Motion sickness, nausea and thermoregulation: The "toxic" hypothesis

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Abbreviations: MS, motion sickness; ACTH, adrenocorticotropic hormone; SCL, skin conductance level.

Principal symptoms of motion sickness in humans include facial pallor, nausea and vomiting, and sweating. It is less known that motion sickness also affects thermoregulation, and the purpose of this review is to present and discuss existing data related to this subject. Hypothermia during seasickness was firstly noted nearly 150 years ago, but detailed studies of this phenomenon were conducted only during the last 2 decades. Motion sickness-induced hypothermia is philogenetically quite broadly expressed as besides humans, it has been reported in rats, musk shrews and mice. Evidence from human and animal experiments indicates that the physiological mechanisms responsible for the motion sickness-induced hypothermia include cutaneous vasodilation and sweating (leading to an increase of heat loss) and reduced thermogenesis. Together, these results suggest that motion sickness triggers highly coordinated physiological response aiming to reduce body temperature. Finally, we describe potential adaptive role of this response, and describe the benefits of using it as an objective measure of motion sickness-induced nausea.

Introduction

Principal symptoms of motion sickness (MS) in humans include facial pallor, nausea and vomiting, and sweating; these are accompanied by gastric awareness and discomfort. Among biochemical markers, a relatively specific physiological measurement is the increases in plasma vasopressin accompanied by non-specific rises in plasma ACTH, cortisol and catecholamines (see¹ for a more detailed review). Although sweating has been a common symptom of MS, thermoregulation-related measurements have not been part of the main assessment of MS as compared with subjective ratings (e.g., rated nausea² and Simulator Sickness Questionnaire³). The purpose of this review is 3-fold: (i) to present and discuss existing data relating thermoregulation and MS leading to identification of research gaps; (ii) to address the ‘where’ and ‘why’ questions related to MS-induced thermoregulatory changes (the toxic hypothesis); and (iii) to highlight the benefits of thermoregulation-based bio-markers for the study of MS among human and animals. We initially present a critical review of studies examining hypothermic effects of MS in humans and animals; this is followed by a review of studies that provide mechanistic insight into how MS induces hypothermia: this includes cutaneous vasodilation, sweating and thermogenesis.

Gaps in the current knowledge are identified. The potential sites of interaction where nausea-related neural pathways may affect thermoregulatory pathways are explored. The discussion focuses on potential sites of interaction between pathways and considers how such interactions take place during MS.

General overview of association between motion sickness and hypothermia

A causative link between MS and reductions of core body temperature has been documented in a number of studies. To the best of our knowledge, the first report of this phenomenon was made by Hess⁴ who noted that in subjects experiencing seasickness, body temperature dropped by about half a degree. Likewise, Ogata⁵ reported that during a long sea voyage, his body temperature was lower on the days of rough sea, when he experienced nausea, compared to normal days. Several experimental studies of MS also noted this phenomenon,⁶,⁷ although they were not designed to specifically focus on temperature changes.

At the beginning of last decade, several interrelated investigations were specifically designed by Canadian and Swedish Defense research institutions to assess combined effects of provocative motion and hypothermia. All of them used similar experimental paradigm – induction of MS by means of pseudo-Coriolis intervention (rotation of a subject sitting in a chair
Motion sickness and thermoregulatory behavior

While a sensation of body warmth and a desire for fresh (cool) air may be common observation among those who experienced MS, only one study specifically addressed and documented this phenomena. It was conducted in a thermoneutral environment (28-29°C), where MS was provoked by pseudo-Coriolis intervention; subjects separately rated their nausea, perception of temperature, and their thermal comfort/discomfort. Prior to the provocation, ratings indicated that the environment was perceived as comfortable and neutral or slightly warm; and at the end of provocation, when all subjects experienced intense nausea, the ambient temperature was perceived as uncomfortable and too warm. These distorted sensations were paradoxical, as core body temperature actually fell during and after the provocation, suggesting that a distortion occurred in the physiological mechanisms responsible for the conscious perception of sensory information from body thermoreceptors. It is obvious that such distorted temperature sensation in subjects with MS could motivate and induce cold-seeking thermoregulatory behavior.

In a cited above rodent study, no effect of provocative motion on the preferred ambient temperature was found; however temperature preference could be assessed only after the termination of the provocation, due to technical reasons. It is thus remains unknown whether provocative stimuli cause behavioral thermoregulatory effects in species others than humans.

Motion sickness and sweating

Sweating is a well recognized symptom of the MS, and its quantitative assessment was performed in a number of studies. In the current section we initially focus on several relevant methodological issues; this is followed by a summary of results obtained in the previous studies. The latter are grouped by i) provocative stimulation; and ii) correlation of the sweating data with the subjective rating of MS.

Studies discussed below employed one of 2 different methods for assessing sweating – detection of MS-induced changes in skin conductance that is dependent on the activity of sweat glands, and a direct assessment of changes in sweating rate. The former approach (termed skin galvanic response or skin conductance level, SCL) is based on measuring skin resistance/conductance by passing a low-intensity constant current between 2 electrodes attached to the skin. In contrast, sweating rate detection is based on assessing changes in the content of water vapor in the dehumidified air flushed through a capsule attached to the skin. It is surprising that the first paper reporting a direct methodical comparison of both methods has just appeared. Its results are highly relevant to this review. Sweating was elicited by a whole-body thermal stimulus, and after reaching temperature threshold for sweating, only a fall in skin resistance was initially observed, whereas changes in sweat rate occurred after a delay of several
Provocative motion leading to nausea also robustly increased the sweating rate in the forehead.\(^8,11,13\)

The first study of visually-induced MS by Parker\(^26\) used playback of a film that was captured from a car driving on a winding road. Measurements of SCL enabled the discrimination of MS-susceptible individuals from MS-resistant individuals. These findings were reproduced (with a different visual stimulus).\(^22\) A rise in SCL has been reported during another common MS provocation - optokinetic stimulation (movement of black/white vertical strips in a visual field).\(^21,27-29\)

One of the authors of the present paper has recently tested the hypothesis that nausea rating and symptoms of sweating would be correlated. Twelve participants (6 male and 6 female) were exposed to a 30 minute rotating drum pattern (vertical black and white stripes projected to a panoramic screen). The original objective of the study was to examine the effects of eye movements on motion sickness and sweating was measured as one of the standard dependent variable.\(^30\)

During the exposure, rated nausea levels were measured every 2 minutes using a 7-point nausea scale.\(^2\) Before and after the exposure, all participants filled in a set of simulator sickness questionnaire.\(^3\) Results of the 12 participants indicated that the nausea rating correlated significantly with the levels of sweating as measured by the questionnaire (\(r = 0.67, P < 0.01\)). This suggests that symptoms of nausea and sweating go hand in hand during visually-induced motion sickness.

A number of studies focusing on simulator sickness or virtual reality-induced motion sickness reported rise in tonic SCL associated with MS.\(^31,32\) Others did not observe changes in SCL in subjects experiencing simulator sickness.\(^33\) This was probably due to relatively mild MS symptoms and by the fact that only tonic level was measured with electrodes attached to the palmar surface of the fingers – the least sensitive experimental configuration (see above). Besides physical and visual stimuli, dizziness or nausea are common effect of caloric ear stimulation – an otonerological test for assessing the integrity of vestibular function. Cui et al.\(^34\) reported that subjects experiencing nausea during caloric ear stimulation also exhibit increases in tonic skin conductance in fingers and in sweating rate on the forehead.

Some of the cited above studies were able to discriminate MS-susceptible from MS-resistant individuals,\(^6,22,26\) while others specifically aimed to determine whether there is a correlation between subjectively perceived nausea and associated changes in physiological parameters, including skin conductance levels. Such correlation was found,\(^18,21,25,27,28\) with the highest correlation (0.62) being between phasic SCL changes in the forehead and MS rating. Negative results\(^23\) were most likely due to the location of electrodes in this study on the fingers (see above).

**Motion sickness and cutaneous vasodilation**

Heat loss through skin is a major thermoregulatory mechanism in mammals possessing reasonable areas of glabrous skin with developed arterio-venous anastomoses. Dilution of these anastomoses allows a substantial amount of warm blood to get in close proximity with the ambient air to dissipate heat in sub-thermoneutral environment. Conversely, constriction of superficial
skin vessels leads to heat conservation. Existing human data on the link between motion sickness and cutaneous vascular tone are controversial, limited and inconclusive. The first study where skin blood flow was assessed during MS provocation, reported a 50-60% fall in finger pulse volume indicative of vasoconstriction. Several other early studies demonstrated that MS is associated with an increase in forearm blood flow. However, they were conducted by means of venous occlusion plethysmography (a method based on the volume changes in the forearm), and thus could not determine whether blood flow increased in the skin or in the muscles of the forearm. Using the difference between forearm and finger temperature as a surrogate measure of cutaneous vascular tone, Nobel and colleagues concluded that MS attenuates cutaneous vasoconstriction provoked by immersion in the cold water. A transient vasodilation in the forearm and calf during MS provocation has been reported in a study employing direct measurement of cutaneous blood flow by laser Doppler. Interestingly, in the Cheung’s study, cutaneous blood flow remained unchanged in 2 subjects who did not report nausea. Overall, further experiments are definitely required to verify and describe the link between nausea and cutaneous vascular tone in humans.

In contrast to human studies, our recent animal experiments, conducted in 3 different laboratories, revealed that provocative motion (rotation around vertical axis at 45 rpm) causes a very robust vasodilatory response in rat cutaneous (tail) vascular bed. A transient vasodilation in the tail vascular bed mediated by heat loss due to vasodilation in thermoregulatory tail vascular bed. Changes in the tail temperature in rats that were determined by means of infrared imaging; present 2 images of a rat taken just before (C) and 20 min after the onset of provocative motion (D). (C) Fall in the core (abdominal) temperature induced by a provocative motion; telemetric recordings. Note that tail vasodilation preceded hypothermia. Similar effects were observed in mice before provocation; during provocation. In rats, the provocation was a rotation in a home cage at 45 rpm; in mice—placing them in their home cages on an orbital laboratory shaker (1 Hz, 4-cm circular motion). Inset in (E) shows temperature coding in pseudo-colors. (A–D) Modified from Ref. 15; (E and F) unpublished observation.

Motion sickness and thermogenesis

Only few studies questioned whether motion sickness affects thermogenesis in humans. For assessing this function, researchers employed indirect calorimetry – measurement of the minute volume of consumed O2 (VO2) that directly reflects changes in heat production. In the initial work, after MS provocation or corresponding control periods, subjects were immersed in a pool with warm (28°C) water; this resulted in about 2-fold increase in VO2 during 90 min of immersion, without any difference between MS and control conditions. In subsequent work, the same research group found that cold-induced VO2 rise was reduced by MS provocation, and argued that this difference was due to the temperature of the water during immersion, such that the larger increase in thermogenesis represented larger substrate for MS-provocation.

Figure 2. In rats and mice, provocative motion causes hypothermia that is mediated by heat loss due to vasodilation in the thermoregulatory tail vascular bed. (A) Changes in the tail temperature in rats that were determined by means of infrared imaging; (C and D) present 2 images of a rat taken just before (C) and 20 min after the onset of provocative motion (D). (C) Fall in the core (abdominal) temperature induced by a provocative motion; telemetric recordings. Note that tail vasodilation preceded hypothermia. Similar effects were observed in mice before provocation; during provocation. In rats, the provocation was a rotation in a home cage at 45 rpm; in mice—placing them in their home cages on an orbital laboratory shaker (1 Hz, 4-cm circular motion). Inset in (E) shows temperature coding in pseudo-colors. (A–D) Modified from Ref. 15; (E and F) unpublished observation.
induced effects. This appears quite plausible providing that in this second study, with water temperature of 15°C, the rise of VO₂ was more than 4-fold. However, in another follow-up study, where the water temperature during immersion was also 15°C, no effects of motion provocation on VO₂ were seen. Here, authors offered a potential explanation for the discrepancy: in their 2006 study, where the effects of MS were present, in addition to pseudo-Coriolis MS provocation prior to immersion, subjects were exposed to the optokinetic drum stimulation during the immersion to maintain the MS at steady state. Thus it may be that thermogenesis is affected mainly during, but not after provocative stimulation.

In summary, published human data suggest that even if MS affects cold-induced thermogenesis, these effects are relatively minor. Also, indirect calorirometry did not allow to determine whether MS affected shivering or non-shivering thermogenesis as a electromyogram was not recorded in the cited studies. There are currently no animal data on the link between MS and thermogenesis, and this gap of knowledge awaits further experimentation.

Where motion sickness could interfere with temperature control?

We believe that answering this question will shed light on the poorly understood neural substrate of nausea. During the last decade, it became apparent that some drugs that efficiently suppress vomiting, have only moderate effects against nausea. This differential action on nausea vs. vomiting led to the realization that there may be different pathways and control systems for nausea and emesis. Indeed, evidence suggests the essential neural circuitry for vomiting reflex is within the lower brainstem, and emesis could be elicited in decerebrated animals. Consequently, a search for the neural substrate of nausea must be focused on the supra-medullary level. There is currently only one human brain imaging studies of nausea. Visually-induced nausea was associated with cortical activation in the prefrontal areas responsible for emotional processing and the insula (responsible for conscious interoceptive awareness); subcortical regions included amygdala, striatum and dorsal pons. In animals, brain activation could be assessed by immunohistochemical detection of Fos protein. A straightforward approach for identifying nausea-related brain regions in animals would be to compare where there is an overlap between chemically- and vestibularly-activated brain regions in animals would be to compare where there is an overlap between chemically- and vestibularly-activated brain regions in animals.

Why motion sickness causes integrative hypothermic response?

Compelling evidence presented in the previous sections suggests that MS triggers coordinated cognitive, behavioral and physiological changes that act synergistically to cool down the body. In fact, it is quite remarkable that seemingly all available bodily resources are mobilized for this purpose: changed perception of and preference for ambient temperature and preference for a cooler environment indicates that this interference occurs quite high in the neuraxis. Functional analysis of afferent input to this brain structure thus might be a fruitful approach to elucidate where in the brain occurs the sensory mismatch leading to MS.
natural or artificial provocations prior to the beginning of sea voyages; one could speculate that there were some traditional tribal dances (akin to Sufi whirling – a form of Islamic physically active meditation,\textsuperscript{48} but it is difficult to imagine that they could have major influences on the physiological response that we discuss. Consequently, it seems that MS-related hypothermia is not a product of evolutionary pressure; this is however not to say that it has no adaptive physiological significance.

It may be that potential answer to the “why” and “how” question could be found by comparing MS-induced hypothermia with hypothermic responses produced by other means. If we exclude pharmacologically- and cold-induced hypothermia, the only other situation when it occurs in response to environmental stressors, both in humans\textsuperscript{49-51} and in experimental animals,\textsuperscript{52,53} is the toxic/septic shock; all other imaginable influences cause either hyperthermia or no effect on body temperature. Another common feature between MS and toxic shock is the presence of nausea, a sensation that is a part of defense against intoxication. Experiments using rats have shown that hypothermia and cold-seeking behavior during toxic shock is not only defensive but actually critical for survival.\textsuperscript{54,55} The adaptive value of these reactions is in reducing tissue demands for oxygen that is critical for survival during intoxication.\textsuperscript{56} Thus, one could speculate that if both nausea and hypothermia develop during MS, they might reflect an activation of the same defense mechanism. Given this assumption, the question now is: defense against what during motion sickness? An intriguing proposal has been made by Osenkopp who was the first to observe motion-induced hypothermia.\textsuperscript{14} The essence of Treisman’s and Ossenkopp’s ideas is complemented with few of our thoughts and is presented in the following paragraph.

Our bodies possess several lines of defense against intoxication.\textsuperscript{57} The first level is distant – unpleasant smell or unappealing appearance of the food would prevent us from its ingestion. The second level is represented by gustatory receptors – we spit out anything with nasty taste. Level 3 comprises the protective mechanisms in the stomach which is vomiting (including 5-HT3 receptors on the afferent vagal ending that, when activated, cause nausea and vomiting). If a neurotoxin passes this line of defense, it may then activate nausea/vomiting and hypothermia by acting in certain “sensor” brain areas, e.g., area postrema\textsuperscript{58} – a fourth line of defense. Taking into account Reason and Brands’ sensory mismatch theory of motion sickness,\textsuperscript{59} Treisman made 2 suggestions: i) that another “sensor” area comprises “the systems involved in controlling movement, including eye movements, and determining the location of the body in space” that are “almost continually in action and highly susceptible to even a minor degree of disruption; they constitute an ideal warning system for detecting early central effects of neurotoxins, where these have not activated more basic levels of defense;” and ii) that stimuli that elicit motion sickness, just by accident, activate this last level of defense.\textsuperscript{60} In other words, vestibular and/or visual stimuli capable to provoke motion sickness do so by accidentally activating integrated response primarily designed to attenuate effects of toxins (by reducing metabolism) and to prevent their ingestion in the future (by inducing nausea that is extremely efficient in producing aversive conditioning). Speaking about nausea, Treisman concludes: “If this suggestion is correct, motion sickness is an adaptive response evoked by an inappropriate stimulus”\textsuperscript{60}; we believe this statement is equally applicable to MS-induced hypothermia.

**Benefits of thermoregulation-related indices as measures of MS-induced nausea**

The evidence for the close link between nausea and thermoregulation has one important practical implication. Currently, assessing nausea in preclinical research is a major technical problem. Measuring retching/vomiting in species that possess emetic reflex has limited value for studying nausea; most commonly used laboratory animals – rats and mice – do not possess vomiting reflex. Common symptoms in humans – sweating and facial pallor – cannot be measured in rodents. There is no real-time physiological biomarker of nausea in animals. The only established and relatively specific biochemical marker of nausea in humans, elevated plasma vasopressin\textsuperscript{61,62} have not been confirmed in rats.\textsuperscript{63} Consequently, rodent studies of nausea have to rely on indirect indices, often with poor temporal resolution and specificity (locomotor activity, food consumption) or, in addition, with limited face validity (pica – an unconventional consumption of kaolin.\textsuperscript{64} Conditioned taste aversion is a powerful method, but the measure is not real-time and could not be used for assessing unconditioned responses. There is thus no real-time physiological biomarker of nausea. Future work in both humans and animals is required to determine whether assessment of thermoregulation-related indices (core and surface temperature, skin blood flow, sweating and basic metabolic rate) during vestibularly- or visually-induced motion sickness could represent the first real-time unconditioned markers of nausea. If so, this will open new opportunities for revealing the neural substrate of nausea and for the search for efficient anti-nausea substances.

**Conclusions and Perspectives**

This review presents ample evidence to suggest that disturbances in thermoregulation play a central role in the pathophysiology of motion sickness. Looking from this angle at so-called “cold

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**Table 1. Objective signs of motion sickness in humans and motion-induced effects in rodents.** It is obvious that most of changes that occur in humans fit into a “thermoregulatory cluster” (dashed line). The table also identifies potential directions for further validation of the rodent model of motion sickness.

| Humans          | Rodents       |
|-----------------|---------------|
| Facial pallor   | N/A           |
| Sweating        | N/A           |
| Fall in body T  | Fall in body T|
| Skin vasodilation| Skin vasodilation |
| Reduced thermogenesis | ? |
| Preference for cooler environment | ? |
| Gastric dysrhythmia | ? |
| Rise in plasma vasopressin | No |

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sweating,” during nausea, one would immediately realize that it is a part of integrated physiological response aimed to reduce body temperature. With this in mind, one would realize that most of objective signs of MS are related to thermoregulation (Table 1). Providing that nausea is a part of natural defense against poisoning, body cooling following the detection of a toxin possibly represents an evolutionary beneficial “defensive hypothermia.” This is supported by the fact that such “defensive hypothermia” occurs during toxic shock, in both humans and in animal models. It may be that provocative visual or vestibular stimuli accidentally trigger this coordinated defensive response. Testing this hypothesis may be a productive way to advance our knowledge about the neural substrate of nausea.

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No potential conflicts of interest were disclosed.

Supplemental Material
Supplemental data for this article can be accessed on the publisher’s website.
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