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Variables of Movement Amplitude and Frequency in the Development of Motion Sickness in *Suncus murinus*

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JAVID, F. A. AND R. J. NAYLOR. *Variables of movement amplitude and frequency in the development of motion sickness in* Suncus murinus. PHARMACOL BIOCHEM BEHAV **64**(1) 115–122, 1999.—The aim of the present study was to investigate the effect of different frequency and amplitude of horizontal movements to induce motion sickness and to identify gender differences and adaptation to motion stimulus in adult *Suncus murinus*. Each animal was subjected to a horizontal motion stimulus of 3, 7, 13, or 40 mm amplitude at a frequency of 0.5, 1, 2, or 3 Hz. The number of vomiting episodes and the latency of onset were recorded over a 10-min period. For the study of adaptation, different groups of males were exposed to repeated motion sickness (using 0.5 or 1 Hz frequency and the amplitude of 40 mm) either every 2 days for a period of 30 days, or once every week for a period of 28 days. In all animals the number of emetic episodes obtained at 1 and 2 Hz were significantly higher by 40–80% than those at 0.5 and 3 Hz using either 13 or 40 mm amplitude of movements; this was followed by shorter latency of emesis. Age-matched females were shown to be more responsive to the emetic stimuli than males as the number of emetic episodes at 1, 2, and 3 Hz (amplitude of 40 mm) were significantly higher by 33%, 42%, and 75%, respectively, than in males; this also was followed by a shorter latency of emetic response. In the study of adaptation, when used once every 2 days, by the second challenge (at 0.5 Hz) the number of emetic episodes was reduced by 62%, and to subsequent challenges emesis was absent or greatly reduced. Also, a reduction in responsiveness was observed at 1 Hz, which attained a maximum effect by the third challenge. The present results indicated that *Suncus murinus* is sensitive to horizontal motion stimulus, the emetic episodes were significantly greater at 1 and 2 Hz than at either a lower or higher frequency, a repeated challenge once every 2 days but not weekly reduced the number of emetic episodes, and in all experiments, age-matched female animals were more responsive than males to motion stimulus and in some experiments this achieved significance. © 1999 Elsevier Science Inc.

Motion sickness Frequency and amplitude of movements Adaptation *Suncus murinus*

THE malaise or nausea and emesis that is associated with motion was probably first observed in humans. While there are undoubtedly individual susceptibilities to "motion sickness," it is likely that almost everyone will succumb if the duration and intensity of stimulation exceeds a certain threshold (21). Although "motion sickness" has been regarded as synonymous as occurring with land, sea, air, and more recently space travel, this is probably misleading. For example, the incautious motion or movement of a postoperative patient in the recovery room, disturbance to patients receiving chemotherapy or radiation treatment or during pregnancy, may provide an additional noxious stimuli that may alter the emetic threshold or intensity of other emetic stimuli (23). Thus, an understanding of the mechanisms involved in motion or movement sickness may contribute directly to rational antiemetic paradigms, based on novel drug design or behavioral therapy, for the problems caused both during travel and in medical practice.

The central component of motion sickness is the vestibular apparatus that is a complex sensorimotor system concerned with the generation of compensatory eye movements (vestibulo-ocular reflexes), changes in body posture (vestibulo-spinal reflexes), the sensation of head movements/acceleration, and through cortical and thalamic projections to the perception of

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self-motion (27, 29). The "sensory conflict" theory of motion sickness suggests that sensory conflict can occur between (a) the vestibular and visual sensors of motion that cannot be related to a stable visual scene, (b) the utricular and saccular components of the otolithic system when changing stimuli on the components does not summate to 1 G (gravity, 9.8 m/s^2), and (c) the otolithic and canal components of the vestibular system when rotation of the head out of the horizontal plane is not associated with a corresponding change in the otolith-sensed direction of gravity (29).

The treatment of movement sickness relates to attempts to (a) reduce sensory conflict, for example, reduce head movements (which can both disorientate and induce nausea) and adopt a posture that requires a minimum postural regulatory activity, (b) reduce motion sickness susceptibility over a period of days or weeks by repeated exposure to motion stimuli, and (c) pharmacologically prevent the nausea and vomiting using muscarinic and histamine H_1 receptor antagonists, for example, hyoscine, dimenhydrinate, cyclizine, or cinnarizine (19,23). The antimotion sickness potential of these drugs was discovered by chance, and does not provide a complete protection in all subjects, particularly when the intensity of the stimulus increases. Further, in some subjects and patients, the intensity of nausea and vomiting provides an intractable problem. More effective treatments are clearly required, and recent advances in an understanding of the vestibulo-ocular reflex system is beginning to identity many transmitter systems and their receptors that may offer future opportunities for the rational design of novel antiemetic treatments (27,29).

In preclinical emesis research, the failure of small laboratory animals such as mice and rats to vomit has necessitated the use of much larger animals. While numerous species have been shown to be susceptible to motion sickness, including horses, cows, sheep, seals, birds and fish (21), the majority of experiments have used cats, ferrets, dogs, and primates (3,7,8, 10,11,35). The availability, purchase, use, and holding of such animals has considerable resourcing implications. Also, in motion sickness research, animals of such size require large-scale apparatus for inducing sickness. Furthermore, sophisticated equipment may be required to combine two directional movements or rotations to elicit symptoms of nausea or vomiting. Therefore, the use of small animals in motion sickness research would provide many advantages.

Suncus murinus is a species of insectivora that has the appearance of a small rodent weighing less than 100 g, but is phylogenetically closer to primates than rodents (20). Various emetogenic drugs will induce vomiting in *Suncus murinus* (20,31–33), and more restricted studies have shown it to be sensitive to motion sickness (16,34). *Suncus murinus* has been reported to be more sensitive to horizontal than vertical movements (16), and this has been confirmed in preliminary studies (Naylor, unpublished observations).

The aim of the present study is to investigate the effect of different amplitude and frequency of horizontal movement to induce motion sickness in *Suncus murinus*, the possibility of adaptation or tolerance to motion sickness on repeated challenge, and the importance of gender difference in such experiments.

METHOD

Animals and Housing Conditions

The experiments were carried out using both adult female (38.6 ± 1.0 g) and adult male (71.2 ± 1.3 g) Japanese House Musk shrew, *Suncus murinus* (Bradford University strain); the animals were age matched. Animals were housed in groups of not more than six in each cage, and were allowed food (AQUATIC 3, trout pellets) and water ad lib. Animals were also fed with cat food three times per week. The cages were floored with sawdust and cleaned twice a week; water and food were checked every day. The animal room was maintained at a humidity between 45 to 50% at 24°C and illuminated between 2100 and 0700 h on a reversed light–dark cycle.

Behavioral Testing

Each animal was placed individually in a transparent cage [100 (W) × 150 (L) × 150 (H) mm] of six linked units. After a 3-min adaptation to the caging, a horizontal motion stimulus was commenced with various amplitudes (peak-to peak displacement: 3, 7, 13, or 40 mm) and frequencies (0.5, 1, 2, or 3 Hz). In all experiments the motion stimulus was applied for 10 min. The emetic episodes were easily observed as a highly characteristic behavioral change: marked abdominal contractions, ventroflection of the head, and a wide gaping mouth with protrusion of the tongue and licking, with vomiting occurring as the passage of solid material following the burst of sustained abdominal contractions. In many cases the gastric material was stained yellow with bile. Vomiting usually occurred for the first two to four episodes until the gastric contents had emptied. In subsequent emetic episodes the above behavioral profile was apparent, but generally without the passage of solid material, i.e., an episode of retching occurred. No attempt was made to measure the number of retches, because intrathoracic pressure measurements in *Suncus murinus* have shown that retching movements can occur very rapidly within each episode but are unlikely to be accurately measured by observation alone (4). Hence, in the present study an "emetic episode" is defined as a discrete period reflecting the characteristic behavioral changes identified above. The latency of onset to the first emetic episode was also recorded. It should be noted that the animals were kept and tested in exactly the same environment to obviate confounding differences of olfactory, visual, and other cues. In addition, all the experimental procedures are in compliance with the UK Animals Scientific Procedures Act 1986.

Experimental Design

Groups of male or female animals were exposed to different amplitudes (3, 7, 13, or 40 mm) and frequencies (0.5, 1, 2, or 3 Hz) once or either every 2 days (for 22 or 30 days) or weekly (for 28 days).

The responsiveness of animals to repeated challenge to motion sickness was also examined 50, 100, and 150 days after cessation of the experiments.

The number of emetic episodes and the latency of onset (the time from the start of shaking to the first vomit) were recorded over a 10-min period. Data were expressed as the mean ± SE and analyzed using a paired–unpaired *t*-test or one-way ANOVA, which was followed by Bonferroni-Dunnett's *t*-test, as appropriate.

RESULTS

The Effect of Varying the Amplitude of Movement to Induce Motion Sickness in Adult Male Animals

In preliminary experiments, the effect of different amplitudes of shaking at a fixed frequency of 1 Hz was investigated in male animals. During a 10-min observation period, no ani-

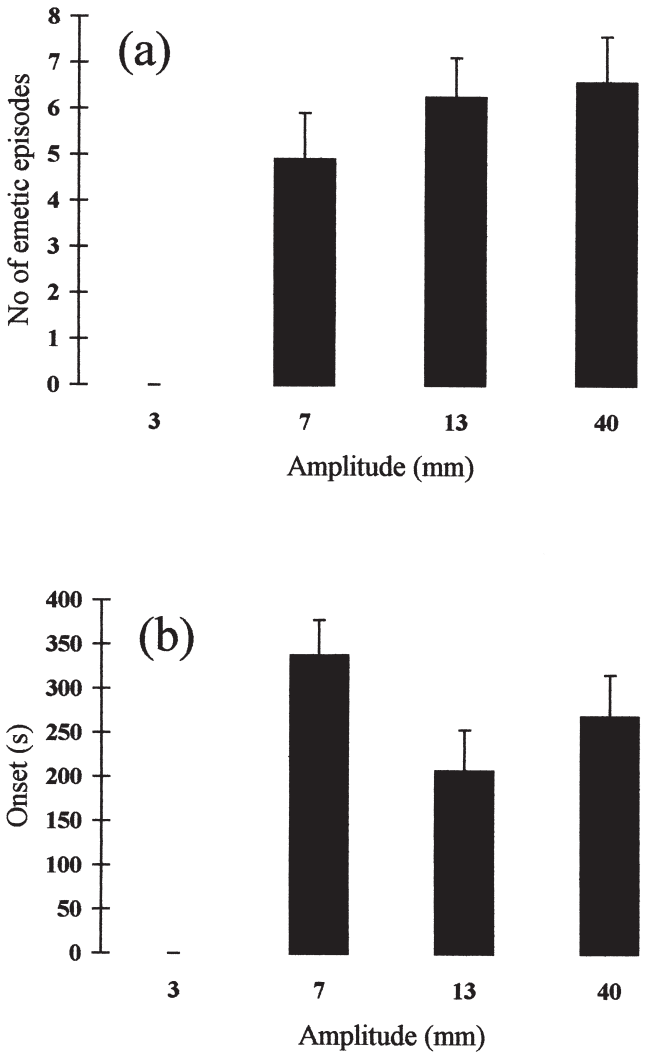

FIG. 1. The effect of different amplitudes of shaking (3, 7, 13, and 40 mm) at a fixed frequency (1 Hz) in adult males *Suncus murinus,* (a) the number of emetic episodes, and (b) the latency to first emetic episode during repeated shaking over a 10-min period. If there was an animal that did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean ± SE mean; $n = 6$.

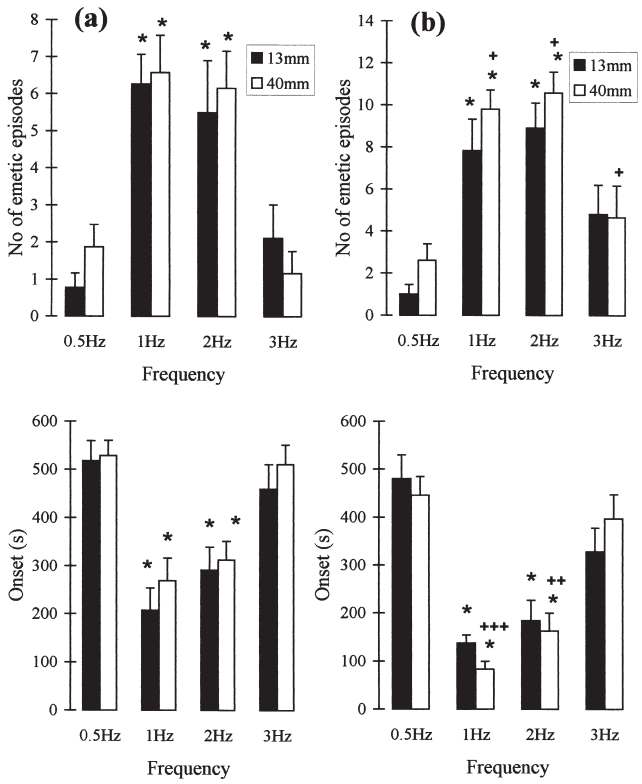

FIG. 2. A comparison of the intensity of emesis induced by an amplitude of displacement of 13 and 40 mm at frequencies of 0.5, 1, 2, and 3 Hz in (a) adult male, and (b) adult female *Suncus murinus*. The number of emetic episodes and the latency to the first emetic episode were measured during a 10-min shaking period. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean + SE mean; $n = 6$. *$p < 0.001$ compared to the data obtained at 0.5 or 3 Hz. +$p < 0.05$ and ++$p < .01$ and +++$p < 0.001$ compared to the data obtained from male animals.

mal developed emesis in response to a 3-mm amplitude of movement. All animals responded using a 7-mm amplitude, and a maximal intensity of response was obtained using a 13- and 40-mm displacement (Fig. 1). The latter amplitudes were used in subsequent studies.

The Effect of Varying the Amplitude of Movement (13 and 40 mm) and Frequency (0.5, 1, 2, and 3 Hz) to Induce Motion Sickness in Male and Female Animals

Using male animals a displacement amplitude of 13 mm and a frequency of 0.5 Hz caused a low intensity of emesis, which occurred with an onset of action just within the observation period. The number of emetic episodes increased approximately sixfold at 1 Hz, was not further increased at 2 Hz, and was reduced to twofold at 3 Hz. The increased intensity of emesis was associated with a shorter onset at 1 and 2 Hz. This profile of action was also observed using an amplitude of 40 mm, the intensity of response being indistinguishable from that obtained at 13 mm (Fig. 2a).

The above profile of motion sickness induced in male animals was also observed in females (Fig. 2b). But the number of emetic episodes at 1, 2, and 3 Hz was approximately 33–75% greater in female than in male animals, and this achieved significance ($p < .05$) using an amplitude of 40 mm.

The Effect of a Weekly Challenge to Motion Sickness over a 4-Week Period in Male and Female Animals

Both male and female animals were subjected to a weekly motion stimuli of a displacement amplitude of 40 mm, with different groups receiving a different frequency (0.5, 1, 2, or 3 Hz) of stimulation.

The profile of onset and the number of emetic episodes at the different frequencies to the first challenge was generally comparable to that observed in the earlier experiment (see Fig. 2a and b). Thus, 0.5 Hz either failed or induced a low-intensity response; the number of emetic episodes at 1 and 2 Hz achieved a maximum intensity, which was of lesser intensity at 3 Hz. This profile of response to the first challenge was generally observed to the challenge in the second, third, and fourth week (Fig. 3a and b). Thus, a weekly challenge to motion

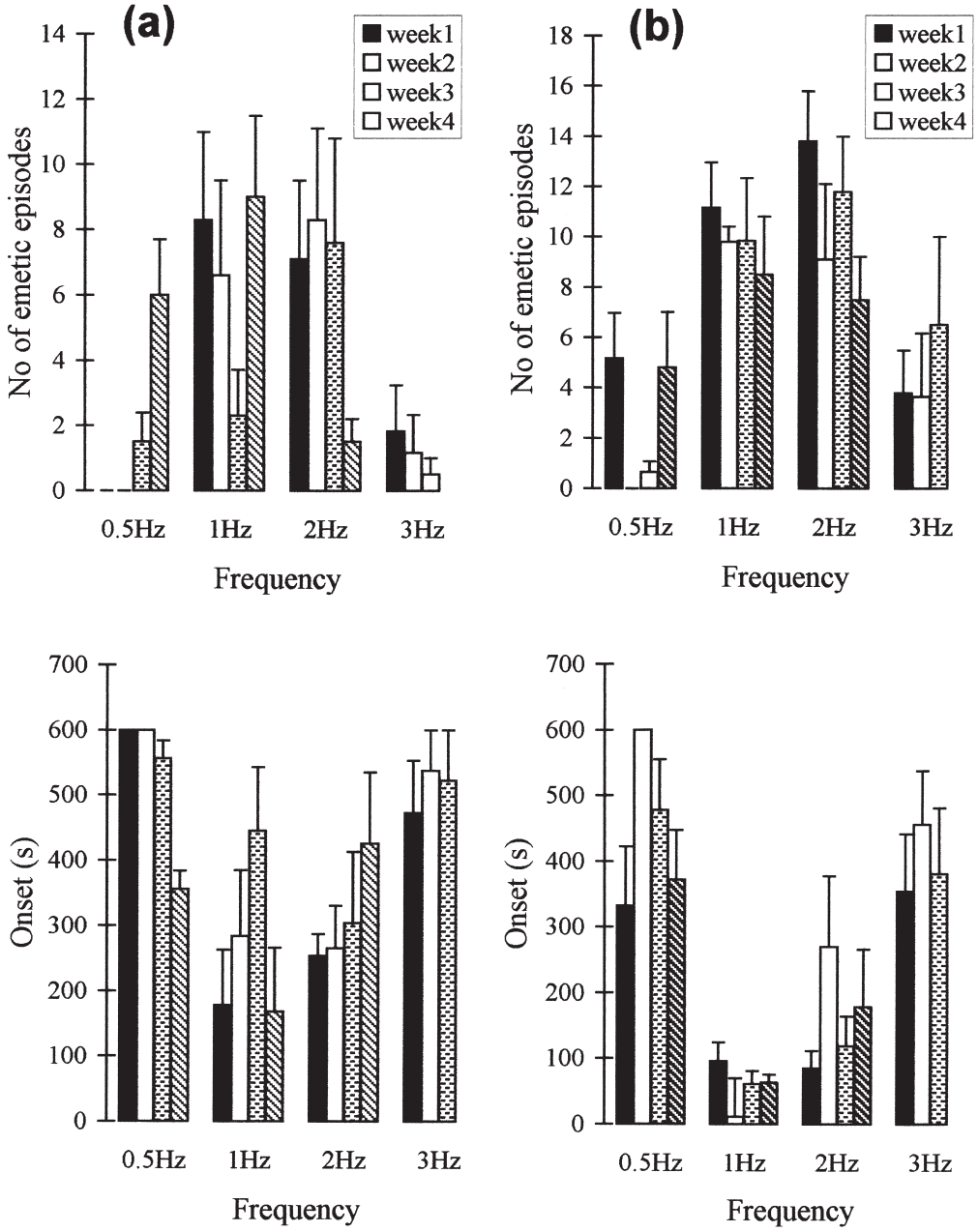

FIG. 3. The effect of a repeated weekly challenge over 4 weeks to motion stimulus in (a) adult male (b) adult female *Suncus murinus.* The number of emetic episodes and the latency to the first emetic episode were measured during a 10-min shaking period at frequency of 0.5, 1, 2, or 3 Hz with an amplitude of displacement of 40 mm. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean ± SE mean; $n = 6$.

sickness did not appear to significantly change the responsiveness of male or female animals to the emetic challenge.

The Effect of a Repeated Exposure of Male Animals to Motion Sickness Once Every 2 days for 13 (0.5 Hz, 40 mm Amplitude) or 17 (1 Hz, 40 mm Amplitude) Trials

The animals challenged with the motion stimulus of 0.5 Hz and 40 mm amplitude responded on the first occasion with 4.2 ± 2 emetic episodes and an onset of 336 ± 120 s. This was reduced to 1.6 ± 0.7 emetic episodes and an onset of 493 ± 61 s on the second trial; no emesis was observed on the third trial. Subsequently, the repeated testing of these animals every 2 days for a total of 22 days indicated an absence or marked reduction of vomiting (Fig. 4). When tested on three further occasions, trials 12, 13, and 14, i.e., at 50, 100, and 150 days, respectively, after the initial testing, emesis was absent or markedly reduced.

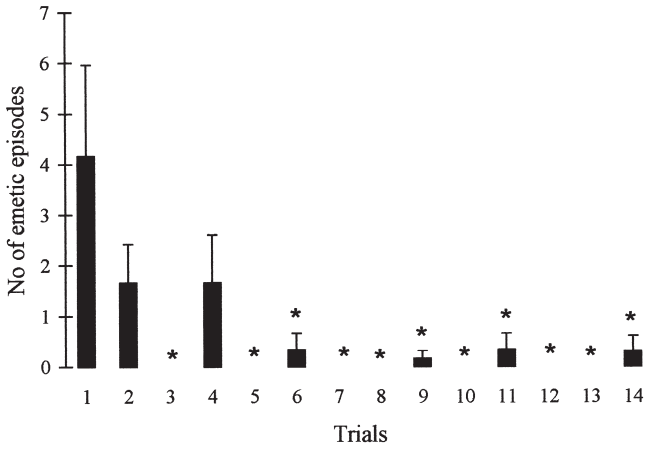

FIG. 4. Adaptation to motion sickness in adult male *Suncus murinus.* Animals experienced a fixed motion stimuli (0.5 Hz, 40 mm amplitude of shaking) once every 2 days with a total number of 11 trials; the 12th, 13th, and 14th trials were carried out 50, 100, and 150 days after the cessation of the 11th trial. The number of emetic episodes were recorded over a 10-min shaking period. Each histogram represents the mean ± SE mean; $n = 6$. $+p < 0.05$ compared to the data obtained at the first trial.

The animals challenged with the motion stimulus of 1 Hz and 40 mm amplitude responded on the first occasion with 12.3 ± 4 emetic episodes and an onset of 109 ± 28 s (Fig. 5a and b). During the second trial there was a tendency for a reduction by approximately 40%, which was reduced again but significantly in the third trial by approximately 64% to 4.5 ± 1 emetic episodes. During the first three trials the onset of vomiting increased from 109 ± 28 to 303 ± 89 s. During the subsequent testing every 2 days, until 15 trials had been completed, emetic episodes were observed in all animals but the intensity of emesis generally remained at a level no greater than 45% of the initial value. This was associated with increases in the onset of vomiting (Fig. 5b). These animals were subjected to three further trials 16, 17, and 18 at 50, 100, and 150 days, respectively, after the initial testing. On these occasions, while the reduced intensity of emetic episodes 6 ± 2, 7 ± 2, and 6 ± 2 was approximately 45–50% below the values recorded in the first trial (12.3 ± 4), and the values of the latency of onset of emesis at 176 ± 86, 204 ± 88, and 260 ± 104 s were greater than the onset in the first trial (109 ± 28 s), such differences were not statistically significant.

DISCUSSION

This study has confirmed that an emetic response can be reliably induced in *Suncus murinus* in response to a horizontal motion stimulus (33). The emetic episodes were easily observed as a characteristic behavioral change of marked abdominal contractions, ventroflection of the head, and a wide gaping mouth with protrusion of the tongue, licking, and vomiting. Although salivation is also a frequent concomitant to emesis in dogs, cats, and primates (15,21,30), salivation was not a pronounced feature in *Suncus murinus* in response to motion stimulus.

Using an amplitude of 40 mm, a value frequently used in other studies (4,16,22,33), the number of emetic episodes appeared to be dependent on the frequency of stimulation. Increasing the frequency of stimulation from 0.5 Hz to 1 Hz significantly increased the number of emetic episodes with an earlier onset of response. Increasing the stimulation to 2 Hz caused no further increase of significance, while increasing the frequency to 3 Hz was actually associated with a reduced incidence of emesis. In a previous comparison of various motion stimuli to induce sickness in *Suncus murinus*, the frequency range was restricted to 2 Hz (16). The present study indicates a narrow range of 1 to 2 Hz that is required to induce a maximal emetic response in *Suncus murinus*, and the lesser effect of 3 Hz stimulation is discussed below in terms of neuroinhibition (37).

The amplitude of horizontal motion was also important, but not as critical as the frequency. Thus, emesis was absent from all animals challenged with a 3-mm reciprocal oscillation but present in all animals using 7-mm amplitude. The number of emetic episodes increased slightly but not significantly upon increasing the amplitude first to 13-mm and then to 40 mm. Therefore, the latter amplitudes were chosen for all subsequent studies investigating the effects of a repeated exposure to motion stimulus in *Suncus murinus.*

A repeated exposure every 2 days to motion sickness caused a rapid decline in the emetic response; this was observed for both the robust stimuli of 1 Hz and the mild shaking at 0.5 Hz. Thus, using either challenge, the response was reduced as early as the second trial by some 40–60%, and whiIe this did not achieve significance, by the third challenge the emetic response was absent in the 0.5 Hz-treated group and significantly reduced by 64% using the 1 Hz treatment. Subsequent testing for a period as long as 150 days after discontinuing a repeated 2-day challenge for 22 days, revealed the abolition or reduction of response at 0.5 Hz to be long lasting. Similar comments would apply to the reduction in response at 1 Hz, although after 50, 100, or 150 days the reduction that had been maintained at some 49–55% just failed to achieve significance ($p \geqslant 0.07$).

The rapid development of tolerance to motion stimuli in *Suncus murinus* during the second and third trial occurred more rapidly than reported by Kaji et al. (16), who used a repeated daily challenge of "severe shaking" (40-mm amplitude, 2 Hz, duration 15 min) for 14 days; five trials were required to demonstrate a reduction in the emetic response with a longer latency of onset. The pattern of temporal challenge may be an important factor in the development of tolerance (see below). However, both the present and the previous study show that *Suncus murinus* may be a useful species to determine the neuronal mechanisms influencing the adaptive response to the emetic challenge. The studies also indicate that caution must be used in the repeated use of *Suncus murinus* in motion sickness experiments using short treatment intervals.

The interval of treatment is an important variable in the development of an adaptative response because the repeated use of *Suncus murinus* at weekly intervals for 4 weeks using stimuli of 0.5, 1, 2, or 3 Hz induced a number of emetic episodes with an onset of response that could not be reliably distinguished at any time of testing. The present paradigms of a weekly treatment would allow the use of *Suncus murinus* on more than one occasion, a useful feature for its laboratory use.

The adaptive response of *Suncus murinus* to motion stimulus remains of considerable interest in an understanding of the mechanisms controlling emesis. This is an important subject because adaptation has been used as a successful therapeutic procedure in humans in the treatment of air, sea, and space sickness, particularly for military personnel (28). It is known that incremental exposure in humans provides a faster rate of adaptation or desensitization, and a grading of the in-

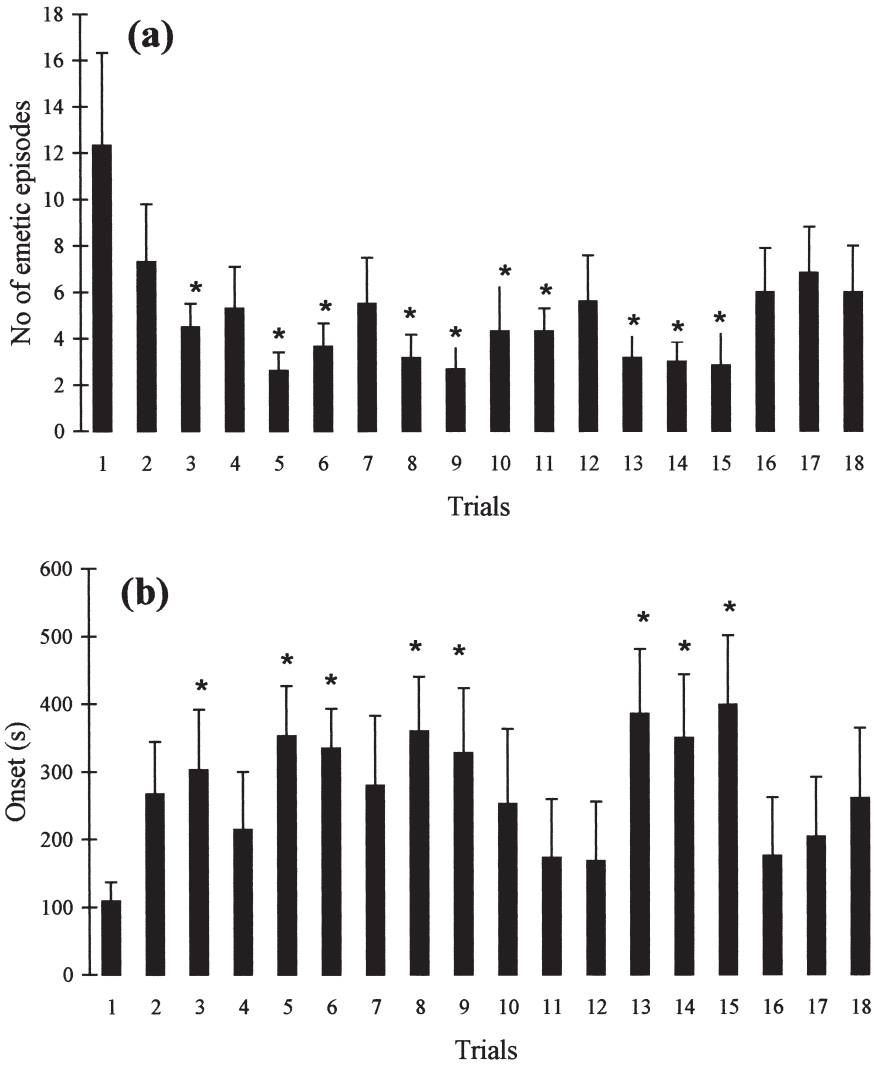

FIG. 5. Adaptation to motion sickness in adult male *Suncus murinus*. Animals experienced a fixed motion stimuli (1 Hz, 40 mm amplitude of shaking) once every 2 days, with a total number of 15 trials; the 16th, 17th, and 18th trials were carried out 50, 100, and 150 days after the cessation of the 15th trial, (a) the number of emetic episodes, and (b) the latency to the first emetic episode over a 10-min shaking period. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each bar represents the mean ± SE mean; $n = 6$. $^*p < 0.05$ compared to data obtained at the first trial.

tensity of the stimuli can also vary the desired malaise end point (12–14). The data obtained in both *Suncus murinus* and humans indicates a profound change in the sensitivity of the emetic reflex in response to repeated challenge. However, it is not known how this is achieved, although it can be hypothesized to involve a change in endogenous neurochemical transmitter or modulatory function, and/or a change in the function of the pathways mediating nausea and vomiting.

Andrews and colleagues (2) have reported that there may be some reorganization or plasticity of the emetic response following abdominal vagotomy in the ferret. While such a drastic change may not be immediately relevant to the present findings, the authors also reported that naloxone can enhance radiation- and drug-induced emesis to support previous observations in the dog (19). Naloxone can also antagonize the antiemetic effects of morphine and precipitate an emetic response to loperamide in *Suncus murinus* (26). Naloxone can also enhance emesis in patients receiving chemotherapy (17). In addition, naloxone has also been shown to enhance the susceptibility to motion sickness in the cat (9), and to enhance the malaise of motion sickness in humans, a response that persisted for 3 days (1).

All these observations implicate endogenous opiates with an endogenous protective or adaptive role in the control of drug induced and motion sickness in animals and humans. In future experiments using opioid agonist and antagonist drugs, *Suncus murinus* may play a useful role in facilitating an understanding of the relevance of opioid systems in adaptation to motion sickness.

Adaptation to motion stimuli may also involve other possibilities, including vagal afferent feedback inhibition. The inhibitory effects of vagus stimulation on reflex actions and be-

havior appear to have been first reported by Schweitzer and Wright (25). Stimulation of the dorsal or ventral branches of the vagus nerve at the supradiaphragmatic level normally causes emesis by triggering the emetic reflex. However, cervical stimulation probably involving respiratory vagal afferents will prevent emesis caused by stimulation of abdominal afferents in the dog, central chemoreceptor stimulation in the cat, and, of particular interest to the present study, motion sickness in squirrel monkeys (36). Further, repeated stimulation of vagal afferents appear to be cumulative in their inhibitory effectiveness. The neurotransmitters mediating these changes are not known. But again, pharmacological studies in *Suncus murinus* may play a useful role in elucidating the transmitter systems.

Other factors involving stress and hormonal influences are known to influence the response to emetic stimuli (18,24). Female sex steroids may alter the threshold of the emetic reflex (5,6), and in the present experiments in a comparison of the response of male and female *Suncus murinus* there was a consistent trend for a greater intensity of emesis and reduced onset of response in all groups of female animals compared to the males; in some of the experiments the differences achieved statistical significance. The influence of stress and hormonal influences on the adaptation to motion stimuli remains to be investigated.

In conclusion, our results confirm that male and female *Suncus murinus* provide a reliable model to demonstrate motion sickness, that emesis in female animals is more intense than in males, that adaptation to motion sickness can occur and is dependent on the frequency of challenge, and that *Suncus murinus* may provide a useful model to investigate the neuronal mechanisms mediating motion sickness and the processes of adaptation.

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