Autonomic Neuroscience: Basic and Clinical 129 (2006) 67–76

AUTONOMIC NEUROSCIENCE: Basic & Clinical

www.elsevier.com/locate/autneu

# Motion sickness susceptibility

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**Abstract**

Motion sickness can be caused by a variety of motion environments (e.g., cars, boats, planes, tilting trains, funfair rides, space, virtual reality) and given a sufficiently provocative motion stimulus almost anyone with a functioning vestibular system can be made motion sick. Current hypotheses of the '*Why?*' of motion sickness are still under investigation, the two most important being 'toxin detector' and the 'vestibular–cardiovascular reflex'. By contrast, the '*How?*' of motion sickness is better understood in terms of mechanisms (e.g., 'sensory conflict' or similar) and stimulus properties (e.g., acceleration, frequency, duration, visual–vestibular time-lag). Factors governing motion sickness susceptibility may be divided broadly into two groups: (i) those related to the stimulus (motion type and provocative property of stimulus); and (ii) those related to the individual person (habituation or sensitisation, individual differences, protective behaviours, administration of anti-motion sickness drugs). The aim of this paper is to review some of the more important factors governing motion sickness susceptibility, with an emphasis on the personal rather than physical stimulus factors.


*Keywords:* Motion sickness; Vestibular; Individual differences; Evolution; Personality; Pharmacology; Perception

## 1. Introduction

More than two thousand years ago the Greek physician Hippocrates observed that '… sailing on the sea proves that motion disorders the body …' (Reason and Brand, 1975). Indeed the term 'nausea' derives from the Greek root word 'naus', hence 'nautical' meaning a ship. The last hundred years innovation of transport and industry have extended the range of provocative motion environments, to cars, tilting trains, funfair rides, aircraft, weightlessness in outer-space, virtual reality, and simulators. The general term 'motion sickness' is best applied across all of those stimulus specific terms such as car-sickness, air-sickness, space-sickness or sea-sickness.

The primary functions of the vestibular system are spatial orientation, maintenance of balance, and stabilising of vision through vestibular–ocular reflexes. An additional vestibular function has been proposed, which is that it acts as a toxin detector. Thus, the evolutionary purpose of what we call 'motion sickness' is postulated to be the same as for any emetic response, which is to protect the organism from the toxic effects of potentially harmful substances that it may have ingested (Treisman, 1977). The "toxin detector" hypothesis proposes that the brain has evolved to recognise any derangement of expected patterns of vestibular, visual, and kinaesthetic information as evidence of central nervous system malfunction and to initiate vomiting as a defence against a possible ingested neurotoxin, i.e., it provides a 'backup' to the main toxin detector system of chemoreceptors of the afferent vagal nerves and the chemoreceptor trigger zone of the brainstem. According to this hypothesis, motion sickness in pedestrian man or other animals is simply the inadvertent activation of this ancient defence reflex by the sensory conflicts induced by the novel altered visual and force environments of sea, air, land transport or virtual reality. This evolutionary-based hypothesis is consistent with the observation that motion sickness is evolutionarily well preserved from man down to the level of the fish (ironically, fish can become seasick during aquarium transport) (Reason and Brand, 1975). It is also consistent with the observation that people who are more susceptible to motion sickness are also more susceptible to toxins, chemotherapy, and post-operative nausea and vomiting (e.g., Morrow, 1985). Finally, this theory has been experimentally tested with evidence of

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doi:10.1016/j.autneu.2006.07.019

reduced emetic response to challenge from toxins after bilateral vestibular ablation (Money and Cheung, 1983).

An alternative hypothesis is based on the observation that tilt stimulation of the otoliths in the cat, which transduce linear accelerations, provoke a pressor response (increased blood pressure and cardiac output) mediated via vestibular–cardiovascular projections. It has been proposed that motion sickness is caused by the inappropriate activation of such vestibular–cardiovascular reflexes "… the vestibular and visual systems … influence autonomic control for the purpose of maintaining homeostasis during movement and changes in posture… motion sickness results from an aberrant activation of neural pathways that serve to maintain a stable internal environment and it is not a poison response to eliminate toxins from the body, as has been suggested by others…" (Yates et al., 1998 page 402). A somewhat similar, non-functional explanation has been proposed by Balaban (1999) that motion sickness might be regarded as referred visceral discomfort after activation of vestibular autonomic reflexes due to the convergence of vestibular and autonomic afferent information in the brainstem and cerebellum. The vestibular–cardiovascular reflex hypothesis has a good historical pedigree in the 19th Century concept of 'cerebral anaemia' as the cause of motion sickness (Nunn, 1881). More recent support comes from an observation that cerebral hypoperfusion preceded nausea during gravito-inertial force variation induced by centrifugation (Serrador et al., 2005). However there is a considerable overlap between sick and non-sick individuals' pressor responses to the gravito-inertial force variation induced by parabolic flight (Schelgel et al., 2001). The importance of the vestibular–cardiovascular reflexes in maintaining blood pressure seems limited since bilateral labyrinthectomised patients' pressor responses to rapid tilts are only minimally slower than normals (<500 ms) (Radtke et al., 2003). The importance of such a hypothesis is undermined also by the observation that these patients do not appear to be fainting frequently as they adjust their posture during everyday activity as they walk around, lay down and stand up. Moreover, although not a formal disproof, this hypothesis does not predict the relative nauseogenicity of the various gravity and body referenced directions of nauseogenic provocative motion, which would be expected to alter blood pressure (Golding et al., 1995, 2003).

Both the so-called toxin detector and vestibular–cardiovascular reflex hypotheses remain in contention to provide explanations for the 'why' of motion sickness. Another hypothesis, which has received less attention, postulates that motion sickness is a punishment system which has evolved to discourage development of perceptual–motor programmes that are inefficient or cause spatial disorientation (Guedry et al., 1998). At present, the balance of evidence favours the toxin detector hypothesis.

## 2. Provocative stimuli

Although the '*Why?*' of motion sickness is uncertain (see above), the '*How?*' of motion sickness mechanisms (qualitative types of stimuli, physical characteristics, engineering standards, sensory conflict, etc) is much better understood. The variety of stimuli that can provoke motion sickness is wide (see Table 1).

The key observation is that the physical intensity of the stimulus is not necessarily related to the degree of nauseogenicity. For example, with optokinetic stimuli the motion is implied but not real, as when a person sitting at the front in a wide screen cinema experiences self-vection and 'cinerama sickness' despite the lack of any motion in the real physical world. In this example, the vestibular and somatosensory systems are signalling that the person is sitting still, but the visual system is signalling illusory movement or self-vection. Consequently the generally accepted explanation of the 'how' of motion sickness is based on some form of sensory conflict or sensory mismatch. The sensory conflict or sensory mismatch is between actual versus expected invariant patterns of vestibular, visual and kinaesthetic inputs (Reason and Brand, 1975). These also include intra-vestibular conflicts between rotational accelerations sensed by the semi-circular canals and linear-translational accelerations (including gravitational) sensed by the otoliths. A variety of detailed models have been developed to explain the nature of sensory conflict or sensory mismatch (e.g., Oman, 1990; Benson, 1999) as well as simplified rule based models. With regard to the latter, Stott (1986) proposed a useful set of simple rules which if broken, will lead to motion sickness:

Rule 1. Visual–vestibular: motion of the head in one direction must result in motion of the external visual scene in the opposite direction;

Table 1
Provocative stimuli

| Context | Examples of provocative stimuli |
|---|---|
| Land | Cars, coaches, tilting trains, ski, camels, elephants, funfair rides |
| Sea | Boats, ferries, survival rafts, divers' lines undersea |
| Air | Transport planes, small aircraft, hovercraft, helicopters, parabolic flight |
| Space | Shuttle, Spacelab |
| Optokinetic | Wide-screen cinemas, microfiche-readers, 'haunted swing', simulators, virtual reality (HMD), rotating visual drums or spheres, pseudo-Coriolis, reversing prism spectacles |
| Laboratory | Cross-coupled (Coriolis), low frequency translational oscillation (vertical or horizontal), off vertical axis rotation (OVAR), counter-rotation, *g*-excess in human centrifuges |
| Correlated stimuli | Emetic toxins, chemotherapy, post operative nausea and vomiting (PONV), extreme arousal (fear increases, fight decreases) |

'Laboratory' stimuli evoking motion sickness are simply refined elements of those provocative stimuli found in the outside world. 'Optokinetic' stimuli are classed separately since they do not need additional physical transportation of the person under all definitions, although some might be also classed under 'Laboratory'. 'Correlated' stimuli are included to indicate the basic evolutionary functions served by nausea and vomiting.

Rule 2. Canal–otolith: rotation of the head, other than in the horizontal plane, must be accompanied by appropriate angular change in the direction of the gravity vector;

Rule 3. Utricle–saccule: any sustained linear acceleration is due to gravity, has an intensity of 1 *g* and defines 'downwards.'

In other words, the visual world should remain space stable, and gravity should always point down and average over a few seconds to 1 *g*.

Bos and Bles (1998) proposed an even more simplified rule. This is that there is only one conflict of interest, between the subjective expected vertical and the sensed vertical. However, although this single rule appears simple, the underlying model is very extensive, as are all the models using or implying frames of reference.

The application of such rules to explain the mechanism of motion sickness in any given environment can be complex because multiple stimuli and conflicts may be involved. One example may suffice. Airsickness in a pilot produced by the flight of an agile military aircraft may be due to several sources. Flying straight and level through air turbulence frequently encountered close to the ground or sea, produces low frequency translational oscillation of the aircraft, which may cause airsickness. During co-ordinated aircraft turns there may be simultaneous provocation from the four following sources: (a) visual–vestibular mismatches as the pilot senses 'down' to remain through the axis of the body but the external visual world to be tilted; (b) sustained changes in the scalar magnitude of gravito-inertial force due to centripetal acceleration; (c) cross-coupling (Coriolis) due to head movements during rotation of the aircraft if the turn is tight enough; and (d) also the *g*-excess illusion if the pilot tilts the head during increased gravito-inertial force.

Whereas there has been much success in explaining the mechanisms of motion sickness, progress has been more limited in providing quantitative models to predict the severity of nausea and the incidence of vomiting. In virtual reality systems (and simulators), self-vection and poor eye collimation may be an important provocative stimulus, but phase lag between real motion and the corresponding update of the visual display may be equally or more important. Compensatory vestibular–ocular reflexes to head movements are as fast as 10 ms or so, consequently visual update lag disparities not much longer than this may be easily detectable by subjects. If update lags are much longer than this then they may provoke sickness, since it has been shown that virtual reality sickness has been induced with update lags as short as 48 ms (Draper, 1998). These numbers at least give some potential for a future quantitative standard. In other circumstances, for example during cross-coupling (Coriolis) or off-vertical axis rotation, quantitative estimates for predicted motion sickness may be made based on parameters such as rotational velocity rates, incremental rates of increase in rotation, angles of tilt or head movements, and duration of exposure. Unfortunately these are often particular to a given class of motion device or even a particular laboratory and the procedures used. Consequently, they are not generalizable for a standard.

It is only with low frequency translational motion, which is a major source of motion sickness in land vehicles, ships, and aircraft, that models are sufficient to provide engineering design parameters (exposure time, acceleration, frequency) and be incorporated for standards regulated by the International Standards Organisation (ISO). This success is seen in the International Standards Organisation standard for human exposure to whole-body vibration, part of which deals with motion sickness produced by low frequencies (ISO 2631, 1997). The frequency weighting function is of great theoretical as well as applied interest.

Controlled laboratory (O'Hanlon and McCauley, 1974; Golding et al., 2001) and ship motion surveys (Lawther and Griffin, 1987, 1988) have shown that lower frequencies (<1 Hz) are more nauseogenic than higher frequencies and that nauseogenicity increases as a function of exposure time and acceleration intensity. Nauseogenicity peaks at the low frequency motion of around 0.2 Hz. Such low frequency motions are present in transportation in ships, coaches, aircraft flying through air turbulence, and on camels and elephants, all of which can provoke motion sickness. However, during walking, running, horse riding, riding off-road trail bikes, etc., the frequencies are higher than 1 Hz. Consequently, although these motions can be quite severe (capable of bruising the person), they are not nauseogenic.

Hypotheses for the frequency dependence of nauseogenicity of translational oscillation are a phase-error in signalling motion between canal–otolith and somatosensory systems (Von Gierke and Parker, 1994; Benson, 1999), or a frequency dependent phase-error between the sensed vertical and the subjective or expected vertical (Bos and Bles, 1998). It has also been proposed that a zone of perceptuo–motor ambiguity around 0.2 Hz triggers sickness, since at higher frequencies imposed accelerations are usually interpreted as translation of self through space, whereas at lower frequencies imposed accelerations are usually interpreted as a shift in the main force vector, i.e., tilt of self with respect to the assumed gravity vertical (Golding et al., 2003; Golding and Gresty, 2005). The region of 0.2 Hz would be a cross-over between these two interpretations and, thus, a frequency region of maximal uncertainty concerning the correct frame of reference for spatial orientation.

## 3. Limitations to the concept of motion sickness susceptibility

Individual differences in motion sickness susceptibility are great. However, the concept of motion sickness susceptibility must acknowledge the multi-factorial nature of motion sickness susceptibility itself. At least three processes are thought to be at work: initial sensitivity to motion, rate of natural adaptation, and the ability to retain

protective adaptation in the longer term (Reason and Brand, 1975). Moreover, correlations among various types of motion challenges are not high (Lentz, 1984), implying differential sensitivity in individuals to different types of motion; e.g., the correlation between susceptibility to translational versus cross-coupled (Coriolis) motion can sometimes be very low (Golding, 1993). Factor analysis of self-report questionnaires, designed to assess susceptibility to motion sickness, suggests the existence of independent latent susceptibilities to different types of provocative environments, usually forming factors that might be termed transportation by land, air, sea, or funfair rides (Golding, 1998). This might seem to contradict the notion of a general motion susceptibility dimension. Nevertheless these apparently contradictory views can be argued to be both true, i.e., a general motion susceptibility factor and specific factors exist.[1] Other limitations are imposed by the reliability of response to a motion challenge, which may be estimated from repeated exposures in the laboratory to be around $r=0.8–0.9$. Finally it is worth noting that the concept of motion sickness susceptibility may overlap with sickness susceptibility to other, non-motion emetic stimuli. These relationships among susceptibilities to motion sickness, migraine, chemotherapy, post operative nausea and vomiting are often used as evidence for the involvement of the vestibular system in the response to non-motion emetogenic stimuli (Money and Cheung, 1983). But, alternatively, they might reflect individual differences in excitability of a postulated common final emetic pathway (Hasegawa et al., 1992).

## 4. Predictors of individual differences in motion sickness susceptibility

Given a sufficiently provocative stimulus nearly all people can be made motion sick. (This assumes of course that the person has not been subjected to prior habituation or desensitisation to the stimulus or pre-medicated with high doses of anti-motion sickness drugs.) Indeed, almost the only individuals who are immune to motion sickness are those who have complete bilateral loss of labyrinthine (vestibular apparatus) function. Even this may not be absolutely true under all circumstances. There is evidence that bilateral labyrinthine defective individuals are still susceptible to motion sickness provoked by visual stimuli designed to induce self-vection during pseudo-Coriolis stimulation, i.e., pitching head movements within a moving visual field (Johnson et al., 1999). It is also worth noting that blind or blind-folded normally sighted individuals can be made motion sick using real motion, although obviously optokinetic stimuli (Table 1) are ineffective. With regard to the contribution of aspects of other individual differences in vestibular function to motion sickness susceptibility, the evidence is limited. Otolith asymmetry between left and right labyrinths, as measured during parabolic flight, has been proposed as an indicator of susceptibility for space sickness (Diamond and Markham, 1991). *Mal de debarquement* is the sensation of unsteadiness and tilting of the ground when a sailor returns to land. A similar effect is observed in astronauts returning to 1 *g* on Earth after extended time in weightlessness in space. In severe cases this can lead to motion sickness but symptoms usually resolve within a few hours as individuals readapt to the normal land environment. Individuals susceptible to *mal de debarquement* may have reduced reliance on vestibular and visual inputs and increased dependence on the somatosensory system for the maintenance of balance (Nachum et al., 2004). However, in a more general sense, individual variation in sensory thresholds to angular or translational accelerations does not seem to relate to susceptibility in any obvious fashion. The evidence that individual differences in postural stability or perceptual style (e.g., Riccio and Stoffregen, 1991) are major predictors of motion sickness susceptibility seems limited (Golding and Gresty, 2005). Similarly, individual variation in the vestibular ocular reflex does not seem to be a reliable predictor of susceptibility, although the ability to modify readily the time constant of vestibular 'velocity store' may be a candidate marker for success in motion sickness habituation (Golding and Gresty, 2005).

Certain groups with medical conditions may be at elevated risk. Many patients with vestibular pathology and disease and vertigo can be especially sensitive to any type of motion. The well known association among migraine, motion sickness sensitivity, and Meniere's disease dates back to the initial description of the syndrome by Prosper Meniere in 1861. It has been proposed that there may be a (genetic) link caused by defective calcium ion channels shared by the brain and inner ear leading to reversible hair cell depolarization, producing vestibular symptoms and that the headache might just be a secondary phenomenon (Baloh, 1998). An alternative explanation has been proposed based upon different functioning of the serotonergic system in the brains of migraineurs (Drummond, 2005; Brey, 2005).

Doubtless there is a genetic contribution to the individual differences in susceptibility, but the evidence is limited and open to various interpretations. An example is the observation that a single-nucleotide polymorphism of the $\alpha_2$-adrenergic receptor increases autonomic responses to stress and contributes to individual differences in autonomic responsiveness to provocative motion (Finley et al., 2004). However, it is unclear whether this is a marker for motion sickness susceptibility, per se, or a general marker for autonomic sensitivity. There is some evidence for Chinese hyper-susceptibility to motion sickness, and this may provide some indirect evidence for a genetic contribution

[1] The historical analogy is with the measurement and the factor analysis of 'intelligence' where it is now generally accepted that, depending on how one wishes to regard the data, there exists a general intelligence quotient (IQ) factor, or just two oblique factors called verbal versus spatial and numerous specific ability factors. As with IQ, for many practical purposes the single general factor solution is the most useful for predicting an individual's overall susceptibility.

to such differences (Stern et al., 1993; Klosterhalfen et al., 2005).

Sex and age are two main predictors in the general population of individual susceptibility. Surveys of transportation by sea, land, and air, indicate that women are more susceptible to motion sickness than men; women show higher incidences of vomiting and reporting a higher incidence of symptoms such as nausea (Kennedy et al., 1995). This increased susceptibility is likely to be objective and not subjective because women vomit more than men. For example, large scale surveys of passengers at sea indicate a 5 to 3 female to male risk ratio for vomiting (Lawther and Griffin, 1988). It does not seem related to extra habituation to greater ranges of motion environments experienced by risk-taking males (Dobie et al., 2001), nor to gender biased differential self-selection between males and females when volunteering for laboratory motion sickness experiments (Flanagan et al., 2005). Moreover, this sex difference is not exclusive to humans because in animals, such as *Suncus murinus*, females show significantly more emetic episodes and shorter latencies to emesis in experimental exposures to motion (Javid and Naylor, 1999). The cause of greater motion sickness susceptibility in women has been suggested to involve the female hormonal cycle. However, although susceptibility probably does vary over the menstrual cycle, it is unlikely that this can fully account for the greater susceptibility in females because the magnitude of fluctuation in susceptibility across the cycle is only around one third of the overall difference between male and female susceptibility (Golding et al., 2005). The elevated susceptibility of females to motion sickness or indeed to post-operative nausea and vomiting or chemotherapy induced nausea and vomiting (Morrow, 1985; Golding, 1998), may serve an evolutionary function. Thus, more sensitive sickness thresholds in females may serve to prevent exposure of the foetus to harmful toxins during pregnancy, or subsequently through milk. This elevated susceptibility in females may be 'hard-wired' but capable of up-regulation albeit variably by hormonal influences during the menstrual cycle and even further during pregnancy.

Infants and very young children are immune to motion sickness. However they have no difficulty vomiting. Motion sickness susceptibility begins from perhaps around 6 to 7 years of age (Reason and Brand, 1975) and peaking around 9 to 10 years (Turner and Griffin, 1999). The reasons for this are uncertain. Puberty begins later (around 10–12 years) than the age 6–7 years for onset of motion sickness susceptibility. This implies that sex hormonal changes per se are not a direct explanation for the onset of motion sickness susceptibility. Another possibility is that the perceptuo–motor map is still highly plastic and not fully formed until around 7 years of age. Most models of motion sickness propose that this perceptuo–motor map provides the 'expected' invariant patterns for detecting possible sensory mismatches in the relationships between vestibular, visual and kinaesthetic inputs. Following the peak susceptibility, there is a subsequent decline of susceptibility during the teenage years towards adulthood around 20 years. This doubtless reflects habituation. Although it is often stated that this decline in susceptibility continues in a more gradual fashion throughout life towards old age, the evidence is weak given that older people may avoid motion environments if they know that they are susceptible. Indeed, longitudinal evidence from individuals who have been studied objectively in the laboratory suggests that towards older age, susceptibility may increase in some individuals (personal communication, Michael Gresty, Medical School Imperial College, London, 2006).

A multiplicity of other possible predictors of susceptibility have been examined over the years, with relatively few being found to be of significance. Cross-sectional surveys show that individuals with high levels of aerobic fitness appear to be more susceptible to motion sickness, and experiments show aerobic fitness training increases motion sickness susceptibility (e.g., Cheung et al., 1990). The reasons are unclear, with one suggestion being that a more reactive autonomic nervous system (including hypothalamic–pituitary–adrenal axis) in aerobically fit individuals may sensitize them. Psychological variables such as mood may modify susceptibility in contradictory directions: 'state' variables such as extreme fear or anxiety conditioned to motion, may contribute indirectly to motion sickness susceptibility, although by contrast, extreme arousal 'fight–flight' such as observed in warfare may suppress motion sickness (Reason and Brand, 1975). Personality 'trait' variables such as extraversion or neuroticism do not strongly predict motion sickness susceptibility, with only minor correlations being observed between extraversion or similar personality traits with reduced susceptibility (Reason and Brand, 1975; Gordon et al., 1994). A recent study using the 'Big Five' personality inventory revealed no significant correlations for any personality factor with motion sickness susceptibility in one hundred and twelve participants (Nieto and Golding, 2006).

## 5. Behavioural countermeasures

Habituation offers the surest counter measure to motion sickness. Habituation is superior to anti-motion sickness drugs, and it is free of side effects (Cowings and Toscano, 2000). The most extensive habituation programmes, often denoted "motion sickness desensitisation," are run by the military, where anti-motion sickness medication is contra-indicated for pilots because of side-effects including drowsiness and blurred vision. These programmes have success rates exceeding 85% (Benson, 1999) but can be extremely time consuming, lasting many weeks. Critical features include: (a) the massing of stimuli (exposures at intervals greater than a week almost prevents habituation), (b) use of graded stimuli to enable faster recoveries and more sessions to be scheduled, which may help avoid the

opposite process of sensitization, and (c) maintenance of a positive psychological attitude to therapy (Yen Pik Sang et al., 2005).

Anti-motion sickness drugs are of little use in this context, since both laboratory (Wood et al., 1986) and sea studies (van Marion et al., 1985) show that although such medication may speed habituation compared to placebo in the short term, in the longer term it is disadvantageous. This is because when the anti-motion sickness medication is discontinued, the medicated group relapses and is worse off than those who were habituated under placebo.

Habituation, itself, is often stimulus specific, producing the problem of lack of generalisation and transfer of habituation from one type of motion to another. Thus, to foster transfer, it is useful to use as wide a variety of provocative motions as possible (see Table 1 'Laboratory' stimuli). The studies by Kaufman (2005) underline the specificity of habituation to different types of motion, with different anatomical patterns of neuronal functional changes (presumably reflecting learning) in the vestibulo–olivo–cerebellar network to different classes of provocative stimuli. Research continues to optimise habituation approaches (Cheung and Hofer, 2005; Stroud et al., 2005). The scope of applications extends to habituation training to reduce motion sickness produced by short arm rotors intended to provide artificial gravity in future space flight (Young et al., 2003). Neural structures such as the amygdala as well as such areas as the nucleus tractus solitarius are thought to be important in processes of induction of and habituation to motion sickness (Nakagawa et al., 2003; Pompeiano et al., 2004).

More immediate and short-term behavioural counter measures include reducing head movements, aligning the head and body with gravito-inertial force (Golding et al., 2003) or laying supine (Golding et al., 1995). However, such protective postures may be incompatible with task performance. It is usually better to be in control, i.e., to be the driver or pilot rather than a passenger (Rolnick and Lubow, 1991). Obtaining a stable external horizon reference is helpful (Bos et al., 2005). With regard to the latter, a direct view out of a car window reduced sickness but a real time video display of the view ahead failed to reduce sickness in rear seat car passengers (Griffin and Newman, 2004). Controlled regular breathing has been shown to increase significantly motion tolerance to provocative motion, being approximately half as effective as standard anti-motion sickness drugs yet rapid to implement and free of side effects. The mechanism by which controlled breathing has its effect is uncertain but may involve activation of the known inhibitory reflex between respiration and vomiting (Yen-Pik-Sang et al., 2003a, 2003b). Some report acupuncture and acupressure to be effective against motion sickness (Bertalanffy et al., 2004). However, well controlled trials find no evidence for their value (Miller and Muth, 2004). Anecdotally, modification of diet has been said to alter susceptibility to motion sickness. Unfortunately, the evidence is contradictory; for example, a recent study suggesting that protein-rich meals may inhibit motion sickness (Levine et al., 2004) may be contrasted with a study which drew the opposite conclusion that any meal of high protein or dairy foods 3–6 h prior to flight should be avoided to reduce airsickness susceptibility (Lindseth and Lindseth, 1995). Supplemental oxygen may be effective for reducing motion sickness in patients during ambulance transport. By contrast, it does not alleviate motion sickness in individuals who are otherwise healthy. This apparent paradox is perhaps explained by the suggestion that supplemental oxygen may work by ameliorating a variety of internal states that sensitize for motion sickness (Ziavra et al., 2003).

## 6. Pharmacological countermeasures

Many of the drugs currently used against motion sickness were identified during World War 2, and certainly most had been proven over 30 years ago (Wood and Graybiel, 1969). They may be divided into the categories: antimuscarinics (e.g., scopolamine), $H_1$ anti-histamines (e.g., dimenhydrinate), and sympathomimetics (e.g., amphetamine). However, these drugs, alone or in combination (e.g., scopolamine+dexamphetamine) are only partially effective. The other newer potent antiemetics, $D_2$ dopamine receptor antagonists and $5HT_3$ antagonists, used for side effects of chemotherapy, are not effective against motion sickness (Levine et al., 2000), probably because their sites of action may be at vagal afferent receptors or the brainstem chemoreceptor trigger zone, whereas anti-motion sickness drugs act elsewhere.

All anti-motion sickness drugs can produce unwanted side effects such as drowsiness, promethazine being a classic example (Cowings and Toscano, 2000). Although it is generally accepted that some drugs, such as transdermal scopolamine or the calcium channel antagonist cinnarizine, are significantly less sedating than others (Gordon et al., 2001), the consequent performance decrements may still not be acceptable in challenging occupations such as piloting aircraft.

Motion sickness induces gastric stasis (Stewart et al., 2000) preventing drug absorption. Consequently, oral administration must anticipate motion. Injection overcomes the various problems of slow absorption kinetics and gastric stasis or vomiting. Other routes such as transdermal also offer advantages providing protection for up to 72 h with low constant concentration levels in blood, consequently reducing side effects. Its slow onset time can be offset by simultaneous administration of oral scopolamine enabling protection from 30 min onwards (Nachum et al., 2001). However, there may be variability in absorption via the transdermal route which alters effectiveness between individuals (Gil et al., 2005). Buccal absorption is effective with scopolamine but an even faster route is nasal scopolamine sprays (Klocker et al., 2001); with higher (alkaline) pH buffered formulations to promote absorption, peak blood levels may be achieved in 9 min (Ahmed et al., 2000). 'Chewing gum' formulations offer the prospect of

adequate motion sickness prophylaxis with reduced side effects compared to tablets, due to a more sustained release (Seibel et al., 2002).

Investigations of 'new' anti-motion sickness drugs include re-examination of 'old' drugs such as phenytoin, as well as the development of new agents such as Neurokinin-1 antagonists. Phenytoin has anti-motion sickness potential (Albert, 2003), although its complex pharmacokinetics and side effects limit practicality. Betahistine has been proposed to have anti-motion sickness properties but a number of studies (Gordon et al., 2003) indicate that its action is too weak to be effective for practical purposes. Chlorphenir-amine is an antihistamine synthesised many years ago which has anti-motion sickness actions without major side effects (Buckey et al., 2004), but comparison with established medication has not been made. Cetirizine and fexofenadine antihistamines are ineffective against motion sickness, perhaps because of their failure to have sufficient central versus peripheral nervous system actions (Cheung et al., 2003). The anti-psychotic Droperidol is shown to have useful anti-motion sickness action and may merit further study (Weichenthal and Soliz, 2003), but its practical value may be offset by side effects. Benzodiazepines and barbiturates have long been known to have anti-motion sickness actions but their sedating actions preclude routine use (Yates et al., 1998), a conclusion supported by recent research comparing lorazepam with other anti-motion sickness drugs (Dornhoffer et al., 2004). Corticosteroids such as dexamethasone attracted some interest as a potential anti-motion sickness agents over fifteen years ago, but evidence for their value is indirect (Lee et al., 2003). A recent observation suggests the drug tamoxifen (used in breast cancer treatment) may prevent motion sickness (Gianni et al., 2005), raising the possibility that pathways involving the estrogens may be capable of modulating motion sickness. Although opioids often elicit emesis, they have been shown in animals to have broad antiemetic actions for motion sickness, the balance of effect may reflect relative actions at the chemoreceptor trigger zone and the nucleus tractus solitarius, or their differential actions on mu and delta opioid receptors (Yates et al., 1998). Work on the animal model *S. murinus* suggests that endogenous opioids may play a role in habituation to provocative motion (Javid and Naylor, 2001), and one study has shown that the mu-opioid receptor agonist loperamide affords some motion sickness protection in humans (Otto et al., 2006). It has been suggested that ginger (main active agent gingerol) acts to calm gastrointestinal feedback (Lien et al., 2003), but studies of its effects on motion sickness have been equivocal making it an unlikely potent anti-motion sickness agent.

The new neurokinin $NK_1$ receptor antagonists are potent broadband antiemetics. They are highly effective against motion sickness in animals, but unfortunately are ineffective in humans. The discrepancy may not be a species difference but rather implies that the $NK_1$ pathway is involved in mediating vomiting but not nausea (Reid et al., 2000). Vasopressin $V_{1a}$ receptor antagonists (Yates et al., 1998), NMDA antagonists (Yates et al., 1998), and $5HT_{1a}$ receptor agonists (Javid and Naylor, 2002) have all been shown to be effective against motion sickness in animals, but published data on humans are lacking with the exception of one study showing anti-motion sickness actions of the anti-migraine triptan rizatriptan (Marcus and Furman, 2005). Unpublished observations of the present author suggest that Vasopressin $V_{1a}$ receptor antagonists are not effective against motion sickness in man. A recent finding is that 3-hydroxypyridine derivatives appear to have anti-motion sickness effects (Iasnetsov et al., 2005). One of the few novel drugs with proven anti-motion sickness properties in humans is the selective muscarinic $M_3/m_5$ receptor antagonist zamifenacin, which has a side effect profile lower than for scopolamine (Golding and Stott, 1997). This opens new possibilities for drug development since antimuscarinics are possibly the most effective and well proven of any class of anti-motion sickness drug.

## 7. Conclusions

The types of stimuli which can provoke motion sickness and the nature of the sensory conflicts are now better understood. Non-pharmacological countermeasures have been increasingly refined, including behavioural modifications, autogenic techniques such as controlled breathing and desensitisation training. At a neurophysiological level, there has been much progress in defining the critical pathways in the central nervous system involved in motion sickness. However there has been less progress in a number of other areas. At the most general level, there is still no consensus as to the reason why motion sickness should occur, although an evolutionary explanation in terms of a 'toxin detector' is the most accepted. Equally the reasons for the great individual differences in motion sickness susceptibility are still only poorly understood. They are probably multiple. The ability to modify readily the time constant of the vestibular 'velocity store' has emerged as a potential candidate marker for rapidity of habituation. The role of genetics is doubtless important but has received little attention as yet. Many of the anti-emetics developed for other types of sickness such as in chemotherapy, have proved ineffective for motion sickness. This suggests a divergence at some level in pathways responding to emetic chemical versus motion stimuli. New anti-motion sickness drugs continue to be developed with the aim of producing greater efficacy with fewer side-effects. Selective anti-muscarinics, opioid antagonists and serotonergic agonists may be of promise. The development of new pharmacological countermeasures and a greater knowledge of possible genetic factors will feedback into our understanding of the neural mechanisms of motion sickness.

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