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Motion sickness may be caused by a neurohumoral action of acetylcholine

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SUMMARY

The mechanism by which motion stimulation results in the autonomic responses, known as motion sickness, has remained somewhat of an enigma. Neural connections between the vestibular nuclei and the autonomic and emetic centers in the brainstem have been described, but these appear to be relatively sparse. Thus, new or additional mechanisms seem warranted to account for this curious relationship.

A new hypothesis is herein presented which posits that acetylcholine (ACh) acts as a neurohumeral agent to bring about the symptoms associated with motion sickness. Motion stimulation will activate primary vestibular afferents leading to activation of secondary vestibulocerebellar fibers, some of which are cholinergic, projecting to the vestibulocerebellar region of the posterior cerebellum. The acetylcholine, once released from these synaptic terminals diffuses into the CSF in the 4th ventricle. From there it gains access to the autonomic and emetic centers within the dorsal brainstem and can activate the cholinergic receptors in these nuclei to produce the symptoms characteristic of motion sickness. In similar fashion ACh would have access to the vestibular nuclei where it will facilitate transmission in these nuclei further reinforcing the vestibulocerebellar activity. This would serve as a positive feedback loop which will result in additional release of ACh from the cerebellum and further activation of the brainstem nuclei that result in the symptoms of motion sickness.

Introduction

The mechanism by which motion stimulation resulting from sea, train, air travel, etc., results in the visceral discomfort, commonly know as "motion sickness", has remained an enigma. It is still not entirely clear how motion stimulation activates the visceral centers in the brainstem to produce the behavioral and autonomic responses, including "stomach awareness", nausea, cold sweating, peri-oral and facial pallor, feeling of body warmth, dizziness, retching and recurrent vomiting experienced during motion sickness. As an explanation for these phenomena it might be surmised that there are extensive connections between the vestibular system and the autonomic and emetic centers in the brainstem. While there is some evidence for this anatomical linkage, it appears to be fairly limited [1–7]. Therefore, it seems reasonable to seek additional or other mechanisms by which the curious linkage between vestibular stimulation and motion sickness might arise.

It is not intuitively obvious why such a linkage should exist at all. Emesis understandably results from the body's attempt to eliminate ingested toxins. Why emesis should be linked to a motion induced conflict between sensory inputs is unclear. One evolutionary hypothesis suggests it may be an accidental by-product of "sensory conflict" [8]. This theory of motion sickness suggests that conflicting sensory inputs are necessary for motion sickness to develop [9–11]. The evolutionary explanation as to why vestibular stimulation would result in such a debilitating condition, namely motion sickness, remains an open question.

In this paper an alternative explanation is offered in the hope that it will be of heuristic value and stimulate further experimentation to determine its validity. The hypothesis is based on the premise that motion sickness is an accidental result of the anatomical relationships between the cerebellum, ventricular system and the dorsal brainstem. It encompasses the idea of a neurohumoral linkage, rather than direct synaptic connections between vestibular inputs and the visceral motor outputs [12]. In the present paper this concept is revisited and revised to incorporate acetylcholine (ACh) as the neurohumoral agent. Whereas previous work has suggested neural areas surrounding the 3rd ventricle as the site from which the suspected neurohumoral substance is released, the present hypothesis suggests the vestibulocerebellum as the proposed site from which the neurohumoral agent, ACh is released. In the following discussion the hypothesis will be presented first and then selected pertinent data will be reviewed in the light of this new mechanism for motion sickness.

The hypothesis

The hypothesis described below is summarized in Fig. 1. The peripheral vestibular apparatus, including the semicircular canals and the otolithic organs (utricle and saccule) provide an abundant input to the vestibular nuclei, located in the dorsal medullary

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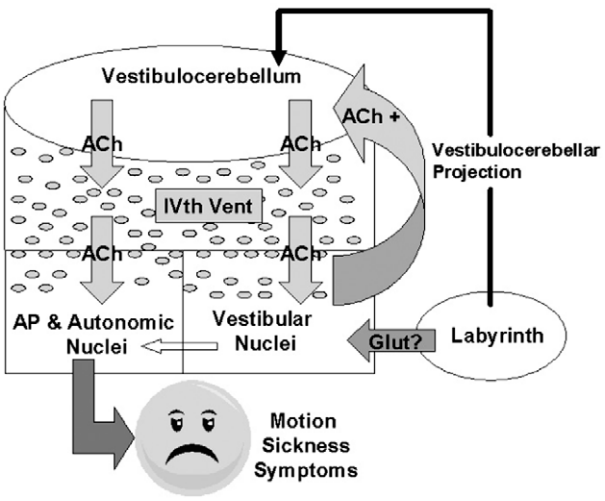

Fig. 1. This is a diagrammatic representation of the hypothetical framework for the generation of motion sickness symptoms as a result of motion stimulation. The labyrinth sends primary vestibular afferents to the vestibular nuclei (block arrow) and the vestibulocerebellum (thin black arrow). The presumed neurotransmitter in this pathway is glutamate (block arrow). The vestibular nuclei project to the autonomic nuclei in the dorsal brainstem (thin clear block arrow) and also to vestibulocerebellum via axonal projections and part of this pathway is cholinergic (curved arrow – ACh). The ACh released in the vestibulocerebellum diffuses (light gray block arrows – ACh) into the CSF of the 4th ventricle (IVth ventricle). ACh then diffuses (light gray block arrows-ACh) into the neurophil of the dorsal brainstem where there are nicotinic and/or muscarinic cholinergic receptors within the area postrema (AP) and the autonomic nuclei (e.g. NTS, DMX and ECRF). In addition, ACh diffuses into the vestibular nuclei in the dorsal brainstem where it interacts with cholinergic receptors to fascilitate the transmission of afferent input to the vestibulocerebellum. In this latter action it provides a positive feedback to enhance the further release of ACh from the vestibulocerebellar fibers. The end result is the activation of the autonomic and emetic nuclei and the genesis of motion sickness symptoms (sad face).

brainstem and also to the ventral regions of the posterior cerebellum, known as the vestibulocerebellum. In addition to these primary afferents there is also a robust projection from the vestibular nuclei to this same region of the cerebellum. This latter secondary projection system uses acetylcholine as one of its neurotransmitters [13,7]. It is highly probable that vigorous motion-induced vestibular stimulation would result in significant release of ACh from secondary vestibulocerebellar cholinergic mossy fiber afferents to the vestibulocerebellum. In many mammals and primates, including the human, the vestibulocerebellum is positioned directly over the 4th ventricle, which is situated between cerebellum and the brainstem. In particular, nuclei involved in autonomic regulation are situated within the dorsal portion of the brainstem immediately below the 4th ventricle. These nuclei include the nucleus of the tractus solitarius (NTS), dorsal motor nucleus of the vagus (DMX), emetic centers located in the reticular formation (EMRF) and also the area postrema (AP), a circumventricular organ that is known to be a chemoreceptor trigger zone for emesis [14–16]. The present hypothesis suggests that ACh released by the vestibulocerebellar afferents acts not only synaptically, to affect it's postsynaptic targets, the granule cells in the vestibulocerebellar region, but that under the influence of vigorous vestibular stimulation sufficient ACh is released and diffuses into the underlying CSF in the 4th ventricle. Once in the 4th ventricle ACh would have access to neurophil in the dorsal brainstem and the autonomic nuclei where it could bind with cholinergic receptors found on many of the neurons in these visceral nuclei [17,18]. The neurohumoral activation of both synaptic and potentially extrasynaptic, ACh receptors would then mediate autonomic responses associated with motion sickness. In addition, ACh could also bind to cholinergic receptors found on the neurons within the vestibular nuclei [19,17,20]. This would establish a positive feedback loop further activating the vestibulocerebellar afferents to the vestibulocerebellum resulting in additional release of ACh into the CSF. The positive feedback would potentiate the ACh effects on the neurons in the dorsal brainstem visceral nuclei and thus exacerbate motion sickness symptoms. This positive feedback loop might also account for the residual effects of motion sickness still present after the vestibular stimulation is no longer present, e.g. when someone experiencing motion sickness due to sea travel continues to feel queasy and uncomfortable when once again on dry land.

Does it fit with existing data?

It is well known that an intact vestibular system is essential for the generation of motion sickness [9,21,22]. Thus, activation of vestibular afferents is necessary, but how does this input then activate the autonomic nuclei (NTS, DMX, EMRF, AP etc.) in the dorsal medullary brainstem that form an integral part of the emetic circuitry [23,19,24]? These autonomic and emetic areas are in close proximity to the vestibular nuclei, especially the medial and inferior vestibular nuclei. The most reasonable conclusion would be that there are neuroanatomical connections between the vestibular system and the visceromotor nuclei in the brainstem that account for the effects of vestibular stimulation on the generation of autonomic symptoms associated with motion sickness. However, while there is neuroanatomical and electrophysiological evidence that such linkages exist, these studies suggest that the connections are surprisingly sparse especially given the robust and long duration of the motion sickness response [1,2,4–6]. This raises the question as to whether vigorous motion stimulation might result in the activation of a different mechanism by which such stimulation affects dorsal brainstem structures responsible for the autonomic responses associated with motion sickness.

Cerebellar involvement

Primary vestibular afferents project to the vestibular nuclei and cerebellum. These primary vestibular afferents appear to use glutamate as their neurotransmitter [25]. Second order fibers from the vestibular nuclei project to the spinal cord, cerebellum, oculomotor centers and thalamus. With regard to the cerebellar target, it has been demonstrated that some of these projections are cholinergic [13,26].

Although the suggestion has been made that the vestibulocerebellar region is necessary for the elicitation of vomiting and other symptoms related to motion sickness, these data are inconsistent [27,28]. It is quite clear however, that this vestibulocerebellar region receives abundant input from the vestibular system [29]. Anatomically, the vestibulocerebellar region forms part of the roof over the posterior aspect of the IVth ventricle, which is situated between the cerebellum and the dorsal brainstem. Vestibular stimulation would therefore result in the activation of cholinergic synapses within the vestibulocerebellum. The released ACh could bind with receptors on postsynaptic granule and unipolar brush cells within the vestibulocerebellar region and then be degraded by cholinesterases. In addition to this however, it is proposed that certain types of vigorous motion-induced vestibular stimulation would result in significant release of ACh from these presynaptic terminals permitting its diffusion into the CSF. Once in the CSF high levels of ACh would be rapidly hydrolyzed by acetylcholinesterase before it could reach the dorsal brainstem. However, it appears that high concentrations of ACh inhibit acetylcholinesterase [30]. Thus, sufficient ACh may remain and allow to function in a neurohumoral fashion. If this were the case then ACh could have access to neurons in the dorsal brainstem that possess both synaptic and