Pharmacology, Biochemistry and Behavior 99 (2011) 381–384

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

# Guamanian *Suncus murinus* responsiveness to emetic stimuli and the antiemetic effects of 8-OH-DPAT

Rachel E.L. Brame, James B. Lucot *

*Department of Pharmacology and Toxicology, Wright State University, 3640 Colonel Glenn Highway, Dayton, OH 45435 USA*

ARTICLE INFO

*Article history:*
Received 24 February 2011
Received in revised form 11 May 2011
Accepted 14 May 2011
Available online 23 May 2011

*Keywords:*
*Suncus murinus*
Emesis
8-OH-DPAT
Nicotine
Motion

ABSTRACT

The Japanese *Suncus murinus*, the house musk shrew, is a small insectivore commonly used in emetic research. The Guamanian *S. murinus* has not had extensive testing as an emetic model, but it is readily available for use in emetic experiments in the United States, unlike the Japanese *Suncus*. This study determined that Guamanian *S. murinus* is an acceptable model for emesis research and its differences from the Japanese strain were examined. Motion and nicotine were used as emetic stimuli and comparable doses of 8-OH-DPAT were used to compare emetic susceptibility to the Japanese strain. The Guamanian strain had decreased susceptibility to motion and increased susceptibility to nicotine as compared to the Japanese, as well as increased sensitivity to 8-OH-DPAT, with lower doses of the recovery drug eliminating retching episodes. The study also determined that Guamanian *S. murinus* are smaller and more aggressive than the Japanese strain, but just as effective as a model for emetic research.

© 2011 Elsevier Inc. All rights reserved.

## 1. Introduction

The house musk shrew, *Suncus murinus*, is an animal commonly used in laboratory studies of emesis and anti-emetics drugs. It is a member of the order Insectivora, and is closer phylogenetically to humans than the more typical laboratory animals, such as mice and rats (Okada et al., 1994; Ueno et al., 1987).

Due to USDA restrictions on importing new species, researchers in the United States have found importing Japanese *S. murinus* for emesis research to be prohibitively difficult. Instead, American researchers must use a different strain of the same species, Guamanian *S. murinus*, for laboratory use. The *S. murinus* available in the United States come from Dr. Emilie Rissman's colony of Guamanian shrews at the University of Virginia (Temple, 2004). The original colony of Guamanian shrews were brought over from Guam in the 1960s by Dr. Gil Dryden, then given to Dr. Rissman in the 1980s (Temple, 2004).

Until now, no one had compared the Guamanian *Suncus* to the Japanese *Suncus* to evaluate its emetic susceptibility and response to anti-emetics. The purposes of this study were to determine if the Guamanian *S. murinus* strain is a useful model in emetic research and to quantify any differences between the strains.

There are five pathways (oculo-vestibular, area postrema, vagal afferents, gut pathologies, and cerebral cortex stimuli) through which nausea and vomiting can occur, although only the first three pathways are typically tested in a laboratory setting (Horn, 2007; Sanger and Andrews, 2006). In this study, the sensitivity of the oculo-vestibular (motion sickness) and area postrema (nicotine) pathways were measured and the ability of a 5-$HT_{1A}$ agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide, (8-OH-DPAT) to block the response was compared with studies using the Japanese *Suncus* (Javid and Naylor, 1999; Kaji et al., 1990; Matsuki et al., 1997; Okada et al., 1994; Ueno et al., 1988). 8-OH-DPAT has been used to successfully prevent vomiting in the cat induced by motion, xylazine, and cisplatin, vomiting in the ferret induced by apomorphine, morphine, copper sulfate, and cisplatin, vomiting in the pigeon induced by ditolyguanidine, and vomiting in the Japanese *S. murinus* induced by motion, nicotine, and cisplatin (Lucot and Crampton, 1989; Rudd et al., 1992; Okada et al. 1994; Wolff and Leander, 2010).

Motion sickness is thought to occur through the combination of visual, proprioceptive, and vestibular sensors providing a different pattern than usual situations that generates a mismatch signal to update the neural store (Javid and Naylor, 1999). Mismatch signals are necessary to adjust muscles and maintain normal balance and movement, but if the signal is prolonged, it will reach sufficient magnitude to trigger an emetic reflex, which, according to the poison hypothesis, may have evolved as a response to ingestion of neurotoxins and attempts to recalibrate the sensors through emesis (Money and Cheung, 1983; Oman, 1998).

The optimized method of inducing motion sickness varies from species to species. For example, squirrel monkeys respond best to rotation and dogs and cats to swinging, but *S. murinus* responds best to linear, side-to-side, horizontal motion at a frequency of 1.0 Hz and linear displacement of 40 mm (Javid and Naylor, 1999; Kaji et al.,1990; Matsuki et al., 1997; Ueno et al. 1988).

* Corresponding author. Tel.: +1 937 775 4595; fax: +1 937 775 7221.
*E-mail address:* james.lucot@wright.edu (J.B. Lucot).

0091-3057/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2011.05.012

Area postrema-induced emesis occurs through the direct action of an absorbed toxic substance or intracellular constituent on the area postrema, where the blood-brain barrier is relatively easy to pass through (Sanger and Andrews, 2006). Nicotine and xylazine are two chemicals commonly used to activate this pathway depending on the species.

## 2. Materials and methods

Male and female *S. murinus* were housed in separate rooms that were both kept at 24 °C, on a 0500–1900 h light cycle. Adult shrews, weighing 20–50 g, were given water and food (3 parts Purina Cat chow: 1 part Specialty Mink Complete Pellets) ad libitum. Shrews were housed in standard cages with shaved pine bedding and a cardboard tube. All activities were approved through the Wright State University IACUC and were in accordance with the EC Directive 89/609/EEC for animal experiments. All tests were given at one week intervals to prevent conditioned emesis and post tests with either motion alone or nicotine alone were given to confirm the lack of habituation to emetic stimuli. The presence of either was evaluated by suitable testing after determination of the 8-OH-DPAT (Sigma Aldrich®, St. Louis, MO) dose response curve. All shrews in the motion group retched/vomited in at least two out of three pre-motion trials. Males responded well to the motion stimulus and they were assigned to motion. Female shrews responded poorly to the motion stimulus and they were assigned to the nicotine stimulus.

Motion induced vomiting (oculo-vestibular pathway) was elicited by placing each male shrew in a separate, closed, clear 13 cm × 5 cm × 15 cm container inside a shaker machine calibrated to linear, reciprocating horizontal, side-to-side motion of 33 mm at 1 Hz for 10 min. 8-OH-DPAT was dissolved in sterile saline and injected subcutaneously (sc) 15 min prior to motion in a volume of 0.5 ml/100 g body weight. Shrews were given 5 min in the test chamber at rest to adjust to the container before motion commenced. The latency to each retch/vomit was verified by video recording.

Drug induced vomiting (area postrema pathway) was induced in female shrews by dissolving nicotine hydrogen tartrate (Sigma Aldrich®, St. Louis, MO), 10 mg/kg, in sterile saline. The nicotine was injected sc in a volume of 0.5 ml/100 g body weight. Each shrew was placed in a separate, closed, clear 30 cm × 18 cm × 15 cm container with clean bedding and observed for 30 min. 8-OH-DPAT was dissolved in sterile saline and injected sc 15 min prior to nicotine injection. The latency to each retch/vomit was recorded and verified by video recording.

All experiments and handling of female Guamanian *Suncus murinus* were conducted wearing latex or nitrile gloves, covered with leather gardening gloves to prevent bites to the hands. Male Guamanian *Suncus murinus* were able to puncture the skin through nitrile gloves and leather gardening gloves with their teeth, so HexArmor SharpsMaster 7080 gloves were worn over nitrile gloves for protection.

The results of this study used standard deviation and standard error from the mean (S.E.M.) to determine variability between values.

## 3. Results

For the purpose of the study, it was necessary to characterize what consisted of a retching episode to quantify experimental results. A retching episode was defined as the distinct period of behavior wherein the shrews exhibited: dramatic and rapid abdominal contractions, ventroflexion of the head, dorsiflexion of the hindquarters, splayed feet, and an open mouth with a protruded tongue, without the expulsion of vomit (Andrews et al., 1996; Javid and Naylor, 1999; Javid and Naylor, 2006). On the occasion that vomit was produced, it was usually colored yellow from bile, as was noted in other studies (Andrews et al., 1996; Javid and Naylor, 1999).

During the experiments, clear behavioral changes due to the emetic stimuli were noted. After the commencement of the stimulus, there was a brief period where normal behavior continued. Then, motor activity would decline and the shrews typically stayed in the same place in the container, as though resting. This lack of motor activity either continued up to the first retching episode, or the shrews would briefly and rapidly move about the container until their first retching episode. After the first retch, the shrews tended to repeat the cycle of brief and rapid movements and subsequent retching episodes. After a series of retches, the shrews gradually resumed normal levels of motor activity. In the case of a nicotine experiment, the shrews exhibited strong tremors prior to retching episodes and the retching episodes tended to occur at a frequency of every 10–12 s, as also seen by Ueno et al. (1987) and Andrews et al. (1996). Periodically, the nicotine + 8-OH-DPAT (but not the 8-OH-DPAT alone) treated shrews would exhibit the flattened body posture associated with the serotonin syndrome that was documented by Okada et al. (1994).

Guamanian shrews were less susceptible than Japanese shrews to motion sickness. Motion elicited fewer average retches in Guamanian shrews than in Japanese shrews. The $ED_{50}$ of the Guamanian shrews was comparable to the $ED_{50}$ of the Japanese shrews, and the 100% effective dose for Guamanian shrews was 25% of the effective dose of Japanese shrews (Table 1). The Japanese shrews had an increase in retching episodes per responding shrew and then a decrease as the drug dose increased, whereas the Guamanian shrews steadily decreased in number of retching episodes as the drug dose increased. The latency to first retch was greater in Guamanian shrews. For both 0.113 mg/kg and 0.226 mg/kg of 8-OH-DPAT, the Guamanian shrews had latencies that were roughly 4 and 3.6 times the length of the latencies of their Japanese counterparts, respectively (Table 1). It is important to note that the Guamanian experiments used a consistently larger number (4 or 5 shrews) than used in the Japanese experiments (1 to 5 shrews).

Nicotine alone produced fewer retches per shrew and a longer latency to the first retch in Guamanian shrews compared with Japanese shrews (Table 2). 8-OH-DPAT was slightly more effective in inhibiting the response in Guamanian shrews than in the Japanese shrews. The $ED_{50}$ of the Guamanian shrews was 30.6% lower than the $ED_{50}$ of the Japanese shrews, and the 100% effective dose for Guamanian shrews was 50% lower than the effective dose of Japanese shrews. The latency to first retch was greater in Guamanian shrews. For both 0.025 mg/kg and 0.05 mg/kg, the Guamanian shrews had of the latencies that were roughly 1.3 and 1.9 times the length of their

**Table 1**
Motion vs. 8-OH-DPAT results in Japanese and Guamanian *Suncus murinus*.

| Shrew strain | 8-OH-DPAT dose (mg/kg) | % vomit | Retch episodes | Average latency to 1st retch episode (min) | ED 50 (mg/kg) | n |
|---|---|---|---|---|---|---|
| Japanese | motion only | 90 | n/a | n/a | – | n/a |
| Japanese | 0.113 | 100 | 4 | 2.3 | – | 1 |
| Japanese | 0.226 | 100 | 5 ± 1.7 | 2.6 ± 0.6 | – | 4 |
| Japanese | 0.452 | 20 | 1 | 4.5 | – | 5 |
| Japanese | 0.904 | 0 | 0 | 5 | – | 1 |
| Japanese | – | – | – | – | 0.0367 | – |
| Guamanian | motion only | 25 | 1.25 | 0.59 | – | 4 |
| Guamanian | 0.113 | 20 | 0.2 | 1.89 | – | 5 |
| Guamanian | 0.226 | 0 | 0 | 10 | – | 5 |
| Guamanian | motion only | 75 | 2.5 ± 1.19 | 4.20 ± 0.99 | – | 4 |
| Guamanian | negative control | 0 | 0 | 10 | – | 4 |
| Guamanian | – | – | – | – | 0.0398 | – |

Comparison of Guamanian and Japanese *Suncus Murinus* dose response curves for inhibition of motion sickness by 8-OH-DPAT. Japanese shrew results from Okada et al. (1994). Number of retching episodes and latency per retching shrew are given as mean ± S.E.M. If there were no retches for Guamanian shrews, the latency to first retching episode was given as 10 minutes. If there were no retches for Japanese shrews, the latency to first retching episode was given as 5 minutes.

**Table 2**
Nicotine vs. 8-OH-DPAT results in Japanese and Guamanian *Suncus murinus.*

| Shrew strain | 8-OH-DPAT dose (mg/kg) | % vomit | Retch episodes | Average latency to 1st retch episode (min) | ED 50 (mg/kg) | n |
|---|---|---|---|---|---|---|
| Japanese | nicotine + saline | 100 | 20, 18 | 2, 8 | – | 2 |
| Japanese | 0.025 | 100 | 5.3 ± 1.9 | 2.7 ± 0.3 | – | 3 |
| Japanese | 0.05 | 40 | 2, 1 | 16, 8 | – | 5 |
| Japanese | 0.1 | 0 | 0 | 30 | – | 2 |
| Japanese | 0.2 | 0 | 1 ± 0 | 30 | – | 1 |
| Japanese | – | – | – | – | 0.0467 | – |
| Guamanian | nicotine + saline | 62.5 | 9.25 ± 2.9 | 2.57 ± 0.04 | – | 8 |
| Guamanian | 0.025 | 87.5 | 5.75 ± 1.39 | 3.57 ± 0.67 | – | 8 |
| Guamanian | 0.03125 | 62.5 | 2.75 ± 1.11 | 4.32 ± 1.43 | – | 8 |
| Guamanian | 0.0375 | 12.5 | 0.25 | 0.52 | – | 8 |
| Guamanian | 0.05 | 0 | 0 | 30 | – | 8 |
| Guamanian | nicotine only | 87.5 | 11.75 ± 2.34 | 4.76 ± 1.35 | – | 8 |
| Guamanian | – | – | – | – | 0.0324 | – |

Comparison of Guamanian and Japanese *Suncus Murinus* dose response curves for inhibition of nicotine-induced emesis by 8-OH-DPAT. Number of retching episodes and latency per retching shrew are given as mean ± S.E.M., but actual values are given when number of shrews with retching episodes < 3. Japanese shrew results from Okada et al. (1994). If there were no retching episodes (for both strains of shrew), the latency to first retching episode was given as 30 min.

Japanese counterparts, respectively (Table 2). Both the Japanese and Guamanian shrews had reductions in the number of retching episodes as the dose of 8-OH-DPAT increased. It is important to note that the Guamanian experiments always used a larger number (8 shrews) than used in the Japanese experiments (1 to 5 shrews).

## 4. Discussion

Tests of motion sickness across species provide a variable baseline because while all subjects in a group may retch or vomit, they will not do so on every control test. One possible reason for this variability, especially in *Suncus*, is that increased stress can impede the emetic response through unknown pathways (Javid and Naylor, 1999). Guamanian *Suncus* are highly aggressive and it is sometimes very difficult to handle the shrews while they are trying to fight, bite, and escape through all stages of an experiment (unpublished data). If the researchers determined that a shrew was too stressed by this process, the shrew was pulled from the experiment and the results nullified.

Guamanian females were found in this study to be unreliable in producing a retching or vomiting response, and were not used for motion sickness. However, studies conducted by Javid and Naylor (1999) as well as Matsuki et al. (1997) conflict on whether female or male Japanese *Suncus* have higher incidence of retching episodes and latency to onset of retching. It is unclear at this time whether such discrepancies exist in Guamanian females because research has not been published with them previously.

The outcomes of the motion tests with the Guamanian shrews varied significantly from the Japanese results. Guamanian *Suncus*, when exposed to provocative motion, have fewer average retching episodes. While they have an$ED_{50}$ for 8-OH-DPAT comparable to the Japanese, they do have a smaller 100% effective dose than Japanese suncus which is less than 25% of the Japanese dose (Table 2). 8-OH-DPAT significantly increases the delays to the onset of retching in male Guamanian shrews not only compared to their motion control results, but also to the latencies due to 8-OH-DPAT of male Japanese shrews (Table 2). The amount of retching episodes in Japanese shrews at first increased, and then sharply decreased as the dose of 8-OH-DPAT increased (Table 2). This is contrary to the number of retching episodes of the Guamanian shrews that steadily declined with increasing doses of 8-OH-DPAT.

It is possible that Guamanian shrews absorbed 8-OH-DPAT more rapidly, causing higher peak concentrations at the 5-HT1A receptors. However, it is more likely that Guamanian shrews are less susceptible to provocative motion and therefore require lower concentrations of 8-OH-DPAT to fully halt retching than Japanese shrews that have a higher susceptibility to motion suggestive of a stronger emetic signal. The Japanese shrews had a dose response curve between 0.113 mg/kg and 0.904 mg/kg of 8-OH-DPAT (Okada et al., 1994). The Guamanian shrews had a steeper dose response curve between 0.113 mg/kg and 0.226 mg/kg of 8-OH-DPAT. Similar results with a steep drug response curve of 8-OH-DPAT were seen in the cat, as found by Lucot and Crampton (1989). When 8-OH-DPAT was tested against motion optimized for vomiting in the cat, it was found to have a dose response curve between 0.01 mg/kg and 0.04 mg/kg of 8-OH-DPAT (Lucot and Crampton, 1989).

Nicotine alone elicited more average retching episodes from Japanese shrews than it did Guamanian shrews, but once 8-OH-DPAT was introduced into the experiment, Guamanian shrews had the greater number of retching episodes per each low dose (Table 2). There was not as large of a difference between the $ED_{50}$ of Guamanian and Japanese shrews as there was with motion, but the Guamanians still had the lower $ED_{50}$, and the dose of 8-OH-DPAT that completely alleviated retching episodes was ½ of the dose that the Japanese shrews required (Table 2). At low doses of 8-OH-DPAT, the Guamanian shrews had larger latencies to their first retching episode than the Japanese shrews, although with nicotine alone, the Japanese had a larger average latency to first retching episode (Okada et al., 1994). However, the values for the nicotine alone with the Japanese shrews had high variability and there were only 2 shrews in that experiment, making an accurate estimate of the baseline latency to first average retch difficult to determine (Okada et al., 1994).

With the increasing 8-OH-DPAT doses, both Guamanian and Japanese decreased their average number of retching episodes, although their drug response curves varied widely. The Guamanian shrews had a sharp dose response curve between 0.025 mg/kg and 0.05 mg/kg of 8-OH-DPAT. The Japanese shrews had a more gradual dose response curve, which was between 0.025 mg/kg and 0.1 mg/kg of 8-OH-DPAT (Okada et al., 1994).

In 1989, Lucot and Crampton found analogous results with a drug response curve of 8-OH-DPAT in the cat. Nicotine acts upon the chemical trigger zone within the area postrema, the same location where xylazine activates in the brain stem. When 8-OH-DPAT was tested against xylazine in the cat, it was found to have a much shallower dose response curve, between 0.01 mg/kg and 0.64 mg/kg (Lucot and Crampton, 1989).

The purpose of this study was to do a side by side comparison of Guamanian *Suncus* and Japanese *Suncus* with a few emetic stimuli and one anti-emetic to make the comparisons clear and simple to comprehend. Two of the main three emetic pathways were tested: the oculo-vestibular system and the area postrema. The use of cisplatin to test the vagal afferents is a lethal and time consuming experiment. We are currently determining their baseline response and the ability of 8-OH-DPAT to reverse it as the shrews come near the end of their useful breeding potential. Other emetic stimuli could be tested, but most use the same transduction pathways as those tested in our laboratory. The emetic responses can be extrapolated to other stimuli within the same pathway because they will give similar emetic reactions. We propose that the stimuli used establish the utility of the Guamanian strain as a useful laboratory tool.

Besides the differences in emetic response to stimuli and anti-emetic drugs, the Guamanian shrews were found to differ profoundly from the Japanese shrews in several parameters. One of the most distinct differences is the size of the shrews. Journal articles written about Japanese shrews list the shrews as being between 30 and 90 g in mass, with the average female weighing 30–50 g and the average male weighing 50–90 g (Andrews et al., 1996; Javid and Naylor, 1999; Kaji et al., 1990; Matsuki et al., 1997; Okada et al., 1994; Ueno et al., 1987; Ueno et al., 1988). The Guamanian shrews only weigh 20–50 g, with the average female shrew weighing 20–30 g and the average male shrew weighing 30–40 g, similar to what was described in 2009 by De Jonghe and Horn (2009). There was one male individual that weighed approximately 47 g, but he was the only shrew of his size and weight.

Another obvious difference is the behavior of the shrews. Japanese shrews have been described by Ueno et al. (1987) and Ueno et al. (1988) as being easy to handle and care for, where as Guamanian shrews are intensely aggressive in their behavior, with repeated biting and vocalizing being common responses to putting a gloved hand in the cage of the shrew (unpublished data). In fact, Guamanian shrews cannot be housed in groups because they display same-sex hostility (Temple, 2004). Throughout the study, researchers noted that the shrews would sometimes become more aggressive after the injection of 8-OH-DPAT, just before the emetic stimulus was given. This could have been due to the stress of injections and handling or being in a different container, but another reasonable cause could have been the 8-OH-DPAT itself. In a study of cats given 8-OH-DPAT to prevent motion sickness, the cats exhibited strong defensive behaviors and anxiety in response to the drug, which is one of the reasons why it is not used in humans (Lucot, 1994). It would be highly advantageous if an anti-emetic drug similar to 8-OH-DPAT could be developed that was similar in its efficacy but devoid of anxiety and aggression as a side effects because it would have the potential for use in both animals and humans.

It is possible that Guamanian shrews may be trained to be less aggressive through repeated exposure. Unpublished data from the author observed that if shrews were handled from a young age regularly, they tended to be "friendly", meaning that they did not bite or vocalize when handled, and they could be handled with nitrile gloves alone. The nursing mother was also not aggressive towards the frequent handler, which is remarkable considering that many mammalian mothers will vigorously defend their young from any perceived threat. There were only three pups in the litter being handled without gloves, and as they grew older they were not as willing to be handled as when they were young, but they were still easier to handle than other shrews in their age group. The handling of mice and other laboratory animals to acclimate them to handling and injections is a common practice, so the handling of all infant shrews may be the best solution for dealing with their hostile behavior.

## 5. Conclusion

There are several distinct differences between Guamanian and Japanese *S. murinus*, which up until now have not been documented. These differences include that Guamanian shrews have decreased susceptibility to motion and an increased susceptibility to nicotine, and require smaller doses of 8-OH-DPAT than the Japanese shrews to eliminate retching episodes. The $ED_{50}$ of Guamanian shrews is comparable to the $ED_{50}$ of Japanese shrews for 8-OH-DPAT against both motion and smaller than the Japanese $ED_{50}$ for nicotine induced emesis. The doses of 100% effectiveness for both motion and nicotine are dramatically different, with the Guamanians using a lower dose in both tests. Guamanian shrews are much smaller and more aggressive than Japanese shrews, and while they are both suitable for emesis research, the possibility of identifying more differences between the strains is an area that needs more in-depth study.

## Acknowledgements

The authors would like to thank Teresa Garrett, Abigail Schwartz, Amber Braddock and Dr. Emily Dudley DVM for their excellent assistance.

## References

Andrews PR, Torii Y, Saito H, Matsuki N. The Pharmacology of the emetic response to upper gastrointestinal tract stimulation in *Suncus Murinus*. Eur J Pharmacol 1996;307:305–13.

De Jonghe BC, Horn CC. Chemotherapy agent cisplatin induces 48-h Fos expression in the brain of a vomiting species, the house musk shrew (*Suncus Murinus*). Am L Physiol Regul Integr Comp Physiol 2009;296:R902–11.

Horn CC. Is there a need to identify new anti-emetic drugs? Drug Discov Today Ther Strateg 2007;4:183–7.

Javid FA, Naylor R. Variables of movement amplitude and frequency in the development of motion sickness in *Suncus Murinus*. Pharmacol Biochem Behav 1999;64:115–22.

Javid FA, Naylor R. The effect of the 5-HT1A receptor agonist, 8-OH-DPAT, on motion-induced emesis in *Suncus Murinus*. Pharmacol Biochem Behav 2006;85:820–6.

Kaji T, Saito H, Ueno S, Matsuki N. Comparison of various motion stimuli onmotion sickness and acquisition of adaptation in Suncus murinus. Exp Anim 1990;39:75–9.

Lucot JB, Crampton GH. 8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin, or xylazine. Pharmacol Biochem Behav 1989;33:627–31.

Lucot JB. Antiemetic effects of flesinoxan in cats: comparisons with 8-hydroxy-2-(di-n-propylamino) tetralin. Eur J Pharmacol 1994;253:53–60.

Matsuki N, Wang CH, Okada F, Tamura M, Ikegaya Y, Lin SC, et al. Male/female difference in drug-induced emesis and motion sickness in *Suncus murinus*. Pharmacol Biochem Behav 1997;57:721–5.

Money KE, Cheung BS. Another function of the inner ear: facilitation of the emetic response to poisons. Aviat Space Environ Med 1983;54:208–11.

Okada F, Torii Y, Saito H, Matsuki N. Antiemetic effects of serotonergic 5-HT1A-receptor agonists in *Suncus Murinus*. Jpn J Pharmacol 1994;64:109–14.

Oman CM. Sensory conflict theory and space sickness: our changing perspective. J Vestib Res 1998;8:51–6.

Rudd JA, Bunce KT, Naylor R. The effect of 8-OH-DPAT on drug-induced emesis in the ferret. Br J Pharmacol 1992;106:101.

Sanger GJ, Andrews PL. Treatment of nausea and vomiting: gaps in our knowledge. Auton Neurosci 2006;129:3-16.

Temple JL. The musk shrew (*Suncus murinus*): a model species for studies of nutritional regulation of reproduction. ILAR J 2004;45:25–34.

Ueno S, Matsuki N, Saito H. *Suncus murinus*: a new experimental model in emesis research. Life Sci 1987;41:513–8.

Ueno S, Matsuki N, Saito H. *Suncus Murinus* as a new experimental model for motion sickness. Life Sci 1988;43:413–20.

Wolff MC, Leander JD. Antiemetic effects of 5-$HT_{1A}$ agonists in the pigeon. Pharmacol Biochem Behav 2010;49:385–91.