Invited Review: The Neurobiology of Facial and Dental Pain: Present Knowledge, Future Directions

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INVITED REVIEW

The Neurobiology of Facial and Dental Pain: Present Knowledge, Future Directions

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This review outlines recent research which has identified critical neural elements and mechanisms concerned with the transmission of sensory information related to oral-facial pain, and which has also revealed some of the pathways and processes by which pain transmission can be modulated. The review highlights recent advances in neurobiological research that have contributed to our understanding of pain, how acute and chronic pain conditions can develop, and how pain can be controlled therapeutically. Each section of the review also identifies gaps in knowledge that still exist as well as research approaches that might be taken to clarify even further the mechanisms underlying acute and chronic oral-facial pain.

The properties of the sense organs responding to a noxious oral-facial stimulus are first considered. This section is followed by a review of the sensory pathways and mechanisms by which the sensory information is relayed in nociceptive neurones in the brainstem and then transmitted to local reflex centers and to higher brain centers involved in the various aspects of the pain experience—namely, the sensory-discriminative, affective (emotional), cognitive, and motivational dimensions of pain. Reflex and behavioral responses to noxious oral-facial stimuli are also considered. The next section provides an extensive review of how these responses and the activity of the nociceptive neurones are modulated by higher brain center influences and by stimulation of, or alterations (e.g., by trauma) to, other sensory inputs to the brain. The neurochemical processes involved in these modulatory mechanisms are also considered, with special emphasis on the role of neuropeptides and other neurochemicals recently shown to be involved in pain transmission and its control. The final section deals with recent findings of peripheral and central neural mechanisms underlying pain from the dental pulp.

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Introduction: The nature and problems of orofacial pain.

Pain is the most common symptom of disease or injury that compels patients to seek medical and dental advice and therapy. It affects many aspects of our being, and because of its great frequency, it constitutes a serious health and economic problem. In terms of economics alone, the cost of pain is staggering. Several years ago, it was estimated that over 60 billion dollars are spent annually in the U.S.A. alone (Bonica, 1983) for pain and related health services; the associated loss of work and productivity results in an even greater economic burden. In terms of effects of pain on our health and lifestyle, chronic pathologic pain in particular serves no clear biological function, yet imposes severe emotional, physical, and social stresses (in addition to economic hardships) on the patient, on the family, and on society in general. In contrast, acute symptomatic pain does serve a biologic function, since it warns the patient that something is amiss in the particular body part(s) manifesting the pain; it is also of considerable diagnostic value to the attending clinician. However, acute pain does share some of the emotional, physical, and social stress impositions that are characteristic of chronic pain states, *e.g.*, it can be very unpleasant, and many patients avoid dental care because of their fear of pain.

Pain in the face and mouth has special emotional, biologic, and psychologic meaning to the patient. Furthermore, apart from headache, which may also involve structures in the mouth and face, acute orofacial pain accompanying acute pathologic states in the teeth and associated structures is probably the most common pain in all the body. Moreover, the face and mouth represent frequent sites of chronic and referred pains. The mechanisms underlying acute pain, and chronic pain in particular, and the processes which account for the efficacy of the various therapeutic procedures presently in use for controlling orofacial pain, have still not been completely clarified. This is partly a reflection of the multidimensional nature of pain, since pain is now conceptualized as a complex, multifactorial experience encompassing sensory-discriminative, affective (emotional), cognitive, and motivational dimensions. It is also partly a reflection of the dearth of investigation on orofacial pain mechanisms until the last decade. Nonetheless, initial and exciting steps have already been taken in unraveling some of the mysteries of acute and chronic orofacial pain, and the following pages will consider the advances in neurobiology in the last few years that have contributed to this partial understanding, and also identify present gaps in knowledge and approaches that might be taken in the future to expand our understanding even further. Because of the special place that dental pain occupies in dentistry, a separate section will be devoted to tooth pulp pain. The reference list is not meant to be exhaustive, but representative; the reader should refer to Darian-Smith (1966, 1973), Anderson *et al.* (1970), Dubner *et al.* (1978), and Byers (1984) for the relevant literature published prior to 1970, since the emphasis here will be on advances that have occurred in the last 15 years.

Nociceptors and primary afferents.

With respect to the neural elements providing sensory-discriminative information about the intensity, location, and duration of a noxious stimulus in the mouth or face, it has been demonstrated that the noxious stimulus excites certain types of receptors in oral-facial tissues, and that the detailed signals from the receptors are carried by specific afferent nerve fibers into the brainstem. As elsewhere in the body, free nerve endings in the face and mouth are seen as providing the peripheral structural basis for pain. Many of these free nerve endings act as nociceptors, that is, they are the peripheral sense organs or receptors that respond to noxious orofacial stimuli. Free nerve endings have long been recognized in virtually all orofacial tissues, including facial skin, oral mucosa, temporomandibular joint (TMJ), periodontium, tooth pulp, periosteum, and muscles, and they are associated with small-diameter myelinated

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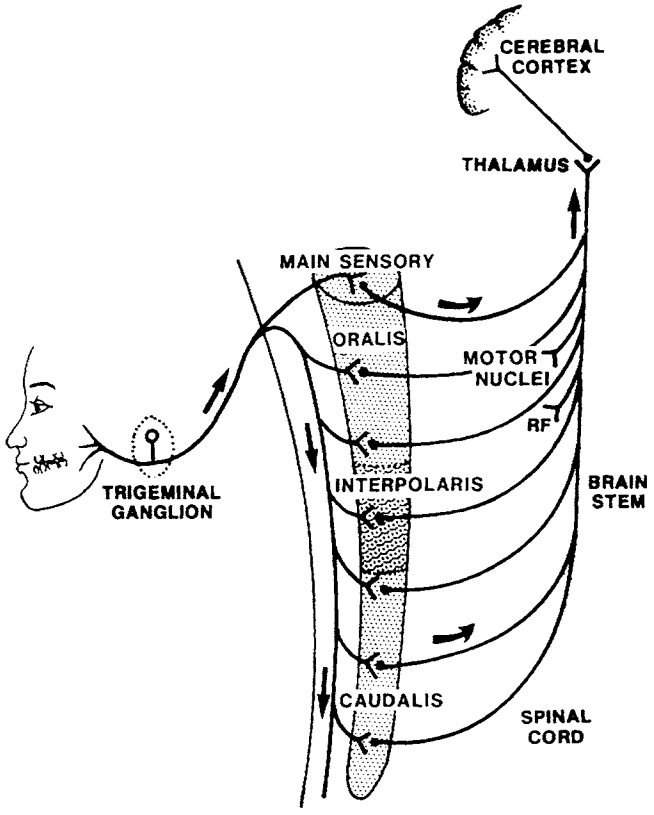

Fig. 1 — Transmission of sensory information from the mouth and face to the somatosensory areas of the cerebral cortex. The major pathway involves the trigeminal nerve, the primary afferent cell bodies of which are in the trigeminal (semilunar) ganglion. The peripheral processes of these cells innervate oral-facial tissues, whereas the central processes enter the brainstem and synapse on second-order neurones at various levels of the trigeminal brainstem sensory nuclear complex. This complex may be subdivided, from rostral to caudal, into the main (or principal) sensory nucleus and the spinal tract nucleus, which consists of three subnuclei: oralis, interpolaris, and caudalis. From the brainstem complex, sensory information may then be relayed directly to third-order neurones in the thalamus and from there to the cerebral cortex, or less directly by multisynaptic pathways involving, for example, the reticular formation (RF). The sensory information relayed from a particular region of the complex may also pass to other brainstem structures (*e.g.*, cranial nerve motor nuclei involved in reflex responses to oral-facial stimuli), or to the spinal cord or other regions of the complex (not shown). From Sessle (1986).

(A-delta) and unmyelinated (C) fiber afferents (see Dubner *et al.*, 1978). It appears that there is a greater proportion of unmyelinated fibers in trigeminal (V) compared with spinal nerves, but the significance of this is unclear. Unmyelinated afferents have also been recently described in spinal ventral (motor) roots (see Willis, 1985) and in the V motor root (Young and Kruger, 1981). While these findings raise the possibility that these afferents may be an additional source of nociceptive afferent input to the CNS, their precise role in somatic sensation has yet to be ascertained.

It is only in the last 10 years that any concerted effort has been made to examine the physiological properties of the small-diameter afferent nerve fibers associated with the free nerve endings in the orofacial region. In the facial skin of monkeys (*e.g.*, Dubner and Bennett, 1983; Dubner, 1985) and cats (Hu and Sessle, 1987), three major classes of nociceptive afferents have been described and invoked as providing the input to the brain that is necessary for pain perception. These three classes are: (i) the A-delta mechanothermal nociceptive afferents, which respond to intense thermal and mechanical stimuli and which seem to exist only in primates; (ii) C polymodal nociceptive afferents, which occur in primates and subprimates and which are excited by strong mechanical, thermal, and chemical stimuli; and (iii) high-threshold mechanoreceptive afferents, which respond best to intense mechanical stimuli but which may sometimes also respond to noxious heat after sensitization, *i.e.*, if the threshold of the nociceptors is lowered by chemical agents or repeated noxious stimuli (these occur in subprimates and primates, and nearly all of these afferents conduct in the A-delta range, but some have been reported with an A-beta conduction velocity). A small sample of A-delta afferents has also been studied in the periodontium, and these have properties suggestive of an involvement in nociceptive mechanisms (Mei *et al.*, 1977), but further information is needed on the properties of the periodontal nociceptive afferents as well as on nociceptive afferents supplying other orofacial tissues, such as the jaw muscles and TMJ.

Further study is also needed of the modulation of orofacial nociceptive afferent input to the CNS by factors implicated in a number of pain states and peripheral pain mechanisms. For example, modification of the activity of spinal nociceptive afferents has been produced by sympathetic efferent stimulation and might be related to a number of causalgic conditions in which the sympathetic nervous system appears to be integrally involved (Roberts, 1986). The activity of spinal nociceptive afferents might also be altered by the application of substances or procedures associated with heightened pain sensitivity, *e.g.*, algesic chemicals, nerve transection leading to neuroma formation, injury to peripheral tissues (see Dubner and Bennett, 1983; Devor, 1984; Pubols and Sessle, 1987). Abnormal firing patterns might also occur in nerves after experimentally induced demyelination, and, as pointed out below, such processes have been suggested as factors in V neuralgia through the changes that they may induce in V nociceptive pathways. While some study has been made of pulp afferents with some of these approaches (see below), their application to other types of V nociceptive afferents should considerably help to elucidate the peripheral mechanisms underlying the pain of V nerve injury, TMJ or myofascial pain dysfunction, V neuralgia, inflammation, etc. Some of these studies could be directed at humans as well as utilize experimental animals, since the feasibility of single afferent recordings in humans has been shown for orofacial nerves (Johansson and Olsson, 1976; Ahlquist *et al.*, 1984) as well as for limb nerves (*e.g.*, Torebjörk and Hallin, 1979).

Brainstem relay mechanisms.

This section will first review the pathways conveying pain information from the face and mouth to the brainstem. Nerves supplying facial and oral tissues carry this information predominantly through the V (Gasserian or semilunar) ganglion, where the primary afferent cell bodies are located. They then enter the brainstem and ascend or descend in the V spinal tract before entering the V sensory nuclear complex (Fig. 1). By the process of synaptic transmission, neurones in the complex are excited by this incoming afferent information.

As illustrated in Fig. 1, the sensory complex can be subdivided into the main (principal) sensory nucleus and the spinal tract nucleus. The latter nucleus consists of three subnuclei, the most caudal of which, the subnucleus caudalis, extends into the cervical spinal cord and merges with the spinal dorsal horn. Neurones in each part of the V brainstem complex have axons that may project directly, or indirectly (*e.g.*, *via* reticular

formation), to the thalamus and are thus implicated as critical elements underlying perceptual as well as emotional and motivational responses to orofacial stimuli. Some of the neurones may also connect with other subnuclei of the V complex and provide the basis for the complex interactions (see below) that can occur between the different parts of the complex. It should also be noted that many of the neurones within the complex or adjacent to the complex, as a result of their connections with the cranial nerve motor nuclei, may serve as reflex interneurones in the multitude of reflex responses to oral-facial stimuli (see Dubner *et al.*, 1978).

Role of subnucleus caudalis.—Fifteen years ago, knowledge of V brainstem mechanisms of pain was almost exclusively based on anatomical and clinical observations carried out 30 or 40 years earlier (*e.g.*, Gerard, 1923; Sjoqvist, 1938). Anatomical studies had indicated that small-diameter axons in the V spinal tract, presumed to represent nociceptive primary afferents, terminate primarily in the subnucleus caudalis of the V spinal tract nucleus. These findings went hand in hand with most clinical observations of the effects of the V tractotomy procedure, used for the relief of V neuralgia in humans: A transection near the obex was reported to produce a profound orofacial analgesia (and thermanesthesia), with much less complete loss of tactile sensibility. There are also close parallels in structure and projection sites between caudalis and the spinal cord dorsal horn (see Gobel *et al.*, 1981), which is an integral component of spinal nociceptive mechanisms, *e.g.*, caudalis is a laminated structure with cell types morphologically similar to those found in the spinal dorsal horn, and the thalamus is a major projection site of both regions (see below). These considerations led to the generally held view that caudalis serves as the principal brainstem relay site of orofacial nociceptive information. The more rostral parts of the V sensory nuclear complex, in particular the main (principal) sensory nucleus and the subnucleus oralis of the spinal tract nucleus, were seen as the major relay sites to higher centers of orofacial tactile information.

A large number of the early electrophysiological studies of the V complex (for review, see Darian-Smith, 1966, 1973; Dubner *et al.*, 1978) supported this view of the involvement of the rostral nuclei in tactile sensibility, but they failed to find any evidence of a substantial population of neurones in subnucleus caudalis with properties commensurate with the role of the subnucleus as the primary pain relay of the V complex. This apparent paradox in fact led to the hypothesis (Young and King, 1972) that caudalis exerts a tonic modulatory influence on orofacial sensory transmission through the rostral V nuclei and thereby determines the orofacial sensory input reaching higher perceptual levels of the brain. While this hypothesis has received support from subsequent studies (see below), electrophysiological research in the last 15 years has also provided data supporting the view that subnucleus caudalis is the essential V brainstem relay for orofacial pain. Buoyed by the success of electrophysiological findings that substantial numbers of nociceptive neurones exist in laminae I/II and V/VI of the spinal cord dorsal horn, and that many of these dorsal horn nociceptive neurones send their axons *via* the spinothalamic tract directly to the thalamus (*e.g.*, reviewed by Albe-Fessard *et al.*, 1985; Willis, 1985), V brainstem studies have clearly shown the existence of comparable neurones in the analogous laminae of subnucleus caudalis of anaesthetized, decerebrate, or unanaesthetized animals; some may also occur within the V spinal tract lateral to caudalis, the so-called interstitial neurones (*e.g.*, Mosso and Kruger, 1973; Price *et al.*, 1976; Dawson *et al.*, 1980; Hoffman *et al.*, 1981; Hu *et al.*, 1981; Azerad *et al.*, 1982; Yokota and Nishikawa, 1982; Bushnell *et al.*, 1984). The morphological and functional similarities between caudalis and the spinal cord dorsal horn have led some workers in the field to view the former as the "medullary dorsal horn" (Gobel *et al.*, 1981; Hoffman *et al.*, 1981; Hu *et al.*, 1981).

On the basis of their cutaneous (facial) response properties, the nociceptive neurones have been classified into two main groups: the high-threshold or nociceptive-specific (NS) neurones, which respond exclusively to noxious stimuli (*e.g.*, pinch, heat); and wide-dynamic-range (WDR) neurones, which are excited by non-noxious (*e.g.*, tactile) stimuli as well as noxious stimuli (Fig. 2). In addition to these cutaneous nociceptive neurones, which predominate in laminae I/II and V/VI, low-threshold mechanoreceptive (LTM) neurones comprise the third major group of caudalis neurones. They do not respond to noxious cutaneous stimuli (although, as pointed out below, some are excited by electrical stimulation of the tooth pulp) but are activated by light tactile stimuli applied to skin, mucosa, or teeth; they predominate in laminae III/IV. These non-nociceptive neurones have properties comparable with those of the principal neurone type reported in the rostral V brainstem nuclei, although there may be differences in their ability to transmit precise information related to a tactile stimulus (Darian-Smith *et al.*, 1968; *cf.* Kirkpatrick and Kruger, 1975).

To date, the information gained has centered on afferent inputs to these three cell types from skin, oral mucosa, and tooth pulp (see below), and only recently has study been directed at their input characteristics from muscle and TMJ afferent inputs evoked by natural stimulation. Many of the neurones in caudalis that respond to cutaneous (or tooth pulp) stimulation can also be excited by electrical and noxious mechanical or algesic chemical (*e.g.*, hypertonic saline, bradykinin) stimulation of afferents supplying jaw and tongue muscles and the TMJ (Amano *et al.*, 1986; Sessle *et al.*, 1986). These excitatory effects are particularly directed at those caudalis cells functionally identified on the basis of their cutaneous/mucosal receptive field properties as nociceptive neurones (*i.e.*, WDR and NS). Very few neurones appear to be exclusively activated by these deep afferent inputs. These observations are consistent with other findings, that V brainstem neurones excited by electrical and natural (*e.g.*, thermal) stimulation of the tooth pulp (Hu and Sessle, 1984) and spinal dorsal horn neurones receiving deep inputs (see Cervero, 1985; Willis, 1985) are primarily WDR and NS nociceptive neurones with cutaneous afferent inputs.

In keeping with analogous findings of the spatial organization of afferent inputs in the spinal somatosensory system, these observations of deep inputs to neurones relaying cutaneous nociceptive information suggest mechanisms which may underlie the poor localization of deep noxious stimuli, *e.g.*, as in TMJ or myofascial pain (Amano *et al.*, 1986; Sessle *et al.*, 1986). Sessle and colleagues have further proposed that the large proportion of the nociceptive neurones in caudalis (as well as those in rostral components of the V brainstem complex) showing extensive convergence from skin, mucosa, visceral (laryngeal), TMJ, jaw or tongue muscle, tooth pulp, and even neck afferents may also underlie the *spread and referral of pain* which are frequently seen in many craniofacial and intra-oral pain conditions. The recent demonstration (Davis and Dostrovsky, 1986b; Strassman *i.e.*, 1986) of convergence of dural vessel afferents and cutaneous afferents preferentially onto nociceptive neurones in caudalis is consistent with these observations and may underlie the poor localization of pain and referral that is typical of headache. Since many of these convergent afferent inputs can only be demonstrated with electrical stimulation (*i.e.*, natural stimulation, such as pinch, tactile, and chemical stimuli, does not evoke responses in the

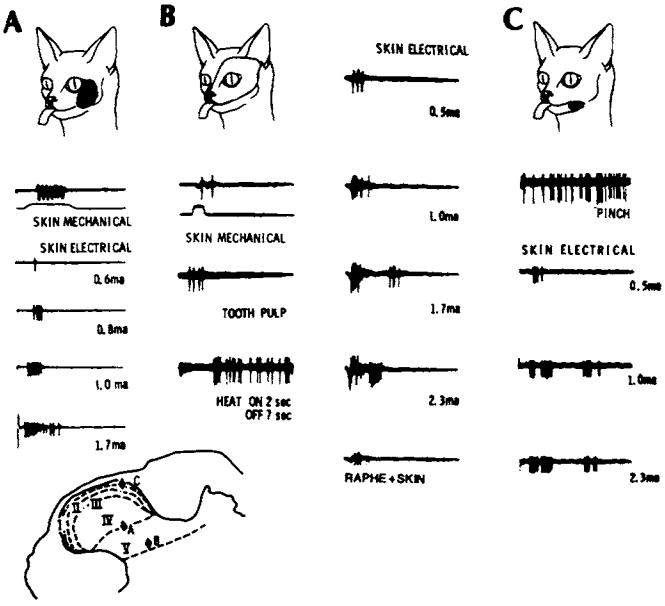

Fig. 2 — Characteristics of the major types of neurones in the trigeminal brainstem sensory complex. The neurone in A is an example of a low-threshold mechanoreceptive neurone that could be activated by mechanical (light tactile) stimulation of a localized area of the cat's face or mouth. The neurone illustrated could be activated by mechanical and electrical stimulation of its mechanoreceptive field outlined in black on the face figurine. The short latency of its electrically evoked responses is indicative of afferent input to the neurone from large-diameter afferent fibers. B shows an example of a wide-dynamic-range neurone; it could be activated by mechanical stimulation of the area of skin outlined on the cat's face, as well as by electrical stimulation of the tooth pulp and by heating and (not shown) pinching of this receptive field on the face. Electrical stimuli applied to the receptive field produced an early burst of activity at low intensities of stimulation (0.5 mA, 1.0 mA), but increasing the intensity further also produced a later burst of discharges. The early burst is attributed to activation of the neurone by large-fiber afferent input (*e.g.*, which carries tactile information to the neurone), whereas the later input probably reflects excitation by the slower-conducting small-fiber afferent inputs carrying nociceptive information to the neurone. Also note that this neurone's responses to noxious stimuli could be suppressed by influences from the periaqueductal gray-raphe system. As shown in the lower part of the Fig., interacting the noxious stimulus with conditioning electrical stimulation of the raphe completely suppressed this neurone's response to the noxious skin or (not illustrated) tooth pulp stimulus. C illustrates an example of a nociceptive-specific neurone; it could only be excited by noxious stimulation (*e.g.*, pinching) of its receptive field on the mandibular facial skin (outlined in black). Since these neurones receive only small-diameter slowly-conducting nociceptive afferent inputs, note that electrical stimulation evokes responses of longer latency than those evoked in wide-dynamic-range neurones; the different bursts of activity probably reflect activation from different sizes of A-delta and C nociceptive afferent inputs to the neurone. As mentioned in the text, many of the two types of nociceptive neurones can be activated not only by electrical and natural stimulation of superficial sites (*e.g.*, skin) but also by stimulation of deep structures (*e.g.*, TMJ, muscle). These three neurones were located in the V subnucleus caudalis: Their locations are indicated (diamonds) in lamina IV (neurone A), lamina V (neurone B), and lamina I (neurone C). The time durations of the traces are 50 msec (A), 100 msec (B), and 200 msec (C), except heat and pinch traces (10 sec).

neurones from sites supplied by the afferents), Sessle and coworkers have proposed that these hard-wired yet relatively ineffective convergent connections may provide a basis for central neural plasticity. As pointed out below, they have suggested that many of these so-called 'long-range' afferent inputs may become operational in pathophysiological situations (*e.g.*, inflammation; deafferentation) and thereby account for the spread and referral of pain that may occur in toothache, TMJ/myofascial pain disorders, and other craniofacial pain conditions.

Those caudalis WDR and NS neurones that can only be excited by localized natural stimulation of cutaneous or mucosal tissues, in contrast, have properties consistent with a role for them in the detection, localization, and discrimination of superficial noxious stimuli. Recent studies of the activity of WDR and NS neurones during behavioral tasks that require monkeys to discriminate among noxious thermal stimuli applied to facial skin indeed indicate that many of them do code specific neural information essential for these tasks and for detection of stimulus quality, intensity, location, and discrimination (Hoffman *et al.*, 1981; Bushnell *et al.*, 1984; Maixner *et al.*, 1986). For example, the activity of the WDR neurones indicates their involvement particularly in the encoding process underlying perception of the intensity of near-threshold noxious heat stimuli.

The afferent inputs to these neurones have been studied not only by electrophysiological techniques but also by anatomical techniques that involve degeneration of afferent nerves or labeling of the nerves (*e.g.*, autoradiography; immunohistochemistry; enzymes such as horseradish peroxidase, HRP). These studies have shown that cutaneous nociceptive afferents (Gobel *et al.*, 1981; Hayashi, 1985; Jacquin *et al.*, 1986a) as well as tooth pulp (Arvidsson and Gobel, 1981; Marfurt and Turner, 1984; Ishidori *et al.*, 1986; Hu *et al.*, 1987; Johnson *et al.*, 1987) and small-diameter muscle afferents (Nishimori *et al.*, 1986) terminate in laminae I and II, and V and VI of caudalis. Low-threshold mechanosensitive primary afferents are primarily large-diameter and rapidly-conducting axons (*e.g.*, A-beta) which terminate in laminae III-VI of caudalis, as well as in more rostral parts of the V brainstem complex (*e.g.*, Gobel *et al.*, 1981, 1982; Hayashi, 1985; Jacquin *et al.*, 1986b). These input patterns to caudalis are thus consistent with the electrophysiologically documented laminar location and responses to low- or high-threshold afferent inputs of the LTM, WDR, and NS neurones.

Anatomical studies have also provided some information on the morphology of the different neurones in caudalis or more rostral V nuclei. These studies have utilized the methods of Golgi impregnation, neuronal labeling by retrograde transport in the neurone's axon of one or more substances (*e.g.*, HRP) deposited in one or more of its projection sites, and the more recently applied technique of intracellular labeling of an electrophysiologically identified neurone (*e.g.*, Gobel *et al.*, 1981, 1982; Dubner and Bennett, 1983; Falls, 1984; Nishikawa and Yokota, 1985; Jacquin *et al.*, 1986c; Renehan *et al.*, 1986). Fig. 3 shows an example of such an intracellularly labeled neurone in caudalis. The caudalis neurones projecting out of the nucleus to various sites (see below) are found mainly in laminae I, III-VI of caudalis. In lamina II, the so-called substantia gelatinosa (SG), several other morphologically distinct cell types have been described, the most common being the stalked cells and islet cells (see Gobel *et al.*, 1981, 1982; Dubner and Bennett, 1983). Some of these SG neurones receive low-threshold peripheral afferent inputs, others nociceptive inputs; noradrenaline and serotonin-containing terminals of inputs from higher brain centers involved in somatosensory modulation are also especially apparent in the SG (Gobel *et al.*, 1981, 1982; Dubner and Bennett, 1983; Basbaum, 1985). Because the axons of most of the SG neurones arborize locally within the V complex, the SG represents a critical interneuronal system underlying the powerful sensory and descending modulation of somatosensory transmission that occurs in subnucleus caudalis and more rostral components of the V complex (see below).

A limited amount of study has been directed at the *neuro-*

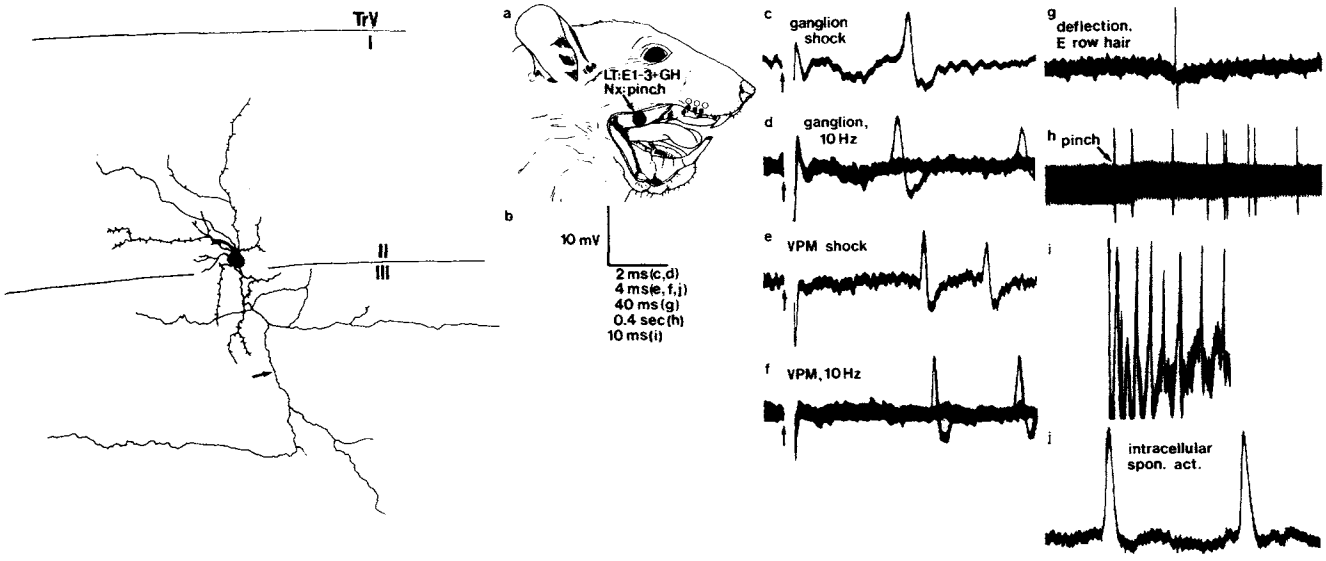

Fig. 3 — Response properties and morphology of an intracellularly stained and recorded nociceptive neurone in subnucleus caudalis of the rat. This lamina II wide-dynamic-range neurone shown in (a) was activated both by gentle deflection of certain vibrissae (so-called E row) and adjacent guard hairs (GH), as well as by a noxious pinch of adjacent intra-oral skin (a). The innocuous stimuli resulted in a phasic discharge (g), while the noxious pinch gave a tonic discharge (h); the pinch was maintained for the duration of the trace. The neurone's response latency to stimulation of the trigeminal ganglion was 3.8 msec (c), with the cell unable to follow 10 Hz (d) at twice-threshold current levels. The neurone responded to thalamic shock with a latency of 8.2 msec (e), and was unable to follow 10 Hz (f). An irregular spontaneous activity (j) was exhibited when the cell was impaled by the electrode. Responses to 3 nA positive injection current are also shown in (i). From Renehan *et al.* (1986).

chemical mechanisms underlying nociceptive transmission in the V brainstem complex; this represents an area of future research crucial to our clarification of V nociceptive mechanisms. The possibility that an improved understanding of the neurochemistry of the V complex and the spinal dorsal horn might aid in the development of better analgesic drugs and other therapies to relieve pain has resulted in an extensive research effort in recent years. The discovery of and recent focus on neuropeptides and other neurochemical substances naturally occurring in the brain have resulted in the documentation of several of them in the V complex and other areas involved in pain transmission and control. Not surprisingly, most focus has been directed at the opioid peptides, of which three major families have now been shown to exist (for review, see Terenius, 1985). Each of these naturally occurring substances is synthesized from one of three different precursor molecules or prohormones: Proenkephalin A gives rise to one family including leu- and met-enkephalin, Proenkephalin B to the dynorphin opioid peptides, and Proopiomelanocortin to beta-endorphin. Within the CNS, there exist several opiate receptors to which these endogenous opioid peptides may bind. The opiate receptors which exist in neural pathways involved in pain and its control are the mu, delta, and kappa receptors. The classic opiate drugs appear to act mainly *via* the mu receptor, and their effects can be blocked by the opiate antagonist naloxone; the delta and kappa receptors are relatively insensitive to naloxone. Enkephalins have a high affinity for both mu and delta receptors, and dynorphin for kappa receptors, but beta-endorphin may be largely non-selective.

Whereas the role of these peptides in pain appears to be mainly directed toward analgesia (see below), other neuropeptides have been discovered which may represent the neurotransmitter(s) underlying excitatory nociceptive transmission. While excitatory amino acids (*e.g.*, glutamate) are major neurotransmitter candidates in several central excitatory pathways, including those pathways transmitting information from low-threshold tactile afferents, evidence does not so far favor a major role for them in nociceptive transmission (*e.g.*, see Salt and Hill, 1983). An important role for the polypeptide substance P in pain pathways, however, has received considerable support from iontophoretic, electrophysiological, and immunocytochemical studies (for review, see Andersen *et al.*, 1978; Henry *et al.*, 1980; Dubner and Bennett, 1983; Salt and Hill, 1983). For example, substance P is found in small-diameter afferents (the spectrum of afferents carrying nociceptive information) of cutaneous and tooth pulp nerves and in ganglion cells, and it is concentrated in terminals in laminae I/II and V of caudalis and spinal dorsal horn, where the nociceptive neurones predominate. It has been implicated in peripheral injury and inflammation, and its depletion by capsaicin (a major ingredient of hot pepper) is accompanied by a reduction in responsiveness to noxious stimuli. When applied iontophoretically, substance P is especially effective in exciting WDR and NS neurones. Nonetheless, it is still unclear whether it is associated with a specific somatosensory modality and if it acts as a neurotransmitter or as a neuromodulator.

Several other endogenous neurochemicals have also been implicated in the excitatory processes underlying nociceptive transmission. Their involvement is based, for example, on their occurrence in primary afferents and/or the regions of the V brainstem complex and spinal dorsal horn containing the nociceptive neurones and the internal neural circuitry involved in regulating their activity (*e.g.*, Basbaum, 1985). These neurochemicals include somatostatin, VIP, and ATP, as well as possibly other substances (*e.g.*, enkephalin, dynorphin, 5-HT) thought to be more involved with suppression of nociceptive transmission. In this context, it should be noted that some of these neurochemicals found in afferents may have roles other than directly in nociceptive transmission. For example, lesioning of small-diameter afferents with capsaicin (Wall *et al.*, 1982) or by tooth pulp deafferentation (Hu *et al.*, 1986a) results in central changes in V somatosensory pathways, which suggests that neurochemicals occurring in these afferents may exert neurotrophic influences on the growth and maintenance

of somatosensory pathways. Further consideration of these and related observations is provided below.

The projection sites of the different output neurones in caudalis have been elucidated by numerous anatomical observations (*e.g.*, Tiwari and King, 1974; Fukushima and Kerr, 1979; Craig and Burton, 1981; Gobel *et al.*, 1981; Matsushita *et al.*, 1982; Shigenaga *et al.*, 1983; Panneton and Burton, 1985) and by recent electrophysiological findings based on antidromic activation of caudalis neurones (Price *et al.*, 1976; Hoffman *et al.*, 1981; Hu *et al.*, 1981) or on the input characteristics of more central neurones (*e.g.*, Woda *et al.*, 1975; Pearl and Anderson, 1980). Caudalis neurones, especially those in lamina I and V/VI, project to the posterior thalamus, cerebellum, periaqueductal gray (PAG), parabrachial area of the pons, brainstem reticular formation, spinal cord, and to rostral regions of the V brainstem complex such as subnucleus oralis; individual neurones may project to more than one of these sites. Some of these sites represent loci involved in the relay of orofacial sensory information from caudalis (*e.g.*, thalamus), whereas others (*e.g.*, PAG; parabrachial area; subnucleus oralis) more likely utilize the information ascending from caudalis for modulating or gating sensory transmission and behavior, as outlined below.

Role of rostral V nuclei.—While in the last 15 years considerable evidence has accumulated in support of the view that subnucleus caudalis is an important relay site of orofacial nociceptive information, support has also been forthcoming for the view that it functions, by means of electrophysiologically and anatomically defined intranuclear projections (*e.g.*, Gobel *et al.*, 1981; Hu *et al.*, 1981; Panneton and Burton, 1982; Falls, 1984), as a gating mechanism capable of modulating sensory transmission through rostral parts of the V complex (Young and King, 1972; Greenwood and Sessle, 1976). Implicit in the latter view is a role also for the rostral V nuclei in nociceptive mechanisms. The following briefly outlines recent evidence which suggests that the rostral components of the complex may have a role in V nociception.

First, some rostral neurones have recently been shown to project directly to caudalis (Hockfield and Gobel, 1982; Falls, 1984), which suggests that they might transmit, or modulate transmission of, somatosensory information through caudalis. A more direct role for the rostral nuclei in nociception is indicated by findings that some tooth pulp (see below) and cutaneous nociceptive (Hayashi, 1985) afferents may terminate in the rostral components, and both WDR and NS neurones have been found in interpolaris, oralis, and the main sensory nucleus (*e.g.*, Azerad *et al.*, 1982; Hayashi *et al.*, 1984; Campbell *et al.*, 1985). Moreover, lesions in or adjacent to caudalis do not necessarily completely eliminate all orofacial nociceptive reflex or behavioral responses (Azerad and Woda, 1976; Greenwood and Sessle, 1976; Vyklicky *et al.*, 1977; Young and Perryman, 1984; Broton and Rosenfeld, 1985), whereas rostral lesions may interfere with pain behavior evoked by noxious thermal or mechanical stimuli applied to facial or intra-oral tissues (Young and Perryman, 1984; Broton and Rosenfeld, 1986; Pickoff-Matuk *et al.*, 1986). It should also be noted that the rostral regions project to some of the same regions mentioned above as the projection sites of caudalis neurones; many of these sites are implicated in pain transmission or its control, and rostral neurones with tooth pulp or facial nociceptive inputs may be involved in the projection (*e.g.*, Sessle and Greenwood, 1976; Gobel *et al.*, 1981; Azerad *et al.*, 1982; Matsushita *et al.*, 1982; Shigenaga *et al.*, 1983; Hayashi *et al.*, 1984). The presence in the rostral nuclei of scattered remnants of what appear to be rostral extensions of lamina I or interstitial neurones, plus the occurrence of pharmacological modulation of neural activity and immunoreactivity indicative of endogenous neurochemical mechanisms implicated in pain (see below), also collectively point to a role for the rostral components in pain.

The two views on the importance of the caudal and rostral components of the V brainstem complex are not mutually exclusive, and more research is required to ascertain the relative contribution of each to V brainstem mechanisms of nociception. For example, the recent method of intracellular labeling of a functionally identified primary afferent or central neurone which has been used successfully in the spinal cord (*e.g.*, Gobel *et al.*, 1981, 1982; Dubner and Bennett, 1983) should be particularly useful and has recently been applied successfully to determine the central arborization patterns of physiologically identified V primary afferents (Hayashi, 1985; Jacquin *et al.*, 1986a, b) and to illustrate the morphology of physiologically defined brainstem neurones (Gobel *et al.*, 1982; Dubner and Bennett, 1983; Nishikawa and Yokota, 1985; Jacquin *et al.*, 1986c). Future efforts in the rostral brainstem should also use the single neurone recording technique in awake animals, since this has been shown to be feasible and productive in relating single neuronal activity evoked by noxious or non-noxious orofacial stimuli to perceptive and behavioral responses made by the awake functioning animal.

The information acquired from these approaches should not only greatly increase our understanding of nociceptive mechanisms related to acute pain but also elucidate chronic pain states and pain syndromes characteristic of the orofacial region. Such aspects are primarily covered in later sections, but it should be emphasized in the present context that many of the suggested approaches are also amenable to physiological or structural manipulations (*e.g.*, de-afferentation; release of tonic modulatory effects by antagonistic drugs; lesioning of peripheral or central neural paths) which are likely to provide findings of clinical relevance to the etiology or control of a number of pain states.

Thalamocortical relay mechanisms.

The roles of the thalamus and cerebral cortex in nociceptive mechanisms, particularly those pertaining to pain perception, are still poorly understood and controversial. A small number of studies several years ago had indicated the presence of a few scattered nociceptive neurones in the posterior thalamus of rats, cats, and monkeys, and possibly in cortical area SII (for review, see Darian-Smith, 1966, 1973; Dubner *et al.*, 1978; Albe-Fessard *et al.*, 1985; Willis, 1985). Since that time, more studies have been directed at these areas to examine possible nociceptive inputs and mechanisms, but only limited information is available of thalamic and cortical neurones excited by orofacial nociceptive inputs or of the precise anatomical loci in the thalamus, where ascending axons from caudalis or the more rostral V brainstem nuclei terminate.

A major input to the posterior thalamus originates from the dorsal column-medial lemniscal system and the rostral components of the V brainstem complex which transmit primarily non-nociceptive information from the spinal and orofacial regions, respectively. Another important input is the spinothalamic tract, which originates in the spinal dorsal horn: Its V analogue is the thalamic projection from subnucleus caudalis. According to many of the anatomical investigations reviewed above, axons originating in caudalis represent a substantial proportion of the V input to the posterior thalamus. Albe-Fessard *et al.* (1985) and Willis (1985) have reviewed several recent studies which have shown the presence of WDR and NS neurones in various parts of the thalamus, including the ventrobasal complex (VB), posterior nuclei (PO), and intralaminar nuclei; recently, the nucleus submedius in the medial

thalamus has also been proposed as an important pain relay in view of the projection to submedius of many lamina I neurones in the spinal dorsal horn and V subnucleus caudalis. Those nociceptive neurones associated with VB have properties (*e.g.*, localized receptive field, somatotopic organization) indicative of a role in pain localization and discrimination, where those in PO and intralaminar nuclei have properties suggestive of a role more in the affective-motivational aspects of pain; tooth pulp-activated neurones also occur in these regions (see below). Whereas most studies describe WDR and NS neurones scattered throughout the VB proper (see Albe-Fessard *et al.*, 1985; Willis, 1985), Yokota *et al.* (1987) have reported that WDR and NS neurones receiving V or spinal nociceptive information occur in a shell region surrounding VB, and that the V input to the WDR and NS neurones relaying orofacial nociceptive information is dependent on an intact subnucleus caudalis. Further study is required to clarify whether this pattern of nociceptive representation is a general principle of thalamic organization, and whether the interruption of the V input to these neurones by a caudalis lesion is indicative of an interference of the V nociceptive relay through caudalis or of the demonstrated modulating influence that caudalis exerts on sensory transmission through more rostral V neurones.

Some of the WDR and NS neurones can be antidromically activated from the somatosensory cerebral cortex, *i.e.*, they project directly to the cortex. These findings are consistent with recent observations of WDR and NS neurones in somatosensory cortical region SI (especially areas 1 and 3b) that respond to noxious limb stimuli; some have properties consistent with a role in pain localization and discrimination (see Albe-Fessard *et al.*, 1985; Willis, 1985). Although little information is available on somatosensory cortex neurones responding to noxious facial stimulation, a number of studies have described cortical neurones responding to electrical stimulation of the tooth pulp (see below).

Related reflex and behavioral responses.

In addition to the interest that has centered on the V brainstem complex, processes involved in other nociceptive responses to noxious orofacial stimuli have also been investigated in humans and experimental animals. The jaw-opening reflex (JOR), which can be recorded in the digastric muscle of animals, has served as a frequent model of nociceptive reflexes, particularly when elicited by stimulation of the tooth pulp, a presumed source of exclusively nociceptive afferents (see below). Study has also been made of the reflexly induced silent periods in the jaw-closing musculature that usually accompany the digastric reflex excitation (Dubner *et al.*, 1978; Mason *et al.*, 1985). Recent use has also been made of pulp-evoked cerebral potentials (Chapman *et al.*, 1979; Fernandes de Lima *et al.*, 1982; Dong and Chudler, 1984) and operant conditioning and avoidance paradigms utilizing stimulation of the tooth pulp (*e.g.*, Vyklicky *et al.*, 1977; Nord and Ross, 1977; Oleson *et al.*, 1980; Young and Perryman, 1984) or noxious facial heat (Hoffman *et al.*, 1981; Bushnell *et al.*, 1984; Broton and Rosenfeld, 1985, 1986; Maixner *et al.*, 1986).

These approaches, especially using the pulp-evoked JOR, have been applied to investigations of various exogenous and endogenous modulatory influences on nociceptive transmission and will be outlined below. In addition, Nord and Ross (1977) and Dubner and colleagues (*e.g.*, Hoffman *et al.*, 1981; Bushnell *et al.*, 1984) have used single neurone recording in the V brainstem complex of awake monkeys trained to discriminate between and escape noxious facial thermal stimulation or tooth pulp stimulation to substantiate more clearly the roles of the various neuronal types in nociception and its control. The responses of the neurones to noxious orofacial stimuli were consistent with a role for caudalis WDR and NS cells in nociception.

The information provided by Nord and Ross also has a bearing on the question raised above of the relative importance of caudalis and the more rostral V brainstem nuclei in pain. Their study indicated that caudalis responses to electrical pulp stimuli may be involved in overt dental pain responses, and more rostral neuronal responses in so-called "pre-pain" sensations. As outlined earlier, other recent reflex and behavioral studies bearing on this question have, in contrast, provided evidence down-playing the importance of caudalis in dental and facial pain. Further investigation utilizing reflex and behavioral paradigms is needed to help elucidate orofacial pain mechanisms and the relative importance of caudalis and the rostral nuclei.

Modulation by sensory stimulation.

As pointed out above, it is only in the last 15 years that substantial numbers of V nociceptive primary afferents and brainstem neurones have been identified and characterized. Consequently, it is hardly surprising that, until recently, only a very limited knowledge base existed regarding the sites and mechanisms of modulation of orofacial pain, and of pain in general. Information had been gathered in the 1960's on afferent- and cortical-induced modulation in the V system, but this was restricted to modulatory influences on brainstem, thalamic, and cortical cells that have now become known as LTM neurones (*e.g.*, see Darian-Smith, 1966, 1973; Dubner *et al.*, 1978).

Several reasons account for the recent increased focus on the modulatory mechanisms underlying the control of orofacial pain. These include the discovery, outlined above, of substantial populations of nociceptive neurones in the brainstem and spinal cord, as well as findings of endogenous pain-suppressive neurochemical mechanisms, and the demonstrated therapeutic effectiveness of peripheral stimulation procedures such as acupuncture and transcutaneous electrical nerve stimulation (TENS). An additional factor has been the research interest generated by the Gate Control Theory of Pain (Melzack and Wall, 1965), which has drawn attention to possible mechanisms capable of modulating nociceptive transmission in the CNS by way of sensory interactions between large-diameter and small-diameter afferent inputs to the CNS and by descending controls from higher brain centers.

With respect to sensory-induced modulation, investigations have centered on documenting the efficacy of therapeutic procedures such as acupuncture and TENS in suppressing orofacial reflexes (*e.g.*, JOR), evoked potentials, or perceptive responses in humans and laboratory animals (again predominantly with the use of electrical stimulation of the tooth pulp as the presumed noxious stimulus), and on examining the suppressive effects of these procedures or other sensory stimuli on central nociceptive neuronal responses. Before one considers in detail the suppressive effects of sensory inputs on nociceptive transmission, it should be pointed out again that recent research has also revealed facilitatory influences of some sensory inputs to brainstem nociceptive neurones, and these excitatory interactions have been implicated in pain sensitization, spread, and referral.

It has been clearly demonstrated that pain perception can be suppressed in humans and laboratory animals by acupuncture and TENS, and the interested reader is referred to Melzack (1984) and Woolf (1984) for details. While the mechanisms and types of stimulated afferents responsible for these effects are still conjectural, the efficacy of a particular site (*e.g.*, Hoku point on hand; infra-orbital area) seems to depend, at least in

part, on the peripheral innervation density at that site. Melzack and colleagues, for example, have demonstrated significant post-operative dental pain suppression as a result of excessive cold stimulation of superficial sites, and acupuncture or TENS stimulation at several sites may have this effect (see Melzack, 1984).

Some of the possible central mechanisms involved in these effects are suggested by findings that neurones in subnucleus caudalis that are excited by noxious or non-noxious facial stimuli can be suppressed by stimuli applied outside their cutaneous receptive field (Yokota and Nishikawa, 1979; Sessle *et al*, 1981a). Muscle-, TMJ-, and pulp-evoked responses of caudalis or rostral V neurones can also be suppressed, even by stimuli applied to sites as remote as the limbs (*e.g.*, Nord and Young, 1975; Khayyat *et al.*, 1975; Sessle and Greenwood, 1976; Sessle *et al.*, 1981a). Dickenson and LeBars (1983) have also reported that WDR neurones in caudalis are preferentially inhibited by noxious stimulation of widespread parts of the body, in keeping with the concept of Diffuse Noxious Inhibitory Controls (DNIC) of spinal dorsal horn WDR neurones by way of a supraspinal loop. While some doubt has been cast on the selectivity of this effect for WDR neurones (Tomlinson *et al.*, 1983), it has been suggested that the effect may underlie some forms of acupuncture (Dickenson and LeBars, 1983). Acupuncture itself has been reported to have suppressive effects on caudalis neurones (Kerr *et al.*, 1978; Toda *et al.*, 1979).

It is still not clear the extent to which the analgesic effectiveness of acupuncture and TENS can be explained by "segmental" mechanisms or by recruitment of descending influences from higher brain regions (*e.g.*, from PAG). Also unclear is the relative contribution made by pre-synaptic and post-synaptic inhibitory mechanisms to afferent-induced suppression. However, the use of putative pre- and post-synaptic inhibitory blockers (Yokota and Nishikawa, 1979) has implicated both mechanisms. Moreover, sensory nerve stimulation can evoke primary afferent depolarization (PAD), which is generally considered a reflection of pre-synaptic inhibition. Although PAD can be elicited in the brainstem endings of tooth pulp afferents (Davies *et al.*, 1971; Lisney, 1979; Dostrovsky *et al.*, 1981) and nociceptive facial afferents (Hu and Sessle, 1987), the effects are not restricted to nociceptive afferents, since afferent-induced PAD can be readily induced in non-nociceptive (*i.e.*, LTM) afferents as well (*e.g.*, Darian-Smith, 1966; Dubner *et al.*, 1978; Hu and Sessle, 1987). Post-synaptic inhibitory mechanisms cannot be excluded as making a contribution to afferent-induced suppression (*e.g.*, Hubbard and Hellon, 1980), but detailed intracellular studies of V brainstem neurones are needed to establish their existence and characteristics clearly.

Afferent-induced modulation of nociceptive responses has received little attention at other levels of the V system. Some modulation may occur in the reticular formation, and the activity of thalamic and cortical neurones evoked by electrical pulp stimulation can be suppressed by acupuncture or other orofacial stimuli (*e.g.*, Lund and Sessle, 1974; Pearl and Anderson, 1980; Toda *et al.*, 1980). Pulp-evoked cortical potentials recorded from humans are also subject to suppression by acupuncture and TENS (*e.g.*, Chapman *et al.*, 1979).

Afferent-induced suppressive effects have also been described on the JOR evoked by orofacial stimuli (*e.g.*, Sessle, 1977; Fung *et al.*, 1978; Ha *et al.*, 1978; Tal *et al.*, 1981); the presumed noxious stimulation site used to evoke the JOR in these studies has been the tooth pulp. The suppressive effects have been implicated in mechanisms underlying the analgesic effectiveness of TENS and acupuncture, and recent findings that noxious stimuli applied to remote sites (*e.g.*, hind limb) are particularly effective in suppressing the pulp-evoked JOR are consistent with the concept of DNIC (see Cadden, 1985). Some, but not all, of these suppressive effects have also been reported to be partly reversible by the opiate antagonist naloxone, which implies that endogenous opiate-related mechanisms may be at least in part involved, in accordance with some views on acupuncture- or TENS-induced analgesia of spinal nociception (*e.g.*, Melzack, 1984; Woolf, 1984). However, other neurotransmitters are very likely involved in the afferent-induced effects in the V system, *e.g.*, 5-HT, noradrenaline, and GABA (Chan and Yip, 1979; Lovick and Wolstencroft, 1983; Salt and Hill, 1983; Basbaum, 1985). Thus, there is still a clear need for further study of the underlying mechanisms of the afferent-induced effects, their loci of action(s), the relative importance of segmental and descending influences in the effects, and the neurotransmitter mechanisms, afferents, and central pathways involved.

Modulation by sensory alterations.

It has become increasingly apparent that alterations to the afferent input to the CNS (other than by the experimentally induced stimulation procedures that have been reviewed above) may result in morphological and functional changes within the CNS and thereby in behavior. Such changes induced, for example, by trauma or inflammation are on the one hand a reflection of neuroplasticity, and the brain's capacity for regeneration and repair. On the other hand, such alterations in structure and function, particularly if they are prolonged or not fully reversible, are also seen as factors involved in the etiology of a number of chronic pain conditions.

Several of the clinical conditions which may manifest chronic pain (*e.g.*, causalgia, neuralgia, and sensory neuropathy) have indeed been linked to *deafferentation* (see Sunderland, 1978; Kerr, 1979; Tasker, 1984), a term which refers to the partial or total loss of a sensory nerve supply to a particular body region. Deafferentation may occur, for example, as a result of trauma to a limb, or damage to the dental nerves during oral surgical procedures. The concept of deafferentation was alluded to earlier when the possibility was raised that the long-range convergent afferent inputs demonstrated in the V brainstem complex may become especially operational after deafferentation and inflammation. Morphological and physiological changes subsequent to deafferentation have been noted in the spinal somatosensory system, and while some of these changes have been disputed by others, they have been demonstrated in several studies in adult animals and are especially prominent in neonatal animals (*e.g.*, for review, see Kaas *et al.*, 1983; Wall, 1984; Pubols and Sessle, 1987). The changes include degenerative-like alterations in CNS neuronal morphology, and physiological alterations in somatotopic organization and response properties of somatosensory neurones. The mechanisms underlying these deafferentation-induced changes are still unclear, and relate primarily to either sprouting of CNS collaterals of non-affected afferent inputs or to unmasking of existing long-range afferent inputs. Since the deafferentation interferes with the flow of neurochemicals as well as nerve impulses in the damaged axons, neurotrophic factors may be involved in these mechanisms, as pointed out above.

Recently, some studies have looked at the possibility that central alterations may be induced by peripheral deafferentation in the adult V system. It has been clearly shown that peripheral nerve lesions or removal of tooth pulps lead to well-documented degeneration of peripheral V nerves and their central endings in the brainstem (*e.g.*, Gobel, 1984; Arvidsson, 1987; Johnson *et al.*, 1987). The degeneration induced by tooth pulp removal or inferior alveolar nerve transection does not necessarily end at the central terminations of the afferents but

may also be associated with transneuronal alterations in the V brainstem complex which can be pharmacologically enhanced by certain convulsant drugs (Gobel, 1984; Sugimoto, 1987).

So-called hyperactivity of V brainstem neurones following V deafferentation has been reported by Anderson *et al.* (1971), Black (1974), and Macon (1979). Macon also noted alterations in the sensitivity of the neurones to iontophoretically applied neurotransmitters, and Yokota (1985) has reported firing of caudalis neurones evoked by stimulation of a neuroma produced by V nerve transection. Sessle and his colleagues have noted changes (compared with control unoperated animals) in the functional properties of neurones in the V spinal tract nucleus (see Sessle, 1985; Hu *et al.*, 1986a). For example, they found that endodontic removal of the tooth pulp results, from 7 to 15 days later, in a statistically significant increase in the incidence of subnucleus oralis neurones having an expanded mechanoreceptive field, habituating tap-sensitive responses to orofacial stimuli, and spontaneous activity (Fig. 4); the level of neuronal spontaneous activity was, however, not higher than that noted in the few spontaneous firing neurones occurring in control animals, *i.e.*, the neurones were not really "hyperactive". These data are consistent with the view that many of the existing convergent afferent connections referred to earlier may account for the receptive field changes, and that the changes may occur too early to involve collateral sprouting (Sessle, 1985; Hu *et al.*, 1986a). These changes in oralis neurones do not necessarily involve a change in central inhibition from the nucleus raphe magnus (Hu *et al.*, 1986b), which is normally a source of powerful modulation of V somatosensory transmission (see below). They are nonetheless consistent with an increased excitability of the neurones which could result from a decrease in afferent-induced inhibition: Peripheral deafferentation can reduce afferent inhibition in the spinal dorsal horn (see Wall, 1984). It should also be noted that the effects on oralis neurones are reversible, at least with a single deafferentation procedure of the pulp (Sessle, 1985; Hu *et al.*, 1986a; and see Fig. 4).

The brainstem alterations that can be induced by V deafferentation in the adult are also probably reflected in changes at higher levels of the V somatosensory system, since thalamic and cerebral cortical changes may occur as a result of spinal nerve deafferentation (*e.g.*, Wall, 1979, 1984; Kaas *et al.*, 1983), and thalamocortical as well as brainstem alterations in rodents may be induced by whisker removal (*e.g.*, Kaas *et al.*, 1983; Jacquin and Rhoades, 1985; Killackey, 1987). The effects of whisker removal are especially evident in, but not restricted to, neonatal animals; the consequence of the 'natural' deafferentation process of the shedding of the teeth in infant animals is considered below.

These changes have elicited considerable interest in terms of CNS development, neuroplasticity, and regenerative phenomena. They are also of potential significance in the etiology of certain pain states. Some authors have suggested that sensory alterations induced by nerve trauma may initiate events leading in some cases to painful sensory neuropathies, V neuralgia and atypical facial pain, burning mouth syndrome, TMJ/myofascial pain dysfunction, etc., and some of the evidence bearing on such a view has recently been reviewed (Kerr, 1979; Loeser, 1984; Tasker, 1984; Sessle, 1985; Grushka *et al.*, 1987). Such trauma-related deafferentation may not be the only factor precipitating these alterations in the CNS. It is possible that other factors which ultimately lead to an alteration in the afferent input to the brain might result in CNS changes associated with the development of certain chronic pain states. For example, inflammation of peripheral tissues can lead to expressions of neuroplasticity in ascending or reflex spinal somatosensory pathways associated with pain (*e.g.*, Benoist *et al.*, 1985; Woolf, 1985). In the V system, compression (*e.g.*, by carotid arterial loops) or demyelination of V sensory root afferents has been viewed (Jannetta, 1977; Calvin, 1979; Kerr, 1979) as being of prime etiological significance in V neuralgia. It has also been reported that peripheral sensory nerve alterations might also result from microbial agents and dental and oral pathoses (*e.g.*, Wepsic, 1973; Ratner *et al.*, 1979) and lead to post-herpetic neuralgia, V neuralgia, and atypical facial pain.

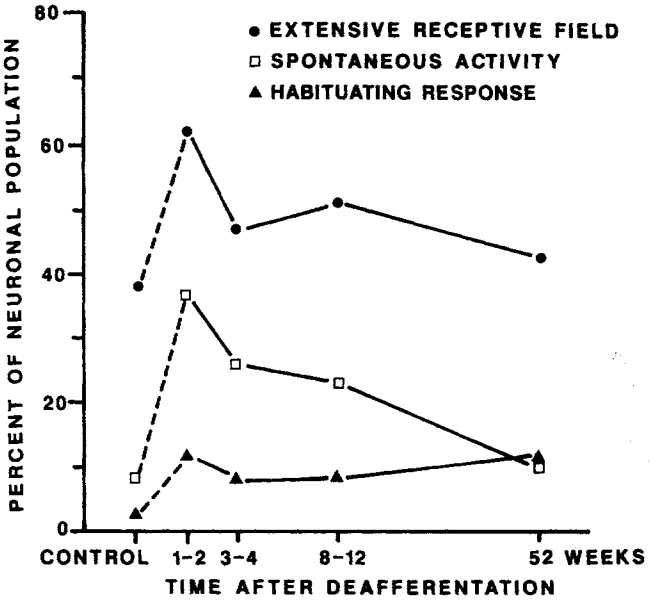

Fig. 4 — Effects of deafferentation of the tooth pulp on the properties of brainstem neurones recorded in the cat's trigeminal spinal tract nucleus (subnucleus oralis). Routine aseptic procedures comparable with those carried out for human endodontic therapy were used to remove the ipsilateral maxillary or mandibular canine, pre-molar, and molar pulps. Neuronal properties were subsequently assessed in each cat at a single post-operative time, varying from 1-2 weeks to a year or more, and were statistically compared with properties of neurones recorded in control (unoperated) cats. The three properties illustrated are based on data acquired from over 1500 single neurones; they are the incidence of: (i) neurones with an extensive mechanoreceptive field involving two or all three trigeminal nerve divisions on the face and mouth; (ii) neurones having spontaneous activity (*i.e.*, tonic firing unrelated to any peripheral stimulus); and (iii) neurones showing a rapidly habituating response to oral-facial tactile stimuli and a sensitivity only to a brisk tap applied to facial or intra-oral sites. As the control values indicate, about one-third of the neuronal population normally shows the extensive receptive field property, and well below 10% shows spontaneous activity or the habituation response. The marked increase in the incidence of these neuronal properties after deafferentation is statistically significant for the initial post-operative period, but it gradually returns to control levels.

While, in general, data from control subjects have not been included in these clinical observations related to orofacial pain conditions (to rule out confounds of normal anatomical variability, the aging process, etc.), some recent support for these possibilities comes from the abovementioned studies of the changes in central somatosensory pathways that may ensue after peripheral nerve damage (*e.g.*, deafferentation, inflammation), as well as from observations in peripheral nerves. Abnormal firing patterns in peripheral V nerves have been observed after experimentally induced demyelination in animals, and it has been postulated that abnormal discharges evoked in large-diameter fibers by tactile stimulation can induce a heightened primary afferent depolarization (PAD) of V nociceptive endings in the brainstem, which paradoxically may

facilitate the production of excessive activity in orofacial nociceptive pathways, and the explosive pain of V neuralgia which is usually triggered by a light tactile stimulus (see Calvin, 1979; Burchiel, 1980). The paradoxical nature of such a proposed mechanism stems from the general view that PAD underlies pre-synaptic inhibition, which is normally associated with a suppression of activity. While research in the last decade has revealed that large-fiber input can pre-synaptically influence the small-diameter V nociceptive afferents (Davies *et al.*, 1971; Young and King, 1972; Lisney, 1979; Dostrovsky *et al.*, 1981), the net effect of this interaction, at least in normal animals, is that the V large-fiber input suppresses, not facilitates, the activity of V brainstem nociceptive neurones (Sessle *et al.*, 1981a). However, damage to peripheral nerves and resulting deafferentation can lead to a reduction in the large-fiber-mediated pre- and post-synaptic inhibition of spinal dorsal horn neurones (see Wall, 1984); therefore, the increased excitability of V brainstem neurones occurring after deafferentation could result from a loss of afferent-induced inhibition (see above) and thereby conceivably account for increased excitability of V nociceptive neurones. Thus, the inhibition that the large-fiber input normally exerts on the neurones may be counteracted by the increased excitability of the neurones.

Such electrophysiological considerations, plus the clinical features of many of these chronic pain conditions, such as V neuralgia, indicate that while the primary initiating factor may be mainly of a peripheral nature, central brainstem mechanisms are undoubtedly also involved. The signs and symptoms of V neuralgia, for example, suggest the involvement of factors related to central neuronal properties of summation, convergence, and inhibition. The WDR neurones in particular may be involved in these processes, since (i) these central properties are a feature of these neurones, (ii) the WDR neurones are critically important in the encoding of noxious stimuli (see above), and (iii) they alone of the three general classes of central mechanosensitive neurones (LTM, WDR, NS) receive, as well as nociceptive afferent inputs, inputs from large-diameter afferents that are activated by tactile stimuli of the form that precipitate a V neuralgia attack. The changes that alterations such as V deafferentation can induce in central neurones (see above), the effects of convulsive (*e.g.*, strychnine) and anticonvulsive (*e.g.*, carbamazepine, baclofen) drugs on somatosensory transmission and afferent-induced inhibition (see Fromm *et al.*, 1984), and the analgesic effects that certain chemicals might induce as a result of possible changes in endogenous nociceptive neuromodulators (see Monks and Merskey, 1984) also point to changes in central mechanisms controlling nociceptive transmission in the etiology of chronic pain conditions such as V neuralgia. Future studies aimed at the further examination of the central consequences of peripheral nerve lesions or alterations, as well as at factors that influence the central processing of nociceptive information, should be very helpful in clarifying the mechanisms underlying chronic orofacial pain states.

Modulation by intrinsic central influences.

As well as being subject to regulation by stimulation of or alterations in afferent inputs into the CNS, neurones involved in pain transmission may also be modulated by influences exerted by neural pathways intrinsic to the CNS, many of which emanate from higher brain centers involved in cognition, and in motivational and emotional behavior. The sensory inputs responsible for the afferent or segmental inhibitory effects outlined above may also access these pathways and mechanisms (*e.g.*, DNIC, acupuncture). With the impetus provided by the concept of Descending Central Controls, espoused in 1965 in the Gate Control Theory of Pain (Melzack and Wall, 1965), and the even more recent discovery of enkephalins, endorphins, and other neurochemicals endogenous to the CNS that are capable of modulating pain, a vast amount of recent pain research has been directed at intrinsic influences on pain transmission and behavior. While much greater study has been directed at mechanisms of spinal nociceptive control (*e.g.*, for review, see Basbaum and Fields, 1984; Dubner and Bennett, 1983; Willis, 1985), most of the techniques utilized in the spinal system have now been used over the last 10 years in the V system.

First, mention should be made of the influence referred to earlier that is intrinsic to the V brainstem complex, namely, the intranuclear pathways that connect different components of the complex and the tonic ascending influence that caudalis has been shown to exert on more rostral V neurones. Further research in this area might be directed at the functional importance of these connections in the awake animal, and at possible modulatory influences exerted by the rostral nuclei on more caudal neurones, taking into account the recent descriptions of descending as well as ascending connections between the rostral nuclei and caudalis.

Because the nucleus raphe magnus (NRM), periaqueductal gray matter (PAG), and adjacent reticular formation have been especially emphasized in studies of the descending modulatory influences on spinal nociceptive transmission, a great deal of the research focus on intrinsic modulatory control of V nociceptive transmission has been directed at these pathways and their influences (Fig. 5). Direct projections to the V spinal nucleus from the NRM have been reported (Lovick and Robinson, 1983; Basbaum and Fields, 1984), and, although the effect of PAG stimulation could also be due to a direct projection from PAG to the V sensory or motor nuclei (*e.g.*, Beitz *et al.*, 1983), there is evidence that at least some of the suppressive effects of PAG are mediated *via* NRM (Basbaum and Fields, 1984; Mason *et al.*, 1986).

Enkephalin, noradrenaline, and 5-HT-containing terminals, possibly originating from the raphe and other brainstem loci, have been described within subnucleus caudalis (Hokfelt *et al.*, 1977; Gobel *et al.*, 1981, 1982; Dubner and Bennett, 1983; Basbaum, 1985), and have been implicated in these descending influences. Nonetheless, it should be noted that some of these effects appear to involve the neural circuitry which is intrinsic to the V spinal nucleus (*e.g.*, substantia gelatinosa of subnucleus caudalis) and which may involve local interneurones containing these substances and other neurochemicals such as the inhibitory neurotransmitter GABA (see Dubner and Bennett, 1983; Basbaum, 1985). These same local or segmental circuits and neurochemicals might also be brought into operation by other descending influences as well as by the sensory inputs that can induce analgesia (see above).

Stimulation of the PAG or NRM has been shown to be effective in suppressing the JOR in the awake, decerebrate, or anaesthetized animal (see Oliveras *et al.*, 1977; Sessle *et al.*, 1981a; Dostrovsky *et al.*, 1982; Mason *et al.*, 1985, 1986). Such stimulation may also reduce nociceptive behavioral responses to noxious facial stimuli (Hayes *et al.*, 1979; Morris *et al.*, 1982) or tooth pulp stimulation (Oleson *et al.*, 1980) in the awake monkey and rat, and may relieve chronic pain states in human patients (Gybels, 1979; Turnbull, 1984). While it cannot be ruled out that some of these effects may result from relatively direct actions of the PAG or NRM influences on digastric motoneurones, at least contributing to these suppressive effects on nociceptive reflex and behavioral responses are the demonstrated inhibitory influences exerted by PAG and NRM on V nociceptive neurones (*e.g.*, Sasa *et al.*, 1975; Sessle *et al.*, 1981a; Dickenson and LeBars, 1983; Dostrovsky *et*

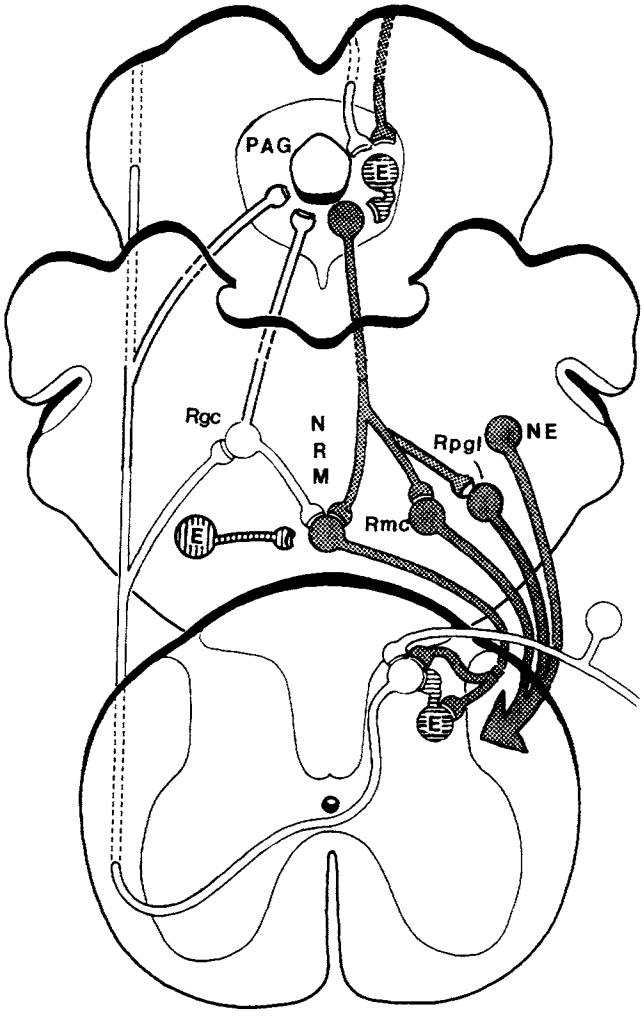

Fig. 5 — Diagram of the major components of a descending system that contributes to the analgesic action of opiates and of electrical brain stimulation. Highlighted (stippling) are the connections between the projection neurones of the periaqueductal gray (PAG) and various subregions of the rostral ventral medulla [the nucleus raphe magnus (NRM), the nucleus reticularis magnocellularis (Rmc), and the nucleus reticularis paragigantocellularis lateralis (Rpgl)]. The latter project to the trigeminal brainstem complex and to the spinal dorsal horn, where they inhibit nociceptive neurones. The inhibitory action may be *via* direct post-synaptic inhibition, or *via* an opioid peptide-containing interneurone (indicated by stripes and "E"). There are other such links illustrated at the level of the PAG and the rostral medulla; however, their connections are not indicated. The noradrenergic (NE) contribution to bulbospinal control, as well as inputs to the PAG, are also illustrated. Ascending components of this system are indicated by the unfilled symbols. These include afferent inputs, projection neurones of the V brainstem complex and the spinal dorsal horn and their collaterals into PAG and medulla, *e.g.*, to neurones of the nucleus reticularis gigantocellularis (Rgc). From Basbaum and Fields (1984).

al., 1983; Hayashi *et al.*, 1984), since many of these serve as interneurones in these responses (*e.g.*, Dubner *et al.*, 1978). NRM stimulation also suppresses pulp-evoked responses of neurones in the medial bulbar reticular formation, an effect which appears to be mediated by GABA (Lovick and Wolstencroft, 1983).

In their awake monkey preparation, Hayes *et al.* (1979) noted that a prolonged period of PAG stimulation results in suppression of nociceptive behavior and caudalis nociceptive neurones that may last several minutes. These effects may be partly related to changes in the nociceptive response properties of caudalis neurones induced by different behavioral contingencies that an animal may be carrying out (*e.g.*, Bushnell *et al.*, 1984). Thus, the behavioral relevance of a noxious stimulus and factors related to attention can modify the responses of caudalis nociceptive neurones. Such effects at the very first synaptic relay in V pain pathways may contribute to the well-recognized effects that motivation, anxiety, attention, distraction, etc., may have on pain, and are indicative of the involvement of multiple descending and segmental influences on V nociceptive transmission; further support for the concept of multiple influences is provided below. These studies in behaving monkeys also indicate that some caudalis nociceptive (and non-nociceptive) neurones can exhibit activity during a behavioral task that is unrelated to the noxious facial stimulus parameters and pain discrimination. These task-related neuronal activities suggest that they may reflect the animal's evaluation of behaviorally important sensory signals that the animal must detect or among which it must discriminate in order to perform the task successfully.

Apart from these demonstrations in behaving monkeys that might partly involve the raphe system and associated structures, other studies have also recently examined how these descending influences might be recruited in normal physiological or pathophysiological situations. It has been shown that analgesia can be produced by certain stressful situations (*e.g.*, footshock, centrifugal rotation), although all stressors do not necessarily produce analgesia. While a noxious input is not critical to initiate the subsequent analgesic effect, most current behavioral models involving these descending influences require a noxious input as the initiating factor (for review, see Dubner and Bennett, 1983; Basbaum and Fields, 1984). Simplistically speaking, pain inhibits pain. Support for such a concept comes, for example, from the findings referred to above regarding DNIC. In this concept, diffuse noxious inputs to the CNS result in the activation of an intrinsic descending pathway that produces suppression of nociceptive transmission. Other studies suggest that additional descending influences may also be involved in analgesic effects of noxious stimuli. In view of the relevance to pain control, studies addressing the physiological roles and circumstances in which these various descending influences are functional represent important avenues of future pain research.

What mechanisms underlie these suppressive influences? Since PAD is thought to underlie pre-synaptic inhibition (see above), pre-synaptic regulatory mechanisms may be involved: PAG or NRM stimulation induces PAD in the brainstem terminals of tooth pulp primary afferents (Dostrovsky *et al.*, 1981) and nociceptive facial afferents (Hu and Sessle, 1987). Some raphe-induced pre-synaptic regulation of ascending V pathways could also be reflected at thalamic levels as well as at the brainstem (Sessle and Hu, 1981). Post-synaptic inhibition, which appears to be involved in raphe-induced suppression of spinal nociceptive neurones, may underlie some of the suppressive effects, since PAG or NRM stimulation blocks antidromic invasion and glutamate-evoked activity of V neurones (Sessle and Hu, 1981; Shah and Dostrovsky, 1982).

Several findings indicate that endogenous opiate-related neurochemicals are involved in these modulating effects: (i) Some of the suppressive effects of PAG or NRM stimulation on the JOR and V neurones are naloxone-reversible (Sessle and Hu, 1981; Sessle *et al.*, 1981a); (ii) enkephalin or morphine micro-iontophoretically applied within caudalis may suppress caudalis neurones (Andersen *et al.*, 1978; Henry *et al.*, 1980; Morris *et al.*, 1982); (iii) morphine micro-injected into caudalis attenuates the perceived intensity of noxious orofacial heat in monkeys trained to discriminate among noxious heat stimuli (Oliveras *et al.*, 1986), which findings are also con-

sistent with observations in humans that the effects of opiates are not only directed at the affective dimension of pain, as previously proposed, but that opiates can also influence the sensory-discriminative aspect of pain (Gracely *et al.*, 1979); (iv) enkephalin and opiate receptor sites are concentrated in caudalis (*e.g.*, Hokfelt *et al.*, 1977; Basbaum, 1985), which may reflect enkephalin-containing cells or terminals within the complex (Gobel *et al.*, 1982; Basbaum, 1985); and (v) enkephalin is reported to suppress the release of substance P from the subnucleus (Jessel and Iversen, 1977). It is still uncertain to what extent these opiate-related effects operate on V brainstem neurones by relatively direct circuits (*e.g.*, enkephalin-containing interneurones in the V complex) or by indirect pathways involving higher centers such as the PAG, which contains enkephalinergic neurones (Fig. 5). Also unclear is their mode of action (see Dubner and Bennett, 1983; Basbaum, 1985): Some authors have suggested a pre-synaptic modulation of nociceptive primary afferent input (*e.g.*, Jessel and Iversen, 1977; Snyder, 1978), but the lack of an anatomical correlate of this effect (see Basbaum, 1985) and the failure of naloxone to reverse PAG and NRM-induced PAD of tooth pulp afferent endings in the brainstem (see Dostrovsky *et al.*, 1981) do not support this concept. Moreover, the failure of naloxone to modify the PAD or to reverse many of the PAG- and NRM-induced suppressive influences also indicates the involvement of other neurochemical modulatory processes. These processes may utilize opiate receptors insensitive to naloxone, or other neurochemicals altogether. An example of the latter would be 5-HT, which is contained in some NRM neurones (*e.g.*, see Dubner and Bennett, 1983; Basbaum and Fields, 1984; Basbaum, 1985); it and other neuromodulators also appear to be involved in the suppressive effects induced from other brainstem regions (see below).

It should be noted that these descending influences and neurochemicals may have effects in CNS systems unrelated to nociception, *e.g.*, memory, certain mental disorders, cardiorespiratory function, and feeding and sexual behaviors (see Eldridge and Millhorn, 1981; Henry, 1982; Sessle and Lucier, 1983; Akil *et al.*, 1984). Furthermore, the effects of PAG or NRM stimulation are not limited to caudalis neurones or the JOR that are activated by tooth pulp or noxious facial stimuli. Stimulation of PAG or NRM can induce profound suppression of JOR responses evoked by low-threshold afferent inputs and inhibition of the majority of LTM neurones throughout the V brainstem complex that are excited by non-noxious orofacial stimuli (Lovick and Wolstencroft, 1979; Sessle *et al.*, 1981a; Sessle and Hu, 1981; Dostrovsky *et al.*, 1983; Hayashi *et al.*, 1984). These effects on non-nociceptive low-threshold afferent inputs are consistent with recent findings of PAG- and NRM-induced suppression of neurones of the spinal cord dorsal horn (*e.g.*, Gray and Dostrovsky, 1983; Willis, 1985), dorsal column nuclei (Dostrovsky, 1980), and respiratory-related neurones in the solitary tract nucleus (Sessle *et al.*, 1981b), and of PAG- and NRM-induced PAD of LTM primary afferent endings in the V brainstem complex (Hu and Sessle, 1987).

In keeping with the concept that there are multiple descending influences modulating nociceptive transmission, JOR and V brainstem neuronal responses to both noxious and non-noxious orofacial stimuli can also be suppressed by stimulation of the somatosensory cerebral cortex (Sessle *et al.*, 1981a); cortical stimulation also induces PAD in the brainstem endings of LTM and tooth pulp primary afferents (*e.g.*, see Darian-Smith, 1966, 1973; Dubner *et al.*, 1978; Dostrovsky *et al.*, 1981). Stimulation of a number of reticular formation sites in the brainstem has also been shown to be capable of suppressing the JOR and both nociceptive and non-nociceptive V brainstem neurones (Chan, 1980; Sessle *et al.*, 1981a; Dostrovsky *et al.*, 1982, 1983; Mason *et al.*, 1985) and producing PAD of the brainstem endings of V afferents (Chan, 1980; Dostrovsky *et al.*, 1982); other effective sites include locus cœruleus, cerebellum, orbital cortex, and a number of thalamic areas (*e.g.*, Sasa *et al.*, 1979; Oleson *et al.*, 1980; Basbaum and Fields, 1984). Neurochemicals implicated in the effects include endogenous opioids, 5-HT, and catecholamines.

These studies have been complemented by a small number of investigations of the effects of systemically administered chemical substances. One of the serious limitations of this approach, as opposed to micro-injection into specific brain loci or local iontophoresis, is that little information is gained on the site(s) of action of the systemically administered chemical. Nonetheless, in accordance with the findings of endogenous opiate-related mechanisms (see above), it has been shown that the JOR and the activity of V nociceptive and non-nociceptive neurones can be suppressed by the intravenous administration of morphine and the effect reversed by naloxone (*e.g.*, Sasa, 1969; Chan and Fung, 1976; Hayes *et al.*, 1979); central catecholaminergic and cholinergic processes may also be involved in these effects (Chan and Yip, 1979). The inhibitory neurotransmitter GABA, which may exist in axonal endings in the spinal cord dorsal horn and subnucleus caudalis (*e.g.*, Basbaum, 1985), has also been implicated in modulatory processes within the V brainstem complex and adjacent reticular formation areas by virtue of the systemic action of GABA antagonists or agonists (Lovick and Wolstencroft, 1983; Fromm *et al.*, 1984). One of these, baclofen, as well as the anticonvulsant drugs carbamazepine and phenytoin, have been found to be very effective when administered systemically in suppressing the activity of V brainstem neurones and in relieving V neuralgia, perhaps through an action on segmental inhibitory mechanisms in the brainstem (see Fromm *et al.*, 1984). Neurones relaying orofacial information at higher CNS levels (*e.g.*, VB and PO thalamus, somatosensory cerebral cortex) can also be affected by intravenously administered chemicals such as morphine (*e.g.*, Mitchell, 1970; Shigenaga and Inoki, 1976), but the relative contribution of brainstem *vs.* direct thalamocortical effects has received little attention in these studies.

These various findings of descending modulation of orofacial sensory transmission are in keeping with comparable findings in the spinal cord dorsal horn and dorsal column nuclei, and point to the existence of multiple descending influences that can potentially influence nociceptive transmission by utilizing several neurochemical mechanisms. They also point to a number of means by which these influences and mechanisms could be studied further, and by which other important intrinsic systems capable of modulating orofacial pain might be revealed. For example, modulatory influences from other areas of the brain, such as those implicated in affective aspects of pain behavior (*e.g.*, limbic system, hypothalamus), might be explored further (Oleson *et al.*, 1980). This is especially important in view of the increasing credence given to so-called "psychological" factors (*e.g.*, related to stress, motivation, emotion, depression) in chronic orofacial pain conditions, such as TMJ/myofascial pain syndromes and atypical facial pain (Dubner *et al.*, 1978; Zarb and Carlsson, 1979; Laskin *et al.*, 1982). Emphasis should also be given to the greater use of immunocytochemical, micro-injection, iontophoretic, and other neuropharmacological techniques to explore the role played by other neuromodulators (*e.g.*, neurotensin, somatostatin, angiotensin, 5-HT) in V nociceptive transmission. Study should also be directed at the interconnections between the raphe, reticular formation, and the V system, and the differential effects of the descending systems on A-beta, A-delta, and C-fiber V afferent inputs. Related investigations should aim at elucidating the relative importance of pre-synaptic *vs.* post-synaptic inhibitory

mechanisms in the effects. Attention should also be given to possible ascending influences from the brainstem and midbrain on nociceptive relays and processing at higher perceptual and affective levels of the CNS, and of the functional circumstances in which the ascending and descending influences come into operation. Implicit in this latter approach is the greater use of awake, behaving animal models in elucidating orofacial pain control mechanisms.

Tooth pulp nociception.

A number of the aspects covered above apply to tooth pulp nociception and so will require little reiteration in the present section. Here, emphasis will be given to peripheral mechanisms in the pulp, and to particular questions or peculiarities pertaining to the pulp and its central processing. Extensive reviews of the neural mechanisms underlying tooth pulp function are available for readers requiring detailed information (Anderson *et al.*, 1970; Dubner *et al.*, 1978; Sessle, 1979; Byers, 1984; Johnsen, 1985; Närhi, 1985; Olgart, 1985).

Tooth pulp sensation.—There has been a recent research focus on the neurobiology of the tooth pulp, largely because of the clinical relevance of the pulp to orofacial pain and the concept that the pulp is a most useful, if not indeed unique, model for studying pain by virtue of its being a "pure" source of nociceptive input to the CNS. The concept of the exclusive sensory role of the tooth pulp in pain has been, and continues to be, reiterated almost *ad nauseum* in the majority of the studies that have utilized the tooth pulp as the model system for pain. It has been pointed out (Dubner *et al.*, 1978; Sessle, 1979) that the concept is primarily based on uncontrolled, anecdotal clinical observations and on anatomical and electrophysiological observations that are purported to reveal that the pulp is supplied exclusively by A-delta and C nerve fibers which elsewhere in the body are concerned with nociceptive transmission. However, it is clear from recent (*e.g.*, Lisney, 1978; Dostrovsky *et al.*, 1981; Cadden *et al.*, 1983; Närhi, 1985) as well as much earlier observations (*e.g.*, Pfaffman, 1939; Graf and Bjorlin, 1951) that fibers with conduction velocities and diameters greater than the A-delta range occur in the pulp. It is also noteworthy that some A-delta and C fibers in the skin subserve functions other than nociception (*e.g.*, temperature, touch), and that many of the pulp C fibers may be autonomic efferents accompanying the pulp's vascular supply (see below). Further study is indicated to clarify the roles that the different types of tooth pulp afferents may play in pain and possibly other sensory functions of the tooth, and how their activity is influenced by conditions (*e.g.*, inflammation) that alter the environment in which they reside.

Other recent studies reviewed by Dubner *et al.* (1978), Sessle (1979), Byers (1984), Kollman and Mijatovic (1985), and Mason *et al.* (1985) have examined the threshold sensation and reflex effects elicited by electrical and thermal pulp stimulation and the CNS regions in which pulp-evoked activity can be recorded (see below). Collectively, these studies also indicate the inadvisability of assigning a role in nociception to *all* neuronal and behavioral responses evoked by pulp stimuli, although it does seem clear that the *predominant* influences of pulp stimulation are related to the sensory-discriminative and affective-motivational aspects of dental pain. Finally, while another potential confound with pulp stimuli is the possible activation of non-pulpal afferents which could make non-nociceptive contributions to observed responses, it is now clear that with appropriate precautions, stimulus spread can be limited to pulpal tissues; however, this limit might not be possible for the continuously erupting rat incisor (Hayashi, 1980; Engstrand *et al.*, 1983; Rajaona *et al.*, 1986), which has unfortunately been used in a number of studies.

Peripheral mechanisms.—Fifteen years ago, the picture of the morphology and the physiological and pharmacological characteristics of the innervation of pulp and dentin was primarily derived from a number of anatomical studies describing the spectrum of nerves supplying the pulp and a few electrophysiological studies of the responses of pulp afferents to peripheral dental stimuli (see Anderson *et al.*, 1970). At the heart of this research was the question, "Is the dentin of the tooth innervated, and if so, does it account for dentinal sensitivity?" In the 1960's, the anatomical studies of Fearnhead (1961, 1963), Frank (1968) and others, and the electrophysiological studies of Scott and co-workers (*e.g.*, Scott, 1972) had provided data suggesting that the dentin is innervated. This prompted a flurry of investigations in the 1970's utilizing more modern and often more rigorous histological and electrophysiological investigation of the innervation of the pulp as well as of the dentin. As a result of these research efforts, the answer to the first part of the question posed above appears to have been answered in the affirmative, although the second part of this question has still not been resolved.

It is clear that a large proportion of the nerve fibers supplying the pulp in both deciduous and permanent teeth are unmyelinated and that the myelinated fibers are not limited to the A-delta conduction velocity range (see Dubner *et al.*, 1978; Byers, 1984; Johnsen, 1985; Närhi, 1985). In contrast to earlier studies (*e.g.*, Fearnhead, 1961, 1963), it has now been shown that myelinated and unmyelinated fibers become apparent very early in tooth development, and a proportion enter the dentinal tubules even before completion of root formation and tooth eruption (Avery, 1979; Byers, 1980, 1984; Fried, 1982).

Whereas synapses, tight junctions, or gap junctions between pulp nerves and odontoblasts appear to be lacking in the pulpodentinal border region, a close apposition may occur between the membranes of structures that may be neural and odontoblastic in nature (*e.g.*, Frank *et al.*, 1972; Avery, 1979; Byers, 1984; Holland, 1985). However, the precise morphology, quantification, characterization, and functional role of these junctional elements must still be established.

Junctional contacts within the dentinal tubule that were reported in some of the initial electronmicroscopic studies (*e.g.*, Frank, 1968) have not been substantiated by subsequent workers. A number of recent investigations have nonetheless verified that dentinal tubules of several species may contain neural elements (*e.g.*, for review, see Holland, 1976; Avery, 1979; Byers, 1984; Johnsen, 1985). While most of the investigations to date have lacked rigorous controls and quantitative data, it is clear that the numbers of these neural elements do vary considerably from tubule to tubule and from tooth site to tooth site (Fig. 6); species differences may also occur.

It should be noted that autonomic efferents as well as somatic afferents supply the pulp, and some of these unmyelinated efferents might enter dentinal tubules (Feher *et al.*, 1977; Avery, 1979). Although there is recent electrophysiological evidence of C-fiber afferents in pulp (see Närhi, 1985), the relative proportion of unmyelinated somatic afferents to autonomic efferents is unclear.

Even less certain is whether the dentinal nerves subserve dentinal sensitivity. For example, it is not inconceivable that they may subserve neurotrophic functions (see Dubner *et al.*, 1978). Virtually all reports have demonstrated their restriction to the inner one-third of dentin (*e.g.*, Fig. 6), with no extension to the enamel-dentin junction, which is clinically reputed, but with no controlled experimental evidence, to be the most sensitive part of the dentin. The application of immunocytochem-

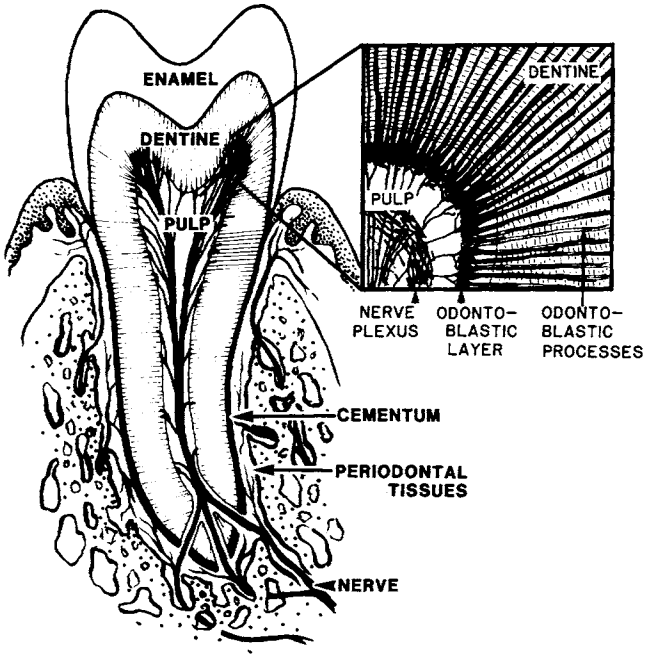

Fig. 6 — Nerve supply of the tooth. The nerves supplying the tooth can be seen innervating the periodontal tissues, which are the supporting tissues of the tooth, as well as the tooth pulp. After entering the pulp at the root apex of the tooth, the pulpal nerves arborize extensively, especially in the crown of the tooth, and form a nerve plexus in the periphery of the pulp beneath the layer of odontoblast cells, which have processes which extend into the tubules in the overlying dentin. Note that some individual nerve fibers leave the subodontoblastic plexus; a number enter the dentinal tubules, although many terminate in the odontoblastic layer. It has been reported that the dentinal nerve fibers are limited to the inner (*i.e.*, pulpal) third of the dentin, and that not every tubule contains a nerve fiber. Modified, with permission, from Byers (1984).

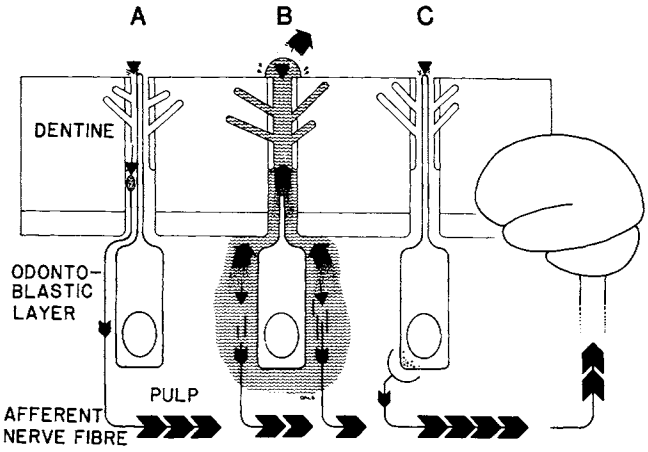

Fig. 7—The three major theories for activation of dental nerve fibers by stimuli applied to enamel or dentin. Stimuli are indicated by arrowheads. The so-called neural theory (A) attributes activation to an initial excitation (arrow) of those nerves ending within the dentinal tubules. These nerve signals are then conducted along the parent primary afferent nerve fibers in the pulp into the dental nerve branches and then into the brain. The hydrodynamic theory (B) proposes that the stimuli cause a displacement of the fluid which exists within the dentinal tubules. The displacement occurs in either an outward direction (as shown) or an inward direction (not shown), and this mechanical disturbance activates the nerve endings in the dentin or pulp. The third theory (C), the odontoblastic transduction theory, proposes that the stimuli initially excite the process or body of the odontoblast, the membrane of which may come into close apposition with that of nerve endings in the pulp (as shown) or in the dentinal tubule (not shown), and that the odontoblast transmits this excitation to these associated nerve endings. From Ten Cate (1985).

istry to this problem seems timely, since this technique has recently been used to demonstrate the extension of the odontoblast process to the dentinoenamel junction (Sigal *et al.*, 1984).

Physiological studies have done little to clarify these issues and answer the question whether these dentinal structures could account for dentinal sensitivity — the so-called "neural theory" (Fig. 7). No clear and undisputed evidence has yet been presented to indicate that activity evoked by dental stimuli and recorded by electrodes applied to dentin or to dental nerve branches arises from an intradentinal source. Nonetheless, these studies have provided other important information pertinent to the peripheral basis of dental pain. Afferents supplying the dental pulp have been shown in early and more recent studies to be sensitive to a variety of thermal, mechanical, chemical, and pharmacologically active agents (*e.g.*, see Scott, 1972; Haegerstam, 1976; Matthews, 1977; Dong *et al.*, 1985; Närhi, 1985; Olgart, 1985). Recent work in this area, in particular by Edwall, by Olgart and associates, and by Närhi, has also documented an association among pulpal blood flow, vasoactive substances, and pulp afferent discharges. Except possibly for 5-HT, many vasoactive substances implicated in pain, such as substance P, bradykinin, and histamine, appear to have no direct effect on pulp A-delta afferents (Närhi, 1985; Olgart, 1985) but may activate C-fiber pulp afferents (Närhi, 1985). Sympathetic nerve stimulation and changes in blood flow can alter pulp afferent activity (*e.g.*, Edwall and Scott, 1971; Matthews, 1976; Närhi, 1985; Olgart, 1985), and it now seems likely that these substances may have indirect effects by altering blood flow (see Närhi, 1985; Olgart, 1985). Vasoactive polypeptides may be released in the pulp during inflammation, and thereby be intimately involved in peripheral mechanisms underlying toothache. Several neuropeptides implicated in pain transmission and its control in the CNS (*e.g.*, substance P, somatostatin, met-enkephalin) have recently been found in the pulp (Mohamed and Atkinson, 1982; Olgart, 1985). Elucidation of their actions at the periphery represents a fascinating area for future pain research. In view of its potential clinical significance, further research in this area should also be encouraged to clarify the relationship among blood flow, vasoactive substances, afferent nerve activity, and pain. An interesting adjunctive approach that potentially could provide compelling data is the possibility that some of these approaches can be applied to human studies, *e.g.*, relating sensations induced by pulp stimuli with pulp afferent activity recorded from the surface of the tooth (Ahlquist *et al.*, 1984) or from the inferior alveolar nerve (Johansson and Olsson, 1976). Further study is also required to clarify the specificity of response of single pulp afferents to different physical and chemical stimuli.

Such doubts about the anatomical and electrophysiological basis of the neural theory indicate that more of a research focus is needed to test the other two major viable hypotheses of dentinal sensitivity (Fig. 7). The concept that the odontoblast, and/or its process within dentin, plays a transductive role between the excitant stimulus and the activated intradental nerves met with some opposition in the 1960's (see Anderson *et al.*, 1970; Dubner *et al.*, 1978). However, the observations mentioned above of the close approximation of odontoblast membranes and apparent nerve fiber membranes, as well as other considerations (see Byers, 1984), have given this theory a transductive (!) boost. Transduction involving the odontoblast might conceivably be an integral component of the third major concept of dentinal sensitivity (Byers, 1984). This concept,

which represents the most generally held view today of the basis of dentinal sensitivity, ascribes sensitivity to a hydrodynamic mechanism whereby a stimulus-produced inward or outward flow of the contents of the dentinal tubules produces, in turn, a mechanical disturbance which excites nerves in the tooth (Brännström, 1968, 1986). Most of the evidence in support of this theory is indirect and stems from the many investigations of Brännström and his colleagues, and from some electrophysiological studies suggesting that some pulpal afferents may be mechanically sensitive (*e.g.*, Haegerstam, 1976; Dong *et al.*, 1985; Närhi, 1985). Not all studies in the last 15 years that bear on this theory, however, support all details of the mechanism (*e.g.*, Horiuchi and Matthews, 1973), and further independent research is called for.

One final point on peripheral mechanisms relates to morphological and functional plasticity of the tooth pulp afferents and their connections with brainstem neurones. The regenerative capacity of the peripheral afferents has been investigated in cats by Robinson and Holland in a series of experiments (*e.g.*, Robinson, 1981; Holland and Robinson, 1985); they provided electrophysiological and morphological evidence of re-innervation of the cat canine tooth pulp 6-9 weeks after the inferior alveolar nerve had been transected. If the nerve was prevented from regenerating, the re-innervating axons originated from other ipsilateral (*e.g.*, lingual) and contralateral nerves. Byers and colleagues also found a correlation between the return of electrophysiological activity and re-innervation of pulp and dentin in re-innervated rat molars, and noted a good correlation between these findings and the return of sensitivity of replanted human teeth (see Byers, 1984).

While such information bears on the regenerative potential of peripheral pulp nerves, it also suggests that some of the bizarre sensory phenomena that sometimes accompany peripheral trauma to orofacial tissues may be partly related to the re-innervation of the injured tissues by nerves supplying quite distant orofacial sites. The central consequences of such trauma must also be considered. As mentioned earlier, recent studies have shown that tooth pulp deafferentation by aseptic endodontic therapy leads to morphological and functional changes not only in the pulp primary afferents but also in V brainstem neurones of the adult cat, and such effects may be involved in the development of chronic pain. It should also be noted, however, that there may be few differences in the properties of these neurones between normal adult cats and kittens at the mixed-dentition stage (Hu *et al.*, 1987). These findings raise the possibility that, during the shedding of the deciduous teeth and eruption of the permanent dentition, either the maturing V brainstem system is inherently more resistant to changes than the adult system, or the central endings of the deciduous pulp afferents may not undergo the extensive degenerative changes seen in the adult after pulp deafferentation. Unfortunately, remarkably little study has been made of the interrelationship of the innervations of the deciduous and permanent dentitions to clarify this matter, or indeed to answer the related question of whether the permanent tooth is supplied by collaterals of the same afferent fibers that supply its predecessor (or other orofacial tissues) or by a whole new set of afferents that innervate the permanent tooth after the deciduous pulp afferents degenerate. Some tooth pulp afferents, at least in permanent teeth, do in fact have collaterals supplying adjacent tissues (Lisney and Matthews, 1978), and during the resorption of the deciduous teeth and associated degeneration of the pulp, there is little evidence of degenerating afferents in the inferior alveolar nerve (Fried, 1982). While this favors the possibility that the same afferent may supply both the permanent tooth and its predecessor, degeneration has been reported in certain parts of the V brainstem complex during the mixed-dentition stage in kittens (Johnson *et al.*, 1987); however, it is not clear whether this degeneration derives from pulp afferents. Obviously, much more research is needed in this interesting area of V neuroplasticity.

Brainstem mechanisms. — From the pulp, afferents pass *via* the V (Gasserian) ganglion to several areas in the brainstem (see Dubner *et al.*, 1978). In the last few years, a number of studies have addressed the question of bilateral innervation of the pulp. There is at present no consensus, since some workers (Anderson *et al.*, 1977; Avery, 1979) have reported electrophysiological and anatomical evidence for such innervation, whereas similar studies by others have found little if any evidence of a bilateral supply (see Matthews and Lisney, 1978; Nord and Rollince, 1980; Arvidsson and Gobel, 1981; Dostrovsky *et al.*, 1981; Byers, 1984); technical problems (*e.g.*, spread of histological label from the pulp to contralateral tissues) might account for the discrepancy in observations. Another related area that also needs clarification through more careful and rigorous investigation is whether pulp afferents, once they enter the brainstem, terminate bilaterally or only ipsilaterally, and whether there is a preferential distribution of large- *vs.* small-diameter pulp afferents. Again, some workers favor a bilateral projection (*e.g.*, Anderson *et al.*, 1977; Nord and Rollince, 1980), whereas findings obtained with several different labeling techniques support only an ipsilateral termination of pulp afferents of deciduous or permanent teeth (*e.g.*, Arvidsson and Gobel, 1981; Marfurt and Turner, 1984; Ishidori *et al.*, 1986; Hu *et al.*, 1987; Johnson *et al.*, 1987). Future anatomical studies need to consider the possibility that each of the different methodologies may reveal only a limited proportion of the total pulp afferent projection to the brainstem, the proportion varying with the survival time selected, the sensitivity of the method, etc.; the possibility that the contralateral (and perhaps some ipsilateral) endings reflect second- or higher-order transneuronal afferents must also be considered and controlled for in future studies.

Although the areas of terminations of pulp afferents vary somewhat depending on the particular anatomical technique used, the areas of concentration of the ipsilateral terminals of pulp afferents in the V brainstem complex correspond in general with the distribution of neurones that can be excited by electrical stimulation of the pulp of permanent or deciduous teeth in electrophysiological experiments (*e.g.*, Nord, 1976; Sessle and Greenwood, 1976; Hu *et al.*, 1981; Azerad *et al.*, 1982; Yokota and Nishikawa, 1982; Dostrovsky, 1984; Hayashi *et al.*, 1984; Hu *et al.*, 1987). Many of the findings of the neuronal properties, as well as the existing gaps in knowledge, that are outlined above for V nociceptive neurones apply also to these pulp-activated neurones. While such features do not warrant reiteration here, the distribution of these neurones requires some further consideration. In view of the integral role that subnucleus caudalis plays in V nociceptive mechanisms, it is not unexpected to note that in the electrophysiological studies referred to above, many neurones have been found in caudalis that can be excited by tooth pulp stimulation; pulp-evoked responses have also been reported in the interstitial islands of cells lateral to caudalis (Dawson *et al.*, 1980). An apparent paradox stemming from these studies is the existence of numerous LTM neurones in rostral regions of the complex that also can be excited by electrical stimulation of the pulp. Their presence in these rostral components (areas of the main sensory nucleus, subnucleus oralis, and subnucleus interpolaris) is consistent with the pulp afferent endings in these areas demonstrated in the anatomical studies indicated above.

Such findings have been viewed by some as supporting the concept that the rostral regions are directly involved in orofacial nociception, whereas others suggest an involvement in

"pre-pain" dental sensations (see above). But the exact functional significance of these rostral responses still needs to be ascertained. Are they directly, or indirectly, implicated in tooth pulp pain or its control? Or, do they merely represent a response to an electrical stimulus that is not normally apparent in the presence of natural pulp stimuli? Hu and Sessle (1984) tested oralis and caudalis neurones, under comparable experimental conditions in the cat, for their responsiveness to thermal as well as electrical stimulation of the pulp. In this acute preparation, they noted consistent and reproducible responses to both electrical and thermal (especially heat) stimulation only in caudalis, and only in WDR and NS (*i.e.*, nociceptive) neurones. Whereas studies of effects of caudal or rostral V brainstem lesions favor a role for the rostral regions in tooth pulp (and facial) pain (*e.g.*, Young and Perryman, 1984; Broton and Rosenfeld, 1985, 1986; Pickoff-Matuk *et al.*, 1986), these observations of oralis and caudalis neurones argue in favor of subnucleus caudalis having a particularly important role in tooth pulp pain, in keeping with its demonstrated role in facial nociception (see above). Hu and Sessle raised the possibility that the responses they documented that could be evoked in oralis LTM neurones by electrical but not by natural stimulation of pulp afferents might reflect inputs analogous to 'long-range' afferents that only become effective in pathophysiological situations. Campbell *et al.* (1985) have recently reported that oralis neurones in cats with minimal surgical preparation can be activated by thermal (especially cooling) as well as by electrical pulp stimulation; they suggested that trauma associated with the surgical and anaesthetic preparation of the animal may depress neuronal responsiveness to pulp stimuli and thereby account for the lack of oralis responses noted in the acute preparation. While it is conceivable that trauma may activate some central inhibitory mechanism, perhaps akin to DNIC, it is difficult to understand why it should be selective for oralis neurones, given the powerful suppression that occurs in oralis as well as caudalis with DNIC or descending central influences from NRM, PAG, somatosensory cerebral cortex, etc. (see above). Further studies using natural pulp stimuli in different types of experimental preparations are obviously called for to clarify this matter, and to determine the relative importance of caudal and rostral V brainstem neurones in pulp pain.

Thalamocortical mechanisms. — At the higher CNS levels, numerous studies have recorded pulp-evoked neuronal activity in many sites, but again only electrical stimulation has been utilized. Consequently, questions and points of clarification similar to those just mentioned apply to these responses as well. Evoked responses have been recorded in the VB and PO thalamus, hypothalamus, and midline nuclei of the thalamus (*e.g.*, Mitchell, 1970; Woda *et al.*, 1975; Shigenaga and Inoki, 1976; Pearl and Anderson, 1980) and in the specific somatosensory cerebral cortex and adjacent association or orbital cortex (*e.g.*, see Mitchell, 1970; Lund and Sessle, 1974; Biedenbach *et al.*, 1979; Roos *et al.*, 1982; Dong and Chudler, 1984; Iwata *et al.*, 1986); responses evoked from human scalp recordings also probably represent mainly thalamocortical activity (*e.g.*, Chapman *et al.*, 1979; Fernandes de Lima *et al.*, 1982). In most of these studies, the responses and modulatory effects tested upon them have been related to mechanisms of pain and its control. However, as indicated earlier, this association can only be presumed; indeed, recent studies of cortical-evoked potentials (*e.g.*, Dong and Chudler, 1984) suggest that these potentials may involve projections of non-nociceptive pulp afferents that do not evoke aversive behavior. Obviously, more definitive methodology is required to show unequivocally the relationship of pulp-evoked CNS activity to pain.

Reflex and behavioral responses and modulation. — Reference has been made above to the frequent use of the tooth pulp for evoking reflex and behavioral responses and for studies of modulatory mechanisms on these responses and pulp-evoked CNS responses. Again, the rationale behind most of these studies has been the assumption that the pulp is a "pure" source of nociceptive input. It would be repetitious to consider the significance of the reflex and behavioral responses to pain mechanisms and the processes involved in sensory and intrinsic modulation. Nonetheless, brief mention should be made here of the need to utilize natural pulp stimuli in such future approaches, *e.g.*, using thermal (Hu and Sessle, 1984; Campbell *et al.*, 1985) or algesic chemical (Foong *et al.*, 1982) stimuli. Reflex and behavioral studies in anesthetized or unanesthetized animals or humans could also be directed at the relative importance of various CNS sites (*e.g.*, subnuclei caudalis *vs.* oralis; somatosensory cortex *vs.* sub-cortical areas) in tooth pulp nociception, at the possible role(s) of pulp afferents in functions other than nociception, at the role of learning and operant conditioning in dental pain phenomena, and at clarification of the central mechanisms underlying therapeutic or endogenous control of dental pain.

Final comment.

The foregoing descriptions relate primarily to neurobiological studies that have used methodologies appropriate to investigate mechanisms of *acute* orofacial pain. Some of these same mechanisms undoubtedly are involved in *chronic* pain, but the pathophysiological bases of V neuralgia, atypical facial pain, TMJ/myofascial pain dysfunction, burning mouth syndrome, and most other chronic pain conditions manifested in the orofacial region are still largely hypothetical. While there have been some advances in our understanding of the factors involved in some of these conditions and their control (*e.g.*, Dubner *et al.*, 1978; Zarb and Carlsson, 1979; Laskin *et al.*, 1982; From *et al.*, 1984; Grushka and Sessle, 1987), the hypotheses that existed over a decade ago have undergone remarkably little modification despite the considerable research focus on mechanisms of pain and its control during this period. Because most of this focus has been directed at "acute" pain mechanisms, the knowledge gained can only be indirectly applied to an explanation of the processes underlying the chronic pain state. Although a detailed outline of these conditions and their possible etiological mechanisms is beyond the scope and space limitations of this review, some limited attempt has been made above to show the possible role in chronic pain of some of the neural mechanisms outlined. I hope that this has also shown the potential clinical relevance of these mechanisms to chronic orofacial pain as well as underscoring the crucial need to expand our current neurobiological research approaches to considerations of mechanisms underlying chronic pain. Important relevant information could be gained by several approaches: (a) defining more clearly the reflex and central consequences of electrical and especially natural stimulation of afferents supplying TMJ, muscles, and teeth as well as facial skin; (b) exploring the long-term effects of such stimuli and of sensory alterations on nociceptive transmission and neuromuscular functions; (c) obtaining more basic information on the role of brain centers involved in the affective aspects of pain and behavior (stress, emotion, etc.) and in their descending influences on nociceptive transmission and neuromuscular functions; (d) clarifying, within this milieu of reflex and CNS controls, the consequences of experimentally induced regional pathology or pathophysiological changes (*e.g.*, to TMJ, muscles, or dentition); (e) determining whether and how the autonomic nervous system may be involved in modulating these

effects; and (f) placing a greater emphasis on the development of experimental animal models for clarifying neural mechanisms underlying chronic pain.

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