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THE PSYCHOPHYSIOLOGY OF NAUSEA*

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Nausea is an unpleasant sensation usually referred to the stomach and sometimes followed by vomiting. Little is known about the subjective aspects of nausea because like pain and fatigue, it is a private sensation. We conceive of nausea as a complex control mechanism that signals us when not to eat. Our research in the areas of motion sickness and chemotherapy has led us to propose that we each have a dynamic threshold for nausea, which depends on the interaction of inherent factors and more changeable psychological factors, and that this threshold effects the individual's cognitive appraisal of both the nauseogenic stimulus and his/her bodily change in response to the nauseogenic stimulus. Inherent factors that are described are age, gender and race; psychological factors that are included are anxiety, expectation, anticipation and adaptation. The physiological responses that have been found to accompany nausea include an increase in sympathetic nervous system activity, a decrease in parasympathetic activity, an increase of abnormal dysrhythmic gastric activity, and an increase in plasma vasopressin. It is concluded that beneficial selective reduction of nausea will depend on a greater knowledge of the interaction of the psychological and physiological variables.

Keywords: Nausea – chemotherapy – motion sickness – gastric dysrhythmia – autonomic nervous system

INTRODUCTION

According to a recent survey, 15% of the American population has experienced nausea during the past three months. But what is nausea? Scientists usually respond much like everyone else: nausea is that sometimes-difficult-to-describe sick or queasy sensation accompanied by loss of appetite and sometimes followed by vomiting. When asked to point to where in their body nausea occurs, some people point to their throat, some to their head, and most to their stomach. Sensations such as nausea, pain, and fatigue are a challenge for psychologists, physiologists, and other

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investigators interested in mind-body interaction to understand and alleviate for a variety of reasons. Number one, they are private and, therefore, not directly observable. Secondly, they are not to be prevented or excluded in all instances, since in some cases they signal danger if certain behavior is continued, such as consuming food that has previously made one ill.

Nausea as a control mechanism

Nausea is a complex control mechanism with multiple detectors that inhibits food intake in situations such as when the available food is perceived as disgusting, or when the available food has been previously associated with nausea and/or vomiting-conditioned taste aversion. Nausea also inhibits food intake when one's stomach and the related control mechanisms are not functioning normally because of pathology or the ingestion of a toxin. Motion sickness is a special case of a nauseogenic stimulus. It is believed that it provokes nausea because it brings about a dissociation of sensory inputs to the brain that is similar to the neurological reaction to the ingestion of a toxin.

Of particular interest to psychologists is the fact that individuals often report nausea in threatening situations that have little to do with eating, e.g., immediately prior to delivering an important speech or performing in the opening night of a play. This is not surprising since in threatening situations, people generally show a specific pattern of autonomic nervous system (ANS) activity – increased sympathetic nervous system (SNS) activity and decreased parasympathetic nervous system (PNS) activity – that results in a decrease or cessation of gastric motor activity, similar to that which accompanies both the nausea of chemotherapy and the nausea of motion sickness [6, 20]. In summary, nausea signals one not to eat when the food is toxic, when the stomach is malfunctioning, and/or when a threat is perceived that decreases stomach activity.

The concept of a dynamic nausea threshold

After studying several of the factors that effect the nausea of both motion sickness and chemotherapy, it is proposed that each individual has a dynamic threshold for the complex control mechanism – nausea – that may change from moment to moment. The threshold depends on the interaction of certain relatively fixed characteristics, e.g. age, gender and race, and certain more changeable psychological factors. It is the contribution of the latter factors such as anxiety, expectation, anticipation, and adaptation that probably accounts for much of the inter- and intra-individual variation in the response to nauseogenic stimuli. It is hypothesized that the threshold level effects the individual's cognitive appraisal of both the nauseogenic stimulus and his/her bodily changes in response to the nauseogenic stimulus. The appraisal is thought to affect both selective attention, as well as one's evaluation of threat and coping ability, and

it is this changing appraisal that modulates the response to the chemotherapy drug, spoiled food, motion, etc.

In our laboratory we use a rotating optokinetic drum that provokes nausea and other symptoms of motion sickness in 50% of healthy adults. The drum is a cylinder 91.5 cm in height and 76 cm in diameter. The interior of the drum is lined with alternating 3.8 cm (5.7°) black and 6.2 cm (9.3°) white vertical stripes. (See Figure 1 and Ref. 20 for a description of the optokinetic drum and its use in motion sickness research.) We collect both subjective reports of symptoms and electrogastrographic (EGG) data. Electrogastrograms reflect gastric myoelectrical activity recorded from the abdominal surface with cutaneous electrodes. EGGs appear as sinusoidal waves recurring at a rate of 3 cycles per minute (cpm) when recorded from healthy humans. Acute or chronic shifts from normal 3 cpm EGG signals to gastric dysrhythmias, usually 4–9 cpm, are associated with a variety of clinical symptoms, particularly nausea [19].

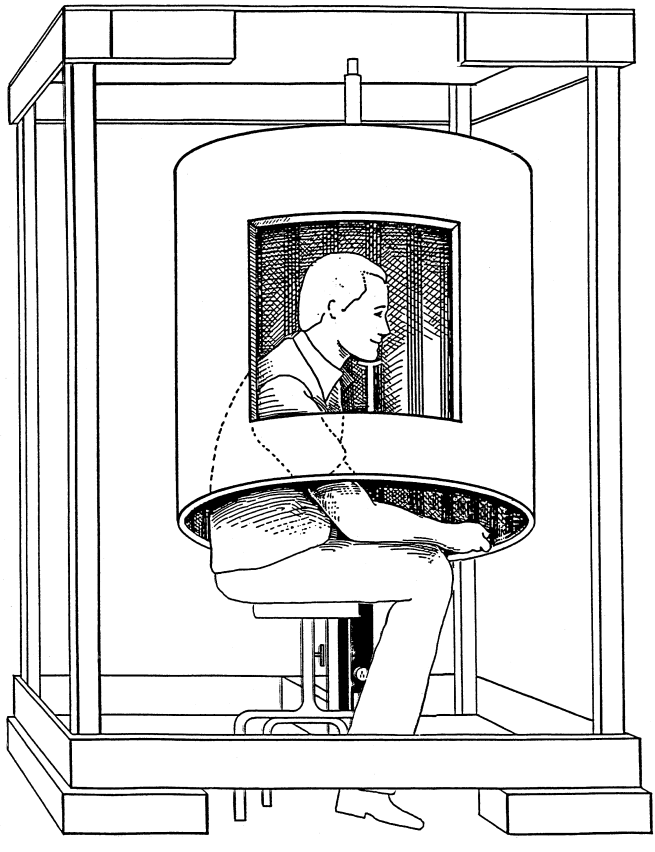

Fig. 1. Optokinetic drum used to stimulate circular vection. The cutout in the drum does not exist; it is shown here for illustrative purposes

What follows is a description of some of the factors that have been studied and are thought to effect one's nausea threshold, but the list is neither exhaustive nor are the factors included here thought to be independent.

Inherent factors

There are at least three inherent factors that have been found to affect the nausea threshold of healthy individuals: age, gender and race.

Age

We have observed that older participants report less nausea and fewer other motion sickness symptoms in the rotating drum than subjects age 16–60. Reason and Brand [17], based on a review of the literature, reported that infants below the age of two are generally immune to motion sickness, susceptibility is greatest between two and twelve, and motion sickness is rare beyond the age of 50. Researchers studying the nausea of chemotherapy (e.g. 16) have also indicated that older patients report less nausea than young patients.

Gender

Numerous reports in the motion sickness literature indicate that women report more symptoms than men. However, we [10] recently completed a study using an optokinetic drum and concluded that, indeed, women reported more symptoms than men, but they did not show greater disturbances in EGG (stomach activity). The chemotherapy literature also indicates that women report more nausea than men receiving the same drugs, but we reserve judgment as to whether this so-called gender effect is physiological or cultural.

Race

In the first of three studies, we reported [21] that 15 Chinese subjects experienced significantly more symptoms of motion sickness than 15 European-American or 15 African-American subjects. Furthermore, the Chinese subjects showed significantly greater abnormal gastric activity during drum rotation than the other two groups. Since the Chinese subjects in this study had recently come to the USA, it was possible that non-biological factors such as child-rearing practices or diet may account for the difference in susceptibility. To rule out this possibility, in another study we tested Asian-Americans, USA-born children of Asian parents, and obtained similar results [22].

Psychological factors

Our theory of why the same nauseogenic stimulus may cause different responses in the same individual on different days is based on our assumption that psychological factors interact with the inherent physiological factors to modulate the response on different days. For example, if a person were particularly anxious on the third day of a series of six days of chemotherapy treatment, he/she might be expected to have a very low nausea threshold and, therefore, appraise the chemotherapy procedure and/or his/her bodily reactions to it as a greater threat than usual and experience more nausea and vomiting than usual.

There is great overlap among the following psychological factors, and, indeed, what one psychologist refers to as, for example, "anticipation," another investigator may label as "expectation." We have decided to preserve the terminology as used by original investigators and describe their research briefly in separate sections of this review.

Anxiety

Reports of nausea are common in patients with various anxiety conditions such as generalized anxiety disorder [15]. Research has shown that anxious individuals are hyper-alert to any type of threat and, therefore, extreme anxiety would be expected to lower one's threshold for the detection of toxins, among other things, resulting in loss of appetite and/or nausea. It has been found that high anxiety contributes to greater side-effects, including more nausea and vomiting, from chemotherapy [9] and from the anticipation of chemotherapy [1]. In the hypothetical example given above, the person who was very anxious on the third day of his/her chemotherapy may have appraised the procedure as more threatening on that particular day and paid more attention to the procedure and to his/her bodily responses to the chemotherapy drug, in essence, getting caught up in a positive feedback loop that resulted in severe nausea and vomiting.

Expectation

Several studies have found that expectations about nausea prior to initial chemotherapy treatment can lower that individual's nausea threshold and in so doing affect appraisal of the procedure and one's bodily responses. This would be predicted by response expectancy theories such as proposed by Kirsch [12]. Specifically, Kirsch states that if an individual is presented with information that indicates that sickness may result due to exposure to some new stimulus (such as information from clinic staff about potential chemotherapy side-effects before the first treatment) and the stimulus exposure itself supports that prediction, then the (nausea) response to the stimulus is likely to be augmented more so than if either the response expectation or

the stimulus were not present together. The results of a recent study in our lab [14] demonstrate the importance of the strength of the expectation and the strength of the nauseogenic stimulus in determining the results. Prior to being exposed to a rotating optokinetic drum, three groups of subjects were given placebos. One group was told that the pills would reduce nausea, a second group was told that the pills would increase nausea, and a third group was told that the pills were a placebo. The first group reported the same degree of nausea as the placebo-control group. The surprise finding was that the group that was told that the pills would increase their nausea reported significantly less nausea than the other two groups and significantly less of the abnormal gastric activity that usually accompanies nausea. Our tentative explanation is that these subjects had a strong negative expectation that was not supported by the actual stimulus, and when their bodily reaction was not very great, the contrast caused an increase in their nausea threshold, an appraisal of the stimulus as not very noxious, and reports of little nausea.

In another recent study [5], it was reported that the greater the amount of abnormal gastric activity immediately prior to chemotherapy, the greater the probability that the patient experienced nausea during and/or following the chemotherapy. One interpretation of this finding is that prior to treatment, those subjects who had an expectation of experiencing nausea during chemotherapy had a lowered threshold for nausea. This may have contributed to the abnormal pretreatment gastric activity, to which they paid attention and appraised as evidence of the seriousness of the threat and/or their inability to cope. And this may have led to the development of nausea during their subsequent chemotherapy. This would be another example of nausea resulting from a positive feedback loop. It should be noted that in Greece, health care providers are not required to tell patients what side effects they may experience from chemotherapy. Anecdotal reports from the chief of the oncology department at the Athens Naval Hospital indicate a much lower incidence of nausea following the same chemotherapy treatment as is commonly used in the USA.

Anticipation

Approximately 25% of cancer patients report nausea in anticipation of chemotherapy following treatment sessions during which they experienced nausea. Anticipatory nausea is thought to be a learned response; it is seldom reported by patients who do not experience nausea during previous treatments. Data tend to support a classical conditioning model with the chemotherapy nurse or the sight or smell of the clinic acting as the conditioned stimulus, the chemotherapy drugs acting as the unconditioned stimulus, and nausea and vomiting being the unconditioned response. The precise role of anxiety in increasing anticipatory nausea is not understood at this time, but there are several possibilities including increasing post-treatment nausea and vomiting (which has been shown to increase subsequent anticipatory nausea), and/or increasing the classical conditioning process by alerting or sensitizing the patient.

Adaptation

Our first attempt to adapt subjects in a rotating optokinetic drum by bringing them back for a second session one week later was a complete failure. However, comments from two astronauts concerning their pre-space flight training in the KC-135 aircraft that they refer to as the Vomit Comet were most helpful. The astronauts indicated that almost everyone gets nauseated and/or vomits the first time they ride in the roller-coaster-like training plane that gives them their first experience of weightlessness; and if they don't get to ride in it again for several days, it is like starting all over and they get sick again. With new insight, we redesigned our adaptation study in the rotating drum and instead of a seven-day inter-session interval, substituted 48 hours. With the shorter inter-session interval most subjects showed a significant reduction in abnormal gastric activity and symptoms of motion sickness, and by the third session were practically asymptomatic [23]. One interpretation of these results is that the recent experience was not as negative as expected, therefore raising the threshold for nausea. Apparently with time, the initial expectation is not sufficiently decreased by subsequent but distant experience and the resulting response is similar to the initial response. Perhaps cancer patients who receive a series of chemotherapy treatments don't adapt, in the sense that they often continue to experience nausea following each treatment, because the inter-treatment intervals are usually too long for adaptation to take place.

Physiological changes that accompany nausea

Figure 2 depicts our working hypothesis of the physiological changes that lead up to the sensation of nausea in susceptible subjects who are exposed to the sensory conflict created by a rotating optokinetic drum. Subjects who experience nausea in the drum, as mentioned at the beginning of this article, show an increase in SNS activity and a decrease in PNS activity, followed by a change in gastric myoelectric activity from a regular 3 cycles per minute (cpm), the normal gastric frequency of humans, to dysrhythmic 4–9 cpm activity, or gastric tachyarrhythmia [19]. We record the frequency of gastric myoelectric activity using non-invasive EGG. The disruption in normal gastric myoelectric activity is usually followed by reports of nausea and an increase in vasopressin levels in the blood [3].

Vasopressin, an anti-diuretic hormone, is released by the posterior pituitary and increases in the blood of individuals who report nausea after injection of apomorphine [4], after cancer chemotherapy agents [2], and after the stimulation of sitting in a rotating chair [3]. It is not clear in these situations whether plasma vasopressin increases immediately before or immediately after the experience of nausea. Several authors (e.g. Robertson [18]) have stated that nausea causes an increase in vasopressin release. Verbalis et al. [24] state, "Nausea, with or without emesis, is one of the most potent stimuli to arginine vasopressin (AVP) secretion known in humans." However, we have not seen any publications in which there are data which demon-

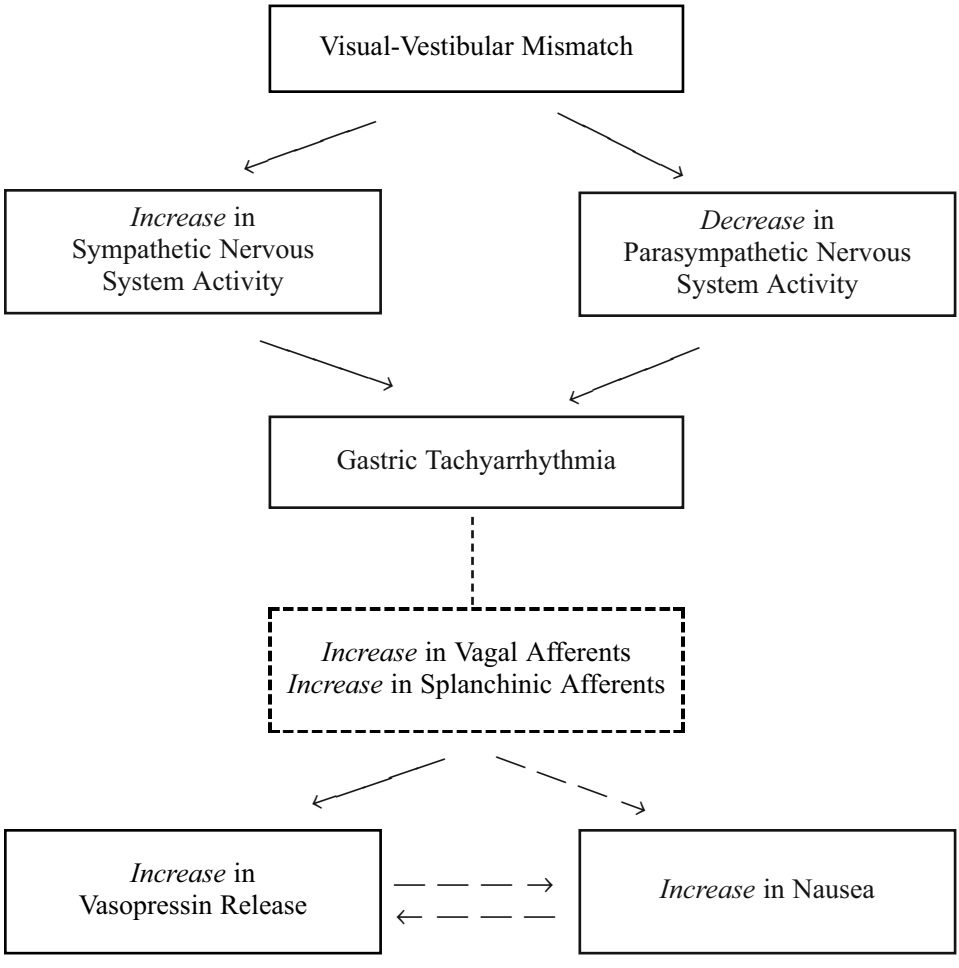

Fig. 2. A working hypothesis of the temporal order of physiological changes that occur in susceptible subjects between exposure to a rotating optokinetic drum and reports of nausea. Solid lines indicate established relationships, dotted lines indicate hypothesized relationships

strate that the temporal sequence of events is a report of nausea followed by an increase in vasopressin levels. Rather, in the typical experiment [e.g. 7], vasopressin levels were found to increase from baseline to the post-stimulus point at which subjects reported nausea. In those few experiments in which several vasopressin measurements were made over time rather than just one pre-stimulus and one post-stimulus measurement [13, 25], reports of nausea do not usually precede increases in vasopressin levels but rather covary. It is conceivable that through classical conditioning, the sensation of nausea has come to stimulate an increase in vasopressin release, but this is thought to be a relatively weak effect since the conditioned stim-

ulus (nausea) and the unconditioned stimulus (vomiting) often don't follow one another, and even when they do, the nausea-vomiting interval is quite long.

Returning to the model depicted in Figure 2, there are several published reports showing that in animals an increase in SNS activity and a decrease in PNS activity often leads to gastric tachyarrhythmia [11]. We know of no studies which demonstrate that gastric tachyarrhythmia leads to increased vagal afferent activity, but we suspect that it does. It has been demonstrated [25] that increased vagal afferent activity stimulates the release of vasopressin.

In studies in our laboratory, for most subjects gastric dysrhythmias preceded the onset of nausea and vasopressin release [23]. We suggest that the shift to gastric dysrhythmias alters ongoing gastric vagal afferent activity, which then modulates neuronal activity in the tractus solitarius and hypothalamus, and ultimately results in vasopressin secretion. Vasopressin levels in the blood of our symptomatic subjects increased along with reports of nausea, and decreased as nausea subsides. In contrast, levels of stress hormones such as epinephrine increased with reports of nausea, but did not decrease until long after nausea subsided. Asymptomatic subjects developed neither gastric dysrhythmias nor increased vasopressin release during drum rotation.

To summarize, the physiological measures that correlate highly with the development of nausea and other symptoms of motion sickness are increased SNS and decreased PNS activity, increased gastric tachyarrhythmia, and increased plasma vasopressin levels.

CONCLUSIONS

Nausea signals us not to eat when we are exposed to a variety of nauseogenic stimulus situations such as being served spoiled meat, receiving chemotherapy, being in a small fishing boat during a storm, or being exposed to certain threatening situations. Individual differences in the experience of nausea can be explained by the complex interaction of factors that determine one's nausea threshold at a certain point in time. Psychological factors such as anxiety, expectation, and anticipation are thought to lower the threshold, and adaptation raises it. We hypothesize that the threshold changes effect cognitive appraisal of the nauseogenic stimulus and/or the bodily changes that follow exposure to the nauseogenic stimulus. And we believe that it is the appraisal that modulates the response to the nauseogenic stimulus. A difficult problem facing health care providers is how to reduce selectively this very effective control mechanism, nausea, when it is not needed, e.g. following chemotherapy, during the first trimester of pregnancy, during threats such as speech preparation, and during provocative motion. This will only be accomplished after we gain a greater understanding of the psychophysiology of nausea.

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