New Zealand Journal of Psychology, 1991, 20, 25–32

Behavioural Recovery from Peripheral Vestibular Lesions as a Model of Recovery from Brain Damage*

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Physiological psychologists and neurobiologists are interested in animal models of central nervous system (CNS) plasticity as a means of studying the mechanisms of behavioural change. This paper describes an animal model of lesion-induced CNS plasticity, known as vestibular compensation, which results from the destruction of the vestibular receptor cells in the inner ear. Unilateral inner ear lesions of this sort cause dramatic eye movement and postural deficits in humans and other animals, many of which disappear within 2-3 days due to some form of CNS plasticity. The advantages of the vestibular compensation model in relation to other models of CNS lesion-induced plasticity are discussed.

Plasticity is the term used to describe the ability of the central nervous system (CNS) to modify its function in response to changes in environmental stimuli or in response to changes in its own structure (see Kandel, 1985 for a review). In adults of most species, CNS neurons are constantly dying but are not replaced, i.e., the structure of the CNS is continuously changing. These normal structural changes require the continuous modification of CNS function in order to maintain the normal function of the organism as a whole. When damage to the CNS occurs, for example, as a result of trauma or stroke, the system has a remarkable capacity for functional recovery due to its inherent plasticity, provided that the damage is not to a vital area, e.g., respiratory or cardiac control centres. The recovery process following damage is known as 'lesion-induced plasticity'.

The mechanisms which underlie lesion-induced plasticity in the CNS are not well understood. In order to study these mechanisms systematically, experimental animal models are required which allow precise quantification of both the *stimulus* for the plasticity and the *response* to that stimulus, at behavioural, neurophysiological, neuroanatomical or neurochemical levels. In the case of brain damage, establishing models which fulfil these criteria can be difficult.

*The preparation of this review was supported by a grant from the Health Research Council of New Zealand.
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When a lesion in the CNS occurs, two distinct types of deficits may result (Fig. 1) (see Steward, 1982 for a review). First, deficits may be produced by the loss of neurons at the site of the lesion. The type of behavioural deficit which results from this neuronal loss will directly reflect the function of the lesioned area, e.g., a lesion in the occipital lobe may result in a "blind spot" in the visual field associated with that particular part of the visual cortex (see Kelly, 1985 for a review). Second, behavioural deficits may be produced by the deafferentation of groups of neurons remote from the site of the lesion. These deficits are due to the loss of afferent input from the lesioned neurons or the disruption of fibre tracts running through the lesioned area. For example, lesions in the region of the lateral ventricle may also result in visual deficits by disrupting the fibres of the optic radiation projecting to the visual cortex. In many cases, deafferentation results in a loss of ongoing neural activity, so called spontaneous activity, of neurons in the deafferented area. Behavioural recovery is often associated with the return of spontaneous activity to the deafferented neurons. In many cases, a CNS lesion will produce behavioural deficits resulting from both the 'local' and 'remote' effects of

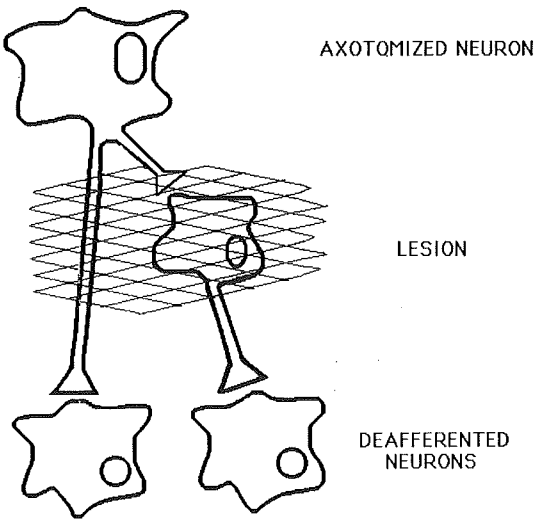

Fig. 1. Schematic representation of the types of damage produced by lesions of the CNS. Shaded area represents lesion.

cell loss. It is the 'remote' effects of lesions caused by deafferentation of CNS nuclei which are the focus of this paper.

In order to study the recovery of neural activity following deafferentation it is desirable to restrict the lesion to a particular fibre tract leading to a well defined area of the CNS. With most CNS lesions, this is almost impossible to achieve. An alternative is to interrupt the transmission of information along a fibre tract before it enters the CNS, e.g., transect a sensory cranial nerve or remove the receptor cells with which it synapses. This method allows the removal of the specific input being studied, without interference with other areas of the CNS. The eighth cranial nerve (VIIIth nerve), the vestibulo-cochlear nerve, is ideal for this purpose.

The VIIIth nerve carries signals from the auditory and vestibular receptors in the inner ear to their corresponding nuclei in the brainstem, the cochlear and vestibular nuclei, respectively. Removal of the vestibular receptors in one inner ear, unilateral labyrinthectomy (UL), or transection of the VIIIth nerve, removes normal sensory input (ie., deafferents) to the ipsilateral vestibular nuclei (VN). The result is a severe syndrome of ocularmotor and postural symptoms which interferes with even the most elementary behaviours. Within a few days, however, many of these symptoms disappear (see Precht & Dieringer, 1985; Schaefer & Meyer, 1974; Smith & Curthoys, 1989 for reviews) in a process of behavioural recovery known as vestibular compensation. This recovery, which is quite rapid compared to behavioural recovery following other types of CNS lesions (e.g., diencephalic hemisection, 24 days (Benelli, Zanoli, Botticelli, & Bertolini, 1988); nucleus accumbens lesions, 3 to 4 weeks (Wolterink, Van Zanten, Kamsteeg, Radhakishun, & Van Ree, 1990)) is not due to regeneration of the vestibular receptors or to recovery of activity in the VIIIth nerve (Jensen, 1983; Sirkin, Precht, & Courjon, 1984; Smith & Curthoys, 1988) and is, therefore, due to CNS plasticity (Precht, 1974; Schaefer & Meyer, 1974).

HISTORY OF THE VESTIBULAR COMPENSATION MODEL

The effects of UL were first investigated experimentally in 1824 by Flourens. Immediately following unilateral damage to the vestibular receptors in pigeons, Flourens observed that the animals exhibited repetitive reflexive eye movements (spontaneous nystagmus) and horizontal head movements (head nystagmus), as well as ataxia. These abnormal behaviours were not permanent, however, but disappeared over a period of days in a process later referred to as *vestibular compensation* (Flourens, 1824, cited in Schaefer and Meyer, 1974). These early observations have since been confirmed in every species studied, from tadpole to human (Rayer & Horn, 1986; Fisch, 1973), although the specific symptoms and the rate of compensation vary between species.

In mammalian species, the symptoms of UL can be divided into two categories based on their relationship to head movement: *static symptoms,* which persist when the head is stationary (see Curthoys, Smith, & Darlington, 1988 for a review), and include spontaneous nystagmus and postural asymmetries (tilting of the head about the vertical *and* horizontal axes); and *dynamic symptoms,* which occur as a result of head movement (Fisch, 1973; see Smith & Curthoys, 1989 for a review) and include deficits in the amplitude and timing of vestibulo-ocular and vestibulo-spinal reflexes. In most mammalian species, the static symptoms compensate almost completely within 2-3 days following UL, whereas the dynamic symptoms compensate more slowly, if at all. Of the static symptoms, the compensation of spon-

taneous nystagmus is the most similar within and between mammalian species. Spontaneous nystagmus is also the easiest behavioural symptom to measure. Since the quick phase of the nystagmus is easy to observe even in albino animals, it is a relatively simple matter to count visually the number of these eye movements per interval of time (Jensen, 1979; Schaefer & Meyer, 1974; Smith, Darlington, & Curthoys, 1986). The measurement of spontaneous nystagmus provides a direct behavioural index of the CNS plasticity responsible for vestibular compensation.

THE STIMULUS FOR VESTIBULAR COMPENSATION

The stimulus for vestibular compensation is the loss of VIIIth nerve input to the brainstem VN. There are two ways this can be achieved, either by UL or surgical transection of the VIIIth nerve. The UL procedure has usually been done surgically, by opening the temporal bone using a dental drill and removing the receptors within the vestibular labyrinth of the inner ear (Cawthorne, 1943; Schuknecht, 1973). This technique has the advantage that the extent of the lesion can be determined visually, at the time it is made, using an operating microscope. Histological evidence shows that the vestibular receptors do not regenerate following this procedure (Fermin & Igarashi, 1984; Igarashi, Watanabe, & Maxian, 1970; Schuknecht, 1982) and electrophysiological evidence indicates that the primary afferent neurons in the VIIIth nerve do not regain their normal resting activity (Sirkin et al., 1984; Smith & Curthoys, 1988). Surgical UL therefore results in a permanent loss of input from the vestibular receptors which can be demonstrated and quantified empirically.

Another type of UL sometimes used is a chemical labyrinthectomy. Using this procedure, a mixture of chloroform and mineral oil is injected into the middle ear (e.g., Azzena, 1969). From the middle ear, the chloroform seeps into the inner ear where it is assumed to destroy the vestibular hair cells. Due to the anatomical complexity of the inner ear it is difficult to be certain that the chloroform reaches and destroys all of the vestibular receptors. Some studies suggest that the chemical UL method may result in incomplete lesions (Jensen, 1979).

A more direct method of removing input from the inner ear is to transect the vestibular nerve before it enters the brainstem (Fisch, 1973b). This is a more difficult technique and requires an intracranial approach, with the associated risk of injury to the cerebellum and/or brainstem.

EVIDENCE FOR CNS PLASTICITY

Under normal circumstances the vestibular system maintains tonic posture and eye position when the head is stationary (static control) and initiates ocularmotor and spinal reflexes which stabilize the position of the eyes and body during head movement (dynamic control) (see Wilson & Melvill Jones, 1979 for a review). For each of these types of ocularmotor and postural control, the VN is the critical CNS site which integrates input from the inner ear (via the VIIIth nerve) and relays this integrated information to the motorneurons innervating the various muscle groups responsible for eye and body movement. Consequently, the search for the CNS site responsible for vestibular compensation has concentrated, primarily, on the VN ipsilateral to the UL, i.e., the deafferented VN.

The first single neuron recordings from the VN of compensated animals were reported by Precht, Shimazu and Markham in 1966. Recording in the cat, these investigators found that although VN neurons ipsilateral to the UL were virtually silent immediately after the UL, 4-6 weeks later, when vestibular compensation of the static symptoms was complete, resting activity in these neurons had regenerated. The regeneration of activity occurred despite the complete absence of input from the ipsilateral ear. Since 1966 this result has been replicated in several different species and it is generally accepted that the regeneration of resting activity in the ipsilateral VN is at least partially responsible for the compensation of the static symptoms of UL. Recently it has been shown that this regeneration of neural activity can occur within 52 hours in species such as guinea pig in which compensation of the static symptoms also occurs during this time (De Waele, Serafin, Muhlethaler, & Vidal, 1988; Smith & Curthoys, 1988).

Despite numerous studies, the mechanism of the rapid regeneration of resting activity in the VN is unknown. A similar recovery of resting activity following denervation has been documented in other areas of the CNS, such as the

lateral cuneate nucleus (Kjerulf & Loeser, 1973), the trigeminal nucleus (Anderson, Black, Abraham, & Ward, 1971), the dorsal horn of the spinal cord (Loeser & Ward, 1967) and the hippocampus (Reeves & Steward, 1988), suggesting that the mechanism responsible for vestibular compensation may be related to lesion-induced plasticity in other parts of the CNS (see Smith & Curthoys, 1989 for a review).

ADVANTAGES OF THE VESTIBULAR COMPENSATION MODEL

In any animal model of lesion-induced plasticity, it is important that both the stimulus for plasticity and the response to the stimulus be quantifiable. In the case of vestibular compensation, the stimulus is an isolated lesion in the peripheral nervous system which deafferents a known region of the CNS without interfering with tissue surrounding that region, or disrupting fibres of passage. The lesion is both histologically and physiologically verifiable.

The response to the stimulus for plasticity can be quantified on a behavioural level as well as by using neurophysiological, neuropharmacological and biochemical techniques. Symptoms such as spontaneous nystagmus produce a direct behavioural measure of the plasticity induced by UL; the rate of the decrease in frequency of nystagmus (Fig. 2A) is tightly correlated with the physiological change occurring in the VN (Fig. 2B) (Smith & Curthoys, 1988). The time course and pattern of the compensation of spontaneous nystagmus within species has also been shown to be highly consistent, so that deviations from the expected pattern, for example as the result of drug treatment, are easily discernable. The deafferented VN is easily identified, facilitating electrophysiological, biochemical or histo-logical analysis.

UL also has the advantage of being a relatively 'natural' stimulus for lesion-induced plasticity. Vestibular receptor loss can occur in humans as a result of accident or ingestion of ototoxic drugs (e.g., aminoglycoside antibiotics (Kimura, Iversen, & Southard, 1988). The UL operation is performed on human patients in order to alleviate the symptoms of disorders such as Meniere's disease or to remove VIIIth nerve tumours (Schuknecht, 1973). Clinical studies of human patients who have received UL or transsection of the vestibular nerve (Schuknecht, 1973; Dai, Curthoys, & Halmagyi, 1989; Halmagyi et al. 1990) complement the information gained from experimental studies.

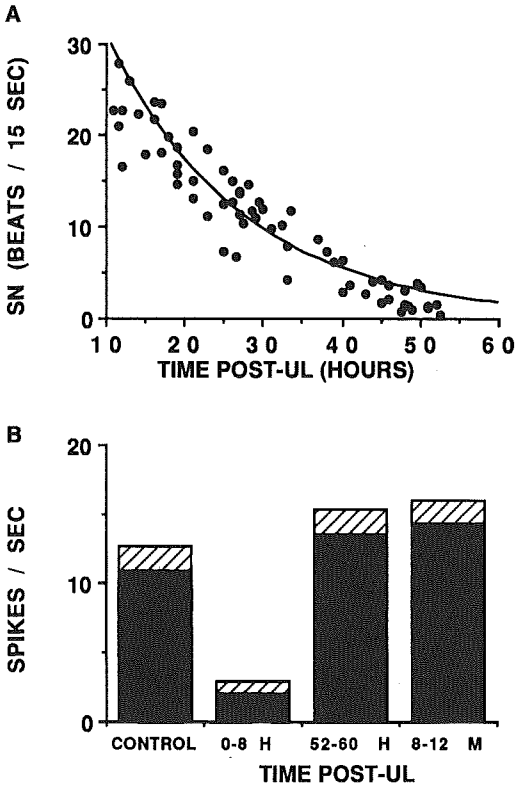

Fig. 2. (a) Time course of compensation of spontaneous nystagmus (SN) (in beats per 15 sec interval) in the guinea pig. The dots represent mean nystagmus for a group of animals (n = 8) during the post-UL recovery period. Modified from Smith and Darlington (1988). (B) Recovery of resting activity (in spikes per sec) in single medial vestibular nucleus neurons (n= 273) ipsilateral to the UL at specific times post-UL. Solid bars represent mean resting activity, hatched areas represent standard error of the mean. Modified from Smith and Curthoys (1988).

MECHANISMS OF COMPENSATION AND ITS RELATIONSHIP TO OTHER FORMS OF CNS PLASTICITY

The mechanism of the regeneration of VN resting activity which is responsible for vestibular compensation is not known. One line of research has focused on the possible involvement of neuropeptide hormones, especially those related to the stress-related hormone, adrenocorticotrophic hormone (ACTH). It has been demonstrated that removal of the pituitary gland in frog, which results in almost total loss of ACTH, retards vestibular compensation, but the administration of ACTH-(4-

10) restores the compensation process to normal (Flohr & Luneburg, 1982). In frog (Flohr, Luneburg, & Richter-Landsberg, 1985), squirrel monkey (Igarashi & Ishikawa, 1985) and guinea pig (Gilchrist, Darlington, & Smith, unpublished manuscript; Gilchrist, Smith, & Darlington, 1990) with pituitary gland intact, it has been demonstrated that administration of specific fragments of the ACTH molecule, for example ACTH-(4-10), may shorten the time required for vestibular compensation to occur. Recent evidence suggests that ACTH-(4-10) may act directly on the vestibular nuclei (Darlington, Smith, & Hubbard, 1990). Administration of an altered form of ACTH-(4-10), (D-Phe^7) ACTH-(4-10), which acts as an ACTH-(4-10) antagonist, retards compensation (Flohr et al., 1985; Gilchrist et al., unpublished manuscript). In other models of CNS lesion-induced plasticity, for example, dopaminergic depletion of the nucleus accumbens (Wolterink et al., 1990), diencephalic hemisection (Benelli et al., 1988) and hippocampal lesions (Hannigan & Isaacson, 1985), neuropeptides related to ACTH have also been effective in accelerating behavioural recovery. In the peripheral nervous system, ACTH related neuropeptides have been shown to enhance recovery from experimentally induced lesions (see Strand, Rose, King, Segarra, & Zuccarelli, 1990 for a review) and to improve recovery from chemotherapy-induced neuropathies in women undergoing cisplatin therapy for cervical cancer (Gispen, 1990).

The role of excitatory amino acids (EAA) has also been studied in vestibular compensation and recent evidence suggests that there may be links between many different models of CNS plasticity at the level of EAA neurotransmitter receptors. Drugs which block the EAA receptor type known as the N-methyl-D-aspartate (NMDA) receptor have been shown to disrupt vestibular compensation (Darlington & Smith, 1989; De Waele, Vibert, Baudrimont, & Vidal, 1990; Sansom, Darlington, & Smith, 1990; Smith & Darlington, 1988), long-term potentiation (Collingridge, Kehl, & McClennan, 1983; see Abraham, 1988 for a review) and kindling (Holmes, Bilkey, Laverty, & Goddard, 1990; Vezzani, Wu, Moneta, & Samanin, 1988) as well as experience dependent plasticity in the visual cortex (Kleinschmidt, Bear, & Singer, 1987), plasticity in the olfactory bulb (Lincoln, Coopersmith, Harris, Cotman, & Leon, 1988) and spatial learning (Abraham, 1988; Morris, Anderson, Lynch, & Baudry, 1986; Tan, Kirk, Abraham, & McNaughton, 1989; Ward, Mason, & Abraham, 1990).

Recent research has concentrated on biochemical events associated with the compensation process, specifically the modification of existing protein within CNS neurons (phosphorylation) and the manufacture of new protein (protein synthesis). Most activities of neurons are dependent to some extent upon the phosphorylation of proteins within the cell, e.g., the synthesis and release of neurotransmitter, the regulation of synapses and ion channels and the growth of axons (see Nestler & Greengard, 1989 for a review). Because of the speed with which vestibular compensation occurs in most species (2-3 days), it seems likely that phosphorylation rather than protein synthesis, is responsible for the rapid neuronal plasticity which causes the behavioural recovery.

The steps leading to protein phosphorylation are usually triggered by the binding of a first messenger, e.g., a neurotransmitter, to a receptor on the neuronal membrane. The binding of the first messenger activates a second messenger inside the cell, e.g., cyclic adenosine-3',5'-monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) or calcium, which in turn activates an enzyme, a protein kinase. The activation of the protein kinase moves a phosphate group onto a target protein. The addition of the phosphate group changes the structure of the protein which accomplishes some specific task, e.g., changing the configuration of an ion channel or altering a synapse. It is possible to identify different phosphorylated proteins by their weight (expressed in kilodaltons, kD) and so identify the particular proteins being phosphorylated under different conditions.

Flohr et al., 1985 studied the changes in the pattern of whole brain phosphorylation which occur during vestibular compensation in the frog. Although there are many phosphoproteins affected by the compensation process, two particularly distinct changes in phosphorylation were observed at 1-3 days, and 7-14 days post-UL. At 1-3 days post-UL, there was an increase in a 21kD phosphoprotein which was independent of cAMP and cGMP but modulated by calcium (Flohr et al., 1985), calmodulin (a calcium dependent second mes-

senger) (Janssen, Richter-Landsberg, & Flohr, 1987) and the neuropeptide hormone, ACTH-(1-24) (Flohr et al., 1985). At 7-14 days, an increase in a 48kD phosphoprotein was observed which was modulated by the calcium-dependent protein kinase, protein kinase C (Janssen et al., 1989). These results suggest that the compensation process, at least in the frog, is dependent upon intracellular calcium. Preliminary results from our laboratory suggest this may also be the case in mammals: intraventricular injections of a calcium/calmodulin antagonist (calmidazolium chloride) during the first 6 hours after the UL drastically reduce the observed spontaneous nystagmus in guinea pigs (Darlington, Sansom, Keenan, Smith, & Gilchrist, unpublished data).

There is also increasing evidence to support the idea that VN neurons are capable of pacemaker-like electrical activity, and that this behaviour may contribute to their capacity to generate electrical activity in the absence of afferent input from the VIIIth nerve. Recent in vitro studies using isolated slices of the brainstem have revealed that VN neurons can generate resting activity in the absence of their normal afferent inputs (Darlington, Smith, & Hubbard, 1989; Darlington, Smith, & Hubbard, 1990; Lewis, Phelan, Shinnick-Gallagher, & Gallagher, 1989; Serafin, Khateb, DeWaele, Vidal, & Muhlethaler, 1990; Smith, Darlington, & Hubbard, 1990; Smith, Darlington, & Hubbard, 1991). Future studies will explore the ionic basis of this in vitro activity in order to make predictions about the contributions of different ion channels to the eye movement and postural behaviour which is initiated by the VN (De Waele, Vibert, Baudrimont, & Vidal, 1990).

How these various mechanisms may contribute to the process of vestibular compensation is unknown. If phosphorylation of intracellular proteins is ultimately responsible for compensation, then neuropeptide hormones and EAAs may affect the compensation process by altering protein phosphorylation. Recent evidence suggests an interaction between the NMDA receptor and ACTH release (Iyengar et al., 1990), so it is possible that the neuropeptide hormones and EAAs might influence phosphorylation via a common mechanism, possibly the sigma receptor in the NMDA-receptor associated ion channel (Iyengar et al., 1990).

Conclusion

Vestibular compensation is a model for the study of recovery from brain damage which offers the advantages of a specific, isolated lesion and a consistent, quantifiable behavioural measure of recovery. The reproducability of the behavioural results obtained using the vestibular compensation model makes it particularly useful for testing the effects of drugs on the recovery process. The results obtained from studies of neuropeptide hormones and EAAs in vestibular compensation and other types of CNS lesion-induced plasticity suggest that similar mechanisms may be involved. It is therefore possible that results obtained using the vestibular compensation model of recovery from brain damage may be useful in the study of CNS lesion-induced plasticity generally.

The preparation of this review was supported by a grant from the Health Research Council of New Zealand.

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