NEUROANATOMIC SUBSTRATES FOR VESTIBULO-AUTONOMIC INTERACTIONS

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Abstract — Recent anatomical studies have identified a network of central neural circuits that appear to integrate vestibular and autonomic information. Like vestibulo-ocular and vestibulospinal circuits, these pathways appear to be under inhibitory modulation by distinct regions in the medial aspect of the cerebellar cortex. These central circuits have the potential to explain the known influence of vestibular stimulation on autonomic motor responses through descending effects on brain stem autonomic regions. In a more global context, the extensive convergence of vestibular and autonomic information in both vestibular and autonomic brain regions is consistent with the concept that vestibular and visceral information (for example, blood pooling and visceral proprioception) are used to form a central representation of gravito-inertial parameters during movements. This representation can influence neural circuitry involved in postural control, cardiovascular control, perception of the spatial vertical and emotional or affective responses. © 1998 Elsevier Science Inc.

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Introduction

The clinical observation that vertigo is accompanied by gastrointestinal discomfort, nausea, and vomiting has long been the basis for speculations regarding mechanistic links between vestibular and visceral function. Prior to the 19th century, this observation was evident in the descriptions of the etiology of vertigo in the medical literature, which often recommended vertigo therapies directed at both the stomach (or other viscera) and brain. For example, a mid-17th century English translation of Paracelsus' Of the Mysteries of the Signs of the Zodiac contained the following discussion of vertigo:

Many who labour with this disease, the Heaven and Earth seems to them to turn like a wheel, and all things to run around . . . For there is such a Convulsion of the Brain, that the Spirits of the Sight and the Brain, are impeded by a certain gross thick vapour ascending from the Stomach to the head, through the optic nerves. (1)

This theme was also evident in a 17th century English edition of Ambrose Paré's works, which recognized a role of optic flow stimulation ("wheels running round, or whirl pits in water"): visual cliff effects and tinnitus ("noyse in the ears") as factors germane to the etiology of vertigo:

The Vertigo is a sudden darkening of the eyes and sight by a vaporous & hot spirit which ascendeth to the head by the sleepy arteries [carotid arteries], and fills the brain, disturbing the humours and spirits which are conveyed there, & tossing them unequally, as if one ran round, or had drunk too much wine. This hot spirit oft-times riseth from the heart upwards
by the internal sleepy arteries to the Rete mirabile, or wonderfull net; otherwhiles it is generated in the brain, its selfe being more hot than is fitting; also it oftentimes ariseth from the stomack, spleen, liver and other entrals being too hot. The signe of this disease is the sudden darkening of the sight, and the closing up as it were of the eyes, the body being lightly turned about, or by looking upon wheels running round, or whirlie pits in waters, or by looking down any deep or steep places. If the originall of the disease proceed from the braine, the patientes are troubled with the head-ache, heart-nesse of the head, the noise in the ears and oftentimes they lose their smell... (2)

Based upon these etiologic schemata, treatments included a combination of measures directed at the stomach and central nervous system:

Fyrst let ye pacient beware of dryntkyng of wine or strong drynkes, they must beware of eatynge of chibolles, garlyke, and onyons, and all vaporous meates & drynkes, and let them use pilles of cochie to purge the stomake and the hed, and gargariccs be good for this matter, and yerapigra, and suche men havynge this passion let them beware of clymnge or goynge up upon highe hyUes or rounde stayres. (3)

This communication reviews recent advances in our understanding of pathways in the central nervous system that receive vestibular and visceral information. These pathways appear to be neural substrates for vestibular influences on the nervous system and bowel reflexes, manifestations of vestibular dysfunction, motion sickness and the perception of one’s relationship to gravitoinertial forces.

Previous studies (for a review, see reference 4) indicate that there are several basic principles of organization of vestibular nuclear pathways that mediate vestibulo-ocular and vestibulospinal responses (Figure 1, panel A). At the core of each pathway is a pool of neurons in the vestibular nuclei, which receives inputs from specific combinations of afferents from vestibular endorgans and projects to either motoneurons or interneurons that mediate the motor responses (for example, see references 4,7). These pools of vestibular nucleus cells are also modulated by direct projections from cerebellar Purkinje cells, which form a second major component of these circuits. Different brain stem pathways receive projections from different cerebellar regions. For example, vestibulo-ocular reflex pathways are affected by the flocculo-nodular lobe, while vestibulospinal pathways are influenced by the anterior lobe. We will develop an initial working hypothesis that vestibulo-autonomic pathways follow these same basic principles of organization.

Detailed studies of the relationship between the flocculo-nodular lobe and vestibulo-ocular reflex relay neurons have generated the hypothesis that cerebellar circuits can be divided into discrete modular units that modulate activity in highly specific vestibulo-ocular reflex pathways (for example, 4–15). These data gave rise to the microcomplex hypothesis (4), which stated that the cerebellum is organized into basic units, termed microcomplexes (Figure 1, panels B and C). Microcomplexes are defined anatomically by a network of specific interconnections between groups of cells in the inferior olive, sagittal groups of cerebellar Purkinje cells (microzones) and pools of cells in the cerebellar nuclei and/or the vestibular nuclei. The inferior olivary component is defined by crossed projections of their axons (climbing fibers) to both a pool of Purkinje cells in cerebellar cortex and the target neurons of the same Purkinje cells in the cerebellar or vestibular nuclei. The cerebellar component, or microzone is defined both by efferent projections of Purkinje cells to specific pools of cerebellar or vestibular nuclear neurons and by
Figure 1. Schematic diagram of the organization of cerebellar microcomplexes involved in vestibular information processing. (A) Block diagram of the basic organization of these pathways. (B) Basic form of the microcomplex hypothesis (4). Microcomplexes are modular circuits defined by a specific pattern of connections between a pool of inferior olivary cells, a sagittal group of cerebellar Purkinje cells, and a pool of neurons in the vestibular (or, in the general case, cerebellar) nuclei. (C) Modified form of the microcomplex hypothesis based on more recent data. Two additional features are incorporated. First, ipsilateral nucleo-olivary connections may provide a substrate for bilateral coordination of activity in microzones. Second, collateralized projections of climbing fibers to multiple cerebellar microzones may be a substrate for coordination of activity in parallel motor pathways.

magnocellular medial vestibular nucleus (reviewed in reference 4).

The results of recent neuroanatomical studies are consistent with the hypothesis that vestibulo-ocular and vestibulo-autonomic pathways in the brain stem and cerebellum show similar principles of organization. Following the example of studies of vestibulo-ocular circuits, these studies have proceeded in two logical steps: (a) identification of the topographic organization of cells in the vestibular nuclei that project to central autonomic pathways and (b) identification of connections between "autonomic" sites in the cerebellar cortex and vestibular nuclear regions that influence brain stem autonomic regions. These studies have provided the first anatomical characterization of direct vestibular nucleus projections to brain stem autonomic pathways (17–22) and have identified connections between these vestibulo-autonomic regions and several regions of the cerebellum. These findings are consistent with the basic organizational features.
of vestibulo-ocular pathways and provide a basis for identifying features of cerebellar microcomplexes that influence the activity of striated muscle (somatic motor system) versus smooth muscle (autonomic nervous system). These findings also may provide insights into neural mechanisms that coordinate somatic and autonomic motor activity during gravito-inertial challenges imposed by changes in posture, by aircraft maneuvers, by travel on ships, or by space travel.

Vestibular Nuclei and Vestibulo-Autonomic Pathways

A major result from recent studies has been the characterization of a network of vestibulo-autonomic projections in the brain stem of rabbits, rats, and cats (17–22). The results are summarized schematically in Figure 2, which divides brain stem vestibulo-autonomic circuits into three components: (a) a vestibulo-autonomic region in the vestibular nuclei, (b) a direct descending pathway to brain stem circuitry for vestibulo-autonomic "reflexes", and (c) an ascending pathway to the parabrachial nucleus. This latter pathway can influence both the medullary autonomic regions (termed the indirect descending vestibulo-autonomic pathway) and more rostral regions of the hypothalamus, amygdala and neocortex, which are likely to mediate neuroendocrine and affective responses to vestibular and autonomic stimulation (see reference 20 for further discussion).

Anatomical data indicate that vestibulo-autonomic pathways originate from a region that includes the dorsal aspect of the superior vestibular nucleus (SVN), pars alpha (or caudalventral aspect) of the lateral vestibular nucleus (Lo), the caudal half of the medial vestibular nucleus and the inferior vestibular nucleus (17–22). Two subdivisions of this vestibular nuclear region can be distinguished on the basis of efferent connectivity. A caudal region (caudal medial vestibular nucleus and the inferior vestibular nucleus) contributes both (a) light descending pro-

Figure 2. Diagram of central vestibulo-autonomic pathways. Abbreviations: Amb/PAmb—nucleus ambiguus/nucleus parambigiuous complex, DM Vagus—dorsal motor nucleus of the vagus nerve, L Tegmentum—lateral tegmental field of the medullary reticular formation, VLM—rostral ventrolateral medulla.
jections to the nucleus of the solitary tract, the dorsal motor vagal nucleus, the nucleus ambiguous, the ventrolateral medullary reticular formation (rVLM), the nucleus raphe magnus, and the lateral medullary tegmentum and (b) ascending projections to the parabrachial nucleus. A rostral region (the superior vestibular nucleus and the rostral pole of the medial vestibular nucleus), though, contributes only ascending projections to the parabrachial region. The two vestibular nuclear regions appear to have distinct and reciprocal connections. However, there is evidence that they differ in the relative density of noradrenergic and serotonergic afferents. In rats (23), rabbits, and monkeys (24), the density of noradrenergic innervation is substantially greater in the rostral region (superior vestibular nucleus) than caudally. By contrast, the limited evidence to date suggests that the caudal region receives a denser serotonergic innervation (25,26).

The connection diagram in Figure 2 presents the hypothesis that descending vestibulo-autonomic projections represent a final common output of the "vestibular nucleus relay" to brainstem autonomic output circuits. A corollary is that these pathways mediate the so-called "vestibulo-sympathetic reflex" (27,28). This hypothesis is consistent with the replicated observation that lesions of the caudal medial vestibular nucleus abolish vestibular-evoked autonomic responses (28–30). It also appears that interspecies differences in the organization of descending vestibulo-autonomic projections are associated with different autonomic responses during vestibular dysfunction and motion sickness. For example, the projection to nucleus tractus solitarius shows a common pattern in rats and rabbits, with relatively heavy innervation to the ventrolateral subnucleus (dorsal respiratory group) and to the ventral and intermediate subnuclei. By contrast, there are negligible vestibular nuclear projections to the medial subnucleus, a region that receives gastrointestinal inputs (31–33). It is interesting that the projections to the dorsal respiratory group and a lack of input to the medial solitary subnucleus are present in species with extremely prominent respiratory responses to vestibular stimulation (35–36), but no emetic responses. Cats show the opposite pattern of organization of vestibulosolitary projections: the medial subnucleus receives the densest vestibular nucleus inputs, with few terminations in the ventrolateral subnucleus. These differences are consistent with reported behavior during vestibular dysfunction in these species. These findings are consistent with the failure of dorsal respiratory group lesions to alter vestibulorespiratory responses in cats (38). In addition, the prominent projections to the medial solitary subnucleus may contribute to prominent gustatory and esophageal responses during vestibular dysfunction in cats (37).

An hypothesis implicit in Figure 2 is the existence of an equivalence relationship between vestibular and visceral information in portions of classically defined vestibular and autonomic pathways, such that both acceleration of the head and visceral consequences of changes in body orientation are integrated in these pathways to control somatic and visceral responses. Both anatomic and physiologic evidence indicate a direct convergence of vestibular and visceral information on neurons in sites such as the nucleus of the solitary tract (17,18,21) and the rostral ventrolateral medullary reticular formation (21,37), which may be a factor in the well-noted similarities between motion sickness and responses to ingestion of toxins (38). Anatomical data predict a similar convergence within the parabrachial nuclear complex (20,21). Finally, recent data suggest a direct convergence of vestibular and autonomic information with the vestibular nuclei via parabrachiovestibular connections (39). The potential convergence of vestibular and autonomic information in vestibular nuclear circuits is analogous to the convergence of oculomotor (eye position and eye velocity) and vestibular signals on vestibular nuclei cells mediating vestibulo-ocular reflexes (40, 41). These interactions provide a potential anatomic basis for Mittelstaedt's experimental evidence that psychophysical determinations of the spatial vertical reflect an interaction between vestibular and visceral signals (42). However, in a broader sense, these data are consistent with the hypothesis that vestibular and autonomic pathways use both vestibular (semicircular canal and otolith) and visceral (for example, blood pooling and visceral proprioception) to construct central representations of the gr. Ito-
inertial forces. These central representations then influence vestibular and autonomic function.

The ascending projections to the parabrachial nucleus appear to represent an integrated vestibular and autonomic influence on ascending limbic, prefrontal, and hypothalamic pathways. These pathways may form a neural substrate for affective, cognitive, and neuroendocrine manifestations of vestibular dysfunction, motion sickness, and responses to altered gravitational environments (20,21). In particular, circuitry linking the vestibular and parabrachial nuclei may provide a neural substrate for the interactions between predisposing cognitive and affective factors in the development of both motion sickness and psychiatric disorders (for example, panic disorder with agoraphobia and height phobia) that are characterized by space and motion discomfort (43,44).

Cerebellar Modulation of Vestibulo-autonomic Circuits

It is well-known that the effects of vestibular nucleus circuits on somatic motor function are under cerebellar modulation (see reference 4 for a review). An extensive literature has characterized discrete regions of the cerebellar cortex that contribute direct projections to vestibuloocular and vestibulospinal reflex circuitry in the vestibular nuclei (reviewed in reference 4). For example, different parasagittal groups of Purkinje cells in the cerebellar flocculus are connected with pools of vestibular nucleus neurons that mediate vestibulo-ocular reflexes in the plane of coplanar pairs of semicircular canals (4,13). Two properties of these circuits are useful as general criteria for identification of cerebellar regions that directly influence vestibular nuclear circuits. First, stimulation of the cerebellar region produces effects consistent with inhibition of the post-synaptic vestibular nucleus circuit. In the case of the flocculus, microstimulation of sites in different zones both inhibits discrete canal–ocular reflexes (4,6,7) and produces slow eye movements (for example, 45), presumably by inhibiting the tonic discharge rates of cells that mediate plane-specific reflexes. Secondly, inactivation or ablation produces both an increase in the gain of the vestibulo-ocular reflex (due to disinhibition) and an attenuation of adaptive changes in reflex performance. For example, microinjections of GABA agonists in the flocculus depress the gain of both vestibuloocular and optokinetic responses (46), and lesions impair the adaptive modification of vestibulo-ocular reflexes (reviewed in reference 4).

Previous studies have identified four regions of the medial aspect of cerebellar cortex that affect autonomic function (Figure 3): 1) an intermediodorsal site on the border of lobule IX and the nodulus, 2) a dorsal posterior lobe region in zone A of lobule IX, 3) a rostral posterior lobe region in zone A of lobules VIIa through VIIIa, and 4) an anterior lobe region within zone A of lobules I through III (reviewed in reference 47). Electrical stimulation of different sites in these regions produces either pressor of depressor responses, probably through inhibition of brain stem autonomic circuits that influence tonic adrenergic (sympathetic) outflow to the periphery. The data also suggest that both the anterior lobe and caudal posterior lobe regions can alter the gain (sensitivity) of brain stem cardiovascular reflexes. These medial cerebellar regions, particularly the anterior lobe and the uvula-nodulus, also subserve a role in control of posture and locomotion (reviewed in reference 4). Since the cerebellar cortex plays an important role in the coordination of somatic movements, it is possible that these regions contribute differentially to the coordination of somatic and autonomic motor activity (reviewed in reference 47). The existing evidence suggests that the rostral posterior lobe region within zone A of lobules VIIa (47) contributes to the selection of stimulus criteria for triggering orienting responses and assists in coordination of the visceral and somatic motor components of orienting responses (reviewed in reference 47). However, the published evidence suggests that the intermediodorsal nodulus–uvula, caudal posterior lobe, and anterior lobe areas are strong candidates for cerebellar regions that directly inhibit the sites of origin of vestibulo-autonomic pathways.

Three convergent lines of evidence suggest that a zone in the intermediodorsal aspect of the nodulus and ventral uvula is the cerebellar component of circuitry mediating vestibulo-auto-
Figure 3. Diagram of cerebellar regions related to autonomic function. Four medial cerebellar regions (shaded) appear to influence autonomic function: 1) an intermediolateral site on the border of lobule IX and the nodulus (Lateral Nodulus–Uvula Region), 2) a caudal posterior lobe region in zone A of lobule IX (Medial Uvula Region), 3) a rostral posterior lobe region in zone A of lobules Vila through Viii (Rostral Posterior Lobe Region), and 4) an anterior lobe region within zone A of lobules I through III (reviewed in reference 47). A region in lobules IV and V that influences respiratory movements is also indicated. Arrows schematically indicate the efferent connectivity of three regions that are likely to affect regions of the vestibular nuclei that contribute ascending and descending vestibulo-autonomic connections.
cardiac responses are mediated via projections through the inferior cerebellar peduncle to either the medial parabrachial nucleus (59) or the superior, rostral medial and inferior vestibular nuclei (for example, 10,59,60). Although Paton and colleagues (59) presented autoradiographic evidence that tritiated amino acid injections into lobule IXb produce anterograde labeling in the caudal aspect of the lateral and medial parabrachial nucleus, it is unclear whether this represents axon terminal or uvulo-vestibular fibers of passage in the anocerebellar fasciculus (50). Thus, the existing data are consistent with the hypothesis that zones of uvula Purkinje cells may be components of central vestibulo-autonomic circuits.

The medial aspect of the anterior lobe is a third potential cerebellar component of vestibulo-autonomic circuits. Beginning with pioneering studies by Moruzzi (61-63) and Wiggers (64), both depressor responses and pressor responses have been elicited from sites within the medial aspect of lobules I through III (57,65,66). These blood pressure changes are not accompanied by heart rate responses (61,62), which suggests that activation of these regions may also depress baroreceptor reflexes. Two other lines of evidence suggest that the anterior lobe may contribute to control of blood pressure lability. First, anterior lobe stimulation suppresses both spontaneous Meyer waves (fluctuations in mean blood pressure with a period of 10 s) and carotid sinus reflexes (61–64). Second, these effects of cerebellar stimulation on cardiovascular lability are selective because Meyer waves are enhanced by anterior lobe ablation (67) without a concomitant effect on Hering–Traube waves (spontaneous blood pressure variations at respiratory frequency). Nisimaru and colleagues (66) reported that stimulation sites that produce cardiovascular effects are located predominantly in zone A, a region that reportedly projects to the rostral fastigial nucleus (for example, 4,68), rostral medial vestibular nucleus (10) and parabrachial region (69). However, more detailed studies are needed to determine whether anterior lobe Purkinje cells influence vestibulo-autonomic pathways.

**Conclusion**

In conclusion, recent studies have identified both vestibular nuclear and cerebellar regions that appear to integrate vestibular and autonomic information. These central circuits have the potential to explain the strong association between vestibular stimulation and autonomic motor responses through descending effects on brain stem autonomic regions. In addition to providing substrates for autonomic manifestations of vestibular dysfunction (70) and motion sickness (71), these pathways provide potential substrates for documented effects of vestibular stimulation on cardiovascular (72,73) and respiratory responses (74). Similarly, convergence of vestibular and autonomic information in these pathways is consistent with the concept that perception of the spatial vertical is determined as a function of both vestibular and visceral inputs (42). Even more intriguing is the emerging recognition that vestibular dysfunction can have major affective consequences, contributing to the symptomatology of several anxiety disorders, such as panic disorder with agoraphobia, agoraphobia without panic, and height phobias (43.44). Further studies of the ascending vestibulo-autonomic pathways have the potential to provide important insights into the neurobiologic bases for these disorders.

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**REFERENCES**


39. Balaban CD. Projections from the parabrachial nucleus to the vestibular nucleus in rabbits: a possible visceral relay to vestibular circuits [abstract]. In: Abstracts of...
58. Wiggers K. The influence of the cerebellum on the heart and the circulation of the blood. 2. Physiological Laboratory, University of Amsterdam, Archives de Physiol 1943;27:301–3.