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# Dynamic Sensorimotor Interactions in Locomotion

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**Rossignol, Serge, Réjean Dubuc, and Jean-Pierre Gossard.** Dynamic Sensorimotor Interactions in Locomotion. *Physiol Rev* 86: 89–154, 2006; doi:10.1152/physrev.00028.2005.—Locomotion results from intricate dynamic interactions between a central program and feedback mechanisms. The central program relies fundamentally on a genetically determined spinal circuitry (central pattern generator) capable of generating the basic locomotor pattern and on various descending pathways that can trigger, stop, and steer locomotion. The feedback originates from muscles and skin afferents as well as from special senses (vision, audition, vestibular) and dynamically adapts the locomotor pattern to the requirements of the environment. The dynamic interactions are ensured by modulating transmission in locomotor pathways in a state- and phase-dependent manner. For instance, proprioceptive inputs from extensors can, during stance, adjust the timing and amplitude of muscle activities of the limbs to the speed of locomotion but be silenced during the opposite phase of the cycle. Similarly, skin afferents participate predominantly in the correction of limb and foot placement during stance on uneven terrain, but skin stimuli can evoke different types of responses depending on when they occur within the step cycle. Similarly, stimulation of descending pathways may affect the locomotor pattern in only certain phases of the step cycle. Section II reviews dynamic sensorimotor interactions mainly through spinal pathways. Section III describes how similar sensory inputs from the spinal or supraspinal levels can modify locomotion through descending pathways. The sensorimotor interactions occur obviously at several levels of the nervous system. Section IV summarizes presynaptic, interneuronal, and motoneuronal mechanisms that are common at these various levels. Together these mechanisms contribute to the continuous dynamic adjustment of sensorimotor interactions, ensuring that the central program and feedback mechanisms are congruous during locomotion.

## I. GENERAL INTRODUCTION

Previous reviews in the field of locomotion have mainly covered the mechanisms of spinal central pattern generation (244) and sensory as well as supraspinal contributions to the initiation or control of this central pattern generation (15, 244, 246, 477, 486). Major reviews (158, 611) and a book (415) published more recently have also dealt with some aspects of sensorimotor interactions

during locomotion. The present review attempts to give a broad view of the dynamic sensorimotor interactions during locomotion from cutaneous and proprioceptive afferents coursing through the spinal cord as well as from sensory inputs reaching supraspinal structures through ascending spinal pathways or through special senses (visual, vestibular, auditory) that may interact dynamically with pattern-generating networks through descending pathways. Some of the basic and common mechanisms of

dynamic sensorimotor interactions such as afferent excitability changes, interneuronal pathway selection, and locomotor-related membrane properties of neurons will be discussed in relation to afferent and descending inputs acting on locomotor networks. We have tried to give a balanced view of several concepts that have emerged in recent decades. To achieve this, we report studies in sufficient details with appropriate citations that the readers should have the tools to make their own interpretation of the sometimes conflicting results, while at the same time we express our own views on some of the apparent conflicts.

At the onset, it should be stated that removal of all or most sensory afferents by dorsal rhizotomy does not prevent the expression of rhythmic patterns such as locomotion (223–225, 255, 589). Similarly, after pyridoxine intoxication, which destroys large-diameter sensory fibers, cats do eventually recover locomotion even though the large afferents have not recovered (430). In humans, the permanent loss of large sensory fibers below the neck leads to important impairment of walking (reduced joint excursion, enlarged base of support), although slow walking, under visual guidance, is still possible (324). Other work has also clearly shown that after paralysis, induced by a chemical neuromuscular blockade, a complex and detailed rhythmic pattern can be recorded from muscle nerves (“fictive locomotion”) when decerebrate and spinal cats are injected with L-DOPA (254, 433) (see also Fig. 7). These basic findings led to the proposal of the existence of a central pattern generator (CPG) for locomotion, i.e., spinal networks of neurons capable of generating a detailed rhythmic locomotor pattern in the absence of descending or afferent inputs (244).

If not needed to generate the basic locomotor pattern, what then are the roles of sensory information during locomotion? Afferent feedback plays a crucial role in adapting and modulating the operation of the CPG in the real environment. Sensory inputs can have global influences in allowing, preventing, or selecting motor patterns. Through dynamic interactions, sensory inputs can participate in the correct positioning of the feet in uneven terrain or in response to obstacles. They can also modify the frequency of the pattern, its intrinsic structure, or the amplitude of muscle discharges within its component subphases. One immediately realizes the complexity of a situation in which sensory inputs of different modalities must be correctly interpreted while the limbs are continuously changing position during walking. There is thus a need for a great flexibility in the motor responses to sensory inputs during locomotor movements (dynamic sensorimotor interactions).

The expression “dynamic interactions” is taken here to include various conditions in which afferent inputs and the CPG exert a reciprocal influence so that both are changed by the activity of one another. More generally,

the term *dynamic* refers to situations in which evoked responses change as a function of state (or task) or as a function of the phases of the task. Generally, state-dependent modulation refers to a modulation of reflex responses occurring during a “locomotor state” relative to a “resting state.” Task-related modulation, on the other hand, refers to different locomotor tasks (walking, running, walking backward or forward). State- or task-dependent interactions could result in a change of response characteristics (inhibitory to excitatory or vice versa) at transition from rest to locomotion (state) or from forward to backward locomotion (task), or from standing to walking or running (tasks). For instance, an inhibitory response in one state or task may become excitatory in another state or vice versa. Responses that vary systematically as a function of the various phases or subphases of cyclical movements are referred to as phase-dependent responses. Thus an excitatory response in some muscles in one phase can be absent in the opposite phase, or become inhibitory or excitatory to another set of muscles. A less obvious type of dynamic sensorimotor interaction is observed when an afferent input is maintained tonically (for instance, a tonic flexion of a joint or a continuous pinch of the skin) or when afferent inputs are removed, as in the case of a chronic neurectomy or nerve block with a local anesthetic. In these conditions, the tonic input is the same throughout all phases of locomotion, but since locomotion continues, the tonic input dynamically interacts with each subphase of the centrally generated cycle. These dynamic interactions may also evolve with time, for instance, in cases of permanent neurectomy, in which condition sensorimotor motor interactions must undergo some plastic changes.

Mechanisms and sites of dynamic interactions are numerous, and Figure 1 points to some of the possibilities. Afferent inputs from muscles or the skin reach the spinal cord, project to motoneurons directly or through interneurons (influenced by the CPG), or through the CPG itself. Afferents also send collaterals through ascending pathways (directly or via relay interneurons) reaching supraspinal structures (telencephalon, brain stem), which in turn project down to the spinal cord on neurons that may or may not also be contacted by the same primary afferent. Through various mechanisms for selecting motor patterns (locomotion, scratching, fast paw shake), sets of membrane properties (i.e., locomotor drive potential, plateau potentials) are activated. In Figure 1, these mechanisms are only shown for motoneurons in the spinal cord and for one idealized cell in supraspinal structures. For instance, at the brain stem level of the lamprey, sensory inputs of graded strength evoke graded potentials in the reticulospinal cells leading, eventually, to a sustained plateau potential and cell discharges and to the initiation of swimming. There is thus a dynamic transformation of a sensory signal into a motor command, and

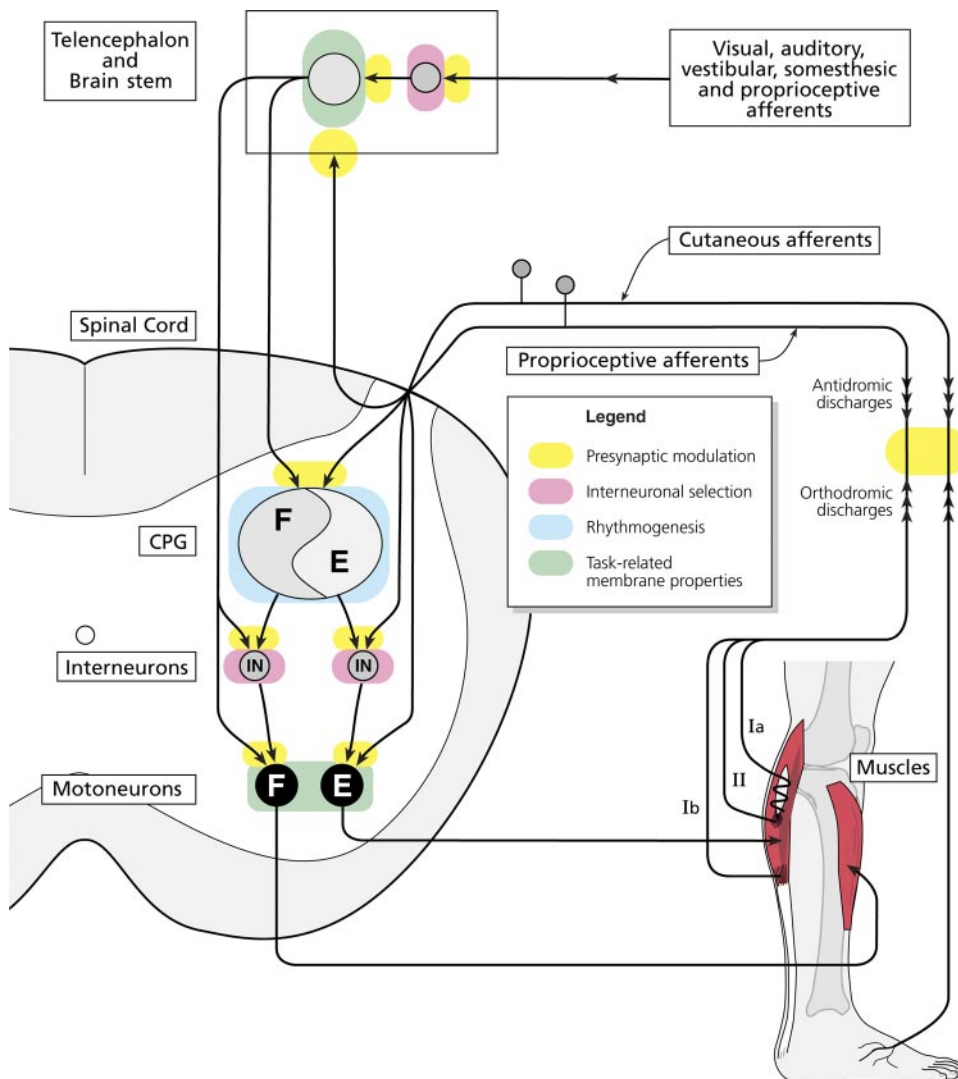


FIG. 1. Some sites for dynamic sensorimotor interactions during locomotion. Sensory inputs of various modalities reach the spinal cord or the brain stem and are generally subjected to a phasic presynaptic inhibitory control (yellow) at their entry (which can even lead to antidromic discharges). Afferent inputs make contact with second-order neurons that are themselves modulated by the rhythmic process such that some pathways may be opened or closed in different phases of the cycle or else the same input may give rise to excitatory or inhibitory responses in the various phases of the cycle (interneuronal selection in pink). This is achieved either by inputs processed by those interneurons implicated directly in the pattern generation or through interneurons whose excitability is modulated cyclically by the central pattern generator (CPG). Interneurons enclosed within the dashed area are considered to be cyclically influenced by the CPG but are not part of the rhythm generation process itself of the CPG. Membrane properties of motoneurons and interneurons apparent only during locomotion (locomotor drive potentials) can also change the gain of the responses to sensory stimuli.

this relies on intrinsic membrane properties of brain stem neurons. At the spinal cord level, sets of interneurons will be selected (interneuronal selection) to allow or block transmission during a given task or else control the transmission in a phase-dependent manner. Finally, through presynaptic inhibition that may occur at different sites (see yellow areas for selected examples), the efficacy of transmission in different tasks and phases of the task may be regulated. It is fascinating to think that probably all these regulatory mechanisms giving rise to a vast repertoire of purposeful dynamic sensorimotor interactions are at play simultaneously during locomotion.

The study of dynamic sensorimotor interactions during locomotion is of interest not only to determine how various reflex responses may give rise to coherent corrections of locomotion to perturbations, but it may also reveal basic mechanisms of sensorimotor integration during movement. First, it is more than likely that the dynamic regulation of responses to unexpected perturba-

tions also applies to the regulation of the normal step cycle by the same afferents during unperturbed walking. Thus the increased or decreased gain of some reflex pathways observed by using perturbations to evaluate such reflex gain may also apply when the same afferents are activated by the locomotor movements themselves (re-afference). Second, the planning and execution of movement must include a set of "ready-to-go" corrections in response to perturbations that may interfere with the various parts or phases of the movement. Studying reflexes during rhythmic processes thus permits the understanding of many of the processes occurring in the background that are revealed only if unexpected events occur. These "behind-the-scenes" processes may be important in pathological conditions in which they may be absent or reduced. Thus it might well be that after neurotrauma or neurological diseases, the ability to correct planned movements is also impaired as well as the movements themselves (608). Work in patients with polyneuropathy



affecting mainly A $\beta$  fibers reveals both abnormalities in gait pattern as well as a great reduction in compensatory adaptive reflexes (572). Parkinsonian patients have also been shown to have a reduced proprioception, which might account for part of their characteristic locomotor deficits (133).

The plan of the review is as follows. In section II, we describe, in various animal preparations, and humans when applicable, state- and phase-dependent spinal reflexes during locomotion in response to various types of sensory inputs (cutaneous and proprioceptive) and indicate their potential contributions not only to adapt locomotion to unexpected perturbations but also to the elaboration of the normal locomotor pattern. Some pathways and mechanisms are suggested to explain certain types of sensorimotor interactions, but some of these common mechanisms are discussed in more detail in the last part of the review. In section III, we describe dynamic sensorimotor interactions between supraspinal structures, activated by sensory inputs either relayed from the spinal cord or by "special senses" pathways reaching supraspinal structures directly. These illustrate how such interactions, together with spinal interactions, lead to a system of coherent corrective responses that will be integrated with the ongoing locomotion. In section IV, a particular emphasis will be put on presynaptic, interneuronal selection, and motoneuronal mechanisms which may, in isolation or in combination, control some of the dynamic sensorimotor interactions during locomotion described in sections III and IV.

## II. SENSORIMOTOR INTERACTIONS IN THE SPINAL CORD DURING LOCOMOTION

This section mainly concentrates on the effects of cutaneous and muscle afferent stimulation in animal preparations, but a number of studies in humans showing similar principles of dynamic sensorimotor interactions are also mentioned. Two fairly recent and extensive reviews have been published on the functional roles of proprioceptive and cutaneous reflexes in the animal kingdom, including humans, during locomotion or other tasks (611) and on load receptors (158).

### A. Cutaneous Afferents

The natural activation of cutaneous fibers can be assessed by recording the actual discharges of single cutaneous afferents or whole cutaneous nerves during locomotion. Only a few studies were performed on the activation of single cutaneous fibers during treadmill locomotion of intact cats (348, 351). Although most of the units discharged as predicted from the direct activation of their receptive field with the external milieu, other units

fired probably as a result of movement-related skin stretches. Some of these units discharged two bursts per cycle. Recording of cutaneous nerves with chronically implanted electrodes (266) also showed whole nerve discharges in distinct phases of the cycle (449). The newly developed method to record multiple single units with electrode arrays inserted in dorsal root ganglia in walking decerebrate cats (14) should provide a wealth of new data on the discharges of cutaneous units especially in relation to proprioceptive afferent units and clarify their relative importance in signaling sensory inputs during various subphases of the locomotor cycle.

For the time being, however, the majority of the work for assessing the role of cutaneous information during locomotion was performed using neurectomies/anesthesia or mechanical stimulation of the skin or electrical stimulation of the skin or skin nerves in different parts of the step cycle.

#### 1. Removal of cutaneous inputs

Early work of Sherrington (531) showed that removing cutaneous inputs from the hindlimbs did not prevent locomotion even after spinalization. This was largely supported by others who reported little deficits when cutting cutaneous nerves in otherwise intact cats (163) or infiltrating the central foot pad with a local anesthetic (190). Anesthesia of the dorsum of the foot in chronic spinal cat (207) or intact cat (462) does not prevent locomotion. However, unpublished observations (S. Grillner and S. Rossignol, unpublished data) showed that anesthesia of the foot pad in chronic spinal cats interfered with foot placement.

Recent work on denervation of the foot pads shed more light on the issue of the contribution of cutaneous inputs to locomotion (48–51, 481). Five cutaneous nerves innervating the hindfeet were cut and prevented from regenerating by capping their proximal end with a polymer cuff. After the denervation, cats with an intact spinal cord could walk almost normally on a treadmill (Fig. 2, A–D). Detailed electromyogram (EMG) and kinematic analyses of treadmill walking showed a long-term adaptation to the denervation consisting essentially in a faster swing (accompanied by an increase in knee and ankle flexors EMG activity), an increased foot lift, as well as a 5–10% increase in double support. The main deficit, however, occurred during precision walking when cats tried to walk on the rungs of an horizontal ladder. Early after the denervation, cats were unable to place their feet on the rungs, and this lasted for 3–7 wk. Eventually, ladder walking recovered but was never quite normal, with cats tending to grip the rungs of the ladder with a clawlike position of the paws. It is thus reasonable to think that cutaneous sensory inputs normally provide the sensory cues necessary to adjust walking, on a step by step basis,

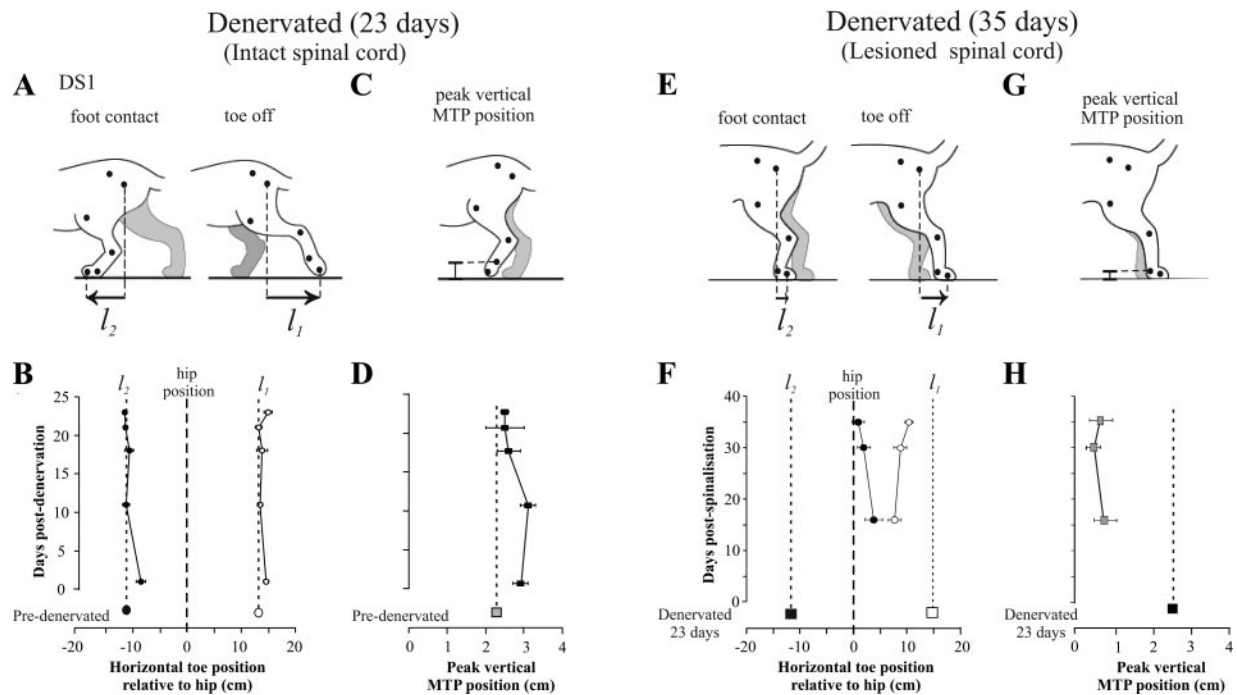


FIG. 2. Details of metric of left hindpaw during treadmill locomotion in a cat, first with the spinal cord intact (*A–D*) and second after a complete spinalization at  $T_{13}$  (*E–H*). *A* and *E*: line drawings from video images. *A*: 23 days after complete cutaneous denervation with the spinal cord intact. *E*: same cat, 35 days after complete spinalization at  $T_{13}$ ;  $l_1$  represents the horizontal distance between the hip and the toe marker at toe off, and  $l_2$  represents the horizontal distance between the hip and the toe marker at foot contact. The sum of  $l_1$  and  $l_2$  is a measure of the step length. *C* and *G*: line drawings representing how peak vertical position of metatarsophalangeal (MTP) joint with respect to treadmill surface was measured and plotted in *D* and *H*. In all graphs each point represents the mean  $\pm$  SD. For *B* and *D*, the vertical dotted lines represent mean predenervation values, and in *B* and *F*, the vertical dashed lines represent the hip position. For *F* and *H*, the vertical dotted lines also represent mean prespinalization values. [Modified from Bouyer and Rossignol (50, 51).]

i.e., dynamically. It is very likely that the kinematic methods used in that study were not precise enough to assess the fine positioning of the foot during ordinary walking on a treadmill or over ground. Increasing the walking difficulty probably enhanced a subtle deficit undetected during level treadmill walking. Further evidence for this comes from the observation that walking on a tilted treadmill was also mildly deficient after denervation, suggesting that the cycle-to-cycle cutaneous inputs from the pads provide a regulatory input to assess load on the limbs during up- and down-going slopes. The vertical and antero-posterior (fore-aft) force distribution measured on a walkway equipped with force platforms was similar before and after denervation, whereas the medio-lateral force during stance doubled after denervation (50). This increase in medio-lateral force may represent a strategy toward a more secure walk by increasing the base of support. It could however also represent a deficit in the correct positioning of the foot secondary to the cutaneous denervation of the hindpaws.

However, after spinalization at  $T_{13}$ , the same cats that had recovered good treadmill locomotion and had regained walking on the horizontal ladder were incapable of placing the foot correctly on the plantar surface (Fig. 2, *E–H*). This was in contrast to nondenervated spinal cats

that had recovered correct foot placement during stance after spinalization (29, 33). The main deficit in the control of the foot was an initial drag at the onset of the swing phase. The animals dragged their foot on the surface of the belt (compare Fig. 2, *D* vs. *H*) during swing and, during stance, their toes doubled up under the foot, which generally remained caudal to the line of projection of the hip joint to the ground (compare Fig. 2, *F* vs. *B*) (51). Of great interest in the context of spinal plasticity, it was found that after partial cutaneous denervation, spinal cats could also adapt their locomotion so that, even with a minimal cutaneous input, spinal cats could “learn” to correctly place the foot (51). This ability was abolished when the denervation was complete. The role of cutaneous inputs thus appears to be crucial for the expression of spinal locomotion and probably for the recovery of locomotion after spinal injury.

The transmission of cutaneous inputs was also found to be modified following locomotor training on a treadmill of spinal cats, indicating the important role of cutaneous feedback for locomotor recovery (104). The amplitude of several cutaneous responses evoked in motoneurons by three different cutaneous hindlimb nerves was significantly modified following 1 mo of locomotor training. The main effect was a decrease in cutaneous transmission

excitability mainly from the medial plantar nerve (MPL) innervating the plantar surface of the foot. This reduction in cutaneous reflex sensitivity by locomotor training may somewhat offset the hyper-reflexia that tends to occur after chronic spinalization (see Ref. 571 for rats).

The experiments in spinal animals have shown the importance of cutaneous inputs for locomotion. The fact that intact cats can walk without cutaneous inputs should not be interpreted to mean that cutaneous inputs are not normally used but rather that other sensory modalities (i.e., proprioceptive) can substitute the missing cutaneous inputs, a substitution which most probably depends on supraspinal controls and cannot be achieved in the spinal state.

## 2. Tonic cutaneous stimulation: triggering, inhibiting, or enhancing locomotion

It has been reported in most studies on spinal locomotion (479) that tonic stimulation of the perineal region (scrotum, vulva, and base of the tail as well as inguinal fold; Ref. 531) is most effective in triggering alternate rhythmic activity of the hindlimbs in cats within the first 7–10 days after a complete spinalization at T<sub>13</sub> or in strengthening weak movements later on when spinal cats have regained spontaneous locomotor movements. The activation of unspecific afferents from the perineal region presumably underlies some important survival function (such as escape from a predator), but the mechanisms of interactions of these perineal afferents with the CPG are not known.

In decerebrate rabbits, electrical stimulation of low-threshold skin afferents (A $\alpha$  and A $\beta$ ) and C fibers from the lumbosacral back regions can increase the amplitude of bursts and frequency of the fictive locomotor rhythm (577). Tonic stimulation of the dorsum of the foot in paralyzed rabbits (575) or of sural nerve in cats (201) can also induce fictive locomotion together with pharmacological stimulation with monoamines.

Although tonic cutaneous stimuli may enhance the vigor or frequency of the locomotor rhythm, stimulation of some specific skin areas can also evoke rhythmic motor patterns other than locomotion. For instance, pinching the toes of a chronic spinal cat elicits brisk alternating movements of the limb with a strong simultaneous activation of several flexor muscles predominantly in the ipsilateral limb. A very similar pattern was observed in paralyzed preparations with the same type of stimulation (433). On the other hand, dipping the foot of a spinal cat in water generates a very brisk paw shake as does the placement of a piece of tape on the foot (28). In paralyzed spinal cat preparations, fictive paw shake can also be elicited by squirting water on the foot pads (433). Finally, stimuli placed on various body parts can generate scratching movements (551). It is thus clear that stimulation of

specific areas and sensory modalities of the skin can induce locomotor movements or other movements that may be more appropriate.

Other types of tonic stimuli can inhibit completely either real or fictive locomotion. Pressing or pinching the skin of the lumbar region of rabbits (576) will instantly abolish locomotion and induce a state of “hypnotic” akinesia. The area of effective stimulus in the rabbit has to be wide (surfaces less than 0.3 cm<sup>2</sup> are ineffective), and the best regions appear to be centered at the lumbar level (220). With well-controlled electrical stimulation (577), it was found that A $\delta$  fibers innervating the dorsal skin areas (probably related to slowly adapting pressure receptors) on one side can block locomotion on both sides while larger (A $\alpha$  and A $\beta$ ) and smaller C fibers may on the contrary exert an excitatory effect as mentioned above. However, after removal of the skin, pressure on a spinous process can also block locomotion. It must therefore be concluded that other modalities than cutaneous inputs also have this capacity to arrest locomotion.

## 3. Phasic cutaneous inputs: correcting the steps

Although cutaneous inputs may have some general roles to play in locomotion such as triggering walking (perineal stimulation) or inhibiting walking (inhibitory inputs from the skin of the back), the main role of cutaneous inputs appears to be the correct positioning of the foot during normal walking or the correct adaptive limb responses to perturbations in different phases of the step cycle. This role requires a great deal of plasticity to adapt multijoint limb responses to a variety of possible perturbations according to the initial static position of the limbs or to the continuously changing limb position during locomotion.

There are several examples in the literature of the adaptability of cutaneous reflexes to initial conditions of the limbs (56, 215, 243, 250, 483, 484, 530); the same stimulus may give rise to responses in flexor muscles or extensor muscles depending on the initial posture of the limb, and this might be relevant to the dynamically changing positions of the limbs during locomotion. A stimulus on one side gives rise to a flexion response if the limb is extended and, conversely, to an extension response if the limb is flexed. Similar observations had originally been made by von Uexkull (584) on the starfish appendage. When hanging on one side, a stimulus would flip the appendage upwards; rotating the appendage by 180°, the same stimulus flipped the appendage upwards, activating the antagonist muscle. This reflex reversal was interpreted on the basis that the stretched muscle of an antagonist pair was more excitable than the other and therefore, whichever muscle was most stretched by the bend of the appendage responded to the stimulus.



Using a tonic stimulation such as a clip on the skin or a tonic electrical stimulation of an afferent nerve, Sherrington (531) noted that the ongoing stimulus after starting locomotion was alternately activating flexors and extensors, i.e., that the same stimulus was effective in exciting one group of muscle in one phase and the group of antagonists in the opposite phase. The expression *reversal* has been used to describe responses that are excitatory in one muscle group in one phase and excitatory to the antagonist muscles in the opposite phase. It has also been used to describe responses that are excitatory in one phase and inhibitory in the opposite phase, or vice versa. Several examples of phase-dependent reflex reversal during rhythmic activity such as locomotion have been described using either mechanical or electrical stimulation of the skin itself or electrical stimulation of specific cutaneous nerves and are detailed in the following paragraphs.

A) MECHANICAL SKIN STIMULATION IN CATS: STUMBLING CORRECTIVE REACTION. Responses to mechanical stimulation of the foot are phase dependent (swing/stance) as well as task dependent (forward/backward walking) and also site dependent (ventral/dorsal). This complex and refined reflex control is absolutely essential to generate avoidance responses appropriately tuned to the specific locomotor phases.

Early studies on the modulation of cutaneous reflexes during locomotion were first performed on chronic spinal cats (206–208). A rod equipped with a micro switch to indicate contact with the dorsum of the foot was used to mechanically obstruct the limb in different phases of the step cycle.

Similar responses were also studied in intact cats with a similar device or even only with air puffs (203). A contact on the dorsum of the foot during swing, as when hitting an obstacle, evokes a robust response of the limb characterized by a prominent knee flexion that rapidly withdraws the foot and then a flexion of the ankle and hip to step over the obstacle and place the foot in front of it (Fig. 3A*b*). During this initial knee flexion, conflicting results have been obtained in ankle muscles. In some studies (462, 587), there was a short latency (10 ms) activation of the ankle flexor tibialis anterior (TA) presumably due to the muscle stretch imposed by the mechanical perturbation. This was immediately followed (at ~25 ms) by an activation of the ankle extensor gastrocnemius lateralis (GL). These specific responses were abolished by local anesthesia, but stretch-induced responses of the ankle flexor remain. It was hypothesized (462) that the early cutaneous responses prevented such stretch responses of ankle flexors that could be counterproductive by inducing an ankle flexion risking to catch the foot in the obstacle instead of avoiding it. In another study (65), a GL activation was also seen during the knee flexion while the TA which is normally active during swing was

actively inhibited. Whether the ankle was locked or extended, the net result was to prevent a further ankle flexion. It is interesting that a similar mechanical stimulus applied to the dorsum of the foot during backward walking in intact cats (65) did not induce the same complex sequential pattern but rather evoked a simultaneous co-activation of the knee and ankle flexors leading to a modestly increased backward swing. When an obstructing perturbation is applied to the ventral surface of the paw during backward walking, there was an initial excitatory response in the ankle flexor and knee extensor which withdraws the foot forward in front of the obstacle followed by an increased knee flexion and eventually knee and ankle extension to place the foot on the supporting surface (65) (Fig. 3A, *e* and *f*). The pattern of muscle activation is thus here different from that of the obstructing perturbation during forward walking swing but achieves the same function of withdrawing the foot from the obstacle. Again, nonobstructive perturbation of the dorsal surface during swing in backward walking elicited more or less the same response as stimulation of the ventral surface during swing in forward walking.

When the same mechanical stimulus is given during stance, in the chronic spinal cat (206), flexor muscles do not respond but, on the other hand, there is a short latency increase of reflex amplitude of the already active extensor muscles at the ankle and knee. Because these stimuli occur during a phase of weight support, the actual limb movements appear less obvious than with perturbations during swing (see also Ref. 65). However, in the spinal cat there is a distinct increase in the ankle and knee angular velocity in the extension direction that could accelerate the movement of the foot in the backward direction. These excitatory extensor responses (often preceded by a short inhibitory response) are more prominent in spinal than in intact cats (32, 462).

B) MECHANICAL SKIN STIMULATION IN HUMANS: TRIPPING. Similar studies using mechanical obstruction of the limb have been performed in humans. Experiments designed to reproduce conditions in which stumbling could occur were performed in subjects walking on a walkway equipped with a force platform. Two 8-cm metal strips embedded in the walkway were flipped upwards in early swing or late swing at times where the toe velocity was about equal so as to generate a similar stimulus when the foot touched the strip (189). When the foot touched the strip in early swing, there was an early response in biceps femoris (BF) of the ipsilateral leg in the swing phase followed by a later response in rectus femoris (RF) and a more variable response in TA. This altogether removed the foot from the obstacle and placed it in front of it. At the same time, short latency responses in hip, knee, and ankle extensor muscles were observed in the contralateral limb in the stance phase, producing an elevation of the whole body, which again allowed for a better clearance of the foot



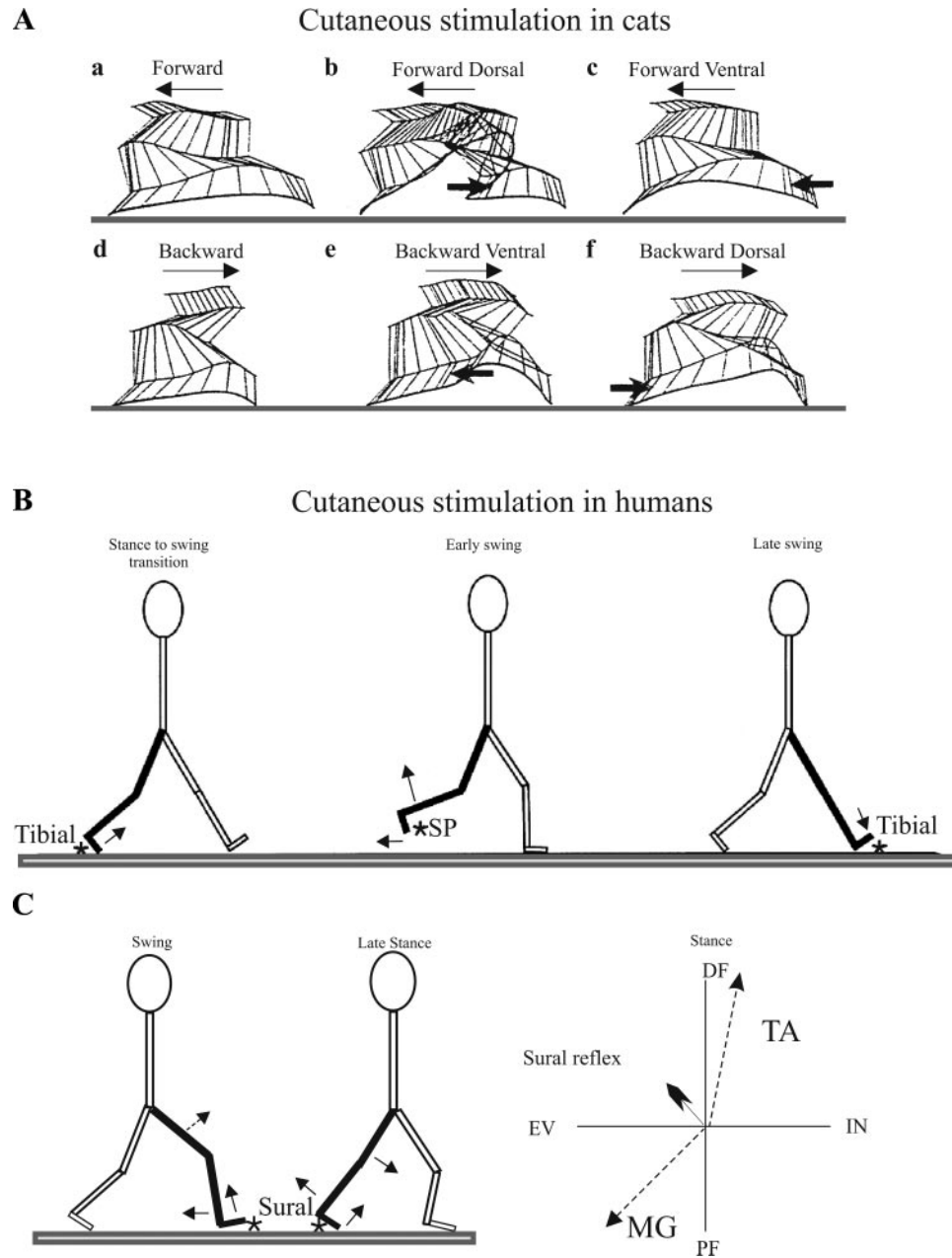


FIG. 3. Cutaneous stimulation in the cat and human: effects of tasks and stimulation site. *A*: hindlimb trajectories before and after mechanical stimulation during swing for backward and forward walking. Locations of the digitized joint coordinates were adjusted for treadmill velocity to create the appearance of over ground locomotion. Normal, unperturbed swing-phase trajectories are illustrated in *a* and *d*, responses to obstructing stimuli are illustrated in *b* and *e*, and responses to nonobstructing stimuli are illustrated in *c* and *f*. Stick figures illustrate hindlimb positions at 30-ms intervals, with an extra stick figure drawn to represent the position at the time of stimulation, indicated by the solid arrows. Direction of walking is indicated above each figure by thin left- or right-directed horizontal arrows. [From Buford and Smith (65).] *B*: schematic diagram of the functional effects of cutaneous reflexes from tibial nerve at the stance to swing transition and late swing and from superficial peroneal (SP) nerve during mid swing. The direction of the induced movements is represented by arrows. Note that after SP nerve stimulation there is a stumbling corrective response involving a linkage between knee and ankle joint mechanics. A phase-dependent reflex reversal (see movement direction indicated by arrows) in the ankle response can be seen when comparing the stance to swing transition and the late swing reflex after tibial nerve stimulation. \*General cutaneous field activated by the electrical stimulation for each nerve. [From Zehr et al. (610).] *C*: schematic illustration indicating proposed functional roles of sural cutaneous reflexes during gait. In stance and late stance, the effect of the reflex is to accommodate to uneven terrain, whereas during swing the reflex avoids a trip. \*Activation of the sural cutaneous field. [From Zehr et al. (612).] The graph on the right combines EMG responses as well as direction of movement. During swing phase, the knee flexion and ankle dorsi-flexion (DF) predominate. During late stance, the hip and knee flexion as well as ankle DF are key features, and during stance (large arrowhead), a net effect of lower leg responses is observed, wherein medial gastrocnemius (MG) and tibialis anterior (TA) responses act in concert to evert (EV) and DF the foot. The putative contributions of MG to plantar-flexion (PF) and EV and TA to DF and inversion (IN) are shown by dotted lines.

from the obstacle. In late swing, the perturbation was more threatening to the equilibrium and evoked a lowering strategy to shorten the swing and put the foot down as soon as possible. This strategy was achieved through either inhibition of the knee extensor or an activation of BF, which would indeed bring the foot down in that configuration of the limb. A third and rarer strategy also occurring in the late swing was termed a *reaching strategy* in which the subject increased or prolonged the hip flexion to increase toe clearance.

In a different study, instead of using a tripping device, an obstacle was released from a magnet on a treadmill at different times after heel strike (508). An elevating strategy was used in early swing, and a lowering strategy was used in late swing. In the first strategy, the foot was brought up by an early flexion at the ankle and at the knee caused by reflex activity in TA and BF. In the lowering strategy, the foot was rapidly put down and then overcame the obstacle in the next cycle. This was brought about by a short latency response in RF and Soleus. The strategy used in mid swing could be an elevating one or a lowering one. The exact afferent source for these responses was not clear. As will be detailed later, electrical stimulation of nerves responsible for the innervation of the same skin area caused a suppressive response of TA in late swing, whereas in the study reported here using mechanical contact, TA was excited. Therefore, other afferent inputs resulting from the abrupt contact of the foot with the obstacle may be responsible for these responses.

C) ELECTRICAL STIMULATION OF CUTANEOUS AFFERENTS IN CATS. Given the difficulty of applying mechanical stimulation to the skin in the different phases of walking, early work used electrical stimulation of the skin and also reported phase-dependent responses in spinal kittens (206, 208). The electrically evoked responses were generally very similar to those evoked by mechanical stimulation. An early work showed that trains of stimuli applied to the tibial or sural nerves (156) had profound effects on rhythm generation in decerebrate cats walking on a treadmill and even entrained the fictive locomotor rhythm (485). Indeed, stimulating large cutaneous fibers with short trains of pulses reduced the duration of flexion and induced a premature initiation of extension, i.e., resetting the rhythm whereas high-threshold fibers would rather prolong the flexor bursts. It was also shown that stimulating the pad and plantar surface during the stance phase increased both the amplitude and duration of the ongoing extensor activity, an action interpreted as helping to compensate for extra load (161). When given during the swing phase, the same stimulation prolonged the flexion or shortened the following extension. These early observations were followed by a number of more detailed studies establishing more precisely the phase-dependency modulation of such responses. Figure 4 illustrates a methodol-

ogy often used to determine the phase dependency of reflex responses during locomotion. To retrieve the phasic modulation of amplitude of the reflex responses in a given muscle independently of the locomotor discharge of that muscle, the reflex responses at a fixed latency must be subtracted from the locomotor electromyographic signal occurring within the locomotor burst at the same time. It can thus be observed that the reflex responses in a given muscle may follow or not the locomotor activation profile of that muscle.

I) *Hindlimbs*. i) Swing phase. With electrical stimulation of the dorsum of the foot (nerve or skin) during the swing phase, short latency responses ( $\sim 10$  ms) are seen in the knee flexor semitendinosus (St) [P1 responses (159)], and very often a second response, P2, appears ( $\sim 25$  ms) in chronic spinal as well as in intact cats (203) (see also Fig. 4). This pattern is seen in several flexor muscles. These two reflex responses at different latencies can be modulated differentially within the step cycle (1) and reach their peaks in different phases of the cycle (159, 203) (see Fig. 4E). The P2 responses are also seen without preceding P1 responses. In GL of intact cats, short latency responses (10 ms) were observed during swing (1, 203), although these were not seen by all investigators (159, 462). A similar pattern of response was also observed in decerebrate cats (161, 203).

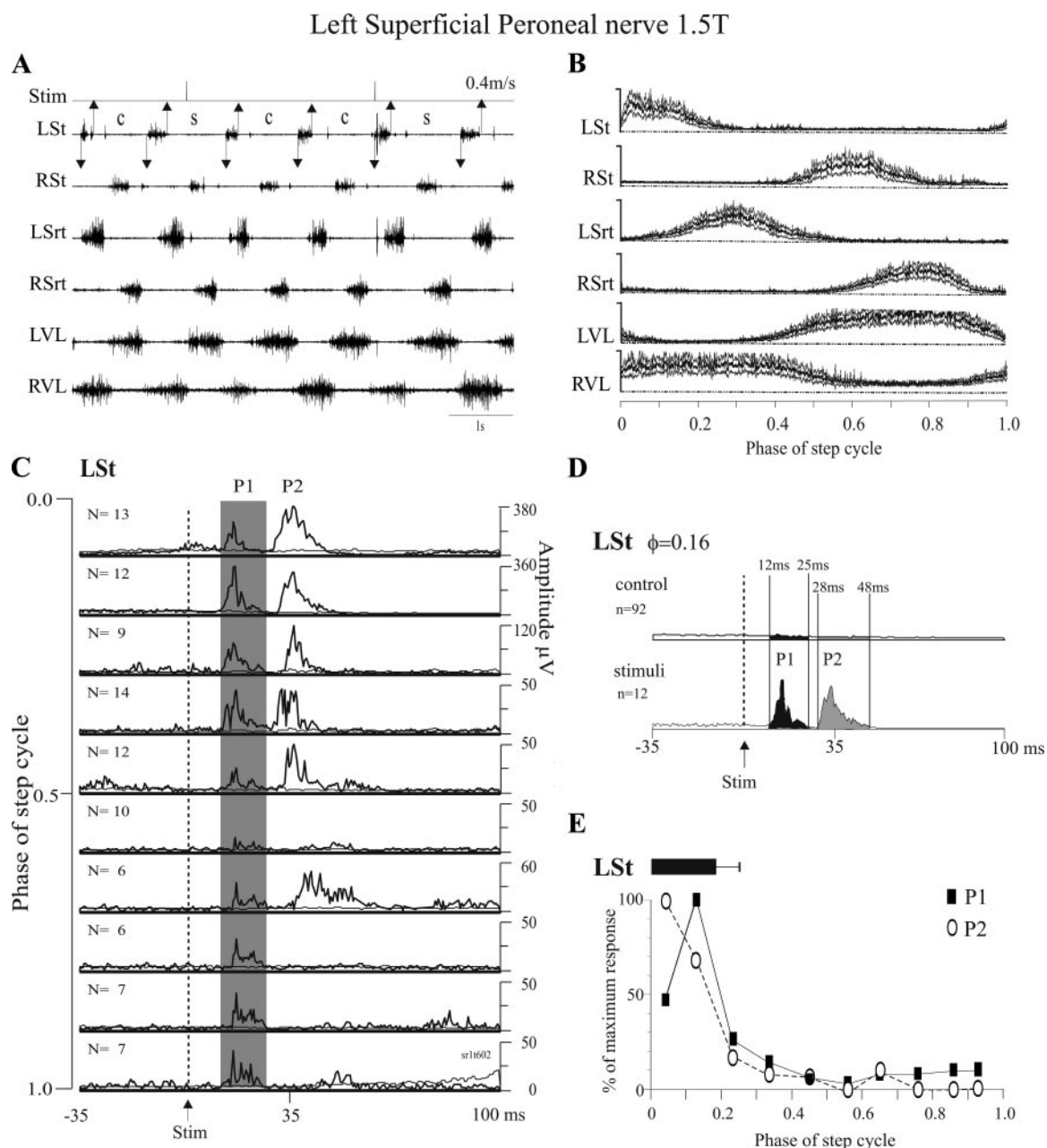
Stimuli applied during the ipsilateral swing also gives rise to P2 responses in the contralateral limb of decerebrate cats (159) and chronic spinal cats (207). In the latter, the crossed extension reflex usually had a shorter latency than the ipsilateral excitatory responses observed in extensors (see below). Finally, crossed flexor as well as crossed extensor responses occur in decerebrate (216) and intact cats (159, 160), again suggesting a variety of crossed cutaneous pathways (268) leading to the phase-dependent activation of antagonist motoneuron pools.

The period of reflex responsiveness in a given muscle does not necessarily coincide with the period of locomotor activation of the muscle. For instance, P2 in St may reach its maximal amplitude before the muscle is activated. P1 responses may also be present well after the first St burst has ended (207) and are often absent during the second St burst which occurs at foot contact. Such discrepancies have also been well documented also by others (439) using stimulation of dorsal root filaments and recording from muscles such as St, flexor hallucis longus (FHL) (410), and extensor digitorum longus (EDL). There is thus good evidence that the reflex modulation during locomotion does not primarily result from an automatic gain control of reflexes, i.e., a condition in which reflex amplitude would simply follow the amplitude changes of the underlying locomotor EMG (see Fig. 4). Similar evidence obtained in the forelimbs will be reviewed later and will be discussed more thoroughly in section IV. Moreover, the reflex excitability and locomotor recruitment of distal

hindlimb muscles may be significantly different among animals, and this may be related to the variability of mechanical action of certain muscles in different animals (350).

ii) Stance phase. Electrical stimulation during stance also gives a rather complex sequence of responses. In the intact cat, stimulation of the dorsum of the foot or specific cutaneous nerves evokes predominantly a short latency inhibition followed by a longer latency excitatory response at a P2 or P3 latency ( $\sim 35$  ms) (1, 32, 159, 203, 207, 350, 462). This short latency inhibition is less pronounced in chronic spinal cats (203), and even shorter latency excitatory responses appear in gastrocnemius medialis

(GM) and flexor digitorum longus (FDL) with sural nerve stimulation (1) and sometimes in vastus medialis (VM) motor units (356). It is of interest to link these observations to previous studies that have described short latency excitatory pathways from cutaneous afferents to extensor motoneurons (69, 201, 258, 322, 323, 595). Therefore, the predominance of short latency inhibitory responses in intact cats and the often preponderant excitatory responses in spinal cats might simply reflect the fact that multiple alternate pathways are recruited by these stimuli and that the transmission in the various pathways may vary according to the preparations (268). At longer latency, the effects of cutaneous inputs from the hindpaws



(pads and sural territory) are predominantly excitatory to extensor muscles during locomotion (161, 201, 344).

The dominant excitatory effects on extensor muscles from the foot may participate in the regulation of stance together with muscle proprioceptors as will be discussed in more details below (161). On the other hand, if a moving object touches the dorsum of the foot, the excitatory responses in extensors may serve to push the foot backwards and shorten the stance to reduce the period of contact with the obstacle. Furthermore, an object touching the foot laterally in the receptive field of the caudal sural nerve can generate responses in GM to remove the foot in a specific direction. These responses would be related to specific excitatory pathways from sural nerve to GM (304, 322). Such site-specific responses (classically described as local sign) elicited during locomotion (157, 159, 163) would thus be highly purposeful. A series of experiments in the rat suggested that precise withdrawal patterns of the foot were subserved by an elaborate set of spinal modules (519, 520) that could play a role in avoidance responses during locomotion. Such an organization has also been suggested to be present in humans, as will be discussed below.

iii) Effects of phasic stimuli on overall changes of the step cycle. One remarkable function of complex phase-dependent responses is to optimize the compensatory movements and minimize perturbation of walking. If flexion reflex responses to the stimulation of the dorsum of the foot would occur in stance, that is, when the foot is on the ground and the contralateral limb is swinging forward, profound perturbations of the rhythm would ensue. In such case, the stimulated limb would rapidly flex and curtail the stance phase, while the contralateral limb would have to rapidly be brought downward to support weight. This is not the case with the responses described here in which flexion responses are inhibited during

stance or replaced by ipsilateral extension. Therefore, the kinematic changes are limited to the on-going phase, and the corrections are over within one step cycle (156, 216). Stimulation of the dorsum of the foot during swing in the chronic spinal cat (207) usually slightly increases the duration of that phase. Stimulation in E3 may shorten the cycle up to ~20%. The contralateral cycle is only slightly changed. Similarly, in the thalamic cats, stimulation of the foot pad or sural nerve shortened the ipsilateral cycle by ~10–15% unless applied in early swing and in the late stance phase (157, 161). In the intact cat (203) there are only very limited changes in cycle duration. Therefore, these well-adapted phase-dependent reflex responses allow corrections to occur within the locomotor phase where they occur and minimize the perturbation to the overall locomotor progression.

iv) Phase-dependent responses in fictive locomotion. It is of interest to ask whether the phase-dependent modulation of reflex responses results from cyclical changes of central excitability or from concomitant interactions with afferents activated during locomotor movements of the limbs themselves. This was addressed using preparations with fictive locomotion in which there is no movement.

During fictive locomotion induced by noradrenergic drugs in cats spinalized a week before an acute experiment (321), the amplitude of short latency reflexes was also modulated in a phase-dependent manner. Specific cutaneous nerves were stimulated, and the response pattern to stimulation of low-threshold afferents was determined in various flexor and extensor muscle nerves. As was described before for real locomotion, phase-dependent reversal was shown, i.e., the same stimulus producing a short-latency excitation in the flexor St during and somewhat after its period of activity and excitatory responses in ankle extensor nerves in the opposite phase,

FIG. 4. Method for measuring size, latency, and duration of cutaneous reflexes during locomotion. *A*: raw recording of various muscles recorded chronically from the hindlimbs of a cat (more detailed methodology in Ref. 33) during a locomotor sequence. The muscles are as follows: semitendinosus (St, a knee flexor and hip extensor), sartorius (Srt, anterior part being a hip flexor and knee extensor), and vastus lateralis (VL, knee extensor). L, left; R, right. A cycle is defined as the period between the onset of two successive St bursts as detected by a Schmitt trigger. Stimuli occur at every third step cycle(s) after two control cycles (c). The up and down arrows indicate the computer selected onset and offset of the St bursts, respectively, with stimuli (stim) indicated by ticks. The stimulus is delivered at random times (in 100-ms intervals) within the step cycle according to a random preprogrammed sequence. Thus, in one stimulated cycle, the stimulus may occur at time 0 ms relative to the onset of St, or at time 200 ms. At each interval, ~10 stimuli are delivered for further averaging of responses (see below). *B*: template of locomotor EMGs of 92 control cycles (c) used to subtract the reflex responses of each muscle in the different phases. The cycle is normalized to 1. The mean EMG amplitude and standard deviation allow one to determine the significance of the reflex responses in various phases of the step cycle. It is important in reflex responses to subtract the mean EMG amplitude in the exact phase in which the stimulus is delivered to differentiate increase in reflex amplitude from the increase of the underlying EMG burst. *C*: all the responses obtained are grouped into the normalized step cycle in 0.1 phase increments. The 10 records represent averages of all St responses within each 0.1 phase of the cycle ( $N$  = number of stimuli given). The displayed responses represent the difference between the integrated value of the reflex response and the integrated value of the control EMG occurring within that phase as obtained from the template shown in *B*. The scales on the right represent an arbitrary value of integration and allow one to optimize the display at each phase even though the amplitude of the responses may vary. *D*: the alignment of onsets and offsets of the responses allows one to clearly define the time intervals for integration of the responses. Clearly in this case there are two peaks labeled P1 (between 12 and 25 ms) and P2 (28 to 48 ms) responses (see text) that will be integrated and from which the integrated background activity of EMG (here 92 cycles) occurring at equivalent intervals in the control cycles will be subtracted. All the bins within those windows are averaged to give a single value. *E*: the P1 and P2 responses are plotted for each of the 10 phases of the normalized step cycle as a percentage of the maximal averaged response in one phase. The locomotor burst duration ( $\pm 1$  SD) of the responding muscle (in this case L St) is represented as a black rectangle above the box.



with a predominance of some inputs from specific cutaneous nerves to certain motoneuronal pools. P1 and P2 responses could clearly be seen in these spinal cats, and their respective amplitude modulation was different in the various phases of the fictive locomotor cycle. The importance of this study, as well as that of others (8) in paralyzed cats, was to show that these refined dynamic interactions rely on central mechanisms rather than on concomitant afferent mechanisms as could be the case when sensory afferents are activated during real movements of the limbs.

The extent of complex central mechanisms in phase-dependent reflex modulation was highlighted by an important study that illustrated the differential responsiveness of two synergistic muscles during fictive locomotion. Anatomically, the FDL muscle acts as an extensor of the toes in parallel with the FHL muscle. However, during stepping, FHL is active as an antigravity muscle during the extensor phase, whereas FDL is active in early flexion except for rare bursts of activity in extension presumably associated with perturbed steps (410). This difference is striking because FDL and FHL share common monosynaptic Ia excitation (201), which is usually an indication of synergistic action (177). During fictive locomotion, intracellular recordings show that disynaptic excitation from superficial peroneal (SP) to FDL is facilitated in early flexion, when FDL is bursting and motoneurons depolarized (510), whereas di- and trisynaptic excitation from the medial plantar nerve (MPL) innervating the ventral surface of the foot is depressed. However, the trisynaptic excitation from the MPL nerve is enhanced during extension in unusual or perturbed steps when FDL fires in extension (201, 394). In contrast, the SP responses in FHL motoneurons consisted mainly of inhibitory postsynaptic potentials (IPSPs) with little or no excitatory postsynaptic potentials (EPSPs) (201). These contrasting modulation patterns and the ensemble of results on these pathways indicate that SP and MPL cutaneous inputs to FDL cells are transmitted through completely different sets of interneurons that can be driven by the CPG (67, 68). Remarkably, the excitation in FDL is trisynaptic at rest or in extension but disynaptic in early flexion. The stimulation of the red nucleus or pyramidal tract can also decrease the latency of cutaneous responses in FDL motoneurons (510, 510). However, disynaptic linkage is also seen during rhythmic activities in spinal cats injected with nialamide and L-DOPA (510), and the spinal mechanism rerouting the SP inputs onto the last-order interneurons is unknown. Candidate interneurons have been located in laminae V and VI of segments L6 and upper L7 (395), but there are yet no recordings during fictive locomotion.

Short-latency responses to SP and MPL inputs were also studied in motoneurons of EDL and TA, two synergist ankle flexor muscles (120). In EDL motoneurons, SP evoked mostly disynaptic IPSPs in early flexion and had

very little effect in extension or at rest. EDL motoneurons are depolarized in mid and late flexion. In contrast, SP produced oligosynaptic EPSPs at rest and also during extension in TA motoneurons, but these were suppressed in flexion. On the other hand, MPL evoked disynaptic EPSPs in both EDL and TA cells that were suppressed in flexion. Together with previous data, the MPL excitation is suppressed in FDL, EDL, and TA cells during flexion, and common interneurons may be involved in these pathways. Also, SP interneurons projecting to FDL and EDL appear to be driven during flexion. Moreover, disynaptic EPSPs in FDL and IPSPs in EDL are enhanced during the early flexion phase of fictive locomotion, but markedly depressed during fictive scratching indicating a clear state-dependent transmission in these pathways (121, 121).

Two recent papers by the group of McCrea (469, 470) have extended significantly our knowledge of the spinal pathways involved in stumbling corrections evoked in the flexion phase or the preventive stumbling reactions triggered by the same stimulation applied during the extension phase. The first remarkable finding is that the details of functional stumbling responses can be observed during fictive locomotion evoked by mesencephalic locomotor region (MLR) stimulation (see sect. III) in the decerebrate cat (469) by stimulating the superficial peroneal nerve with trains of pulses and recording several nerves acting at the various hindlimb joints. First, the ankle (except TA which is briefly activated) and hip flexors are initially inhibited (possibly to prevent further contact with the stimulus). This is followed by a knee flexion and ankle extension to actively remove the foot and then a later activation of flexors at different joints that would presumably bring the limb in front of the obstacle. Interestingly, the cutaneous nerve stimulation applied during stance also evoked excitatory responses in ongoing extensor muscle nerves (see also Ref. 321) and a subsequent large activation of the hindlimb flexor discharges in the next flexor phase of the fictive locomotor cycle. Corresponding intracellular events were also recorded from various types of motoneurons (470). Of great interest in this study is the predominance of di- and trisynaptic excitation of knee flexor and ankle extensor motoneurons. Concerning the latter, the excitation starts at the same time as in the knee flexors, but the actual motoneuronal discharges (and hence electroneurographic responses) are somewhat delayed because this excitation first has to offset the locomotor-related hyperpolarization of the extensor motoneurons in that phase. There is also a clear increase in amplitude of IPSPs in ankle flexor motoneurons and a reduced inhibition of extensors. Finally, late responses occurring in the following flexor phase after a stimulus applied in the previous extensor phase are thought to represent complex responses evoked by the SP nerve through the CPG.

Together, these intracellular studies of motoneurons clearly suggest complex mechanisms of reflex pathway selection (see Fig. 1) by which afferents reaching synergistic muscles give rise to appropriate phase-dependent responses either through the CPG itself or through interneuronal pathways whose excitability is modulated by the CPG. This is discussed further in section IVB.

*II) Forelimbs.* Although most studies on dynamic sensorimotor interactions were performed on the hindlimbs of cats, some studies on the forelimbs shed new light on such interactions. As was the case for the hindlimbs, cutaneous afferents of one forelimb were also removed (534), and 1 wk later the cat could walk well on the treadmill, suggesting that these afferents are not essential for the control of forelimb walking.

Responses to cutaneous stimuli of the forelimbs during unrestrained walking are also phase-dependent in intact cats (146–148, 482) and thalamic cats (535). Figure 5 illustrates an interesting combination of responses to electrical stimulation of the superficial radial nerve during the swing and stance phases in four muscles with different biomechanical actions at different joints. Figure 5 illustrates, with raw EMGs (on the left side), typical responses evoked by a single stimulus given during either the swing or stance phases (left column). The responses to 10 stimuli given in swing and stance are displayed in a raster form in the two middle columns to illustrate their general phase dependency. On the right of Figure 5, *A–D*, the responses are plotted as a function of the cycle phase using the method described in Figure 4. Note that the duration of activity of other muscles acting at the same joint are also displayed (open bars) on the right side for comparison. The latissimus dorsi muscle (a shoulder retractor) has a large response to the stimulation of the radial nerve during swing but is unresponsive during stance. On the other hand, there is a large excitatory response in triceps brachii (long head, elbow extensor) during swing where this muscle is normally inactive during locomotion and an inhibitory response during the stance phase. As mentioned previously for the hindlimb, when the forelimb hits an obstacle the elbow flexors and extensors are strongly coactivated leading to a virtual lock of the elbow while the shoulder retracts the limb first and then, at a longer latency, the shoulder protracts and brings the limb in front of the obstacle. The large out-of-phase excitatory response in triceps during swing, in a period where this muscle is inactive during locomotion, indicates again that the reflex responsiveness of a muscle may be under separate control from its locomotor activation. In Figure 5C, the elbow flexor yields an important excitatory response during swing followed by a clear inhibition and is unresponsive during stance. Palmaris longus (Fig. 5D), which is normally active during stance, shows a large response in swing and a slight excitatory response during stance followed by inhibition. These responses are undoubtedly related to the positioning of the foot.

Finally, it should be pointed out that the responses in a given set of muscles are not only dependent on the main phase of the step cycle (swing/stance) but also on their subphases. Thus a perturbation of the forelimb in the early swing phase is compensated for mainly by retraction of the proximal shoulder joint, whereas the same stimulation applied in late swing when the foot is just about to touch ground, evokes a variety of responses, either flipping the foot upwards or else speeding up the contact with ground. This is very similar to hindlimb responses and illustrates the refinement of the control of reflex responses that must be optimized to best compensate for an obstacle in all phases of the movement.

It is of interest to mention that, during fictive locomotion, when there is no movement, the out-of-phase responses occurring in triceps could not be observed (504) and only excitatory responses during the period of locomotor activity obtained with stimuli applied to the superficial radial nerve. This might implicate that, for this particular cutaneous pathway, the out-of-phase responses may depend on a balance between central drive and concomitant peripheral inputs generated during active locomotor movements.

*D) ELECTRICAL STIMULATION OF CUTANEOUS AFFERENTS IN HUMANS.* In humans, nonnociceptive electrical stimulation during walking also yields phase-dependent responses that induce withdrawal responses during swing and stabilizing responses during stance (610) (see Fig. 3, *B* and *C*). As was indicated in previous animal work (206, 207), such phase-dependent reflex reversal makes functional sense. For instance, tibial nerve stimulation, which mimics a stimulation of the plantar surface of the foot (Fig. 3B, *left*), yields an ankle flexion at the stance to swing transition to remove the foot, whereas it produces an ankle extension in late swing (Fig. 3B, *right*) to accelerate foot placement on the ground (165, 610). Stimulation of SP, resembling a stimulation of the dorsum of the foot such as when encountering an obstacle, produces a suppressive response in TA in early swing which translates mechanically into a plantar-flexion, whereas there is an excitatory response in SOL, GL, and GM later in swing (610) (Fig. 3B, *middle*). If the stimulation evokes a larger flexion of the ankle, it could increase the likelihood that the foot would catch the obstacle instead of clearing the obstacle (168). Thus the site of cutaneous stimulation determines largely the type of functional reflex responses evoked to clear an obstacle or to prevent further contact with the obstacle. Other studies, stimulation during stance of the sural nerve which innervates the lateral part of the foot, have shown (165, 612) an activation of GM and TA, and these responses are believed to result in a dorsi-flexion and eversion of the foot (see large arrow in Fig. 3C, *right*). Presuming that the sural nerve stimulation here mimics a stimulation of the lateral part of the foot on an uneven terrain, the eversion response would counteract the in-

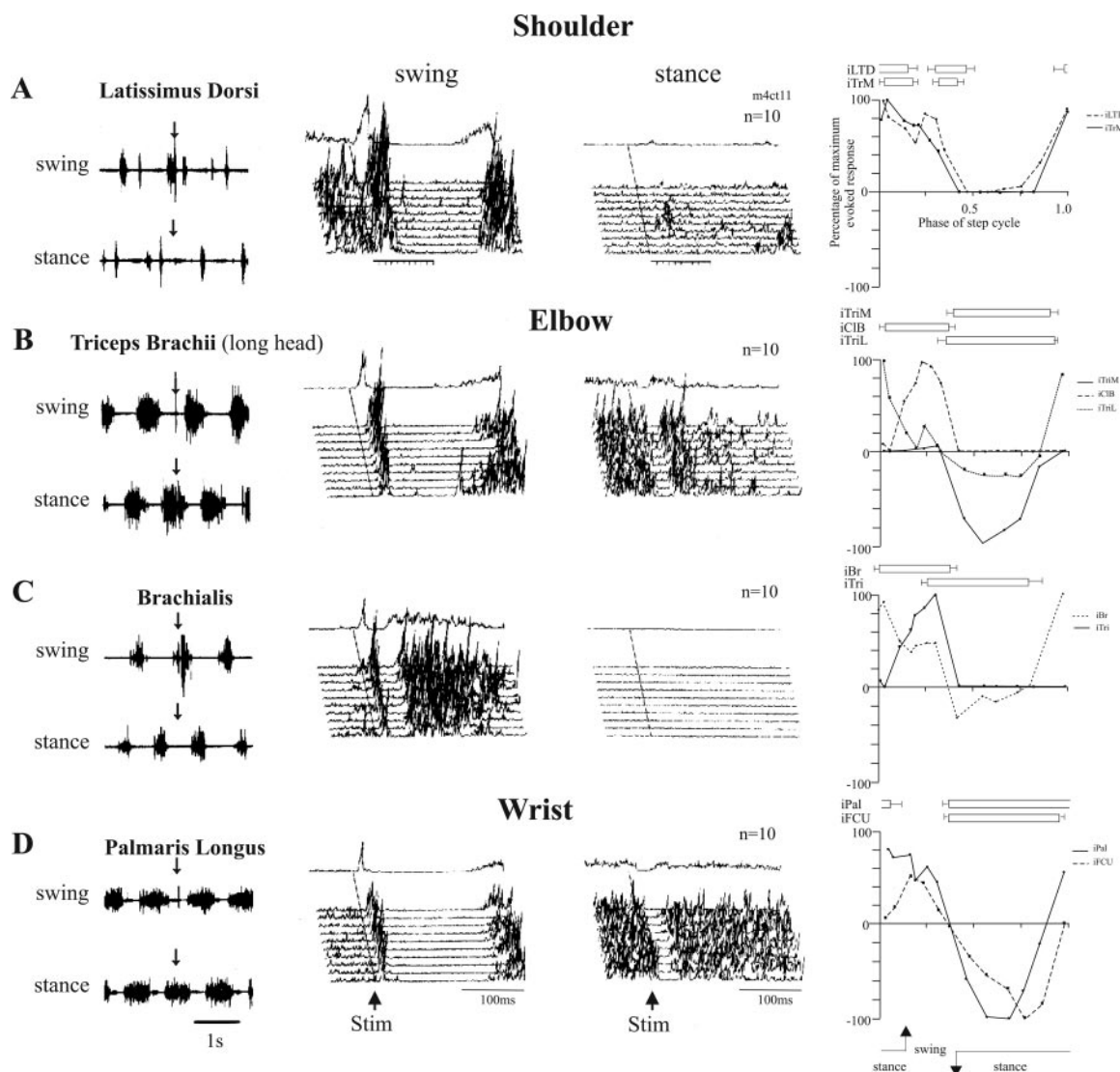


FIG. 5. Reflexes evoked in forelimb muscles by low-strength electrical stimulation of the superficial radial nerve. Four forelimb muscles are illustrated: *A*: latissimus dorsi (LTD) acting as a shoulder retractor. *B*: triceps brachii (Tri, long head) acting as an elbow extensor and shoulder retractor. *C*: brachialis (Br), an elbow flexor. *D*: palmaris longus (Pal), a wrist ventro-flexor. For each muscle, the traces display the following information: on the left, original records of EMG activity showing the effects evoked in the muscle by a stimulus applied either during swing or stance. The arrows indicate the time of stimulation. In the next column, swing, the reflexes evoked during swing in each of the muscles during 10 different sequential trials together with the average (top trace) of these 10 trials. The traces are aligned with respect to the time of stimulation, indicated by the oblique line. In column stance, the same display shows the reflex responses evoked during stance. Note the difference in the time bases between the original records on the left and the computer displayed images in the swing and stance columns. On the right, the amplitude of the integrated responses as a function of the time of stimulus application in the normalized step cycle is plotted. Note that the responses in each muscle are expressed as a percentage of the maximal response in that muscle, or for inhibitory responses, to the minimal value. The bar above each graph shows the normal activity of the muscles during more than 30 unstimulated step cycles aligned with respect to the onset of activity in Br. The small horizontal lines give the SD of the average values of EMG activity. The average occurrence of foot contact and foot lift is also indicated under each graph. TrM, teres major; TriM, triceps brachii, medial head; ClB, cleidoBrachialis; FCU, flexor carpi ulnaris. [Modified from Drew and Rossignol (147).]

ward displacement. During swing, the responses to sural stimulation in the ankle and knee flexors would serve to avoid the obstacle.

Although the description of responses has focused mainly on the corrective movements of the ankle, more proximal joints such as the knee and hip were also involved in the evoked reflex responses. There is an inter-

esting difference between quadrupeds such as the cat and humans. In cats, as mentioned earlier, one important strategy is to lock the distal joint and move the foot through flexion at more proximal joints. In humans, in addition to inducing responses in ankle muscles, stimulation of SP, tibial, and sural nerves all give responses in knee muscles such as the knee extensor vastus lateralis



(VL) and knee flexor BF with, however, a resultant knee flexion. The role of the coactivated knee extensor is not clear, although it is postulated to limit the flexion of the knee, which could be destabilizing (610, 612). Therefore, these corrective reactions result in complex movements involving multiple joints (also contralateral) that have to be optimally integrated in the locomotor movement.

Similarly to what was done in cats during forward and backward walking, electrical stimulation of the sural nerve at twice the strength needed to evoke a motor response was applied during forward and backward walking in humans (164). Excitatory and inhibitory responses were seen in both forms of walking but at different times in the cycle corresponding to the biomechanical roles of the muscles in the different tasks. Cutaneous reflexes are generally increased during running compared with standing or tonic contraction (166).

In summary then, although cutaneous inputs have some general roles in facilitating or inhibiting locomotion, they appear to be involved in the correct positioning of the limb (foot) during normal locomotion or after perturbations induced by mechanical obstruction or electrical skin stimulation.

## B. Muscle Afferents

As for cutaneous afferents, muscle afferents have general roles such as providing signals acting as on-off switch to set the range of joint angular excursion within which locomotion can take place. However, an important role of muscle afferent feedback appears to be in setting the overall timing of the step cycle by adjusting the duration of the various phases of the locomotor cycle and facilitating the switch between these phases. Another important role is to regulate the output amplitude of muscles in various phases. This section reports the observations made in animal preparations or humans and, when appropriate, discuss more specific spinal proprioceptive pathways that could be involved in mediating these effects.

### 1. Initiating and blocking the locomotor rhythm

Locomotor movements can only operate efficiently within a certain range of limb position. Outside this range little force can be applied by the feet or the feet may simply lose contact with the walking surface. Afferents signaling the amount of stretch in muscles acting at various joints must therefore play a key role in setting the limits of limb position within which locomotion can occur. Such a role has been demonstrated experimentally in different manners. Early work (532) suggests that hip proprioceptors exert a powerful control over the initiation of the locomotor rhythm because extending the hip in a spinal animal is sufficient to initiate air stepping, whereas flexing the hip can prevent it. Similarly, in

chronic spinal cats, flexion of the hip joint on one side can abolish treadmill stepping on that side, whereas the other side continues to walk (Fig. 6A). Conversely, extending the hip until it reaches approximately the angle normally attained at the end of stance (Fig. 6, B–D) will initiate stepping provided that the contralateral limb is in a position to accept the weight of the animal (251). Similarly, the locomotor rhythm, evoked by stimulation of the MLR (see sect. III) and recorded in ventral roots, can be abolished by passive limb manipulations (418). During real locomotion, retarding or accelerating the movement of the hip joint during locomotion affects the movements of more distal joints (411), suggesting that hip joint afferents exert a global role in the organization of the locomotor sequence at other joints.

In decerebrate cats walking on a treadmill, flexing the ankle increased markedly the extensor bursts and diminished the flexor bursts (162). When a muscle stretch corresponding to that obtained with a load of 4 kg was reached, the ankle extensor bursts of activity became tonic and the flexor activity disappeared. This also abolished rhythmic activity in more proximal muscles. The other limb continued to walk at an even faster rhythm to compensate for the slowing of the ipsilateral limb. The authors concluded that ankle extensor proprioceptors exert an inhibitory effect on the flexor component of the locomotor pattern generating circuit and that unloading of extensors is therefore necessary to initiate the flexor bursts and thus the swing phase. Evidence from ventral root stimulation and muscle vibration established that the force input was the key sensory signal rather than muscle length. Similarly, stimulation of afferents of the plantaris muscle nerve at twice threshold during fictive locomotion accelerated and strengthened the extensor activity while inhibiting the flexor activity in the knee flexor St and hip flexor sartorius (102).

Similar results were obtained with tonic stimulation of proprioceptive afferents of the forelimbs performed in decorticate cats walking on a treadmill (488). A maintained protraction of the shoulder on one side increased markedly the duration of extensor activity, shortened the flexor activity, and prolonged the cycle to the point that rhythmicity was altogether abolished and replaced by a tonic extensor activity in the forelimbs (Fig. 6E). Conversely, a tonic retraction of the shoulder led to a marked increase in the vigor of the locomotion with larger activity in forelimb flexors (Fig. 6F) and complementary changes on the other side. Such complementary bilateral changes in response to tonic perturbations are largely reproducible during fictive locomotion, i.e., in absence of locomotor movements (505). Retractions of one of the forelimbs reduced the ipsilateral extensor bursts and increased the contralateral extensor bursts, and vice versa for a tonic protraction bringing the whole forelimb forward (Fig. 7A). These changes resulted from the interactions be-



## Treadmill locomotion

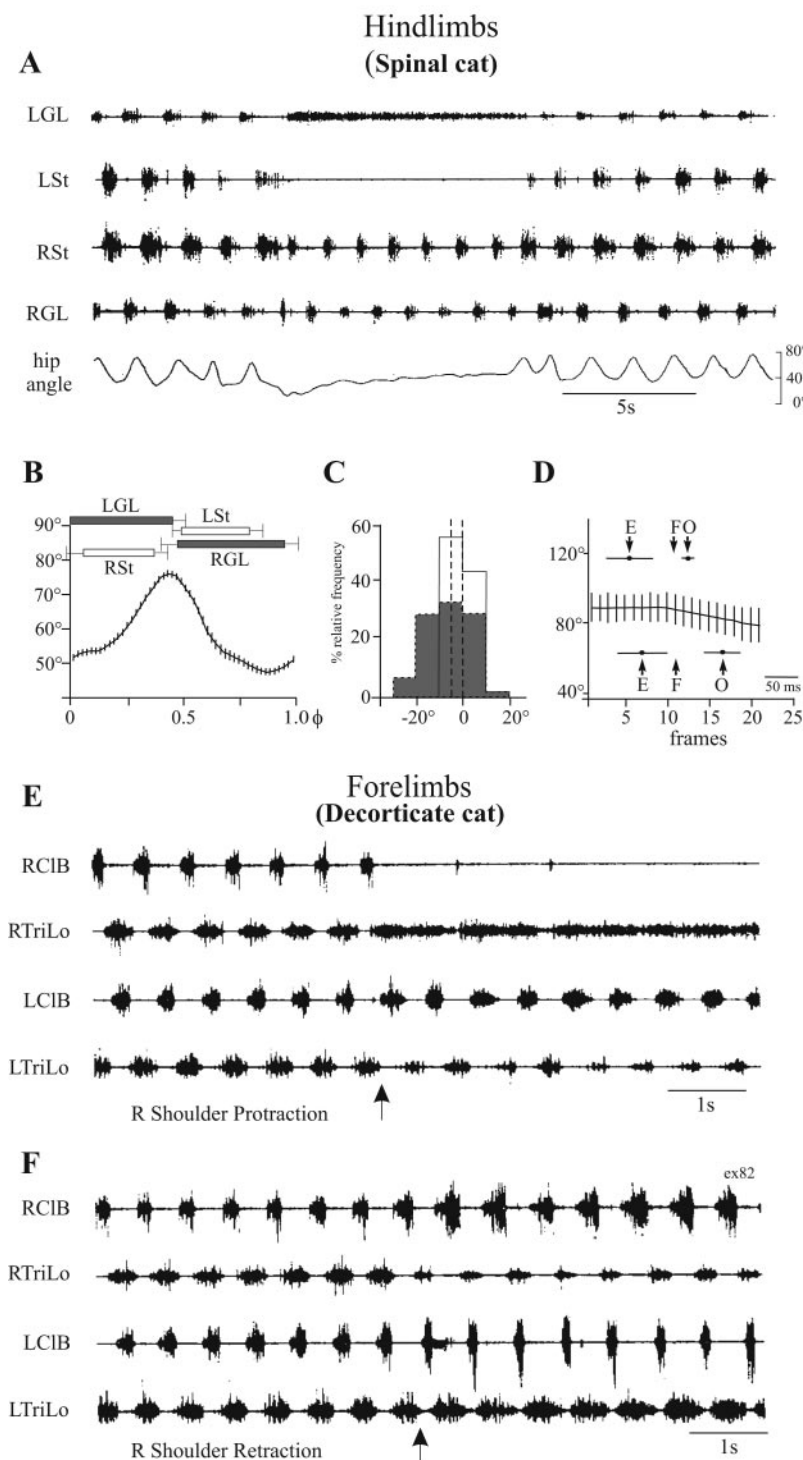


FIG. 6. Effect of tonic hip or shoulder perturbations on treadmill locomotion. *A–D*: obtained in a chronic spinal cat. *A*: EMG and hip angle excursion of the left hindlimb when the left hip is protracted while the knee is also flexed. Left (L), right (R), gastrocnemius lateral (GL), and semitendinosus (St) recordings are shown. When the limb is held, LGL is tonically active and LSt is silenced while the contralateral right leg continues to walk. The continuous trace representing the hip angle was derived from the *X–Y* coordinates of diodes placed on the hip and knee joint (Selspot system). *B*: average hip angle and EMG during 40 normal walking cycles normalized to 1 from the onset of LGL activity. *C*: hip angle at initiation of the swing and lift-off responses, i.e., angle at which the limb starts walking when retracted from its protracted position. The hip angles corresponding to the onset of flexor EMG St were measured in 100 normal walking cycles and 48 lift-off responses. These angles are plotted as a histogram (clear, swing of normal locomotion; grey, lift-off responses), as a percentage of relative frequency. The mean angle at the onset of St during walking was set to  $0 \pm 4.8^\circ$  (SD). The mean angle for lift-off responses was  $-5.6 \pm 10.9^\circ$  (SD). *D*: film and EMG analysis of hip angles during 27 lift-off responses and 11 initiations of swing during normal locomotion. Ten frames before and after St onset (F) were analyzed. The hip angular trace represents the lift-off responses. Termination of LGL (E) and break of contact of the foot (O) at lift-off are displayed together with the SD values of E, F, and O above correspond to the initiation of swing in normal spinal locomotion and those below apply to lift-off responses. [*A–D* from Grillner and Rossignol (251).] *E* and *F*: decorticate cat walking spontaneously on the treadmill belt at  $\sim 0.4$  m/s. In this case the right forelimb is manually protracted tonically in *E* and retracted in *F*. Note that in this situation, the manipulated limb does not touch the treadmill anymore and that the rhythmicity ceases with extreme protraction, whereas the locomotor pattern becomes more vigorous on both sides with retraction. Cleidobranchialis (CIB), a shoulder protractor and elbow flexor; triceps brachii long head (TriLo), a shoulder retractor and elbow extensor. [*E* and *F* from Rossignol et al. (488).]

tween the rhythmic central command and the tonic afferent feedback signaling the same position of the limb irrespective of the phase of the central command. Thus, when the limb was protracted tonically, the locomotor pattern either stopped altogether (as was the case during

real locomotion as seen in Fig. 6*E*) or else generated large extensor bursts as an attempt to retract the limb. It was also shown that the static position of the hip markedly influenced the fictive locomotor pattern recorded in hindlimb muscle nerves after curarization (433). Indeed, a

gradual extension of the hip starting from an initial flexed position led to an increasingly vigorous rhythm until the limit of hip extension was reached (Fig. 7B).

Taken together, these results clearly indicate that the range joint excursion signaled by proprioceptive afferents (especially from proximal joints) determines some of the general characteristics of the pattern (on-off) through rather complex interactions that will be discussed more fully when discussing the effects of phasic perturbations.

## 2. Effects on timing: resetting and entrainment

Besides these global effects that resemble more or less the effect of an on-off switch, various observations suggest that proprioceptive afferents play a significant role in setting the frequency of locomotion in animal preparations and humans. The timing structure of the step cycle is controlled by either prolonging the ongoing phase of locomotion or else by inducing a switch from one phase to the other. Some specific spinal pathways that might carry these effects are also discussed in this section.

A) OBSERVATIONS IN ANIMALS. Proprioceptive afferents can phase-advance or phase-delay components of the step cycle and thus adjust the frequency of stepping. Cats placed on a treadmill adapt their speed to that of the treadmill. Thus the stance phase becomes shorter as speed increases, whereas the swing phase remains relatively constant across the range of walking speeds (244, 259). Although supraspinal commands undoubtedly play an important role in the speed of goal-directed locomotion, it has also been observed that after spinalization, cats can also adapt the walking of the hindlimbs to the speed of the treadmill (29, 204). Moreover, spinal cats can modify the structure of the step cycle of individual limbs when walking on a split treadmill moving at different speeds (205). Although cutaneous receptors of the pads cannot be discarded as an important source of inputs for such speed adaptation, the bulk of evidence suggests that proprioceptive inputs from muscles and/or joints are the main contributors. This is best shown by experiments specifically designed to evaluate how proprioceptive inputs can entrain the locomotor rhythm.

The fictive locomotor rhythm can be powerfully entrained by sinusoidal movements of the hip joint in a 1:1 ratio or in a fractional ratio (2:1, 3:1) depending on the frequency range (10). Joint afferents and muscle afferents of muscles acting at the hip could be responsible for the noted effects. Other studies (320) on entrainment of the MLR-induced fictive locomotor pattern suggested that capsular afferent of the hip joint are not important since 1:1 entrainment persisted after specific hip joint deafferentation. It was suggested that the potential to induce such entrainment was distributed among several muscles acting at the hip joint. A similar conclusion was reached

when investigating the afferent systems responsible for reflex reversal when the position of the hip was changed from a tonic flexion to a tonic extension (483). Group II afferents of flexor muscles acting at the hip joint also have powerful action on the locomotor rhythm (see below).

The role of the hip joint has been studied systematically during fictive locomotion using ramp stretch of the hip (9) in various phases of the step cycle. When ramp movements were applied early during the TA burst (i.e., during early flexion phase), there was an increase in amplitude, but a shortening of, the TA burst. Applied later, both the amplitude and duration of TA increased. The same flexion imposed during late extension terminated extension and phase-advanced the flexor burst. It thus appears that flexion movement imposed during the flexor burst enhances the ongoing activity (positive feedback, i.e., increase of EMG of the muscle producing the movement in the same direction), whereas flexion in the opposite period of extensor activity has a negative-feedback effect. Similar findings were made with ramps in the extension direction. Interestingly, removal of the skin did not prevent these effects, although skin nerve stimulation can also entrain the fictive locomotor rhythm (485, 518).

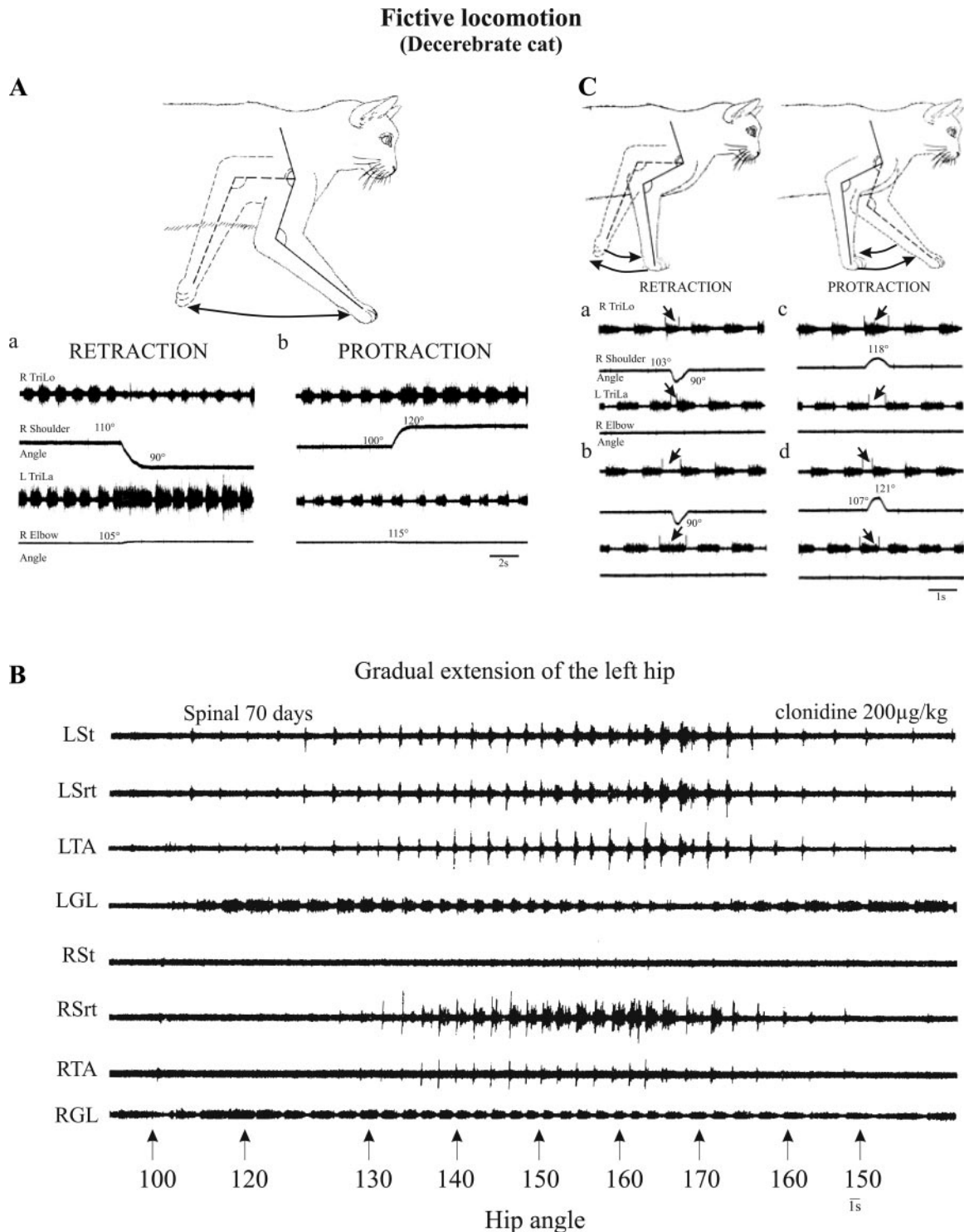
In the cat forelimbs, phasic protractions or retractions of one shoulder yield compensatory changes in both forelimbs in a negative-feedback manner during fictive locomotion. Thus perturbations in the direction of the movements that would have taken place if the animal had not been paralyzed tended to shorten the duration of the burst of activity of the muscles active during that phase, and vice versa in the opposite phase. Changes in the response patterns took place around critical points in the rhythm of fictive locomotion. Past a point corresponding to ~58% of the ipsilateral (i) extensor burst, protractions no longer prolonged the burst and no longer delayed onset of the contralateral (co) extensor. At another point, occurring at 41% of the contralateral extensor burst, ipsilateral protractions maximally shortened the ipsilateral flexor phase. During a critical period extending from the end of the ipsilateral flexor activity until the contralateral flexor onset, retractions could elicit two alternative responses. The activity of the contralateral extensor was abolished or else it persisted for another cycle and the activity of the contralateral flexor was turned on. It was argued that the critical points in the fictive locomotor cycle correspond to critical biomechanical events in real locomotion (such as weight transfer) and may underlie a phase-dependent motor coordination (488, 506).

B) PATHWAYS INVOLVED IN RESETTING AND ENTRAINMENT IN ANIMALS. There are certainly many afferents of different sensory modalities activated by locomotor movements that participate simultaneously in regulating the duration and phases of the step cycle, and for each, possibly many different spinal pathways are involved. Only a few of

these pathways have been investigated by different research groups.

In walking decerebrate cats, perturbation of the hip flexion results in a negative-feedback compensation so that hip protraction during swing reduces the flexion phase and the associated hip flexor EMGs, whereas resisting hip flexion increases the amplitude and duration of

the bursts of activity of iliopsoas (Ip) and sartorius (Srt) (325). These effects are mainly dependent on the activation of afferents from Srt since they are preserved when another hip flexor, Ip, is detached from its femoral insertion. The effects are greatly decreased when sartorius is denervated. It is presumed that several pathways are involved: monosynaptic, disynaptic, and polysynaptic





through the CPG, as detailed later. All flexor afferents are not equivalent in their ability to influence the locomotor rhythm. For example, in decerebrate cats walking on a treadmill, Ia afferents of EDL can reset the rhythm to flexion, but in the case of TA, the stimulation intensity has to be increased to recruit group II afferents to obtain a reset (263). Notably, stretches of Ip or stimulation of TA group II afferents could not increase the duration of the flexion phase, but group II from EDL could (518). Also, repetitive stretches of flexor muscles (usually in combination) could entrain the walking rhythm (263).

Stimulation of specific muscle afferents, especially from Golgi tendon organs of extensors, can also reset the locomotor cycle (102). A brief train delivered to the planaris nerve recruiting group Ib afferents during the flexion phase abruptly terminates the ongoing flexor activity and initiates a new extensor burst. This was shown to be due to an hyperpolarization of motoneurons consequent to a disfacilitation and not to postsynaptic inhibition, since the same input at rest did not produce inhibition of the motoneurons. The stimulus induced a reset of the locomotor rhythm because there was a permanent shift in time of the following cycles. When a similar stimulus was given during the extensor phase, the extensor burst was markedly increased, and again there was a shift of the following cycles (see also below). Resetting effects were seen with proprioceptive inputs from extensors of the ankle and the knee but not with group I afferents of flexor muscles.

Group Ib afferents of extensors not only reset the cycle but can also entrain the rhythm at around the spontaneous locomotor frequency. Indeed, sinusoidal stretches of the muscles of sufficient magnitude could, in spinal paralyzed cats injected with DOPA, entrain the fictive locomotor rhythm and the organization of the pattern was such that maximal extensor activity coincided with peak force (102). The need for stretches generating sufficient tension, as well as electrical stimulation at different strengths of group I afferents in muscle nerves, and the absence of resetting effect with vibration suggested that Ib afferents were necessary for the entrainment. This conclusion was consistent with the suggestion that un-

loading of the ankle extensors was a crucial input that signals the effective termination of stance and triggers the swing phase (162). In a later study (431), in spinal cats pretreated with clonidine, similar conclusions were reached using muscle stretch. This work confirmed that Ib afferents were probably responsible for the entrainment and that Ia afferents did not play a significant role. Moreover, the authors have shown that with triangular stretches of different frequencies, the extensor burst duration followed the duration of the stretch slope, whereas the flexor bursts were triggered at a constant latency (a few hundred milliseconds) after the peak stretch, irrespective of the stretch frequency. If the stretch was prolonged, the flexor burst was further delayed.

The emergence of polysynaptic excitatory group I pathways during locomotion is an elegant example of state-dependent transmission in sensory pathways during locomotion (see Fig. 8). At rest, in decerebrate cats, there are disynaptic IPSPs in extensor motoneurons evoked by group I afferents from extensors corresponding to the classical group Ib "autogenetic" inhibition (176) also called "nonreciprocal group I inhibition" (295). Intracellular recordings revealed that the nonreciprocal disynaptic IPSPs in the extensor motoneurons disappear during an episode of fictive locomotion in the decerebrate or spinal cat and are replaced by polysynaptic EPSPs, a clear example of reflex reversal (232, 239). For example, Figure 8A shows that, as more L-DOPA is injected leading to rhythm generation, there is a progressive change from inhibition to excitation in the extensor motoneuron (FHL) in response to group I stimuli from another extensor (PI). Interestingly, the stimulation of some pyramidal tract fibers (Fig. 8B) evokes a similar change in the response pattern. These two inputs were also shown to converge on common interneuronal pathways (Fig. 8C) with spatial facilitation (336).

As described above, group I signals were also able to entrain and reset the rhythm during fictive locomotion in decerebrate and spinal cats (102, 256, 377, 432). As for hip or shoulder movements, the ability to entrain or reset the rhythmic activities in all limb muscles is clear evidence

FIG. 7. Tonic and phasic perturbations of the limbs during fictive locomotion. *A*: in a paralyzed, anemically decorticated cat and acutely spinalized at T<sub>13</sub>, the humerus is tonically retracted or protracted by 20° on the right side, as shown in the shoulder potentiometer traces, while the scapula and elbow remain fixed. Note the bilateral reciprocal effects of shoulder retraction and to a lesser extent of the shoulder protraction. [From Saltiel and Rossignol (505).] *B*: in a paralyzed, anemically decerebrate cat chronically spinalized for 70 days, the hip was first put into flexion (100°), then gradually extended to full extension (170°) before being flexed again. Note that at the onset there is no rhythmic activity whereas, as the hip is extended, a faint rhythmic pattern first appears on the side of the retraction, and this becomes more and more prominent while the contralateral hindlimb rhythm appears. Note also that the contralateral rhythm disappears and the ipsilateral rhythm peters out. [From Pearson and Rossignol (433).] *C*: in a paralyzed, anemically decorticated cat acutely spinalized at T<sub>13</sub>, phasic protractions or retractions of the right shoulder are applied during the R extensor burst or the R flexor burst. All 4 examples are from the same cat with spontaneous fictive locomotion recorded bilaterally from triceps brachii, long head (TriLo), shoulder retractor and elbow extensor and triceps brachii, lateral head (TriLa), an elbow extensor. The R elbow remained fixed while the R shoulder was manually protracted or retracted as illustrated in the drawing. A downward deflection of the trace corresponds to a retraction. *a*, Retraction during RTrilo burst; *b*, retraction during R flexor phase; *c*, protraction during R extensor burst; *d*, protraction during R flexor phase. In each case, the direction of the small arrows above electroneurographic bursts indicates on each side the effects on duration (shortening or prolongation) of the interval during which the perturbation is given. The perturbations were brief and largely confined to the phase of the cycle in which they were applied. [From Saltiel and Rossignol (506).]



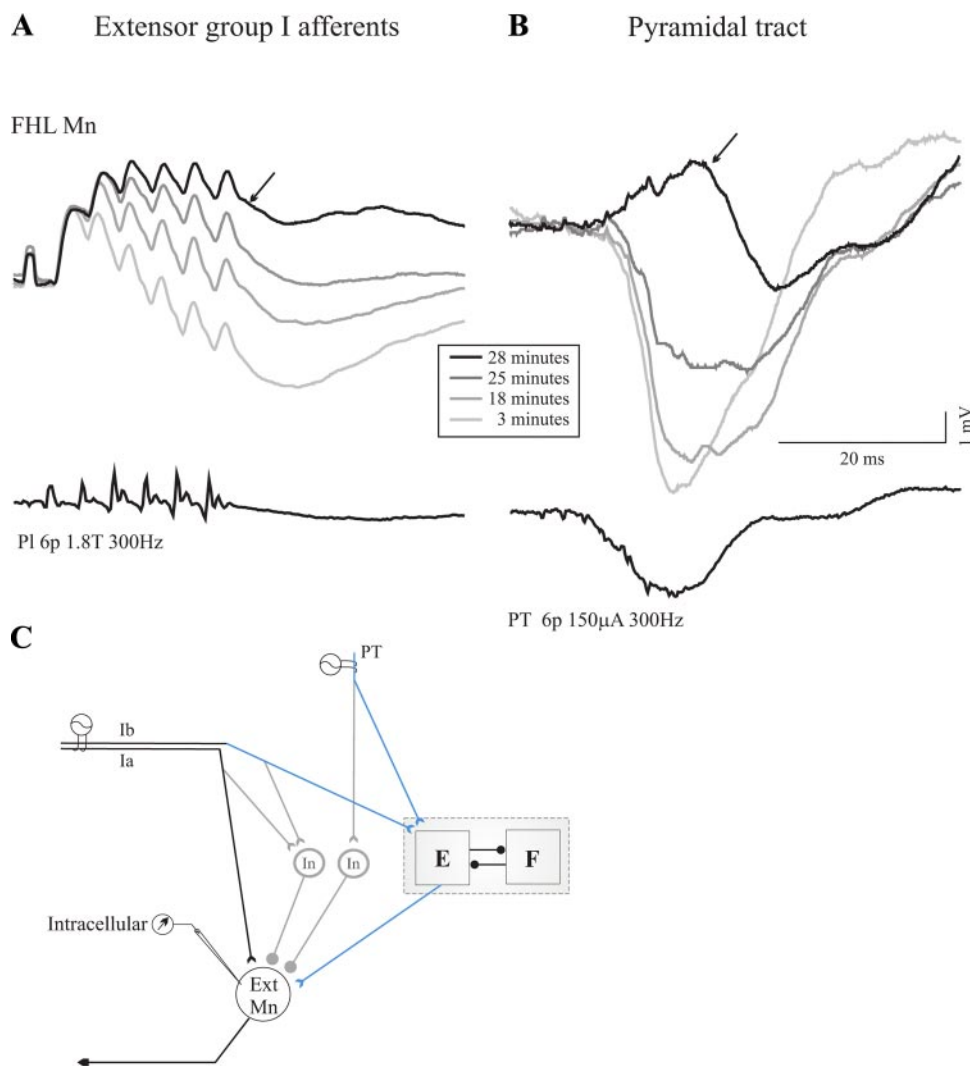


FIG. 8. Task-dependent reflex reversal. Averaged intracellular responses from a FHL motoneuron showing that there is a parallel reversal from IPSPs to EPSPs (arrows) evoked by alternating extensor group I (plantaris, Pl in A) and pyramidal tract (PT in B) stimuli with the progressive injection (3–28 min) of L-DOPA (decerebrate cat with spinal cord transected at T<sub>13</sub> except for the ipsilateral ventrolateral quadrants). C: diagram illustrating that the locomotor activity blocks transmission in disynaptic inhibitory pathways (in gray) from group Ia+Ib and PT fibers and opens a common polysynaptic excitatory pathway (in blue). Also illustrated is the monosynaptic pathway giving rise to 6 positive humps in the recording of A in response to 6 group Ia afferent stimuli.

that these sensory fibers project onto the rhythm-generating networks of locomotion in the spinal cord (see Fig. 10).

Further studies have shown that group I pathways may evoke specific excitation patterns in extensors. For example, inputs from ankle extensor nerves are very efficient in resetting the locomotor rhythm and in increasing the extensor nerve activity, whereas inputs from knee extensor nerves may activate proximal extensor muscle nerves and soleus but inhibit other ankle extensors nerves during MLR-evoked fictive locomotion (256). Moreover, stretch-evoked Ia afferent inputs during the stance phase can prolong that phase but, when given during the flexor phase, cannot reset the rhythm in the same way as group Ia and Ib stimulated together (256). In addition, in walking decerebrate cats, the influence of group I afferents from GL-soleus (GLS) muscles is normally very powerful, whereas the influence of group I afferents from GM muscle is quite weak (591).

During fictive locomotion in the decerebrate or spinal cat, stimulation of group I fibers from flexors has little effect on rhythmicity (102), but a more intense stimulation, recruiting the group II fibers, can reset the rhythm in the same way as group I fibers from extensors (435). However, during real walking of decerebrate cats on a treadmill, stretching flexors, such as Ip, TA, or EDL during stance reduces the duration of extensor activity instead and initiates the onset of flexor activities as described above (263). The graded electrical stimulation of TA and EDL revealed that group II fibers from TA and group I fibers from EDL are involved in the resetting. There is no resetting to extension when flexor afferents are stimulated during flexion. The difference of flexor group II actions during fictive and real locomotion could be attributed to the different reticulospinal activation in the two preparations (263). A similar pattern of resetting of the locomotor-like rhythm in the mudpuppy was seen by stimulating dorsal roots (C2–4); the stimulation inter-

rupted the ongoing extensor phase or prolonged the flexor phase (91). As mentioned above, it was shown that stimulation of sartorius afferents in assisting or resisting the hip flexion in decerebrate cats walking on a treadmill alters not only the amplitude but the duration of IP and Srt EMG bursts of activity (325). It was further shown that these effects were observed only at electrical stimulus strength of 1.6 T and higher, suggesting that the Srt action on the rhythm generator was mediated by group Ia and Ib (polysynaptic) pathways (326). Also, it was found that group II afferents from Srt evoked a mix of excitatory and inhibitory effects on both IP and TA flexor activities. There is thus a great heterogeneity in the effects and pathways from group I and group II afferents of different flexor muscles on the generation of swing activities.

During fictive locomotion in spinal cats injected with DOPA, the stimulation of group II afferents (2–5 T) from hip, knee, and ankle extensors had mixed effects because the stimulation also recruited group I afferents (518). Usually a stronger stimulation (5–10 T) evoked flexor activities as expected from this preparation where group II afferents from all muscles are part of the flexor reflex afferent (historically known as the acronym FRA) pathways that promote the flexion phase (518).

Entrainment of locomotor rhythm by sensory feedback is seen in several species, but the mechanisms of sensorimotor interactions have been particularly well studied in the lamprey. If the caudal part of the lamprey notochord-spinal cord is moved rhythmically back and forth as in swimming, the rhythm of fictive swimming can be entrained above or below the control rate (249, 374). Similar entrainment was observed in the dogfish (252). The intraspinal stretch-sensitive edge cells located along the lateral margin that sense the lateral bending of the cord in the lamprey during each swimming cycle would be the cause of such entrainment. By using paired intracellular recordings, it was found that a class of excitatory edge cells (SR-E) have monosynaptic glutamatergic contacts to ipsilateral interneurons of different types and motoneurons (582) and a class of inhibitory edge cells (SR-I) have monosynaptic glycinergic connections with contralateral interneurons and edge cells. The excitatory and inhibitory connectivity could account for the entrainment effect of edge cells on the rhythmogenesis in the lamprey, which was also modeled (253, 565). It is suggested that this circuitry and its role is analogous to the stretch reflex pathways activated by muscle spindles in mammals.

C) OBSERVATIONS IN HUMANS. Various approaches have been taken to study how the stimulation of proprioceptive afferents can also modify the step characteristics in humans. For instance, tonic vibration of different muscles to activate specifically Ia afferents during walking on a runway shows, on the one hand, an undershoot of the joint excursion on which the muscle is acting and, on the other

hand, a slowing down of the walking speed due to an increased stride time (574). It is of interest to note that tendon vibration does not change the intralimb coupling of joints during the step cycle.

Work in human infants is very instructive, since it allows one to observe how the innate locomotor behavior functions before the corticospinal control is completed (604). The similarities of sensorimotor interactions in infants and cats are remarkable (209). These studies showed that when a limb was halted during swing there was a prolongation of stance in the contralateral limb. In 3- to 10-mo-old infants, blocking one limb temporarily evoked, in the crossed limb, a prolongation of stance (605). Increasing load by pressing on the pelvis or letting more weight being supported by the experimenter also significantly increased the duration of the stance phase. Therefore, it appears that reflex pathways capable of adjusting the step cycle are innate and functional even before the baby has experienced such conditions. The importance of hip position and leg loading was investigated in 5- to 12-mo-old babies walking on a treadmill equipped with two force platforms while their weight was partly supported by the experimenter (421). One limb was perturbed at different times during the step cycle using a cardboard placed under one foot of the baby so as to increase hip extension during late stance, block the limb in mid-stance, or flex the hip during early swing. The results indicated that both the hip position and loading were crucial factors determining the likelihood for the onset of swing. For certain perturbations, the hip position appeared more important, whereas for others, loading of the whole limb achieved by pressing down on the pelvis was more determinant. Other experiments in infants (5–13 mo) were performed to assess the role of sensory afferents in triggering swing in various forward and sideways walking patterns (422). The babies stepped on a cardboard that was removed by the experimenter at different moments in different directions. It was shown that a perturbation that brings the limb in the direction opposite to the ongoing movement was more likely to generate a swing phase. For instance, during forward walking, extension of the hip was the most powerful input to induce a new swing, a finding very much related to the animal work in spinal cats (251).

Which afferent systems are involved in limb responses to load in humans is difficult to determine. However, as in other vertebrates, evidence indicates that the spinal locomotor system in adult humans reacts to different conditions of loading (134, 158) as mentioned before. The importance of load was observed during manually assisted stepping in spinal cord-injured subjects on a treadmill, as well as in normal subjects (260). It was shown that the modulation of EMG amplitude in Sol and GM was more related to the peak load in each step than to muscle-tendon stretch in spinal cord-injured subjects

or velocity of such stretch (260). Thus stretch reflexes were not the sole sensory pathway for EMG modulation, and it is suggested that level of loading on lower limbs was a crucial sensory cue to facilitate emergence of stepping patterns in spinal cord-injured subjects. In clinically complete spinal cord-injured subjects, imposing stepping movements with a driven orthosis at the hip evoked leg muscle EMGs similar (although smaller) to normal patterns (132), but only if there was a level of load bearing (30% body wt). Thus both hip movements and load appear to be important sensory inputs to generate spinal locomotor commands in humans. In another study attempting to distinguish among sensory contributors, the EMG activation in lower limb muscles of spinal cord-injured subjects was studied while one leg was assisted to step on a treadmill and the other was manipulated to modify sensory feedback (199). In one condition, the leg was assisted to do air-stepping (no loading), and in another, the leg was minimally moving but the load (60% weight-bearing) was rhythmically applied. Flexing and extending the joints during air-stepping in the contralateral leg evoked only minimal EMG activation while phasic loading induced clear rhythmic EMG bursts as in walking in three of four clinically complete spinal cord injured (SCI) subjects. However, no EMG activity was found during one leg loading alone in similar SCI subjects (132), and this difference may be due to the different treadmill speed, amount of body weight, and previous locomotor training (199). The results so far suggest that the stretching of the muscles during air-stepping was not sufficient to produce EMG locomotor patterns (as in Ref. 132) but that loading is required for stepping patterns to emerge. This is reminiscent of other results (396, 397) showing that, for chicks with hemisectioned cords to recover proper locomotion, it is necessary to have not only sensory feedback from rhythmic movements (like in swimming) but a good contact or load from the feet. Whether phasic loading alone is sufficient for the human spinal cord networks to generate stepping commands remains to be clarified.

Loading must activate group I afferents from anti-gravity extensor muscles in the legs and similar pathways as described in cats could be operating in humans. Whether there is, as in cats, a reversal of Ib inhibition to excitation in extensors during walking in humans was tested with a conditioning of the Sol H reflex by a GM group I input (555). An early, presumably disynaptic, inhibition of the H reflex (5–28%) was observed in 10 of 15 subjects during quiet sitting. During the stance phase of walking, there was a significant reduction in this inhibition in the 10 subjects. A similar reduction was seen during a matching voluntary isometric contraction of the Sol or during standing. However, there was no excitation in the overall extensor muscle group. Nevertheless, in four subjects, there was an increase in the conditioned H-reflex during walking that was not apparent during

isometric contraction (555). Thus only in the four subjects was there evidence that walking led to an additional excitation from GM to Sol consistent with a reflex reversal as seen in cats. As mentioned above, group I afferents from GM are known to be less effective than other ankle extensors in cats (591), and if the same in humans, the use of GM may partly explain the modest excitation. Also, when the activities of all sensory and descending control systems converge onto spinal networks, it can be expected that the contribution of a single sensory signal will appear quite modest.

Altogether, the results discussed in the above section on cats, lampreys, and humans (infant) strongly indicate that proprioceptive feedback plays a determinant role in adapting the step frequency and structure during walking (426). It is of interest to consider that to proceed with the next part of the step cycle, the central nervous system must take into account several possible states of the limbs. This requirement has led Prochazka (457) to identify different sets of If-Then rules that have to be met at different points in the step cycle. For instance, if the ankle extensors are unloaded, if the hip has reached a certain degree of extension, if the contralateral limb is in a position to accept weight, then the limb may swing forward. This stresses the fact that probably no single afferent input from one limb is sufficient to determine the next phase of the cycle. Rather, several simultaneous conditions must be reached before proceeding to the next part of the step without jeopardizing gait stability.

### 3. Role of muscle proprioceptive afferents on muscle discharge amplitude

The previous sections described how proprioceptors participate in the overall timing structure of the step cycle and its subphases. In this section, we review how the inactivation of muscle afferents by local anesthesia or neurectomies alters locomotor output and how excitation of proprioceptors by muscle stretch might also contribute, through various reflex pathways, in setting the discharge amplitude of muscles in the different phases. At the onset, however, it should be realized that the inherent conduction and neuromechanical delays preclude an efficient sensory compensation in larger mammals occurring within the same phase of the movement (e.g., load compensation) during fast locomotion like a cat gallop or human top-speed running (242). During a leisurely walk, however, sensory feedback can contribute importantly. Different approaches have been taken to evaluate how proprioceptive feedback can participate in determining the muscle output during locomotion.

A) REMOVAL OF MUSCLE AFFERENTS. It is difficult, if not impossible, to remove muscle afferents selectively. Experimental methods such as pyridoxine intoxication can damage all classes of large-diameter afferents including pro-

prioceptive afferents and cutaneous afferents (430). There are however different ways to evaluate the general consequences of removing proprioceptive feedback.

The role of proprioceptors from extensor muscles in setting the EMG amplitude during locomotion can be inferred from the observations made when unloading subjects with a harness during walking. In this condition, subjects all show a major reduction of amplitude of burst discharge in antigravity muscles (133, 134, 260). Similarly, if the ankle extensors are unloaded during stance by mechanically extending the ankle through an external ankle brace, there is a 50% decrease in the amplitude of the ankle extensor muscle. Such a decrease could be attributed to the stretch of ankle flexors by this ankle extension maneuver. However, an ischemic block of the common peroneal nerve innervating the ankle flexor muscles does not abolish the inhibitory response in the extensors, thus suggesting that it is due to a removal of excitatory inputs from the ankle extensor muscles themselves (546).

In cats, elegant experiments have also been performed to evaluate unloading during locomotion, in particular "foot-in-the hole" experiments in which cats suddenly make one step through a trap (227) or walk on a peg that is lower than expected (141). In all those cases where the sensory feedback is reduced, presumably because of a decrease in ankle extensor load, there is a short latency reduction of the ankle extensor muscle activity.

An interesting indirect approach to examine the effect of removing proprioceptive feedback has been through the use of modeling in which it is possible to instantly remove or add proprioceptive feedback as well as central drive (458). These theoretical experiments led to the conclusion that the importance of proprioceptive feedback varied relative to the level of central drive. When the central drive was low and could lead to a collapse of the walking model, adding proprioceptive inputs could come to the rescue. Adding proprioceptive feedback to a central drive that is already sufficient increased the extensor activity leading to an increase in body height and speed of walking. The model suggested that proprioceptive feedback can modify the walking speed by skipping parts of the activation profiles as also suggested later (506).

Cutting peripheral muscle nerves obviously abolishes both sensory and motor functions. However, these nerve sections can give clues as to whether or not the sensory afferent feedback from certain muscles is essential for the overall locomotor pattern. Nerves to ankle flexors were cut on one side in otherwise intact cats that were chronically implanted with EMG electrodes (85). The locomotor movements postneurectomy were very similar to preneurectomy after only a few days, except for a decrease in ankle flexion. Hip and knee flexor EMG amplitude was weakly but consistently increased to compensate for the

reduced ankle flexion. After spinalization however, walking became asymmetric with pronounced dysfunctional knee and hip hyperflexions during swing on the denervated side. The abnormality of the spinal locomotor pattern suggested that the spinal cord compensated for the combined sensorimotor loss. When the neurectomy was performed in a spinal cat that had already recovered locomotion, the deficit consisted only in a reduced ankle flexion with no abnormal dysfunctional hyperflexions as observed when the neurectomy is performed before spinalization. It thus appears that when muscles (and their proprioceptors) are removed from the locomotor sensorimotor apparatus, there is a profound reorganization implicating spinal and supraspinal changes to compensate not only for the missing muscle biomechanical action but also for the lack of proprioceptive inputs that normally arise from this muscle.

In a similar vein, Pearson and co-workers (427, 428, 590) developed a model of muscle neurectomy of the GLS. This neurectomy produced initially a marked yield of the ankle. Five days after such a neurectomy, the agonist muscles (MG and plantaris) rapidly compensated by significantly increasing their output, thus offsetting the ankle yield. In other experiments (52), the GLS nerve was cut on one side in three chronic spinal cats that had regained normal spinal locomotion. After the neurectomy, the ankle also yielded during stance for the first few days, and the GM burst of activity increased markedly. This yield was mostly compensated within a week, but GM activity remained elevated. The mechanisms of such compensation in spinal cats still have to be elucidated. Another study examined in more detail the changes in GM bursts of activity following denervation of both GLS and plantaris (428). There are two components in the GM burst: the initial component precedes foot contact and is thought to be centrally generated by the CPG and the late component, which starts 40 ms after foot contact, and to which sensory feedback contributes (227). The late component of the GM was increased rapidly after neurectomy, and this was postulated to result from the increased stretch of GM which now has to carry more load. The amplitude of the earlier component, which starts before foot contact, took 7–10 days to increase. It was argued that this early component is of central origin and that the compensation probably results from a recalibration of the central drive through the proprioceptive feedback.

Whereas the above experiments dealt with the adaptation to a permanent muscle nerve lesion eliminating both the efferents and afferents, a complementary experiment using botulinum toxin injected in GL, plantaris, and Sol was performed to temporarily inactivate the neuromuscular junction and reproduce the same ankle deficit by only affecting the motor output. As with nerve section, similar deficits were found initially, and this was followed by a later compensation. Interestingly, it was shown that



the central adaptive plasticity induced by the botulinum toxin alone was such that a further section of the peripheral nerves (or other injections of bolulinum toxin) did not produce the usual ankle yield (385). A recent study (430) showed that following a pyridoxine injection that destroyed all large afferents, cats showed severe locomotor dysfunction, but all recovered significantly over a period of 1 or 2 mo. In these animals, a denervation of GM synergists resulted in a large increase in yield at the ankle that persisted almost unchanged for a month after the operation. The magnitude of burst activity in the GM muscle during early stance did not increase or increased only slightly. This corroborates earlier conclusions that proprioceptive feedback from intact agonist muscles is necessary for functional recovery after neurectomy of a given muscle.

**B) FUSIMOTOR DRIVE.** The above sections strongly suggest that removing proprioceptive feedback by nerve section deeply affects the locomotor output. Another more indirect way to alter proprioceptive feedback is to change the gamma drive (fusimotor drive) to primary muscle afferents. It was shown that a selective block of gamma axons by application of a local anesthetic in an ankle extensor motor nerve reduced significantly the EMG amplitude of the muscle burst during locomotion, suggesting that the gamma blockade reduced spindle sensitivity and hence the discharge of muscle afferents (524). In this early study, only primary spindle afferents were shown directly to reduce their discharge during such anesthesia, and no comments were made on secondary spindle afferents. Other direct measurements showed an increase in the discharge of Ia afferents during the phase of passive muscle stretch, but also during the lengthening contraction of muscles during locomotion (140, 349, 352–355, 455, 459, 460, 463, 464, 525). The discharges of the proprioceptors are therefore not only a function of stretch itself but also of the central drive. This intimate control of the CPG on muscle spindles sensitivity through alpha-gamma coupling is a good example of dynamic sensorimotor interactions. The alpha-gamma coactivation varies with the tasks (456, 461). The dynamic and static gamma motoneurons discharges are closely linked to the CPG output since alpha-gamma coactivation was shown in paralyzed DOPA spinal cats (549) as well as in decorticate or high decerebrate walking preparations (76, 399, 437, 438). Recordings of spindle primary afferents during locomotion in thalamic cats indicate a high degree of fusimotor control, since the spindle afferents discharged during the extrafusal discharge and were even active in the absence of overt EMG activity (77). A more direct evaluation of the effect of static and phasic gamma drive on the primary and secondary muscle afferents of uni- and bifunctional flexor or extensor muscles was reported (76). Primary and secondary afferents of pure flexors received a strong static gamma drive, whereas primary afferents (but not

secondary afferents) of pure extensors received a more dynamic gamma drive, and bifunctional muscle afferents were submitted to more balance influences.

Analogous to the efferent gamma control of muscle spindles in mammals is the modulation of stretch-sensitive neurons located in the spinal cord of the lamprey and that show rhythmic potential oscillations (61, 63, 583). During NMDA-induced fictive locomotion (583), two-thirds of these cells display a phasic glutamatergic excitation during the ipsilateral motor activity and a phasic glycinergic inhibition during the contralateral motor activity. During the hyperpolarization, there are also GABA<sub>A</sub>-dependent large unitary IPSPs. The remaining cells are rhythmically inhibited during the ipsilateral motor activity or at the transition phase. Thus, during real swimming, when the contralateral side is contracting, the receptor being stretched and excited would receive a CPG-related inhibition and when unloaded during ipsilateral contractions, the receptors would receive a CPG-related excitation. It is suggested that the centrally generated excitation may ensure a greater sensitivity to stretch. On the other hand, during an episode of sensory-evoked fictive locomotion (triggered by tailfin stimulation), there is a tonic, but no phasic, inhibition of edge cells (6). The application of strychnine revealed a rhythmic excitatory depolarization synchronous with the ipsilateral motor activity, which was also observed in NMDA-induced fictive locomotion. The synaptic control of edge cells under endogenous release of neurotransmitters may thus differ significantly from what is observed during an exogenous application of drugs (6).

Altogether, these centripetal drives on the excitability of receptors are important to consider because they will change significantly the sensorimotor dynamic interactions during locomotion.

**C) LOCOMOTOR TASK-DEPENDENT MODULATION OF STRETCH REFLEX AND H-REFLEX.** The evaluation of state or task dependency of proprioceptive reflexes was done by applying stimuli to specific muscle nerves or by inducing muscle stretches during locomotion or during standing. The underlying hypothesis is that changes in reflex response amplitude observed throughout the step cycle could provide information on the contribution of the muscle afferents, which are themselves activated during the natural movements. As always, however, it is important to clearly differentiate between changes in response amplitude, which simply match the underlying changes of muscle activity themselves (automatic gain control), and changes in reflex gain in which the input-output relationship is altered independently of the change in muscle burst amplitude.

The effects of brief muscle stretches produced by flexing or extending joints during the step cycle were studied in animals and humans. One frequent observation has been that proprioceptive reflexes are tonically depressed during the locomotor "state." Intracellular record-

ings of lumbar motoneurons during fictive locomotion evoked by stimulation of the MLR in decerebrate cat showed a general reduction (by 34%) in the amplitude of EPSPs evoked by group Ia afferents (229). The onset of MLR stimulation decreased the Ia-EPSP amplitude, but there was a further decrease when rhythmic activities began, suggesting that the reduction was due to the locomotor networks and not the descending pathways stimulated by the MLR. In humans, it was also shown that the H-reflex excitability is lower during locomotion than during resting conditions and is even lower during running (81). The implication could be that the stretch reflex is less important during running. However, others suggest that the decrease in the gain of the reflex during running is related to a methodological issue (measurement of the M wave in different conditions) and that there is no reason to believe that the stretch reflex would not participate in the extensor activity during the stance phase of running (138; see also Ref. 609). The overall modulation of the H-reflex is not either just a function of automatic gain control (as further detailed later) because the changes in H-reflex modulation during level, upward, or downward walking are not a straightforward reflection of the muscle discharge profile (545).

Similarly, a comparison in the same subjects of the modulation of the H-reflex and the stretch reflex during standing versus walking indicates that the two might be modulated differently, implying that each could be subjected to differential presynaptic inhibition (7). A task-dependent modulation of the H-reflex was also shown by the comparison of the H-reflex during stance of level walking and beam-walking. The H-reflex was reduced by ~40% in beam-walking (346). This reduction was interpreted as a mean of reducing the excitability of the stretch reflex that may interfere with precise beam-walking. Finally, it was also shown that the form of locomotion (i.e., walking or running at the same overlapping speed range) was more important in determining the H-reflex modulation than the speed itself (179).

Changes in gain of reflexes were explained by a task-dependent increase of tonic presynaptic inhibition in group Ia afferents. Similar findings were made on the modulation of the biceps femoris tendon jerk, which is reduced during treadmill locomotion (192). However, when the stimulation parameters were corrected on-line at every step (according to the M wave), the results showed no change in the gain but an increase in H-reflex threshold during running compared with walking (199, 544).

Because there are no interneurons in the monosynaptic reflex arc, state-dependent differences in H-reflex amplitude are attributed to changes in presynaptic inhibition in Ia afferents when compared for similar EMG levels. This is based on the critical assumption that similar EMG levels represent similar postsynaptic conditions

in all the motoneurons of the pool. Considering the number of possible intrinsic properties of motoneurons engaged in a motor task with several nonlinear input-output relationships (see sect. iv), it is possible to imagine several different recruitment schemes resulting in a similar global EMG output. It is also assumed that Ia transmission is evenly distributed to all motoneurons in the pool (382) at all times. However, as described in section iv, presynaptic inhibitory control of individual collaterals of Ia afferents could deeply modify this distribution.

D) PHASE-DEPENDENT MODULATION OF STRETCH REFLEX AND H-REFLEX. Not only are proprioceptive reflexes modulated in a task-dependent manner, their amplitude is also subject to a phase-dependent modulation and could therefore participate in the regulation of EMG amplitude of various muscles in the different phases of locomotion. Studies on ankle stretch induced by different means during walking (7, 603) suggest that the response to stretch is high during stance and is about one-half during swing. It has been estimated that 30–60% of the Sol muscle activity might be related to the stretch of the muscle during stance. Increases in load augment EMG amplitude in extensors of adult humans (553, 556) but less than in babies (605). However, others (137, 138) have reported that a brief ankle stretch in early stance in humans did generate only a very small monosynaptic reflex compared with the response obtained with the same stimulus in the sitting position.

Another approach was used to examine compensatory reflexes when the walking surface is briefly and abruptly moved. When the surface is withdrawn backwards or the ankle is dorsiflexed, there is a large increase in the amplitude of the ankle extensor bursts. On the contrary, a forward movement or downward rotation of the ankle (plantar-flexion) instead evoked responses in the ankle dorsiflexors. These responses are organized as the synergies described by Nashner (401) for forward or backward sways and are well integrated within the locomotor pattern. Corrective responses to accelerating or decelerating pulses of the treadmill speed are met with either an ipsilateral ankle extensor contraction and contralateral flexion and a bilateral activation of ankle flexors, respectively (43). It is thought that group II muscle afferents are important for these responses (137) because blocking Ia afferents with an ischemic block does not prevent these responses. Similarly, in one study in humans, the Ia afferent contribution to the normal EMG activation was estimated by removing transiently the Ia feedback from ankle extensors (546). With an imposed plantar-flexion, there was a decrease in Sol EMG, but the decrease was unchanged following ischemia that efficiently removed Ia afferent feedback. This decrease was not either influenced by a lidocaine application on the common peroneal nerve innervating the stretched ankle dorsiflexors and which could have been a source of

reciprocal inhibition (546). These results suggest that there is indeed an important contribution of sensory feedback to EMG locomotor burst but that group II (or some group Ib), and not Ia afferents, are major contributors (136).

There is clear evidence showing a phase dependency of the monosynaptic reflex during locomotion in the cat (3, 154, 155, 439, 533) and of H-reflex or stretch reflex during walking in humans (81–83, 106, 135, 179, 345, 552).

Figure 9A represents a clear example of this modulation (513), which follows nicely the underlying locomotor profile of the Sol muscle so that it is maximal during stance and minimal during swing. The modulation of the H-reflex during locomotion is interesting because it raises several issues relevant to the modulation of all reflexes and which will be treated in more depth in section IV of this review. The results are quite consistent in showing that the H-reflex is largest during the period of activity of the muscle

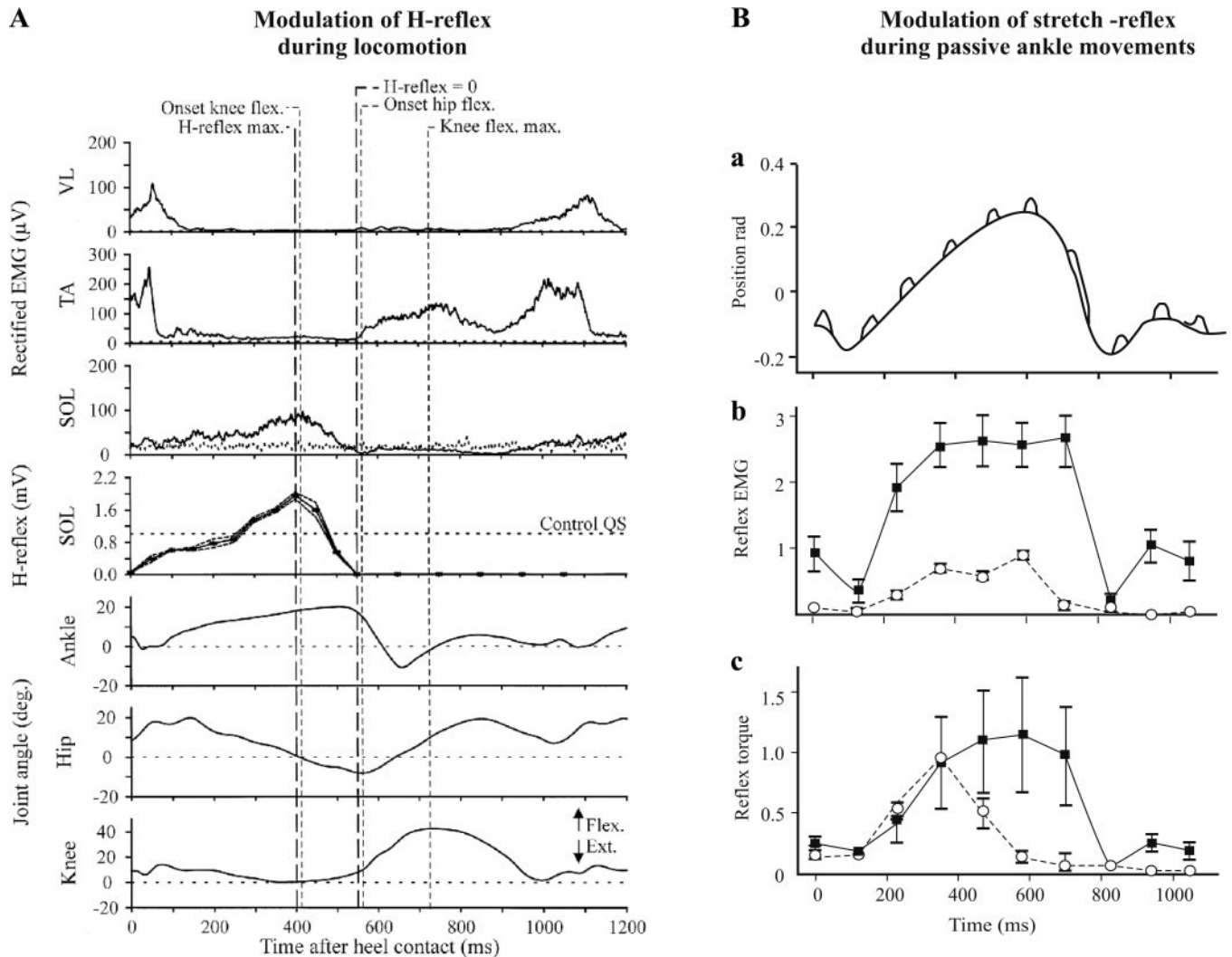


FIG. 9. Modulation of the H-reflex during locomotion or during passive ankle movements in humans. *A*: example from a single subject of the H-reflex modulation pattern during walking. Rectified electromyograph (EMG) activities of the vastus lateralis (VL), tibialis anterior (TA), and soleus (SOL) are shown along with the corresponding soleus H-reflex amplitude ( $\pm$ SE) and the angular displacement of the ankle, hip, and knee. Data are plotted as a function of time after heel contact; step cycle duration is  $\sim$ 1,100 ms. The H-reflex values are plotted against the time of their occurrence, not the time of stimulation in this and all other figures. The H-reflex amplitude during quiet standing is also indicated (control, QS). The rectified EMG traces are averages of 64 successive step cycles, and the superimposed dashed traces are the EMG values during quiet standing. Joint flexion is shown as an upward deflection of the angular displacement trace. The thick dashed vertical lines are markers for the H-reflex maximum and the minimum values. The thin dashed vertical lines are markers of kinematics events: onset of knee and hip flexion, time of full knee flexion. [From Schneider et al. (513).] *B*: influence of passive ankle movements (either imposed ankle angle walking profiles collected during actual walking or trials with imposed static positions of the ankle) on reflex EMG and reflex torque in humans produced by brief pulse displacements. *a*, Average ankle position with the 10 pulse displacements superimposed. *b*, Mean  $\pm$  SE of the normalized reflex EMG for simulated walking ( $\blacksquare$ ) and related static trials ( $\circ$ ). Note the reduction in the reflex EMG during the walking displacement profile of the ankle. *c*, Mean  $\pm$  SE normalized reflex torque for simulated walking ( $\blacksquare$ ) and related static trials ( $\circ$ ). Note that the torque is greater in the second half of the imposed extension with the locomotor profile than in the static profile. [From Kearney et al. (305).]



under investigation (usually Sol) and lowest during the opposite phase while the muscle is actually being stretched and during which a stretch response would be counterproductive (see Fig. 9A).

This raises the question of the mechanisms implicated in the modulation. Is the largest response during stance the result of an automatic gain control? Is the absence of an H-reflex during swing due to an absence of activity of the gastrocnemius during that phase or to the reciprocal inhibition from the agonist or to other mechanisms? It was shown (606) that, when subjects are asked to contract the gastrocnemius muscle during swing, the H-reflex remained depressed and that, even in the absence of activation of the ankle flexors, the H-reflex was depressed. Therefore, it is likely that powerful control mechanisms are responsible for the phasic modulation, such as presynaptic inhibitory mechanisms (see sect. IV) and reciprocal inhibition (556; see also Ref. 547). It is of interest to mention that during backward walking, the H-reflex is increased during swing while the Sol muscle is inactive (513). This modulation can also be trained and, with practice, can disappear (512), suggesting a great deal of supraspinal control of such basic spinal reflexes in different locomotor tasks.

It is also of great interest that passive locomotor-like movements of hip and knee joints can modulate the H-reflex, tonically and phasically (54, 55) and somehow mimic the findings obtained during locomotion (see however Ref. 513). A systematic study of stretch reflexes was performed in humans using ankle movement profiles (previously obtained during walking) and imposed through a hydraulic actuator to the ankle while subjects, lying reclined, were instructed to maintain a constant output force of extensor muscles (305). Brief stretches were imposed by the actuator. It was found that the stretch reflex was tonically diminished during the task and that it was phasically modulated much the same as during real walking. In addition, the EMG and the torque generated by the stretch reflexes could be dissociated during the cycle. The EMG amplitude was smaller in the early stance, whereas the torque was high and vice versa in late stance, suggesting that muscle dynamics may play a significant role in the final mechanical outcome of the contribution of stretch reflexes to locomotion (Fig. 8B). The interest of this study is the demonstration and confirmation that peripheral afferent feedback induced by the passive cyclical movements has the ability to induce changes in the excitability of reflex transmission probably through presynaptic inhibition as presumed to occur during real locomotion. This suggests that sensory-evoked presynaptic inhibition exerts a powerful effect on the modulation of the monosynaptic transmission from Ia afferents as described in section IV. This view has been contested by others (513). It is thus most likely that the modulation of H-reflex during locomotion is due to both central and

reinforcing concomitant peripheral sensory feedback during locomotion (214).

There are also important differences between studies on H-reflex and on stretch reflex. The two reflexes in the Sol were compared during the stance phase of walking and sitting at matched Sol activity (7). No difference was found in the amplitude of the stretch reflex, but there was a significant decrease of the H-reflex during the stance phase of walking. Also, a significantly different modulation of the two reflexes was found in the late stance where the stretch reflex decreased in relation to the H-reflex. The differences in results between H-reflex and stretch reflex could be due to the different presynaptic inhibitory patterns evoked by a synchronous electrical stimulation of Ia afferents in the former and by more dispersed Ia volleys in the latter (392). Furthermore, the amplitude of the short-latency and medium-latency stretch reflexes, presumably due to Ia and group II afferent inputs, respectively, was measured in soleus in normal subjects during walking, pedaling, and sitting. The results indicate a task-specific increase in medium-latency reflex during walking compared with pedaling and sitting but no change in the amplitude of short-latency stretch reflex for the three conditions (241).

In patients with a spinal cord lesion, the modulation of the H-reflex during locomotion is decreased and, in some instances, absent. It was argued that, in these patients who have increased hyperactive H-reflexes, the reduced modulation might have been a function of saturation, although in some cases, H-reflexes evoked by low-intensity stimuli were not modulated either (602).

E) PHASE-DEPENDENT MODULATION AND ROLE OF PROPRIOCEPTIVE PATHWAYS IN CONTROLLING MUSCLE DISCHARGE AMPLITUDE. The evidence reviewed in the above sections clearly indicates that muscle afferents can shape the locomotor pattern and, conversely, that the locomotor networks can modulate the transmission of proprioceptive afferent pathways. Given the existing knowledge of the various proprioceptive pathways, it is of interest to ask what could be the specific contribution to muscle amplitude modulation of the different proprioceptive afferents coursing through various pathways, namely, monosynaptic Ia pathway, group Ia and Ib di- and polysynaptic pathways, and finally group II and other afferents. The reader should refer to a detailed study addressing this question specifically in ankle extensors (140) as well as a more general review on the topic of sensory contribution to ankle extensor activity during stance (141).

1) *Monosynaptic Ia excitatory pathway.* The experimental evidence for a modulation of the excitability of the Ia excitatory pathway is clear, although the underlying mechanisms for this modulation in the "simplest" pathway is still not clear. Indeed, intracellular recordings have provided strong evidence for a phase-dependent modulation of Ia-evoked EPSPs in motoneurons, but neither the



size of the modulation nor the phases where maximum EPSPs occur can fully account for the modulation in amplitude of the monosynaptic reflex. During fictive locomotion of the forelimbs, monosynaptic excitation of flexor motoneurons was found maximal during the flexion phase when motoneurons are depolarized (264). During fictive locomotion in high spinal cats injected with DOPA (516) or in decerebrate cats (230, 529), the Ia-EPSPs in hindlimb motoneurons were larger during the depolarized phase of the flexor and extensor motoneurons (381). In one study however, two-thirds of Ia-EPSPs had no more than a 5% difference in amplitude depending on the phase, and these changes were unrelated to the motoneurons being flexors or extensors.(228).

The considerable variability in the reported phase-dependent modulation of Ia-EPSP amplitude could be due to differences in the preparation, the robustness of the fictive locomotor rhythm, the selected motor pools, the types of motor units, or the statistical analysis used. Nevertheless, there is a consistent and robust phase-dependent modulation of the monosynaptic reflex during locomotion, always peaking during the active phase (see also Ref. 140). Because the monosynaptic reflex phasic modulation is not always matched by a similar modulation of the Ia-EPSPs themselves, it is likely that the locomotor drive potential in motoneurons is mainly responsible for determining whether the Ia-EPSPs will reach the firing threshold or not. All the preceding intracellular investigations on the modulation of monosynaptic excitation used a single shock to elicit the monosynaptic EPSP. The size of such single-shock EPSPs is relatively small (1–3 mV), and it can reach the firing threshold only when it is riding on the underlying locomotor depolarization (up to 30 mV). However, under normal situations, spindle primaries would never fire with a single volley but instead with trains of impulses of varying frequencies. Trains of Ia inputs display additional properties like posttetanic potentiation (101) and can lower the threshold for plateau potentials in motoneurons (40). The excitation resulting from trains of Ia inputs and its modulation during locomotion may thus differ quite significantly from what is observed with only one shock. Further studies using patterns of Ia inputs resembling those from natural stimulation are needed to clarify the role of the monosynaptic reflex pathway in motoneuronal excitability.

Another issue is whether the activation of the monosynaptic Ia pathway contributes to the ongoing muscle discharge amplitude during locomotion. This was addressed specifically (140) for the ankle extensor MG in a preparation in which this muscle can be stretched to different isometric lengths while most of the limb is denervated and the three remaining limbs walk on the treadmill after decerebration. These studies showed that stretching the muscle resulted in an increase in the output amplitude of the MG as well as the GL (but not the Sol).

Recordings of afferents from muscle spindles (group Ia and II) indicate that they reach their lowest frequency during stance, and it was suggested that they could hardly be responsible for the stretch-related amplitude increase. Given the fact that H-reflex can be recorded in that experimental condition, it must be concluded that muscle spindles contribute little to the EMG amplitude of ankle extensors during locomotion. By exclusion, the change in burst amplitude of the ankle extensor muscles resulting from muscle stretch must originate from other muscle proprioceptors such as Golgi tendon organs.

It is important to realize that an H-reflex occurs when a highly synchronous stimulation of all Ia afferents induces an EPSP that reaches the firing threshold in, usually, a fraction of the motor pool. During normal walking, Ia afferent inputs, from spindles located in different regions of the muscle, will be conducted in different sub-phases of the step cycle, transmitted through IA terminals having different profiles of presynaptic inhibition (see sect. IV) and reach different types of motoneurons. The Ia inputs will then activate several different classes of membrane receptors and influence the excitability and properties of motoneurons through several intracellular pathways. They will also reach and influence several classes of spinal interneurons. It would thus be imprudent to determine the role of Ia excitation in locomotion based only on results from H-reflex studies.

*II) Disynaptic group I excitation of extensors and flexors.* At rest or in anesthetized cats, group Ib afferents originating from Golgi tendon organs together with Ia afferents can excite motoneurons of antagonistic muscles (295), but there is very little evidence of oligosynaptic excitation from group I afferents in motoneurons of synergists. Initially, disynaptic EPSP were rarely observed (529) during locomotion in paralyzed decerebrate cats. Later on, group Ia and Ib inputs from extensors were shown to evoke disynaptic EPSPs in synergistic motoneurons that reach maximal amplitude during the depolarized phase (11, 377, 468) or during fictive locomotion induced by nialamide and DOPA in decerebrate high spinal cats (514). However, when fictive locomotion is induced by clonidine (377) or DOPA (232) injection in cats spinalized at T<sub>13</sub>, disynaptic EPSPs are absent. So, transmission in these pathways appears to require not only locomotor network activation but some neuromodulation originating from above the spinal section.

A clear example of task-dependent transmission in group I pathways has been shown for disynaptic excitation in FDL and FHL motoneurons (121). During fictive locomotion, the group I evoked EPSPs are maximal in extension when FDL is hyperpolarized and FHL is depolarized. However, during fictive scratching, EPSPs are maximal in flexion when the polarization patterns in these two groups of motoneurons are reversed. State-dependent disynaptic excitation from group I afferents was also

observed in motoneurons of other flexor and bifunctional muscles in decerebrate cats (121, 468, 514). During MLR-fictive locomotion, a majority of motoneurons (468) innervating ankle, knee, or hip flexor muscles and motoneurons innervating bifunctional muscles received group I-evoked oligosynaptic EPSPs. These were present in some motoneurons in absence of fictive locomotion. In flexor motoneurons, locomotor-dependent excitation was present in both step cycle phases but largest during flexion. In motoneurons of bifunctional muscles, EPSPs were often largest at the transition between flexion and extension phases. Differences in the phase dependence and sources of group I excitation to flexor and extensor motoneurons during locomotion suggest the existence of separate groups of excitatory interneurons exciting flexor and extensor motoneurons.

What could be the contribution of these oligosynaptic excitatory proprioceptive pathways to the amplitude of muscle discharges during locomotion? As mentioned earlier, spindles are unlikely to provide a major excitatory input during stance when the maximal force output is reached. Golgi tendon organs discharge maximally during stance, and their discharge rate is closely linked to the force output (140, 460). Because group Ia has little effect and because electrical stimulation of the muscle nerve at group I strength induce an increase in ankle extensor

output, it must be concluded by exclusion that the Golgi tendon organ afferents play a major role in modulating muscle output during locomotion.

*III) Summary of the modulation in proprioceptive pathways during locomotion.* Overall, if one oversimplifies, the reorganization of group I pathways in extensors in the cat during locomotion appears to follow a simple scheme where the afferent inputs from hip, knee, and ankle extensors are transmitted through similar excitatory polysynaptic pathway (*path 3* in Fig. 10) to all extensors in the hindlimb. The closing and opening of the group I pathways during locomotion result in a net excitatory drive to extensor motoneurons (mono-, di-, and polysynaptic). Group Ia and Ib afferents are active during stance (460) and would thus contribute to the recruitment of extensors for weight-bearing in that phase (429). Figure 10, *left*, summarizes the connectivity involved in extensors during locomotion. The different pathways activated by group Ia, Ib, and group II afferents are drawn. Also, as described above, there is also convergence on interneurons of the polysynaptic excitatory pathways between group I afferents and reticulospinal fibers included in the medial longitudinal fasciculus (MLF) (499) and corticospinal fibers in the pyramidal tract (PT) but not with vestibulospinal tracts from Deiter's nucleus (DN) (335, 336). Some nuances not shown in the diagram include the

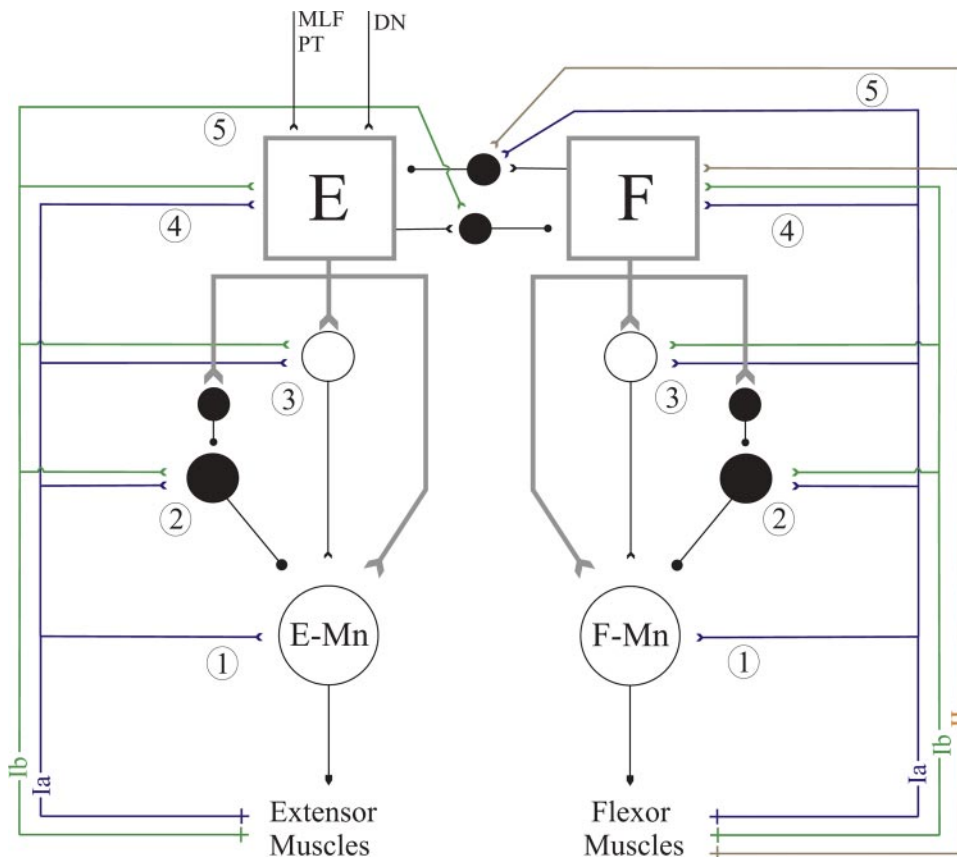


FIG. 10. Schematic representation of proprioceptive pathways from extensors and flexors during locomotion. *Left:* there are 4 pathways projecting to extensor motoneurons (E-Mn): the monosynaptic pathway from Ia afferents (*path 1*), the disynaptic group Ia+Ib inhibitory pathway (*path 2*) which is suppressed by the extensor generator (box E in grey), the disynaptic group Ia+Ib excitation (*path 3*), and the polysynaptic excitation (*path 4*) which are opened by the extensor generator. Group Ib afferent inputs are more powerful than Ia afferents to terminate the activities in flexors, and this is represented by *path 5*. There are also specific projections of supraspinal systems [medial longitudinal fasciculus (MLF), pyramidal tracts (PT), and Deiter's nucleus (DN)] onto group I polysynaptic excitatory pathways. *Right:* there is a similar organization in pathways from group Ia + Ib afferents of flexors for *paths 1-4*. Most flexors using group I or group II afferents can interrupt excitation and reset the rhythm to flexion (*path 5*), but only some can prolong the flexion phase (*path 4*). Inhibitory neurons and axonal projections are black circles. Excitatory neurons are empty circles, and axonal projections are forks. Ia are blue, Ib are green, and group II afferents are brown.

lack of effect of semibromesum with anterior biceps (SMAB) (232, 256; see however Ref. 518), the inhibition of gastrocnemii from quadriceps stimulation during MLR-induced fictive locomotion (256), and the potency of GLS over GM to promote extensor activities (591). Group II inputs from knee and ankle extensors evoke flexion reflex in spinal cats injected with L-DOPA (102, 232, 518).

The reorganization of proprioceptive pathways in flexors is not as global but is more complex. Various flexors have different afferents that are transmitted through selective pathways. For example, the Ia afferent inputs from Srt, Ip, and EDL and group II from TA can interrupt the extension phase and reset the rhythm to flexion (*path 5*). Only inputs from group I afferents of Srt and from group II afferents of EDL can prolong the flexion phase (*path 3*). Figure 10, *right*, summarizes the connectivity involved in flexors during locomotion (excluding the results from MLR-induced fictive locomotion, Ref. 435). Here again, the net synaptic effect resulting from the stimulation of these pathways is to provide an excitatory drive (mono-, di-, and polysynaptic) to flexor motoneurons. In this way, group Ia and II afferents of flexors that are active because of stretch at the end of stance and because of gamma drive (as described above) during swing would contribute to the initiation and recruitment of flexor activities.

F) PLASTICITY OF PATHWAYS FOLLOWING SPINAL INJURIES. Because of the importance of group I inputs from extensors to the control of activities in stance, it has been hypothesized that the repetitive stimulation of load pathways during step training on a treadmill after spinal cord injury could modify the transmission in these pathways (105). This was evaluated by comparing two groups of spinal cats; one group was trained to walk (no drugs) until full weight-bearing (3–4 wk), and the other was not. During an acute experiment, changes in group I pathways, monosynaptic excitation, disynaptic inhibition, and polysynaptic excitation were investigated by measuring the response amplitude in extensor motoneurons before and after clonidine injection. Disynaptic inhibition was significantly decreased by training after clonidine. Also, clonidine could reverse Ib inhibition into polysynaptic excitation (reflex reversal) in both groups of cats, but the level of significance was higher in the trained cats. Longer periods of locomotor training leading to full recovery of stepping (3 mo) (105) further decreased the group Ib disynaptic inhibition in extensors, which was apparent even without clonidine. Moreover, both monosynaptic and polysynaptic group I excitation were significantly increased in cats trained for 3 mo compared with 1 mo. It was also found that quadriceps muscle afferents were particularly effective. Overall, these changes would result in a better recruitment of extensor muscles required for recovering weight support during the stance phase of stepping.

### C. Other Afferents

Very little is known about the role of joint afferents. Loeb et al. (351) recorded three knee joint afferents that discharged during mid range movement of the knee. Two of these discharged during stance. In one study (198) it was shown that intra-articular injection of a local anesthetic could result in some major locomotor deficits such as external limb rotation and pronounced yield during stance. More work is needed to clarify how the locomotor networks interact with signals from joint afferents.

As detailed and reviewed elsewhere (280, 296, 297, 360, 361, 364, 518), after an intravenous injection of L-DOPA in spinal cats, segmental pathways activated by FRA form a reciprocal inhibitory network that was suggested to contribute to the alternating activities between antagonist muscle groups during locomotion. FRAs include joint, large and small cutaneous afferents, and group II, III, and IV (or high-threshold) muscle afferents. During fictive locomotion, it was shown that the stimulation of ipsilateral FRAs could reset the rhythm by initiating or prolonging the flexion phase (518). Similarly a strong stimulation of primary afferents evoked classical flexion withdrawal responses (531) irrespective of the step cycle phase (157, 203, 207). In contrast, the stimulation of contralateral FRAs evoked activities in extensors (102, 232, 296, 297, 360). In DOPA-treated spinal cats, stimulation of C fibers and, stimulation of group III and IV afferents through intra-arterial injections of bradykinin or KCl in the gastrocnemius muscle as well as afferents recruited at high threshold of stimulation of the superficial peroneal nerve led to an enhancement of ongoing rhythmic activity (314, 315).

Even though there is clear evidence that the pathways involved in long-latency and long-duration discharges are implicated in the rhythmic patterns evoked in acute spinal cat injected with DOPA, there is scarce evidence that similar pathways are involved in other walking preparations. For example, the long-lasting discharge evoked by stimulation of these afferents seen in acute spinal cats after DOPA is not evoked in chronic spinal cats capable of stepping on a treadmill (29, 243). These results suggest that pathways transmitting inputs from FRA are markedly reorganized following a chronic spinal cord transection in cats. On the other hand, electrical stimulation of FRAs in humans with a complete spinal cord injury evokes long-latency and long-duration discharges (72, 474). This discrepancy is difficult to understand and may be related to the fact that the hyperreflexia and spasms developing after a spinal lesion in humans are much more pronounced than in cats.

Tonic stimulation applied to the dorsal columns and dorsal roots (64, 254), a stimulation that cannot be related to a particular region and undoubtedly also include afferents of different modalities, can be very effective in in-



ducing locomotion in DOPA-treated spinal cats. Similar work has been performed in animal preparations and in humans using epidural stimulation of the cord or intraspinal microstimulation. This work shows that indeed stimulation of the spinal cord in cats (31, 218, 291, 400) can generate spinal locomotion. The respective role of direct afferent stimulation and motor pools still has to be sorted out in these preparations. Such electrical stimulation in combination with neurotransmitter agonists [ $\alpha$ -2 noradrenergic agonist clonidine for the cat (31) and serotonergic agonist in the rat (289)] can evoke very elaborate locomotor pattern. Of interest is the fact that the electrical stimulation of the upper lumbar region appears to be particularly efficient in triggering locomotion. A similar finding was also reported in humans with spinal cord lesion (139, 398, 448, 471).

### III. SENSORIMOTOR INTERACTIONS AT SUPRASPINAL LEVELS

In section II, dynamic sensorimotor interactions at the spinal level were discussed in details. The complexity of the interactions within the spinal cord has become more and more apparent with time as we have learned more about the processes involved. The underlying mechanisms are numerous, and the interactions can occur at multiple neuronal levels within the spinal cord. Dynamic sensorimotor interactions do not only occur at the spinal level during locomotion; many sources of sensory inputs impinge on neurons located at supraspinal levels and will, by the same token, influence markedly locomotor behavior. Sensory inputs from several modalities are used to adjust locomotion to conditions that prevail in the external environment into which an animal is moving. In turn, the locomotor centers adjust the sensory inflow in relation to the internal state of the organism as well as of other sensory inputs. The sensory inputs reaching supraspinal levels will also contribute importantly to initiate or stop locomotion. In this context, they will influence the dynamic operation of supraspinal locomotor centers as well as neurons involved in the descending control of locomotion. Through such influences, sensory inputs will change the dynamic state of motor behavior from rest to locomotion, and vice versa. In this part of the review, we describe the evidence relative to sensorimotor interactions at the supraspinal level.

#### A. Overview of the Supraspinal Control of Locomotion

The spinal locomotor networks can be turned on and off as well as controlled by supraspinal structures, which also receive sensory inputs directly or indirectly from various sources (Fig. 1). As described in section II for the

spinal cord, there are many potential sites where dynamic sensorimotor interactions can occur: presynaptic excitability changes, interneuronal selections, and changes in intrinsic membrane properties.

Circumscribed brain stem and forebrain regions have been identified to play a key role in the initiation and control of locomotion (for review, see Ref. 15; 246, 247, 302, 303, 415, 477). One such region is the MLR, which was first identified in cats by a Russian group (533). The MLR does not project directly to the spinal cord but initiates and controls locomotion through monosynaptic connections to brain stem reticulospinal neurons, which, in turn, activate the spinal locomotor networks to initiate locomotion. As discussed below, sensory inputs converge extensively at the level of reticulospinal cells, thus providing a site of complex sensorimotor interactions.

Since the discovery of the MLR in the early 1960s, its stimulation was used by many investigators as a means of eliciting real as well as fictive locomotion (see sect. II). The MLR receives inputs from several brain stem and forebrain regions. For instance, the basal ganglia project to the MLR, and the activation of the nucleus accumbens elicits locomotion that is prevented by inactivation of the MLR (59). Projections from the nucleus accumbens to the ventral pallidum and then to the MLR are involved. It is believed that pallidal neurons are tonically active at rest, keeping the MLR under tonic inhibition (247). Activation of the MLR by the nucleus accumbens appears to result from disinhibition as injections of GABA<sub>A</sub> antagonists in the MLR induce locomotion (212). Another pathway, arising from the striatum and projecting to the MLR via the substantia nigra and nucleus accumbens, also operates through disinhibition. The medial hypothalamus projects to the MLR via the periaqueductal grey, a pathway proposed to be involved in locomotion generated for defensive purposes. Another projection from the lateral hypothalamus is proposed to be involved in initiating locomotion for food seeking (548). The organization of these pathways has been reviewed in detail (303). Other locomotor regions have been identified in the diencephalon where stimulation of the zona incerta elicits locomotor activity (383, 424, 548). In the rat, a direct projection exists from this region to the caudal medulla (521). An homologous region was discovered in lampreys and shown to also elicit locomotion via a direct projection to reticulospinal cells of the hindbrain (185). In addition to the MLR and the diencephalic locomotor region, other locomotor regions were described in the cerebellum (42, 389) and in other parts of the brain stem (42, 390, 406). Electrical stimulation of these regions also elicits locomotion in a graded fashion. The cerebral cortex is not a locomotor region per se, but it exerts powerful influences on locomotion. Several studies have demonstrated that the effects are more crucial during precise visually guided walking (38, 144, 145, 371). There is extensive modulation



of sensory transmission to cortical neurons during locomotion, and this is reviewed below.

## B. Modulation of Descending Inputs

Descending inputs activate the spinal locomotor networks to initiate locomotion. They are also subjected to a modulatory action when they reach the spinal neurons. Convergence of sensory and supraspinal inputs onto spinal interneurons was described in anesthetized cats (360). Pathways including the vestibular nucleus, reticulospinal tracts from the medial longitudinal fasciculus, and reticular pathways activated by the MLR have been examined extensively in mammals. Stimulation of the medial longitudinal fasciculus evokes mono- and disynaptic excitation in a majority of lumbar motoneurons. The amplitude of the disynaptic EPSPs displays a strong phase-dependent modulation; they are maximal during the depolarized phase in motoneurons innervating either flexor or extensor muscles (202). This indicates distinct interneuronal populations mediating opposite phase-dependent transmission in flexors and extensors. The disynaptic excitation in FDL motoneurons is maximal during extension, and little convergence occurs between cutaneous (sural, superficial peritoneal, or plantaris) and medial longitudinal fasciculus inputs. There is convergence between the medial longitudinal fasciculus and pyramidal tracts but not vestibulospinal tracts (237). The disynaptic excitation evoked by both the medial longitudinal fasciculus fibers and Deiter's nucleus is maximal during the depolarized phase in flexors and extensors during fictive locomotion (237). The influence of reticulospinal tracts in the medial longitudinal fasciculus and of vestibulospinal fibers from Deiter's nucleus during locomotion is thus transmitted through at least four different interneuronal populations. Moreover, MLR-evoked disynaptic EPSPs in FDL motoneurons are maximal during the depolarized phase at the beginning of the flexion phase, whereas the disynaptic excitation evoked by medial longitudinal fasciculus input is always maximal during extensor activity (121). These distinct patterns of phase-dependent modulation suggest separate interneuronal pathways.

Convergence between supraspinal structures and group I afferents from extensors on the long-latency polysynaptic excitatory pathways (Fig. 10) to extensors have also been studied in partially spinalized decerebrate cats injected with nialamide and DOPA (499). A convergence was found between group I afferents and the medial longitudinal fasciculus (333, 335) or the pyramidal tracts (336), but not for vestibulospinal tracts (331, 332). This is consistent with the lack of convergence observed between the medial longitudinal fasciculus and vestibular tracts on disynaptic excitatory pathways in decerebrate

cats (237) and between Deiter's nucleus and group Ib inputs in anesthetized cats (248). The lack of convergence between vestibulospinal tracts and extensor group I afferents is surprising because both inputs exert the same effect on the locomotor rhythm, a reset to extension (499) and both inputs also converge on contralateral high-threshold afferent (FRA) pathways in the same preparation (333, 562).

Injections of DOPA in spinal cats reorganize spinal networks to generate a locomotor-like rhythm. In this preparation, it was shown that disynaptic group I inhibition was gradually replaced by a growing polysynaptic excitation originating from the same afferents (232) as detailed in section iv. Similarly, an injection of DOPA induced a progressive increase of polysynaptic excitation from Deiter's nucleus, medial longitudinal fasciculus (335), and pyramidal tracts (see Fig. 9B) (336). Thus inputs from extensor group I afferents, Deiter's nucleus, some reticulospinal fibers in the medial longitudinal fasciculus, and the pyramidal tracts are all transmitted through common polysynaptic excitatory pathways that can enhance and promote extensor activities. However, the convergence results described above indicate that these pathways are composed of at least two separate interneuronal populations. These distinct subsystems, which are all involved in promoting extensor activities, could be involved in the differential locomotor and postural adjustments during stepping (554). There are therefore strategically located interneurons in the spinal cord that will likely play a crucial role in dynamic sensorimotor interactions by receiving convergent inputs from both descending and sensory inputs.

In humans, transcranial magnetic stimulation offers new avenues to explore the interactions between descending and sensory inputs at the level of the spinal cord (444). The effects of repetitive transcranial magnetic stimulation were examined on the size of the soleus H-reflex (434). A depression was observed and was explained, at least partly, by an increased presynaptic inhibition of soleus Ia afferents. Whether similar reflex modulation exerted by cortical circuitry is present during locomotion remains to be established in humans.

Studies in mammals and humans have thus provided a general account of the modulation of descending inputs interacting with sensory signals. On the other hand, there has been little information on the specific cellular mechanisms, and the latter have been studied in greater details in lower vertebrates. In lampreys, several neurotransmitter systems are known to modulate the transmission from descending axons to spinal neurons. For instance, serotonin exerts powerful effects on the locomotor output (261, 586), and increases in its endogenous levels in the spinal cord modulate locomotor activity (94). Serotonin was also shown to depress the glutamatergic excitatory

responses elicited by descending reticulospinal axons in spinal neurons (62). The subcellular mechanisms were examined in details through an elegant series of experiments. It was proposed that the depression resulted from the activation of a novel signal transduction pathway directed on the release of glutamate from the presynaptic terminals of descending reticulospinal axons (45, 561). Because serotonin exerts pre- and postsynaptic effects at different levels in the spinal cord, the exact contribution of its modulation on the transmission from descending axons has not been identified yet on the powerful effects that serotonin exerts on locomotion. In the mammalian spinal cord, most of the serotonergic innervation originates from the brain stem raphe nuclei. It would thus be expected that serotonergic modulation of descending inputs and/or sensory transmission would result from the activation of brain stem neurons. Indeed, effects of serotonin on sensory transmission in the spinal cord have been reported in several animal species (46, 340, 358). On the other hand, little is known about effects on descending pathways in mammals.

Other transmitter systems also modulate the transmission from descending inputs. Glutamate ionotropic receptors are present on the membrane of descending reticulospinal axons in lampreys. Both AMPA and NMDA receptors are present on descending axons (98). This indicates that glutamate, likely from spinal neurons, modulates, in turn, glutamatergic transmission from descending reticulospinal axons. NMDA receptors control presynaptic calcium and transmitter release in the descending axons. Large intracellular calcium rises are elicited by NMDA. This causes an increase in neurotransmission in the central network that underlies locomotion in the lamprey spinal cord. This will undoubtedly modulate the descending inputs during locomotion. Group I metabotropic glutamate receptors also exert powerful effects on the transmission from descending axons to spinal cells. These receptors are activated by repetitive activation of glutamatergic terminals. Blocking metabotropic receptors reduces glutamate release during the repetitive activity such as seen during locomotion. Interestingly, it was shown that this can lead to the arrest of locomotion (97, 560). In addition, several neuropeptides have been reported to depress the reticulospinal inputs to spinal neurons of lampreys (423). It appears therefore that there are many possible neuromodulatory systems that regulate the transmission from descending inputs in the spinal cord. However, the exact role of these transmitter-receptor systems in shaping the transmission from descending inputs to spinal cells during locomotion needs to be defined. Whether the same systems will exert effects on sensory inputs in the spinal cord as well as on their interactions with the descending control system also remains to be clarified in the future.

### C. Dynamic Sensorimotor Interactions at the Supraspinal Level

We review the interactions between some sensory systems and supraspinal centers controlling locomotion with an emphasis on the dynamic changes occurring in locomotion. The inputs are not only important to control ongoing locomotor activity, but they have been shown to be involved in initiating locomotion and, in some cases, they will arrest it.

#### 1. Cutaneous inputs

Cutaneous inputs play a crucial role in the control of locomotion. The effects exerted at the spinal level were examined extensively in the past and are reviewed in detail in section II. In addition to their effects at the spinal level, cutaneous inputs also shape the activity of supraspinal neurons, and we now review how this is done at different levels in the brain stem and in the forebrain. It should be mentioned that our understanding of the dynamic interactions between cutaneous inputs and supraspinal centers has remained for a long time very limited compared with that of the spinal interactions. Nevertheless, over the last decades, there have been an increasing number of studies, thus improving our knowledge of the supraspinal interactions in mammals and lower vertebrates.

A) ROLE OF CUTANEOUS INPUTS IN THE INITIATION OF LOCOMOTION. As reported in section II of this review, cutaneous inputs can initiate locomotion in many animal species. Stimulation of the face region elicits locomotion in mammals (576). This observation may be related to the finding that stimulation of trigeminal nuclei is effective in triggering locomotion in decerebrate cats (see Ref. 302 for a review of the relations between the trigeminal complex and locomotor inducing brain stem areas). Stimulation of the dorsal columns or dorsal roots was also shown to be very efficient in eliciting bouts of locomotion in decerebrate cats (42). Although the locomotor effects may result from a direct activation of the spinal CPG, the ascending projections to the brain stem may very well contribute to the initiation of locomotion through a synaptic activation of reticulospinal cells (see below). Moreover, pinna stimulation elicits four-legged locomotion on a treadmill in acute precollicular-postmammillary decerebrate cats (13). The authors proposed that postural tone played a critical role because the same stimulation failed to elicit locomotion when tone was exaggerated or depressed. Although the ascending cutaneous pathways are themselves well described in mammals, little is known about the mechanisms by which cutaneous inputs initiate locomotion in these animal species. In aquatic vertebrate species, this is better understood. For instance, cutaneous stimulation induces bouts of locomotion in zebrafish. These re-

sponses occur very early during development, indicating that the underlying pathways are established early in life (60, 503). In an effort to examine the populations of neurons involved in these responses, the group of O'Malley conducted elegant experiments where they imaged brain stem neurons in response to cutaneous inputs. A large number of ipsilaterally and contralaterally projecting reticulospinal neurons displayed short-latency calcium responses to taps applied to the head (211). This indicated that reticulospinal neurons acted as command neurons to elicit locomotion in response to sensory inputs in these animals (for review, see Ref. 373). Moreover, the large number of reticulospinal cells being recruited indicated that the neural control system for swimming behavior is widely distributed.

The general neural organization responsible for sensory-evoked locomotion has now been described in several vertebrate species. However, the detailed cellular mechanisms involved were not worked out until recently. One useful model for the study of such cellular mechanisms has been the lamprey. As in other vertebrate species, reticulospinal cells constitute the main descending system in these animals. Because they are tightly coupled with sensory inputs and activate CPG neurons in the spinal cord, reticulospinal cells were proposed to act as command neurons (373, 580) not unlike other command neurons described in invertebrates (210, 593). The mechanisms by which reticulospinal cells generate bouts of escape swimming in response to sensory stimulation were identified (580, 581). The authors took advantage of a semi-intact preparation, consisting of the brain stem and rostral spinal cord dissected free from the muscle tissue and the tail left intact to freely swim behind. As the entire preparation is bathed in a Ringer solution, a detailed investigation of the cellular mechanisms underlying active locomotion was made possible with intracellular and/or whole cell patch recordings. In lampreys, excitatory cutaneous inputs are transmitted to reticulospinal cells through glutamate transmission (579). Anatomical studies have indicated that the trigeminal primary afferents do not make monosynaptic contacts with reticulospinal neurons (200, 316, 408). The afferents are restricted to the principal trigeminal sensory nucleus and travel down the descending trigeminal tract where they make synaptic contacts with second-order trigeminal neurons (see Ref. 578 and schematic in Fig. 11A). Stimulation of the skin over the head region induces graded excitatory responses in reticulospinal cells (581). The synaptic responses linearly increase in amplitude with increasing the stimulation strength (Fig. 11B). This linear relationship is maintained until a threshold level is reached at which action potentials are elicited in reticulospinal cells and are propagated to the spinal cord. Swimming is then initiated in the semi-intact preparation, similarly to the bouts of escape swimming produced by intact animals (Fig. 11E).

The depolarization plateaus require the activation of NMDA receptors that are present on the reticulospinal cell membrane.  $\text{Ca}^{2+}$  imaging experiments have shown that the sustained depolarization plateaus are accompanied by large increases in intracellular  $\text{Ca}^{2+}$ . This increase in  $\text{Ca}^{2+}$  leads to the activation of a  $\text{Ca}^{2+}$ -activated nonselective cationic current ( $I_{\text{CAN}}$ ) that maintains the cell into a depolarized state. Release of  $\text{Ca}^{2+}$  from internal stores may also play a role in maintaining the  $I_{\text{CAN}}$  and the brain stem command neurons into a depolarized state. These plateaus do not display voltage dependency and thus differ from those described in spinal motoneurons (274, 308, 309, 311). Once elicited, the reticulospinal cell plateaus cannot be stopped by hyperpolarizing the cell, either with intracellular current injections or through inhibitory synaptic transmission. Because the locomotor bout has to be sufficiently long to allow the animal to escape a threatening stimulus, the reticulospinal cells that act as command neurons likely need to be activated for a long period. This may explain some of the differences in the cellular mechanisms of reticulospinal cell plateaus compared with that observed in spinal motoneurons (see below). Nevertheless, the depolarizing plateaus seen in reticulospinal cells provide an interesting mechanism by which a short-duration sensory input can generate a long and sustained activity in motor command neurons through a calcium-mediated process. The sustained depolarization can last several tens of seconds to minutes. It was recently shown that the spinal locomotor networks do not contribute significantly to maintaining the sustained depolarization. Reversibly blocking conduction between the spinal cord and the brain stem did not modify the duration of the depolarization plateaus induced in reticulospinal neurons by mechanical stimulation of the skin or electrical stimulation of trigeminal primary afferents (197). Whether similar mechanisms occur in other locomotor centers in the brain remains to be established.

**B) ROLE OF CUTANEOUS INPUTS IN STOPPING LOCOMOTOR BEHAVIOR.** Sensory stimuli can stop locomotion in different animal species. In mammals, mechanical stimulation of the skin as well as electrical stimulation of specific afferent fibers can stop locomotion (see above; Refs. 576, 577). The mechanisms by which this occurs have not been identified. Inhibitory connections were also described from the brain stem to spinal neurons (347, 366). Moreover, inhibitory reticulospinal cells exist in the rat (269) and in the cat. Brain stem stimulation in freely behaving cats is thought to stop walking by exciting spinal inhibitory neurons (388). Recently, Roberts and co-workers (341) described interesting findings relative to a mechanism involved in stopping locomotion in response to tactile stimulation in the tadpole. As for lampreys, the nervous system of these animals is relatively simple, and fictive swimming can be initiated by brief cutaneous stimuli



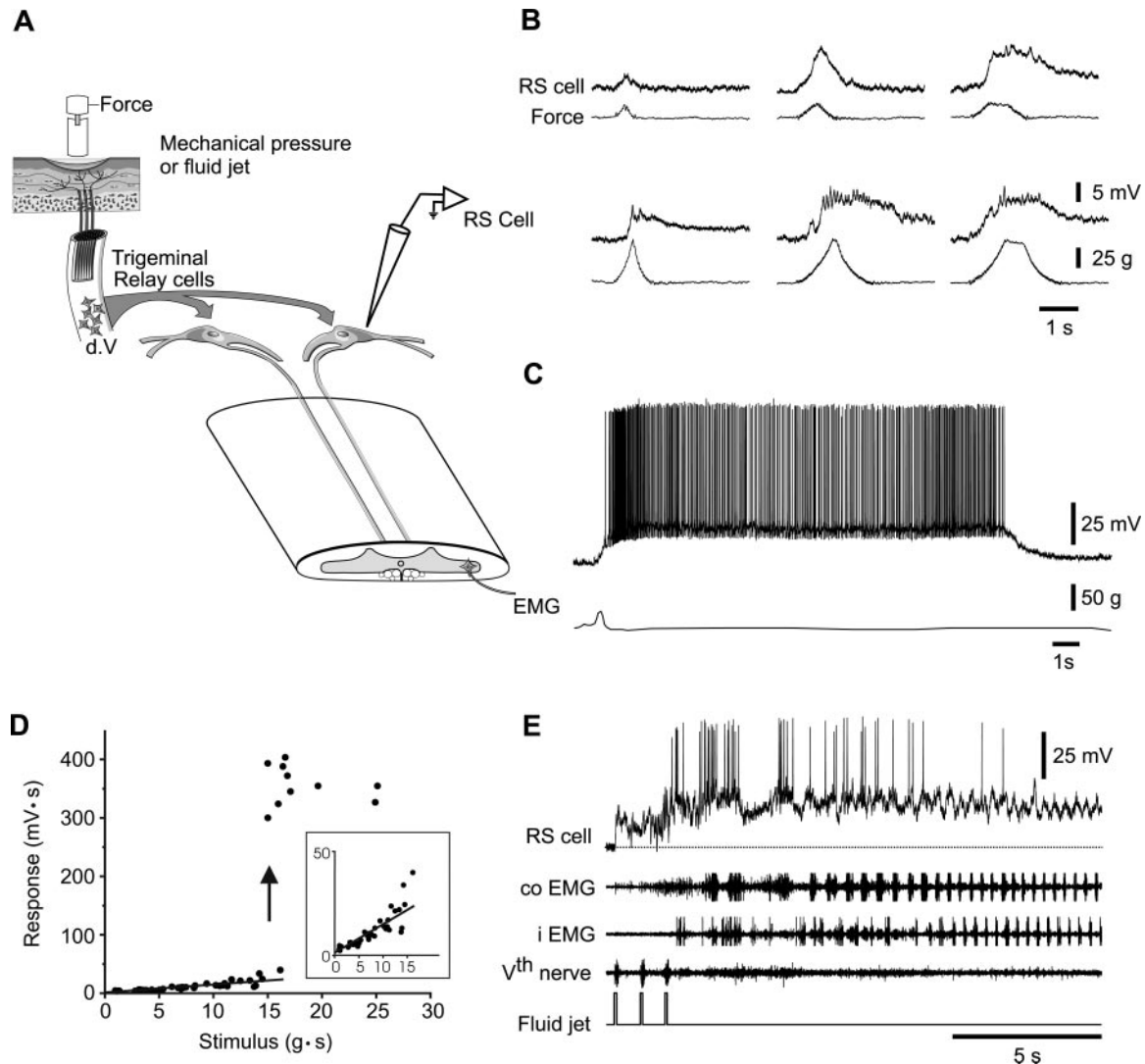


FIG. 11. Responses to mechanical stimulation of the head in lampreys. *A*: schematic representation of the disynaptic pathway from the periphery to reticulospinal cells in the brain stem. Mechanical stimulation or jets of fluid are applied to the skin in a semi-intact preparation where the brain stem and rostral spinal cord are dissected in vitro and a patch of skin is kept intact on the snout. *B*: responses evoked in a reticulospinal cell (*top traces*) by mechanical stimulation of different intensities and durations (force applied to the skin; *bottom traces*). *C*: a suprathreshold mechanical stimulation induces a large and long-lasting depolarizing plateau in a reticulospinal cell. *D*: plot of the stimulus-response relationship in one RS neuron. A linear relationship is observed for low intensities of stimulation (*inset*). *E*: responses to repeated low-intensity fluid jets, directed to the snout in a semi-intact preparation where the brain stem and spinal cord are dissected out and the a part of the body is kept intact to freely swim behind in the Ringer's solution. Note that the repetitive stimulation elicits a buildup of excitation that leads a sustained depolarization in the reticulospinal cell accompanied by spiking activity. As discharges occur in the reticulospinal cell, locomotor activity begins and is illustrated by the presence of alternating EMG bursts between the ipsilateral (i EMG) and contralateral (co EMG) sides. [From Viana Di Prisco et al. (580).]

(473). The authors have described a pathway from the peripheral receptors located in the cement gland from which trigeminal afferents carry cutaneous inputs to reticulospinal cells in the brain stem. Trigeminal afferents from the cement gland activate reticulospinal neurons projecting to the spinal cord (442). The reticulospinal cells in the hindbrain that are excited by pressure or electrical stimulation to the head skin have contralateral descending projections to the spinal cord. Moreover, it was shown that these reticulospinal neurons display GABA immunoreactivity. When spinal neurons receive

GABAergic inhibition, swimming stops. The induction of firing in the inhibitory GABAergic reticulospinal cells by intracellular current injection stops ongoing swimming, an effect that is blocked by the GABA<sub>A</sub> antagonist bicuculline. The same research group identified the spinal neurons that receive a direct descending GABAergic inputs (341). Ventral motoneurons and premotor interneurons involved in generating the swimming rhythm receive GABAergic inhibition, whereas the dorsal inhibitory premotor interneurons are inhibited less reliably. Sensory interneurons did not receive GABAergic inhibition. The



connections are thus more specific to neurons involved in the generation of locomotion. Taken together, these results consisted of a detailed description of a pathway from the periphery to the spinal CPG neurons including the mechanisms involved in stopping locomotor activity in one vertebrate species. This has not been achieved yet in other species of vertebrates. Because inhibitory descending reticulospinal cells exist in other species, it is possible that a similar mechanism operates to stop locomotor activity. Lampreys, for instance, possess glycinergic reticulospinal cells, which inhibit spinal neurons (588). With the use of double-labeling techniques, GABAergic cells projecting down to the lumbar spinal cord were described in the brain stem reticular formation of rats (270). These GABAergic cells could thus influence the entire spinal cord and eventually be involved in stopping locomotion in higher vertebrates as seen in amphibians.

C) ROLE OF CUTANEOUS INPUTS IN THE CONTROL OF ONGOING LOCOMOTOR ACTIVITY. How cutaneous inputs modulate locomotor activity and how gating of these inputs occurs at the spinal level is well documented (see sects. II and III). However, in intact animals, it is difficult to distinguish spinal from supraspinal effects. There are very few studies where cutaneous inputs impinging onto the supraspinal structures involved in the control of locomotion were examined. It was shown that the transmission of cutaneous inputs to the medullary reticular formation is modulated during locomotion (142). The authors suggested that the efficacy of transmission of the afferent information is determined more by the excitability of the spinal relay neurons than by the level of excitability of the reticulospinal neurons in the brain stem. The responses of reticulospinal cells to stimulation of low-threshold cutaneous afferents were maximal during the swing phase of the limb that was stimulated, and the size of the response was largely independent of the discharge pattern of the cell. It was proposed that the base of discharge pattern of reticulospinal neurons is largely determined by their central afferent input, whereas peripheral afferent inputs primarily serve to modify the reticulospinal neuron discharge pattern in response to perturbations. There is thus clear evidence that sensory inputs modulate strongly the discharge pattern of descending brain stem neurons.

The discharge pattern of cat motor cortex neurons was shown to be markedly modified in response to perturbations applied to the contralateral forelimb (371). Cortical inputs are also known to play a crucial role during locomotion. They adapt locomotor activity for accurate foot placement during each step cycle (for review, see Refs. 16, 217, 247). The activity of cortical neuron is also modulated by sensory inputs during locomotion. A perturbation that likely activated proprioceptive inputs as well as cutaneous receptors that were unloaded in reaction to the retraction of the base of support of the foot

produced marked changes in the discharge pattern of neurons in the motor cortex contralateral to the perturbed forelimb. In humans, there is also clear evidence that the inputs from the moving limbs reach cortical areas during rhythmic movements. Cerebral activity was examined during bicycling using positron emission tomography (92). The authors described a bilateral activation of the primary sensory cortex, the primary motor cortex, and the supplementary motor cortex. Interestingly, the responses were very similar during passive bicycling, suggesting that the sensory inputs from the moving limbs modulate strongly the activity of neurons in the motor cortical areas. Evidence for a significant input from the limbs to cortical areas and a strong influence onto motor cortical areas has been reviewed by Christensen et al. (93).

Not only do inputs from the moving limbs modulate the activity of cortical neurons in the motor areas during locomotion, but the responses to sensory inputs show a phasic modulation during the locomotor cycle. Responses of neurons in forelimb motor cortex to the stimulation of the superficial radial and ulnar nerves in the contralateral forelimb of cats walking over a ladder were examined (372). Most responses to both nerves were considerably reduced relative to their size under rest condition. In addition, some responses were phase dependent as they varied in amplitude depending on stimulus timing relative to the locomotor cycle. The findings were interpreted as evidence for central mechanisms that powerfully regulate the excitability of the somatic afferent pathways from the forelimb mechanoreceptors to motor cortex during skilled cortically controlled walking. The authors also showed that an enhancement of responsiveness often occurred (especially for ulnar nerve) around footfall, perhaps reflecting a behavioral requirement for sensory input signaling the quality of the contact established with the restricted surface available for support. These results are compatible with previous findings in the primary somatosensory cortex of rats during locomotion (89, 539). The transmission of sensory inputs from the contralateral limb showed a phase-dependent modulation during the step cycle and tonic depression of the responses during the whole step cycle was observed for some units. The exact site where the modulation takes place has not been established in any of the above studies. On the other hand, there is indication that movement-related gating of sensory transmission takes place in the dorsal column nuclei and the thalamus (90, 219, 359, 536–538).

The role of transmitter systems in modulating cutaneous inputs during locomotion has been examined in lampreys. It was shown that dorsal root and column inputs to reticulospinal cells are subjected to a GABA<sub>B</sub> receptor modulation that can nearly suppress the excitatory responses (151). Whether this modulatory system onto the brain stem command neurons is active during

locomotion remains to be established. There is also evidence for a strong muscarinic modulation of sensory transmission in the brain stem of lampreys (339). Muscarinic agonists significantly depress trigeminal sensory transmission to reticulospinal cells. Antagonists produce a facilitation indicating that there is a muscarinic depression exerted tonically in the brain stem. Interestingly the muscarinic effects are exerted specifically on the NMDA receptor component of the sensory-evoked glutamate response, the AMPA component being nearly unaffected. A muscarinic depression of sensory transmission is also elicited by stimulation of the MLR, which is the main source of cholinergic inputs in lampreys (47). The effects are long lasting and could thus be more state-related than phase-dependent. Muscarinic gating of sensory transmission originating in the MLR could have interesting behavioral consequences. The locomotor drive from the MLR could depress sensory inputs to prevent counterproductive reflexes from perturbing goal-directed locomotion.

## 2. Auditory and vibratory inputs

Acoustic stimuli and vibrations can also elicit locomotion in vertebrates (373). Strong responses to vibrations are, on the other hand, well documented in lampreys as well as in other fish species (107–110). In larval animals, the responses consist of cocontractions on both sides of the body, and there is a rapid withdrawal of the animals. Reticulospinal cells are excited by the vibrations and provide the descending command for the withdrawal response. The responses disappear after a labyrinthectomy. Vibrations also elicit directional responses followed by sustained bouts of linear locomotion in adult lampreys. The reticulospinal cells are responsible for the directional and the locomotor responses (131).

The responses to vibration and the underlying mechanisms have been examined extensively in teleosts. In these fishes, there is ample evidence that vibrations induce bouts of escape swimming. The movements evoked as well as the underlying neural mechanisms were examined in details. Escape swimming is characterized by a body bend in a C-like profile followed by rapid locomotion away from the initial position (170). The escape locomotor bout in goldfish is ballistic in nature. It does not use sensory information from the stimulus once the escape movement is initiated (172). Several approaches have been used to identify the underlying neural pathways responsible for the escape reaction. Mauthner cells are very large reticulospinal cells in these animals and have been shown to play a crucial role in the escape reaction (403). They receive inputs from the eighth nerve (for review, see Ref. 193). Sounds will elicit large excitatory postsynaptic responses in these cells. Under intense stimulation, firing is evoked, leading to muscle contractions (78). They showed that firing of the Mauthner cell

results in a body contraction occurring at a short latency that orients the initial stage of the movement away from the direction of the threatening stimulus (403). It was concluded however that firing of just the Mauthner cell could not account for the precisely tuned direction of the escape trajectory. To form the brain stem escape network, participation of other descending neurons is needed, together with that of the Mauthner cell (171, 173). The reticulospinal system will then act as the final common descending system to activate the spinal locomotor networks for sensory-evoked locomotion in response to different sensory modalities in different vertebrate species.

In mammals, auditory startle responses have been examined extensively. They consist of generalized motor responses to a strong auditory stimulus. The pathway involved has been identified. The acoustic startle reflex in rats and cats is mediated primarily by giant neurons in the nucleus reticularis pontis caudalis of the reticular formation (for review, see Ref. 607). Activation of neurons in this nucleus occurs 3–8 ms after the acoustic stimulus reaches the ear. The auditory inputs are relayed by neurons of the cochlear nuclei that connect to the reticulospinal cells either mono- or disynaptically. Giant neurons in the nucleus reticularis pontis caudalis, in turn, activate motoneurons in the brain stem and spinal cord.

There is considerable data in the literature relative to acoustic startle responses in humans. An intense acoustic stimulus generates a startle response manifesting itself in various parts of the body, including the lower limbs (116). Short-latency responses to acoustic stimulation were also observed in the leg using H-reflex (475, 487). The modulation of the responses can occur at different levels along the pathways from the sensory afferents to the motoneurons in the spinal cord. In humans, it is very likely that such responses result from the activation of reticulospinal pathways as shown in cats (476). A phase-dependent modulation of the responses to acoustic stimuli was also described during walking (402). Startle responses to an auditory stimulus during walking were found in all muscles recorded. This contrasted with the previous findings of Schepens and Delwaide (507) who reported that only a fraction of the subjects responded to the auditory stimuli while standing or sitting. The larger intensity of the stimulus in the former study was considered as the probable explanation for the discrepancy. Responses of various latencies (from 60 to 145 ms) are observed especially in more proximal lower limb muscles, and the various peaks of the responses can be modulated differentially in different parts of the step cycle. This indicates that these responses are, in part, generated by different neural pathways. Excitatory as well as inhibitory responses are seen, but the overwhelming response pattern is one of cocontraction in antagonist muscles presumably, as suggested by the authors, to increase stance stability during the

startle. Modulation could occur at the level of entry in the brain stem and/or within the spinal cord itself. Indeed, the descending inputs from the reticular formation show a phase-dependent modulation during locomotion. The effects of electrical stimulation of reticulospinal pathways in mammals have been examined in cats (149, 150). The cocontractions seen at rest are, to a large extent, replaced by responses in flexor or extensor muscles in the respective swing or stance phases. How much will additional modulation of the sensory inputs to the reticular formation add to a modulation of descending inputs onto spinal neurons remains to be established. This has not been worked out in any animal species yet.

### 3. Vestibular inputs

Appropriate posture is essential for the coordinated control of motor behaviors (for review, see Ref. 365), including locomotion (for review, see Ref. 145). Vestibular transmission during locomotion has been studied extensively in mammals. The effects of vestibular stimulation were examined during locomotion of cats over a treadmill belt (413, 419). Vestibulospinal neuron activity was first examined during locomotion, and it was found that the overall discharge of the cells increased. There was also a clear modulation of discharge with the locomotor activity (412). The same cells decreased their response to tilt during locomotion compared with rest conditions (419). It was proposed that the discharge of vestibular receptors in response to head displacement or perturbations could modify the rhythmic activity of brain stem descending neurons and disrupt locomotor activity. The vestibular influence on the spinal locomotor networks is also attributed in part to transmission to reticulospinal cells. It was shown that procaine microinjection into the ventromedial portion of the medullary reticular formation was accompanied by reduction of vestibular influence on flexor muscle activity evoked by electrical cutaneous and MLR stimulation (370). Vestibular influence on extensor muscle activity remained unchanged after the injection, suggesting that medial bulbar reticular formation is the site of the convergence of MLR and vestibular activity. This is also consistent with the independent pathways transmitting extensor-related commands from reticulospinal tracts and from vestibulospinal tracts in the cat as described above (see Fig. 9). The regulation of vestibular information during locomotion has been examined in humans recently. Galvanic vestibular stimulation was delivered at different times during the locomotor cycle, and the authors provided evidence of phase-dependent modulation of vestibular information during locomotion (41).

Because of the multiple descending systems involved in postural control in mammals, it has remained difficult to elucidate the detailed neural mechanisms underlying

postural control in these animals, including humans. The lamprey system has provided a useful tool to investigate the cellular mechanisms underlying the vestibular interactions on postural and locomotor control. Deliagina and co-workers (123–126, 128–130, 317, 416, 425, 566, 568) worked this out through an elegant series of studies. Lampreys normally maintain a dorsal-side-up orientation of the body during swimming as well as a preferred orientation with respect to the horizon. Vestibular inputs to reticulospinal cells play an essential role in maintaining postural orientation in these animals, and the responses of these cells to rotations in different planes were examined *in vitro* (128, 129, 416). Reticulospinal cells respond to rotations in both roll and pitch planes. The cells display responses that are composed of both dynamic and static components. There is a directional sensitivity to the responses. When rotating the animals in the roll plane, reticulospinal cells on both sides of the body are activated differentially. For instance, vestibular inputs mostly excite contralateral reticulospinal cells, and the roll balance will be maintained by symmetrical activity on both sides. The control of pitch also depends on the balance of activity of two groups of reticulospinal cells, the up and the down groups. The details of the connections from the vestibular apparatus to the descending control neurons have been worked out and modeled (317) (for review, see also Ref. 127). There are also strong interactions with the visual system, and these will be considered below when dealing with vision.

Vestibular inputs to reticulospinal neurons have also been shown to be modulated during fictive locomotion in lampreys (73). As locomotor discharges appear in the ventral roots during NMDA-induced fictive locomotion, the synaptic responses elicited in reticulospinal cells by vestibular nerve stimulation show a clear phasic modulation of their amplitude during the locomotor cycle. Responses to stimulation of the ipsilateral vestibular nerve are smaller during the ipsilateral burst discharge than during the contralateral activity, whilst responses to stimulation of the contralateral vestibular nerve are minimal during contralateral activity and maximal during ipsilateral activity. This opposite pattern of modulation observed in the same reticulospinal neuron was interpreted as evidence for the phasic modulation to occur at a pre-reticular level. More recently, it was shown that the inhibitory vestibular inputs are also subjected to a phase-dependent modulation during locomotion in lampreys (445). The excitatory vestibular inputs had minimal amplitude when the inhibitory ones were maximal. These two tendencies would reduce the influence exerted by vestibular inputs to the reticulospinal cells on one side when the contralateral spinal cord begins to be activated. This could help avoid that the reticulospinal neurons exert a counteractive drive on the ongoing rhythmic activity.



#### 4. Visual inputs

Visual inputs produce powerful modulation of locomotor behavior in most animal species (for review, see Ref. 478). They are used to choose a direction, to avoid obstacles, and in combination with vestibular inputs to set orientation. It has been recognized for a long time that optic flow contributes importantly to the control of locomotion (221, 337). Movements of the body in space generate a continuously changing optic flow field on the retina. These changes are an important source of information used to guide navigation and indicate the direction and the speed at which an individual is moving. Moving objects also contribute to the optic flow and confusion can occur between the self-generated flow and that of external objects. Optical flows produced artificially have been shown to generate locomotion that is perfectly adapted to the speed of the optic flow (117). Changes in the optic flow also profoundly affect locomotor activity. During forward locomotion, if the walls of the room are moved forward, this will create the impression that the subject is moving backward (337). Although considerable progress has been made in understanding how individuals perceive their direction of self-motion from the optic flow, little is known about how these perceptual processes develop in young individuals. It was recently shown that prelocomotor infants discriminate between optic flow patterns only when large changes in head angle are simulated. Changes smaller than  $22^\circ$  are not discriminated. Moreover, the sensitivity to direction changes in optic flow patterns does not improve between 3 and 5 mo (222). The authors proposed that spatial abilities associated with optic flow take time to develop and may depend on locomotor experience.

Visual information is also essential for anticipatory control to avoid obstacles when walking. Several elements need to be taken into consideration to avoid hitting an obstacle, such as the speed of walking and the distance from the object. Individuals will not fixate on the obstacles over which they want to step. This is planned several steps in advance. Feed-forward information is thus very important to guide locomotion in an obstructed path. Recently, the role of distant visual information sampled during locomotion was evaluated in the feed-forward control of locomotion with obstacles (386). The individuals had to approach and step over a single wide object located in the walking path. They used either their lead or trail limbs to step over the obstacle. Both limbs required feed-forward visual information to control stepping over the obstacle. However, only the lead limb elevation was influenced by on-line visual information during obstacle crossing.

The neural mechanisms responsible for the visual control of locomotion have only recently begun to be examined. Lesions of motor cortex lead to little changes

in unobstructed walking over ground or on a treadmill. The effects were far more pronounced when locomotion required stepping over obstacles or precise visually guided foot placement (37, 306; see Ref. 143 for review). Motor cortex conveys important commands during precise visually guided locomotion, which are needed for the proper adjustments of the gait to the features of the environment. Lesions of the corticospinal tract and reversible inactivation of motor cortex lead to the inability for a cat to walk over a ladder or step over obstacles over a treadmill belt (300, 330). Several studies have shown that most of the neurons in the limb regions of the motor cortex are phasically modulated during locomotion. There is a marked increase in discharge when precise foot placement is required such as during walking on narrow surfaces or changing the trajectory of the limbs to step over obstacles (17–19, 37–39, 592). It is clear from those observations that motor cortical discharge will contribute importantly to visually guided locomotion. The activity of red nucleus neurons was also examined in cats trained to walk on a treadmill and to step over obstacles (329). The discharge pattern of the cells was similar to that of pyramidal tract neurons recorded from the motor cortex. However, many cells increased their activity during the step cycle. It was proposed that the red nucleus also contributes to the modifications of the pattern of muscle activity that are required to produce the change in limb trajectory needed to step over an obstacle. The transformations that need to occur to modify the discharge pattern of descending neurons in response to visual cues have not been worked out.

Studies were also carried out to examine the role of movement-related visual feedback in locomotion by removing it. In stroboscopic light, which gives intermittent lighting thus providing positional cues but no optic flow, normal cats can walk on beams (367). Their performance gets better when the frequency of the flashes is increased. Cats were also raised under stroboscopic illumination and tested for locomotion under different conditions (368). The cats displayed slowness under all the experimental conditions. However, they showed no special deficit on narrow rails, indicating that their dynamic balancing abilities were normal. In these animals, the decrease in the use of kinetic visual cues was compensated for by an increase in the use of position cues. When tested after chronic bilateral labyrinthectomy, the cats reared in stroboscopic light had locomotor speeds identical to those of control labyrinthectomized cats, except on wide platforms involving orientation towards a visual goal. These results were interpreted as indicating that, in the absence of motion-vision, vestibular control of dynamic balance can mature normally. On the other hand, aspects of locomotion involving the processing of vestibular and kinesthetic inputs may be impaired. Removal of movement related visual feedback was then tested on the recovery of



cats subjected to a bilateral labyrinthectomy (613). The lack of motion cues resulted in severe alterations of fine posturokinetic balance. The animals displayed inappropriate dynamic motor adjustments and irregular locomotion speed regulation.

It was also shown that removing dynamic visual information with stroboscopic light affected more profoundly Parkinson's patients than normal subjects (22). It was proposed that information about the environment seems to be obtained in discrete samples (21) as shown using stroboscopic light. Measuring eye movements during walking on irregularly placed stones shows that after ~50 ms of landing on each stone, the eyes make a saccade to the next stone. This ensures accurate placement of the foot each step of the way (267). Discrete visual cues are thus obtained at precise time in the step cycle to accurately predict where the foot will land next.

##### 5. *Interactions between visual and vestibular inputs*

The interactions between visual and vestibular inputs to control posture and locomotor behavior have been examined recently. Behavioral and cellular experiments in lampreys have shed light on the cellular mechanism underlying these interactions. Blind and intact lampreys normally swim with their dorsal side up in darkness as long as their vestibular inputs are intact. The stabilization of the dorsal up orientation during swimming is done by the postural control system driven in large part by the vestibular system (123–125, 566, 567). Illumination of one eye in the intact lamprey evokes a roll tilt toward the source of light (566, 567, 569, 570). This behavior is referred to as the dorsal light response (414). The contribution of vestibular and visual inputs in the control of roll has been examined in great detail (126, 568, 569). After a bilateral labyrinthectomy, the swimming lamprey cannot stabilize any definite orientation. The animal continuously loops in different planes, indicating that the vestibular system plays a crucial role in the compensatory responses. A unilateral labyrinthectomy, on the other hand, elicits a motor deficit including loss of equilibrium and continuous rolling during swimming (425). Interestingly, illumination of the eye contralateral to the unilateral labyrinthectomy or repetitive electrical stimulation of the corresponding optic nerve restores equilibrium control. The same result is obtained when the vestibular nerve on the unilateral labyrinthectomy side is stimulated. The impairment of equilibrium control appears to result from the inability of the roll control system to use the information delivered by the remaining labyrinth properly. A conceptual model has been developed to explain the interactions between visual and vestibular inputs in the neural control of roll. The left and right side reticulospinal cells form two subgroups of cells that receive different visual and vestibular inputs. For instance, reticulospinal cells on one

side receive mainly excitatory vestibular inputs from the contralateral side and excitatory visual inputs from the ipsilateral eye. There are also some inhibitory inputs that come from the ipsilateral vestibular apparatus and the contralateral eye (see Ref. 130). At equilibrium, those inputs will generate a postural command allowing the animal to swim with its dorsal side up. Any imbalance in the vestibular inputs will for instance produce roll of the animal, and compensation will be possible by increasing the activity of other sensory inputs, such as seen by illumination of one eye in animals that were subjected to a unilateral labyrinthectomy. This convergence of visual and vestibular inputs at the reticulospinal cell level is an interesting feature for the merging of the two sensory modalities for equilibrium control. Whether similar brain stem mechanisms are present in higher vertebrates remains to be established.

#### IV. CELLULAR AND NETWORK MECHANISMS OF SENSORIMOTOR INTERACTIONS

In this section, we review different mechanisms that may underlie, at the cellular and network levels, some of the dynamic sensorimotor interactions reported in the previous sections. Referring again to Figure 1, it is important to stress that several mechanisms are probably at play when an appropriate response to a perturbation is generated in different phases or subphases of the locomotor cycle. The sensory inputs can be modulated early in the pathway, in the primary neurons themselves through presynaptic modulation that may change the inputs cyclically or may even select collaterals of an afferent that will or will not transmit information to second-order neurons. Similar presynaptic mechanisms may also be involved in modulating sensory inputs that reach the brain stem and in gating descending commands to the spinal cord (see sect. III). Related to presynaptic modulation are antidromic discharges in sensory afferents that can potentially change the state of excitability of the peripheral receptors. Probably the most complex and potent mechanisms for sensorimotor interactions occur at the level of segmental interneurons. The excitability changes of various types of interneurons by the CPG or by rhythmic descending or peripheral inputs offer an almost infinite set of response characteristics needed to interact efficiently with the locomotor pattern. Thus responses to a given input may be excitatory, inhibitory, or without effect depending on the state and the phases of the cycle. Finally, the motoneurons themselves are not only subjected to phasic changes in excitability during locomotion but membrane properties, that are unseen at rest, may participate in the modulation of the responses. These three large classes of mechanisms will now be presented in more details.

## A. Presynaptic Inhibition

Stopping or decreasing sensory feedback before it reaches spinal targets is a very efficient mechanism to control afferent inputs in different motor tasks as well as in different phases of the task. For instance, signals from spindle afferents of ankle extensors during their stretch in early stance may be useful to potentiate the ongoing activity of these muscles. On the other hand, a similar stretch during ankle dorsiflexion during swing could evoke an unwanted stretch reflex unless the afferent inputs are blocked by presynaptic inhibition and by reciprocal inhibition of the motoneurons. Presynaptic inhibition was first described as related to a depolarization in primary afferents (or dorsal root fibers) in response to electrical stimulation of sensory nerve and which was associated with a decrease in afferent transmission. It was later demonstrated (511) that sensory-evoked PAD was produced by a short chain of interneurons (at least 2) with axo-axonic contacts releasing GABA on terminals of primary afferents in the spinal cord. This GABAergic transmission to afferent terminals is mostly mediated by an increased chloride conductance that has a reversal potential significantly more depolarized than the resting potential (86, 95) and thus leads to a primary afferent depolarization (or PAD). In mammals, most of the PAD is mediated by bicuculline-sensitive GABA<sub>A</sub> receptors (111, 498, 511). For a detailed description of PAD pathways and mechanisms in vertebrates, readers should refer to the excellent review by Rudomin and Schmidt (498).

In the case where PAD is evoked by sensory inputs, it can be thus considered as representing a certain amount of presynaptic inhibition. This is referred to as "sensory-evoked PAD" and the GABAergic pathways involved are termed "PAD pathways." Recordings of sensory afferents during locomotion have shown spontaneous depolarizations, but the underlying mechanisms have rarely been investigated. We will refer to this depolarization as "locomotor-related PAD." These are depolarizing events occurring at the level of afferent terminals (presynaptic modulation), but their exact effect on synaptic transmission is unknown in many cases. It is important to realize that during normal stepping, PAD pathways are activated from different sources: sensory feedback, CPG networks, and supraspinal structures (as in most human investigations) and it is the resulting PAD (rarely recorded) that may have a modulatory effect on synaptic transmission. However, investigations of PAD during locomotion have usually focused on one source of PAD only. Therefore, in the following sections, PADs generated by the CPG networks are first reviewed and, then, PADs produced by sensory inputs and PADs evoked by supraspinal pathways are discussed.

### 1. State- and task-dependent locomotor-related PADs

As reviewed above, some studies in humans showed a lower H-reflex for similar EMG levels in SOL when changing from standing to walking and running, and this decrease was attributed to a task-dependent increase in presynaptic inhibition in Ia afferents leading to a lower gain in the monosynaptic transmission (552). Most findings from cat investigation indeed report a generalized PAD increase during locomotion. It was found, with an excitability testing method (585) measuring the amplitude of the antidromic compound action potential in peripheral nerves evoked by electrical stimulation of afferent terminals, that there was a sustained depolarization for several seconds in group Ia and Ib afferents from GS at the onset of fictive locomotion in decerebrate cats. This was interpreted as resulting from an increase of extracellular K<sup>+</sup> (155). Other indirect evidence for a generalized PAD increase during locomotion comes from extracellular field potential recordings. A change in the amplitude of monosynaptic field potential may be considered as being due to a change in afferent transmission (and of presynaptic inhibition; Ref. 559) if one assumes that the postsynaptic properties do not alter significantly the responses. Field potentials were recorded in the dorsal and intermediate laminae throughout the midlumbar to first sacral segments during MLR-induced fictive locomotion in the decerebrate cat (436). The vast majority of group I, II, and cutaneous-evoked field potentials were decreased during fictive locomotion. The reduction in group II field potentials began at the onset of MLR stimulation before the onset of rhythmic alternating locomotor discharges, but the field potential depression increased with the establishment of fictive locomotion. The larger depression found for the intermediate group II field potentials may indicate a preferential reduction in transmission from group II afferents to interneurons located in intermediate spinal laminae. A generalized reduction in Ia-EPSPs in motoneurons was also found in similar preparations (229), and this is in accord with the reported reduction in the amplitude of group I field potential in the ventral horn. Taken together, these results show an overall (but not evenly distributed) depression of synaptic transmission from group Ia and especially from group II in the intermediate zone and motor nuclei of lumbar segments during fictive locomotion in the cat. The mechanism underlying the tonic presynaptic depression during locomotion has not been determined. The reported depression of sensory transmission may participate in the stretch and H-reflex reduction and in the selective activation of group II interneuronal pathways as reviewed above.

A similar tonic reduction in sensory responses is seen during swimming in the tadpole. Bath application of 5-hydroxytryptamine (5-HT) enhances the duration and intensity of motor activity during swimming in *Xenopus* em-

bryo (541), but at the same time inhibits the cutaneous activation of swimming. This inhibition is partly due to a sustained presynaptic control of sensory neurons (Rohon-Beard cells). Recordings of first-order interneurons, the dorsolateral cells, showed an impressive decrease in monosynaptic EPSPs evoked by these sensory neurons after 5-HT application. Also, the rate, but not the amplitude distribution, of spontaneous EPSPs in dorsolateral cells was decreased by bath application of 5-HT (542). This indicates that 5-HT, by acting on receptors located on axonal terminals of the sensory neurons, reduces the probability of excitatory amino acid release and thus sensory transmission to dorsolateral cells. 5-HT also decreases the probability of release from the axonal terminals of dorsolateral cells as well (see sect. IVB). Similar effects of 5-HT were described on lampreys (188). Moreover, 5-HT also modulates sensory transmission in the mammalian spinal cord (213), suggesting that a presynaptic 5-HT modulation may be a generalized phenomenon in vertebrates.

## 2. Phasic locomotor-related PADs

Superimposed on this generalized PAD increase, there is also a spontaneous cyclic fluctuation of PADs during locomotion (in absence of sensory stimulation). For example, using an excitability tracking method, it was found that Ia and Ib afferents of both flexor and extensor muscles were more excitable (i.e., more depolarized) during the flexor phase than the extensor phase of the locomotor cycle (23, 24, 155). The recordings from cut dorsal rootlets (dorsal root potential) during fictive locomotion in thalamic or decerebrate cats and spinal cats (injected with DOPA) showed that the dorsal roots of cervical and lumbar segments were depolarized twice per locomotor cycle (25, 153). A maximum depolarization occurred during the flexor phase and a usually smaller one during the extension phase. The phase relationships between the peaks in depolarization and motor nerve activities indicated that the dorsal root potential fluctuations were well correlated in time with the locomotor cycle variations. Stimulation of dorsal roots in the tadpole has a powerful effect on locomotor networks because it can initiate, accelerate, or decelerate the rate of fictive swimming (550). Conversely, the locomotor networks evoke a tonic and phasic depolarization in dorsal roots synchronous with the ipsilateral motor activity, indicating tonic and cyclic PAD in afferent terminals. Accordingly, the excitability testing method showed a doubling of antidromic discharge in dorsal roots evoked by intraspinal stimulation during fictive swimming compared with rest (550).

Dorsal root recordings during real swimming and walking in rats showed two peaks corresponding to swing and stance (597–599). A larger depolarization was found during the stroke phase in swimming and during the

stance phase in walking, and a significant relationship was found between the magnitude of dorsal root potential and the amplitude of the general sensory inflow. Note that the maximal depolarization occurs in flexion during fictive locomotion in cats but in extension during real walking in rats. The difference is probably due to movement-related sensory feedback in the latter case. Indeed, as discussed below, sensory feedback triggers a dorsal root potential with a maximal amplitude in extension. This suggests that the phasic pattern of depolarization in afferents during walking is the result of interactions between central and sensory afferent inputs on presynaptic pathways.

Cyclic PAD was also investigated with intra-axonal recordings in the cat and lamprey. During spontaneous episodes of fictive locomotion in thalamic cats, large cutaneous axons innervating the dorsal and plantar areas of the hindpaw (234) and muscle group I (and some group II) afferents (236) displayed a wave of depolarization generally occurring during the flexor phase and a smaller wave during the extensor phase. One example of cyclic PAD in a group Ia afferent is illustrated in Figure 12 (*top left inset*). Overall, the relative amplitude of these two waves varied little from one cycle to the other but changed very much from one afferent to another. There was no obvious correlation between the PAD patterns and neither the size of the axon, its receptive field, nor the muscle group. Altogether, the results suggest that locomotor-related PAD patterns in an afferent axon cannot be simply related to its peripheral origin.

The effect of locomotor-related PAD on sensory transmission in the cat spinal cord was directly investigated by recording cyclic PAD in identified group Ia afferents and, simultaneously, the single fiber Ia-EPSPs in a target motoneuron during fictive locomotion (230). It was found that maximal EPSP occurred in TA motoneurons during flexion when the cyclic PAD in group Ia from TA was also maximum. This clearly indicates that patterns of cyclic PAD did not determine alone the amplitude of Ia-EPSPs in motoneurons. On the other hand, a sensory-evoked PAD reduced dramatically the amplitude of single fiber Ia-EPSPs in motoneurons (230, 558). Therefore, cyclic PAD does not appear to change transmission between Ia afferent terminals and motoneurons in this preparation. Supporting this notion is the finding of Misiaszek and collaborators (384) who compared the magnitude of the stretch- and electrically evoked monosynaptic reflexes in ankle extensor muscles in decerebrate cats during periods of tonic contractions and during sequences of rhythmic contractions occurring during the stance phase of walking on a treadmill. Rhythmic contractions and tonic contractions at the same level of background activity had the same effect on these reflexes, and it was suggested that the CPG did not presynaptically inhibit monosynaptic reflexes during the stance phase.



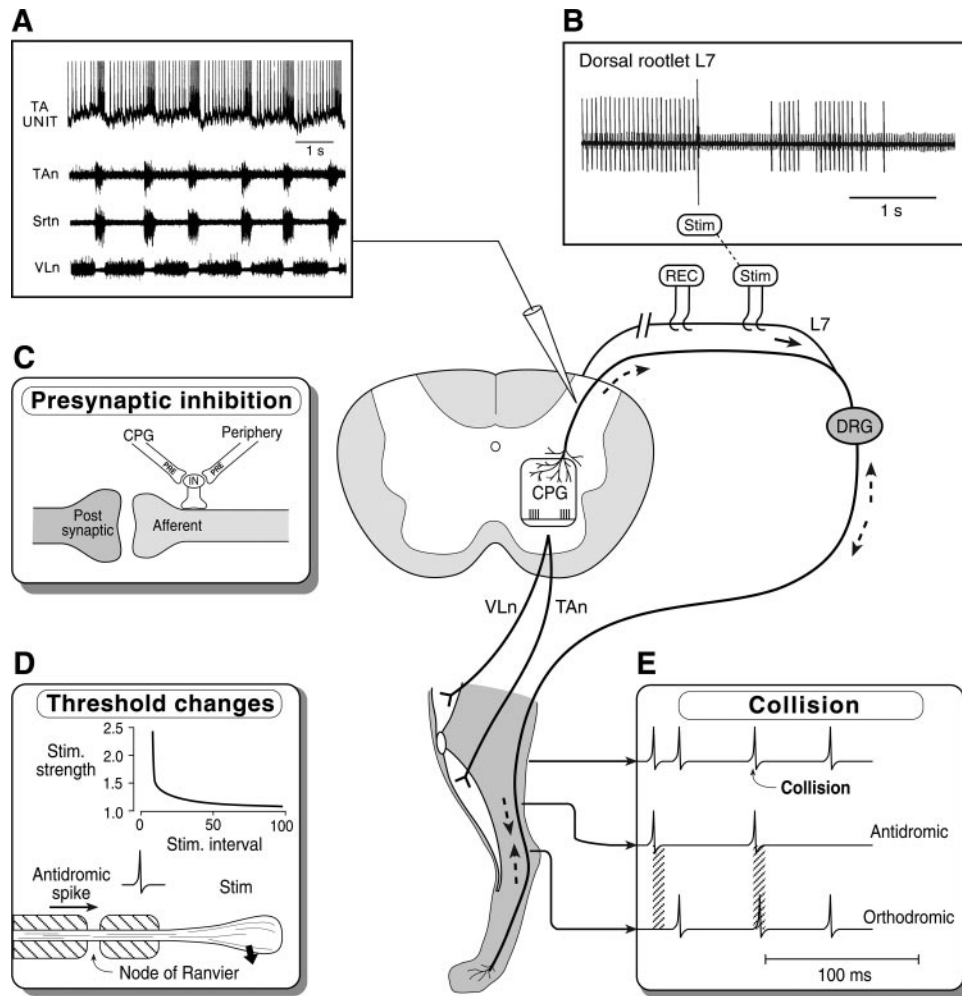


FIG. 12. Rhythmic antidromic discharges in primary afferents during fictive locomotion. *A*: intra-axonal recording of a IA afferent from TA showing high-frequency burst of antidromic spikes riding on a cyclic potential wave peaking during the flexor phase of fictive locomotion. Note the brief period where there are no spikes following the high-frequency burst. The other impulses at lower frequency are orthodromic discharges coming from the TA spindle. [From Gossard et al. (236).] *B*: recording of firing from two afferents in a cut dorsal rootlet from L<sub>7</sub> while stimulating antidromic discharge electrically. The schematic diagram in *B* shows the electrode set-up. A short stimulation train (Stim, 3 pulses 80 Å) stops the orthodromic activity in one unit (large amplitude) but does not affect the other unit (small amplitude). [From Gossard et al. (231).] *C*: diagram of systems modulating presynaptic inhibitory pathways during locomotion. Primary afferent terminals in the spinal cord are contacted by axo-axonic synapses from a short chain of interneurons (represented here by only one) producing PAD and antidromic discharges. PAD reduces the height of the action potentials invading the terminal and increases membrane conductance, leading to a reduced release of neurotransmitters. The interneuronal pathway is modulated by inputs from other peripheral afferents and by inputs from the central pattern generator. *D* and *E*: two peripheral mechanisms may be implicated in the control of orthodromic spikes by antidromic activity during locomotor movement. *D*: threshold changes. A potentially powerful mechanism to modulate orthodromic firing is to change the threshold of sensory transduction in peripheral receptors. In the diagram [redrawn from Lindblom (343)], it is shown that an antidromic spike invading the first node of Ranvier changes the excitability for spike generation for several milliseconds. The graph shows that it takes a stronger stimulus to trigger a spike following an antidromic invasion. The delay in spike generation probably explains the brief period of silence seen with intra-axonal recordings in *A*, and the absence of discharges in *B*, following antidromic activity. *E*: collision: orthodromic spikes are generated by a stimulation of the peripheral sensory field, as during locomotor movements. If antidromic spikes are also generated during the same time in the same afferents, there is a short period of time where some of the orthodromic spikes can “collide” with antidromic spikes and dissipate due to refractoriness they produced in the axon. As can be seen, only a few spikes would be blocked by this mechanism.

At this moment, it is not clear whether cyclic PAD and sensory-evoked PAD are generated by the same mechanism in the cat or whether cyclic PAD has a specific effect on different afferent terminals. In the neonatal rat, bicuculline could not abolish cyclic PAD recorded as dorsal root potential during drug-induced locomotor-like rhythmic activities, indicating that other mechanisms

than GABA<sub>A</sub> receptor activation may be involved, such as K<sup>+</sup> accumulation (319). There are indeed large potassium concentration transients in the isolated neonatal spinal cord in response to afferent stimulation (299a, 586a) that could also be produced by CPG network activity. However, in a later study using the same preparation, bath application of a low concentration of bicuculline blocked



rhythmic antidromic discharge in dorsal roots (195), suggesting that the underlying dorsal root potentials were generated via GABA<sub>A</sub> receptors. It was further proposed that the difference between the two studies was due to bath concentration in bicuculline.

The role of locomotor-related PAD on sensory transmission in cats and rats remains to be elucidated, but it has been investigated more directly in the lamprey. Intracellular recordings of skin-sensitive dorsal cells during NMDA-induced locomotor activity in the lamprey revealed large phasic depolarizations, occurring during the ipsilateral ventral root activity, that were not blocked by specific GABA<sub>A</sub> and GABA<sub>B</sub> antagonists (186). The depolarization was larger in the axon than in the soma located in proximity in the spinal cord and never led to antidromic discharge. It was further shown that the amplitude of the monosynaptic EPSP recorded with a second electrode in giant interneuron was reduced during the peak depolarization in the afferent without change in input resistance in the postsynaptic cell. Locomotor-related PAD in lamprey is thus able to inhibit (or filter) the sensory transmission to postsynaptic targets.

In brief, that cyclic PAD generated by the CPG has an inhibitory action on synaptic transmission has only been shown in the lamprey. Some preliminary evidence in the cat suggests on the contrary that this type of PAD is not able to modulate the IA-motoneuron transmission. However, the role (and mechanisms) of cyclic PAD on other synaptic pathways remains to be investigated. On the other hand, studies in the cat and tadpole indicate that locomotor activity is accompanied by a generalized tonic PAD resulting in a general decrease of sensory transmission.

### 3. Sensory control of PAD pathways

PAD evoked by sensory inputs (174, 498, 511) is also modulated during locomotion, indicating a CPG input onto sensory-evoked PAD pathways. For example, sensory-evoked PADs were recorded in dorsal rootlets (unidentified afferents) during fictive locomotion in thalamic cats (240). The amplitude of evoked dorsal root potentials was generally maximal during the extensor phase and minimal during the flexor phase when the locomotor PAD was maximal. The amplitude of dorsal root potentials evoked by contralateral afferent stimulation was also maximal during the extensor phase. This indicates that the PAD amplitude in a given afferent depends on the CPG phase in which it is engaged (i.e., extension) rather than on the CPG phase of the afferents evoking the PAD. Indeed, during the extensor phase on the ipsilateral side, afferents stimulated on the contralateral side actually show a maximal locomotor PAD during flexion.

Results from measurements of sensory-evoked field potentials have also indicated a phase-dependent modulation

in presynaptic pathways. In half of the recorded field potentials, there was a cyclic variation in amplitude with a depression in flexion for group I and cutaneous fields and a particularly important depression for group II fields in extension (436). This suggests that group II afferents would have a more potent effect on interneurons during flexion and, accordingly, the firing of group II interneurons occurs mainly during flexion during MLR-induced fictive locomotion (527; see below). Intracellular recordings of motoneurons have also shown a phase-dependent modulation of Ia-EPSPs in many motoneurons (229, 381, 515), which is attributed to phasic changes in presynaptic inhibition in Ia afferents. It is interesting that monosynaptic excitation is usually evoked by stimulating the entire population of Ia afferents in a peripheral nerve, and the resulting EPSP is modulated by the sum of PADs occurring in all Ia afferents. However, individual Ia afferents and individual Ia terminals may show different PAD patterns as discussed below.

A phase-dependent pattern of sensory-evoked PAD in cutaneous afferents has also been described in thalamic cats (235). The amplitude of PAD evoked in cutaneous afferents by cutaneous stimulation was maximal during the extensor phase of the step cycle, whether or not there was a concomitant locomotor PAD in the afferent. The results showed clearly that the maximum CPG-related PAD, which occurs during flexion (see above), was out of phase with the maximum cutaneous-evoked PAD. However, intra-axonal recordings showed much more complex PAD patterns in muscle group I afferents during fictive locomotion in decerebrate cats (379). The pattern of PAD modulation (in amplitude and the depth of modulation) varied with each recorded afferent as well as with each stimulated nerve. Group I afferents from the same muscle during the same experiment can display different phase-dependent PAD patterns. The differences in the complexity of PAD patterns between cutaneous and muscle afferents may represent a true distinction between sensory modalities or variations in analysis or preparations (thalamic vs. decerebrate cats).

Of course, during walking, several different sensory modalities can stimulate PAD pathways and determine the amount of presynaptic inhibition in different classes of afferents. Recent work (380) showed that cutaneous volleys could significantly modify the amplitude of PADs evoked by muscle afferent volleys in about half of the group I axons. The most common effect was a decrease in the PAD amplitude, which was operating for a major part of the step cycle and SP was the most potent skin nerve. These results suggest that cutaneous inputs, especially from the skin area on the dorsum of the paw (SP), could reduce presynaptic inhibition in group I afferents during perturbations of stepping (e.g., hitting an obstacle) and could thus adjust the influence of proprioceptive feedback onto motoneuronal excitability. The effects of such

complex PAD patterns on monosynaptic transmission were investigated in motoneurons (381), using the same stimuli as above. In about half of the trials, preceding the muscle afferent volleys by cutaneous volleys increased or decreased the monosynaptic EPSP size but only for a small portion of the step cycle. SP was again the most efficient skin nerve in affecting the EPSP and, in most cases, reduced the presynaptic inhibition of EPSPs. These studies suggest that small changes in sensory feedback during walking (e.g., perturbations) could lead to important modification of Ia transmission via PAD pathways. Moreover, sensory feedback accompanying different motor tasks could also modify the Ia afferent transmission. For example, differences in H-reflex amplitude between sitting, walking, and running (as described above) may be due to different central setting of the Ia transmission, but also, and more importantly, to the differences in sensory feedback accompanying each task (409).

One important finding from PAD studies in anesthetized cats is that different collaterals of the same afferent may be controlled by different last-order PAD interneurons (182, 357, 466). For example, presynaptic inhibition of the terminals of Ia afferents on motoneurons and on DSCT cells is mediated by different populations of PAD interneurons (299). Such organization could exert a focal control of sensory transmission and participate in the selection of interneuronal pathways. It was thus proposed that PAD interneurons during locomotion may be organized to reduce transmission in afferents ending on particular postsynaptic targets and not according to the peripheral origin of afferents (379). This could explain why it is difficult to classify PAD patterns in axons according to their peripheral origin. In addition, variable PAD patterns in terminals could also contribute to signal transmission. A distribution of widely variable PAD to different afferent collaterals could be considered as an increase in input noise to improve sensory function (stochastic resonance, Refs. 88, 453, 454) and/or used to decrease the variability of the H-reflex (238, 490, 491, 496). A differential control of Ia transmission in homonymous and heteronymous motor nuclei was shown for a voluntary ankle movement in humans (285, 286). However, it is not yet known if different collaterals of the same afferent have differential PAD patterns during locomotion.

#### 4. State- and phase-dependent antidromic discharges

When primary afferent terminals reach firing threshold, action potentials are triggered and propagated backward into the axon, i.e., antidromic propagation in peripheral, ascending, and descending branches (287, 409, 447). The so-called "antidromic discharge" can be recorded in proximal stumps of dorsal rootlets cut from their peripheral axons (known as "dorsal root reflex"; Ref. 30), demonstrating their central origin. Antidromic discharges are

observed during fictive and real locomotion in cats and rats. During fictive locomotion in cats, some afferents in cut dorsal rootlets discharged more or less tonically while others exhibited brief bursts either during the flexor phase, the extensor phase, twice per cycle or at phase transitions (152, 153). Bursts of antidromic discharges in afferents were usually coincident with the largest dorsal root potential, and there was a strong correlation between the burst duration and the duration of the locomotor cycle, in both decerebrate and spinal cats. Intra-axonal recordings from identified primary afferents during fictive locomotion in the decerebrate cat revealed that rhythmic antidromic discharges can occur in a minority of large cutaneous axons (234) and in about one-third of group I afferent fibers from flexor or bifunctional muscles (236). Figure 12 gives a schematic representation and recordings of antidromic discharges in sensory afferents. Antidromic discharges generated at the terminals can be modulated by sensory, supraspinal, or CPG networks (Fig. 12C). Once generated at the terminals, they can be recorded when traveling backward into the main axon with a micropipette or in a number of afferents in a dorsal rootlet. An example of rhythmic bursts of antidromic discharge in a group Ia afferent from TA during fictive locomotion is shown in Figure 12A. There are bursts of antidromic discharges riding on cyclic potential oscillations peaking during flexion. The other discharges occurring at lower frequency (during extension) are orthodromic and come from the TA spindle.

Rhythmic antidromic discharges can also be recorded in dorsal rootlets during real locomotion (152, 446). Antidromic discharges recorded during swimming or walking in rats occurred mostly at the onset of extension, and their number increased with the intensity of sensory feedback. Antidromic discharges recorded in GM and GL nerves of decerebrate cats walking on a treadmill, whether occurring spontaneously or when elicited by muscle afferent volleys, occurred during flexion, whereas those elicited by cutaneous volleys were depressed during flexion (154). Recent work (36, 480) using dorsal root recordings in decerebrate cats (Fig. 13) showed that the orthodromic and antidromic discharges can be distinguished in the same rootlet simply by comparison of their polarity (Fig. 13A). It was also found with spike-triggered averaging that antidromic firing can coexist with orthodromic firing in the same dorsal rootlet (35). These recordings showed that the number of afferents displaying antidromic activity increased dramatically during real walking on a treadmill (~80%) compared with fictive locomotion (19% in Ref. 153 and 44% in Ref. 35). The maximal frequency of discharge could occur in different parts of the step cycle, but the distribution indicates two maxima, one in swing and one in stance. Two examples of such rhythmic antidromic discharges are illustrated in Figure 13B. When the orthodromic inflow was blocked by

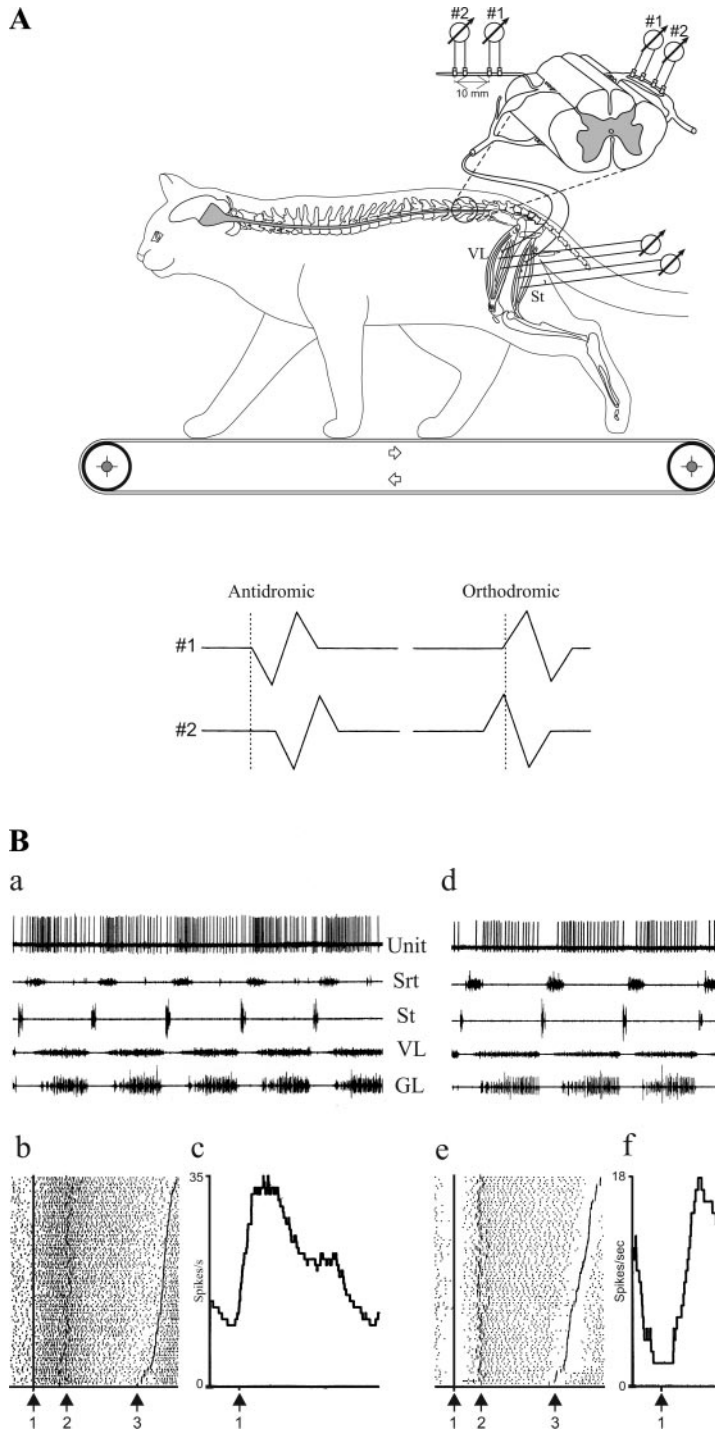


FIG. 13. Rhythmic antidromic discharges in primary afferents during treadmill locomotion. **A**: experimental set-up. Two bipolar Ag/AgCl electrodes are used to record activity in a cut dorsal root filament (such as in the *Ba* and *Bd* below) during locomotion on a treadmill belt in a decerebrate cat. The proximal electrode is labeled #1, and the distal electrode is labeled #2, and in that configuration, there is no doubt that the unit fires antidromically since it is cut from the periphery. To the right of the spinal cord is another configuration in which the filament is dissected but not cut. In this case, the direction of conduction is determined using a spike triggered averaging method. Spikes were labeled as antidromic when the first negative deflection recorded on the distal electrode (#2) occurred later than the one on the proximal electrode (#1). Spikes were labeled as orthodromic when the pattern of direction was opposite. The EMG activity of several hindlimb muscles can be recorded at the same time during treadmill locomotion (two only are shown, VL and St). **B**: antidromic activity of two fibers recorded in proximal stumps of cut dorsal root filaments during locomotion. The top records in *a* and *d* are raw signals from two filaments (Unit), and they are superimposed on the EMG activity of the ipsilateral Srt, St, VL, and GL. In *b* and *e*, the discharges are rank-ordered in raster formats and triggered on the onset of activity in Srt muscle: below the rasters: 1, onset of the Srt activity burst; 2, the end of this burst; 3, the onset of the next Srt burst. In *c* and *f*, the discharge frequency is presented in histogram forms. 1 indicates the onset of activity in Unit. The discharge frequency of the unit shown in *a-c* reaches a peak after the onset of activity in the flexor muscle Srt, i.e., during swing phase of the step cycle, while the discharge frequency of the unit shown in *d-f* increases at the end of the flexor phase and reaches its peak during the time of activity in the extensor muscles VL and GL, i.e., in the stance phase of the step cycle. [From Beloozerova and Rossignol (36).]

lidocaine application or transection, the phase of discharge did not change, but the frequency increased. Thus sensory feedback related to walking movements may increase in general the number of antidromically active afferents but also appears to decrease the firing frequency in single afferents.

One recent study indicates that the amount of antidromic discharge is task dependent. Indeed, the number

of antidromic discharges in lumbar dorsal rootlets slightly increased during fictive locomotion but greatly decreased during fictive scratch compared with rest in the same cat (103). Moreover, there were parallel changes in the amplitude of sensory-evoked PAD and dorsal root potentials. However, the amplitude of cyclic PAD (CPG related) was smaller during locomotion than scratch. These results indicate that antidromic discharges are generated by a



task-dependent modulation of sensory-evoked PAD pathways and not related to the underlying CPG-related PAD oscillations. This corroborates the result obtained in the neonatal rat showing that locomotor-related antidromic discharges were GABA<sub>A</sub> dependent (195). Antidromic discharges can have a powerful depressing effect on sensory volleys when they are propagating back to peripheral receptors as shown in several species (44, 87, 178, 231, 257, 290, 342, 343, 409, 564). Recordings in dorsal rootlets or axons in the cat show that antidromic discharge may have a long-lasting depressing effect on orthodromic propagation (Fig. 12, *inset B*) that likely reflects an inhibitory action on the peripheral receptor function and not spike collisions (Fig. 13, *insets D and E*). There is also evidence that antidromic discharges would not invade the terminals where they are generated (86, 184) but could invade other central collaterals and act on postsynaptic targets (287) or use the branching tree of collaterals as a local interneuronal circuit (573). Although the exact role of antidromic discharges in the control of locomotion is unknown, the present state of knowledge indicates that primary afferents are not just passive messengers but task-specific modulators of sensory information.

### 5. Supraspinal control of PADs

As described above, an elegant study in humans has shown that a voluntary movement of the ankle is accompanied by a differential control of presynaptic inhibition in Ia afferent terminals ending in different motor pools (285), indicating that supraspinal commands are able to set up PAD patterns relevant for the intended task. Evidence from anesthetized cats shows there are indeed several supraspinal systems controlling the PAD pathways (489, 494, 497). For example, stimulation of either the reticular formation, red nucleus or pyramidal tract, but not of the vestibular nuclei, reduces PAD (evoked by sensory inputs) in Ia fibers, but increases PAD in a majority of Ib fibers. Moreover, it has been described recently that some descending activity can exert a differential control on terminals of the same group I afferent ending in the Clarkes' nucleus and others ending in the L<sub>6</sub> intermediate zone (495). Descending terminals from supraspinal structures are not subjected to sensory-evoked PAD (112, 492, 493), but their transmitter release can be controlled by other mechanisms (e.g., glutamatergic and other receptors in reticulospinal tracts as described above).

Surprisingly, there is almost no data on the supraspinal control of PAD pathways during locomotion. A preliminary study (233) on the reticulospinal control of PAD during fictive locomotion in the decerebrate cat has shown that the transmission in PAD pathways activated by reticulospinal input is phasically modulated with a maximum occurring during the extensor phase on the

ipsilateral side with an opposite and larger modulation pattern on the contralateral side. Another study (334) has shown that the transmission in PAD pathways activated by Deiter's nucleus was maximal at the beginning of the extensor phase, by reticulospinal fibers in the medial longitudinal fasciculus during the flexor phase, and by pyramidal tracts in the middle of the flexor phase. It is probable that the phase dependency of PAD evoked by supraspinal systems is mainly due to the CPG drive to PAD interneurons.

PAD connectivity established in studies in anesthetized cats indicates an important convergence between supraspinal structures and sensory afferents on common PAD interneurons acting on group I afferent terminals. Preliminary results with dorsal rootlet recordings showed an absence of facilitation between supraspinal inputs and cutaneous or muscle afferent inputs (233, 334). These preliminary results suggest that supraspinal and sensory inputs could meet at the level of afferent terminals through private PAD pathways. Also, sensory and supraspinal pathways may activate different receptor systems (GABA<sub>A</sub> and GABA<sub>B</sub>) to exert a specific control of PAD transmission (465). Much work is needed to clarify the convergence patterns and mechanisms of supraspinal control of PAD during locomotion and movement in general.

## B. Interneuronal Activity

The complex modulation of sensory pathways has been documented in previous sections usually for one modality. It is of interest that in humans, one can also demonstrate a task-dependent differential regulation of proprioceptive and cutaneous reflexes involving some of the same motoneurons, which can only be achieved through an interneuronal selection (609). Another indication of such fine interneuronal control can be seen in situations where stimulation of cutaneous nerves induces a differential activation of synergistic muscles. For instance, GM is activated more than GL when the sural nerve is stimulated during walking (169) as predicted from interneuronal connectivity established in the cat (322). Similarly, differential phase-dependent modulation of cutaneous reflex pathways in the same muscle during walking or running (167) or between forward and backward walking in humans (164) could not be predicted on the basis of their variations in background activity and were thus due to interneuronal selection.

### 1. Locomotor-related activity of spinal interneurons

During locomotion, the activity of interneurons will result from the mix of convergent inputs from the CPG, sensory feedback, descending commands and of intrinsic properties turned on by different neuromodulators. The



activity of interneurons during locomotion was either recorded directly or inferred from the modulation of response in their postsynaptic targets, most often motoneurons. Varying the firing level of interneurons is certainly the most efficient way to gate sensory signals in reflex pathways. During locomotion, the interneuronal activity is phasically modulated and/or tonically excited or inhibited depending on the reflex pathway. Different patterns of interneuronal activity will thus determine which pathways are open, modulated, or blocked.

An example of interconnectivity between reflex and locomotor interneuronal pathways during locomotion is the initiation of swimming in the *Xenopus laevis* embryo. Swimming in this larva can be initiated by a natural contact on its trunk or tail skin that activates primary sensory neurons (Rohon-Beard cells). These sensory neurons activate mono- and polysynaptically dorsolateral commissural interneurons in the spinal cord that distribute their excitation to several classes of neurons involved in the generation of swimming (541). Dorsolateral commissural interneurons do not fire but receive rhythmic inhibition during fictive swimming, mostly in phase with the ipsilateral motor activity (96, 541). The rhythmic inhibition in these cells is able to block the EPSP evoked by cutaneous stimulation and can thus account for the phase-dependent gating of sensory excitation during swimming (540, 541). Premotor interneurons receiving cutaneous inputs are also rhythmically active, and their phase of inhibition is synchronous to dorsolateral commissural cells (541). The stimulation of contralateral skin at rest evokes subthreshold EPSP in premotor interneurons but, during fictive swimming, the same stimulation occurring on the depolarized phase evokes an extra action potential so the overall gain of the reflex pathway is enhanced (541). In this example, the excitability changes of spinal interneurons that are involved in rhythmogenesis also determine the phase dependency, and set the gain of, cutaneous reflex pathways during locomotion.

Some interneuronal pathways are tonically inhibited during locomotion. An example described above is the transmission in short-latency pathways producing flexion (historically described as flexor reflex afferents or FRA), which is inhibited during fictive locomotion induced by DOPA injection in the spinal cat (296–298, 360). A more recent study has shown that the responses of dorsal horn cells in laminae I, II, and V in lumbar segments of the decerebrate cat to group III muscle afferent inputs are greatly depressed following stimulation of the mesencephalic locomotor region (118). Iontophoretic application of bicuculline and strychnine suppressed the MLR-induced inhibition of transmission of group III afferent input to these cells, indicating a locomotor-related release of GABA and glycine to gate out group III transmission (118, 119).

The main problem in studying interneurons during locomotion in mammals is to obtain a complete functional identification, i.e., to identify both their afferent input and their efferent output to postsynaptic targets (292–294). Many studies recorded unidentified, or partly identified, spinal interneurons in the cat that are rhythmically active during fictive locomotion in lumbar and cervical segments of the cat. Attempts were made to classify these interneurons according to their phase of maximal firing frequency and laminar distribution. Although the firing of many interneurons is confined to either the flexor or the extensor phase, the overall conclusion is that there is a wide distribution of active periods within the locomotor cycle.

A first study recorded unidentified neurons extracellularly during MLR-induced walking on a treadmill (417). All of the selected neurons had locomotor-related firing and the onset and periods of firing could occur anywhere in the step cycle but preferably in stance. When afferents were severed, fewer neurons were active but their firing frequencies were not significantly different. The firing of unidentified interneurons was also analyzed during fictive locomotion in spinal cats injected with nialamide and DOPA (180). Although many cells had a peak firing frequency that coincided with flexion or extension, many others showed a maximal firing occurring anywhere in the step cycle. Unidentified firing interneurons in the cervical enlargement during forelimb locomotion were classified into four categories, two of which were firing during the main locomotor phases and the two others were firing during phase transitions (600, 601). These groups show a loose dorsoventral and rostrocaudal distribution within the C<sub>5</sub>-T<sub>1</sub> segments. Last-order interneurons (presumably both excitatory and inhibitory) to flexor motoneurons are located in C<sub>5</sub>-C<sub>7</sub> segments and those to extensor motoneurons in C<sub>6</sub>-T<sub>1</sub> segments (288). Repetitive stimuli in the upper cervical lateral funiculus used to induce fictive locomotion evoke time-locked disynaptic EPSPs, trisynaptic IPSPs, and trisynaptic EPSPs in forelimb motoneurons with different phasic modulation patterns. These three different modulation patterns suggested three different sets of interneuronal populations projecting to motoneurons: the first for flexion, the second for the onset of extension, and the third to maintain extension. The responses evoked by the third group persisted when the lateral funiculus was cut and could thus be driven by the ventral funiculus.

In the neonatal rat, whole cell recordings of commissural interneurons in L<sub>2</sub>-L<sub>3</sub> segments during fictive locomotion showed that those with descending projections to L<sub>4</sub>-L<sub>5</sub> segments on the contralateral side fired in all phases of the locomotor cycle and exhibited varying degrees of rhythmicity, from strongly rhythmic to nonrhythmic (74). A large proportion of these fired during the ipsilateral L<sub>2</sub> locomotor activity in flexion and could be involved in interlimb coordination. In a later study, these authors

described their postsynaptic actions and how the underlying pathways could be modified from rest to fictive locomotion (75). Commissural interneurons were divided into four groups: two monosynaptically projecting, excitatory and inhibitory, one polysynaptic inhibitory, and one that switched from polysynaptic inhibition at rest to monosynaptic excitation during fictive locomotion. Also, their phasic activity during fictive locomotion could account for the interlimb coordination of flexors and extensors on both sides of the cord. Their modulation by descending or sensory inputs remains to be examined. This remarkable piece of work holds the first description of fully identified CPG interneurons in the mammalian spinal cord. It should be noted that basic rhythmogenesis can be generated without crossing interneurons in the lamprey (79).

The difficulties of interneuronal identification make the relative simplicity of disynaptic pathways quite attractive (67, 68). Thus several disynaptic pathways to motoneurons activated by cutaneous and group I afferents as well as supraspinal descending tracts have been investigated during locomotion in the cat.

## *2. Group I interneuron responses and recurrent inhibition during fictive locomotion*

Ia inhibitory interneurons are not only part of disynaptic pathways, but their unique inhibitory response to recurrent inhibition (by ventral root stimulation) allows them to be identified and recorded during fictive locomotion. The activity of Ia inhibitory interneurons (mainly from quadriceps) was recorded extracellularly during MLR-induced walking in decerebrate cats (194). The period of firing was maximal during the stance phase. In deafferented cats, where the gamma bias is removed and thus phasic Ia inputs eliminated, most interneurons were still firing during the extensor phase (with lower frequencies) as determined by the modulation of the monosynaptic reflex. Similar firing patterns in a few interneurons were obtained during fictive locomotion from another group (376). Also, stretching the quadriceps muscles increased the firing only during the active phase of the interneurons (194). These results demonstrated clearly that Ia inhibitory interneurons were driven both by the CPG and by Ia afferents at the time when the muscle of origin (quadriceps) was normally active and could thus contribute to the inhibition of the antagonists during locomotion. Accordingly, there is a phase-dependent modulation of Ia-evoked IPSPs in motoneurons of antagonists with a maximum occurring during the hyperpolarized phase and a minimum during the depolarized phase during fictive locomotion (121 however see Ref. 452). In humans, the short-latency inhibition of SOL by common peroneal nerve stimulation, attributable to reciprocal inhibitory pathways, was found maximal during the swing

phase of walking (when SOL motoneurons are hyperpolarized) (443) or related to the level of antagonist TA activity (328). However, other studies showed that the magnitude of reciprocal inhibition in soleus actually increased with EMG but decreased with speed (80, 307). The reasons for such discrepancies are still unclear.

Renshaw cells inhibit motoneurons but also Ia inhibitory interneurons and other Renshaw cells (27, 175, 283). The patterns of activity in these cells will thus condition how their targets will react to afferent inputs during locomotion. In this sense, Renshaw cells are key players in determining the sensorimotor interactions occurring in many other spinal neurons. The burst of activity in Renshaw cells was found to occur at the time when the motoneurons from which they receive excitation were active during MLR-induced fictive locomotion (376). There was a small but significant reduction in firing evoked by ventral root stimulation during locomotion compared with rest (as suggested in Ref. 526). However, the inhibitory effects of Renshaw cells by ventral root stimulation on ventral root firing (451) were found comparable during passive cyclic movements and during fictive locomotion. This indicates that the Renshaw cell pathways are still very much operating during walking movements. Moreover, there were no differences in firing whether the ventral root was stimulated during the active or silent phase (376). Renshaw cells were thus mostly responding to the activation of motoneuronal collaterals. On the other hand, the amplitude of recurrent IPSPs in motoneurons evoked by ventral root stimulation was inversely correlated with the membrane potential, being maximal during the depolarized phase and minimal during the hyperpolarized phase. This phase-dependent modulation may be due to the membrane potential oscillations in the motoneuron (e.g., an increased electromotive force on inhibitory conductance during the depolarized phase) and/or to rhythmic Renshaw cell activity driven by the motoneuronal collaterals. Of course, Renshaw cells integrate inputs from many other sources (284, 596) that could participate in shaping their firing pattern of discharge during locomotion.

A further examination of the timing of Renshaw cell firing in relation to motoneuronal activity in the cat indicated that those related to extensors were firing maximally towards the end of the extension phase and those related to flexors, in the middle and late flexion (452). It was suggested that one role of such firing would be to help terminate the activity of motoneurons and of Ia inhibitory interneurons and thus help the transition to the antagonist phase of activity (376, 452). It is noteworthy that the rhythmic activity of 5/6 Renshaw cells was abolished following a nicotinic antagonist (mecamylamine) injection during fictive locomotion, indicating that the rhythmicity was derived mostly from motoneuron axon collaterals (407), unless there is also a CPG cholinergic

input. Moreover, with most of the recurrent inhibition blocked, the firing of motoneurons and of Ia inhibitory interneurons from quadriceps persisted and with increased frequencies. Also, the injection of strychnine blocking glycinergic inputs from Renshaw cells and Ia inhibitory interneurons did not eliminate MLR-induced fictive locomotion (452). Thus recurrent inhibition when present is limiting the activity of these two targets but is not required for locomotor activities to develop. It is obvious that recordings of large numbers of Renshaw cells and of Ia inhibitory interneurons associated with several different motor nuclei in several different preparations are needed to gain a complete picture of the roles of these cells in locomotor control.

Interneurons interposed in disynaptic group I pathways to extensors were recorded in the intermediate nucleus in  $L_6$ – $L_7$  at rest and during MLR-induced fictive locomotion (375). Interneurons with response characteristics typical of nonreciprocal inhibitory group I pathways hardly responded to group I inputs during fictive locomotion demonstrating a locomotor-related tonic inhibitory drive. This corroborates the abolition of disynaptic IPSPs in extensor motoneurons (Fig. 10, *path 3, left*) in response to extensor group I afferent stimulation during fictive locomotion as described above. On the other hand, more interneurons were found in  $L_7$  to have the response patterns appropriate for mediating excitation in disynaptic pathways to lumbar motoneurons (12, 467). These cannot be activated by group I inputs at rest but become responsive, and fire spontaneously, during the extensor phase of fictive locomotion. These interneurons are thus clearly activated, or disinhibited by, the activity of the CPG (Fig. 10, *path 2, left*). However, because locomotion can be evoked in the absence of such disynaptic excitation, these interneurons may not be considered as essential parts of the CPG network.

### 3. Group II interneurons responses and activities during fictive locomotion

Two groups of interneurons preferentially responding to group II afferent stimulation are distinguished, one located in caudal lumbar segments (362–364, 472) and one located in midlumbar segments (181). The latter group located in the intermediate zone and motor nuclei of  $L_4$  segment has drawn attention because of their direct projections to motoneuronal pools in more caudal segments, thus allowing an antidromic identification of these cells as last-order interneurons. Injection of monoamines or stimulation of monoaminergic descending tracts in the locus coeruleus can induce presynaptic inhibition of group II afferent terminals (53, 404) without affecting group I terminals as much. Because most of these interneurons also respond to group I inputs, the release of monoaminergic modulators could preferentially reduce group II sensory

feedback so that group I feedback would dominate. Two-thirds of the group II interneurons in  $L_4$  segment fired during the flexor phase during MLR-induced fictive locomotion in decerebrate cats (527). There were phase-dependent responses to group I, group II, and/or cutaneous stimuli in many of these interneurons occurring only during the flexor phase. The remaining one-third of interneurons were silent and inhibited during fictive locomotion, and their responses to group II afferents were suppressed at the onset of the MLR stimulation. It is truly remarkable that some neurons that were classified as “group II interneurons” (according to their responses at rest or in anesthetized animals) did not respond to group II inputs when involved in a locomotor network. Various recent evidence points to the potential importance of such interneuronal elements located in midlumbar segments. Indeed, intraspinal injections of noradrenergic agonists restricted to the midlumbar segments evokes spinal locomotion in cats spinalized 1 wk before the acute experiment (369); chronic spinal lesions below  $L_4$  abolish all spinal locomotion (327), and locomotion evoked by electrical stimulation of the spinal cord requires the integrity of these midlumbar segments (31).

### 4. Cervical interneurons in forelimb sensory pathways

Cervical interneurons mediating disynaptic cutaneous reflexes to  $T_1$  motor pools have been identified and found widely distributed in laminae IV–VII of  $C_6$ – $C_8$  segments (271, 272, 313). However, their responsiveness and firing patterns during fictive locomotion have not yet been defined. Candidate interneurons in the forelimb were partly identified by their cutaneous input (264) or partly identified as last-order interneurons projecting to the motor pools of elbow flexors (563) and studied during fictive locomotion. The stimulation of cutaneous afferents in the superficial radial nerve and of muscle afferents in the deep radial nerve during fictive locomotion evokes reflexes and intracellular responses in elbow flexors that are phasically modulated (264). The trisynaptic EPSPs and excitatory reflexes evoked by superficial radial nerve were maximal during flexion and suppressed in extension. The oligosynaptic EPSPs and excitatory reflexes evoked by the deep radial nerve were increased during flexion and decreased during extension while a longer-latency response was suppressed during the entire episode of fictive locomotion. This differential effect suggested that the modulatory mechanisms were occurring at a premotoneuronal level. The firing of interneurons mono- or disynaptically activated by muscle and cutaneous afferents, respectively, was modulated while the firing of interneurons monosynaptically activated by both types of afferents was not (265). The periods of firing were widely distributed in the step cycle but tended to be mostly in flexion or mostly in extension. It was concluded that



these two groups of interneurons could be involved in excitation and inhibition of elbow flexors, respectively (265).

Propriospinal neurons in C<sub>3</sub>-C<sub>4</sub> segments were also studied during fictive locomotion, and there was a disappearance of their phasic discharge after cooling the cervical area, suggesting a spinal origin for their firing modulation (20). Their firing frequency was found to be much higher than that observed during passive forelimb movement, but the phase during which maximum firing occurred was not reported. Thus the results suggest that these propriospinal neurons are more concerned with the transmission of intraspinal events (as CPG-related activities) than with sensory feedback.

### 5. Presynaptic inhibition of interneuronal axons

Recent studies indicate that the release from axonal terminals of spinal interneurons could be controlled presynaptically. For example, it was shown in the lamprey that axons of interneurons coursing through the ventrolateral quadrant displayed locomotor-related axonal depolarization (4) similar to locomotor PAD in sensory axons as described above. These depolarizations were found to be mediated by both GABA<sub>A</sub> and GABA<sub>B</sub> receptors. The peak depolarization (up to 10 mV) in axons was in phase with the ipsilateral motor activity. Because depolarizations were seen only with long piece of spinal cord (10 segments), it is suggested that the reduced transmission from these interneuronal terminals would contribute to intersegmental coordination.

The alternation of activity on each side of the *Xenopus* embryo during swimming is produced by reciprocal inhibitory connections via glycinergic commissural interneurons (543). In the absence of swimming, there were spontaneous IPSPs in motoneurons due to quantal glycinergic release. It was found that NA increased, and 5-HT decreased, the frequency, but not the amplitude distribution of, spontaneous IPSPs in tetrodotoxin-treated preparations. This result indicates that the neuromodulators act at a presynaptic level by decreasing and increasing the probability of transmitter release of commissural interneurons (378). It was also shown that 5-HT increased the duration of motor activity, by retarding burst termination, while NA reduced swimming frequency by delaying burst onset. There is also evidence of presynaptic inhibition of Ia inhibitory interneuronal axons in the anesthetized cats. Conditioning sensory volleys able to depress reciprocal inhibition reduce transmission from the Ia afferents as well as from the axons of Ia inhibitory interneurons activated by quadriceps afferents (191). Another study showed that last-order interneurons located in L<sub>4</sub>-L<sub>5</sub> had their axonal terminals into gastrocnemius-soleus lateralis (GLS) or posterior biceps-semitendinosus (PBSt) motor nuclei more excitable following sensory volleys and par-

ticularly from group II inputs (2). Whether there is a presynaptic control of release from interneuronal axonal terminals during locomotion in mammals is still unknown.

## C. Membrane Properties

Experimental evidence clearly indicates that motoneurons as the output elements of the spinal cord participate actively in the patterning of motor commands during locomotion. Because of synaptic and neuromodulatory influences, several intrinsic properties of motoneurons are turned on during locomotion that result in nonlinear input-output relationships (cf. Refs. 66, 281, 312, 450, 523). For example, there is a locomotor-dependent reduction in the threshold for spike generation (113, 318) and of afterhyperpolarization duration (58, 187, 509), which results in higher motoneuronal excitability. Two other motoneuronal properties susceptible to interact significantly with afferent inputs are the membrane potential oscillations known as "locomotor-drive-potential" and plateau properties.

### 1. Locomotor-drive potential

Membrane potential of motoneurons in vertebrates shows, during locomotion, a wave of depolarization during the active phase that alternates with a wave of hyperpolarization during the antagonist phase of activity, a rhythmic membrane oscillation also called "locomotor drive potential" or LDP (26, 180, 194, 301, 405, 420, 439, 452, 500, 515-517, 529). In the cat, the depolarizing phase is generated by an excitatory synaptic drive while the hyperpolarized phase by inhibitory synaptic inputs (180, 301, 439, 452, 528). Also in the lamprey, phasic excitation is mediated by glutamatergic synaptic inputs to both AMPA and NMDA receptors alternating with phasic inhibition mediated by a glycinergic chloride conductance (5, 114, 115, 245, 387). However, rhythmic activities can persist after glycinergic inhibition by antagonists as strychnine in the cat (452), and thus phasic inhibitory conductances are not a requirement for rhythmogenesis to occur (99). Another example comes from whole cell current-clamp recordings of motoneurons during fictive swimming in the zebrafish (70) that showed a rhythmic cationic drive (probably glutamatergic) with a tonic shunting anionic input (probably glycinergic). Fictive swimming in the stingray (594) and dogfish motoneurons (393) do not include phasic inhibition either.

Independent of the underlying mechanism, the mere amplitude of the locomotor drive potential (up to 30 mV in cat motoneurons) is crucial in deciding if a postsynaptic response will reach firing threshold or not (referred to as "automatic gain control"). The depolarized phase in motoneurons is thus a key factor in the facilitation of re-



sponses occurring during the period of activity of the muscle. However, the phase-dependent modulation of postsynaptic responses does not always match the excursions of the locomotor drive potential. As exemplified above for several spinal pathways, the largest reflex may occur outside the phase of activity in the muscle or of the motoneurons. If there is little or no change in somatic input resistance that can explain the postsynaptic response modulation, then out-of-phase patterns are taken as evidence for interneuronal and/or presynaptic modulation of transmission.

## 2. Plateau potentials

Plateau potentials have been described in motoneurons of vertebrates including the turtle (277), cat (275, 338, 522), mouse (84), frog (440), and humans (100, 226, 310). Plateau potentials have been the focus of intensive studies in the last 20 years, and excellent reviews have covered the subject (183, 273, 279, 281, 311, 450). As described in details in such reviews, ionic currents giving rise to plateau potentials in motoneurons are predominantly occurring in dendrites (276) because they possess voltage-sensitive L-type calcium conductances (Cav1.3) that induce a persistent inward current. These currents are turned on or unmasked by a variety of neuromodulators acting on various conductances and second messenger cascades (e.g., inositol trisphosphate pathway; Refs. 273, 441). It was shown recently that synaptic inputs on dendrites are quite efficient in recruiting plateau potentials and to evoke sustained discharge (40, 122). Increasing synaptic inputs can activate persistent inward currents in dendrites in a graded fashion, and the apparent bistability of earlier studies was mostly due to the artificial activation of plateaus by intrasomatic current injection (282). Thus local dendritic activation of these currents can amplify dramatically the effect of the synaptic inputs from sensory or descending afferents. Their dendritic activation is probably responsible for the apparent voltage-dependent enhancement of motoneuronal responses during fictive locomotion in the cat (57, 262). Also in zebrafish motoneurons, whole cell recordings have revealed plateau potentials that presumably play a role in patterning the synaptically driven motoneuron output in these rapidly swimming fish (71).

Another remarkable finding was that a strong excitatory synaptic input could recruit a plateau potential below the spike threshold. Thus during normal synaptic activation of motoneurons, the threshold for plateaus and for spike initiation may be quite similar (281). It was also shown that cells displaying self-sustained firing (>3 s) in the decerebrate cat had lower spike threshold and conduction velocities, suggesting that plateau potentials are more prevalent in motoneurons innervating fatigue-resistant muscle fibers (338). It is thus easy to imagine that

motor tasks like posture or stepping recruit fatigue-resistant motor units readily with sustained discharge produced by persistent inward currents without continuous network inputs.

Preliminary evidence indicates that plateau potentials and sustained discharge are also found in some classes of spinal interneurons in the ventral horn (278) and the dorsal horn (391, 501). As in motoneurons, these plateaus are facilitated by 5-HT and NA (275, 276), metabotropic glutamate receptors (391) and depressed by ionotropic and metabotropic inhibition (502). Long-lasting plateau potentials in reticulospinal cells of the lamprey, controlled by different sets of membrane conductances, have already been described and so was their central role in initiating locomotion. As in motoneurons, plateau potentials activated in interneurons by the neuromodulators released during locomotion may permit the amplification of synaptic inputs in particular dendrites. Because interneurons often integrate sensory, segmental, and supraspinal information, this would be a very effective mechanism to favor the transmission of inputs relevant for the generation or corrections of motoneuronal activities during stepping. Future research will likely reveal other types of neurons, including CPG interneurons, that possess membrane conductances underlying plateau potentials and how these may interplay with the neural locomotor network to efficiently integrate sensory and motor commands.

## V. CONCLUDING REMARKS

During movement, the brain can selectively open appropriate afferent pathways to motoneurons such that their command signals to muscles are appropriate for the task at hand (557). This simple and elegant statement summarizes very well the goal achieved by a host of rather complex mechanisms. This review has indeed aimed at discussing several aspects of the dynamic interactions between sensory afferents (from spinal or supraspinal origins) and the central motor program for locomotion so as to achieve adequate correcting responses during the various phases and subphases of locomotor movements while preserving the locomotor progression. There are several sensory modalities that impinge at various levels in the central nervous system and that are used to initiate, stop, or modulate ongoing locomotor activity. Feed-forward information is critical to adapt locomotion to the environmental conditions taking into account the internal state of the neural circuitry as well as that of the locomotor apparatus. The phase-dependent modulation of the corrective responses is not seen as discrete steps between phases but rather as a continuum between and throughout the various locomotor phases and subphases. It should also be stressed that the responses to perturba-

tions represent only one (although crucial) aspect of the role of afferents. Obviously, beneath it all, is the idea that these responses to experimental perturbations also reveal mechanisms through which sensory afferents activated by the normal locomotor movements will contribute to control the characteristics of the movement themselves (frequency, amplitude, coordination) in a phase- and task-dependent manner.

These fine controls are exerted through different mechanisms. Presynaptic inhibition of the afferents themselves allows the afferent inputs to be reduced during certain phases to prevent, for instance, undue responses to muscle stretch in a given part of the cycle (i.e., stretch of ankle extensor muscles during swing). By varying presynaptic inhibition it is also conceivable that the importance of stretch afferents can be adjusted to the various parts of the stance phase, being smaller in early stance and larger towards the end when the muscle is being shortened and producing less force. Interneuronal selection of alternative pathways will allow a given input (e.g., group Ib afferents) to exert an excitatory effect during stance, whereas they normally produce an autogenic inhibition at rest. Such interneuronal selection can also differentially distribute the same cutaneous input to different muscles acting in the same phase (FDL vs. FHL, medial vs. lateral gastrocnemius) or produce an excitatory response in extensor muscles during swing, a period during which they are normally inactive (triceps in forelimbs, gastrocnemius in hindlimbs). Moreover, membrane properties (locomotor drive potentials, plateau potentials) revealed during locomotion in motoneurons and interneurons will also contribute to modulate certain responses. One could also postulate that during locomotion the relative balance between sensory inputs to dendrites and soma could be dynamically changed so that the responses during locomotion may be quite different than at rest.

Although the various mechanisms and pathways have been dissected in small parts, it should again be stressed that during real locomotor movements or perturbations several afferent pathways are stimulated and that interactions occur in different neural elements at different levels of the central nervous system. The more we dig into the details of these sensorimotor interactions, the more it seems improbable that they should work so smoothly, but they do.

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