The pathophysiology of motion sickness: A review

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ABSTRACT

Motion sickness (MS) is known to mankind from the time he started moving by means other than on his own two feet. It is an important problem in aviation, more so during the initial training stages of flying. Literature suggests that up to 70% of student aviators suffer from MS and 10% find the symptoms overpowering. Despite the long history of MS, its exact aetiology is not known, though the neural mismatch hypothesis, is indeed logical. This paper brings out the neural mismatch hypothesis, strengths and weaknesses in explaining the aetiology of MS and the neural mechanisms, which result in vomiting. It also attempts to answer which drugs are effective against motion sickness and their most probable mechanisms of action.

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Motion sickness (MS) is a syndrome characterized by drowsiness, pallor, sweating, nausea and vomiting in response to unfamiliar motion, which gradually reduces in intensity as familiarity with the motion increases. Though, MS has been known for centuries there is still no proven theory for its causation. All hypotheses, including the most popular neural mismatch hypothesis, leave some unanswered questions. This paper reviews the available literature to explain the signs and symptoms of MS and the cause for their occurrence. It discusses the neural mechanisms, which may be responsible for the symptom complex of MS. Finally, it outlines the pharmacological or other interventions, which would help in reducing the incidence or severity or help in early adaptation to motion.

Hypotheses for Aetiology of MS

As has been mentioned above, there is still no proven theory explaining the causation of motion sickness or the signs and symptoms of MS. This is mostly due to the varied symptomatology of MS and the various neural mechanisms involved in its causation. Any hypothesis for the causation of MS would have to explain the following:-

(a) MS is usually not seen before 2 yrs or after 60 yrs of age.
(b) MS can be precipitated by abnormal visual or auditory stimulation even in the absence of any motion.
(c) The lack of gravity alone results in Space MS (SMS), even in the absence of motion. Active head movements increase the severity of SMS.
(d) Labyrinthectomized patients do not suffer from MS. Labyrinthectomy causes severe MS in the first few days after the procedure.
(e) MS is usually accompanied by drowsiness.

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Neural Mismatch Hypothesis

This hypothesis was first proposed by Claremont in 1931 and widely accepted after publication of studies by Reason in 1975 [1, 2]. In simple terms, this states that each individual has a neural model, built early in life, for vestibular inputs and related visual, proprioceptive, kinaesthetic and auditory cues i.e. what cues to expect for each type of vestibular cue and vice versa. When an orientational cue is received, it is compared against this neural model for the other cues. If the cue and the model do not match, two things happen[1, 2]:-

(a) A neuro-hormonal cascade occurs, resulting in the MS syndrome.

(b) The neural model is updated.

The neural mismatch hypothesis satisfies most points brought out above. In addition, it can explain the symptoms of pathological (e.g. Meniere’s disease) and surgical (e.g. Labyrinthectomy) disturbances of the vestibular system [1, 2, 4]. It, however, fails to answer a few questions:-

(a) Why MS results in nausea and vomiting (and not something else)?

(b) Why does MS result in drowsiness?

(c) Why some weak anti emetics like anti-histamines or sympathomimetics like Dexamphetamine are effective in controlling MS, while powerful anti-emetics like Domperidone and Metoclopramide are ineffective?

(d) Which situation will give rise to MS and which will not, or why is it that some individuals get MS while others in the same situation do not?

The balance of this paper attempts to answer these questions from the literature available at present. Human experimentation for motion sickness, especially for neurotransmitter studies is difficult, requiring researchers to resort to animal experimentation.

Motion sickness is seen in almost all mammals. However, of the five or more symptoms constituting the MS syndrome, only vomiting can be detected in other animals, and that too is not quantifiable. Rats are unable to vomit, but instead develop pica, which can be demonstrated by their eating non-nutritious substances like Kaolin [4, 5].

Rat Model

For the following reasons it is believed that pica is the equivalent of vomiting in rats [6]:-

(a) Pica develops with unusual motion in a double axis with changing centrifugal and angular accelerations. It develops to a much lesser degree during motion about a single axis i.e. more complicated motion causes a greater degree of pica.

(b) Double labyrinthectomized rats do not develop pica i.e. the vestibular system is required for pica to develop.

(c) The amount of Kaolin ingested (severity of pica) increases with the duration of rotation, indicating summation.

(d) Rats recover from pica within 4 h of rotation (cf motion sickness in humans).

(e) Rotation for 1 hr for 8-10 days results in habituation of rats, after which, rotation does not result in pica.

(f) Pica in rats is suppressed by Anti-MS drugs.

(g) It also develops with the ingestion of opioids and other poisons.

Using behavioural methods (like pica) for research has advantages over using emesis as an index of MS. These are as under [6]:-

(a) The amount of kaolin consumed is quantifiable. Emesis is an all-or-none phenomenon, difficult to grade in severity. Latency of emesis is better, but still an all-or-none phenomenon.

(b) Vomiting is dependant upon stomach contents, and comparison between different studies is difficult. On the other hand, Kaolin ingestion has been seen to occur despite a full stomach.

(c) Kaolin ingestion increases with the duration of rotation, thus indicating the effects of summation. On
the other hand, once the stomach is empty, vomiting is unreliable for assessing the severity of sickness and thus the effects of summation.

**Neural Mechanisms of MS**

As has been described in the neural mismatch hypothesis above, three steps are involved in the development of MS [1, 2] Fig 1:-

(a) Receipt of cues from vestibular, visual, proprioceptive and auditory systems.

(b) Formation of a percept of and comparison of this percept with a stored neural model.

(c) Generation of nausea, emesis and other symptoms, in case of a mismatch.

Such mismatch can be produced in the laboratory by provocative motion on a parallel swing or gimble-mounted tumbling device. On the other hand, unilateral caloric stimulation also produces motion sickness because of a vestibular-vestibular mismatch. This has the advantage of being quantifiable, even to the extent of whether the vestibular system is firing more (with warm stimulation) or less (with cold stimulation).

**Causation and Suppression of MS: The Role of Acetylcholine**

Scopolamine, an antagonist of acetylcholine (ACH) muscarinic receptors, is a potent Anti-MS medicine, indicating that ACH is an important neurotransmitter for the development of MS [8]. Scopolamine Butylbromide, which does not cross the blood-brain barrier is unable to prevent MS in humans, indicating that CNS (and not peripheral) acetylcholine mediated pathways form a link in the MS chain [9].

Studies conducted during sea-sickness and SMS indicate that scopolamine is more effective when started before the trip or early in the trip. It is usually not effective in preventing vomiting once sickness has developed. This indicates that while ACH is involved in the neural mismatch, it is perhaps not responsible for the final symptoms of MS (nausea and vomiting) [10].

Morita et al using a Transdermal Therapeutic System (TTS) found that scopolamine administration hastens the development of habitation to MS. Physostigmine, a centrally acting Cholinesterase inhibitor has been found to retard habitation. Neostigmine, which acts only peripherally has no such action, further indicating that central ACH receptors are important for causation of MS [11].

Horii et al showed an increase of ACH secretion from the hippocampus on stimulating the vestibular system using micro-dialysis. The same researchers later demonstrated that ACH secretion from the hippocampus increased with unilateral caloric stimulation, whether the vestibular system fired more (warm stimulation) or less (cold stimulation).
From the above it appears that secretion of ACH results from the actual process of neural mismatch and not with suppression of vestibular signals (otherwise habituation would have been retarded), nor with suppression of vomiting (in which case, habituation would not have been affected). Blocking of this secretion with scopolamine prevents MS [12, 13]. This further indicates that scopolamine is a good prophylactic against MS, since it prevents sickness while hastening habituation.

The Role of Catecholamines in MS

Amphetamine is a clinically proven Anti-MS medicine and prevents rotation induced pica in rats [9, 14], indicating that catecholamines have a role to play in the causation of MS. Pharmacologically, amphetamine results in release of nor-epinephrine (NE) and dopamine. Thus, it is likely that either NE or dopamine is a part of the MS chain. The two have been discussed below.

Since the vestibular nuclei have few noradrenergic (NA) nerve fibres, catecholamines are unlikely to affect them directly. The locus ceruleus (LC) is the largest noradrenergic nucleus in the brain. Unilateral caloric stimulation reduced NE release from the LC irrespective of whether the canal fired more or less [15, 16]. Thus, it appears that neural mismatch and not vestibular stimulation results in lesser NE release from the LC. Administration of Bicuculline, which is a GABA-A receptor antagonist, blocks the NE suppression at LC in response to unilateral caloric stimulation [16]. It has been established that the ventro-lateral medulla is connected to the LC through GABA-ergic neurons and that electrical and chemical lesions of ventro-lateral medulla stopped inhibition of LC cells.

An important symptom of MS is intense and persistent drowsiness. It has been established that the LC is responsible for inducing arousal. It has also been established that unilateral caloric stimulation results in long lasting suppression of the LC. It is thus likely that suppression of the noradrenergic system due to vestibular mismatch may be the cause of sopite syndrome, which is a form of MS involving only persistent drowsiness[3]. Amphetamine is very effective in countering the drowsiness of sopite syndrome [17].

The other neuro-transmitter stimulated by amphetamine is dopamine. Domperidone and Metoclopramide are dopaminergic D2 antagonists and potent antiemetics and yet unable to control vomiting due to MS [4, 18, 19]. It thus appears that the dopaminergic neuron system does not play an important role in the vomiting of MS.

The Role of histamine in MS

Histamine H-1 receptor blockers are effective in stopping vomiting due to MS [9], indicating the role of histamine in the vomiting due to MS. However, non-sedating antihistamines like Astemizole that do not cross the blood-brain barrier have not been found to be effective against MS [20]. It thus appears that centrally acting histaminergic neurons are responsible for the symptoms of MS.

Takeda et al used Fluromethylhistidine (FMH), an irreversible inhibitor of histidine decarboxylase and found it to be a very potent Anti-MS medication in rats, cats and Suncus murinus [21, 22]. FMH was found to have no effect on the development of habituation to provocative motion. Thus it appears that histamine(HA) has little role to play in the neural mismatch but is important in the final event of emesis.

Takeda et al studied the effects of single and double rotation on histaminergic systems. They found that double rotation, resulted in increase in histamine content of both the hypothalamus and the ponto-medullary junction, while single rotation (which does not result in MS) did not alter the histamine content. The histamine content was also seen to increase as a result of unilateral caloric stimulation irrespective of whether the canals fired more (warm stimulation) or less (cold stimulation). It thus appears that histamine increases in response to neural mismatch rather than in response to vestibular stimulation [21].

Takeda et al developed an artificial microgravity environment for rats in order to study SMS. Using microdialysis they found that a negative change in gravity increased the histamine content, indicating that histamine may be an important factor in the development of SMS [23].
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The exact location of the emetic centre is not known. However it is hypothesized to be encompassing the parvocellular reticular formation, the nucleus of the tractus solitarius, the dorsal motor nuclei of the vagus and the nucleus ambiguous. These are found to be innervated by histaminergic neurons. It has been demonstrated that injection of histamine into the cerebral ventricles induced H-1 receptor induced vomiting in dogs [4].

Cholinergic projection have been reported from the limbic system (the seat of memory, neural model), to the tuberomammillary nucleus of the hypothalamus, from which histaminergic neurons originate. It has been demonstrated that AF64A, which causes destruction of cholinergic neurons, suppressed vestibular induced histamine release from the hypothalamus. On the contrary, giving FMH did not reduce the cholinergic output. This finding suggests a cholinergic to histaminergic transmission in the chain of MS rather than the other way round [4].

Intracerebroventricular introduction of histamine in release of vasopressin and oliguria in dogs. This theory also explains the oliguria associated with MS, which has been found to be associated with an increase in vasopressin levels [24].

Seti et al have demonstrated that histamine applied to the para-ventricular nucleus results in yawning and have likened this to the yawning associated with MS [25]. They have postulated a common pathway perhaps through the LC, for MS, drowsiness and yawning, mediated through histamine.

Antihistamines have been found to be effective in controlling the symptoms of MS even after they have developed. This indicates that they perhaps act on the final pathway for emesis, rather than on the pathway for development of neural mismatch.

The Role of Anxiety

‘Motion sickness’ has been known to be precipitated by sights, sounds and smells associated with aircraft (air-sickness) and ships (sea-sickness) even in the absence of actual motion. Such vomiting is, however, not accompanied by drowsiness which is otherwise a characteristic of MS. Similar anticipatory nausea and vomiting is known to occur in cancer patients on chemotherapy. In both these cases, the vomiting is considered a conditioned reflex. Not surprisingly, patients with a known history of MS have been known to be at a higher risk for developing anticipatory vomiting to chemotherapy [26].

As any other conditioned reflex, this is modified when the stimulus condition (bell in the classic Pavlovian reflex), does not result in the effect. Thus, desensitization to aircraft sights and sounds has a role to play in preventing anticipatory MS. Similarly, reducing anxiety may have a role to play. Behavioural modification, desensitization, relaxation exercises and amxiolytics are known to help in the anticipatory nausea and vomiting of both MS and chemotherapy.

Some Conjectures

None of the facts brought out above bring out why MS presents with nausea and vomiting. Treisman has postulated that since several poisons result in an abberant vestibular stimulation, the discordant signals are interpreted by the brain as an evidence of poisoning and have been teleologically programmed to induce vomiting as a protective reflex [1, 2]. This would perhaps also explain the development of pica in rats who are unable to vomit. Ingestion of non-nutritious substances like Kaolin would result in dilution and chelation of the poison and would have been protective in case of ingestion of a poison if the animal is unable to vomit.

Why does the vestibular system suppress the noradrenergic discharge from the LC? It has been demonstrated that the LC receives inputs from the visual auditory and somato-sensory systems as well. Studies have suggested that the LC is responsible for selective attention to some stimuli in the presence of many (conflicting) stimuli. Thus in case of a neural mismatch, the LC is designed to suppress the noradrenergic system to suppress the discordant inputs, which may be a result of poisoning, in order to focus attention to more important life saving activities.

Where is the comparator for neural mismatch? Several theories have been extended.
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(a) O’Keefe found ‘place units’ in the hippocampus strongly correlated with the spatial position of the animal and suggested that the hippocampus was the seat of spatial orientation and information. There is evidence to suggest that the cholinergic system of the hippocampus is involved with associative learning. Stimulation of the cholinergic system facilitates acquisition of associative memory through enhancing a new input pattern and suppressing the old stored patterns. Thus, cholinergic antagonists would impair the discrimination of novel from stored sensory patterns thus preventing MS, while allowing a new sensory pattern to develop speedily (leaky integrator?).

(b) Another strong contender for the comparator is the cerebellum, which receives inputs from the vestibular as well as other orientational senses. Opinions are divided as to whether the cerebellum has a major role in development of MS. However, it has been demonstrated in rats that surgical ablation of the vermis and flocculus does not provide any immunity from MS [4]. On the other hand it has been reported that removal of the whole cerebellum confers immunity from MS [1].

We know that some individuals are more susceptible to MS, but are not clear whether the susceptibility is to vestibular cues, the mismatch or to vomiting. It has been shown that people susceptible to MS show a higher incidence of vomiting in response to chemotherapy, anticipatory vomiting in anticipation to chemotherapy, and post anaesthetic vomiting. It would thus appear that the susceptibility to vomit is, by itself, an important determinant towards the development of MS [26, 28].

The statistically higher incidence of vomiting in females has been attributed to their willingness to vomit [1]. Studies have been done to correlate the incidence of MS in virtual reality environments with female hormone levels [27]. It has been found that high oestrogen states have higher susceptibility for MS. Similarly, mothers pregnant with female babies have a higher propensity for MS. It thus appears that the higher incidence of MS in females is a result of hormonal influences rather than just the willingness to vomit.

Summary

It appears that the vestibular, visual, auditory and somato-sensory information is relayed to the hippocampus. Here it is compared with a stored model, using a cholinergic neuron system. A mismatch in this is conveyed to the locus ceruleus using cholinergic efferents and to the emetic centre using histaminergic afferents. The norepinephric system in the LC is depressed by this mismatch signal, leading to drowsiness. The emetic centre is excited and this results in vomiting. Anxiety appears to have a role in directly stimulating the emetic centre resulting in anticipatory vomiting.

Scopolamine blocks the cholinergic neurons in the comparator and thus is effective before actual nausea and vomiting occur. Amphetamines stimulate the LC and prevent the drowsiness of MS. Antihistamines act on the histaminergic system and block the final pathway from the comparator to emetic centre, thus preventing vomiting. For this reason, antihistamines are effective in MS even after vomiting has developed, but do not facilitate habituation.

Ideal Drug Therapy for MS

From the above, the following would emerge:-
(a) Before exposure to motion stimulus, Scopolamine is the ideal drug, as it would suppress sickness and hasten habituation at the same time. If combined with Dexamethasone, it would prevent the drowsiness of MS.
(b) If sickness has already developed, Scopolamine is of little use. Antihistamines, especially the sedating ones of older generation will stop the vomiting most effectively.
(c) Metoclopramide and Domperidone though powerful antiemetics, have little role to play in reducing MS.
(d) Reduction of anxiety has a definite role to play and relaxation exercises and Yoga would be helpful.
References


