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# The Effects of Cannabidiol and Tetrahydrocannabinol on Motion-Induced Emesis in *Suncus murinus*

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*Abstract:* The effect of cannabinoids on motion-induced emesis is unknown. The present study investigated the action of phytocannabinoids against motion-induced emesis in *Suncus murinus*. *Suncus murinus* were injected intraperitoneally with either cannabidiol (CBD) (0.5, 1, 2, 5, 10, 20 and 40 mg/kg), $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC; 0.5, 3, 5 and 10 mg/kg) or vehicle 45 min. before exposure to a 10-min. horizontal motion stimulus (amplitude 40 mm, frequency 1 Hz). In further investigations, the $CB_1$ receptor antagonist, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (AM 251; 5 mg/kg), was injected 15 min. prior to an injection of $\Delta^9$-THC (3 mg/kg). The motion stimulus was applied 45 min. later. The number of emetic episodes and latency of onset to the first emetic episode were recorded. Pre-treatment with the above doses of CBD did not modify the emetic response to the motion stimulus as compared to the vehicle-treated controls. Application of the higher doses of $\Delta^9$-THC induced emesis in its own right, which was inhibited by AM 251. Furthermore, pre-treatment with $\Delta^9$-THC dose-dependently attenuated motion-induced emesis, an effect that was inhibited by AM 251. AM 251 neither induced an emetic response nor modified motion-induced emesis. The present study indicates that $\Delta^9$-THC, acting via the $CB_1$ receptors, is anti-emetic to motion, and that CBD has no effect on motion-induced emesis in *Suncus murinus*.

The signs and symptoms of motion sickness including vomiting, nausea, pallor and general malaise are seen, to some degree, in most people on sufficient exposure to a motion stimulus [1]. As such, motion sickness is a significant problem not only in civilian transport, but also in military training and travel, and also in space travel. The most widely accepted hypothesis regarding the initiation of motion sickness is the sensory conflict or sensory mismatch theory [2].

It is proposed that sensory conflict occurs when vestibular, visual and non-vestibular information from somatosensory receptors concerning motion and balance of the body do not relate to each other or to what is anticipated from previous exposure; this leads to motion sickness. The neuronal pathways and the degree of their involvement in the mediation of motion sickness are not fully known. Experiments involving deaf-mutes [3] were the first to show that a functional vestibular system is critical for the development of motion sickness. This was confirmed when labyrinthine-defective individuals [4,5] and labyrinthectomized dogs [6] were shown to possess a total immunity to seasickness. Following discrete removal of the *area postrema* (the chemosensitive trigger zone for emesis), it was demonstrated that although this structure is involved in the development of motion-induced emesis, it is not an essential component [7]. The vestibulocerebellum conveys information from the vestibular system regarding the position of the head and is involved in the generation of reflex eye movements and changes in posture. Like the *area postrema*, the vestibulocerebellar pathway is involved in the induction of motion sickness, but it is not essential for its development [8,9]. The available antimotion sickness drugs do not completely protect individuals against emesis and their anti-emetic site of action is not fully understood.

$\Delta^9$-Tetrahydrocannabinol ($\Delta^9$-THC; dronabinol) and a synthetic cannabinoid (nabilone) are authorized for use in the USA and UK, respectively, as anti-emetics in patients undergoing cytotoxic chemotherapy. The anti-emetic effects of cannabinoids in models of drug-induced emesis are well established and have been shown to be both $CB_1$ receptor-mediated [10–14] and non-$CB_1$ receptor-mediated [12]. The role of the cannabinoids and their receptors is still to be determined in motion-induced emesis. Previous studies have implicated the anti-emetic action of the phytocannabinoid cannabidiolic acid on motion-induced emesis in the *Suncus murinus* [15].

The aim of the present study was to investigate the anti-emetic potential of cannabidiol (CBD) and $\Delta^9$-THC on motion-induced emesis using *S. murinus* (house musk shrew). Furthermore, the involvement of the cannabinoid $CB_1$ receptor in the mediation of motion-induced emesis and the action of $\Delta^9$-THC on motion-induced emesis was investigated using the $CB_1$ receptor antagonist *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (AM 251). *Suncus murinus* is an insectivore that is closer phylogenetically [16] and physiologically [17,18] to

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primates than rodents and lagomorphs. This animal model has been shown to be a robust model of motion sickness [19,20].

## Materials and Methods

*Animals and housing conditions.* Japanese house musk shrews *S. murinus* (University of Bradford strain) were bred and maintained at the University of Bradford animal facilities. Age- and gender-matched adult *S. murinus* (males 66.6 ± 0.5 g) were used throughout the investigations. Animals were housed up to three per cage, with an *ad libitum* supply of food (AQUATIC 3, trout pellets) and water, in a temperature- and humidity-controlled room (22°, 35–38%) on an 8:30–19:00-hr light:dark cycle. Cages, containing sawdust and shredded paper, were cleaned twice weekly with cat food introduced once a week.

*Emesis study.* The apparatus used to measure emesis consisted of six, linked, transparent cages [100 (W) × 150 (L) × 150 (H) mm] on a track that was set to move horizontally at a frequency of 1 Hz and an amplitude of 40 mm for 10 min. Previous experiments have shown that these are the optimum settings to evoke a reliable and reproducible emetic response to a motion stimulus in S. murinus [19].

All experiments were carried out at the same time of the day (8:00 a.m. to 4:00 p.m.) and under the same experimental conditions. This reduced the possibility of any changes in emetic behaviour being influenced by a change in visual, olfactory or other stimuli.

Motion sickness was quantified by an emetic response. An emetic episode was characterized by strong repeated abdominal contractions and wide opening of the mouth, initially coupled with the passage of solid or liquid matter from the upper gastrointestinal tract. As the inter-retch interval has been shown to be approximately 260 msec. [21], it is not possible to observe and count the number of retches in an episode. Thus, a bout of retching was recorded as an emetic episode. In all experiments, the number of emetic episodes experienced by each animal and the latency of onset from the start of the shaking stimulus to the first emetic episode were recorded by a non-blinded observer.

All the experiments were carried out in accordance with the UK Animals Act (Scientific Procedures) 1986, and were approved by the University of Bradford animal ethics committee.

*Experimental design. Suncus murinus* were injected intraperitoneally with scopolamine (2 mg/kg), CBD (0.5, 1, 2, 5, 10, 20 or 40 mg/kg), $\Delta^9$-THC (0.5, 3, 5 or 10 mg/kg), AM 251 (5 mg/kg) or vehicle (control) and were immediately placed individually in a cage of the shaker. The animals were observed for displays of emesis (the number of emetic episodes and latency of onset to the first episode were recorded) and for any other overt behavioural changes for 45 min. (except animals receiving AM 251 that were observed for 1 hr). In another set of experiments, animals received AM 251 (5 mg/kg) or vehicle 15 min. prior to the administration of $\Delta^9$-THC (3 mg/kg) or vehicle. Animals were then observed for 45 min. with emesis parameters being recorded as described above.

In all the experiments, following the observation period, motion was applied for 10 min. (at a frequency of 1 Hz and an amplitude of 40 mm) and the number of emetic episodes and latency of onset to the first episode were recorded. Animals were observed for a further 2 min. before being returned to the housing cage.

*Drugs.* Crystalline CBD and $\Delta^9$-THC were supplied by GW Pharmaceuticals Ltd. (Wiltshire, UK). AM 251 and scopolamine hydrobromide (HBr) were purchased from Tocris Cookson Limited, Bristol, UK. Dimethyl sulphoxide (DMSO) and polyoxyethylenesorbitan monooleate (Tween-80) were purchased from Sigma (Poole, Dorset, UK).

Scopolamine was dissolved in distilled water. All other drugs were dissolved in a vehicle of 2% DMSO plus 1% Tween-80. Preliminary experiments showed that the emetic response induced by motion in vehicle-treated animals was not significantly different ($P > 0.05$) to the response in saline-treated animals. Drugs were administered intraperitoneally in a volume of 1 ml/100 g body weight.

*Data analysis.* Data were expressed as the mean ± S.E.M. of n = 5–10 and analysed using Student's t-test or a one-way ANOVA followed by Bonferroni's *post hoc* test where appropriate. P-values of <0.05 were taken as significant.

## Results

*The effect of scopolamine on motion-induced emesis.*

Intraperitoneal administration of scopolamine at a dose of 2 mg/kg significantly ($P < 0.01$) attenuated the emetic response induced by motion from 7 ± 1.4 episodes in control animals to 2 ± 0.7 episodes in scopolamine-treated animals. The time of onset of emesis was significantly ($P < 0.001$) increased from 196.6 ± 52.5 sec. in control animals to 502.1 ± 42.1 sec. in test animals.

*The effect of cannabidiol on motion-induced emesis.*

Pre-treatment with 0.5, 1, 2, 5, 10, 20 and 40 mg/kg CBD did not modify the emetic response to the motion stimulus. The number of emetic episodes and the latency of onset of emesis were comparable to those recorded in the vehicle-treated animals ($P > 0.05$) (fig. 1). The administration of CBD in its own right did not induce emesis in any of the doses examined.

*The effect of $\Delta^9$-tetrahydrocannabinol on motion-induced emesis.*

The intraperitoneal administration of $\Delta^9$-THC (3, 5 and 10 mg/kg) induced an emetic response, in its own right, during the 45-min. observation period before the application of the motion stimuli (table 1). The lower dose of 0.5 mg/kg $\Delta^9$-THC did not induce emesis (table 1).

Pre-treatment with $\Delta^9$-THC at a dose of 0.5 mg/kg had no effect on motion-induced emesis, with both the number of emetic episodes and the onset to the first emetic episode being comparable ($P > 0.05$) to those in the vehicle-treated control animals (fig. 2). The higher doses of 3 and 10 mg/kg $\Delta^9$-THC induced a significant ($P < 0.05$ and $P < 0.01$, respectively) reduction in the number of emetic episodes compared to vehicle-treated animals. This was not associated with an effect on the latency of onset to the first emetic episode, which was comparable to those recorded in control animals (fig. 2). At 5 mg/kg, $\Delta^9$-THC significantly ($P < 0.001$) attenuated the emetic response to motion, reducing the number of emetic episodes and increasing the latency of onset to emesis (fig. 2). Indeed, $\Delta^9$-THC at 5 mg/kg significantly ($P < 0.05$) reduced the number of animals displaying emesis to motion from 5/5 animals, in the control group, to 1/5 animals in the drug treated group.

*The effect of a $CB_1$ receptor antagonist on motion-induced emesis.*

Pre-treatment with 5 mg/kg AM 251 had no effect on the emetic response to the motion stimulus. The number of

 

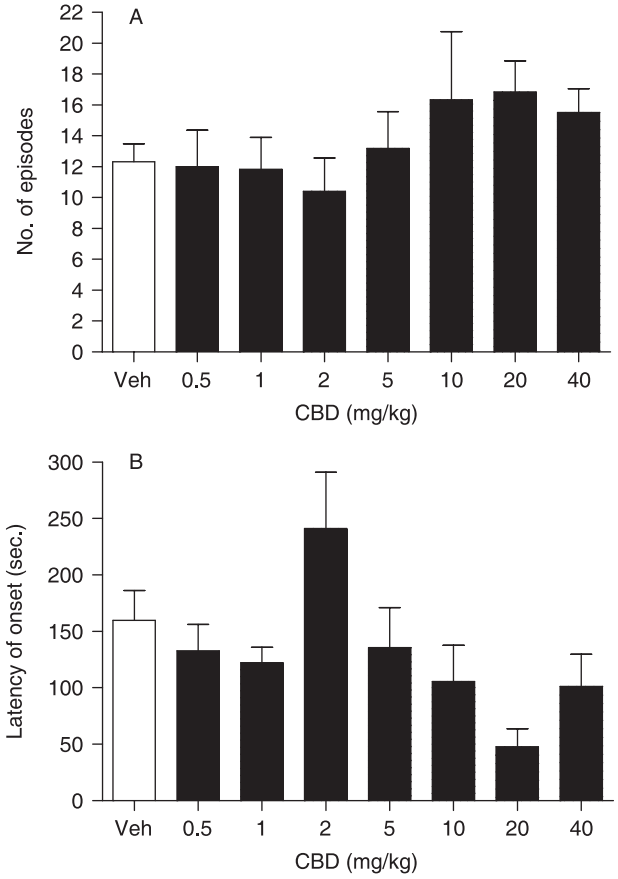


Fig. 1. The effect of cannabidiol (CBD) (0.5, 1, 2, 5, 10, 20 and 40 mg/kg) and vehicle (Veh) administered intraperitoneally 45 min. prior to the application of motion. The number of emetic episodes (A) and latency of onset to the first emetic episode (B) induced by a 10-min. horizontal motion stimulus (of a frequency of 1 Hz and an amplitude of 40 mm) were measured in *Suncus murinus*. If emesis was not observed the latency of onset was recorded as 600 sec. Each bar represents the mean ± S.E.M., n = 5–15.

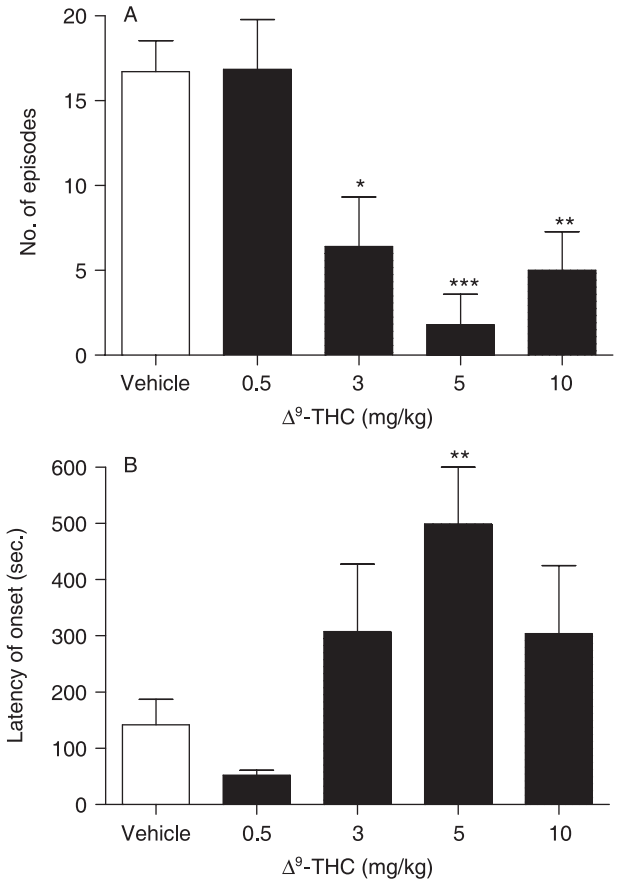


Fig. 2. The effect of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) (0.5, 3, 5 and 10 mg/kg) and vehicle, administered intraperitoneally 45 min. prior to the application of motion. The number of emetic episodes (A) and latency of onset to the first emetic episode (B) induced by a 10-min. horizontal motion stimulus (of a frequency of 1 Hz and an amplitude of 40 mm) were measured in *Suncus murinus*. If emesis was not observed, the latency of onset was recorded as 600 sec. Each bar represents the mean ± S.E.M, n = 5–10. *P < 0.05, **P < 0.01 and ***P < 0.001 indicate a significant difference to the vehicle-treated control animals using one-way ANOVA followed by Bonferroni's *post hoc* analysis.

emetic episodes and the latency of onset of emesis were comparable to those recorded in the vehicle-treated animals (P > 0.05) (fig. 3). The administration of AM 251 did not induce an emetic response compared to vehicle-treated control animals.

### *The effect of a $CB_1$ receptor antagonist on $\Delta^9$-tetrahydrocannabinol-induced emesis.*

The intraperitoneal administration of AM 251 15 min. before $\Delta^9$-THC (3 mg/kg, intraperitoneally) significantly

*Table 1.*

Emetogenic profile of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), including number of emetic episodes (mean ± S.E.M.), latency of onset to the first emetic episode (mean ± S.E.M.) and the number of animals per group displaying emesis, observed for 45 min. following intraperitoneal administration of drug or vehicle in *Suncus murinus*.

| Vehicle or $\Delta^9$-THC (mg/kg) | Number of emetic episodes | Latency of onset (sec.) | Number of animals vomited per group |
|---|---|---|---|
| Vehicle | 0 ± 0.0 | 2700 ± 0 | 0/10 |
| $\Delta^9$-THC (0.5 mg/kg) | 1 ± 0.6 | 2088 ± 387.5 | 2/5 |
| $\Delta^9$-THC (3 mg/kg) | 15.2 ± 1.4[2] | 468.8 ± 71.5[2] | 5/5[1] |
| $\Delta^9$-THC (5 mg/kg) | 8.6 ± 2.4[2] | 322.6 ± 31.8[2] | 5/5[1] |
| $\Delta^9$-THC (10 mg/kg) | 11.2 ± 0.9[2] | 572.2 ± 64.1[2] | 5/5[1] |

If emesis was not observed, the latency of onset was recorded as 2700 sec. n = 5–10. [1]P < 0.01 and [2]P < 0.001 indicate a significant difference to the vehicle-treated control group following one-tailed statistical analysis.

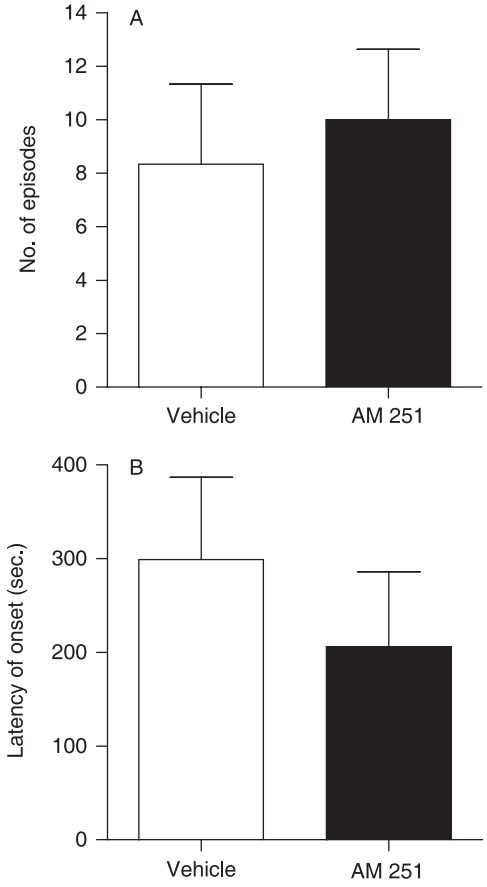


Fig. 3. The effect of AM 251 (5 mg/kg) and vehicle, administered intraperitoneally 45 min. prior to the application of motion. The number of emetic episodes (A) and latency of onset to the first emetic episode (B) induced by a 10-min. horizontal motion stimulus (of a frequency of 1 Hz and an amplitude of 40 mm) were measured in *Suncus murinus*. If emesis was not observed, the latency of onset was recorded as 600 sec. Each bar represents the mean ± S.E.M., n = 6.

($P < 0.001$) reduced the number of emetic episodes displayed by *S. murinus* compared to $\Delta^9$-THC-treated animals (table 2). The administration of AM 251 plus $\Delta^9$-THC did not induce a significant ($P > 0.05$) number of emetic episodes compared to vehicle-treated control animals. The intraperitoneal administration of 5 mg/kg AM 251 alone did not induce an emetic response compared to vehicle-treated control animals ($P > 0.05$) (table 2).

*The effect of a $CB_1$ receptor antagonist on motion-induced emesis in animals treated with $\Delta^9$-tetrahydrocannabinol.*

$\Delta^9$-Tetrahydrocannabinol-induced attenuation of emesis evoked by a motion stimulus was reversed by AM 251 (5 mg/kg), with both the number of emetic episodes and the latency of onset to the first episode being comparable ($P > 0.05$) to vehicle-treated animals (fig. 4).

## Discussion

The present study investigated the effects of the phytocannabinoids CBD and $\Delta^9$-THC on motion-induced emesis in *S. murinus*. The study further confirmed the findings of others [19,20,22] that motion-induced emesis is reliably initiated in *S. murinus* under the influence of horizontal shaking. Furthermore, motion-induced emesis was significantly inhibited by the muscarinic receptor antagonist scopolamine. This may relate to the action of scopolamine to attenuate motion-induced emesis in human beings [1] and further confirms the literature [20,23,24] that motion-induced emesis in *S. murinus* can reliably be antagonized by a reference pharmacological agent.

In an attempt to investigate the effects of cannabinoids on motion sickness, initially the study was designed to investigate the effects of CBD. In such experiments, CBD did not modify motion-induced emesis in *S. murinus*; both the intensity (the number of emetic episodes) and the delay in the onset of the first emetic episode were comparable to those in control animals. It has also been reported in the least shrew that CBD, at comparable doses to the present study, had no effect on emesis induced by 2-arachidonoylglycerol (2-AG) [25].

Cannabidiol is a non-psychoactive constituent of *Cannabis sativa* [26] and as such presents a more desirable option than other cannabinoids as a therapeutic agent. It has been reported that CBD induced a biphasic effect on lithium-induced emesis in *S. murinus* attenuating vomiting at low doses (5–10 mg/kg) and potentiating vomiting at high doses of 25–40 mg/kg with neither effect being mediated via $CB_1$ receptor activation

*Table 2.*

Emetogenic profile of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) (3 mg/kg) in the presence and absence of AM 251 and AM 251 (5 mg/kg) alone, including number of emetic episodes (mean ± S.E.M.), latency of onset to the first emetic episode (mean ± S.E.M.) and the number of animals per group displaying emesis, observed for 45 min. following the second injection of drug or vehicle in *Suncus murinus*.

| Vehicle or drug treatment (mg/kg) | Number of emetic episodes | Latency of onset (sec.) | Number of animals vomited per group |
|---|---|---|---|
| Vehicle | 0 ± 0.0 | 2700 ± 0 | 0/5 |
| AM 251 (5 mg/kg) | 0.6 ± 0.4[3] | 1818 ± 543.8 | 2/5 |
| $\Delta^9$-THC (3 mg/kg) | 15.2 ± 1.4[2] | 468.8 ± 71.5[1] | 5/5[1] |
| AM 251 (5 mg/kg) + $\Delta^9$-THC (3 mg/kg) | 4.4 ± 2.1[3] | 1164 ± 627.7 | 3/5 |

If emesis was not observed, the latency of onset was recorded as 2700 sec. n = 5. [1]$P < 0.01$ and [2]$P < 0.001$ indicate a significant difference to the vehicle-treated control group following one-tailed statistical analysis. [3]$P < 0.001$ indicates a significant difference to the $\Delta^9$-THC-treated group following one-tailed statistical analysis.

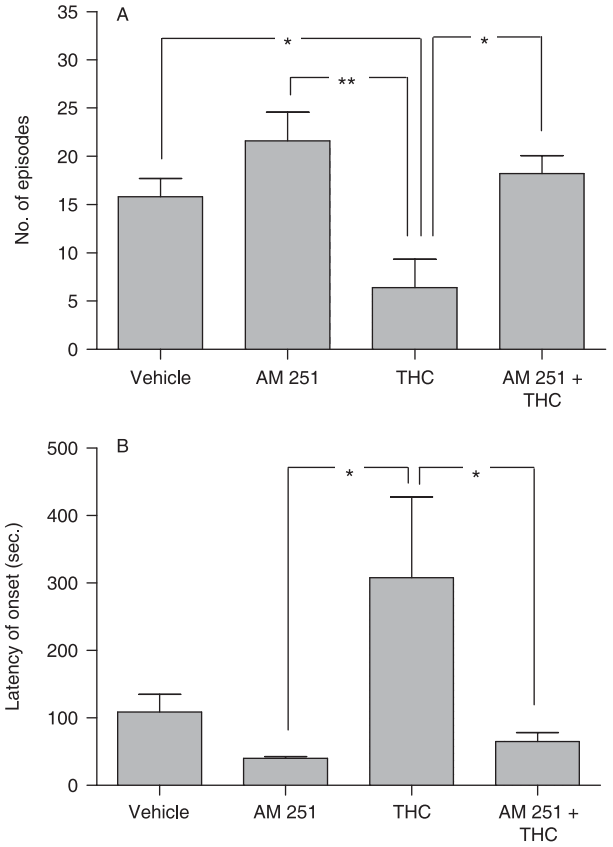


Fig. 4. The effect of vehicle or AM 251 (5 mg/kg) administered intraperitoneally 15 min. prior to vehicle or $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) (3 mg/kg) on the number of emetic episodes (A) and latency of onset to the first emetic episode (B) induced by a 10-min. horizontal motion stimulus (of a frequency of 1 Hz and an amplitude of 40 mm), applied 45 min. after the second vehicle or drug injection in *Suncus murinus*. If emesis was not observed, the latency of onset was recorded as 600 sec. Each bar represents the mean ± S.E.M., n = 5–10. *P < 0.05 and **P < 0.01 indicate a significant difference between treatments groups using one-way ANOVA followed by Bonferroni's *post hoc* analysis.

[12]. The same biphasic action of CBD has been reported in cisplatin-induced emesis in *S. murinus* [27]. However, in the present study, CBD applied at the doses that produced bi-phasic effects in lithium- and cisplatin-induced emesis in other studies, did not modify emesis induced by motion. This might be due to the differing neuronal pathways involved in the induction of emesis by these emetogenic stimuli; with lithium acting via the *area postrema* [28] and cisplatin acting via vagal afferents and the *area postrema* [29], pathways that are not essential to the development of motion sickness [7,30]

In further experiments, the effects of $\Delta^9$-THC were investigated. The intraperitoneal administration of $\Delta^9$-THC demonstrated an emetogenic effect in *S. murinus*. This was in line with previous experiments where $\Delta^9$-THC was shown to be emetogenic in the dog [31,32]. However, $\Delta^9$-THC was not reported to be emetogenic in the ferret [10,11] or in the pigeon [33], suggesting some species differences may occur.

The $CB_1$ receptor antagonist AM 251 attenuated the emetic action of $\Delta^9$-THC in the present study, suggesting that the emetogenic action of $\Delta^9$-THC is mediated via $CB_1$ receptor stimulation.

In the present study, in addition to the action of $\Delta^9$-THC to induce an emetic response, pre-treatment with $\Delta^9$-THC administered intraperitoneally induced a dose-related attenuation of emesis induced by motion. In such data, $\Delta^9$-THC at a dose of 5 mg/kg induced the greatest inhibition of the emetic episodes, and that was associated with a significant increase in the latency of onset of the first emetic episodes. Furthermore, while the single application of AM 251, a $CB_1$ receptor antagonist, failed to modify motion-induced emesis, in a combined study, it reversed the anti-emetic effects of $\Delta^9$-THC on motion sickness. The increase in the latency of onset to the first emetic episode afforded by $\Delta^9$-THC was also antagonized by pre-treatment with the antagonist. These data suggest the involvement of $CB_1$ receptors in mediating the anti-emetic action of $\Delta^9$-THC on motion sickness in *S. murinus*.

Indeed, the psychoactive cannabinoid $\Delta^9$-THC has been reported to demonstrate anti-emetic efficacy to emesis induced by a plethora of emetogens, including morphine [11], cisplatin [10,14,27], 2-AG [25], lithium [12], SR141716A [34], 5-hydroxytryptophan [35], dopamine agonists [36] and radiation [37] in the *S. murinus*, ferrets and the least shrew. Such an anti-emetic activity was reported to be through $CB_1$ receptors located in the brain stem [11] and at specific regions of the dorsal vagal complex [10]. The present study has furthered the current knowledge by revealing an anti-emetic action of $\Delta^9$-THC against motion-induced emesis via $CB_1$ receptors in *S. murinus*.

It was interesting to note that in the present study, the action of $\Delta^9$-THC to inhibit motion-induced emesis in the house musk shrew was observed at doses that also inhibited cisplatin- [14,27], 2-AG- [25] and SR141716A-induced [34] emesis. It may be hypothesized that the anti-emetic action of $\Delta^9$-THC in motion-induced emesis is mediated by the same mechanism as in emesis induced by cisplatin, 2-AG and SR141716A. That these emetic stimuli act via different neuronal pathways suggests that the anti-emetic actions of $\Delta^9$-THC are mediated via common downstream pathways of emesis.

Furthermore, it has been reported that $\Delta^9$-THC, acting via both central and peripheral actions, inhibited 5-hydroxytryptophan-induced emesis via activation of $CB_1$ receptors [35]. As motion-induced emesis is hypothesized to be initiated by central mechanisms [38] with peripheral inputs being non-essential to its induction [30], it may be suggested that the antimotion sickness action of $\Delta^9$-THC in the present study may be centrally mediated.

Immunohistochemistry and Western blotting studies have shown the distribution of $CB_1$ receptors in the vestibular nucleus complex, which is one of the key areas involved in mediating motion sickness [39]. Furthermore, such studies confirmed that $CB_1$ receptors exist in significant densities in the vestibular nucleus complex and are likely to contribute

 

to the neurochemical control of the vestibular reflexes [39]. Whether $\Delta^9$-THC induces emesis in *S. murinus* via centrally or peripherally located $CB_1$ receptors remains to be elucidated. Furthermore, scopolamine, the reference antimotion sickness drug used in the present studies, inhibits motion sickness via antagonism of acetylcholine receptors. $CB_1$ receptor activation has been shown to inhibit the release of various neurotransmitters from neurons in both the brain and the periphery [40,41]. Whether $\Delta^9$-THC is mediating its antimotion sickness effects through actions on cholinergic neurotransmission remains to be determined.

In the present study, the emetogenic action of $\Delta^9$-THC may contribute to the action of $\Delta^9$-THC to inhibit emesis induced by motion via a possible desensitization of a common down stream pathway involved in the emetic reflex that may follow the depolarisation of $CB_1$ receptors. Further experiments are required to investigate the desensitisation of $CB_1$ receptors.

The ability of $\Delta^9$-THC to induce two opposing effects was not surprising, since the same phenomenon has already been reported for some chemicals, such as serotonin and resiniferatoxin. Indeed, it has been shown in *S. murinus* that while serotonin was emetic, it could also induce an anti-emetic effect on motion sickness and that this was possibly due to a desensitization of the emetic pathway or activation of a different sites or pathways [23]. Furthermore, studies by Andrews *et al*. [42] revealed that while resiniferatoxin was emetic, it also had an anti-emetic effect to emesis induced by nicotine, cisplatin, motion and copper sulphate in *S. murinus*, possibly via depletion of the neurotransmitter substance P [42].

In the present study, the $CB_1$ receptor antagonist AM 251 did not induce an emetic response in *S. murinus*, suggesting the unlikely involvement of an endocannabinoid tone, mediated by the $CB_1$ receptors in the emetic reflex. This supports other investigations where $CB_1$ receptor antagonists did not induce emesis in the ferret [11], least shrew [13,34] and house musk shrew [12]. Furthermore, AM 251 did not modify motion-induced emesis in the present study, suggesting the unlikely involvement of an endocannabinoid tone, mediated by the $CB_1$ receptors, activation of which prevents motion-induced emesis.

In conclusion, the present study has revealed an anti-emetic potential of $\Delta^9$-THC on motion-induced emesis and demonstrated that the non-psychoactive cannabinoid CBD had no effect on motion sickness. Furthermore, it was shown that the action of $\Delta^9$-THC to inhibit motion-induced emesis might have been mediated by cannabinoid $CB_1$ receptors. This contributes to growing evidence that $\Delta^9$-THC may act as a broad spectrum anti-emetic.

Acknowledgements

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## References

1 Spinks AB, Wasiak J, Villanueva EV, Bernath V. Scopolamine for preventing and treating motion sickness. Cochrane Database Syst Rev 2004;**3**:CD002851.
2 Reason JT, Brand JJ. Motion Sickness. Academic Press, London, 1975.
3 James W. The sense of dizziness in deaf-mutes. Am J Otol 1882;**4**:239–54.
4 Kennedy RS, Graybiel A, McDonough RC, Beckwith FD. Symptomatology under storm conditions in the North Atlantic in control subjects and in persons with bilateral labyrinthine defects. NSAM-928, NASA Ord. No. R-P3, Naval School of Aviation Medicine, Pensacola, FL, May 25, 1965.
5 Reynolds TT. On the nature and treatment of seasickness. Lancet 1884;**1**:1161–2.
6 Sjoberg A. Experimental studies of the eliciting mechanism of sea sickness. Acta Otolaryngol 1929;**13**:343–7.
7 Wilpizeski CR, Lowry LD, Goldman WS. Motion-induced sickness following bilateral ablation of area postrema in squirrel monkeys. Laryngoscope 1986;**96**:1221–5.
8 Miller AD, Wilson VJ. Vestibular-induced vomiting after vestibulocerebellar lesions. Brain Behav Evol 1983;**23**:26–31.
9 Stoffregen TA, Smart LJ, Jr. Postural instability precedes motion sickness. Brain Res Bull 1998;**47**:437–48.
10 Van Sickle MD, Oland LD, Mackie K, Davison JS, Sharkey KA. $\Delta^9$-Tetrahydrocannabinol selectively acts on $CB_1$ receptors in specific regions of dorsal vagal complex to inhibit emesis in ferrets. Am J Physiol 2003;**285**:G566–76.
11 Van Sickle MD, Oland LD, Ho W, Hillard CJ, Mackie K, Davison JS *et al*. Cannabinoids inhibit emesis through $CB_1$ receptors in the brainstem of the ferret. Gastroenterology 2001;**121**:767–74.
12 Parker LA, Kwiatkowska M, Burton P, Mechoulam R. Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew). Psychopharmacology (Berl) 2004;**171**:156–61.
13 Darmani NA. The cannabinoid $CB_1$ receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55, 212-2. Eur J Pharmacol 2001;**430**:49–58.
14 Darmani NA. $\Delta^9$-Tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB(1) receptors in the least shrew. Pharmacol Biochem Behav 2001;**69**:239–49.
15 Javid FA, Wright C, Naylor RJ, Whittle BA. The role of cannabinoids in the mediation of motion sickness in *Suncus murinus*. FENS Abstr 2002;**1**:A142.14.
17 Hoyle CHV, Hill J, Sanger GJ, Andrews PLR. Analysis of pancreatic polypeptide cDNA from the house musk shrew, Suncus murinus, suggests a phylogenetically closer relationship with humans than for other small laboratory animal species. Regul Pept 2003;**114**:137–44.
16 Colbert EH. Evolution of Vertebrates, 2nd edn. John Wiley & sons, New York, NY, 1969.
18 Hoyle CHV, Chakrabarti G, Pendleton NP, Andrews PLR. Neuromuscular transmission and innervation in the urinary bladder of the insectivore *Suncus murinus*. J Auton Nerv Syst 1998;**69**:31–8.
19 Javid FA, Naylor RJ. Variables of movement amplitude and frequency in the development of motion sickness in *Suncus murinus*. Pharmacol Biochem Behav 1999;**64**:115–22.
20 Ueno S, Matsuki N, Saito H. *Suncus murinus* as a new experimental model for motion sickness. Life Sci 1988;**43**:413–20.
21 Andrews P, 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.
22 Andrews P, Dovey E, Hockaday J, Hoyle CH, Woods AJ, Matsuki N. The development of the emetic reflex in the house musk shrew, *Suncus murinus*. Brain Res Dev Brain Res 2000;**121**:29–34.
23 Javid FA, Naylor RJ. The effect of serotonin and serotonin receptor antagonists on motion sickness in *Suncus murinus*. Pharmacol Biochem Behav 2002;**73**:979–89.

 

24 Nakayama H, Yamakuni H, Higaki M, Ishikawa H, Imazumi K, Matsuo M *et al*. Antiemetic activity of FK1052, a 5-HT3- and 5-HT4-receptor antagonist, in Suncus murinus and ferrets. J Pharmacol Sci 2005;**98**:396–403.
25 Darmani NA. The potent emetogenic effects of the endocannabinoid, 2-AG (2-arachidonoylglycerol) are blocked by $\Delta^9$-tetrahydrocannabinol and other cannabinoids. J Pharmacol Exp Ther 2002;**300**:34–42.
26 Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol 1981;**21**:417S–27S.
27 Kwiatkowska M, Parker LA, Burton P, Mechoulam R. A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the Suncus murinus (house musk shrew). Psychopharmacology (Berl) 2004;**174**:254–9.
28 Billig I, Yates BJ, Rinaman L. Plasma hormone levels and central c-Fos expression in ferrets after systemic administration of cholecystokinin. Am J Physiol Regul Integr Comp Physiol 2001;**281**:R1243–55.
29 Leslie RA, Reynolds DJM. Functional anatomy of the emetic circuitry in the brainstem. In: Bianchi AL, Grelot L, Miller AD, King GL (eds). Mechanisms and Control of Emesis. Colloque INSERM, London, 1992;19–27.
30 Lang IM, Sarna SK, Shaker R. Gastrointestinal motor and myoelectric correlates of motion sickness. Am J Physiol 1999;**277**:G642–52.
31 Shannon HE, Martin WR, Silcox D. Lack of antiemetic effects of $\Delta^9$-tetrahydrocannabinol in apomorphine-induced emesis in the dog. Life Sci 1978;**23**:49–53.
32 Loewe S. Studies on the pharmacology and acute toxicity of compounds with marihuana activity. J Pharmacol Exp Ther 1946;**88**:154–61.
33 Feigenbaum JJ, Richmond SA, Weissman Y, Mechoulam R. Inhibition of cisplatin-induced emesis in the pigeon by a non-psychotropic synthetic cannabinoid. Eur J Pharmacol 1989;**169**:159–65.
34 Darmani NA. $\Delta^9$-Tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB(1) receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacology 2001;**24**:198–203.
35 Darmani NA, Johnson JC. Central and peripheral mechanisms contribute to the antiemetic actions of $\Delta^9$-tetrahydrocannabinol against 5-hydroxytryptophan-induced emesis. Eur J Pharmacol 2004;**488**:201–12.
36 Darmani NA, Crim JL. $\Delta^9$-Tetrahydrocannabinol differentially suppresses emesis versus enhanced locomotor activity produced by chemically diverse dopamine D2/D3 receptor agonists in the least shrew (*Cryptotis parva*). Pharmacol Biochem Behav 2005;**80**:35–44.
37 Darmani NA, Janoyan JJ, Crim J, Ramirez J. Receptor mechanism and antiemetic activity of structurally-diverse cannabinoids against radiation-induced emesis in the least shrew. Eur J Pharmacol 2007;**563**:187–96.
38 Kennedy RS, Graybiel A, McDonough RC, Beckwith FD. Symptomatology under storm conditions in the North Atlantic in control subjects and in persons with bilateral labyrinthine defects. Acta Otolaryngol 1968;**66**:533–40.
39 Ashton JC, Zheng YW, Liu P, Darlington CL, Smith PF. Immunohistochemical characterisation and localisation of cannabinoid $CB_1$ receptor protein in the rat vestibular nucleus complex and the effects of unilateral vestibular differentiation. Brain Research 2004;**1021**:264–71.
40 Schlicker E, Kathmann M. Modulation of transmitter release via presynaptic cannabinoid receptors. Trends Pharmacol Sci 2001;**22**:565–72.
41 Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA *et al*. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;**54**:161–202.
42 Andrews PL, Okada F, Woods AJ, Hagiwara H, Kakaimoto S, Toyoda M *et al*. The emetic and anti-emetic effects of the capsaicin analogue resiniferatoxin in *Suncus murinus*, the house musk shrew. Br J Pharmacol 2000;**130**:1247–54.

 