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Current status: animal models of nausea

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SUMMARY

The advantages, and possible benefits of a valid, reliable animal model for nausea are discussed, and difficulties inherent to the development of a model are considered. A principle problem for developing models arises because nausea is a subjective sensation that can be identified only in humans. Several putative measures of nausea in animals are considered, with more detailed consideration directed to variation in cardiac rate, levels of vasopressin, and conditioned taste aversion. Demonstration that putative measures are associated with reported nausea in humans is proposed as a requirement for validating measures to be used in animal models. The necessity for a "real-time" measure of nausea is proposed as an important factor for future research; and the need for improved understanding of the neuroanatomy underlying the emetic syndrome is discussed.

Les modèles animaux dans l'étude de la nausée: état de la question

Résumé: Les avantages et bénéfices possibles d'un modèle animal dans l'étude de la nausée sont discutés; les difficultés inhérentes au développement de ce modèle sont abordées. Un problème de principe pour développer de tels modèles (animaux) réside dans le fait que la nausée est une sensation subjective qui ne peut être identifiée que chez l'homme. Plusieurs indices pouvant permettre de détecter la nausée chez l'animal sont présentés, en insistant plus particulièrement sur les variations du rythme cardiaque, le taux sérique de vasopressine et le comportement de réulsion alimentaire conditionné. La démonstration que ces indices sont aussi associés à une nausée avérée chez l'homme est proposée comme une condition de validation de ces indices chez l'animal. La nécessité d'objectiver la nausée en temps réel est proposée comme un facteur important pour les futures recherches. Le besoin d'une meilleure connaissance neuroanatomique des circuits qui sous-tendent le syndrome émétique est discuté.

INTRODUCTION

Nausea generally is not life threatening, but it can have significant negative impact in clinical procedures (Wetchler, 1991) and chronic nausea may lead to a marked reduction in the quality of life (Stewart, 1991). Patients with predisposition to prolonged gastric emptying or those undergoing laparoscopy are at high risk for nausea and intractable vomiting when anesthesia

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or sedation are required (Kapur, 1991). Nausea and vomiting also are severe side effects of chemotherapy and contribute importantly to noncompliance with treatment regimens, particularly in adolescents (Zelter *et al.*, 1991). In addition, anticipatory nausea is a significant problem with up to one fourth of pediatric patients undergoing chemotherapy (Dolgin *et al.*, 1985).

A valid animal model of nausea would contribute importantly to the study of the neural and physiological systems involved in this state. Miller and Kucharczyk (1991) noted that the lack of such a model has hampered investigation of both the etiology of nausea and the relationship of nausea to vomiting. Development and verification of an animal model of nausea is difficult, however, for both practical and theoretical reasons. Practical difficulties arise because there is no accepted physiological method for identifying the subjective state of nausea in animals, or for that matter in humans. Self-reports of nausea are accepted in humans, but there are no reliable, direct measures of either the presence or degree of this state. Several putative measures of nausea have been suggested, but as is discussed below, none has been convincingly demonstrated as reliable, workable, and valid. This absence of direct measures of nausea creates a significant problem for the validation of animal models.

Development of animal models is complicated further by the fact that species differences in this response are unknown. Vomiting, the culminating event of the emetic syndrome, can be identified directly and is widespread in the animal kingdom. However, the wide variety of stimuli that elicit, or fail to elicit vomiting in various animals (Corcoran, Fox, & Daunton, 1990; Daunton, 1990; King, 1990) might imply that variations are to be expected in nauseogenic responses as well. The observation of vomiting may *not necessarily* indicate that nausea is, or has been, present. Nausea and emesis are not inextricably linked in humans (Harm, 1990) and there is no *a priori* reason to believe that they would be linked in a possible animal model.

Current theoretical interpretations of the neurophysiological mechanisms of vomiting indicate another problem for the development of models. The traditional concept that effector activation of vomiting is coordinated by a localized group of neurons, or vomiting "center" (Borison & Wang, 1949) is now questioned (Miller & Wilson, 1983a). Current interpretations of possible mechanisms for the nausea-emetic syndrome propose that this state may be mediated via multiple pathways (Miller & Wilson, 1983b) rather than a single emetic center. Such schemes may involve predominant pathways for a given emetic stimulus or species (Harding, 1990) or a hierarchical cascade of effector systems that may vary for different animals (Lawes, 1991). Evolutionary development of multiple pathways provides diverse opportunities for variation in the mechanisms of nausea and vomiting among species.

DETECTION OF NAUSEA WITH INDIRECT MEASURES

Following the suggestion of Borison and Wang (1953), indirect measures for nausea have been chosen to reflect autonomic responses thought to accompany this state. Several responses have been used as prodromal signs of nausea. Applications of this approach range from the development of formal rating scales to the reporting of individual responses thought to be prodromal symptoms of sickness. Demonstration that a putative measure is associated with reported nausea in humans is crucial to the validation of measures to be used in animal models.

Rating scales are based on the concept that various autonomic responses (e.g., increased

salivation, disruptions of cardiac rhythm, defecation) that often precede vomiting are associated with nausea. An implicit assumption of this approach is that autonomic signs of sickness reflect an underlying serial process progressing from mild disturbance through nausea toward frank vomiting. Formal rating scales were developed for human studies of motion sickness (Graybiel, Wood, Miller, & Cramer, 1968) so that stimulation could be terminated prior to frank vomiting, and to provide a graded measure of sickness. A scale of one form or another, and self-reported nausea, are used in virtually all studies of motion sickness in man. Analogous scales have been developed to assess the development of motion sickness in cats (Suri, Crampton, & Daunton, 1979), squirrel monkeys (Igarashi *et al.*, 1983) and chimpanzees (Meek, Graybiel, Beischer, & Riopelle, 1962). Several observations indicating that the individual responses comprising rating scales fail to reflect a serial, unitary emetic mechanism in motion sickness are reviewed by Daunton (1990). This lack of evidence of a serial mechanism in motion sickness raises serious concerns regarding the use of rating scales to assess the development of sickness (i.e., nausea) in animal models.

A wide variety of individual responses have been used to assess sickness in animals. Some of these are included in typical rating scales, while others are not. A partial summary of the responses used with various species is outlined in Table 1. Several of these responses (e.g., reduced activity or food intake, defecation, pica) are observed in humans during activation of the emetic syndrome and were adopted as measures to be used with species that do not possess a complete emetic reflex. The use of such species (e.g., the rat) is motivated, in part, by the utility of these standard laboratory animals for physiological investigations. Although the use of these species to assess emetic mechanisms is questionable, these measures continue to receive consideration as multiple, or supplemental indices of sickness (Ossenkopp & Ossenkopp, 1985).

Table 1. Several putative measures of sickness (nausea) and the species that have been tested with each measure.

MEASURE	SPECIES
Arginine Vasopressin (AVP)	human, monkey, cat, rat
Burrowing and Backing	ferret
Cardiac Rhythm	human, squirrel monkey
Conditioned Taste Aversion (CTA)	human, squirrel monkey, cat rat, guinea pig, mouse
Defecation	cat, ferret, rat
Gastric Rhythms	human, dog
Pica	human, rat
Reduced Activity	ferret, rat
Reduced Intake of Food or Water	human, rat
Skin Color Changes	human, squirrel monkey

POSSIBLE MARKERS FOR NAUSEA

Some measures have been adopted specifically to assess nausea. Three of these are discussed in the following sections.

Cardiac Rhythm

A relationship between cardiac irregularity and the emetic reflex has long been suspected (Crittenden & Ivy, 1933). Ishii *et al.* (1987) used beat-to-beat variation in cardiac rhythm to assess autonomic nervous system effects related to "motion sickness" induced by vestibulo-visual conflict in squirrel monkeys. Monkeys were secured in a primate chair to avoid movement artifacts. Variation in beat-to-beat intervals increased immediately prior to vomiting, perhaps reflecting nausea. Two effects indicate these changes could arise from altered parasympathetic activity: injections of atropine reduced variations in animals in control conditions and counteracted increased variation in animals subjected to vestibulo-visual conflict. Demonstration of a relationship between these changes and other possible indices of nausea (i.e., see changes in AVP discussed below) should be considered to investigate these effects further. Cardiac arrhythmia can be processed in real time by computer analysis, and thus could provide a direct, "on-line" measure of parasympathetic activity in conditions when effects from other factors such as stress or blood pressure can be controlled or eliminated.

Release of Vasopressin

The level of systemic vasopressin (AVP) has been investigated as a possible objective marker for nausea or activation of emetic pathways. AVP is elevated during nausea and after vomiting in man (e.g., Koch *et al.*, 1990; Miaskiewicz, Striker, & Verbalis, 1989; Rowe *et al.*, 1979), and after vomiting in cats (Fox *et al.*, 1987) and monkeys (Verbalis, Richardson, & Striker, 1987). However, most examinations of the relationship between nausea and AVP have been correlational in nature, and there is no definitive explanation of the physiological events underlying it. AVP is excitatory to neurons of the chemoreceptive trigger zone (Carpenter, Briggs & Strominger, 1984), but an emetic effect of AVP is not well documented. Infusion of AVP has produced emesis in humans (Thomford & Sirinek, 1975), but infusion also has failed to produce emesis in man (Williams *et al.*, 1986) and in cats (Fox, unpublished data). Explanation of any cause and effect relationship between nausea and elevated levels of AVP is crucial to the use of AVP as a marker for nausea in an animal model.

Two recent studies have addressed the relationship between nausea and AVP. Koch *et al.* (1990) induced malaise using illusory self-motion. Koch (1991) notes that both reported nausea and the release of AVP in this study are related to gastric arrhythmia, and proposes that either of two possible sequences, arrhythmia \rightarrow nausea \rightarrow AVP release or arrhythmia \rightarrow AVP release \rightarrow nausea, are possible. Miaskiewicz *et al.* (1989) stimulated nausea and vomiting in humans by injection of cholecystokinin octapeptide (CCK). Doses of CCK that caused epigastric cramping and mild visceral discomfort were associated with increased levels of AVP, however, these effects occurred without reports of nausea. This result was interpreted as suggesting that AVP secretion can occur with minor visceral malaise even prior to nausea or emesis, perhaps indicating that secretion of AVP precedes nausea.

The efficacy of AVP as a marker for nausea has not been demonstrated convincingly for animal models. Two factors should be considered prior to using AVP to identify nausea or the activation of emetic pathways. First, large individual differences in the range of the AVP response have been observed in studies with humans (Edwards, Carmichael, Baylis, & Harris, 1989; Koch *et al.*, 1990; Miaskiewicz *et al.*, 1989), monkeys (Verbalis *et al.*, 1987), and cats (Fox *et al.*, 1987). Second, not all cases of nausea are associated with AVP secretion. A dissociation of AVP and nausea was shown when nausea, induced by rapid food intake, failed to be associated with elevated AVP (Miaskiewicz *et al.*, 1989). Neither is the association

between emesis and AVP secretion obligatory, since elevation of AVP fails to occur in man when emesis is induced with ipecacuanha syrup (Nussey *et al.*, 1988).

Technological issues also complicate the use of AVP as a marker of nausea in animal studies. Assays for AVP require blood volumes which prohibit serial sampling in small animals. This is a serious problem with very small animals like shrews, where it may not be possible to obtain even single samples without producing changes in blood pressure or plasma osmolality. Obtaining repeated samples from cats may impact other indices of general stress such as cortisol (Fox *et al.*, 1987). In addition, significant processing is required to conduct the assay, so assessment of AVP cannot provide an "on-line" index of the nauseous state.

Conditioned Taste Aversion

The avoidance of flavored substances consumed just prior to the onset of sickness (a conditioned taste aversion, or CTA) was first demonstrated in the laboratory by Garcia and colleagues (e.g., Garcia & Ervin, 1968). Because many of the stimuli used to induce CTA in early experiments produce gastrointestinal distress or nausea, CTA was thought to be mediated by neural mechanisms important to the emetic syndrome. The observation of CTA in patients made nauseous while undergoing chemotherapeutic (Bernstein, 1985; Bernstein & Webster, 1980) or radiation treatments (Smith *et al.*, 1984) for cancer provides further support for this position.

Few direct, systematic evaluations of the assumption that visceral distress, or nausea promote CTA have been conducted. In a retrospective evaluation conducted by reviewing the literatures on vomiting and CTA, Grant (1987) argued that if nausea or other pre-emetic components of the emetic syndrome are responsible for CTA, then CTA should depend on neural structures important to the emetic syndrome (assessed by vomiting). Available studies that investigated whether neural pathways important to emesis also are important to the production of CTA neither confirm nor reject convincingly a role for emetic structures in CTA. Some blood-borne agents such as lithium chloride (McGlone, Riner, & Kelly, 1980; Rabin, Hunt, & Lee, 1983), copper sulfate (Coil & Norgren, 1981), or xylazine (Fox, Corcoran & Brizzee, 1990) that produce CTA do depend on the area postrema. The disruptive effects of AP lesions on CTA induced by toxins are sufficiently reliable that both lithium chloride (Sutton, Fox, & Dauntun, 1988) and scopolamine methyl nitrate (Ossenkopp, 1983) have been used to screen for the completeness of AP lesions in rats. For other agents, however, CTA and vomiting do not depend on the same neural mechanisms. Morphine, for example, produces vomiting via the area postrema (Borison *et al.*, 1962) but produces CTA via the periaqueductal gray (Blair & Amit, 1981).

Several factors require that conclusions from Grant's review be made with care. Grant acknowledged that emetic circuitry is incompletely understood and that most research on CTA has been conducted with rats while that on emetic mechanisms has been on cats, dogs, and monkeys. (Ferrets must now be added to the list of animals used to study emetic mechanisms). Because there are species differences in sensitivity to emetic treatments, cross-species comparisons can be difficult. However, cross-species comparisons are required because the relationship between CTA and the emetic syndrome has been investigated directly in very few studies (Fox *et al.*, 1990; Rabin *et al.*, 1986; Roy & Brizzee, 1979; Wilpizeski *et al.*, 1985). These studies generally show that vomiting does not predict the formation of CTA precisely. CTA may occur without vomiting and vomiting may occur without CTA being produced. Additional studies directly assessing CTA and the emetic syndrome in the

same species (or animals) will be required to clarify whether the emetic syndrome and CTA share common neural circuitry.

Because CTA is a learned response, several control conditions for the study of learning mechanisms are required when this measure is used (Fox, 1990). Procedures to eliminate pseudoconditioning and other artifactual effects that could be incorrectly interpreted as CTA can significantly increase the effort and cost involved in using this measure. The possibility that exposure to the emetic stimulus prior to testing could reduce the strength of CTA, and thus lead to incorrect inferences about the effect of the stimulus, can restrict methods for conducting experiments.

CONCLUSIONS

Development of a valid animal model of nausea requires the identification of motor, hormonal, neural, or behavioral events that are associated with nausea. Because nausea is a subjective state that can be identified only in man, potential measures for animal models must be based on demonstrations that the same measures reliably identify nausea in man. Thus, a coordinated research strategy that integrates information from studies in humans and animals is required. Confidence in a given measure could be enhanced by the accumulation of convergent validation data from multiple assessments (i.e., motor and hormonal).

Each of the potential measures of nausea discussed above is affected by one or more detrimental factors. All of these potential measures require better validation. Technical requirements for assaying systemic AVP can produce general stress effects, or even prohibit application of the measure in very small animals. Concern about neural circuitry crucial to CTA, requirements for control procedures, and the observation that nausea and/or vomiting can occur independently of CTA indicate reservations about this measure. In addition, investigation of the effects of antiemetic drugs on CTA have produced positive (Coil *et al.*, 1978) and negative (Goudie *et al.*, 1982) results, and some of the compounds used as antiemetics can produce CTA themselves (i.e., scopolamine).

Neither AVP nor CTA can provide a real-time assessment of sickness. Variation in cardiac rhythm could provide real-time assessment, but this measure needs to be validated with additional studies. The source or type of other possible measures for nausea are not readily forthcoming. Incomplete characterization of the neuroanatomy that underlies the emetic syndrome complicates identification of prodromal signs sufficiently independent of emesis that they might serve as measures of other components of the syndrome. Thus, recent research has characterized gastrointestinal precursors of vomiting (Lang *et al.*, 1986; Lang, Sarna, & Condon, 1986) but has not provided a clear candidate for an index of nausea. Gastric relaxation could be a candidate (Andrews & Wood, 1988; Hulse & Patrick, 1977; Willems & Lefebvre, 1986) but this response also occurs as part of the normal sequence of feeding (Young & Deutsch, 1980), and not all forms of gastric distention produce nausea (Miaskiewicz *et al.*, 1989). If this response is related to nausea, an explanation of why it leads to the sensation of nausea in some instances but not in others is required.

Improved understanding of the neurocircuitry of the emetic syndrome is a primary requirement for the development of a model for nausea. The neural mechanisms underlying nausea will not be identified until the events that converge to elicit vomiting are described more fully. Improved understanding of interrelationships between prodromal signs of vomiting and identification of the mechanism coordinating the neural activity that produces the complicated

pattern of motor events leading to expulsion would be very beneficial. At the present time there is little evidence indicating whether the mechanisms underlying nausea should be sought in central or peripheral sites.

The species best suited for a model is not obvious. Each species traditionally used to study emetic mechanisms (dogs, cats, ferrets and monkeys) has advantages for specific purposes. The extensive knowledge of neural, receptor, and gastrointestinal mechanisms in these animals is invaluable. But other tractable animals that readily can be bred for purpose to insure availability at reasonable cost would be advantageous. The ferret has been very useful in recent years, and the house shrew, *Suncus murinus*, is a relatively new candidate on the scene that shows promise (Matsuki *et al.*, 1988; Ueno, Matsuki, & Saito, 1987; Ueno, Matsuki, & Saito, 1988). The shrew is very small for some procedures, such as blood assays and instrumentation, but this small size is an advantage for housing and testing of chemical agents that are difficult to produce in large quantities. If detailed description of neuroanatomy and physiology are forthcoming this may prove to be a useful animal. Certainly the rat is not an ideal model. Thorough knowledge of anatomy and physiology are a valuable asset, but the lack of an emetic reflex leads to complex issues of species differences that complicate understanding.

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