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Mechanisms of recovery following unilateral labyrinthectomy: a review

Paul F. Smith and Ian S. Curthoys

Vestibular Research Laboratory, Department of Psychology, University of Sydney, 2006, NSW (Australia)

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CONTENTS

Correspondence: P.F. Smith, Department of Psychology, University of Otago, P.O. Box 56, Dunedin, New Zealand.

1. INTRODUCTION

In all classes of vertebrates, deafferentation of one labyrinth (in this review, referred to as unilateral labyrinthectomy or UL) results in a characteristic syndrome of ocular motor and postural disorders. These disorders can be divided into two categories on the basis of their relationship to head movement: *static* symptoms, such as deviation of the eyes towards the lesioned side and spontaneous nystagmus (in mammals) which persist in the absence of head movement; and *dynamic* symptoms, such as a reduced amplitude and abnormal timing of the vestibulo-ocular and vestibulo-spinal reflexes, which occur in response to head movement[50]. Over 2–3 days following UL, some of these symptoms diminish in a process of behavioral recovery known as *vestibular compensation*. Since the labyrinthine receptors do not regenerate following UL and peripheral neurons in Scarpa's ganglion do not regain their normal resting activity[84,162,164], vestibular compensation has been attributed to plasticity in the central nervous system (CNS) (see Schaefer and Meyer[153] for a review).

Although vestibular compensation has been documented for many species and single neuron recording has shown that it is associated with a recovery of neural activity in the vestibular nucleus ipsilateral to the UL, the CNS mechanism which is responsible for the fast behavioral recovery is still unknown. However it seems likely that the mechanism responsible for recovery from UL will be involved in other forms of CNS plasticity, therefore vestibular compensation may serve as a model of CNS plasticity in general and has been proposed as such[59]. Vestibular compensation is necessary for the recovery of human patients who receive a peripheral vestibular neurectomy as treatment for conditions such as Meniere's disease or acoustic neuroma, or in whom vestibular deafferentation occurs as a result of accident. Understanding the mechanisms of vestibular compensation may eventually lead to ways of accelerating the compensation process in these patients by pharmacological means and to ways of initiating the compensation process in patients who do not compensate spontaneously.

The purpose of this review is to summarise and critically evaluate the current state of knowledge of vestibular compensation. The review will be divided into the following 3 main sections:

(1) 'the uncompensated stage', which will consider the immediate behavioral and neural consequences of UL;
(2) 'the partially compensated stage', which will consider behavior and neural activity during vestibular compensation;
(3) 'mechanisms of vestibular compensation', which will discuss and evaluate the current hypotheses on the causes of compensation.

2. THE UNCOMPENSATED STAGE

In this review, the stage immediately following UL, when the ocular motor and postural symptoms are most severe, will be referred to as the 'uncompensated stage'.

2.1. *Behavior*

2.1.1. *Static symptoms.* In mammalian species, the most prominent ocular motor effect of UL is a high frequency, mainly horizontal, spontaneous nystagmus (SN), with its quick phase directed to the intact side (see Schaefer and Meyer[153] for a review). Reports from humans suggest that SN in light causes retinal slip, resulting in vertigo[15,116,117,138]. Whilst this may be the case for some reports of vertigo, such patients also report feeling vertiginous in total darkness, showing that retinal slip is not necessary for the sensation of vertigo.

In submammalian species such as the frog, SN does not occur, however the eyes undergo a tonic deviation toward the side of the lesion (see Schaefer and Meyer[153] for a review). Tonic eye deviations toward the lesioned side have also been reported in the rat[175], guinea pig[170], rabbit (De Kleyn, as cited in Schaefer and Meyer[153]), monkey (Magnus, as cited in Schaefer and Meyer[153]), and human[67]. These tonic deviations usually occur with decreased alertness.

In mammals, the static postural symptoms of UL are more variable between species than the ocular motor symptoms. Common to most mammalian species and also to some submammalian species is a tilt of the head toward the lesioned side in the roll plane, which has been referred to as roll head tilt (RHT)[35]. RHT is often accompanied by a roll tilt of

the body in the same direction. Some mammalian species also exhibit a tilt of the head toward the lesioned side in the yaw plane, which has been referred to as yaw head tilt (YHT)[35]. This symptom has been reported consistently in the guinea pig[82, 153,170] and has also been reported in the rabbit[11]; it is questionable however whether it occurs in the rat[162,175]. In higher mammalian species these symptoms are not invariably present and human patients postneurectomy may show no RHT or YHT. Other symptoms which have been reported following UL include a yaw curvature of the spine, with mid-scapular point and sacrum directed to the lesioned side, circling and rolling toward the lesioned side, extension of the contralateral forelimb and head nystagmus (see Schaefer and Meyer[153] for a review). Studies in the baboon have revealed an hypoexcitability of the limb extensor muscles ipsilateral to the UL[92].

2.1.2. *Dynamic symptoms.* At present, the effects of UL on the vestibulo-ocular reflex have been quantified mainly for the horizontal vestibulo-ocular reflex (HVOR). In mammalian species, UL results in severe abnormalities in the gain, symmetry and phase of the HVOR. For rotation to the lesioned side, the velocity of the slow phase compensatory eye movement toward the intact side in proportion to the peak angular velocity of the head (defined as gain re velocity) is reduced compared to normal, therefore eye movement is not sufficient in amplitude to compensate for head movement[11,13,33,47, 70,107,108,120,142,174,184]. There have been contradictory reports regarding the gain of the HVOR for rotation to the intact side immediately following UL. Some authors have reported a clear decrease in gain[47, 107,108,142] while others have reported a gain similar to normal[33,173,174]. It is worth noting that in all of the former studies, the SN slow phase to the lesioned side was subtracted from the HVOR slow phase to the lesioned side, whereas apparently this was not done in the latter studies. This methodological difference may account for the discrepancy in the results of the two sets of studies since subtracting the SN slow phase for rotation to the intact side will effectively reduce the gain of the HVOR for rotation in that direction. Differences in stimulus waveform and frequency may also contribute to the discrepancy. Recent results in human patients using impulsive head rotations to stimulate the canals have shown there is a clear and significant reduction in HVOR gain for rotations toward the intact side. This gain reduction is not as large as the gain reductions for head rotations towards the lesioned side but it is significantly different from the preoperative results in the same patients (Halmagyi and Curthoys, 1988, unpublished observations).

Irrespective of whether the HVOR gain for rotation to the intact side is normal or less than normal, it is consistently found to be greater than that for rotation to the lesioned side, resulting in an asymmetry in HVOR gain for the two directions of rotation[11,12,32,33,47,107,108,120,142,173,174,183,184].

Following UL, the HVOR also develops an increased phase lead re velocity at low frequencies in sinusoidal testing[11,13,70,107,108,120,142,173,174] and a reduced time constant[13,47] in response to velocity steps. Moran[120] reported that the increased phase lead re velocity is greater for rotation to the lesioned side, while Maioli et al.[108] (also in the cat) reported a symmetrical increase in phase lead re velocity.

Using sinusoidal testing, the deficits in the gain, symmetry and phase of the HVOR which follow UL are generally more substantial at low frequencies of rotation[11,70,120,142,184]; they have been demonstrated at frequencies as low as 0.01 Hz[183,184] and as high as 1.80 Hz[11]. It has been shown that the HVOR gain deficits are larger at high amplitudes of velocity steps[47,108,142] and sinusoids[108,173] than at low amplitudes.

UL results in a decrease in the gain of the vertical VOR which is symmetrical for the two directions, as well as a decrease in time constant[4]. UL also results in deficits in the ocular counter rolling response to roll head tilt, presumably due to the loss of the otoliths on the lesioned side[37].

Such ocular motor deficits result in an instability of gaze which causes oscillopsia, the apparent movement of the visual world during head movement[14]. Although oscillopsia may result in blurred vision[15], it does not necessarily have this effect[69,133,138]. The persistence of clear vision despite oscillopsia may be due to changes in the visual system which increase the degree of instability of the retinal image necessary for visual blur to occur[69].

UL results in a decrease in the gain (slow phase eye velocity divided by visual stimulus velocity) of

the horizontal optokinetic reflex[107,142,144].

In the frog, UL causes a large reduction in the HVOR for rotation to the lesioned side but only a slight reduction in the HVOR for rotation to the intact side[139].

There have been few studies of the dynamic postural symptoms of UL i.e. deficits in the response of the vestibulo-spinal reflexes to head movement which parallel the deficits of the VOR.

Lacour et al.[93] have demonstrated that UL causes a reduction in the response of the soleus extensor muscles in the ipsilateral limb and increase in the response of the same muscles in the contralateral limb to fall; the antagonist tibialis anterior muscles show the opposite change in response. In addition, the ipsilateral soleus muscles show a longer than normal latency of response. These defective responses to fall are correlated with the hypoexcitability of spinal reflexes ipsilateral to the UL and the hyperexcitability of spinal reflexes on the contralateral side[92,93].

It has also been shown that UL causes a reduction in the response of the tibialis anterior muscle in the ipsilateral limb to backward pitch[3], a reversal of the response of the medial triceps in the contralateral limb to head rotation in pitch[99] and an impairment of the righting reflex[72]. The severe disturbance of locomotion which follows UL[75,77,92,93] is probably a result of deficits in both static and dynamic functions of the vestibulospinal system, as well as distorted visual input due to the ocular motor symptoms.

In frogs (see Dieringer and Precht[42] for a review) and turtles (Trendelenburg and Kuhn, cited in Precht and Dieringer[140]), UL results in an asymmetrical vestibulo-collic reflex with head movements being evoked only toward the lesioned side (i.e. only by rotation to the intact side).

2.2. *Neuronal activity*

Since vestibular nucleus (VN) neurons receive mono- or polysynaptic input from the ipsilateral labyrinth and project to motoneurons innervating the ocular and skeletal muscles (see Wilson and Melvill Jones[180] for a review), the VN are usually regarded as mediating the onset and disappearance of the symptoms of UL. However, to date, single neuron recording studies following UL have been undertaken only in the medial and lateral vestibular nuclei (MVN and LVN, respectively).

2.2.1. *Medial vestibular nuclei (MVN).* The main labyrinthine input to the MVN is from the ipsilateral semicircular canals and many neurons, especially in the rostral areas of the nucleus, are responsive to horizontal angular acceleration[159] (see Wilson and Melvill Jones[180] for a review). MVN neurons fall into two major categories, Type I and Type II, with Type I neurons outnumbering Type II neurons[160]. Type I neurons are defined by an increase in firing rate for horizontal angular acceleration to the ipsilateral side and a decrease for horizontal angular acceleration to the contralateral side; Type II neurons have the opposite response pattern[160]. Most

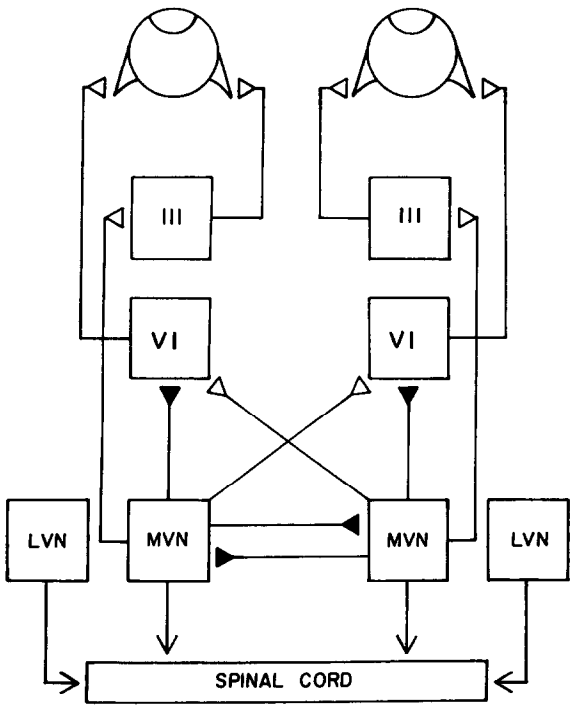

Fig. 1. Schematic summary of the main functional projections in the vestibulo-ocular and vestibulo-spinal pathways from the brainstem vestibular nucleus in mammals. MVN, medial vestibular nucleus; LVN, lateral vestibular nucleus; VI, nucleus of the sixth cranial nerve (abducens nucleus); III, nucleus of the third cranial nerve (oculomotor nucleus). △, functionally excitatory projections; ▲, functionally inhibitory projections.

Type I neurons are excited by galvanic depolarization of the ipsilateral labyrinth and many of these same monosynaptically activated neurons project to the ocular motor nuclei[121] (see Shimazu[158] for a review; see Fig. 1); however, some Type I neurons project to the spinal cord[181] and others project to both targets[118]. By contrast, many Type II neurons are excited monosynaptically by Type I neurons in the contralateral MVN, across the midline of the brainstem, and some Type II neurons inhibit Type I neurons ipsilateral to them[121,160].

Following UL, single neuron recording from the MVN on the ipsilateral side has shown that few Type I responses remain and that those neurons responding as Type Is have a low resting activity[61,68,114,160,164,178]. The loss of Type I responses in the ipsilateral MVN (ipsi MVN) seems to be due both to the removal of the major source of firing rate modulation during rotation and the loss of resting activity, which results from the ipsilateral labyrinthectomy. However, Type II responses remain in the ipsi MVN and the resting activity of Type II cells has been found either to increase[160,164] or remain the same as normal[68].

Recordings from the MVN contralateral to the UL (contra MVN) have revealed a pattern opposite to that of the ipsi MVN: most studies show Type I neurons with an increased resting activity[34,109,110,160,163] (however Hamann and Lannou[68] have recently reported that there is no such change in the albino rat). In addition, Type I neurons have a reduced sensitivity (increase in spikes/s/deg/s^2) to horizontal angular acceleration, a result attributed to the removal of Type II inhibition resulting from the loss of commissural input from Type I neurons on the lesioned side[34,68,109,110,160,163]. It has been reported that the time constant of Type I neurons in the contra MVN is similar to normal[110], however a greater phase lead re velocity (from 0.02 to 0.20 Hz) compared to normal has also been reported[163].

In contradiction to these results, there have been reports that in the cat, at one day following UL, both MVN are electrically silent[113,114]. This bilateral shutdown of activity was attributed to the cerebellum which, in other studies, had been partially removed. It has recently been demonstrated however that, between 12 and 20 h following UL in the guinea pig with cerebellum intact, vigorous Type I activity is present in the contra MVN[34]. This result, together with the fact that with cerebellum intact the lateral vestibular nuclei are not silent following UL[95,136,185], suggests that the 'cerebellum shutdown' hypothesis is incorrect. The presence of ocular motor and postural symptoms both immediately and 24 h after UL in the cat, as in other species, suggests that the contra VN are active and that it is the asymmetry in resting activity between the bilateral VN caused by the reduced activity in the ipsilateral VN, which is responsible for these symptoms[34,137,139,140,170]. The elimination of activity in both VN would be expected to result in a bilateral loss of muscle tone due to a reduction in descending vestibulospinal activity, an effect which is not observed following UL[34].

The results of 2-deoxyglucose (2-DG) studies also suggest that there is a large asymmetry in neuronal activity between the MVN immediately following UL; 2-DG uptake in the ipsi MVN is below normal[54,100,104,126].

2.2.2. *Lateral vestibular nuclei (LVN).* Like the MVN, the LVN receive a distinct pattern of input from the different ipsilateral labyrinthine endorgans, however, a major part of this input arises from the otoliths (see Wilson and Melvill Jones[180] for a review). As a consequence, many LVN neurons respond to roll tilt, either with an increase in firing for side-down tilt and a decrease for side-up tilt (α-neurons), or the reverse response pattern (β-neurons)[21]. Unlike the MVN, the LVN does not have major brainstem commissural connections with its contralateral counterpart[26,57,80,95,96,135,161], however it does receive excitatory input from the contralateral labyrinth through the medullary reticular formation[160,161] and possibly the cerebellar fastigial nucleus[46,179]. Also in contrast to MVN neurons, LVN neurons project primarily to the spinal cord and participate mainly in the regulation of posture (see Pompeiano[134] for a review).

The changes which occur in the LVN immediately following UL vary between the rostroventral and dorsocaudal areas of the nucleus, which project to the cervical-thoracic and lumbosacral segments of the spinal cord, respectively[134]. In the ipsilateral LVN (ipsi LVN), there is a decrease in the proportion of neurons responsive to roll tilt in the rostroventral areas, but not in the dorsocaudal areas, as

well as an overall decrease in the average resting activity of neurons; on the other hand, there are increases in the number of position-sensitive neurons, in the sensitivity (% change of the mean discharge rate per degree) of dorsocaudal neurons to tilt, and the number of β-responses[136,176,185] (increase in firing for side-up tilt, decrease in firing for side-down tilt). The average phase lead re displacement decreases compared to normal[185].

In the contralateral LVN (contra LVN) the proportion of neurons responsive to roll tilt is similar to normal, however the overall resting activity is slightly reduced, especially in rostroventral areas[95, 112]. In a similar fashion to the ipsi LVN, there are increases in the number of position-sensitive neurons and β-responses; the sensitivity of neurons to roll tilt decreases in the rostroventral areas[95]. The results of 2-DG studies suggest that like the bilateral MVN, the bilateral LVN exhibit asymmetrical neuronal activity immediately after UL, with the ipsi LVN exhibiting less 2-DG uptake than the contra LVN[100, 104]. However, the asymmetry may not be as large as for the MVN[104].

2.2.3. *Abducens nuclei.* As yet, the only recordings from the abducens nuclei following UL are from the frog[2] where it is reported that there is no significant change in the resting activity of bilateral abducens neurons, but that the increase in firing rate for rotation to the contralateral side is less than normal in both abducens nuclei, with the greater decrease occurring in the abducens nucleus contralateral to the UL; the decrease in firing rate for rotation to the ipsilateral side is less in the abducens nucleus ipsilateral to the UL. Since SN occurs in mammals but not in frogs (see Agosti et al.[2] for a review), a significant difference in resting activity between the abducens nuclei following UL would be expected in mammals and the gain reductions described above seem consistent with this prediction.

3. THE PARTIALLY COMPENSATED STAGE

The stage of recovery from UL in which the static symptoms are almost completely compensated has been defined as the partially compensated stage, due to the fact that some static symptoms (e.g. roll head tilt) remain and other, dynamic symptoms, continue to compensate over the ensuing months or years[187]. There have been fewer studies of the partially compensated stage than of the uncompensated stage.

3.1. *Behavior*

3.1.1. *Static symptoms.* SN, as measured in light, decreases from its high frequency values immediately following the UL, until by 2–3 days post-op., little SN remains in most species[50,65,82,162].

Studies in which SN was measured in darkness generally suggest a similar time course, although some long-term studies in humans suggest that SN in darkness may persist at a low level for years following UL[50].

In the rat, the tonic vertical eye deviation observed immediately after UL is reported to disappear by 4–6 h post-op.[162], while in the rabbit[11] and guinea pig[152], eye deviation toward the lesioned side is reported to persist for days or weeks. Recently, Petrosini and Gremoli[129] have reported that in guinea pigs, tonic eye deviation in darkness shifts toward the intact side during vestibular compensation.

YHT has been measured systematically only in the guinea pig, where it is reported to compensate at a rate similar to SN[82,152,168].

Systematic measurements of RHT have been confined to the frog, rat and guinea pig. In the frog, RHT compensates very slowly, taking between 40 and 70 days to reach values of around 7° (ref. 54). In the rat, RHT is reduced to around 10° within hours of the UL[100], however, recent studies suggest that it might undergo a secondary increase[162]. Studies in the guinea pig show that RHT decreases to about 15° by 2–3 days post-op., and that many animals retain a permanent RHT of about 10° (refs. 82, 168). Qualitative observations in other species confirm that RHT does compensate, but at a slower rate than SN, and that a small amount of RHT may persist for months or years after UL[11,108,141,187].

Other postural symptoms which have received less attention, for example, yaw curvature of the spine and head nystagmus, have been reported to compensate at a rate similar to SN and YHT (see Schaefer and Meyer[153] for a review).

3.1.2. *Dynamic symptoms.* The majority of the studies of the HVOR during the partially compen-

sated stage suggest that gain does not recover to normal levels, although it may be higher than in the uncompensated stage[11,13,33,47,108,174]. The few studies which have examined the two directions of rotation separately, suggest that the gain for rotation to the lesioned side increases slightly from the uncompensated stage, while the gain for rotation to the intact side stays the same or is even slightly lower than in the uncompensated stage[33,47,108,174]. Fetter and Zee[47] have demonstrated that the HVOR gain deficit for both directions of rotation increases with increasing velocity of rotation.

The increase in the gain for rotation to the lesioned side results in a decrease in the asymmetry in the gain of the HVOR for the two directions of rotation[11,47,108,184]. However, phase retains the increased lead re velocity observed immediately following UL and the time constant remains shorter than normal[13,47].

Recently, Allum et al.[4] have reported that the gain of the vertical VOR recovers to within normal limits in humans by 1–3 months following acute unilateral vestibular paralysis.

Precht et al.[142] have reported that the gain of the optokinetic reflex recovers to approximately normal levels for velocities of optokinetic stimuli below 60°/s (constant velocity) by about 15 months following UL; however, these studies were conducted in animals at 6 weeks of age (at the time of the UL) and compensation is generally more effective in infants than in adults[108,153].

Very few studies of the vestibulo-spinal reflexes have been carried out during the partially compensated stage of recovery from UL. Lacour et al.[93] have found that normal EMG patterns reappear in the soleus and tibialis anterior muscles in response to fall by about 3 weeks post-op.; studies of the Hoffman and tendon reflexes suggest a similar timecourse of recovery[92,93]. Lindsay and Rosenberg[99] have shown that by 8 weeks post-op., the response of the medial triceps in the contralateral limb to head pitch reverts to normal. Igarashi and Guiterrez[72] have shown that recovery of the righting reflex occurs by about 3 weeks post-op.

These few studies suggest that compensation of the dynamic postural symptoms may occur more quickly and completely than the compensation of the dynamic ocular motor symptoms. The general recovery of the vestibulo-spinal reflexes is reflected in the return of approximately normal locomotor behavior by about 4–6 weeks post-op.[75,77].

3.2. *Neuronal activity*

3.2.1. *Medial vestibular nuclei.* Precht et al.[141] reported that the frequency of occurrence and resting activity of Type I neurons in the ipsi MVN had shown some recovery toward normal values by 6–8 weeks post-op. However, the sensitivity of these neurons to ipsilateral horizontal acceleration was still much less than normal. Since the original study of Precht et al., others have confirmed that there is a recovery of resting activity in Type I neurons in the ipsi MVN[107,113,114,146,164,178]. Paralleling the behavioral recovery, Smith and Curthoys[163,164] demonstrated that, in the pigmented guinea pig, recovery of the normal average Type I resting activity occurs by 52–60 h post-op., which correlates with the compensation of the static symptoms in that species[168]. De Waele et al.[178] have recently reported a similar rapid recovery of normal resting activity in the guinea pig. However, Smith and Curthoys found that the frequency of occurrence of Type I neurons remained less than normal up to one year post-op. The recovery of Type I resting activity was accompanied by a recovery of resting activity in neurons unmodulated by horizontal rotation. Consistent with the findings of Precht et al.[141], Smith and Curthoys[164] found no recovery of normal Type I sensitivity to horizontal rotation up to one year after UL. The gain deficit of these neurons seemed to increase with increasing velocity, a result which may account for the finding that the HVOR gain deficit in compensated animals is greater at high velocities[47].

By contrast with all of these studies, Hamann and Lannou[68] have reported that Type I resting activity in the ipsi MVN of the albino rat decreased during compensation, to a level even lower than immediate postoperative values. These authors found similar changes in gain and phase to those reported in studies of cat and guinea pig, however it is not clear in which VN subnucleus they were recording. A further study[68] using pigmented rat showed changes in Type I resting rates and responses to rotation which were similar to those reported in other mammalian species.

Type II neurons in the ipsi MVN do not show any

marked change in their resting activity or response to horizontal rotation from normal values during vestibular compensation[68,124,141,146,164].

Anatomical studies of the ipsi MVN during compensation have reported little transneuronal degeneration[90,146,156], however the appearance of a new kind of synaptic bouton has been reported in the cat at 5 days post-op.[90], which some authors (e.g. Galiana et al.[59]) have interpreted as an indication of axonal sprouting.

As the resting activity of Type I neurons in the ipsi MVN increases to more normal levels, the resting activity of Type I neurons in the contra MVN decreases[34,107,146,163,187]. Curthoys et al.[34] showed that this decrease can occur in the guinea pig with or without the midline cerebellum intact, by approximately 12 h after UL. By contrast, Hamann and Lannou[68] have reported that in the albino rat, the resting activity of Type I neurons in the contra MVN is very similar to normal, both immediately after UL and during vestibular compensation. The resting activity of such Type I neurons is normal in the pigmented rat within 4 days post-op.

As for the ipsi MVN, the sensitivity of Type I neurons in the contra MVN to horizontal rotation remains lower than normal[34,68,187], even up to one year post-op.[163]. Yagi and Markham[187] reported that, in the cat, the time constant of these Type Is was similar to those obtained in uncompensated or normal animals. On the other hand, in the guinea pig, the increased phase lead re velocity observed in contra Type Is immediately after UL, decreases toward normal values by 52 h post-op.[163].

Ried et al.[146] reported that Type II neurons were virtually absent from the contralateral MVN in cats at 4–6 weeks after UL. However, Smith and Curthoys[163] reported that, in the guinea pig, Type II neurons on this side were encountered more frequently at 52–60 h and 8–12 months post-op. than at 0–8 h post-op. Type II neurons have also been reported in the contra MVN of the gerbil at 4–6 weeks post-op., with a significant recovery of gain compared to immediate post-operative values[68,124].

The differences in VN neuronal activity between the cat, guinea pig and rat suggest that some aspects of the neuronal changes underlying vestibular compensation may be species-specific even within mammals. This result would not be too surprising given that the speed of behavioural recovery differs fairly substantially between species.

Single neuron studies in the frog suggest that normal resting activity returns to Type I neurons in the ipsi VN by about 60 days post-op.[39,40].

3.2.2. *Lateral vestibular nuclei.* Xerri et al.[185] and Pompeiano et al.[136], recording from ipsilateral LVN neurons at 2–4 months post-op. in the cat, have reported that the overall average resting activity (α- and β-neurons in the rostroventral and dorsocaudal LVN combined) does not recover from the immediate post-operative levels, although small neurons (identified by slow conduction velocity), which could be antidromically activated from T_{12}–L_1, did show a significant recovery of resting activity. The proportion of neurons in the rostroventral areas responsive to roll tilt increased to an approximately normal level, while the sensitivity of these neurons to this stimulus remained similar to normal and the uncompensated stage; the sensitivity of the dorsocaudal neurons decreased to normal levels. However, the proportion of position-sensitive neurons and β-responses remained similar to the uncompensated stage. The average phase re displacement increased to an approximately normal value.

There are currently no data on the contralateral LVN in the partially compensated animal, however, Lacour et al.[95] found little difference between the contra LVN in uncompensated and normal animals. Whether the contra LVN remains normal during partial compensation remains to be tested.

Consistent with single neuron studies, the results of 2-DG studies of the VN suggest that there is some recovery of symmetry of neural activity between the VN during vestibular compensation[54,100,104]. This recovery of symmetry seems to be greater for the MVN than the LVN[104].

3.2.3. *Abducens nuclei.* The only available data on the abducens nuclei during vestibular compensation are from the frog[2]. At 60 days post-op., abducens neurons on the side contralateral to the UL are more sensitive to horizontal rotation than immediately post-op., while those ipsilateral to the UL are slightly less sensitive, resulting in greater symmetry of response between the two abducens nuclei than during the uncompensated stage; no significant changes in resting activity from the uncompensated stage were reported[2].

With the growing realization of the significance of prepositus hypoglossi in vestibular functioning it is to be hoped that systematic studies of neurons in this nucleus during compensation will soon be published.

4. MECHANISMS OF VESTIBULAR COMPENSATION

The previous sections have described the process of vestibular compensation and the neuronal recovery which accompanies it. The present section will review the hypotheses which have been put forward to explain vestibular compensation and the experimental results which are cited as evidence for these hypotheses. Since lesions of the ipsi VN prevent compensation following UL[170], it is generally accepted that the recovery of neuronal activity within the ipsi VN has a major causal role in the behavioral recovery[71,137,139,140]. However, many hypotheses concerning the causes of vestibular compensation do not relate specifically to the *mechanism* of this neuronal recovery, but merely propose that input from the remaining labyrinth (e.g. Galiana et al.[59]), another sensory modality (e.g. vision[32]), or some other area of the CNS (e.g. cerebellum[31]) causes the neuronal recovery which is necessary for vestibular compensation. Most of these hypotheses are not formally stated and deal only with a specific aspect of the compensation process, for example, the role of the flocculus in HVOR compensation[31] or brainstem commissural influences on neurons in the deafferented VN[40]; since they address vestibular compensation on so many different levels, many of the hypotheses current in the literature are not mutually exclusive, but emphasise different events within compensation. The only formal theory which has been put forward to date is the model presented by Galiana et al.[59] which proposes that the brainstem vestibular commissures are responsible for the neuronal changes which accompany vestibular compensation.

Since the problem which the CNS faces in compensating for UL is essentially similar to that created by injury to other parts of the nervous system, in the following review, data on the causes of compensation will be categorised in terms of the types of explanation which have been used in recent reviews of lesion-induced neuronal plasticity[49,111,172].

4.1. *Initiation versus maintenance of vestibular compensation*

It is likely that the kinds of neuronal processes which are responsible for vestibular compensation do not normally occur, but that some effect of the UL initiates these processes, serving as an error signal to stimulate adaptive changes (see Flohr et al.[53,54] for reviews). Conceivably, this error signal could be any effect of the UL, from the loss of synaptic drive from the vestibular nerve, or its degeneration[87], to the abnormal sensory signals[148] or motor commands[36] which are caused by the symptoms of UL. However, the speed with which compensation of the static symptoms is initiated (i.e. 3–4 h post-op.) suggests that the error signal would have to be generated very quickly following UL, which may exclude extensive anatomical changes in the VIIIth nerve as the source. This error signal would not have to be something unique to UL if, for example, the neuronal processes responsible for compensation were also responsible for other phenomena, such as adaptation of the VOR following a prolonged angular acceleration[116,117].

The factors which initiate vestibular compensation may be distinct from those which maintain it[31,101]; once vestibular compensation is achieved, the error signal should (by definition) dissipate, therefore other mechanisms would be necessary to maintain compensation in the absence of the error signal.

Most experiments on the causes of vestibular compensation are not designed to discriminate the factors which initiate compensation from those which maintain it; demonstrating that a type of lesion or sensory deprivation prevents the development of compensation does not indicate whether the initiation or the maintenance of compensation, or both, was impaired. For this reason, in the present review, it is not possible to categorise experiments according to whether they relate to the initiation or maintenance of vestibular compensation, but only according to the general type of explanation of compensation which they have been interpreted as supporting.

4.2. *Alternate strategies*

It is possible that part of vestibular compensation is achieved through the adoption (perhaps con-

sciously at first) of behavioral strategies which minimise the behavioral deficits introduced by the UL (see Berthoz[16] for a review). This may occur independently of changes in the structure or function of neurons which do not occur under normal circumstances i.e. neuronal plasticity.

It has been noted that bilaterally labyrinthine defective patients may adopt idiosyncratic strategies to offset deficits in gaze holding caused by a defective HVOR, such as the use of catch-up saccades[64,85] or the restriction of head velocity during head movements toward the lesioned side[66]. It has also been shown that if an active head movement is prematurely and unexpectedly terminated in subjects with bilateral labyrinthine loss, the appropriate eye movement may still occur, suggesting that the compensatory eye movement may be centrally pre-programmed[38,64,85]. Similar strategies may be adopted following unilateral labyrinthine loss and may explain why patients with poor VORs do not necessarily experience oscillopsia[64,69,182].

Denise et al.[36] have suggested that following UL, animals may reduce the asymmetry in neck muscle activity and even the asymmetry in VN activity, by consciously shifting gaze to the contralateral side. However, this suggestion is based only on the correlation of gaze and neck muscle EMG following UL in cats, therefore it must be regarded cautiously.

Since compensation of the static symptoms relies on a permanent substitution for the static activity which has been lost from the ipsilateral labyrinth, the adoption of strategies to provide this activity would seem, in the long term, an uneconomical means of bringing about behavioral recovery (unless use of the strategy caused some other mechanism to generate a more permanent change). The use of strategies as a major cause of vestibular compensation also seems unlikely in view of the speed with which compensation of the static symptoms occurs in most species (i.e. 2–3 days); if strategies were responsible for the compensation of the static symptoms, it might be expected that there would be large variability in the degree of compensation achieved by different animals within 2–3 days of the UL, yet typically, the degree of compensation achieved is very similar between different animals of the same species. It seems more likely that the compensation of the static symptoms is a prerequisite for the effective use of strategies in alleviating the poorly compensated dynamic symptoms.

4.3. *Vicarious functioning*

Many authors believe that vestibular compensation is a result of vicarious functioning, the substitution of other sensory inputs for the missing labyrinthine input[31,143]. The sensory inputs which have been suggested for this function include visual, neck proprioceptive and somatosensory inputs, as well as input from the remaining labyrinth (see Precht and Dieringer[140] for a review). Sometimes it is suggested that sensory information from a specific CNS site is substituted, for example, somatosensory information from the spinal cord or visual information from the flocculus.

Most experiments relevant to vicarious functioning have used a sensory deprivation or CNS lesion before or after vestibular compensation has occurred in order to delineate the role of a specific sensory input in compensation. The results of such experiments are, however, difficult to interpret. Failure to compensate or decompensation as a result of sensory deprivation or a lesion, merely suggests that a particular input is *necessary* for compensation, it does not indicate that it is *sufficient*. The term 'sensory substitution' seems to imply that a sensory input is being used in a way which is different from normal, in order to bring about vestibular compensation. However, it is quite conceivable that the normal level of a particular sensory input is necessary for vestibular compensation, and that removing that normal input will prevent compensation or cause decompensation. For example, spinal inputs may be more important for the resting activity of VN neurons in the partially compensated animal simply because the ipsi VN neurons have fewer inputs compared to normal, rather than because spinal inputs are potentiated. Experiments which demonstrate no compensation or decompensation as a result of the removal of a sensory input cannot discriminate between a situation in which the input is necessary but normal and that in which it is sufficient and potentiated, therefore the most that can be concluded is that the sensory input is necessary for vestibular compensation.

However, the nature of sensory deprivation and CNS lesions allows that negative results (i.e. no

compensation) may be obtained for reasons other than because a particular input is necessary for vestibular compensation. In particular, CNS lesions could result in diaschisis (i.e. neural shock[111]) in neurons in the ipsi VN, which could result in a retardation of compensation or transient decompensation, and be mistakenly interpreted as an indication that the lesioned site is necessary for compensation. In fact, more often than not, CNS lesions do not completely prevent compensation or cause permanent decompensation, (e.g. Azzena[7]) which is consistent with the hypothesis that the behavioral effects of these lesions could be due to diaschisis. Furthermore, sensory deprivations or CNS lesions may have widespread consequences which influence compensation only indirectly. For example, visual deprivation eliminates retinal slip information, but it may also reduce alertness and locomotor activity, therefore failure to compensate following visual deprivation does not necessarily indicate that visual information itself is necessary for vestibular compensation.

4.3.1. *Visual input.* It is well known that visual stimulation dampens the frequency of SN during the uncompensated stage, however a level of compensation is eventually reached in animals and humans where SN is either totally absent or slight (2–3°/s slow phase velocity) in dark as well as light[11, 47,50,65,108,132,153].

Data from guinea pig[168], cat[32] and rhesus monkey[48] all suggest that visual deprivation has minimal effect on the compensation of SN, but it does significantly impede compensation of HVOR gain deficits[32,48].

Compensation of YHT in the guinea pig is not affected by visual deprivation, however the compensation of RHT is significantly reduced[168]. Putkonen et al.[143] obtained similar results on RHT in the cat.

Studies using lesions of visual processing areas of the CNS have yielded inconsistent results regarding the compensation of the static symptoms. While some authors report that lesions of the flocculus, nodulus[65] or uvula[65,154,155] do not have any significant effect on the development of compensation of the static symptoms, other authors report a moderate delay in the compensation of SN following lesions of the uvula and nodulus[73] and a severe delay following flocculus lesions[31,81]. These discrepancies cannot be explained simply by species differences, since the studies of Haddad et al.[65], Jeannerod et al.[81] and Courjon et al.[31] were all conducted in the cat. However, Jeannerod et al.[81] and Courjon et al.[31] did not use an appropriate control group (UL only, measured at the same post-operative times) or provide statistical analysis of the results, so their conclusions may be questionable.

Robles and Anderson[149] reported that destruction of the olivocerebellar pathway in the cat did not produce decompensation, while Llinas et al.[101] reported that inferior olive lesions in the rat prevented compensation and caused decompensation in animals already compensated. Azzena et al.[9] confirmed that inferior olive lesions cause decompensation in the guinea pig.

Jeannerod et al.[81] reported that lesions of the superior colliculus prevent compensation of SN and the HVOR; however, only 3 cats were used, without an adequate control group (UL only, measured at the same post-operative intervals) for statistical analysis of the results.

Fetter et al.[48] reported that a bilateral occipital lobectomy in rhesus monkeys did not prevent compensation of SN.

While there are inconsistencies in the data on the effects of lesions of visual processing areas on compensation of the static symptoms, the majority of the evidence is consistent with visual deprivation studies in suggesting that vision is largely unnecessary for compensation of the static symptoms.

Fewer studies are available on the role of vision in the compensation of the dynamic symptoms. It is well-known that following UL, visual information increases the gain of the compensatory eye movement which is evoked by horizontal rotation of the head, although it is not clear that this gain increase is any greater than occurs with the addition of vision under normal circumstances[11,142,144,174]. Since the optokinetic reflexes remain poorly compensated[48, 144], it is unlikely that they could potentiate the compensatory eye movement evoked by head movement. Maioli and Precht[106] have shown that even optokinetic stimulation that would normally increase the gain of the compensatory eye movement in intact animals, results in only a small and transient improvement in gain in unilaterally labyrinthectomized cats. However, Hamann and Lannou[68] have recently

reported that in the compensated pigmented rat, the addition of optokinetic stimulation increases the response gain of vestibular nucleus neurons to head rotation; this enhancement of gain was found to be greater in compensated animals than in normal animals.

Fetter et al.[48] have recently shown that visual deprivation following UL severely impedes HVOR gain compensation in the rhesus monkey: normal compensation does not begin until re-exposure to light. Similar results were obtained by Courjon et al.[32] in the cat. Fetter et al.[48] obtained a similar retardation of HVOR compensation following bilateral occipital lobectomy, suggesting that geniculostriate pathways may be important for this aspect of compensation. It remains to be seen however whether visual inputs are actually potentiated or whether they are simply necessary at their normal level for HVOR compensation to occur.

Lacour and Xerri[94] have shown that visual motion cues augment the reduced soleus muscle response to fall during the early stages of compensation, but that later in the compensation process these cues become unnecessary. Igarashi and Guitierrez[72] have shown that vision improves the compensation of the righting reflex following UL.

4.3.2. *Cervical input.* In guinea pigs, the asymmetrical cervical input which results from YHT apparently accelerates the compensation of the static postural symptoms, since restraint in the 0° YHT position retards compensation of these symptoms[82,132,154,155]. However, whereas previous authors[82,154,155] reported that such restraint had no significant effect on SN, Pettorossi and Petrosini[132] reported that compensation of SN, like the static postural symptoms, was delayed by head restraint in the 0° position. This discrepancy may be due to the fact that Pettorossi and Petrosini's infrared method of eye movement measurement was capable of resolving finer differences in SN than the methods of the previous authors (visually counting nystagmic quick phases) and that their measurements of SN were in darkness, where there is usually more SN to measure. Whether tonic cervical input plays a role in the compensation of the static symptoms in other species remains to be tested.

There are few data on the role of cervical inputs in the compensation of the VOR following UL. There is some evidence from squirrel monkey that the cervico-ocular reflex (COR) may become potentiated following UL[62], however apparently this does not happen in frog[147]. The COR may contribute to improving gaze stability following bilateral labyrinthine loss. Dichgans et al.[38] reported that monkeys which received a bilateral labyrinthectomy showed an improvement to 90% of normal ocular motor compensation when given passive head rotation (body stationary) in darkness and suggested that the COR had become potentiated in order to compensate for VOR deficits. Consistent with this hypothesis is the finding that the proportion of ipsi LVN neurons which are responsive to neck stimulation increases in partially compensated animals[186].

However, other experiments in humans with bilateral labyrinthine loss, suggest that only a modest amount of COR potentiation occurs, and that both the gain and latency of the COR are highly variable even within subjects[20,66,85]. Bles et al.[20] reported that cervical input does not contribute to the stabilization of posture following head movement in patients with bilateral labyrinthine loss.

4.3.3. *Other proprioceptive and somatosensory inputs.* Reduced proprioceptive and somatosensory input may reduce the rate at which the compensation of the static symptoms develops[92,94,152] and produce decompensation during the formative period before the static symptoms are fully compensated[82,152]. It has been reported that guinea pigs lifted from the ground during the first 48 h of compensation show a return of the static postural symptoms seen immediately following UL[82,152,169], but if a surface is placed in contact with their paws, the symptoms diminish and sometimes reverse[82]. Immersion in water is reported to accelerate compensation of the static symptoms[127,128].

These results suggest that afferent input from limb proprioceptors and somatosensory receptors may be important for the compensation of the static postural symptoms. Consistent with this hypothesis is the finding that Xylocaine blockade of limb afferents induces postural decompensation[82], as do transsections of the spinal cord[7,83,152]. In partially compensated animals, a cold block at T_7 is reported to produce a significant reduction in the multi-unit resting activity of neurons in the ipsilateral descending VN[83] and spinal transsection at T_{3-4}, a

reduction in the positive waves in the VN on the lesioned side[8] and an asymmetry in field potentials in the bilateral vestibular cortical areas[10] evoked by electrical depolarization of the intact labyrinth. Spinal transsection at this level also results in a return to the predominantly β response to roll tilt in ipsi LVN neurons[176] seen immediately after UL[185]. Lesions of the lateral reticular nucleus, which receives strong input from the flexor reflex afferents, also result in decompensation of the static postural symptoms[9].

It has been suggested that somatosensory information from the face may serve some function in compensation: transsection of the trigeminal nerve contralateral to the UL is reported to cause decompensation of the static symptoms[130] and an increase in the amplitude of the N1 and N2 waves in the intact VN evoked by electrical depolarization of the intact labyrinth[131].

Despite this evidence, there are no demonstrations that changes in somatosensory input can produce decompensation of the static symptoms in long-term animals (the longest post-operative interval used in these studies was 50 days post-op.). Also, the postural decompensation which results from spinal transsection is not permanent, but lasts only up to one day[7].

The effects of interference with spinal inputs to the VN on compensation may not reflect the importance of specific somatosensory inputs, but rather the general importance of tonic spinal inputs, in the restoration of ipsi VN resting activity; as argued previously, there is no need to assume that a supranormal level of spinal input is necessary in order for decompensation to occur following spinal transsection. However, given the transient nature of the decompensatory effects of spinal transsection and trigeminal neurectomy[130], the possibility must be considered that the decompensation is due to diaschisis in ipsi VN neurons caused by further deafferentation; the recovery of compensation may occur when the diaschisis has subsided.

The case for proprioceptive and somatosensory input serving a function in the formative stages of vestibular compensation of the static symptoms seems to be a stronger one. It is possible that somatosensory information is initially used to determine orientation in the presence of confusing vestibular and visual signals; when somatosensory input might cease to be important in this respect is unclear.

In terms of dynamic postural symptoms, there is evidence that proprioceptive and somatosensory inputs may be necessary for complete compensation. It has been reported that immobilization delays the recovery of locomotor function in cats and baboons[92,94]. This result probably reflects both the reduced compensation of the static postural symptoms caused by reduced proprioceptive and somatosensory inputs[92,94,152] as well as reduced compensation of the dynamic postural symptoms. Conversely, increased motor activity has been reported to improve the compensation of locomotor function and possibly SN[75,77].

Lacour and Xerri[94] have reported that immobilization following compensation does not induce decompensation of locomotor function and Xerri et al.[185] have reported that elimination of fusimotor activity by curarization does not alter the response of ipsi LVN neurons to roll tilt in the partially compensated animal, therefore the proprioceptive and somatosensory inputs which result from motor activity may be necessary only for the initiation of dynamic postural compensation, not its maintenance. However, it should be noted that in all of these studies involving manipulation of the degree of motor activity, other factors such as visual input and alertness may also vary, and the possible contribution of these factors to the results obtained must be considered.

4.3.4. *Input from the intact labyrinth.* If vestibular compensation is the result of sensory substitution, then the most likely sensory input to be substituted would be vestibular information from the intact labyrinth. While there is disagreement about the role of this input in the compensation of the static symptoms, there is universal agreement that it is necessary for effective compensation of the dynamic symptoms[71,138–140].

The finding that a second labyrinthectomy, following compensation for the static symptoms caused by the first, evokes static symptoms in the opposite direction to those evoked by the original labyrinthectomy (the Bechterew phenomenon, Bechterew, (cited in Schaefer and Meyer[153]) suggests that compensation of the static symptoms following UL is not due to input from the intact labyrinth or VN.

The occurrence of the static symptoms in the opposite direction suggests that following the first labyrinthectomy, the resting activity in the ipsi VN is restored (resulting in compensation of the static symptoms) and a contralateral labyrinthectomy then results in a reduction in resting activity in the contra VN, causing a reversed asymmetry in VN resting activity and a reversal of the static symptoms[170]. Recordings from single neurons in the ipsi MVN in partially compensated animals are consistent with the hypothesis that compensation of the static symptoms is not due to input from the contralateral labyrinth or VN: the renewed resting activity in the ipsi MVN persists following removal of the midline cerebellum and transsection of the brainstem commissures[114,141,164]. A similar renewal of resting activity occurs in the bilateral MVN following bilateral labyrinthectomy[151].

The majority of behavioral studies support the idea that commissural input to the ipsi VN is not necessary for static vestibular compensation in mammals. Static postural compensation occurs even if the brainstem (guinea pig[169]; gerbil[122]) or transcerebellar commissures (gerbil[122]) are transsected at the time of the UL. In the guinea pig[165], gerbil[122], and cat[105], removal of the transcerebellar commissures does not result in decompensation. However, the data on the effect of brainstem commissurectomy after compensation has occurred are less conclusive: transsection of the brainstem commissures does not result in postural decompensation in the guinea pig[165], or gerbil[122], however a permanent decompensation RHT has been reported following this operation in the cat[105]. The reason for this discrepancy is unclear, however a recent study suggests that there may be a difference in the anatomical organisation of the brainstem vestibular commissures between the gerbil and cat[123]. In the frog, brainstem commissurectomy is reported to cause permanent decompensation RHT in animals already compensated, suggesting that input from the intact VN is necessary for compensation of the static symptoms[17,54]. One possible explanation for the discrepancy between the effects of brainstem commissurectomy in mammals and frogs is the difference in the functional nature of the brainstem vestibular commissures: in mammals, these commissures are predominantly inhibitory in function (in normal animals[56,160]; in compensated animals[107,141,146]) whereas in frogs, they are predominantly excitatory in function (in normal animals[125]; in compensated animals[39,40]). Consequently, in frogs, the brainstem vestibular commissures could contribute to the restoration of ipsi VN resting activity through excitation, whereas in mammals, this contribution could only be made through disinhibition. It is unlikely that resting activity could be restored to the ipsi VN in mammals by disinhibition alone, since the return of Type I responses to the ipsi MVN would seem to rely on commissural disinhibition during ipsilateral rotation[141] and any release from tonic commissural inhibition to increase resting activity would detract from the modulation of this resting activity during head rotation.

In fact, there is little evidence to suggest that the brainstem commissural input to the ipsi VN in partially compensated mammals is in any way different from normal: no significant change has been found in the resting activity of ipsi Type II neurons[141,146,164] or the threshold or latency for excitation of ipsi Type II neurons by electrical depolarization of the intact labyrinth[141,146]. Precht et al.[141] could find only a slightly lower threshold for the inhibition of ipsi Type I neurons in response to electrical depolarization of the intact labyrinth, a result which Ried, et al.[146] could not confirm. In addition, Ried, et al.[146] could find no change from normal in the response of ipsi Type I or Type II neurons to electrical hyperpolarization of the intact labyrinth.

By contrast, in the frog, it has been reported that the synaptic efficacy of the brainstem commissural input to the ipsi VN is increased during vestibular compensation. Dieringer and Precht[39,40], using electrical depolarization of the intact labyrinth and intracellular recording from neurons in the ipsi VN, reported a shortened rise-time and increased amplitude of EPSPs, as well as an increased number of IPSPs to the same stimulation. Kasik et al.[86] reported that electrical depolarization of the intact VIIIth nerve evoked field potentials in the ipsi VN of the isolated medullae which were of larger than normal amplitude; these authors also reported that application of atropine, an acetylcholine antagonist, had a slightly (but not significantly) larger than normal depressive effect on these field potentials.

Despite these observations, Rayer and Horn[145] have demonstrated that static and dynamic vestibulo-ocular compensation can occur in tadpoles which fail to develop vestibular nuclei on one side, due to UL immediately after hatching. This result suggests that compensation can occur in amphibia without brainstem vestibular commissures.

From these results, it can be concluded that there is little evidence that input from the intact labyrinth is necessary for compensation of the static symptoms in mammals and that, consistent with this, there is no evidence for any change in the efficacy of the brainstem commissural input to the ipsi VN. However, in frogs, brainstem commissural input to the ipsi VN may be necessary for the compensation of RHT; consistent with this result is the finding that the synaptic efficacy of this commissural input is increased in partially compensated frogs.

In terms of the dynamic ocular motor and postural symptoms, there is definitive evidence that input from the intact labyrinth is necessary for compensation. Following complete bilateral labyrinthine loss, there is no VOR (by definition), and any compensatory eye movement which results from head rotation in darkness is usually small compared to normal and must be due to cervical input (if the body is stationary), other proprioceptive or somatosensory input, or prediction[38,66,85]. Following UL in the frog, sectioning the contralateral horizontal canal nerve or plugging the horizontal canal completely eliminates the HVOR[43]. It has been reported that following bilateral labyrinthectomy, the response of the soleus and tibialis muscles to fall and the Hoffman and tendon reflexes remain uncompensated[93,94]; the righting reflex is also incompletely compensated[72]. General locomotor function recovers[74,93], however detailed evaluation on the rail test reveals a permanent impairment[74].

Thus, for both ocular motor and postural dynamic symptoms, the removal of input from the contralateral labyrinth, either eliminates or severely reduces compensation following UL. This is consistent with the results of neuronal studies in partially compensated animals. Responses to horizontal rotation are completely eliminated in the ipsi MVN following transsection of the midline of the brainstem to a depth of about 2 mm (midline cerebellum already aspirated); however, the resting activity of neurons in the ipsi MVN (no longer identifiable as Type Is) increases to approximately the peak firing rate which had previously been recorded for ipsi Type Is during ipsilateral rotation[141,164]. The return of Type I responses to the ipsi MVN is probably the result of resting activity returning to Type I neurons under tonic commissural inhibition, so that during ipsilateral rotation, resting activity is disinhibited to generate an increase in firing, characteristic of Type I neurons[141].

Xerri et al.[185] have reported that LVN neurons do not respond to roll tilt following bilateral vestibular neurectomy, a result which suggests that the recovery of the response of ipsi LVN neurons to roll tilt in partially compensated animals is due to input from the contralateral labyrinth, possibly via the cerebellum or medullary reticular formation.

Taken together, the data on the function of the vestibular commissures in vestibular compensation largely contradict the model of Galiana et al.[59], which proposes that vestibular compensation is due to the altered synaptic efficacy of transcommissural inputs to the ipsi VN. The majority of the evidence suggests that the transcerebellar and brainstem commissures are not necessary for static compensation in mammals, although they may be necessary for this process in frogs. Certainly, commissural input is necessary for the recovery of response to head movement in neurons in the ipsi VN, and this recovery may be important for dynamic compensation in mammals, but there is no evidence that these commissural inputs are in any way potentiated. Fetter and Zee[47] have recently shown that it is possible to mathematically model the VOR changes which occur during vestibular compensation in mammals without assuming any change in the efficacy of the vestibular commissures.

4.3.5. *Cerebellar lesion studies.* Because of its important role in motor coordination in the normal animal, the cerebellum has seemed likely to have a critical function in vestibular compensation. However, lesion studies of the cerebellum during vestibular compensation have yielded inconsistent results.

As described in a previous section, some authors report that lesions of the flocculus[81], nodulus and uvula[73] inhibit compensation of the static symptoms while other authors report that they do not[65]. Magnus (cited in Schaefer and Meyer[153]), reported

that total cerebellectomy prevented compensation, however Schaefer and Meyer[152] reported that it had only a transient retardatory effect, which the authors attributed to the trauma of the operation. Discrete lesions of the posterior vermis are reported to result in a retardation of the compensation of the static postural symptoms[154,155] and locomotor function[73]; compensation of SN is less affected[73,154,155]. Lesions of the anterior vermis are reported to retard compensation of the static ocular motor and postural symptoms less than lesions of the posterior vermis[154,155].

Carpenter et al.[27] have reported that ablation of the fastigial nuclei severely retards compensation, however Robles and Anderson[149], using the same species (cat), reported that ablation of the cerebellar nuclei neither prevented compensation nor caused decompensation in animals already compensated.

The results of these lesion studies do not delineate a very clear role for the cerebellum in vestibular compensation. The results of neuronal studies suggest that the alterations in resting activity which occur in the bilateral MVN during vestibular compensation occur in the absence of the midline cerebellum (which includes the vermis)[34,113,114,141,151,187]. However, it seems likely that cerebellar lesions will have marked effects on the response of VN neurons to head movement during vestibular compensation, and therefore, on the compensation of the dynamic symptoms of UL.

4.3.6. *Conclusions on the role of vicarious functioning.* The evidence reviewed suggests that vicarious functioning (either through sensory substitution or substitution of other neuronal inputs) is not a major contributor to the compensation of the static symptoms in mammals, although sensory inputs, without necessarily being potentiated in any way, are necessary for the compensation of the dynamic symptoms.

Many of the explanations of vestibular compensation in terms of vicarious functioning imply that the cause of vestibular compensation is localized to a specific sensory modality or CNS site[7,59]. However, results from 2-deoxyglucose studies in partially compensated animals suggest that many areas of the CNS have increased glucose uptake during compensation, suggesting the possibility of widespread increased neuronal activity[54,100]. Whether this increased glucose uptake is related to the cause of vestibular compensation, however, remains to be determined.

4.4. *Reactive synaptogenesis*

Reactive synaptogenesis, the sprouting of new synapses in response to a lesion, has frequently been proposed as an explanation for the return of resting activity to the ipsi VN following UL[40,59,71,141,185]. Reactive synaptogenesis is well documented in the CNS[29,52], however few data are available on synaptogenesis in the vestibular system. Dieringer et al.[44] have presented autoradiographic evidence for an increased projection from the dorsal horn to the VN following UL in the frog, however in mammals, the only evidence for sprouting is the finding by Korte and Friedrich[90] that 5 days following UL in the cat, a new type of synaptic bouton appears in the deafferented VN. Although the latter result is often cited as evidence for reactive synaptogenesis following UL in mammals[59], Korte and Friedrich were themselves quite cautious about the implications of the result, suggesting the possibility that the new bouton might actually be a previously existing bouton which was transformed by altered physiological activity caused by UL. Gacek et al.[58] have recently reported that they could find no evidence of sprouting in the ipsi VN up to one year following UL in cat.

Finger and Almli[49] have pointed out that even in cases where sprouting clearly does occur following a lesion, it cannot be assumed that the structural change has a causal relationship with behavioral recovery: the new synapses may not be functional or if they are functional, they could be maladaptive; sprouting could be an irrelevant reaction of a labile developmental process mistakenly triggered by the lesion, or it could be an effect rather than a cause of the behavioral recovery (see Finger and Almli[49] for a review).

Reactive synaptogenesis may be an unlikely explanation of vestibular compensation because of the speed with which compensation occurs in most species: compensation of the static symptoms is almost complete by 2–3 days post-op. The results of studies in the denervated rat hippocampus, where the time-course of reactive synaptogenesis has been plotted, suggest that in adult animals, there is at least

a 5-day delay before new synapses begin to form (see Gall and Lynch[60] for a review), and an even longer delay before the new synapses become functional (up to 9 days, see Cotman and Nadler[30] for a review). The reason for this delay appears to be that the terminals of the lesioned neurons must degenerate and be phagocytosed by glial cells before new synapses can form[119]. Studies of the cat VN following vestibular neurectomy, suggest that while degeneration of the vestibular nerve terminals begins by 24 h post-op. (by which time, SN is at least 60% compensated in the cat[65]) glial cell proliferation is not observed until about 3–4 days post-op., and glial cell phagocytosis of degenerated terminals continues for up to 6 days post-op.[156]. Since in hippocampal studies, synaptogenesis is consistently delayed until phagocytosis is complete[119] (see Gall and Lynch[60] for a review), these results suggest that synaptogenesis may not begin in the VN until at least 6 days following UL. SN has almost disappeared in the cat by 3 days post-op.[65].

Other anatomical studies of the hippocampus suggest that tetanization of the perforant path afferents can generate the formation of new synapses within 10–15 min[97] (see Greenough and Chang[63] for a review). Whether such rapid structural changes, or even longer term structural changes, have any role in vestibular compensation, remains to be determined.

4.5. *Functional alterations in synaptic efficacy*

'Denervation supersensitivity' is the increased excitability of a neuron to neurontransmitter following denervation (see Cannon and Rosenbleuth[25] and Stavraky[171] for reviews). Usually, but not exclusively, the term is associated with the notion that there is an increase in the number of postsynaptic receptors for a neurotransmitter. It has been suggested that following UL, neurons in the ipsi VN may gradually develop denervation supersensitivity to remaining excitatory inputs, and that this might account for the return of resting activity to the ipsi VN which accompanies vestibular compensation[141, 170,185]. However, as with reactive synaptogenesis, there is little direct evidence for the occurrence of supersensitivity in deafferented VN neurons following UL.

Pharmacological studies in the frog have shown that injection (systemic or intracisternal) of cholinesterase inhibitors (physostigmine, paraoxon, parathon, BW 284)[18] or acetylcholine agonists (arecholine, carbachol, nicotine, muscarine, oxotremorine, methacholine[1]) causes decompensation RHT, whereas injection of acetylcholine antagonists results in RHT toward the intact labyrinth (overcompensation). Similar results have been obtained in mammals: cholinesterase inhibitors cause decompensation of the static symptoms in the guinea pig[154], as do acetylcholine agonists in the squirrel monkey[79]. Acetylcholine antagonists also reduce SN during the uncompensated[189] and compensated stages[79] of recovery from UL.

Noradrenaline agonists (clonidine, injected intracisternally) are reported to cause decompensation RHT in the frog, whereas noradrenaline antagonists (phentolamine) cause overcompensation (Abeln and Flohr, cited in Flohr et al.[53]). In the same species, GABA agonists (muscimol) cause decompensation RHT, while GABA antagonists (picrotoxin) cause overcompensation (Abeln and Flohr, cited in Flohr et al.[53]).

These studies suggest an asymmetry in the effect of various neurotransmitter agonists and antagonists on the CNS in partially compensated animals. However, such data do not prove that denervation supersensitivity occurs, since they do not show whether the asymmetry is due to increased sensitivity on one side or a decreased sensitivity on the other; the behavioral effects of these drug manipulations may simply be a result of the reduction in synaptic input to the VN on the side of the lesion, e.g. reduced excitatory or increased inhibitory input to the ipsi VN. Because the injections were systemic or intracisternal, the drugs could be acting on many parts of the CNS other than the VN, so it is not certain that the asymmetrical effects of the drugs are related to the bilateral VN[86].

In a recent study by Kasik et al.[86], bath application of an acetylcholine antagonist (atropine) to the isolated medullae of a partially compensated frog, did not result in a significant reduction in the amplitude of the n-wave in the deafferented VN, elicited by electrical depolarization of the contralateral VIIIth nerve; however, the amplitude of the p-wave increased significantly. This result suggests some alteration in the brainstem cholinergic pathways of the vestibular system, which is consistent

with denervation supersensitivity, however the result could also be due simply to the reduction in synaptic input caused by the UL. The results of recent autoradiographic[190] receptor studies suggest that there is no significant change in the number of muscarinic binding sites in the bilateral VN up to 90 days following UL.

Knopfel and Dieringer[91] have reported that the increased efficacy of brainstem commissural input to the ipsi VN in the frog is not due to increased *N*-methyl-D-aspartate (NMDA) receptor activation, which is responsible for the rapid induction of long-term potentiation in the hippocampus[28] and is implicated in the development of several other instances of CNS plasticity[89,98,177].

Recently, Smith and Darlington[166,167] have reported that the potent NMDA receptor antagonists MK801 and CPP disrupt compensation of spontaneous nystagmus in the guinea pig. Whether the decompensatory effect of NMDA antagonists is due to their action within the VN itself remains to be determined, however, it is possible that the function of NMDA receptors in the ipsi VN increases during vestibular compensation in mammals.

Despite the dearth of empirical data on supersensitivity in the deafferented VN, a great deal of research has been done on supersensitivity in other parts of the nervous system. Denervation supersensitivity is well documented in the peripheral nervous system, where in studies at the neuromuscular junction, it has been shown that the supersensitive response of muscle cells to acetylcholine following lesions of motor axons is due to an increase in the number of acetylcholine receptors on the muscle cell membrane[6]. In the CNS, supersensitivity has been proposed as an explanation for neuronal hyperactivity (i.e. increased spike output) following denervation[5,87,88,102,103]; however, it has proven difficult to show that the hyperactivity is due to supersensitivity (i.e. a postsynaptic change) rather than to some change in synaptic input (e.g. increased excitatory input or disinhibition)[88]. Attempts have been made to test for supersensitivity directly by electrophoretic ejection of neurotransmitter agonists onto partially denervated neurons; studies in the denervated hippocampus[19] and facial nucleus[115] have shown an increased spike output from single neurons in response to selected transmitter agonists. However, it is possible that in these studies, the supersensitive response was due to the continued effect of the transmitter agonist upon the membrane of the denervated neuron in the absence of the presynaptic terminals necessary to inactivate it[19,115]. If the supersensitivity were due solely to the absence of a means of inactivating the transmitter agonist which is artificially inserted, then it is questionable whether this form of supersensitivity would ever occur naturally, since any transmitter which was released into the synaptic cleft by remaining presynaptic terminals might be inactivated by those terminals as normal. Thus, supersensitivity due to loss of inactivation would have no significance for normal behavior unless the remaining presynaptic terminals reduced the inactivation of the transmitter which they released.

With this problem in mind, Yarborough and Phillis[188] have distinguished between supersensitivity due to loss of inactivation (presynaptic or inactivation supersensitivity) and that due to some change in the postsynaptic cell (postsynaptic or true supersensitivity).

Although denervation supersensitivity is the most widely cited functional explanation for the return of resting activity to neurons in the ipsi VN, there are many other possible functional changes which could account for this neuronal recovery (see Burke[22] for a review). Some of these possibilities are presynaptic, like an increase in the amount of transmitter liberated per bouton, and others postsynaptic, such as a change in the electrical excitability of the postsynaptic neuron (see Calvin[23,24]; Burke[22] for reviews) or in the distribution of ions across its membrane[45,157]. Complex interactions between pre- and postsynaptic mechanisms are also likely[45]. The identification of specific pre- and postsynaptic mechanisms responsible for the regeneration of resting activity in partially deafferented vestibular neurons will be an important focus for future studies of the physiological basis of vestibular compensation.

It is possible that the efficacy of synaptic inputs to deafferented neurons in the ipsi VN is increased through hormonal changes which regulate synaptic efficacy (see Flohr et al.[53,55] for reviews). Flohr and Luneburg[51] reported that hypophysectomy significantly retards the compensation of RHT in the frog, while administration of $ACTH_{4-10}$ restores the com-

pensation process. $ACTH_{4-10}$ in the absence of hypophysectomy accelerates compensation[51]. Recently, Igarashi and Ishikawa[76] have reported that compensation of SN and ataxia in squirrel monkeys can be accelerated by administration of $ACTH_{4-10}$. Similar results were obtained with thyrotropin-releasing hormone (TRH)[78]. In both of these cases, however, it is possible that the acceleration of compensation was due to increased arousal caused by the hormones[76,78]. Further work will need to be done to exclude this possibility.

One way that ACTH-like neuropeptides may influence neuronal activity in vestibular compensation is through the phosphorylation of proteins which regulate the activity of neuron membrane channels[55]. Richter-Landsberg and Flohr (unpublished, cited in Flohr et al.[55]) have recently reported increased phosphorylation in the frog brain during vestibular compensation.

The mechanism of the recovery of neuronal activity which occurs in the vestibular nucleus during vestibular compensation may be related to that responsible for the recovery of neuronal activity in other denervated nuclei, in particular, the dorsal horn of the spinal cord following transsection of the dorsal root ganglion[24]. The loss of cutaneous sensation which results from the latter operation may result in phantom limb sensations which, in principle, are similar to the renewal of static vestibular sensation afforded by the recovery of resting activity in VN neurons: in both cases, resting activity returns to the second order sensory neurons but there are no receptors.

5. CONCLUSION

The available data on vestibular compensation suggest that the static symptoms of UL are well compensated by 2–3 days post-op. in most species, whereas the dynamic symptoms compensate more slowly, if at all. Neuronal studies suggest that compensation of the static symptoms is caused by a partial rebalancing of resting activity between neurons in the bilateral VN. In mammals at least, this recovery of resting activity seems to be independent of transcommissural input from the intact labyrinth and VN, and also independent of any remaining input from the ipsilateral Scarpa's ganglion. Recovery of the response to head movement seems better for neurons in the ipsi LVN than those in the ipsi MVN, and this correlates with generally better compensation of vestibulo-spinal reflex deficits compared with vestibulo-ocular reflex deficits. The recovery of response to head movement seems to be entirely dependent upon input from the remaining labyrinth, and, at present, there is no compelling evidence for any increase in the efficacy of that input in mammalian species. Since compensation of the dynamic symptoms is much less complete than the compensation of the static symptoms, and compensation of the dynamic symptoms appears to be mediated by commissural inputs which are normal, the main example of neuronal plasticity occurring in vestibular compensation must be the return of resting activity to the ipsi VN.

The cause of the return of resting activity to the ipsi VN is unknown, however the majority of the available data suggest that it is not due to the substitution of non-vestibular sensory inputs or to increased input from other parts of the CNS which process sensory inputs. The rapid timecourse of the recovery of resting activity suggests that reactive synaptogenesis would be too slow to produce the necessary increased synaptic drive. Denervation supersensitivity, which would increase the sensitivity of deafferented neurons in the ipsi VN to remaining inputs, is a possible candidate to explain the fast recovery of the resting activity. However, currently there are few data to support this hypothesis. Rapid hormonal changes which would regulate the sensitivity of neurons to neurotransmitters may be one way that supersensitivity could occur, and recent experiments suggest that, in mammals and frogs, peptide hormones like $ACTH_{4-10}$ and TRH may modulate vestibular compensation processes. However, the acceleration of compensation which occurs when these hormones are administered to a compensating animal is not large, and other effects that they might have on variables such as arousal need to be considered. Given the preliminary result that NMDA antagonists disrupt compensation in the guinea pig, the possible role of NMDA receptors in the regeneration of VN neural activity in mammals would seem worthy of future investigation.

Since a similar recovery of resting activity occurs in other areas of the CNS with a similar time-course

following denervation (lateral cuneate nucleus[88]; trigeminal nucleus[5], dorsal horn[103]), it is possible that the recovery of resting activity in the ipsi VN following UL is an expression of a general CNS process which functions to offset the long-term changes in tonic synaptic input which would otherwise be caused by denervation. There may exist a type of automatic gain control for firing rate, such that a prolonged reduction in tonic synaptic excitation of a neuron constitutes an error signal, which may be corrected through some form of denervation supersensitivity[23,24]. If this were the case, vestibular compensation would have little to do with the vestibular system itself, and would instead be a particular instance of a general CNS process. Since the recovery of resting activity in the ipsi VN appears to be the major neuronal change occurring during vestibular compensation, general mechanisms for the development of denervation supersensitivity may be the most productive focus for future research on vestibular compensation.

6. SUMMARY

This paper reviews the literature on the mechanisms responsible for the behavioural recovery which occurs following unilateral labyrinthectomy (UL). UL causes a syndrome of ocular motor and postural disorders, which diminish over time in a process of behavioural recovery known as *vestibular compensation*. Electrophysiological studies show that the VIIIth nerve does not undergo a functional recovery, therefore vestibular compensation has been attributed to CNS plasticity. However, the nature of the plasticity responsible for vestibular compensation is not understood. Single-neuron studies have demonstrated that a significant recovery of resting activity has occurred in the vestibular nuclei (VN) ipsilateral to the UL by the time symptoms such as spontaneous nystagmus and roll head tilt (static symptoms) have largely disappeared. However, many of the deficits in the response of VN neurons to head acceleration persist and may be permanent. This lack of recovery in the response of neurons to head acceleration correlates with the incomplete and sometimes poor recovery of the vestibulo-ocular and vestibulo-spinal reflex responses to head movement (dynamic symptoms). The major neuronal change in the VN during vestibular compensation appears to be the recovery of resting activity in the VN ipsilateral to the UL, although this recovery is more pronounced in the medial VN than in the lateral VN. The mechanism responsible for the regeneration of resting activity in VN neurons is unknown. In frogs, there is evidence to suggest that transcommissural synaptic input to the VN, from the contralateral (intact) labyrinth, increases in efficacy. However in mammals, the recovery of VN resting activity seems to be independent of transcommissural influences. The pre- and postsynaptic mechanisms responsible for this neural recovery in mammals remain to be determined.

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