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Chapter 8

INVESTIGATING MOTION SICKNESS USING THE CONDITIONED TASTE AVERSION PARADIGM

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I. INTRODUCTION

The avoidance of foods which are associated with uncomfortable or aversive internal states has long been recognized. Many people are aware, either directly or via anecdotal reports, of individuals who avoid foods which were eaten just before the onset of sickness. Awareness of this phenomenon can be traced to the writings of John Locke.[1] The disruption of diet during cancer therapy is sometimes ascribed to the attribution of an unpleasant quality to foods eaten preceding the sickness induced by therapy itself.[2] In addition, it has long been recognized by the manufacturers of rodent poisons that animals avoid the injection of food treated with nonlethal doses of poison.[3,4]

An important part of the laboratory study of this phenomenon has been directed toward studying the role learning plays in this type of avoidance behavior. Following the lead of Garcia and his associates, this avoidance has come to be interpreted as arising from a form of classical conditioning. In typical laboratory studies of this behavior, a novel food is ingested just prior to exposure to some stimulus, commonly poisoning or irradiation, which produces illness. Following the terminology of classical conditioning, it is common to describe this procedure as one of "pairing" a conditioned stimulus (CS), the novel food, with an unconditioned stimulus (US), the illness induced by toxicosis or irradiation. Avoidance of the food in succeeding feeding opportunities is viewed as a learned response or a conditioned taste aversion (CTA).

Garcia and associates have argued that this form of learning is biologically significant in that it serves to regulate the "internal milieu", presumably by adjusting the hedonic value of food via feedback from the viscera.[5,6] Work by Garcia and collaborators has generated considerable debate in the psychological literature regarding this form of conditioning and its impact on traditional theories of learning.[1,7] Various bibliographies[8,9] and reviews[10-12] dealing with these issues are available in the existing literature. These sources should be consulted for detailed discussion of theoretical issues.

The persistent conception that "illness", particularly visceral illness, serves as the US for the development of CTA is of more importance to the use of CTA in motion sickness research. Early studies of CTA typically used either exposure to irradiation or injection of toxins as the US. Most stimuli used as USs in these studies were known to produce sickness in the form of nausea or vomiting in humans or animals. Thus, the assertion that sickness produced by these treatments was the functional US producing the observed CTA was a natural inference. In addition, Garcia and Ervin[5] discussed the anatomical convergence of gustatory and visceral afferents in the nucleus of the solitary tract, and thus suggested a putative neural system to account for the unique propensity, demonstrated by Garcia and Koelling,[13] for gustatory stimuli to become associated with visceral disruption (i.e., "sickness").

Garcia et al.[14] asserted that motion sickness could produce "gustatory" aversions, but passive motion was first reported as an US to establish CTA by Green and Rachlin.[15] The purpose of this chapter is to review the manner in which CTA has been used to study motion sickness. Numerous reviews concentrating on other aspects of CTA are available in the existing literature. Readers are encouraged to consult the various papers[16-22] and edited books[11,23] for extensive information on other aspects of this literature.

II. RATIONALE FOR USING CTA

The assumption that an unspecified, aversive internal state resulting from exposure to passive motion is the effective stimulus producing CTA underlies the use of CTA to measure motion sickness. Various forms of evidence support the inference that CTA produced using passive motion as the US results from motion sickness. In early studies investigating the use of motion-induced CTA in rats it was noted that lithium chloride, cyclophosphamine, or irradiation have nauseogenic and emetic effects in other animals or in humans, and presumably produce general

malaise which serves as the US in rats. Because nausea and gastrointestinal distress are common components of the motion sickness syndrome, the inference that motion-induced CTA arises from illness is plausible. The presumed importance of an internal state, or illness, as the US was supported further by the demonstration that motion-induced CTA occurs more readily to gustatory cues than to either proprioceptive or exteroceptive cues.[24] This finding is consistent with data for poison-induced CTA[6] and lends plausibility to the inference that exposure to motion disrupts an internal state, thereby producing CTA. In addition, the vestibular system plays a critical role for the efficacy of motion as an US to produce CTA. After surgical damage to the vestibular system, motion-induced CTA is either prevented,[25] or greatly attenuated.[26] Thus, as motion sickness does not occur in labyrinthine-defective humans[27] or animals,[28,29] motion-induced CTA does not occur when the vestibular system is destroyed in rats.

Following this general conception of a plausible relationship between CTA and sickness, two principal applications have evolved for using CTA to assess motion sickness. The most prevalent is to view CTA as a behavioral reflection of motion sickness that may be useful with species such as the rat which are incapable of vomiting.[30] This concept was implied by Hutchison[31] and furthered by Mitchell and colleagues[32,33] who showed that both pica and CTA could be produced by rotation and then argued that these two effects of rotation should be considered species-specific reactions to motion sickness. The second application is to assess subemetic symptoms of motion sickness in animals capable of vomiting. This application was suggested for squirrel monkeys by Roy and Brizzee,[34] and Wilpizeski and Lowry[35] have proposed a theory interpreting nausea as the US for CTA in squirrel monkeys.

III. GENERAL MODEL OF THE CTA PARADIGM

A. DEFINING CHARACTERISTICS

Various aspects of a general model of the CTA paradigm, with particular attention to factors which are important to the application of CTA to the study of motion sickness, are discussed in this section. This model has the following characteristics: (1) A flavored stimulus (often a novel fluid) serving as a CS is offered to the animal. (2) Some form of passive motion, most often involving rotation, is used as a US. Exposure to this motion typically occurs soon (within minutes) after access to the CS is withdrawn. (3) A period during which recovery from the direct effects of the US can occur (perhaps 2 or more days) follows the joint presentation (i.e., "pairing") of the CS and US. (4) The CS is presented by itself (an "extinction trial") to determine the strength of CTA developed by pairing the flavored stimulus with passive motion. Various modifications on this general model may occur for experimental reasons or because of limitations arising from practical considerations in a specific study.

B. A POTENTIAL ADVANTAGE OF CTA OVER OTHER DEPENDENT MEASURES

While vomiting is well defined and universally accepted as the endpoint of motion sickness, the identification of nausea, and the interpretation of the various other effects of motion which accompany motion sickness are less clear, particularly in animals. Of special interest here are the disorientation and disruption of locomotion and motor skill which may be produced by exposure to passive motion. Reason and Brand[27] referred to these accompanying effects as epiphenomena to the "big four" reactions of motion sickness: pallor, cold sweating, nausea, and vomiting. Other putative dependent measures of motion sickness, especially those which reflect sickness via reductions in behavior, are prone to influence by these accompanying effects of motion in addition to being influenced by motion sickness itself. These other measures include spontaneous activity,[36] operant responding for food reinforcement,[37] and fluid intake.[25] While these measures need not necessarily be affected by factors other than sickness,[38] each could be suppressed by accompanying effects and by various exteroceptive stimuli (i.e., noise, vibration, or other stimuli associated with the production of passive motion stimulation).

On the other hand, CTA is produced by exteroceptive cues only with difficulty. In addition, when CTA is used as the dependent variable for assessing motion sickness, disorientation, disruptions of locomotion, and other residual effects dissipate during the recovery period following the pairing of a CS with exposure to passive motion (see number 3 above). Thus, this recovery period between the conditioning and evaluation phases of the CTA paradigm serves to isolate the evaluation of motion sickness from various direct effects of motion which may not be the intended referent of "motion sickness". This characteristic of the CTA paradigm provides CTA with an advantage over some other putative measures of motion sickness. Changes in those putative measures which indicate sickness by increases in behavior (the intake of nonnutritive substances, or pica[32,33]) may be reduced by accompanying effects of motion, but these measures will not provide a false positive indication of sickness. Because the rate of defecation can be affected by general arousal, animals should be acclimated to the experimental conditions before testing.[39]

C. POTENTIAL CONFOUNDING VARIABLES IN CTA

1. Novelty and Salience of the Conditioned Stimulus

The relative novelty of a taste can have a profound influence on the strength of an aversion conditioned to that taste. It is generally the case that stronger aversions are formed to novel tastes than to familiar tastes.[40,41] However, CTAs can be formed to familiar tastes in animals,[42,43] in children,[44] and in adult humans.[2] Thus, it is not imperative that a novel taste be used as a CS. In many cases, particularly when rodents or other small laboratory-bred animals are used, the feeding history of subjects is controlled and known and a novel-flavored food or solution can be used to make a sensitive test for CTA. When primates such as the popular squirrel monkey are used, the selection of palatable, novel-flavored stimuli can be problematic. Caution should be used when pretesting a flavor to assess its palatability because pretesting itself may influence the effectiveness of that flavor as a CS. Exposure to a potential CS preceding conditioning clearly attenuates the strength of an aversion to that cue.[45,46]

The term salience has been used to describe the propensity of a cue to become conditioned. Rozin and Kalat[22] demonstrated that all tastes are not equally associable to the internal consequences of poisoning in rats. Those tastes to which stronger aversions were formed were referred to as more salient. The salience of a cue may be affected by its novelty, intensity, palatability, and intrinsic taste quality (see Kalat[47] for references). Rozin and Kalat[22] demonstrated that palatability order, determined as preference in choice tests, does not necessarily correspond to the salience order for a set of taste cues. Kalat[47] varied the concentration of flavored solutions used for conditioning to investigate the role familiarity may play in determining salience. For rats reared on tap water, the more concentrated of two solutions was associated better with illness. For rats reared on an even more concentrated solution, the less concentrated solution was associated better with illness. Kalat suggested that unfamiliarity (novelty) is a major determinant of salience. Salience also appears to be affected by cue characteristics other than taste alone. Solutions typically used in studies of CTA may differ in odor as well as in taste. By rendering rats anosmic, it has been shown that olfactory cues can combine with taste cues to increase the salience of a "flavored" (i.e., a taste) stimulus.[48]

The novelty and salience of cues used as CSs are clearly related to the strength of CTAs and could impact importantly on studies using CTA to investigate motion sickness. A research objective which requires repeated conditioning with a given animal will be influenced by these effects. The same cue should be used as a CS in successive conditioning attempts using different USs only with caution, and precise matching of cues for novelty/salience is very difficult and costly, if possible. Several investigations of the relative salience of some cues have been conducted for rats,[47-51] but similar studies for other species used in motion sickness research (i.e., dog, cat, and monkey) have not been conducted. Certainly, any comparison of the strength of CTA associated with different phases of an experiment must be made cautiously or avoided

completely. A design where a cue is presented repeatedly but an aversion is not formed simultaneously provides preexposure to the CS, which may reduce the strength of CTA conditioned to that cue later. Thus, the demonstration of CTA in later conditioning conservatively shows CTA can be produced, but it does not pose a sensitive test of the strength of that CTA. In addition, any design using repeated conditioning will also expose animals to aversive internal consequences, either from the same or another US, and such exposure can significantly attenuate the strength of CTAs induced later (see below).

Research investigating the effects of lesions on motion-induced CTA should consider effects of those lesions on salience as well as on the efficacy of the US (i.e., on motion sickness). It has been shown, for example, that lesions of area postrema influence food consumption in rats.[52] While the effects of lesions on other neural structures of interest to motion sickness research are not necessarily known, it should be recognized that surgical interventions could affect the magnitude of CTA by altering reactions of the animals to the CS as well as to the US or its internal effects.

2. Prior Exposure to the Unconditioned Stimulus

The strength of conditioned aversions generally is greatly reduced by exposing animals to an aversion-producing treatment prior to conditioning. That is, animals exposed to an aversion-producing treatment prior to the pairing of that, or a different treatment with a flavored food, commonly form aversions less readily than animals exposed to a control treatment prior to conditioning. In some cases this exposure before conditioning completely prevents the formation of a conditioned aversion. This effect can occur when any of various conditioning procedures and aversion-producing treatments are used.[53] The degree of reduction in magnitude of CTA which is produced by exposure to a treatment prior to conditioning generally increases as the number of exposures prior to conditioning increases, but reduced magnitude of conditioning has been demonstrated with a single exposure preceding conditioning.[53,54]

Braveman[55] referred to experiments in which animals are exposed to one potentially aversion-producing treatment and then conditioned with a different treatment as "crossover" experiments. Experiments of this type have been conducted to exclude addiction or tolerance to the drugs commonly used as aversion-producing treatments as explanatory factors for the effect. However, in a series of crossover experiments of particular importance to the use of CTA as a measure of motion sickness, Braveman[54] (Experiment 5) demonstrated that five exposures to doses of methylscopolamine, d-amphetamine sulfate, or lithium chloride prior to conditioning with motion blocked the formation of an aversion when rotation (60 rpm for 15 min) was used 5 d later as an US.

The blocking of motion-induced CTA by preconditioning exposure to aversion-inducing drugs is a finding of cardinal importance to the use of CTA in studies of motion sickness. Braveman suggested this blocking effect may depend on exposure to a treatment which can be used as an US for producing CTA. The existence of this effect dictates that CTA should not be used to measure motion sickness when animals have been exposed to any of the myriad of drugs known to be an effective US for CTA. This can be of special concern when primates, which are sometimes tested on several occasions over a period of years, are used in motion sickness research. A conservative interpretation would indicate that CTA should not be used, or at least should be used with caution, if animals have been tested previously with emetic drugs, or with other drugs such as scopolamine, which can be used as an US to produce CTA.

In addition, passive motion itself meets Braveman's criterion of being a treatment capable of producing CTA, and the attenuating effect of exposure to a treatment before conditioning is typically robust when animals are exposed to the identical treatment that is to be used for conditioning. Thus, it would appear that CTA might be expected to be weak when conditioning follows several exposures to the motion used later as an US. Haroutunian et al.[25] (Experiment 3b) reported that exposure to interrupted rotation before conditioning prevented the formation

of CTA in rats when that same motion was used as an US. In this experiment preconditioning exposures consisted of rotation of water-deprived rats on five separate occasions in order to study postrotational suppression of drinking. Exposure to rotation before conditioning clearly reduced the magnitude of CTA produced by later conditioning. All animals were exposed to motion the same number of times prior to conditioning, and the parameters of the motion (i.e., speed of rotation, etc.) were not varied. Thus, it is not possible to determine the minimum number of exposures to rotation which will produce this effect or whether this minimum number is affected by the type of passive motion that is used. It is clear from this experiment, however, that serious confounding of effects could arise if the number of exposures prior to conditioning varies for different animals. This potential problem should be considered if animals to be used in a conditioning study may have been used in previous motion sickness research.

3. Interaction Between Unconditioned Stimuli

The efficacy of an US can be influenced by other stimuli present at the time the US is applied. Electric shock typically is not an effective US for establishing CTA. However, Lasiter and Braun[56] have shown that rotation-induced CTA is enhanced when rats are exposed to footshock in conjunction with rotation. In a second experiment reported in this paper it was demonstrated that footshock also enhanced the magnitude of CTA produced using apomorphine as the US. Thus, it appears that the enhancing effect of footshock on rotation-induced aversion is not necessarily due to increased vestibular stimulation arising from movements elicited during rotation. The authors suggest this enhancement is due to increased arousal produced by the footshock. This demonstration of enhanced CTA by a stimulus which is not an effective US for CTA indicates that control groups should be included when the method of exposure to motion might affect the level of arousal of animals.

IV. IMPLEMENTATIONS OF THE PARADIGM

A. PASSIVE MOTION AS AN UNCONDITIONED STIMULUS

Simple, vertical axis rotation is the most common form of passive motion used to produce CTA. Rotation speeds range from as low as 12 rpm (72°/s) to as great as 198 rpm (1188°/s), but most studies have used speeds of 30 to 40 rpm (180 to 240°/s). Because the vestibular system is affected only by accelerations, precise specification of the parameters of motion which comprise the US is complicated when this type of stimulus is used. If animals are restrained and positioned so the vestibular system is directly over the axis of rotation, accelerations will occur only briefly at the beginning and ending of rotation. However, if voluntary movement is permitted during rotation, undefined accelerations are produced when the head is moved. Cross-coupled accelerations, which are especially provocative for producing motion sickness in man, occur if the head is moved in a plane differing from the plane of rotation. No studies requiring animals to make voluntary head movements producing such cross-coupled accelerations have been reported.

Several forms of passive motion have been used to ensure accelerations are applied to the vestibular system independently of voluntary movements made by the animals during rotation. A simple method for accomplishing this is to start and stop, i.e., to interrupt the motion. This method might be called interrupted vertical axis rotation. This form of rotation has been used in experiments with rats,[24,25,39,58,59] quail,[60] and squirrel monkeys.[61] It ensures that accelerations are applied to the semicircular canals each time rotation begins and ends. The occurrence of accelerations can also be ensured easily by tilting the rotation platform so the axis of rotation deviates from earth vertical. When the platform is so tilted, the body axis of rats is oscillated between head up and head down positions during rotation, thereby applying a sinusoidal pattern of accelerations to the otoliths. This method has been used with rats[57] and mice.[38]

Other methods of ensuring the application of accelerative forces to the vestibular system have

involved more-complicated motion devices. The effects of centrifugation have been investigated using forces of 5 to 10 times gravity.[62] Rotation about two axes simultaneously was accomplished using a modified Hobart mixer[33] with the extreme rotary speeds of 198 rpm and 88 rpm combined. Rotation combined with sinusoidal vertical oscillation has been used to produce CTA in squirrel monkeys,[34] but vertical sinusoidal acceleration alone failed to produce CTA in squirrel monkeys.[63] Simple, vertical axis rotation can be used to produce CTA in squirrel monkeys,[35,64] so it appears that rotation may have been the effective stimulus in the earlier study[34] when rotation was combined with a vertical excursion of the apparatus.

Several experiments have demonstrated that the magnitude of motion-induced CTA is affected in a predictable manner by manipulation of parameters of motion which are known to affect the severity of motion sickness in man. Several variables have been manipulated to provide such correlational evidence. Green and Rachlin[15] investigated the magnitude of rotation-induced CTA while varying both the duration of exposure to rotation and the speed of rotation. Their analysis indicated that the absolute number of rotations, not the speed or duration of rotation alone, was the best predictor of the magnitude of aversion. The effect of different forms of passive motion on the magnitude of CTA has been investigated for three different motion profiles.[65] Accelerative forces were varied by using three conditions producing increasing stimulation to the vestibular apparatus. As the degree of presumed vestibular stimulation increased from a condition involving only vertical-axis rotation, to sinusoidal bouncing (seesaw motion), to cross-coupled motion comprised of rotation during seesaw oscillation, the magnitude of CTA also increased. Off-vertical rotation has also been used to address this issue. Off-vertical rotation becomes increasingly provocative for producing motion sickness as the degree of tilt increases and approaches "barbeque spit rotation".[66] Fox et al.[38] demonstrated that the magnitude of CTA increased as the tilt-axis of a rotation platform was increasingly deviated from earth vertical.

B. METHODS OF CAGING DURING EXPOSURE TO MOTION

1. Individual vs. Group Caging

Considerable improvement in methodological efficiency can be accomplished by exposing animals to rotation in groups rather than individually. The amount of savings obtained by this procedure obviously increases as the duration of the rotation period is lengthened or as the number of animals is increased. Because the magnitude of CTA can be influenced by circadian rhythm,[67] conditioning should be conducted during a limited period of the day. This can be facilitated by using several motion devices, by distributing the experiment over several days, or by exposing several animals to motion simultaneously.

These issues are addressed briefly by Harrison and Elkins,[68] who indicated several previous studies using various approaches to expose small groups of rats to rotation. They also describe a simple, easily constructed device for exposing groups of rats to rotation. Their device confines rats in tubes constructed of PVC pipe. Two tubes are placed side by side, and two tiers are stacked so that four rats can be rotated simultaneously. A similar tiered approach has been used with four compartments (18 × 19 × 10 cm) in each of five tiers, permitting the simultaneous exposure of up to 20 rats to off-vertical rotation.[69,70] Placement of animals side by side with the axis of rotation between them permits two animals to be close to the axis of rotation on each level. Placement of animals in chambers constructed as small squares within a larger square pattern with one corner of each of the smaller squares converging over the axis of rotation permits four animals to make voluntary movements close to the axis of rotation on each level of such a device. These approaches facilitate the testing of several animals while confining all animals close to the axis of rotation and thereby minimizing centrifugal forces which increase with increasing displacement from the axis. The total number of animals that can be exposed at a time can then be increased by stacking levels up to the safety limits of the rotation device. The expansion of such devices for use with larger animals should be done with consideration of possible safety

factors resulting from weight of the device and the animals. In addition, as larger confinement chambers are used with larger animals, greater centrifugal forces can result from orientations adopted by the animals. Thus, control of the effective stimulus serving as the US depends increasingly on the orientation adopted by the animal during rotation. Larger animals such as monkeys or cats are typically exposed to motion individually. A device for exposing two cats to motion simultaneously has been described,[71] but this device has not been used in studies of CTA.

2. Restriction of Voluntary Movement

As reflected by vomiting, motion is dramatically less provocative in man when head movements are restricted[72] and in squirrel monkeys when movement is restricted,[73] or prevented by rigid restraint.[61,74,75] From the viewpoint of experimental control, however, the restriction of movement during exposure to motion has the beneficial effect of permitting better specification of accelerations to the vestibular system. This benefit derives from the elimination or reduction of accelerations dependent on movement by the animals. Restriction of movement thus tends, in effect, to equate stimulation which otherwise might vary due to movements elicited or evoked differentially in individual animals exposed to motion.

Restraint has not been used often in studies of motion-induced CTA. The movement of rats has been restricted to avoid uncontrolled, cross-coupled accelerations produced by whole-body movement when investigating CTA induced by centrifugation.[62] In addition, restraint has been used when exposing rats to off-vertical rotation.[76]

The magnitude of CTA induced by off-vertical rotation with whole-body movement of rats permitted or restricted was investigated in an unpublished experiment. Rats in a voluntary movement condition (FREE) were placed in opaque plastic mouse cages (8 × 18 × 28 cm) when exposed to rotation. Rats in the restricted movement condition (RESTRAINED) were placed in plastic tubes 8 cm in diameter and 18 cm long during exposure to rotation. Each of 32 rats was assigned randomly to one of the eight conditions formed by the factorial combination of two treatment conditions (motion or no motion), two novel flavors (sucrose or salt), and two rotation conditions (free or restrained). The rotation profile consisted of off-vertical rotation (rotation axis displaced 20° from earth-vertical) and an angular velocity of 150°/s for 15 min. A discrimination procedure adapted from that used by Braun and McIntosh[57] was used for the conditioning procedure. During an 8-d acclimation period, rats were adjusted to a restricted drinking procedure consisting of 15 min of access to tap water in the home cage every 12 h followed immediately by placement in the appropriate experimental holding cage for 15 minutes. During conditioning, one of two taste solutions, either sucrose or salt, or tap water was offered in each drinking session (i.e., one every 12 h). One taste solution was always followed by exposure to rotation. Tap water was offered in the drinking session 12 h after rotation and the other taste solution was offered in the drinking session 24 hours after rotation. Completion of three consecutive drinking sessions, during which each of the three fluids was offered once for drinking, comprised a conditioning cycle of the procedure. Six conditioning cycles were used in the experiment.

Conditioning was much stronger to the salt taste than to the sucrose taste. The median intake of the paired taste solutions by animals in the FREE and RESTRICTED movement conditions is shown in Figure 1. Each curve is based on data from only four animals and consequently should be interpreted with caution, but there is no evidence in these data of any reduction in the magnitude of CTA when whole-body movement is restricted. Neither parametric nor nonparametric statistical tests indicated a reliable difference between the conditions ($ps > 0.20$). Thus, although the assessment of motion sickness by vomiting indicates reduced sickness under conditions of restricted movement, the magnitude of motion-induced CTA was not reduced when movement was restricted during exposure to off-vertical rotation.

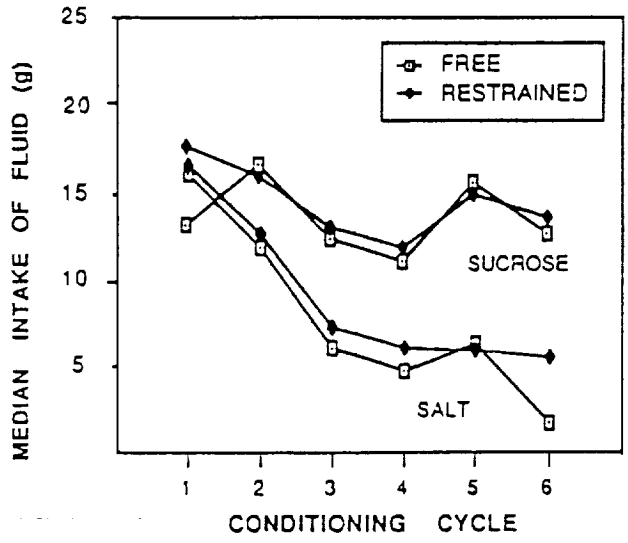

FIGURE 1. Median intake of the solution which was paired with motion when animals were permitted to make voluntary movements (FREE condition) or when movement was restricted (RESTRAINED condition) during motion. The upper curves reflect conditioning when the sucrose solution was paired with motion. The lower curves reflect conditioning when the salt solution was paired with motion. Each curve is based on data from four rats.

C. TYPES OF CONDITIONED STIMULI AND METHODS OF PRESENTATION

Flavored fluids have been used as CSs most commonly, but solid foods have been used with rats[65] and squirrel monkeys.[35,74] Fluids generally are preferred over solid foods as CSs because residual traces are not as likely to be present after the CS is removed at the end of the period of access. Solid foods may remain on the fur of the animal and be encountered during grooming after exposure to motion. When the CS is presented in the home cage of the animal, spilled or smeared food may remain and be eaten after the animal is returned following treatment with motion. Nonnutritive substances are generally preferred over nutritive substances to avoid confounding nutritional consequences with the effects of illness.

Most studies which have used flavored fluid as the CS have assessed the magnitude of CTA with the "two bottle" method. With this method, the CS and tap water are available simultaneously during tests for conditioned aversion. The magnitude of CTA is assessed as preference for the flavored fluid determined as the percentage of total fluid intake accounted for by intake of the CS. With the "one bottle" method, only one fluid is offered for drinking in a single period of restricted access each day. With this method, aversion to the CS is shown either as lesser consumption of the CS after exposure to motion than before that exposure (a within-subjects comparison) or as lesser consumption of the CS by animals exposed to motion than by control animals not exposed to motion (a between-subjects comparison). The two-bottle method is generally considered to be a more sensitive test of CTA than is the one-bottle method.[77,78] However, Ossenkopp[59] found that enhancement of motion-induced CTA in animals with the area postrema lesioned was detected with an intake measure (one-bottle method) but not with a preference measure. He concluded that the preference measure was not sensitive to this enhancement effect in his experiment because preference for the CS was so low that it could not be reduced (i.e., a "floor effect" prevented detection of the enhancement of CTA). Thus, under some conditions the one-bottle method might be preferred.

The discrimination procedure used by Braun and McIntosh[57] and in the unpublished

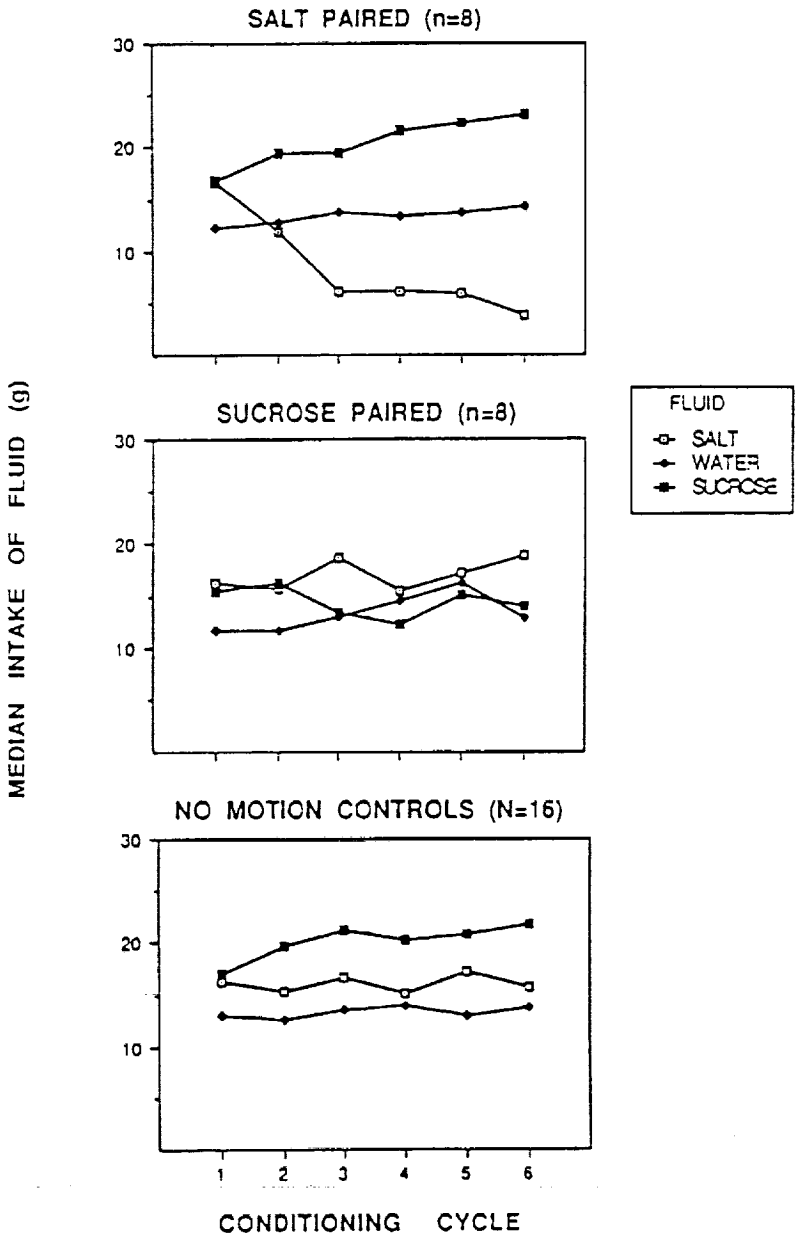

FIGURE 2. Median intake of the three solutions consumed during the experiment. Conditioning effects are shown in the upper panel where the salt solution was paired with motion and in the middle panel where the sucrose solution was paired with motion. Median intake reflecting preferences for the solutions by animals which were never exposed to motion are shown in the bottom panel.

experiment discussed above may be prone to spurious effects arising from repeated exposure to more than one flavored stimulus. Additional data from that unpublished experiment are presented in Figure 2 and show the intake of each fluid with the FREE and RESTRAINED conditions combined. It is apparent from this figure that a stronger aversion was produced when salt was paired with motion (upper panel) than when sucrose was paired with motion (middle panel). When the salt solution was paired with motion, the animals consumed less of that solution

in all tests for aversion (Cycles 2 through 6, $p < 0.01$). However, when the sucrose solution was paired with motion, the consumption of that solution was reduced only in Cycles 3 and 4 ($p < 0.05$). Intake data for the control animals not exposed to motion are shown in the bottom panel of the figure. For these animals both flavored solutions were preferred over tap water in Cycle 1 ($p < 0.01$), but neither flavored solution was preferred over the other ($p > 0.05$). However, after repeated exposure to the three fluids, consumption of the sucrose solution increased and this solution came to be preferred over the salt solution ($p < 0.01$ in Cycle 6) while consumption of the salt solution and tap water did not vary ($p > 0.05$). When these results are combined, it can be seen that a weak aversion developed to the paired solution which became more preferred during the experiment (sucrose), while a strong aversion developed to the paired solution for which preference remained stable during the experiment. This observation indicates that the magnitude of motion-induced aversions may be related to the preference for flavored cues used as CSs.

It should be noted, however, that these results differ from those reported by Braun and McIntosh in two ways: they found aversions of similar magnitude to both flavored solutions and, although the consumption of the sucrose solution was greater than that of the salt solution in their experiment, they did not report a statistically reliable difference in consumption. There is insufficient information available in the Braun and McIntosh paper to perform a post hoc analysis to evaluate more completely the possibility of a shift in preference in their control group. The issue of the strength of aversion to sucrose may be related to the fact that a more severe stimulus was used by Braun and McIntosh. In that experiment, rats were exposed to off-vertical rotation at 150 rpm for 5 min (750 total revolutions) while in this experiment they were exposed to off-vertical rotation at 25 rpm for 15 min (325 revolutions). Thus, if the total number of revolutions is used to evaluate the intensity of the US,[15] there is an intensity ratio of 2:1 in the two experiments. These observations indicate that the effects of preference on the magnitude of motion-induced CTA may become evident only if moderate motion profiles are used. In addition, it appears that there may be complicated interactions between the preferences for solutions used as CSs, the number of exposures to flavored cues and changes in preferences for them, and the intensity of motion which is used as an US.

V. RELATIONSHIP OF CTA TO NAUSEA AND VOMITING

A presumed relationship between gastrointestinal disturbance and the development of CTA is particularly important to the use of CTA for the study of motion sickness. The use of CTA as a putative measure of motion sickness in species which do not vomit (i.e., rats) rests on the assumption that motion-induced CTA is produced via neural and physiological states which either are the same as or are analogous to those which produce vomiting in species with a complete emetic reflex. When CTA is used as an index of subemetic levels of motion sickness[34] or "concomitant" symptoms of motion sickness,[63] it is assumed to reflect states which comprise internal sequelae progressing toward vomiting or internal states comprising the motion sickness syndrome. A relationship between CTA and visceral disturbance in the form of either nausea or vomiting has been implicit in various reports. Wilpizeski and Lowry[35] provide a formal theory of motion sickness in squirrel monkeys in which they propose that CTA reflects the development of a "nausea factor" which is independent of an "emetic factor" that underlies vomiting.

A. CTA PRODUCED BY DRUGS

However, the validity of this assumed relationship between gastrointestinal disturbance and the development of CTA induced in animals by drug treatments remains open to criticism. Ashe and Nachman[16] pointed out that the efficacy of several drugs and of irradiation as USs is not correlated strongly with the effectiveness of those treatments in producing gastric dysfunction. Dose levels of several drugs and irradiation which are too low to produce obvious signs of

sickness in animals can be very effective treatments for producing CTA, and doses of apomorphine which produce indications of extreme sickness may produce a CTA of relatively low magnitude.

Thus, it appears to be more accurate to consider gastric illness to be a sufficient, but not a necessary condition for the production of drug-induced CTA, than to assert that gastric illness is the functional stimulus serving as an US in drug-induced CTA.

Information about the relationship between nausea and CTA induced by toxins can be obtained from reports of nausea in patients studied for the development of CTA while undergoing cancer therapy. Experimental control is very difficult in clinical studies, but it appears from such studies that CTA and nausea are not inextricably interdependent. It has been reported that the likelihood of developing CTA during radiation therapy is related to the site of application of irradiation and that CTA does not always occur when nausea is reported.[3] Conversely, CTA may occur when nausea is not reported. Bernstein and Webster[79] also reported the development of CTA in patients not reporting nausea. The degree of nausea reported by their patients was unrelated to the magnitude of aversion. Thus, the predictability between nausea and CTA appears to be poor, but the reasons for this are unknown. More objective assessment of the degree of nausea in patients might improve predictability. The level of plasma vasopressin has been shown to be related to nausea in humans,[80] and might be used for more objective assessment. However, this technique would require an invasive procedure with patients. While there is evidence that plasma vasopressin is related to the emetic reflex in cats,[81] a convincing demonstration that increased levels of plasma vasopressin reflect nausea in animals remains to be provided, and this technique has not been used in investigations of CTA.

B. CTA PRODUCED BY MOTION

Investigations of motion-induced CTA in animals with a complete emetic reflex provide evidence indicating CTA and vomiting are not directly related. In studies with cats[82] and squirrel monkeys,[34,35] CTA has been reported in animals which did not vomit in response to motion. In addition, not all animals which did vomit developed CTA. Thus, if CTA was produced by visceral illness, vomiting is not a completely reliable index of that illness. That vomiting is not the sole index of motion sickness is acknowledged, of course, when rating scales based on putative prodromal symptoms are used with humans[83] or animals.[84,85]

C. RELATED RESEARCH

Research investigating the effects of antiemetic drugs on CTA in rats provides additional related information on the relationship between nausea and CTA. These studies have used the rationale that if nausea plays an important role in CTA, it might be possible to use antiemetics to prevent either the formation or expression of CTA. One approach might be to prevent CTA by the administration of an antiemetic before exposing the animal to the US and inducing nausea. This procedure is questionable because some antiemetics (i.e., scopolamine) can serve as USs to produce CTA. Thus, an antiemetic administered to counteract a presumed nauseogenic effect of an US might enhance the magnitude of CTA. The antiemetic dose of a drug typically is considerably less than the dose that serves as an US for producing CTA, but the potential for confounding is clearly present in such a procedure. Consequently, most studies have investigated whether antiemetics administered at the time of testing for CTA reduce the magnitude of that CTA. If the magnitude of CTA is attenuated in animals treated with an antiemetic prior to testing, it might be argued that the antiemetic counteracted conditioned nausea elicited by the taste cues (CS) at testing.

Studies which have investigated whether antiemetics administered prior to testing do attenuate CTA have produced inconsistent results. When CTA was induced by lithium chloride injection, the administration of scopolamine, cyclizine, prochlorperazine, or trimethobenzamide before testing was reported to attenuate the magnitude of CTA.[86] However, a later study

failed to replicate this finding.[87] In this second study, no attenuation of CTA was found when prochlorperazine or scopolamine was administered prior to testing for CTA induced by the injection of lithium, amphetamine, or morphine as USs. Replication failed even though strong as well as weak aversions were produced and a range of antiemetic doses was used. This outcome is in agreement with an earlier report of no attenuation of CTA when scopolamine was administered prior to testing for the CTA.[88]

Studies conducted to investigate the role of selected neural structures in CTA induced using motion as the US also provide some information related to the relationship between CTA and vomiting (see work by Fox et al.[89] for a more detailed discussion than is provided here). When exposed to passive motion after complete ablation of the area postrema, rats develop CTA,[59,69] and cats[42] and squirrel monkeys[64] develop CTA and vomit. Thus, the area postrema apparently does not play an essential chemoreceptive role in either CTA or vomiting induced by motion. After selective gastric vagotomy, CTA was not produced in rats when vertical axis rotation was the US.[70] Whether vagal pathways might be shared by CTA and vomiting could not be addressed directly in this experiment because rats are incapable of vomiting, but it seems unlikely that the crucial neural pathways for these two responses are isomorphic because vagotomy does not eliminate motion-induced vomiting in dogs.[90]

These studies of neural structures have not elucidated a single neural mechanism that mediates motion-induced CTA. However, it has been shown that both vagal and vestibular functions[25,26] contribute essentially to the production of CTA in rats when motion is the US. Perhaps motion-induced CTA depends on the convergence of vagal and vestibular functions, or on some unknown neural network which receives inputs from various structures (i.e., vagus nerve, vestibular system, area postrema, etc.). Also, it is known that the rate of gastric emptying is affected by vestibular stimulation,[91] that afferent activity in the vagus nerve is influenced by caloric stimulation,[92] and that tachygastria is associated with prodromal symptoms of motion sickness.[93] Whether the neural structures essential to the development of CTA induced by motion also are essential to vomiting induced by motion is unknown at this time.

VI. SUMMARY AND CONCLUSIONS

CTA was proposed as a measure of motion sickness due, in part, to the commonly accepted concept that visceral sickness is the functional US for drug-induced CTA. In early studies of CTA induced by drugs, it was shown that this presumed visceral illness is associated uniquely with gustatory cues rather than with exteroceptive cues. Several studies have shown that taste aversion is not formed to exteroceptive stimulation present at the time of exposure to motion. Thus, gustatory cues are assumed to be associated uniquely with aversive, interoceptive effects of motion rather than with any of the various exteroceptive effects associated with exposure to motion.

The use of CTA to measure motion sickness also is supported by studies showing that an intact vestibular system is essential for the production of CTA when motion is the US. This finding parallels the well known absence of motion sickness in humans and animals with defective or damaged labyrinths. In addition, the magnitude of CTA is increased by longer exposure to motion and by manipulations which increase vestibular stimulation (i.e., by off-vertical rotation). Thus, certain changes in the parameters of motion that affect the production of motion-induced vomiting also affect the presence or magnitude of motion-induced CTA.

CTA has two principle advantages over some of the other putative measures of motion sickness. The magnitude of CTA is assessed at a time removed from exposure to motion, and therefore is not affected by residual effects of motion (i.e., by disorientation, disruption of locomotion, etc.). Some of the other indices may be affected by these factors and therefore can lead to false positive indications of motion sickness. Second, because the magnitude of CTA is assessed as volume or weight of food or fluid, the degree of sickness is reflected in a continuous

measure rather than in the discrete, all-or-none fashion characteristic of vomiting. A possible third advantage might be that CTA provides a very sensitive measure of motion sickness. The use of CTA to measure subemetic levels of motion sickness is based upon this concept. However, it should be recognized that this application assumes CTA is not only more sensitive than vomiting, but also that CTA reflects prodromal symptoms progressing toward vomiting as the endpoint of motion sickness.

As with other measures, there can be complicating factors and potential disadvantages involved when CTA is used to assess motion sickness. Conditioned aversion is a *learned response*, and therefore is qualitatively different from the universally accepted index of motion sickness, the emetic *reflex*. Because CTA is a learned response, various control conditions commonly used in the study of learning mechanisms may be required in specific applications of the method. Control conditions for assessing psuedoconditioning and various other artifactual effects may require significant additional expense and work in an experiment. The importance of these control conditions is less critical if CTA is used as a discrete assessment of motion sickness (present or absent). However, if an experiment requires precise comparison of the magnitude of CTA produced by different treatments, control conditions become paramount. In addition, repeated testing of animals as conducted in within subjects designs may be contraindicated by the potential for the magnitude of CTA to be affected by both variation in the novelty of the CS and exposure to motion or drugs prior to conditioning.

There are three areas where assessments of motion sickness using CTA and other measures appear to differ. First, neither nausea nor vomiting seem to have an essential, direct relationship to motion-induced CTA. This reflects negatively on the use of CTA to assess motion sickness because both vomiting and nausea are principle indices of motion sickness. Second, the restriction of movement during exposure to motion may not reduce the magnitude of CTA produced by that motion. This is in contradistinction to the reduction in vomiting that occurs when the movement of humans and animals is restricted. This point should be considered cautiously, however, because it is based on a single, preliminary test: conclusive resolution of this issue requires more extensive experiments. Third, it appears that CTA and motion sickness might depend upon different neural structures. The meaning of recent evidence indicating that motion-induced CTA is prevented in rats by selective gastric vagotomy is unclear at this time. Previous research has led to the general conception that abdominal innervation plays no essential role in motion-induced vomiting. This apparent difference in neural mechanisms may arise from differences between the nervous systems of rats and species possessing a complete emetic reflex. Alternatively, a demonstration that motion-induced CTA is prevented by selective gastric vagotomy in species possessing a complete emetic reflex might imply that the abdominal vagal system is involved in some manner, if not essentially, in motion sickness. Although the area postrema was long thought to be essential for the production of vomiting by motion, we now know that both CTA and vomiting can be produced by motion after the area postrema has been completely ablated. Perhaps additional research will elucidate neural systems common to, and different between, motion sickness and CTA.

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