The Remarkable Vestibuloocular Reflex

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lowed production of antibodies against each protease and the inhibitor. The antibodies will be increasingly useful for both biochemical and cellular studies.

Several emerging methodologies in cellular and molecular biology should prove particularly useful in understanding the CDP system. For example, cell microinjection techniques should allow alteration of the level of any one of the system's components and the ability to assess the effect of each on cell function. This technique may also be used to introduce specific, inactivating antibodies into cells. Such techniques, when combined with appropriate physiological studies, hold considerable promise for distinguishing the specific roles of CDP activity and the mechanisms of cellular regulation. These studies will also be aided by the increasing understanding of how calcium is regulated in intact cells.

In related approaches, elucidation of the exact catalytic specificities of the proteases should lead to the design of specific inhibitors for use in intact cells. Recombinant DNA techniques have already provided sequence information about CDP subunits and will eventually provide the exact definition of the relationships among the components of the system. The successful cloning and sequencing of the cDNAs for these proteins will also permit experiments utilizing site-directed mutagenesis, altering any desired amino acid of the protein product to define in greater detail structure-function relationships of the catalytic and regulatory properties of the enzymes.

This molecular genetic approach can also provide a foundation for additional experiments designed to identify the function of this proteolytic system by use of specific antisense RNA, which forms a molecular hybrid with complementary messenger RNA and prevents its being read by the protein-synthesizing machinery, thus selectively inhibiting the translation of a given protein.

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The Remarkable Vestibuloocular Reflex

G. Melvill Jones

The amazing ability of the eye to remain fixed on a target during rapid movements of the head depends on the familiar automatic control mechanism known as the vestibuloocular reflex. This article presents new information about this reflex in the control of eye movement and the stabilization of eye position. The reflex is found to be highly adaptive, including the curious recent finding that imaginary visual information can initiate plastic changes.

In the past, the vestibuloocular reflex (commonly termed the VOR) has been envisaged as a discrete, basically disynaptic reflex arc, epitomising the concept of a stereotyped, short-latency (10–12 ms) sensorymotor response pathway through the brain stem. It served to produce automatic stabilization of the eyes relative to space during head movement, independently of other brain stem mechanisms and irrespective of behavioural context. However, a surge of recent research has substantially changed the picture (reviewed in Refs. 1, 7, 9).

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This article briefly reviews four significant areas in which there have been major recent advances: visual-vestibular interactions, head-eye coordination, adaptive plasticity in vestibuloocular function, and the influence of behavioural context on reflex performance.

Visual-vestibular interactions

Until recently there has been a tendency to study visual and vestibular influences on the oculomotor system independently of one another. However, in many natural conditions, as when the head turns relative to an illuminated scene, these two sensory systems are stimulated simultaneously and thus concurrently feed the central nervous

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system with two different kinds of sensory information about the same physical event, namely head rotation relative to space. It was therefore entirely appropriate to find that in these circumstances the separate visual and vestibular sensory messages about head rotation converge onto common central neurons, first noted in the vestibular nuclei of the brain stem (e.g., Ref. 8).

Figure 1 outlines some general features of this close central integration between the two sensory inputs. The semicircular canals of the vestibular end organ discharge a primary afferent neural response into the vestibular nuclei of the brain stem, which forward their output via a central neural integrator (not shown, but see Refs. 7 and 9) to the nuclei of the oculomotor system for the generation of the compensatory eye movement.

For brief head movements the vestibular response is keyed to the instantaneous speed of head rotation. However, with more prolonged rotations the initial canal's response decays exponentially with a time constant of ~10 s in humans (see "vestibular processing" in Fig. 1). The exponential form of this decay implies as much as 30% attenuation of the peripheral signal after a mere 3 s of continuous turning at constant speed.

How does the central nervous system cope with this apparent deficiency of vestibular sensory transduction? One answer seems to be that, given clear vision of the stationary world, its (i.e., the world's) relative rotation generates a velocity-dependent optokinetic response that is fed into the central nervous system, via the accessory optic system, to find its way onto neurons in the vestibular nuclei that receive the primary vestibular input. Note that for compatibility with the vestibular signal registering head rotation relative to space, the optokinetic signal should also reflect head rotation. One proposal suggests that this is achieved by summation of retinal afferent signals depicting eye movement relative to space with an efferent copy (known to exist) of eye movement relative to the head, as indicated in the diagram.

It was puzzling at first to learn that when studied alone (i.e., by turning the seen world at a steady velocity around the stationary animal) this optokinetic signal in the vestibular nuclei began at a low level and then exponentially increased its intensity toward a plateau level, rising with a similar time constant to that of the previously mentioned decaying vestibular signal (see "optokinetic processing" in Fig. 1). But this is in fact exactly what would be required to generate an internal neural signal that is independent of transduction inadequacies in the two peripheral systems.

As implied at Fig. 1 inset, given this form of visual-vestibular interaction, a stepwise stimulus of head angular velocity, relative to a stationary visual scene, would yield a correspondingly shaped central response derived from algebraic summation of the separate vestibular and optokinetic signals in the vestibular nuclei. This would be exactly what is wanted for generating appropriate compensatory eye movements during the turn, independently of its duration or the frequency content of the stimulus, and also for generating

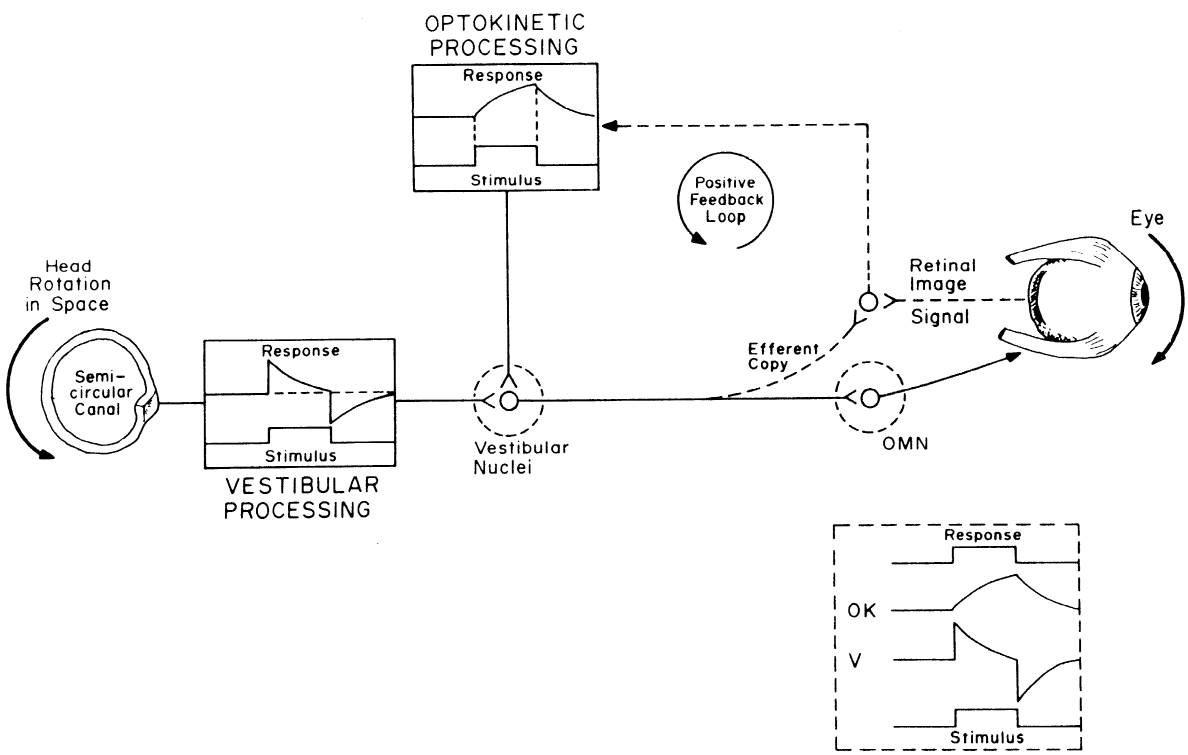

FIGURE 1. Schematic representation of vestibular (V) and optokinetic (OK) interactions during head rotation in light. Note how *curves* shown in boxes labeled "vestibular processing" and "optokinetic processing" represent inverse transfer functions. When acting together (*lower right-hand corner*) they yield an emergent central response that represents behavioural (stimulus) event better than either of peripheral inputs. OMN, nucleus of oculomotor system. (Adapted from Wilson and Melvill Jones (9).)

a reliable cognitive response of perceived head rotation relative to space.

Furthermore, the inverse dynamics of the two inputs would serve to cancel the otherwise inevitable postrotational errors (see postrotational responses in the vestibular and optokinetic processing boxes of Fig. 1) functionally associated on the one hand with postrotational vestibular nystagmus and, on the other hand, so-called optokinetic afternystagmus (commonly termed OKAN).

It is particularly interesting that in the accessory optic system the optokinetic signal proves to be neurally coded in planes parallel to those of the three orthogonal semicircular canals, thus facilitating three-dimensional integration of visual and vestibular signals (reviewed by Simpson and Graf in Ref. 1).

An important additional feature is the implied positive feedback loop formulated in the combined network of Fig. 1. Control of synaptic efficacy (neural "gain") in such a loop offers a powerful means of manipulating both the magnitude and dynamic characteristics (e.g., time constant) governing the overall response. The concept accounts well for the otherwise surprising but advantageous phenomenon that central vestibular signals recorded in the intact, alert animal exhibit an exponential "canal" decay time constant, which may be up to three times longer than that found in the peripheral vestibular afferent pathway. In the alert animal this extended time constant is also evident in vestibular nystagmus.

In summary, the outcome of this form of central integration is the emergence of a completely new central neural message, different from either of the separate peripherally derived inputs, but much better representing the actual behavioural event than either of the primary afferent response signals. Appropriately, it is this emergent central signal that determines the relevant patterns of reflex oculomotor discharge and probably also the relevant cognitive perceptual response.

Head-eye coordination

A decade or so ago, it was generally agreed that when rapid, reorienting eye and head movements were made between two visible targets, simple summation of the saccadic oculomotor discharge and the compensatory VOR incurred by head rotation sufficed to account for all experimentally observed oculomotor phenomena. Recent work has shown that although this is true for small target separations, for larger shifts of gaze (i.e., direction of visual regard relative to space) far more complex patterns of eye-head coordination are invoked. For example, although the initial phase of head rotation usually generates a normal VOR, this may or may not summate with an ocular saccade toward the new target. Indeed, during the mid-phase of movement the VOR may become substantially suppressed, even eliminated, until gaze direction coincides with the intended target. Then, with latency too short for visual input to be a causal factor, the active VOR immediately returns in full force (i.e., with unity gain) to retain the eye on target during the remaining head movement (reviewed in Ref. 2).

What kind of mechanism could account for these elaborate and variable patterns of head-eye coordination? A currently favoured hypothesis proposes that the relevant neural control network resolves into a "gaze control system." A neural correlate of desired gaze direction feeds into a combined saccade-VOR complex, the output of which feeds back a neural correlate of actual gaze direction for comparison with the desired input.

This feedback signal can even be formulated in the absence of vision (as when trying to "look" at a remembered target in the dark), presumably by summation of a vestibular statement of head movement-re-space and an internal statement (probably an "efference copy") of eye position-re-head [gaze angle = (eye angle-re-head) + (head angle-re-space)]. Action in the combined system (eye-plus-head movement) then runs its course until the difference signal (i.e., gaze error) is nulled out, using head movement, ocular saccades, and/or VOR according to need, but not necessarily in a stereotyped fashion.

Adaptive plasticity

Behavioural studies. The intimate interaction of allied mechanisms implied in the previous two sections emphasizes the need for the constant tuning of internal controlling neural parameters such as synaptic efficacy. This would seem necessary to cope with ever-changing conditions incurred, for example, by developmental growth, hormonal and diurnal body cycles, pathological effects of disease, and cell loss due to aging.

It was recently argued that if such adjustment is constantly active in maintaining the normal tuning of reflex responses (i.e., a form of neurological homeostasis) then surely adaptive retuning should occur to meet novel behavioural demands. A common approach has been to call for an altered oculomotor response to a given vestibular stimulus by optical means, i.e., vision reversal with dove prism goggles, magnification of the visual scene by means of binocular goggles, and even a call for horizontal eye movement during vertical rotation of the head in its sagittal plane.

Experimental results have uniformly validated this hypothesis (1, 9). For example, "permanent" reversing optics first attenuates the dark-tested VOR and then, after wk of free movement with continuous left-right reversal of vision, yields a reversed form of vestibular nystagmus. Magnifying lenses gradually augment the reflex, whereas reducing lenses slowly diminish it. Furthermore, prolonged horizontal optokinetic stimulation during vertical (sagittal) head rotation does eventually produce a dark-tested horizontal component of reflex ocular response during vertical head rotation, even though this form of head movement stimulates primarily the vertical rather than horizontal semicircular canals.

The generalized nature of the phenomenon is evidenced by the fact that every reflex system thus far pressed to change its response characteristics by a suitable experimental paradigm has demonstrated these attributes of adaptive plasticity, i.e., the saccadic oculomotor system, the accommodation-vergence linkage, the eye-head coordination system, and even the monosynaptic stretch reflex of the spinal cord (1).

Central mechanisms. What kind of central learning processes are re-

sponsible for these behaviourally induced examples of plastic change in reflex function? Although the matter is still controversial, there are certain commonly agreed findings. Thus removal of the vestibular cerebellum (floccular-nodular lobes) abolishes the adaptive phenomenon, as does ablation of the inferior olive in the brain stem, particularly its dorsal cap that projects climbing fibres to cerebellar cortex. Evidently cerebellar pathways and mechanisms are intimately involved.

These and other findings have led to the hypothesis of Ito (3) outlined in Fig. 2. The VOR is diagrammed as a disynaptic reciprocal pathway connecting the semicircular canals of the vestibular sensory apparatus with the extraocular muscles of the eye (in practice, there are other multisynaptic pathways; Ref. 9). The shaded area encloses selected elements in the cerebellar floccular cortex, through which there is a proven side loop of the VOR, activated by direct vestibular inputs via mossy fibre projections. These in turn synapse with granule cells projecting their parallel fibres onto cortical Purkinje cells, which themselves project back an inhibitory influence onto vestibular nuclear cells receiving direct excitatory input from the canals. Consequently, modulating the efficacy of the cerebellar side loop could serve to modify the net vestibular output to the nuclei of the oculomotor system, even perhaps to the point of reflex reversal given the known level of spontaneous activity of these target cells in the vestibular nuclei.

But how could this cerebellar cortical learning site be taught to change its transmission characteristics appropriately? Ito's suggestion builds on the general concept of Marr's hypothesis whereby (in this case) climbing fibre projections to cerebellar cortex of the floccular lobes would serve to alter the efficacy of vestibularly activated parallel fibre synapses on the Purkinje cell dendritic tree. This in turn would alter the effectiveness of the transcerebellar side loop and thus change the balance of excitatory and inhibitory influences on the vestibular nuclei. To produce an advantageous (i.e., adaptive) change the climbing fibre input should signal the functional error of system performance, presumed to be coded in terms of retinal image slippage incurred by an inappropriate VOR. This error message would then modulate signal strength in the side loop in such a way as to null out the error and hence restore a stable retinal image during head movement.

Experimentally, retinal afferent signals, keyed to direction and velocity of image slip, were indeed found reflected in the climbing fibre input to vestibular cerebellar Purkinje cells. Moreover, more recent work from Ito's laboratory has demonstrated sustained changes of efficacy in parallel fibre synaptic influences after concurrent electrical stimulation of convergent climbing fibre and mossy fibre projections to flocculus (reviewed in Ref. 3). This and allied results certainly invoke strong physiological support for the adaptive mechanism outlined in Fig. 2.

The hypothesis is not without contestants. For example, an alternative idea has recently been suggested by Miles and Lisberger (6). Briefly, they concluded that although the vestibular cerebellum plays an essential role in the adaptive process, it does not itself provide the site of synaptic learning, at least as reflected in their experiments on alert monkeys. Instead they suggest that the predominant signal found in the floccular Purkinje cell neural discharge is one of gaze (defined as above) generated by summation at the Purkinje cell level of the vestibular signal (i.e., head-re-space) and an efferent copy

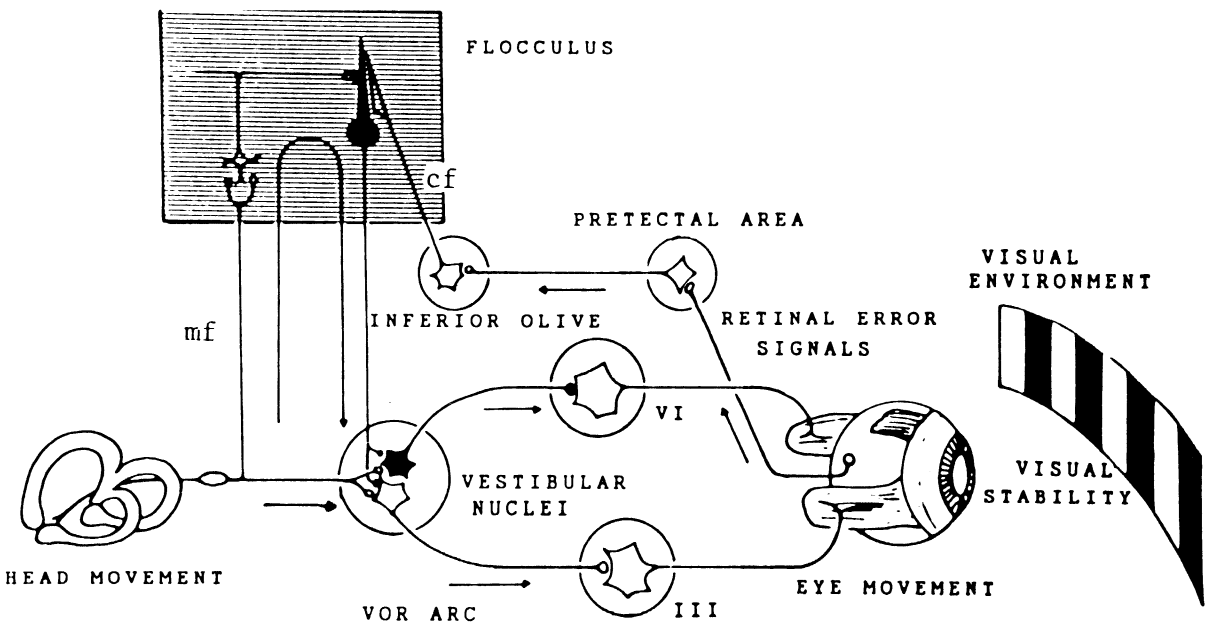

FIGURE 2. Neuronal diagram outlining Ito's hypothesis of adaptive control in the rabbit's vestibuloocular reflex (VOR). Vestibular mossy fibre (mf)-granule cell-Purkinje cell pathway through flocculus acts as a modifiable side path to VOR arc. Modification of side path is effected by retinal error signals conveyed through accessory optic tract acting via inferior olive climbing fibre (cf) pathway. Retinal error signals monitor mismatching of VOR to visual environment. (From Ito (3).)

of eye position-re-head. Consequently, any modulation of Purkinje cell discharge would reflect modulation in gaze direction relative to space and hence provide a measure of gaze destabilization, i.e., an alternative measure of error in desired oculomotor performance. They proposed that it is this error signal (rather than one of retinal image slippage) that acts through Purkinje cell projections on an unidentified learning site located somewhere upstream in the VOR pathway but notably not in cerebellar cortex. Interestingly, Galiana (reviewed in Ref. 1) has recently pointed to modifiable synaptic relays in closed-loop commissural pathways connecting the two vestibular nuclei as a powerful putative site for such an action.

Behavioural context and cognitive control

Volitional control over the VOR. The neurological mechanisms outlined above represent subcortical machinelike processes, responding automatically to the call of new behavioural demands by means of central plastic changes. However, it transpires that over and above these long-term autoadaptive phenomena the human subject can exercise a remarkable degree of immediate volitional control over the VOR, according to the intentionally chosen behavioural goal (7). Thus, if one is turned in the dark while trying to look at a remembered earth-fixed target, compensatory eye movement relative to the head is usually almost equal and opposite to movement of the head relative to space. On the contrary, if the intention is to fixate a remembered target, which is attached to (and hence moves with) the head, then the VOR can be largely suppressed despite the absence of vision.

Although the behaviourally defined cognitive control over subcortical reflexes is now well established, much less is known about central mechanisms than about those responsible for adaptive plasticity. Nevertheless some indexes are beginning to emerge. Thus very recent work points toward voluntary control of efficacy in critical neural relay stations in the brain stem reflex pathway (4), rather than the putative exercise of an opposing "visual pursuit" signal.

Interaction of cognitive and adaptive control. The ability to exercise purely volitional control over VOR output permitted an investigation of whether sensory-motor rearrangement in the absence of vision might of itself suffice to activate adaptive plasticity in the reflex. An affirmative answer would argue against the necessity for a real peripheral visual error signal of the kind implied in Fig. 2. After this lead a recent study did indeed produce lasting adaptive changes after a mere 3 h of voluntary VOR suppression in the dark (5). A thought-provoking corollary was a correspondingly altered conscious percept of self-rotation (reviewed in Ref. 1). Apparently simply thinking about a particular behavioural context during rotation in the dark was sufficient to produce lasting alteration of the subject's perceptual interpretation of the causal physical event!

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Paradigms and Concepts in Thermal Regulation of Homeotherms

Eckhart Simon

This article challenges the belief in a central role for the hypothalamus in temperature regulation. This concept arose from classical experiments that pointed to the hypothalamus as a central regulator where deep body temperature is monitored, integrating incoming signals and controlling effectors such as shivering, sweating, and panting. More recent experimental evidence requires a much broader view of the integrated neural control system for temperature regulation in homeotherms.

Body temperature in homeotherms is maintained by a control system that is typical for autonomic control in general. Thermal imbalance induces changes in generation and dissipation of heat according to the principle of negative feedback. At each stage of the control loop multiple components are involved (9). Ef-

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