

Motion Sickness: Current Knowledge and Recent Advance

Li-Li Zhang,¹ Jun-Qin Wang,² Rui-Rui Qi,² Lei-Lei Pan,² Min Li² & Yi-Ling Cai²

¹ Department of Pharmacology, Second Military Medical University, Shanghai, China

² Department of Nautical Injury Prevention, Faculty of Navy Medicine, Second Military Medical University, Shanghai, China

Keywords

Countermeasure; Evaluation; Motion sickness; Pathogenesis; Prediction.

Correspondence

Y.-L. Cai, Department of Nautical Injury Prevention, Faculty of Navy Medicine, Second Military Medical University, 800 Xiang Yin Road, Shanghai 200433, China.

Tel.: +86-21-81871135;

Fax: +86-21-81871135;

E-mail: yilingcai1@sohu.com

Received 24 July 2015; revision 10 September 2015; accepted 10 September 2015

SUMMARY

Motion sickness (MS) is a common physiological response to real or virtual motion. Numerous studies have investigated the neurobiological mechanism and the control measures of MS. This review summarizes the current knowledge about pathogenesis and pathophysiology, prediction, evaluation, and countermeasures of MS. The sensory conflict hypothesis is the most widely accepted theory for MS. Both the hippocampus and vestibular cortex might play a role in forming internal model. The pathophysiology focuses on the visceral afference, thermoregulation and MS-related neuroendocrine. Single-nucleotide polymorphisms (SNPs) in some genes and epigenetic modulation might contribute to MS susceptibility and habituation. Questionnaires, heart rate variability (HRV) and electrogastrogram (EGG) are useful for diagnosing and evaluating MS. We also list MS medications to guide clinical practice. Repeated real motion exposure and combined visual-vestibular interaction training accelerate the progress of habituation. Behavioral and dietary countermeasures, as well as physiotherapy, are also effective in alleviating MS symptoms.

doi: 10.1111/cns.12468

Introduction

Motion sickness (MS) is a feeling of unwellness caused by motion, especially during traveling and virtual reality immersion. The main symptoms of MS include autonomic reactions (nausea, vomiting, pallor, sweating, hypersalivation, and stomach awareness) and sopite syndrome referring to drowsiness, lethargy, and persistent fatigue [1]. Intact vestibular apparatus and sufficient provocative stimulation are prerequisites for MS. There are great individual differences in MS susceptibility, which is thought to be a result of gene-environment interaction [2]. Although the etiology and precise neurobiological mechanism of MS are still ambiguous, several hypotheses have been proposed in which the sensory conflict hypothesis is the most widely accepted theory. Varieties of countermeasures have been developed and successfully used for decades.

Pathogenesis and Pathophysiology

Sensory Conflict Theory

The “sensory conflict and neural mismatch” theory was originally proposed by Reason and Brand. It is currently accepted for explaining MS [3]. MS will develop when mismatches happened between the integrated pattern of sensory information under real motion (e.g., in boats, cars, and airplanes) or virtual environment

(e.g., watching 3D video films) and the anticipated “internal model” formed under normal or experienced conditions [4]. The physiological significance of “neural mismatch” is to initiate sensory-motor learning and promote self-adjustment, ultimately producing MS habituation under novel locomotion environment [5].

Recent studies have added new knowledge to sensory conflict theory. Cullen and his colleagues recently identified sensory conflict neurons in the VN and cerebellum. They found that “vestibular only” (VO) VN neurons and “unimodal” rostral fastigial nucleus (u-rFN) cerebellar neurons only reacted to passive head movement (exafferent) but not to anticipated active afference (reafference) in primates [6]. These sensory conflict neurons may receive inhibitory innervations canceling “reafference” that matches the experience in the “internal model.” As the sensory conflict theory suggests that neural storage of the experienced motion pattern can produce novel “internal model,” it can be presumed that the “exafference” might also be canceled by novel “internal model” established after habituation induced by prolonged or repeated passive motion exposure (Figure 1).

Several lines of evidence suggest that brain regions involved in space orientation and motion perception (hippocampus and vestibular cortex) are areas where internal model stores [7,8]. As for the hippocampus, forward-backward translocation and passive rotation can induce theta rhythm in dentate gyrus and CA1 regions while lesion in these regions can aggravate MS, suggesting

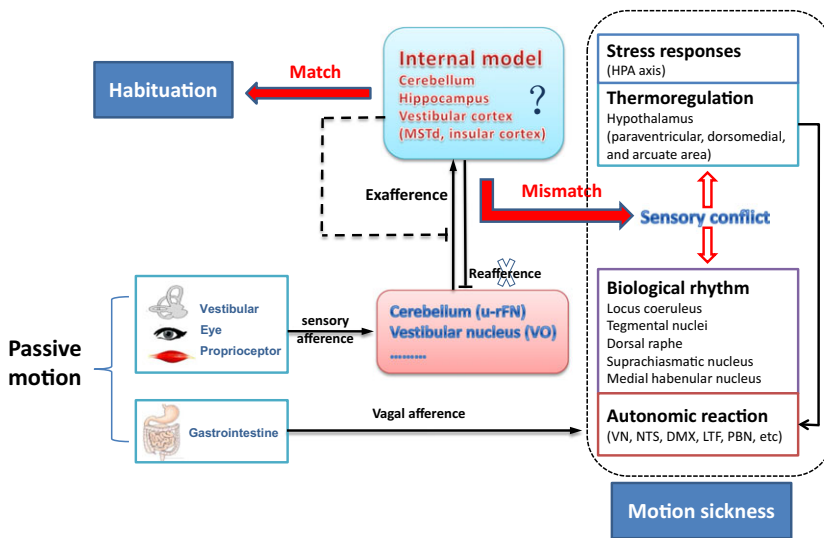


Figure 1 Sensory conflict theory and pathophysiological process of MS.

the hippocampal involvement in processing sensory conflict information [9–11]. In the vestibular cortex, electrophysiological experiments showed that bilateral labyrinthectomy significantly decreased the firing rate of neurons in dorsal part of middle superior temporal (MSTd) during physical rotation and translation in the dark, but not in the visual condition [12]. During large-field visual motion stimulation, inhibitory visual-vestibular interaction was observed in brain regions connected indirectly with MSTd in monkeys [13]. A recent fMRI study showed that long-term spaceflight significantly reduced intrinsic connectivity in insula cortex in a cosmonaut [14]. These lines of evidence supported that the vestibular cortex might play a role in visual-vestibular sensory conflict and possibly in forming “internal model.”

Pathophysiological Mechanisms

Theoretically, activating sensory conflict neurons may trigger autonomic reaction through vestibulo-autonomic pathways that connect the VN complex with central autonomic regions [15,16]. Yates et al. have confirmed that vestibular system regulates cardiovascular function during movement and changes in posture via vestibulo-sympathetic reflex [17]. Although the contribution of sensory conflict neurons to VN-autonomic regulation is still ambiguous, downstream pathophysiological mechanisms of MS are updated by recent studies emphasizing visceral vestibular convergence, vestibulo-thermal regulation, and MS-related endocrine (Figure 1).

It has been demonstrated that brain regions associated with nausea and vomiting not only receive vestibular afference but also converge gastrointestinal (GI) signal [18], suggesting that visceral mechanosensory input might facilitate VN-autonomic reaction during MS. Ossenkopp et al. for the first time reported that MS can induce hypothermia which has recently been proved to be caused by increased heat loss resulting from peripheral vasodilatation [19,20]. Ngampramuan et al. proposed that the vestibular thermoregulatory symptoms may serve as a core pathophysiological element of motion-induced nausea in mammals [21]. As body

temperature and biorhythms are significantly disrupted by chronic hypergravity and bilateral vestibular loss [22], we speculate that vestibular system might participate in keeping homeostasis during MS via connections with thermal and rhythmic regulation centers (Figure 1).

In addition to autonomic reactions, MS also accompanies stress hormones release and endocrine responses habituated over repeated motion exposure [23]. Nevertheless, temporal changes of blood hormones, such as arginine vasopressin (AVP) and adrenocorticotrophic hormone (ACTH), did not synchronize with those of motion-induced nausea, suggesting that activating hypothalamic–pituitary–adrenal axis might be a general stress response to provocative motion [24]. Recently, ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, was observed to be related to acute nausea or vomiting [25]. In animals and humans, ghrelin was found to have gastro-prokinetic activity via facilitating gastric cholinergic activity [25]. Our study revealed that plasma ghrelin levels were positively correlated with severe seasickness-induced autonomic responses in humans (unpublished data), which suggests that gastroenteropancreatic hormones might play a role in MS development. Nevertheless, more detailed evidence is required to verify this hypothesis.

Genetic Contributions

MS is a conserved and a cross-species phenotype (from fishes, amphibia to mammals) with a heritability around 57–70% in humans [5]. Race disparity is also significant. Chinese are more sensitive to MS than Caucasian [2]. Finley et al. for the first time reported that a single-nucleotide polymorphism (SNP) in the α_2 -adrenergic receptor gene correlated with individual differences in autonomic responsiveness to provocative motion and other stressors [26]. Recently, a genomewide association study conducted in 80,494 individuals from the 23 and Me database found that 35 SNPs in genes involved in balance function, eye, ear and cranial development, neurological processes, glucose homeostasis, or

hypoxia were associated with self-reported carsickness susceptibility [27]. Nevertheless, it has been verified that none of these SNPs is related to vestibular function regulation. It is noteworthy that some SNPs are in or near genes implicated in glucose and insulin homeostasis, which links to our previous finding that hyperglycemia is related to the GI symptoms of MS both in human and rodents [28]. Recent studies have found that SNPs in genes of 5-Hydroxytryptamine type 3 receptor (5-HT₃), cholinergic muscarinic receptor type 3 (M3 AChR), morphine (μ) opioid receptor, and neurokinin 1 (NK₁) receptors are associated with background sensitivity to postoperative and chemotherapy-induced nausea and vomiting (PINV and CINV) [29]. These genetic bases for “final common pathway” of nausea and vomiting may also contribute to MS susceptibility.

Patients with migraine and Meniere’s disease are prone to experience MS especially in female patients [30,31]. Mutations in genes related to vasculopathy and cortical spreading depression are responsible for vestibular symptoms and MS hypersusceptibility in migraine patients [32]. Previous studies have found sporadic Meniere’s disease might be associated with mutations in genes of aquaporins and voltage-gated potassium channel expressed in the inner ear [33]. Given that these genes play important roles in endolymphatic homeostasis, their mutations ought to contribute to subnormal or asymmetrical otolith function associated with MS hypersusceptibility in Meniere patients.

Spaceflight and microgravity can affect the expression of genes associated with cellular functions [34,35]. Our study also showed that MS susceptible and insusceptible animals have different gene expression profile in the caudal VN after motion stimulation [36]. Moreover, for human T-lymphocyte cells, simulated microgravity exposure could alter the expression of genes involved in DNA methylation and histone modification, inducing DNA hypomethylation and mutational changes [37]. These lines of evidence indicate that epigenetic modulations might also contribute to MS susceptibility diversity and MS habituation. In addition, MS susceptibility is also influenced by personal characteristics including trait-anxiety, aerobic fitness, and hemodynamic as well as age and sex [38]. The linkage between genetic and epigenetic basis of these phenotypes and MS merits further investigation.

Prediction and Evaluation

Prevalence Prediction

It has been demonstrated that almost all healthy individuals can obtain MS when exposed to appropriate provocative motion. MS prevalence depends on individual threshold to motion stimulation and varies under different situations, which makes it difficult to predict. Lawther and Griffin established mathematical models with dependence on various vertical motion parameters (acceleration magnitude, frequency, and duration) for predicting incidence of seasickness [39]. Perez Arribas and Lopez Pinerio have proposed “sicken passengers ration” which represents variables including ship speed, loading condition, and sea state and includes the effect of passenger behavior and habituation to moving environment [40]. These formulas greatly improve ship design to increase the degree of comfort and the work ability on the sea.

Individual Susceptibility Prediction

Birren and Fisher for the first time provided a questionnaire approach to predict seasickness susceptibility [41]. Pensacola Motion History Questionnaire (PMHQ) and Reason and Brand MS Susceptibility Questionnaire (MSSQ) were nowadays commonly used in MS studies [42–44]. Golding redesigned a MSSQ-Short by simplifying the scoring and adding vital items including the demographic (e.g., age, gender, race), the nauseogenic environments avoidance (e.g., cars, planes, video games), and vestibular disorder comorbidities and anthropometric items (e.g., height, body weight, BMI) to increase the reliability and validity [45,46].

Shupac *et al.* and other groups assessed vestibular function, such as vestibular-ocular reflex (VOR), caloric stimulation, and vestibular-evoked myogenic potential (VEMP), to predict individual MS susceptibility [47–50]. Stoffregen *et al.* recently proposed the postural instability as a precursor of MS susceptibility [51]. Previous studies also demonstrated that computerized dynamic posturography (CDP) data can be used as indicator of seasickness susceptibility and habituation [52,53]. In addition, baseline protein concentration and amylase activity in saliva as well as odor and taster sensitivity were also used as indicators for predicting MS susceptibility in human subjects [54–57] (Table 1).

Diagnosis and Evaluation

MS can be diagnosed according to the manifestations during motion exposure after excluding other pathological disorders. Graybiel *et al.* and Wiker *et al.* established two MS severity grading criteria by scoring 7 categories of cardinal signs and symptoms, and 28 major, minor, or other symptoms, respectively [58,59]. Several research groups developed different questionnaires for assessing the multiple dimensions of MS symptoms [60–62] (Table 1).

Heart rate variability (HRV) and electrogastrogram (EGG) are useful for assessing cardiac sympathovagal interactions and gastric motility during MS, respectively [63,64]. HRV indices might be influenced by motion patterns, intersubject variations, subjects’ self-adjustments, vomiting process, and stress response [65,66]. As for the EGG test, increased 4–9 cpm activity and the absence or decrease of 3 cpm activity may indicate MS-induced nausea and vomiting, respectively [64]. EGG has also been demonstrated to be more sensitive than electroencephalogram, electrocardiogram, and skin conductance in MS evaluation [67].

Fos protein, an indicator of neuronal activity, is considered to be a molecular indicator for MS development and habituation [68,69]. Nevertheless, whether Fos expression can illustrate race and sex difference in MS susceptibility is still unclear. Recently, we found that motion-induced elevation of serum glucose was significantly related to GI symptoms of MS and might serve as a potential MS marker [28] (Table 1).

Motion sickness Medications

In 1869, the first usage of medications for MS is a combination of chloroform and tincture of belladonna [70]. Nowadays, there are at least 9 different kinds of drugs used against MS. Anticholinergics and antihistamines are the most effective MS prophylactics with apparent side effects such as drowsiness and depression. Drug

Table 1 Prediction and evaluation for MS

Category	Description	Application	References
MS Questionnaires			
PMHQ	Coriolis stimulation, very low-frequency ship motion, and simulator stimulation as scoring keys	Predicting SS susceptibility	[42,44]
MSSQ	Childhood and adults history of transport or entertainment exposure and MS experience	Predicting susceptibility to real motion-induced MS	[43,45]
Graybiel rating scales	Rating cardinal symptoms including cold sweating, pallor, increases in salivation, drowsiness, headache, pain, and nausea and vomiting	Evaluating MS of all forms	[58]
Wiker rating scales	Rating MS by rigging up 28 major, minor, and other symptoms	Evaluating MS of all forms	[44,59]
Kennedy rating scales	Factor analysis of oculomotor, disorientation, and nausea dimensions	Evaluating SS	[60]
Muth rating scales	Rating 3 dimensions of nausea including gastrointestinal, somatic, and emotional distress	Assessing MS-induced nausea	[61]
Gianaros rating scales	Rating gastrointestinal, central, peripheral, and sopite-related dimensions	Multidimensional analysis of MS	[62]
Vestibular function			
VOR	Higher gains and lower phase leads	Predicting MS susceptibility; indicator of semicircular canal function	[47,48]
Caloric test	Faster slow-phase velocity	Predicting MS susceptibility; indicator of semicircular canal function	[165]
cVEMPs	Higher threshold; lower peak-to-peak amplitude interval	Predicting MS susceptibility; evaluating MS habituation; indicator of saccular function	[49,50]
Physiological indexes			
CDP	Less stability in condition 5 of SOT; decreased MCT strength	Predicting postural instability of MS susceptibles; evaluating MS habituation	[52,53]
Postural dynamics	Greater positional variability; higher temporal dynamics	Predicting postural instability of MS susceptibles	[51]
Odors and tastes sensitivity	Sensitive to unpleasant odors (e.g., petrol, leather); sensitive to phenylthiocarbamide tasters	Predicting susceptibility to environment incentives	[56,57]
HRV	Reduction in (HF) high-frequency component; increment in low-frequency component (LF) and LF/HF ratio	Evaluating MS-induced sympathovagal disturbance	[63,66]
EGG	Increased 4–9 cpm activity; absence or reduction of 3 cpm activity	Evaluating MS-induced gastric response	[50,64]
Core temperature	Reduction in core temperature	Evaluating MS-induced thermal reaction	[20]
Biochemical test			
Stress hormones	Increment in levels of AVP, ACTH, cortisol, beta-endorphin, etc. after provocative motion stimulation	Evaluating MS-induced stress	[23,166]
Salivary protein and amylase	High baseline salivary protein concentration; high amylase activity	Preceding MS susceptibility	[54,55]
Fos protein	Increase expression	Indicator of MS-related neuronal activation; evaluating vestibular habituation	[69,167]
Serum glucose	Elevated after provocative motion stimulation	Indicator of severity of GI symptoms of MS	[28]

SS, simulator sickness; SOT, sensory organization test; MCT, motor control test.

combinations are thus used to increase efficacy and alleviate side effects (Table 2).

Anticholinergics

Atropine, scopolamine (hyoscine), and hyoscyamine have already been used to treat MS before World War I. A recent cochrane systematic review of 14 randomized controlled trials (RCTs) concluded that scopolamine, the nonselective muscarinic cholinergic receptor (mAChR) antagonist, was more effective than pla-

cebo but not superior to antihistamines in preventing MS and was no more likely to induce drowsiness, blurring vision, or dizziness compared to other agents [71]. Nevertheless, the precise mAChR subtypes (M_1 – M_5) that serve as the targets of scopolamine is still unclear. As we know that all mAChR subtypes are expressed in the brain, while only M_1 , M_2 , and M_5 exist in vestibular ganglia and vestibular end organs in humans [72]. The M_1 , M_3 , and M_5 are postsynaptic excitatory receptors; M_2 and M_4 receptors are inhibitory. Furthermore, selective M_3 and M_5 antagonist zamifenacin was found to be as effective as scopolamine in preventing

Table 2 Antimotion sickness medications

Category	Dosage formation	Usage	Application	References
Anticholinergics				
<i>Scopolamine</i>	p.o. (0.6 mg)	0.5–1 h before MS, effective within 6 h	Seasickness and experimental MS	[71]*
	TTS (1.5 mg/patch)	6–8 h before MS, effective over 72 h	Seasickness, airsickness, ship motion simulator, and experimental MS	[71]* [74,75]
<i>Zamifenacin</i>	IN (0.4 mg)	0.5 h before MS, effective over 6 h	Experimental MS	[76,77]*
	p.o. (0.3 mg) + TTS	1 h before MS, effective over 72 h	Seasickness	[168]
	p.o. (20 mg)	1.5 before MS	Experimental MS	[73]
Antihistamines				
<i>Dimenhydrinate</i>	p.o. (100 mg)	2 h before MS effective for 8 to 12 h	Seasickness and experimental MS	[84]* [169]
	CG (3 × 20 mg)	Chewed for 30 min each during MS	Experimental MS	[82]*
<i>Cinnarizine</i>	Oral (30 or 50 mg)	3 h before MS	Seasickness and flight simulator sickness	[170,171]
<i>Cyclizine (Marezine)</i>	p.o. (50 mg)	2 h before MS	Experimental MS	[172]
<i>Promethazine</i>	p.o. (25 or 50 mg)	2 h before MS, effective within 12 h	Space MS	[91,173]
	i.m. (25 or 50 mg)	1–2 h before MS, effective within 12 h	Space MS, parabolic flight and experimental MS	[92,174,175]
<i>Meclizine (Antivert)</i>	Suppository (25 or 50 mg)	1–2 h before MS, effective within 12 h	Space MS	[175]
	p.o. (25 or 50 mg)	1–2 h before MS, effective within 24 h	Experimental MS	[94,176]
<i>Chlorpheniramine</i> ,	p.o. (4 or 12 mg)	3–4 h before MS	Experimental MS	[83]*
<i>Betahistine</i>	p.o. (32 or 48 mg)	1–2 h before MS	Seasickness and experimental MS	[89] [177]
Dopamine Antagonists				
<i>Metoclopramide</i>	i.v. (20 mg)	15 min after MS initiation	Carsickness	[97]*
5-HT _{1B/1D} receptor agonist				
<i>Rizatriptan</i>	p.o. (10 mg)	2 h before MS	Experimental MS in migraineurs	[103]*
Sympathomimetics				
<i>D-amphetamine</i>	p.o. (10 mg)		Airsickness	[108]
Neuroleptics				
Phenytoin	p.o. (200 mg)	4 h before MS	Seasickness and parabolic flight MS	[117,118]
<i>Baclofen</i>	p.o. (20 mg)	0.5–1 h before MS	Experimental MS	[116]
Calcium channel blocker				
<i>Flunarizine</i>	–	–	Experimental MS	[125]†
μ-Opiate receptor agonist				
<i>Loperamide</i>	p.o. (16 mg)	3 h before MS	Experimental MS	[126]
Hormones				
<i>Dexamethasone</i>	i.v. (0.5 mg)	Every 6 h for 48 h	Experimental MS	[124]
Combination				
<i>Promethazine + d-amphetamine</i>	p.o. (25 mg+10 mg)	2 h before MS	Airsickness	[178]
<i>Scopolamine + d-amphetamine</i>	p.o. (0.4–1.2 mg+5 mg)	0.5–1 h before MS	Parabolic flight MS	[179]
<i>Scopolamine + ephedrine</i>	p.o. (0.3 mg+25 mg)	0.5–1 h before MS or 3 times daily	Seasickness and experimental MS	[180]*
	i.m. (0.2 mg+25 mg)	30 min before MS	Experimental MS	[181]
<i>Chlorpheniramine + ephedrine</i>	p.o. (12 mg+50 mg)	3–4 h MS	Experimental MS	[83]*
<i>Dimenhydrinate + scopolamine</i>	–	–	Air sickness	[182]†

p.o., per os; TTS, transdermal therapeutic system; IN, intranasal; CG, chewing gum; i.m., intramuscular; i.v., intravenous. *Randomized control trials. †Dosage unavailable.

MS [73]. These lines of evidence suggest that scopolamine might exert its antagonistic effect on peripheral M₁ and M₅ and/or central M₁ and M₃ mAChR to prevent MS.

The commonly used dosage forms of scopolamine include oral tablets and liquid, transdermal therapeutic system (TTS), and the

intranasal (IN) aerosol (Table 2). The TTS delivering scopolamine to the mastoid area shows a long-lasting prophylactic effect without psychomotor impairment [74,75]. Noninvasive IN formulation of scopolamine has higher peak plasma concentration and shorter peak time than oral agents [76,77]. In addition, grapefruit

juice can increase the bioavailability of orally administered scopolamine via inhibiting the cytochrome P-450 3A enzymes which are involved in oxidative demethylation of the scopolamine, while the efficacy of IN and TTS of scopolamine are affected by pH value [78,79].

Antihistamines

In 1949, Gray and Carlner for the first time discovered that antihistamine dimenhydrinate was effective in preventing seasickness [80]. Small RCTs have verified the effectiveness of the first-generation H₁ antihistamines against MS, but the second generations were ineffective [81–84] (Table 2). Physiological studies suggested that dimenhydrinate, cinnarizine, and meclizine exerted a central action on the medial VN in which high density of H₁ and H₂ receptor were present [85,86], while the promethazine had global suppression effect on vestibular system, but all these antihistamines had no effect on the central autonomic regions [87]. Betahistine, an H₃ receptor antagonist and a weak H₁ receptor agonist, is effective in the preventing seasickness and increases tolerability to Coriolis accelerations via reducing histamine release in medial VN [88,89]. Recent studies found that H₄ receptors were expressed in rat vestibular ganglia, and H₄ receptor antagonists had a pronounced inhibitory effect on primary vestibular neuron activity and significantly alleviated vestibular deficits in rats [90]. These results highlighted H₄ receptors as potential pharmacological targets for treating MS.

The main dosage forms of antihistamines include oral (all), intramuscular injection (promethazine and cyclizine), suppository (promethazine), chewing gum (dimenhydrinate), and sublingual form (dimenhydrinate) [91]. Putcha *et al.* found that promethazine, as the only drug given by three different routes (orally, intramuscularly, and rectally), was most effective and had minimal side effects when administered intramuscularly in astronauts during space shuttle missions [92]. The diphenhydramine chewing gum has been developed to alleviate antihistamine's adverse effects [82,93]. Recently, a new suspension formulation of meclizine was developed with a more rapid effect and higher maximum concentration than marketed oral tablet [94].

Monoamine Antagonists/Agonist

Dopamine D₂ and D₃ receptors are known to play a role in nausea and emesis. They can alter the amount of cAMP within neurons of the vomiting center via inhibiting adenylate cyclase [95]. Competitive D₂ receptor antagonist metoclopramide, administered through intravenous or intramuscular injection but not oral route, alleviated overall symptoms and restored gastric emptying after the initiation of MS [96,97]. In addition, orally administered domperidone, a peripherally restricted D₂ receptor antagonist and α_1 -adrenoceptor antagonist, failed to prevent spatial disorientation-induced gastric dysrhythmia and MS symptoms in humans [98,99] (Table 2). These results suggest that effectiveness of dopamine antagonists may depend on the administration route and timing. Similarly, although the 5-HT₃ receptor antagonists ondansetron are extensively used to prevent and suppress CINV and PONV [100], oral administration of this drug has no preventive effect against seasickness or experimental MS [101,102]. As MS

can induce delayed gastric emptying and reduce absorption, oral forms are problematic and injection or transdermal formation is recommended.

Additionally, two double-blind, placebo-controlled studies showed that 5-HT_{1B/1D} receptor agonist rizatriptan prevented the development of MS in migrainous patients [103,104]. The 5-HT_{2A} antagonist ketanserin significantly suppressed hypergravity-induced hypophagia in rats, while a 5-HT_{1A} agonist, 8-hydroxy-2-(di-n-propylamino) tetralin hydrobromide (8-OH-DPAT), successfully prevented vomiting induced by motion in cats and *suncus murinus* [105–107]. The precise efficacy of these drugs against MS in humans needs to be verified in the future.

Stimulants and Sedatives

Sympathomimetics d-amphetamine was found to be highly effective against space MS rather than seasickness [108]. Accumulating evidence suggests that d-amphetamine and ephedrine might counteract the sedative side effects of scopolamine and antihistamines, but at the risk of drug addiction and counterbalancing the vestibular suppression effect (Table 2). Nevertheless, scopolamine used in combination with d-amphetamine against MS should be cautioned, for scopolamine impairs decision-making and motivational behavior similar to the effect produced by amphetamine [109]. Modafinil, a potential substitute of amphetamine, significantly enhanced the efficacy of scopolamine when used in combination in rodents [110], but failed to prevent MS in humans when used alone [111]. Caffeine, a much more commonly used psychostimulant, was found to be effective in counteracting scopolamine-induced memory impairment in humans and animals [112,113], while no study has been performed to evaluate efficacy of caffeine in the management of MS alone or in combination with scopolamine and antihistamines. Neuroleptics including barbiturates, diazepam, and baclofen as well as phenytoin were found to be effective in prevention of MS [114–118] (Table 2).

Other Drugs

Clinical studies have demonstrated that powdered ginger was as effective as other anti-emetics in reducing the incidence of nausea and vomiting caused by traveling, while exploratory experimental studies had controversial outcomes possibly due to different stimulation patterns and evaluation methods used [119,120]. Chinese medicinal compound recipe composed of ginger, *pogostemonis herba*, and *radix aucklandiae* and an ancient prescription *Pingandan* are also found to be effective against MS in animals [121,122]. Our study revealed that ginsenosides combined with dexamethasone can significantly increase tolerance to acceleration in rats [123], consisting with early findings that dexamethasone can reduce susceptibility to space MS in humans [124] (Table 2). Flunarizine, a calcium channel blocker, was shown to be a peripherally acting labyrinthine suppressant. It was effective in preventing MS without central depressive side effects [125]. A placebo-controlled, crossover study showed that the peripheral acting μ -opioid agonist loperamide attenuated vertical axis rotation-induced nausea in humans [126]. The NK₁ receptor antagonist aprepitant is successfully used for preventing acute and delayed CINV [127]. The NK₁ receptor antagonists are also effective

tive against MS-induced emesis in animals but not in humans [128–130]. Recent findings have demonstrated that MS is associated with impaired endocannabinoid activity [123,131,132]. CB1 receptor agonist (Δ^9 -tetrahydrocannabinol, Δ^9 -THC) and antagonist (cannabidiolic acid) were observed to inhibit emesis induced by motion in *suncus murinus* via different neural mechanism [133,134].

Nonpharmacological Countermeasures

Habituation Training

Transient MS habituation can be induced in animals and humans by repeated or prolonged motion stimulation and may generally last for several weeks [69,135,136]. The habituation acquired under particular stimulus conditions is normally highly specific, while the time-course of habituation acquirement for linear acceleration is quite different from that for angular acceleration in humans [137]. Repeated exposure may produce more sufficient habituation than single prolonged stimulation, but desensitization to one provocative motion could not be transferred to a more severe motion stimulus [138]. Thus, the objective of habituation training is to reproduce the sensory conflict as close as possible to the provocative environment. For instance, horizontal suspension, parabolic flight, and neutral buoyancy simulation have been used as microgravity simulation methods for astronaut training [139,140]. Recent studies have demonstrated that preflight virtual reality training is also effective against space MS and disorientation [141]. As sufficient activation of vestibular system is the prerequisite to produce novel “internal model,” anti-MS drugs are not recommended during MS habituation training process [137,142].

Compared with conventional ground-based training procedures using revolving chair, winding stair, idler wheel, and swing, combined visual-vestibular habituation training was more effective and can produce long-term effect against travel-induced MS for up to 18 weeks in susceptible subjects [143,144]. Recent prospective studies also showed that optokinetic training comprising vertical, horizontal, and torsional movements of frontally projected bright spots can reconstitute the effects of swell encountered at sea and appears to be an effective training modality for the prevention of disabling seasickness [145]. In addition, the pseudorandom galvanic vestibular stimulation (GVS) is expected to be used in astronaut training against landing sickness, as it accurately replicated the postural instability, locomotor impairment, and reduced dynamic visual acuity observed in astronauts after return from space [146].

Behavioral and other Countermeasures

Forward-looking vision on the distant horizon is effective in alleviating MS symptoms via matching visual and vestibular information in subjects exposed to simulated ship motion [147]. Controlled breathing is also beneficial for managing MS symptoms and promoting habituation [148,149]. Nevertheless, breathing supplemental oxygen had no advantage over breathing air in reducing MS in healthy adults [150]. MS symptoms can be alleviated by autogenic-feedback training exercise for autonomic

responses control as well as the manipulations to enhance predictability and positive expectancy [151–153]. Recently, smoking deprivation, pleasant music, and odors as well as head vibration and mental distraction have been found to be effective in reducing MS symptoms [154–157].

High sodium and energy dense or low vitamin A, vitamin C, and iron diets as well as high frequency of meals in previous 24 h increased the airsickness occurrences in pilots [158]. A protein-predominant beverage taken 5 or 30 min before optokinetic stimulation was found to be effective in suppressing gastric tachyarrhythmia and MS symptoms [159]. A recent double-blind, placebo-controlled crossover study found that vitamin C was effective in suppressing symptoms of seasickness, particularly in youngsters [160].

Acupuncture at the P6 or Neiguan point to treat nausea and vomiting has been practiced in China for many years, but it is still controversial whether SeaBand or ReliefBand designed for acupressure or electrostimulation at P6 are effective in MS treatment [161,162]. Transcutaneous electrical nerve stimulation of the posterior neck and the right Zusanli acupoint was found to be effective in reducing simulator sickness symptoms and alleviating cognitive impairment [163]. Recently, stroboscopic illumination at 8 hertz, by ambient strobe light or by liquid crystal display shutter glasses, reduced the severity of MS symptoms and improved the performance on the vigilance task in soldiers exposed to a nauseogenic flight in a helicopter [164].

Conclusion

This study reviews the progress of sensory conflict theory, vestibular homeostasis regulation and genetic basis of MS. It also summarizes prediction and evaluation, and available countermeasures. In sensory conflict theory, the “sensory conflict neurons” remain activated and ultimately disrupt homeostasis and trigger MS responses if the provocative motion signal or reafference information mismatches the “internal model.” The heredity of MS susceptibility involves genetic and epigenetic regulation on genes participating in cellular metabolism, autonomic regulation, and vestibular function and development. Several methods are used for MS prediction and evaluation, but specific indicator is scarce. The efficacy of anti-MS medications depends on dosage forms and time of administration. Novel drugs in development show no remarkable advantages over traditional medications such as anticholinergics and antihistamines. Visual-vestibular habituation training is the most effective nonpharmacological prophylaxis. Other measures such as acupuncture and stroboscopic illumination could be substitutes for medications when side effects are unacceptable.

Acknowledgment

This study is supported by grants from the National Natural Science Foundation of China (81272178) and the Natural Science Foundation of Shanghai (12ZR1437300).

Conflict of Interest

The authors declare no conflict of interest.

References

- Lackner JR. Motion sickness: More than nausea and vomiting. *Exp Brain Res* 2014;**232**:2493–2510.
- Golding JF. Motion sickness susceptibility. *Auton Neurosci* 2006;**129**:67–76.
- Reason JT. Motion sickness adaptation: A neural mismatch model. *J R Soc Med* 1978;**71**:819–829.
- Tal D, Wiener G, Shupak A. Mal de débarquement, motion sickness and the effect of an artificial horizon. *J Vestib Res* 2014;**24**:17–23.
- Oman CM. Are evolutionary hypotheses for motion sickness “just-so” stories? *J Vestib Res* 2012;**22**:117–127.
- Carriot J, Brooks JX, Cullen KE. Multimodal integration of self-motion cues in the vestibular system: Active versus passive translations. *J Neurosci* 2013;**33**:19555–19566.
- Oman CM, Cullen KE. Brainstem processing of vestibular sensory exafference: Implications for motion sickness etiology. *Exp Brain Res* 2014;**232**:2483–2492.
- Cullen KE. The vestibular system: Multimodal integration and encoding of self-motion for motor control. *Trends Neurosci* 2012;**35**:185–196.
- Aitake M, Hori E, Matsumoto J, et al. Sensory mismatch induces autonomic responses associated with hippocampal theta waves in rats. *Behav Brain Res* 2011;**220**:244–253.
- Zou D, Aitake M, Hori E, et al. Rat hippocampal theta rhythm during sensory mismatch. *Hippocampus* 2009;**19**:350–359.
- Uno A, Takeda N, Horii A, et al. Effects of amygdala or hippocampus lesion on hypergravity-induced motion sickness in rats. *Acta Otolaryngol* 2000;**120**:860–865.
- Takahashi K, Gu Y, May PJ, et al. Multimodal coding of three-dimensional rotation and translation in area MSTd: Comparison of visual and vestibular selectivity. *J Neurosci* 2007;**27**:9742–9756.
- Chen A, DeAngelis GC, Angelaki DE. Convergence of vestibular and visual self-motion signals in an area of the posterior sylvian fissure. *J Neurosci* 2011;**31**:11617–11627.
- Demertzi A, Van Ombergen A, Tomilovskaya E, et al. Cortical reorganization in an astronaut's brain after long-duration spaceflight. *Brain Struct Funct* 2015. doi:10.1007/s00429-015-1054-3 [Epub ahead of print].
- Holstein GR, Friedrich VL Jr, Martinelli GP. Projection neurons of the vestibulo-sympathetic reflex pathway. *J Comp Neurol* 2014;**522**:2053–2074.
- Holstein GR, Friedrich VL Jr, Kang T, Kukielka E, Martinelli GP. Direct projections from the caudal vestibular nuclei to the ventrolateral medulla in the rat. *Neuroscience* 2011;**175**:104–117.
- Yates BJ, Bolton PS, Macefield VG. Vestibulo-sympathetic responses. *Compr Physiol* 2014;**4**:851–887.
- Yates BJ, Catanzaro MF, Miller DJ, McCall AA. Integration of vestibular and emetic gastrointestinal signals that produce nausea and vomiting: Potential contributions to motion sickness. *Exp Brain Res* 2014;**232**:2455–2469.
- Ossenkopp KP, Ossenkopp MD. Animal models of motion sickness: Are nonemetic species an appropriate choice? *Physiolist* 1985;**28**:S61–S62.
- Nobel G, Tribukait A, Mckjavic IB, Eiken O. Effects of motion sickness on thermoregulatory responses in a thermoneutral air environment. *Eur J Appl Physiol* 2012;**112**:1717–1723.
- Ngampramuan S, Cerri M, Del Vecchio F, et al. Thermoregulatory correlates of nausea in rats and musk shrews. *Oncotarget* 2014;**5**:1565–1575.
- Fuller PM, Jones TA, Jones SM, Fuller CA. Neurovestibular modulation of circadian and homeostatic regulation: Vestibulohypothalamic connection? *Proc Natl Acad Sci U S A* 2002;**99**:15723–15728.
- Rohleder N, Otto B, Wolf JM, et al. Sex-specific adaptation of endocrine and inflammatory responses to repeated nauseogenic body rotation. *Psychoneuroendocrinology* 2006;**31**:226–236.
- Otto B, Riepl RL, Klosterhalfen S, Enck P. Endocrine correlates of acute nausea and vomiting. *Auton Neurosci* 2006;**129**:17–21.
- Camilleri M, Papanthanasopoulos A, Odunsi ST. Actions and therapeutic pathways of ghrelin for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* 2009;**6**:343–352.
- Finley JC Jr, O'Leary M, Wester D, et al. A genetic polymorphism of the alpha2-adrenergic receptor increases autonomic responses to stress. *J Appl Physiol* (1985) 2004;**96**:2231–2239.
- Hromatka BS, Tung JY, Kiefer AK, et al. Genetic variants associated with motion sickness point to roles for inner ear development, neurological processes and glucose homeostasis. *Hum Mol Genet* 2015;**24**:2700–2708.
- Mo FF, Qin HH, Wang XL, et al. Acute hyperglycemia is related to gastrointestinal symptoms in motion sickness: An experimental study. *Physiol Behav* 2012;**105**:394–401.
- Janicki PK, Sugino S. Genetic factors associated with pharmacotherapy and background sensitivity to postoperative and chemotherapy-induced nausea and vomiting. *Exp Brain Res* 2014;**232**:2613–2625.
- Persico AM, Verdecchia M, Pinzone V, Guidetti V. Migraine genetics: Current findings and future lines of research. *Neurogenetics* 2015;**16**:77–95.
- Sharon JD, Hullar TE. Motion sensitivity and calorific responsiveness in vestibular migraine and Meniere's disease. *Laryngoscope* 2014;**124**:969–973.
- Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AM. Migraine pathophysiology: Lessons from mouse models and human genetics. *Lancet Neurol* 2015;**14**:65–80.
- Chiarella G, Petrolo C, Cassandro E. The genetics of Meniere's disease. *Appl Clin Genet* 2015;**8**:9–17.
- Taylor WE, Bhasin S, Lalani R, Datta A, Gonzalez-Cadavid NF. Alteration of gene expression profiles in skeletal muscle of rats exposed to microgravity during a spaceflight. *J Gravit Physiol* 2002;**9**:61–70.
- Ward NE, Pellis NR, Risin SA, Risin D. Gene expression alterations in activated human T-cells induced by modeled microgravity. *J Cell Biochem* 2006;**99**:1187–1202.
- Wang JQ, Qi RR, Zhou W, et al. Differential gene expression profile in the rat caudal vestibular nucleus is associated with individual differences in motion sickness susceptibility. *PLoS ONE* 2015;**10**:e0124203.
- Singh KP, Kumari R, Dumond JW. Simulated microgravity-induced epigenetic changes in human lymphocytes. *J Cell Biochem* 2010;**111**:123–129.
- Paillard AC, Quarck G, Paolino F, et al. Motion sickness susceptibility in healthy subjects and vestibular patients: Effects of gender, age and trait-anxiety. *J Vestib Res* 2013;**23**:203–209.
- Lawther A, Griffin MJ. Prediction of the incidence of motion sickness from the magnitude, frequency, and duration of vertical oscillation. *J Acoust Soc Am* 1987;**82**:957–966.
- Arribas FLP, Pineiro AL. Seasickness prediction in passenger ships at the design stage. *Ocean Eng* 2007;**34**:2086–2092.
- Birren JE, Fisher MB. Susceptibility to seasickness: a questionnaire approach. *J Appl Psychol* 1947;**31**:288–297.
- Kennedy RS. Motion sickness questionnaire and field independence scores as predictors of success in naval aviation training. *Aviat Space Environ Med* 1975;**46**:1349–1352.
- Reason JT. Relations between motion sickness susceptibility, the spiral after-effect and loudness estimation. *Br J Psychol* 1968;**59**:385–393.
- Kennedy RS, Fowlkes JE, Berbaum KS, Lillenthal MG. Use of a motion sickness history questionnaire for prediction of simulator sickness. *Aviat Space Environ Med* 1992;**63**:588–593.
- Golding JF. Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. *Brain Res Bull* 1998;**47**:507–516.
- Lamb S, Kwok KC. MSSQ-short norms may underestimate highly susceptible individuals: Updating the MSSQ-short norms. *Hum Factors* 2015;**57**:622–633.
- Nachum Z, Gordon CR, Shahal B, Spitzer O, Shupak A. Active high-frequency vestibulo-ocular reflex and seasickness susceptibility. *Laryngoscope* 2002;**112**:179–182.
- Gordon CR, Spitzer O, Doweck I, Shupak A, Gadoth N. The vestibulo-ocular reflex and seasickness susceptibility. *J Vestib Res* 1996;**6**:229–233.
- Fowler CG, Sweet A, Steffel E. Effects of motion sickness severity on the vestibular-evoked myogenic potentials. *J Am Acad Audiol* 2014;**25**:814–822.
- Tal D, Hershkovitz D, Kaminski-Graif G, et al. Vestibular evoked myogenic potentials and habituation to seasickness. *Clin Neurophysiol* 2013;**124**:2445–2449.
- Variet M, Bardy BG, Chen FC, Alcantara C, Stoffregen TA. Coupling of postural activity with motion of a ship at sea. *Exp Brain Res* 2015;**233**:1607–1616.
- Shahal B, Nachum Z, Spitzer O, et al. Computerized dynamic posturography and seasickness susceptibility. *Laryngoscope* 1999;**109**:1996–2000.
- Tal D, Bar R, Nachum Z, Gil A, Shupak A. Postural dynamics and habituation to seasickness. *Neurosci Lett* 2010;**479**:134–137.
- Igarashi M, Reschke MF, Henley C, et al. Salivary total protein and experimental Coriolis sickness. *Acta Otolaryngol Suppl* 1993;**504**:38–40.
- Gordon CR, Jackman Y, Ben-Aryeh H, et al. Salivary secretion and seasickness susceptibility. *Aviat Space Environ Med* 1992;**63**:356–359.
- Sharma K, Sharma P, Sharma A, Singh G. Phenylthiocarbamide taste perception and susceptibility to motion sickness: Linking higher susceptibility with higher phenylthiocarbamide taste acuity. *J Laryngol Otol* 2008;**122**:1064–1073.
- Paillard A, Jacquot L, Millot JL. Olfactory perception and motion sickness. *Chem Senses* 2011;**36**:E35–E36.
- Graybiel A, Wood CD, Miller EF, Cramer DB. Diagnostic criteria for grading the severity of acute motion sickness. *Aerosp Med* 1968;**39**:453–455.
- Wiker SF, Kennedy RS, McCauley ME, Pepper RL. Susceptibility to seasickness: Influence of hull design and steaming direction. *Aviat Space Environ Med* 1979;**50**:1046–1051.
- Fowlkes JE, Kennedy RS, Hettinger LJ, Harm DL. Changes in the dark focus of accommodation associated with simulator sickness. *Aviat Space Environ Med* 1993;**64**:612–618.
- Muth ER, Stern RM, Thayer JF, Koch KL. Assessment of the multiple dimensions of nausea: The Nausea Profile (NP). *J Psychosom Res* 1996;**40**:511–520.
- Gianaros PJ, Muth ER, Mordkoff JT, Levine ME, Stern RM. A questionnaire for the assessment of the multiple dimensions of motion sickness. *Aviat Space Environ Med* 2001;**72**:115–119.
- Lin CT, Lin CL, Chiu TW, Duann JR, Jung TP. Effect of respiratory modulation on relationship between heart rate variability and motion sickness. *Conf Proc IEEE Eng Med Biol Soc* 2011;**2011**:1921–1924.
- Lang IM, Sarna SK, Shaker R. Gastrointestinal motor and myoelectric correlates of motion sickness. *Am J Physiol* 1999;**277**:G642–G652.
- Lin CL, Jung TP, Chuang SW, et al. Self-adjustments may account for the contradictory correlations between HRV and motion-sickness severity. *Int J Psychophysiol* 2013;**87**:70–80.
- Lacout L, Napadow V, Kuo B, et al. Dynamic cardiovascular response to motion sickness: A point-process

- heart rate variability study. *Comput Cardiol* 2009;**36**:49–52.
67. Hu S, McChesney KA, Player KA, et al. Systematic investigation of physiological correlates of motion sickness induced by viewing an optokinetic rotating drum. *Aviat Space Environ Med* 1999;**70**:759–765.
 68. Pompeiano O, d'Ascanio P, Balaban E, Centini C, Pompeiano M. Gene expression in autonomic areas of the medulla and the central nucleus of the amygdala in rats during and after space flight. *Neuroscience* 2004;**124**:53–69.
 69. Cai YL, Wang JQ, Chen XM, et al. Decreased Fos protein expression in rat caudal vestibular nucleus is associated with motion sickness habituation. *Neurosci Lett* 2010;**480**:87–91.
 70. Schmal F. Neuronal mechanisms and the treatment of motion sickness. *Pharmacology* 2013;**91**:229–241.
 71. Spinks A, Wasiak J. Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database Syst Rev* 2011;CD002851.
 72. Ishiyama A, Lopez I, Wackym PA. Molecular characterization of muscarinic receptors in the human vestibular periphery. Implications for pharmacotherapy. *Am J Otol* 1997;**18**:648–654.
 73. Golding JF, Stott JR. Comparison of the effects of a selective muscarinic receptor antagonist and hyoscine (scopolamine) on motion sickness, skin conductance and heart rate. *Br J Clin Pharmacol* 1997;**43**:633–637.
 74. Noy S, Shapira S, Zilbiger A, Ribak J. Transdermal therapeutic system scopolamine (TTSS), dimenhydrinate, and placebo—a comparative study at sea. *Aviat Space Environ Med* 1984;**55**:1051–1054.
 75. Gleiter CH, Antonin KH, Bieck PR. Transdermally applied scopolamine does not impair psychomotor performance. *Psychopharmacology* 1984;**83**:397–398.
 76. Klocker N, Hanschke W, Toussaint S, Verse T. Scopolamine nasal spray in motion sickness: A randomised, controlled, and crossover study for the comparison of two scopolamine nasal sprays with oral dimenhydrinate and placebo. *Eur J Pharm Sci* 2001;**13**:227–232.
 77. Simmons RG, Phillips JB, Lojewski RA, et al. The efficacy of low-dose intranasal scopolamine for motion sickness. *Aviat Space Environ Med* 2010;**81**:405–412.
 78. Ebert U, Oertel R, Kirch W. Influence of grapefruit juice on scopolamine pharmacokinetics and pharmacodynamics in healthy male and female subjects. *Int J Clin Pharmacol Ther* 2000;**38**:523–531.
 79. Renner UD, Oertel R, Kirch W. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. *Ther Drug Monit* 2005;**27**:655–665.
 80. Gay LN, Carliner PE. The prevention and treatment of motion sickness I. seasickness. *Science* 1949;**109**:359.
 81. Cheung BS, Heskin R, Hofer KD. Failure of cetirizine and fexofenadine to prevent motion sickness. *Ann Pharmacother* 2003;**37**:173–177.
 82. Seibel K, Schaffler K, Reitemir P, Golly I. A randomised, placebo-controlled study comparing two formulations of dimenhydrinate with respect to efficacy in motion sickness and sedation. *Arzneimittelforschung* 2002;**52**:529–536.
 83. Buckley JC Jr, Alvaranga DL, MacKenzie TA. Chlorpheniramine and ephedrine in combination for motion sickness. *J Vestib Res* 2007;**17**:301–311.
 84. Pyykko I, Schalen L, Jantti V. Transdermally administered scopolamine vs. dimenhydrinate. I. Effect on nausea and vertigo in experimentally induced motion sickness. *Acta Otolaryngol* 1985;**99**:588–596.
 85. Zhou L, Zhou W, Zhang S, et al. Changes in histamine receptors (H1, H2, and H3) expression in rat medial vestibular nucleus and flocculus after unilateral labyrinthectomy: Histamine receptors in vestibular compensation. *PLoS ONE* 2013;**8**:e66684.
 86. Zhang XY, Yu L, Zhuang QX, et al. Postsynaptic mechanisms underlying the excitatory action of histamine on medial vestibular nucleus neurons in rats. *Br J Pharmacol* 2013;**170**:156–169.
 87. Weerts AP, De Meyer G, Pauwels G, et al. Pharmaceutical countermeasures have opposite effects on the utricles and semicircular canals in man. *Audiol Neurootol* 2012;**17**:235–242.
 88. Wang JJ, Dutia MB. Effects of histamine and betahistine on rat medial vestibular nucleus neurones: Possible mechanism of action of anti-histaminergic drugs in vertigo and motion sickness. *Exp Brain Res* 1995;**105**:18–24.
 89. Matsnev EI, Sigaleva EE. Efficacy of histaminergic drugs in experimental motion sickness. *J Vestib Res* 2007;**17**:313–321.
 90. Desmadril G, Gaboyard-Niay S, Brugeaud A, et al. Histamine H4 receptor antagonists as potent modulators of mammalian vestibular primary neuron excitability. *Br J Pharmacol* 2012;**167**:905–916.
 91. Murdin L, Golding J, Bronstein A. Managing motion sickness. *BMJ* 2011;**343**:d7430.
 92. Putcha L, Berens KL, Marshburn TH, Ortega HJ, Billica RD. Pharmaceutical use by U.S. astronauts on space shuttle missions. *Aviat Space Environ Med* 1999;**70**:705–708.
 93. Valoti M, Frosini M, Dragoni S, Fusi F, Sgaragli G. Pharmacokinetics of diphenhydramine in healthy volunteers with a dimenhydrinate 25 mg chewing gum formulation. *Methods Find Exp Clin Pharmacol* 2003;**25**:377–381.
 94. Wang Z, Lee B, Pearce D, et al. Meclizine metabolism and pharmacokinetics: Formulation on its absorption. *J Clin Pharmacol* 2012;**52**:1343–1349.
 95. Sanger GJ, Andrews PL. Treatment of nausea and vomiting: Gaps in our knowledge. *Auton Neurosci* 2006;**129**:3–16.
 96. Kohl RL. Failure of metoclopramide to control emesis or nausea due to stressful angular or linear acceleration. *Aviat Space Environ Med* 1987;**58**:125–131.
 97. Rubio S, Weichenthal L, Andrews J. Motion sickness: Comparison of metoclopramide and diphenhydramine to placebo. *Prehosp Disaster Med* 2011;**26**:305–309.
 98. Takeda N, Hasegawa S, Morita M, et al. Neuropharmacological mechanisms of emesis. I. Effects of antiemetic drugs on motion- and apomorphine-induced pica in rats. *Methods Find Exp Clin Pharmacol* 1995;**17**:589–590.
 99. Kono T, Tokumaru O, Mizumoto C, Tatsuno J, Chen JD. Impaired gastric slow waves induced by spatial disorientation and effect of domperidone. *Am J Gastroenterol* 1999;**94**:1224–1229.
 100. Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2006;CD004125.
 101. Hershkovitz D, Asna N, Shupak A, et al. Ondansetron for the prevention of seasickness in susceptible sailors: An evaluation at sea. *Aviat Space Environ Med* 2009;**80**:643–646.
 102. Levine ME, Chillias JC, Stern RM, Knox GW. The effects of serotonin (5-HT₃) receptor antagonists on gastric tachyarrhythmia and the symptoms of motion sickness. *Aviat Space Environ Med* 2000;**71**:1111–1114.
 103. Furman JM, Marcus DA, Balaban CD. Rizatriptan reduces vestibular-induced motion sickness in migraineurs. *J Headache Pain* 2011;**12**:81–88.
 104. Marcus DA, Furman JM. Prevention of motion sickness with rizatriptan: A double-blind, placebo-controlled pilot study. *Med Sci Monit* 2006;**12**:P11–P17.
 105. Abe C, Tanaka K, Iwata C, Morita H. Vestibular-mediated increase in central serotonin plays an important role in hypergravity-induced hypophagia in rats. *J Appl Physiol* (1985) 2010;**109**:1635–1643.
 106. Lucot JB, Crampton GH. 8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin or xylazine. *Pharmacol Biochem Behav* 1989;**33**:627–631.
 107. Brame RE, Lucot JB. Guamanian *Suncus murinus* responsiveness to emetic stimuli and the antiemetic effects of 8-OH-DPAT. *Pharmacol Biochem Behav* 2011;**99**:381–384.
 108. Wood CD, Kennedy RE, Graybiel A, Trumbull R, Wherry RJ. Clinical effectiveness of anti-motion-sickness drugs. Computer review of the literature. *JAMA* 1966;**198**:1155–1158.
 109. Silveira MM, Malcolm E, Shoaib M, Winstanley CA. Scopolamine and amphetamine produce similar decision-making deficits on a rat gambling task via independent pathways. *Behav Brain Res* 2015;**281**:86–95.
 110. Yu XH, Cai GJ, Liu AJ, Chu ZX, Su DF. A novel animal model for motion sickness and its first application in rodents. *Physiol Behav* 2007;**92**:702–707.
 111. Hoyt RE, Lawson BD, McGee HA, Strompolis ML, McClellan MA. Modafinil as a potential motion sickness countermeasure. *Aviat Space Environ Med* 2009;**80**:709–715.
 112. Botton PH, Costa MS, Ardaís AP, et al. Caffeine prevents disruption of memory consolidation in the inhibitory avoidance and novel object recognition tasks by scopolamine in adult mice. *Behav Brain Res* 2010;**214**:254–259.
 113. Riedel W, Hogervorst E, Lebourg R, et al. Caffeine attenuates scopolamine-induced memory impairment in humans. *Psychopharmacology* 1995;**122**:158–168.
 114. Noble RL. The effect of barbiturates and other substances on motion sickness in dogs. *Can J Res E Med Sci* 1948;**26**:283–294.
 115. McClure JA, Lyceet P, Baskerville JC. Diazepam as an anti-motion sickness drug. *J Otolaryngol* 1982;**11**:253–259.
 116. Cohen B, Dai M, Yakushin SB, Raphan T. Baclofen, motion sickness susceptibility and the neural basis for velocity storage. *Prog Brain Res* 2008;**171**:543–553.
 117. Chelen W, Kabrisky M, Hatsell C, et al. Use of phenytoin in the prevention of motion sickness. *Aviat Space Environ Med* 1990;**61**:1022–1025.
 118. Knox GW, Woodard D, Chelen W, Ferguson R, Johnson L. Phenytoin for motion sickness: Clinical evaluation. *Laryngoscope* 1994;**104**:935–939.
 119. Chrubasik S, Pittler MH, Roufogalis BD. Zingiberis rhizoma: A comprehensive review on the ginger effect and efficacy profiles. *Phytomedicine* 2005;**12**:684–701.
 120. Palatty PL, Haniadka R, Valder B, Arora R, Baliga MS. Ginger in the prevention of nausea and vomiting: A review. *Crit Rev Food Sci Nutr* 2013;**53**:659–669.
 121. Chen Y, Zhang C, Zhang M, Fu X. Three statistical experimental designs for enhancing yield of active compounds from herbal medicines and anti-motion sickness bioactivity. *Pharmacogn Mag* 2015;**11**:435–443.
 122. Pei JS, Tong BL, Chen KJ, Li CS, Zhang GX. Experimental research on antimotion sickness effects of Chinese medicine “pingandan” pills in cats. *Chin Med J (Engl)* 1992;**105**:322–327.
 123. Zheng Y, Wang XL, Mo FF, Li M. Dexamethasone alleviates motion sickness in rats in part by enhancing the endocannabinoid system. *Eur J Pharmacol* 2014;**727**:99–105.
 124. Kohl RL, MacDonald S. New pharmacologic approaches to the prevention of space/motion sickness. *J Clin Pharmacol* 1991;**31**:934–946.
 125. Lee JA, Watson LA, Boothby G. Calcium antagonists in the prevention of motion sickness. *Aviat Space Environ Med* 1986;**57**:45–48.
 126. Otto B, Riepl RL, Otto C, et al. mu-Opiate receptor agonists – a new pharmacological approach to prevent motion sickness? *Br J Clin Pharmacol* 2006;**61**:27–30.
 127. Hargreaves R, Ferreira JC, Hughes D, et al. Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. *Ann N Y Acad Sci* 2011;**1222**:40–48.

128. Mathis A, Lee K, Alibhai HI. The use of maropitant to prevent vomiting induced by epidural administration of preservative free morphine through an epidural catheter in a dog. *Vet Anaesth Analg* 2011;**38**:516–517.
129. Reid K, Palmer JL, Wright RJ, et al. Comparison of the neurokinin-1 antagonist GR205171, alone and in combination with the 5-HT₃ antagonist ondansetron, hyoscine and placebo in the prevention of motion-induced nausea in man. *Br J Clin Pharmacol* 2000;**50**:61–64.
130. Lucot JB, Obach RS, McLean S, Watson JW. The effect of CP-99994 on the responses to provocative motion in the cat. *Br J Pharmacol* 1997;**120**:116–120.
131. Chouker A, Kaufmann I, Kreth S, et al. Motion sickness, stress and the endocannabinoid system. *PLoS ONE* 2010;**5**:e10752.
132. Strewé C, Feurercker M, Nichiporuk I, et al. Effects of parabolic flight and spaceflight on the endocannabinoid system in humans. *Rev Neurosci* 2012;**23**:673–680.
133. Cluny NL, Naylor RJ, Whittle BA, Javid FA. The effects of cannabidiol and tetrahydrocannabinol on motion-induced emesis in *Suncus murinus*. *Basic Clin Pharmacol Toxicol* 2008;**103**:150–156.
134. Bolognini D, Rock EM, Cluny NL, et al. Cannabidiolic acid prevents vomiting in *Suncus murinus* and nausea-induced behaviour in rats by enhancing 5-HT_{1A} receptor activation. *Br J Pharmacol* 2013;**168**:1456–1470.
135. Wilpizeski CR, Lowry LD, Miller R. Intensification and habituation of experimental motion sickness in squirrel monkeys by repeated horizontal rotation. *Otolaryngol Head Neck Surg* 1986;**94**:628–632.
136. Hu S, Stern RM. The retention of adaptation to motion sickness eliciting stimulation. *Aviat Space Environ Med* 1999;**70**:766–768.
137. Wood CD, Stewart JJ, Wood MJ, et al. Habituation and motion sickness. *J Clin Pharmacol* 1994;**34**:628–634.
138. Cheung B, Hofer K. Desensitization to strong vestibular stimuli improves tolerance to simulated aircraft motion. *Aviat Space Environ Med* 2005;**76**:1099–1104.
139. Strauss S. Space medicine at the NASA-JSC, neutral buoyancy laboratory. *Aviat Space Environ Med* 2008;**79**:732–733.
140. De Witt JK, Perusek GP, Lewandowski BE, et al. Locomotion in simulated and real microgravity: Horizontal suspension vs. parabolic flight. *Aviat Space Environ Med* 2010;**81**:1092–1099.
141. Chen W, Chao JG, Chen XW, Wang JK, Tan C. Quantitative orientation preference and susceptibility to space motion sickness simulated in a virtual reality environment. *Brain Res Bull* 2015;**113**:17–26.
142. Wood CD, Manno JE, Manno BR, Odenheimer RC, Bairnsfather LE. The effect of antimotion sickness drugs on habituation to motion. *Aviat Space Environ Med* 1986;**57**:539–542.
143. Dai M, Raphan T, Cohen B. Prolonged reduction of motion sickness sensitivity by visual-vestibular interaction. *Exp Brain Res* 2011;**210**:503–513.
144. Stroud KJ, Harm DL, Klaus DM. Preflight virtual reality training as a countermeasure for space motion sickness and disorientation. *Aviat Space Environ Med* 2005;**76**:352–356.
145. Ressiot E, Dolz M, Bonne L, Marianowski R. Prospective study on the efficacy of optokinetic training in the treatment of seasickness. *Eur Ann Otorhinolaryngol Head Neck Dis* 2013;**130**:263–268.
146. Dilda V, MacDougall HG, Moore ST. Tolerance to extended galvanic vestibular stimulation: Optimal exposure for astronaut training. *Aviat Space Environ Med* 2011;**82**:770–774.
147. Tal D, Gonen A, Wiener G, et al. Artificial horizon effects on motion sickness and performance. *Otol Neurotol* 2012;**33**:878–885.
148. Stromberg SE, Russell ME, Carlson CR. Diaphragmatic breathing and its effectiveness for the management of motion sickness. *Aerosp Med Hum Perform* 2015;**86**:452–457.
149. Yen Pik Sang F, Billar J, Gresty MA, Golding JF. Effect of a novel motion desensitization training regime and controlled breathing on habituation to motion sickness. *Percept Mot Skills* 2005;**101**:244–256.
150. Zivara NV, Yen Pik Sang FD, Golding JF, Bronstein AM, Gresty MA. Effect of breathing supplemental oxygen on motion sickness in healthy adults. *Mayo Clin Proc* 2003;**78**:574–578.
151. Cowings PS, Toscano WB. Autogenic-feedback training exercise is superior to promethazine for control of motion sickness symptoms. *J Clin Pharmacol* 2000;**40**:1154–1165.
152. Levine ME, Stern RM, Koch KL. The effects of manipulating expectations through placebo and nocebo administration on gastric tachyarrhythmia and motion-induced nausea. *Psychosom Med* 2006;**68**:478–486.
153. Levine ME, Stern RM, Koch KL. Enhanced perceptions of control and predictability reduce motion-induced nausea and gastric dysrhythmia. *Exp Brain Res* 2014;**232**:2675–2684.
154. Bos JE. Less sickness with more motion and/or mental distraction. *J Vestib Res* 2015;**25**:23–33.
155. Keshavarz B, Hecht H. Pleasant music as a countermeasure against visually induced motion sickness. *Appl Ergon* 2014;**45**:521–527.
156. Golding JF, Prosyaniikova O, Flynn M, Gresty MA. The effect of smoking nicotine tobacco versus smoking deprivation on motion sickness. *Auton Neurosci* 2011;**160**:53–58.
157. Keshavarz B, Stelzmann D, Paillard A, Hecht H. Visually induced motion sickness can be alleviated by pleasant odors. *Exp Brain Res* 2015;**233**:1353–1364.
158. Lindseth G, Lindseth PD. The relationship of diet to airsickness. *Aviat Space Environ Med* 1995;**66**:537–541.
159. Williamson MJ, Levine ME, Stern RM. The effect of meals of varying nutritional composition on subjective and physiological markers of nausea in response to optokinetic motion. *Digestion* 2005;**72**:254–260.
160. Jarisch R, Weyer D, Ehlert E, et al. Impact of oral vitamin C on histamine levels and seasickness. *J Vestib Res* 2014;**24**:281–288.
161. Miller KE, Muth ER. Efficacy of acupressure and acustimulation bands for the prevention of motion sickness. *Aviat Space Environ Med* 2004;**75**:227–234.
162. Stern RM, Jakerst MD, Muth ER, Hollis C. Acupressure relieves the symptoms of motion sickness and reduces abnormal gastric activity. *Altern Ther Health Med* 2001;**7**:91–94.
163. Chu H, Li MH, Huang YC, Lee SY. Simultaneous transcutaneous electrical nerve stimulation mitigates simulator sickness symptoms in healthy adults: A crossover study. *BMC Complement Altern Med* 2013;**13**:84.
164. Webb CM, Estrada A, Athy JR. Motion sickness prevention by an 8-Hz stroboscopic environment during air transport. *Aviat Space Environ Med* 2013;**84**:177–183.
165. Cui J, Mukai C, Iwase S, et al. Response to vestibular stimulation of sympathetic outflow to muscle in humans. *J Auton Nerv Syst* 1997;**66**:154–162.
166. Drummer C, Stromeyer H, Riepl RL, et al. Hormonal changes after parabolic flight: Implications on the development of motion sickness. *Aviat Space Environ Med* 1990;**61**:821–828.
167. Cai YL, Ma WL, Li M, et al. Glutamatergic vestibular neurons express Fos after vestibular stimulation and project to the NTS and the PBN in rats. *Neurosci Lett* 2007;**417**:132–137.
168. Nachum Z, Sahal B, Shupak A, et al. Scopolamine bioavailability in combined oral and transdermal delivery. *J Pharmacol Exp Ther* 2001;**296**:121–123.
169. Muth ER, Elkins AN. High dose ondansetron for reducing motion sickness in highly susceptible subjects. *Aviat Space Environ Med* 2007;**78**:686–692.
170. Doweck I, Gordon CR, Spitzer O, Melamed Y, Shupak A. Effect of cinnarizine in the prevention of seasickness. *Aviat Space Environ Med* 1994;**65**:606–609.
171. Lucertini M, Mirante N, Casagrande M, Trivelloni P, Lugli V. The effect of cinnarizine and cocculus indicus on simulator sickness. *Physiol Behav* 2007;**91**:180–190.
172. Weinstein SE, Stern RM. Comparison of marezine and dramamine in preventing symptoms of motion sickness. *Aviat Space Environ Med* 1997;**68**:890–894.
173. Gandia P, Saivin S, Le-Traon AP, Guell A, Houin G. Influence of simulated weightlessness on the intramuscular and oral pharmacokinetics of promethazine in 12 human volunteers. *J Clin Pharmacol* 2006;**46**:1008–1016.
174. Cowings PS, Toscano WB, DeRoshia C, Miller NE. Promethazine as a motion sickness treatment: Impact on human performance and mood states. *Aviat Space Environ Med* 2000;**71**:1013–1022.
175. Davis JR, Jennings RT, Beck BG. Comparison of treatment strategies for Space Motion Sickness. *Acta Astronaut* 1993;**29**:587–591.
176. Wood CD, Graybiel A. Evaluation of sixteen anti-motion sickness drugs under controlled laboratory conditions. *Aerosp Med* 1968;**39**:1341–1344.
177. Gordon CR, Doweck I, Nachum Z, et al. Evaluation of betahistine for the prevention of seasickness: Effect on vestibular function, psychomotor performance and efficacy at sea. *J Vestib Res* 2003;**13**:103–111.
178. Weerts A, Pattyn N, Van de Heyning P, Wuys F. Evaluation of the effects of anti-motion sickness drugs on subjective sleepiness and cognitive performance of healthy males. *J Psychopharmacol* 2013;**28**:655–664.
179. Makowski AL, Lindgren K, Locke JP. Visual side effects of scopolamine/dextroamphetamine among parabolic fliers. *Aviat Space Environ Med* 2011;**82**:683–688.
180. Tokola O, Laitinen LA, Aho J, Gothoni G, Vapaatalo H. Drug treatment of motion sickness: Scopolamine alone and combined with ephedrine in real and simulated situations. *Aviat Space Environ Med* 1984;**55**:636–641.
181. Wood CD, Stewart JJ, Wood MJ, Mims M. Effectiveness and duration of intramuscular antimotion sickness medications. *J Clin Pharmacol* 1992;**32**:1008–1012.
182. Chinn HI, Strickland BA, Waltrip OH, Gainer SH. Prevention of air sickness by benadryl-scopolamine mixtures. *US Armed Forces Med J* 1951;**2**:401–404.