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The effect of the 5-HT_{1A} receptor agonist, 8-OH-DPAT, on motion-induced emesis in *Suncus murinus*

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Abstract

In the present study we evaluated the role of 5-HT_{1A} receptors in mediating the inhibitory action of 8-OH-DPAT, a 5-HT_{1A} receptor agonist, in motion sickness in *Suncus murinus*. 8-OH-DPAT (0.1 mg/kg, i. p) attenuated motion-induced emesis which was associated with an increase in the latency of the onset to the first emetic episode. Pre-treatment with methysergide (a 5-$HT_{1/2/7}$ receptor antagonist, 1.0 mg/kg, i. p.), WAY-100635 (a 5-HT_{1A} receptor antagonist, 1.0 mg/kg, i. p.), SB269970A (a 5-HT_7 receptor antagonist, 1.0 and 5.0 mg/kg, i. p.), ondansetron (a 5-HT_3 receptor antagonist, 1.0 mg/kg, i. p) or GR13808 (a 5-HT_4 receptor antagonist, 0.5 mg/kg, i. p) failed to modify the inhibitory action of 8-OH-DPAT on motion sickness. Furthermore, the application of either methysergide, WAY-100635, SB269970A, ondansetron or GR13808 alone had no effect on motion sickness in its own right. These data indicate that neither 5-HT_{1A} nor any 5-HT_2 receptor subtypes, 5-HT_3, 5-HT_4 and 5-HT_7 receptors are likely to be involved in the inhibition of motion-induced emesis mediated by 8-OH-DPAT.

Keywords: Motion sickness; 8-OH-DPAT; *Suncus murinus*

1. Introduction

In humans an essential requirement of movement is that they remain orientated to their surroundings. This is achieved through the vestibular and occular systems and a proprioceptive input. The communication between these systems does not enter consciousness unless there are unusual conditions of movement or orientation of either the body or environment (see review by Golding, 2006; Spinks et al., 2004). Such conditions are readily observed in many subjects during land, sea, air or space travel and create powerful and conscious sensations generally described as 'motion sickness.' The exact mechanism or neuronal circuitry involved in motion sickness is not fully understood. It is thought that motion sickness occurs as a result of a mismatch or conflict between the information arising from the semicircular canals and otolith organs of the vestibular system and the visual and proprioceptive inputs, that is expected on the basis of past experience (see review by Golding, 2006). The most unpleasant sensations are described as vertigo, dizziness and nausea with the frequent appearance of vomiting and changes in gastrointestinal motility and autonomic function.

Receptors such as M_3/M_5 muscarinic acetylcholine receptors, D_2 dopaminergic receptors, 5-HT_2 serotonergic receptors, H_1 and H_2 histamine receptors, mu and delta opioid receptors and the 5-HT_{1A} receptors have been implicated in motion sickness (Golding and Stott, 1997; Smith and Darlington, 1996). Thus, drugs acting at many different types of receptors could affect the neuronal emetic mechanism within the vestibular system. Research on emesis has revealed the value of the 5-HT_3 receptor antagonists as anti-emetics for cancer chemotherapy, however, they do not block the emetic response to motion (see Andrews, 1994). However, this does not negate a role for the serotonergic system in the mechanism of motion sickness since previous studies have shown the involvement of serotonergic 5-HT_{1A} receptors in motion sickness (Lucot, 1995; Okada et al., 1995; Javid and Naylor, 2002).

More recently postsynaptic 5-HT_{1A} receptors are also attributed to moderate emesis as the specific 5-HT_{1A} receptor agonist, 8-OHDPAT has been shown to induce protection against drug and motion-induced emesis in species such as the

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pigeon and cat (Wolff and Leander, 1994; Lucot and Crampton, 1989). However, most studies did not attempt to reverse the inhibitory action of 8-OHDPAT on motion sickness and assumed the involvement of 5-HT_{1A} receptors in mediating this inhibition.

The aim of the present studies was to further evaluate the role of 5-HT_{1A} receptors in mediating the inhibitory action of 8-OHDPAT to reduce motion-induced emesis in *Suncus murinus*.

2. Methods

2.1. Animals and housing conditions

The experiments were carried out using both adult female (35.6±1.2 g) and adult male (68±1.5 g) Japanese House Musk shrew, *S. 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 libitum'. Animals were also fed with cat food three times per week. The floor of the cages was covered with sawdust and cleaned twice a week. The animal room was maintained at a humidity between 45 to 50% at 24 °C and illuminated between 21.00 and 07.00 on a normal light–dark cycle.

2.2. Behavioural observations

Immediately after the administration of a drug or vehicle each animal was placed individually in a transparent cage (100 $W \times 150$ $L \times 150$ H mm) of 6 linked units and observed for any behavioural change. Animals were observed for any behavioural change and also emesis immediately after receiving the drugs. After a defined period for each drug (stated as pre-treatment time), animals were exposed to a horizontal motion stimulus of 1 Hz and a 40 mm amplitude of shaking for 10 min, during which the number of emetic episodes (vomiting/retching) and the latency of onset to the first emetic episode were recorded. The shaker was then turned off and animals remained under observation for 30 min. Preliminary experiments showed that the shaking parameters were suitable to induce a reliable and reproducible emetic response (Javid and Naylor, 1999). The emetic episodes were easily observed as a highly characteristic behavioural 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 semi-solid material following the burst of sustained abdominal contractions. Vomiting usually occurred for the first two to four episodes until the gastric contents had emptied. In subsequent emetic episodes the above

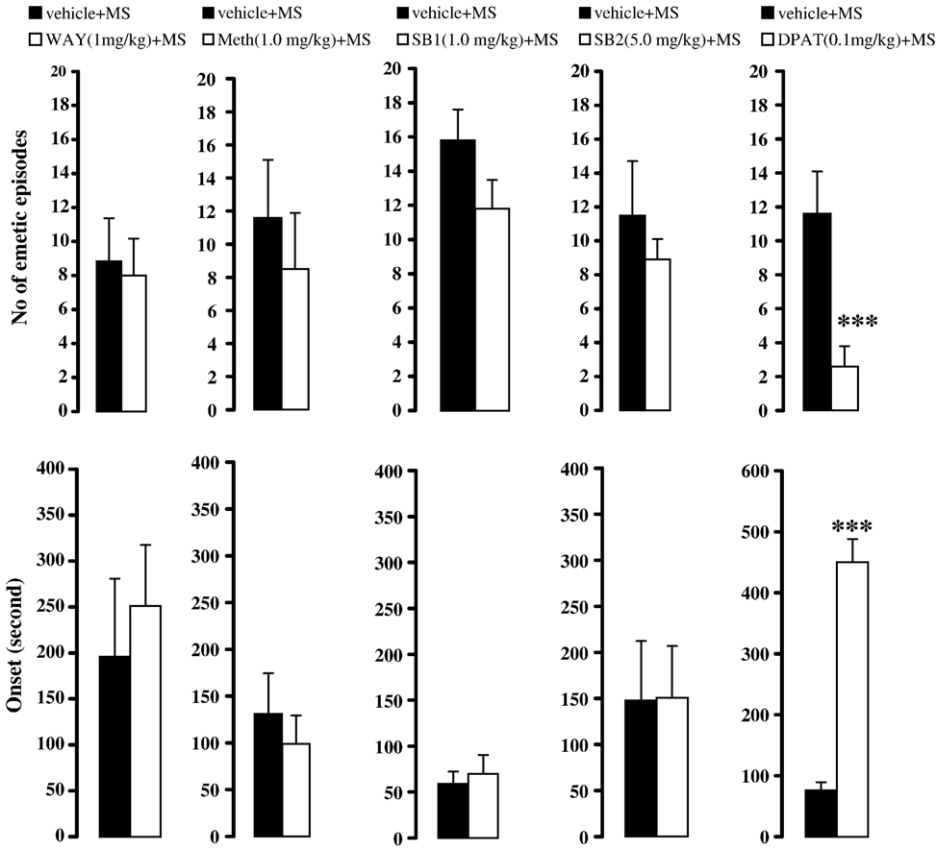

Fig. 1. The effects of WAY100635 (WAY,1.0 mg/kg, i. p., 60 min pre-treatment), methysergide (meth, 1.0 mg/kg, i. p., 60 min pre-treatment), SB269970A (SB1, 1.0 mg/kg, SB2, 5.0 mg/kg, i. p., 60 min pre-treatment) and 8-OHDPAT (DPAT, 0.1 mg/kg, i.p., 30 min pre-treatment) on motion-induced emesis using male *Suncus murinus*. The number of emetic episodes and the latency of onset to the first emetic episode were measured during a 10 min shaking period at a frequency of 1.0 Hz with an amplitude of 40 mm movement are shown. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean (drug or vehicle)±s.e. mean, $n=6$; $^{**}p<0.01$ and $^{***}p<0.001$ compared to the vehicle treatment; MS=motion stimulus.

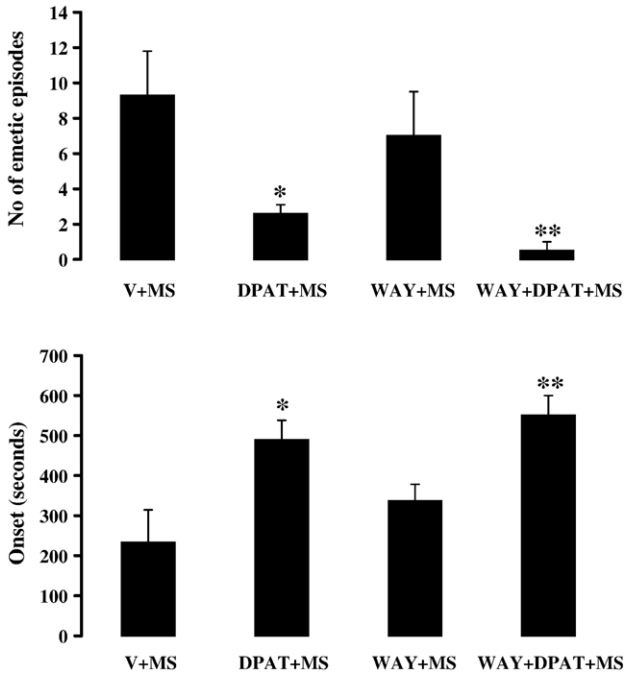

Fig. 2. The effect of 8-OH-DPAT (DPAT, 0.1 mg/kg, i.p, 30 min pre-treatment), WAY100635 (WAY, 1.0 mg/kg, i. p., 60 min pre-treatment), a combination of 8-OHDPAT plus WAY100635, or vehicle on motion-induced emesis using male *Suncus murinus*. The number of emetic episodes and the latency of onset to the first emetic episode were measured during 10 min shaking period at a frequency of 1.0 Hz with an amplitude of 40 mm movement are shown. 10 min observation period commenced from the first emetic episode. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean (drug or vehicle)±s.e. mean, $n=6$.; *$p<0.05$ and **$p<0.01$ compared to the vehicle treatment; MS=motion stimulus.

behavioural profile was apparent, but generally without passage of solid material, i. e. an episode of retching occurred. No attempt was made to measure the number of retches, because intrathoracic pressure measurement in *S. murinus* have shown that retching movements can occur very rapidly within each episode but are unlikely to be accurately measured by observation alone (Andrews et al., 1996). Animals were used only on one occasion. 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. Emesis induced by motion did not occur outside the period for which the animals were exposed to motion stimulus nor did they vomit prior to the application of motion stimulus.

2.3. Experimental design

Animals received 8-OHDPAT (0.1 mg/kg, i. p. 30 min pre-treatment) or vehicle and were observed for any behavioural change. In another set of experiments, animals were injected with either vehicle, methysergide (1.0 mg/kg, i. p.), WAY-100635 (1.0 mg/kg, i. p., Fletcher et al., 1994), SB269970A (1.0 and 5.0 mg/kg, i. p., Lovell et al., 2000), ondansetron (1.0 mg/kg, i. p.) or GR13808 (0.5 mg/kg, i. p.,) 30 min prior to the administration of 8-OHDPAT (0.1 mg/kg, i.p.) which itself was applied 30 min prior to a motion stimulus.

In other experiments animals received either vehicle, methysergide (1.0 mg/kg, i. p.), WAY-100635 (1.0 mg/kg, i. p.), SB269970A (1.0 and 5.0 mg/kg, i. p.), ondansetron (1.0 mg/kg, i. p.) or GR13808 (0.5 mg/kg, i. p.) 60 min prior to the to a motion stimulus.

In all experiments a motion stimulus of 1.0 Hz and 40 mm amplitude of shaking was used for a 10 min period. The number of the emetic episodes and the latency of onset to the first emetic episode were recorded. All the experimental procedures were in compliance with the UK Animals Scientific Procedures Act 1986.

2.4. Drugs

8-OH-DPAT(8-hydroxy-2(di-*n*-dipropyl-2-aminotetralin hydrobromide (RBI), WAY-100635 (*N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride) (Sigma), SB269970A (*R*)-3-(2-(2-(4-Methyl-piperidin-1-yl)ethyl)-pyrrolidine-1-sulphonyl)-phenol (Glaxosmithkline), ondansetron (Glaxosmithkline) and GR13808 [[1-[2-methylsulphonyl)amino]ethyl-4-piperidinyl] methyl 1-methyl-1 *H*-indole-3-carboxylate] (Almirall) were dissolved in distilled water. All doses of the drugs used were calculated on the basis of the weight of drug base and administered in a volume of 1 ml/100 g body weight.

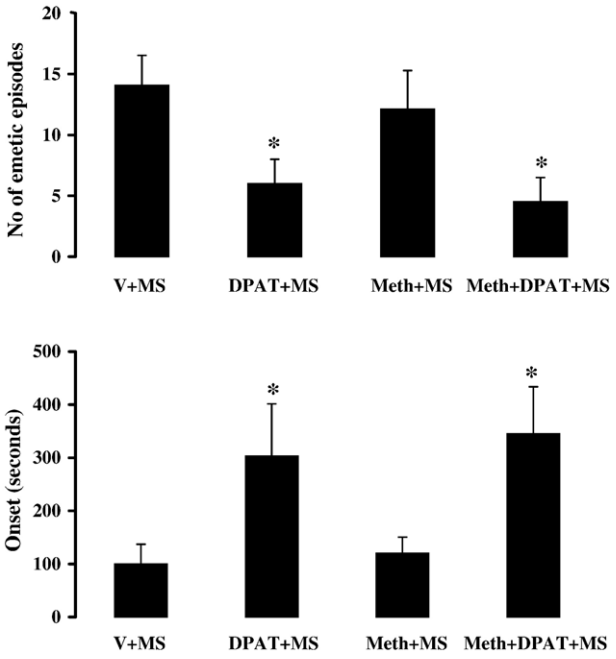

Fig. 3. The effect of 8-OH-DPAT (DPAT, 0.1 mg/kg, i.p, 30 min pre-treatment), methysergide (meth, 1.0 mg/kg, i. p., 60 min pre-treatment), a combination of 8-OHDPAT plus methysergide, or vehicle on motion-induced emesis using male *Suncus murinus*. The number of emetic episodes and the latency of onset to the first emetic episode were measured during 10 min shaking period at a frequency of 1.0 Hz with an amplitude of 40 mm movement are shown. 10 min observation period commenced from the first emetic episode. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean (drug or vehicle)±s.e. mean, $n=6$.; *$p<0.05$ and **$p<0.01$ compared to the vehicle treatment; MS=motion stimulus.

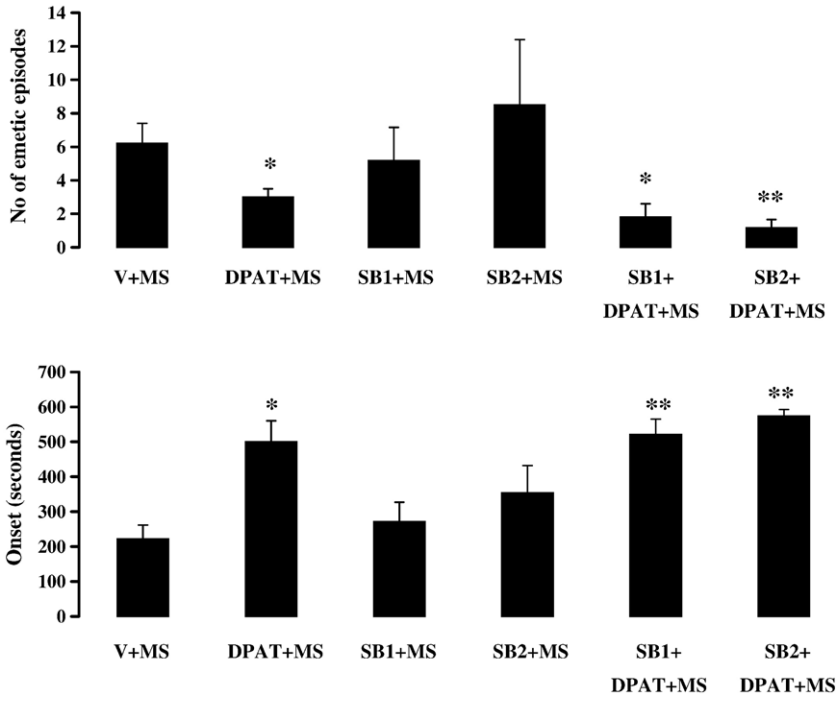

Fig. 4. The effect of 8-OH-DPAT (DPAT, 0.1 mg/kg, i.p, 30 min pre-treatment), SB269970A (SB1, 1.0 mg/kg, SB2, 5.0 mg/kg, i. p., 60 min pre-treatment), a combination of 8-OHDPAT plus SB269970A, or vehicle on motion-induced emesis using female *Suncus murinus*. The number of emetic episodes and the latency of onset to the first emetic episode were measured during 10 min shaking period at a frequency of 1.0 Hz with an amplitude of 40 mm movement are shown. 10 min observation period commenced from the first emetic episode. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean (drug or vehicle)±s.e. mean, $n=6$.; *$p<0.05$ and **$p<0.01$ compared to the vehicle treatment; MS=motion stimulus.

2.5. Statistical analysis

Data were expressed as the mean±s.e. mean and analysed using a paired *t*-test or analysis of variance which was followed by Bonferroni–Dunnett's *t*-test as appropriate, where *$p<0.05$, **$p<0.01$ and ***$p<0.001$ were taken as significant.

3. Results

3.1. Effects of 8-OHDPAT and 5-HT receptor antagonists on motion-induced emesis

The intraperitoneal administration of 8-OHDPAT (0.1 mg/kg) 30 min prior to the motion stimuli significantly ($p<0.001$) reduced the number of emetic episodes as compared to the saline treated animals (Figs. 1 and 2). For example, the number of emetic episodes was reduced from 9.3±2.0 to 2.6±0.5; this was associated with a significant ($p<0.001$) increase in the latency of onset of emesis from 233.2±81.1 s to 489.0±49.3 s (Fig. 2). There were no other overt changes in behaviour of the animals.

The administration of the 5-HT receptor antagonists WAY-100635 (a 5-HT_{1A} receptor antagonist, 1.0 mg/kg) (Figs. 1 and 2), methysergide (a 5-$HT_{1/2/7}$ receptor antagonist, 1.0 mg/kg) (Figs. 1 and 3), SB269970A (a 5-HT_7 receptor antagonist, 1.0 and 5.0 mg/kg) (Figs. 1 and 4), ondansetron (a 5-HT_3 receptor antagonist, 1.0 mg/kg) (Fig. 5) or GR113808 (a 5-HT_4 receptor antagonist, 0.5 mg/kg) (Fig. 5) 60 min prior to the motion stimulus of 1.0 Hz and a 40 mm amplitude of movement, did not inhibit motion-induced emesis. Also, the onset of the emetic episodes was not affected by these antagonists. None of the 5-HT receptor antagonists in their own right induced an overt behavioural change in the animals.

3.2. Effect of 5-HT receptor antagonists on the inhibitory effects of 8-OHDPAT on motion-induced emesis

In these experiments different groups of animals were used to assess possible interactions between 8-OHDPAT and different serotonergic antagonists such as WAY-100635, methysergide, ondansetron, GR113808 and SB269970A. Animals were injected with either vehicle, antagonist alone, or 8-OHDPAT (0.1 mg/kg, i. p.), in the absence or presence of a 30 min pre-treatment with the antagonist, 30 min prior to the application of a motion stimulus. The intraperitoneal administration of 8-OHDPAT at 0.1 mg/kg significantly ($p<0.05$) reduced the number of emetic episodes induced by a subsequent motion stimulus (Fig. 2); 8-OHDPAT also significantly increased the latency of onset of emesis as compared to the control animals ($p<0.05$). Whilst pre-treatment of the animals with WAY-100635 (1.0 mg/kg, i. p.), methysergide (1.0 mg/kg, i. p), ondansetron (1.0 mg/kg, i. p, GR113808 (0.5 mg/kg, i. p) or SB269970A (1.0 and 5.0 mg/kg, i. p.), alone failed to modify motion-induced emesis (see Figs. 1 and 5), they also failed to modify the inhibitory action of 8-OHDPAT on motion sickness when used in a combination with the agonist. (Figs. 2–5).

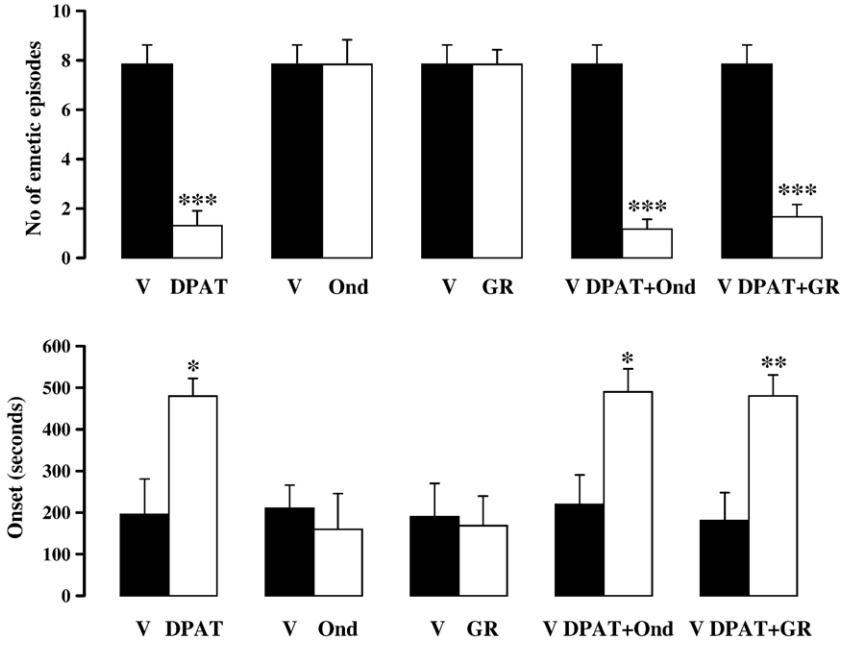

Fig. 5. The effects of 8-OH-DPAT (DPAT, 0.1 mg/kg, i.p, 30 min pre-treatment), ondansetron (ond, 1.0 mg/kg, i. p., 60 min pre-treatment), GR13808 (GR, 0.5 mg/kg, i. p., 60 min pre-treatment), a combination of ondansetron plus 8-OHDPAT, a combination of GR13808 plus 8-OHDPAT, or vehicle on motion-induced emesis using male *Suncus murinus*. The number of emetic episodes and the latency of onset to the first emetic episode were measured during 10 min shaking period at a frequency of 1.0 Hz with an amplitude of 40 mm movement are shown. 10 min observation period commenced from the first emetic episode. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean (drug or vehicle)±s.e. mean, $n=6$.; ***$p<0.01$ compared to the vehicle treatment; MS=motion stimulus.

None of the antagonists produced any other overt behavioural change in the animals. In particular, the animals did not look sedated.

4. Discussion

In the present study we have further confirmed that 8-OH-DPAT attenuates motion-induced emesis in *S. murinus* and is in agreement with previous studies in different species such as the cat, ferret and pigeon (Lucot and Crampton, 1989; Lucot, 1992; Okada et al., 1994; Rudd et al., 1992; Wolf and Leander, 1994). This may suggest the involvement of 5-HT_{1A} receptors in mediating an inhibitory response. In the brain the population of 5-HT_{1A} receptors is divided into somatodendritic autoreceptors with a high sensitivity to pharmacological stimulation (Golzan et al., 1983; Verge et al., 1989) and postsynaptic receptors with lower sensitivity (Pompeiano et al., 1992; Verge et al., 1989). The 5-HT_{1A} receptors located on 5-HT cell bodies function as autoreceptors, whereas 5-HT_{1A} receptors on postsynaptic nerve terminals modulate activity in non-serotonergic neurones (Blier et al., 1993a,b; Chen and Rieth, 1995). 5-HT_{1A} autoreceptor activation decreases 5-HT activity and has an anti-serotonergic effect, whereas 5-HT_{1A} postsynaptic receptor activation would promote serotonergic effects. 8-OHDPAT is a specific and full 5-HT_{1A} receptor agonist, which has been shown to have major impact on behaviour of the animals through the activation of either pre-synaptic, post-synaptic or both receptors (Arvidsson et al., 1981; Berendsen et al., 1989; Ahlenius et al., 1999; Hillegaart et al., 1996; Karamanakos et al., 2004; Mignon and Wolf, 2002).

The vestibular nucleus in the brainstem receives 5-HT-containing projections from the dorsal raphe nucleus, and binding studies have demonstrated the presence of 5-HT_{1A}, 5-HT_{1B} and 5-HT_2 receptors on vestibular nucleus neurones (Zanni et al., 1995). The application of 5-HT to the mouse lateral vestibular nucleus *in vivo* using the iontophoretic technique, has shown in the majority of cases an increase in the neuronal firing rate and in some cases a reduction followed by an increase. The increase in the firing rate is believed to be mediated by 5-HT_2 receptors due to its sensitivity to antagonism by methysergide and ketanserin (Licata et al., 1990). However, activation of 5-HT_{1A} receptors is believed to cause the reduction in the firing rate as this effect could be blocked by the 5-HT_{1A} receptor antagonist NAN-190 (Kishimoto et al., 1994). The decrease in the firing rate was mimicked by 8-OH-DPAT (Licata et al., 1993).

In emesis research it has been suggested that the anti-emetic activity of 8-OH-DPAT may affect a common neuronal effector pathway of the emetic reflex in the central nervous system. If the anti-emetic action of 5-HT_{1A} receptor agonists is due to the stimulation of the pre-synaptic somatodendritic autoreceptors in the raphe nuclei (Vander Maelen et al., 1986; Sprouse and Aghajanian, 1987), then the reduction of 5-HT release could be indicative of the importance of a 5-HT pathway downstream in the emetic reflex. If this hypothesis is correct, then attempts to reduce the neurotransmitter role of 5-HT by depleting the stores of 5-HT should reduce emesis. However, depletion of 5-HT in the cat with the 5-HT synthesis inhibitor parachlorophenylalanine (PCPA) failed to antagonise the emesis induced by motion; indeed, it decreased the latency to the first retch (Lucot, 1992). However, another possibility is the activation of post-synaptic

5-HT_{1A} receptors which may in turn activate an inhibitory mechanism.

Whether 8-OH-DPAT administered peripherally acts on the dorsal raphe nuclei or directly on neurones in the vestibular nucleus remains to be investigated. However, according to the results of the present study, the direct involvement of 5-HT_{1A} receptors in the inhibitory action of 8-OHDPAT seemed to be unlikely as pre-treatment with WAY-100635, a potent and selective 5-HT_{1A} receptor antagonist (Fletcher et al., 1994) failed to reverse the inhibitory action of 8-OHDPAT on motion sickness. If the 5-HT_{1A} receptors were not involved in the mediation of the effects of 8-OHDPAT, could other 5-HT_1 receptors contribute to such a role? This was investigated using methysergide. In such experiments pre-treatment with methysergide, a 5-$HT_{1/2/7}$ receptor antagonist also failed to modify the action of 8-OHDPAT and further confirmed the unlikely involvement of both 5-HT_1 and 5-HT_7 receptors in mediating the inhibitory action of 8-OHDPAT on motion sickness.

As it has been shown that 8-OH-DPAT could act as an agonist at the 5-HT_7 receptor as well as the 5-HT_{1A} receptor (Eglen et al., 1997), attempts were made to investigate further the possibility that 8-OHDPAT induces its inhibitory action through the activation of 5-HT_7 receptors. Although the results from pre-treatment with methysergide provided preliminary evidence for an unlikely involvement of 5-HT_7 receptors, further experiments were carried out using a highly selective and specific 5-HT_7 receptor antagonist. However, pre-treatment with a selective and potent 5-HT_7 receptor antagonist SB269970A (Lovell et al., 2000), failed to modify the action of 8-OHDPAT. This strongly suggests the unlikely involvement of 5-HT_7 receptors in mediating the anti-motion sickness effect of 8-OHDPAT.

It has been proposed that the activation of 5-HT_{1A} receptors could induce an inhibitory action on the 5-HT_2 receptor-mediated response (Darmani et al., 1989). However, it has been shown that DOI, a non-selective 5-HT_2 receptor agonist could attenuate motion sickness (Javid and Naylor, 2002; Baxter et al., 1995). This negates the involvement of 5-HT_2 receptors in the inhibitory action of 8-OHDPAT on motion sickness. Again, further support for this came from the present studies where pre-treatment with methysergide, a non-selective 5-$HT_{1/2/7}$ receptors failed to modify the action of 8-OHDPAT on motion sickness.

The present study also confirmed the unlikely involvement of 5-HT_3 and 5-HT_4 receptors in mediating a response to 8-OHDPAT as pre-treatment with ondansetron and GR13808 failed to reverse the inhibition of motion sickness mediated by 8-OHDPAT.

It can then be hypothesised that the action of 8-OHDPAT on motion sickness is mediated possibly through a non-5-HT receptor system. Indeed previous electrophysiological studies have shown that serotonergic agents act on neuronal nicotinic acetylcholine receptors (Garcia-colunga and Miledi, 1995). Such studies have shown that 8-OHDPAT was the most potent blocker, even more potent than 5-HT, of acetylcholine currents when tested on Xenopus oocytes expressing neuronal nicotinic acetylcholine. It was then concluded that 5-HT and its related agents such as 8-OHDPAT have an important modulatory function at nicotinic acetylcholine receptors in a wide variety of neurones. Moreover, the effects of serotonergic agents on neuronal nicotinic acetylcholine receptors occur at such concentrations that they need to be considered when we try to understand the normal and pathophysiological processes of synaptic transmission, as well as the mode of action of the many serotonergic agents presently used to alleviate brain malfunctions (Garcia-colunga and Miledi, 1995). If 8-OHDPAT induces an inhibition of motion-induced emesis through the cholinergic system then this may not be surprising since an anti-cholinergic agent such as scopolamine is one of the most currently used drugs in reducing motion sickness (Yates et al., 1998; Stott et al., 1989; Ueno et al., 1988; Javid and Naylor, 2002). Further experiments using anti-nicotinic receptor antagonists are required to substantiate the present findings.

In conclusion, the results of this study suggest that the ability of 8-OHDPAT to inhibit motion sickness is not due to the activation of WAY-100635 sensitive site, i.e. 5-HT_{1A} receptors, nor is it via the activation of the SB269970A sensitive site, i.e. 5-HT_7 receptors, or via methysergide sensitive sites, i.e. 5-$HT_{1/2/7}$ receptors, or via ondansetron and GR113808 sensitive sites, i. e. 5-HT_3 and 5-HT_4 receptors. Further experiments are required to explore the site of action of 8-OHDPAT in attenuating motion-induced emesis.

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