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Pharmacology, Biochemistry and Behavior 68 (2001) 761–767

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Opioid receptor involvement in the adaptation to motion sickness in *Suncus murinus*

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Received 12 June 2000; received in revised form 9 January 2001; accepted 9 January 2001

Abstract

The aim of the present study was to investigate an opioid receptor involvement in the adaptation response to motion sickness in *Suncus murinus*. Different groups of animals were treated intraperitoneally with either saline, morphine (0.1 and 1.0 mg/kg), naloxone (1.0, 10.0 and 5.0 mg/kg) or a combination of naloxone plus morphine in the absence or 30 min prior to a horizontal motion stimulus of 1 Hz and 40 mm amplitude. For the study of adaptation, different groups received saline on the first trial, and in subsequent trials (every 2 days) they received either saline, naloxone (1.0 and 10.0 mg/kg, ip) or morphine (0.1 mg/kg, ip) 30 min prior to the motion stimulus. Pretreatment with morphine caused a dose-related reduction in emesis induced by a single challenge to a motion stimulus. Pretreatment with naloxone alone did not induce emesis in its own right nor did it modify emesis induced by a single challenge to a motion stimulus. However, pretreatment with naloxone (5.0 mg/kg, ip) revealed an emetic response to morphine ($P < .001$) (1.0 mg/kg, ip) and antagonised the reduction of motion sickness induced by morphine. In animals that received saline or naloxone (1.0 mg/kg), a motion stimulus inducing emesis decreased the responsiveness of animals to a second and subsequent motion stimulus challenge when applied every 2 days for 11 trials. However, the animals receiving naloxone 10.0 mg/kg prior to the second and subsequent challenges showed no significant reduction in the intensity of emesis compared to the first trial. The data are revealing of an emetic potential of morphine when administered in the presence of a naloxone pretreatment. The administration of naloxone is also revealing of an additional inhibitory opioid system whose activation by endogenous opioid(s) may play a role in the adaptation to motion sickness on repeated challenge in *S. murinus*.

Keywords: Motion sickness; Adaptation; Opioid; *Suncus murinus*

1. Introduction

The symptoms of motion sickness have caused considerable concern in the military and particularly in aviation and during space travel (Lathers et al., 1989; Oman, 1990). The intensity of the symptoms can vary considerably between individuals, and therefore no one pharmacological approach has afforded a reliable control of motion sickness in all individuals (Lathers et al., 1989). For example, the traditional antimotion sickness drugs, such as the muscarinic and histamine H_1 receptor antagonists, do not provide a complete protection in all subjects (Stott, 1992; Yates et al., 1998).

Motion sickness is generally attributed to a mismatch of sensory information from the vestibular, proprioceptive and the visual systems (Yates et al., 1998; Money, 1990). Motion stressors have been shown to act directly on the vestibular apparatus of the inner ear, as the emetic response to motion can be prevented by a bilateral loss of the vestibular nucleus in man (Graybiel, 1964) and in animals (Money and Cheung, 1983; Money and Friedberg, 1964). It has also been shown that a discordant visual stimulus can precipitate sickness in a stationary subject (Money, 1970) and the symptoms of motion sickness decline or even disappear after a repeated exposure to either a moving visual stimulus or a moving subject (Bergstedt, 1965; Graybiel and Knepton, 1978a,b). A repeated experimental exposure to motion stimuli has been shown to reduce the responsiveness to the stimulus especially in air and space travel (Stott, 1990). It has been reported that adaptation occurred in small groups of subjects placed in a rotating

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0091-3057/01/$ – see front matter
PII: S0091-3057(01)00470-1

chair who were required to make a head movement (see Hu et al., 1991). It is also reported that the symptoms of motion sickness decreased when subjects made repeated head movements in a slowly rotating room (Guedry, 1965); when the same subjects made head movements with the room rotating in the opposite direction, symptoms reappeared but at a reduced severity as compared to the original exposure. However, and similarly to the pharmacological attempts to control movement sickness, the desensitisation techniques have not afforded a complete control (Lathers et al., 1989).

Biochemical studies revealed a significant rise in the level of β-endorphin in the plasma of individuals after a rotation motion stimulus (Yasnetsov et al., 1985). It was hypothesised that the change in the level of β-endorphin indicated an involvement of endogenous opioids in the genesis of motion sickness.

The emetic effect of opioid drugs is considered to be due to an action on the chemoreceptor trigger zone as ablation of the area postrema in dogs prevented morphine-induced vomiting (Wang, 1965; Wang and Glaviano, 1954). However, the emetic action of the opiates is complicated further by an antiemetic effect possibly located at a more distal location in the emetic reflex (Michelson, 1992). Furthermore, it has been shown that ambulatory patients receiving opiates are more affected than nonambulatory patients indicating the existence of a vestibular component in the emetic effects mediated by opiates (Jaffe and Martin, 1980). The present study was designed to investigate the role of opiates in motion sickness. In previous studies, we have shown that an emetic response can be reliably induced in *Suncus murinus* (house musk shrew) in response to a horizontal motion stimulus (Javid and Naylor, 1999). Furthermore, it has been shown that animals developed adaptation on a repeated exposure to a motion stimulus (Javid and Naylor, 1999). The aim of the present study was to investigate the role of the opioid system in the adaptation response to motion sickness in *S. murinus*.

2. Methods

2.1. Animals and housing conditions

The experiments were carried out using both adult female (30.5 ± 1.2 g) and adult male (70.1 ± 1.4 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 were covered with sawdust and cleaned twice a week. The animal room was maintained at a humidity between 45% and 50% at 24°C and 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 ($100W \times 150L \times 150H$ mm^3) of six linked units and observed for any behavioural change. After a described time, a horizontal motion stimulus of 1 Hz and a 40-mm amplitude of shaking was commenced for 10 min. Preliminary experiments showed that these parameters were suitable to induce a reliable and reproducible emetic response (Javid and Naylor, 1999). In all experiments, the number of the emetic episodes (vomiting/retching) and the latency of onset to the first emetic episode were 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. All the experiments were conducted at the same time every day.

2.3. Experimental design

In all experiments, a motion stimulus of 1 Hz and 40-mm amplitude of shaking was used for a 10-min period.

Animals received naloxone at 1.0, 5.0, or 10.0 mg/kg (ip), nicotine (5.0 mg/kg), morphine at 0.1 or 1.0 mg/kg (ip) or vehicle alone as a single challenge or 30 min prior to the application of a motion stimulus and were observed for any overt behavioural change. In another set of experiments, animals were injected with either vehicle or naloxone (5.0 mg/kg, ip) 30 min prior to the administration of morphine (0.1 or 1.0 mg/kg, ip) and observed for 90 min; different groups of animals also received naloxone (5.0 mg/kg, ip) 30 min prior to the administration of morphine (0.1 or 1.0 mg/kg, ip), which itself was administered 30 min prior to a motion stimulus.

An assessment of emesis was made over a 30-min observation period following the administration of any drug unless otherwise stated. The doses of drugs were selected on the basis of previous investigations (Selve et al., 1994; Kakimoto et al., 1997) and preliminary studies.

For the study of adaptation, different groups of animals were exposed to a motion stimulus every 2 days with a total number of 6–12 trials, with a 30-min prior treatment with naloxone (1.0 or 10.0 mg/kg, ip), morphine (0.1 or 1.0 mg/kg, ip) or vehicle. Preliminary experiments revealed that adaptation can reliably develop if the animals are exposed to a motion stimulus on more than one occasion in a 1-week period (Javid and Naylor, 1999). All the experimental procedures were in compliance with the UK Animals Scientific Procedures Act 1986.

2.4. Drugs

Naloxone HCl (RBI), morphine HCl (Merck) and nicotine HCl (Sigma) 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.

2.5. Statistical analysis

Data were expressed as the mean ± S.E. mean and analysed using analysis of variance, which was followed by Bonferroni–Dunnett's *t* test as appropriate, where * $P < .05$, ** $P < .01$ and *** $P < .001$ were taken as significant.

3. Results

3.1. The emetic effects of nicotine and the actions of naloxone and morphine when administered alone

The intraperitoneal administration of nicotine at 5.0 mg/kg induced 13.8 ± 3.2 emetic episodes (Fig. 1) with a latency of onset of 209.0 ± 78.7 s. The emetic action of nicotine did not last more than 5 min.

The intraperitoneal administration of either naloxone at doses of 1.0 and 10.0 mg/kg or morphine at a dose of 1.0 mg/kg did not induce emesis in their own right (Fig. 1). There were no other overt changes in behaviour of the animals.

3.2. The emetic activity of morphine in the presence of naloxone

It has been shown that naloxone at 5.0 mg/kg could reveal an emetic response to fentanyl in the cat (Costello and Borison, 1977). Experiments were carried out to investigate the effect of morphine in naloxone-treated animals.

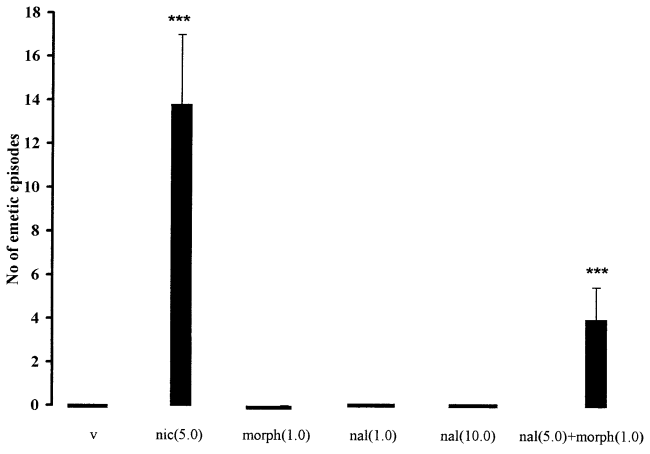

Fig. 1. The emetic potential of nicotine and the effect of morphine and naloxone and their interaction in *S. murinus*. Animals were treated intraperitoneally with either vehicle (v), nicotine (nic, 5.0 mg/kg), morphine (morph, 1.0 mg/kg), naloxone (nal, 1.0 or 10.0 mg/kg) or a combination of morphine (1.0 mg/kg) plus naloxone (5.0 mg/kg, as a 30-min pretreatment). The number of emetic episodes was measured during a 90-min observation period. Each histogram represents the mean ± S.E. mean; $n = 6$. *** $P < .001$ compared to vehicle- and morphine-treated animals.

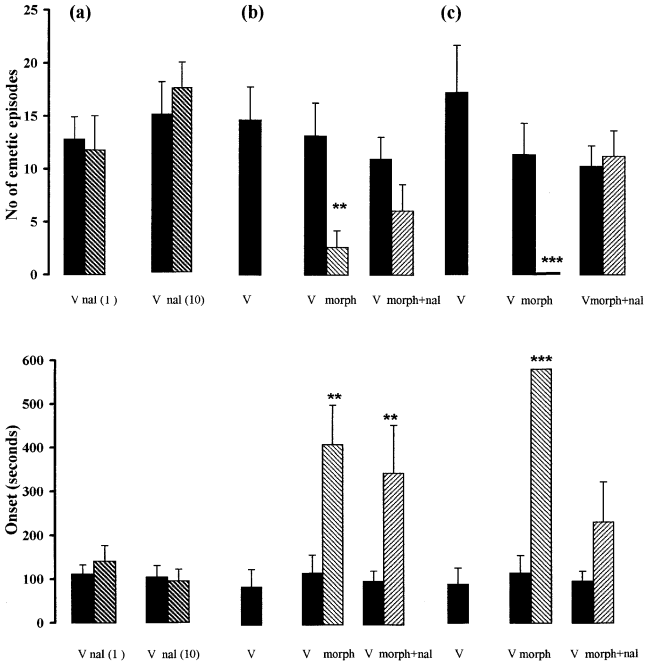

Fig. 2. The effect of a 30-min pretreatment with vehicle, (a) naloxone (nal, 1.0 and 10.0 mg/kg, ip) (b) 0.1 mg/kg morphine and (c) 1.0 mg/kg morphine (ip) or a combination of naloxone (nal, 5.0 mg/kg, ip) plus morphine on the development of motion sickness in *S. murinus*. The number of emetic episodes and the latency of the onset to the first emetic episode to motion stimuli (a single challenge) were measured during a 10-min shaking period at a frequency of 1 Hz with an amplitude of 40-mm movement. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean ± S.E. mean; $n = 6$. ** $P < .01$ and *** $P < .001$ compared to the saline-treated animals.

Animals were injected with naloxone (5.0 mg/kg, ip) 30 min prior to the administration of morphine (1.0 mg/kg, ip) and observed for any behavioural changes over a 90-min period.

While the administration of morphine alone at 1.0 mg/kg (ip) failed to induce emesis or any overt behavioural changes in its own right, morphine (1.0 mg/kg, ip) induced a significant number of emetic episodes of 4.0 ± 1.5 ($P < .001$) in animals pretreated with naloxone (5.0 mg/kg, ip) (Fig. 1).

3.3. The effects of naloxone and morphine and their interaction on emesis induced by a single challenge with a motion stimulus

A 30-min pretreatment with naloxone (1.0 or 10.0 mg/kg) prior to a motion stimulus challenge failed to modify motion-induced emesis (Fig. 2). There were no other overt changes in animal behaviour. However, the 30-min pretreatment with morphine (0.1 and 1.0 mg/kg) significantly ($P < .01$ and $P < .001$) reduced the intensity of emesis induced by a motion stimulus. The dose of morphine 0.1 mg/kg reduced the emesis from a value of 12.5 ± 3.1 emetic episodes in vehicle-treated controls to 2.5 ± 1.5 emetic

episodes ($P<.01$) in the drug-treated group. The latency of onset of emesis was also significantly increased ($P<.01$). The higher dose of morphine 1.0 mg/kg abolished emesis ($P<.001$), the control animals recording 11.6±3.0 emetic episodes (Fig. 2).

In the presence of a 30-min pretreatment with naloxone, the administration of morphine at both 0.1 and 1.0 mg/kg failed to significantly ($P>.05$) reduce motion-induced emesis. The 80% reduction in emesis afforded by morphine alone was reduced to approximately 45% by the naloxone pretreatment. The naloxone treatment was even more effective to antagonise the antiemetic effects of the higher dose of morphine ($P<.001$). The 100% antagonism afforded by 1.0 mg/kg morphine was completely inhibited, the intensity of emetic episodes in control animals (11.1±2.4) being indistinguishable from the naloxone/morphine-treated group (12.0±2.6) (Fig. 2). Similarly, the latency of onset of emesis in the higher dose morphine-treated group was significantly reduced ($P<.001$) (Fig. 2).

3.4. Effect of naloxone on adaptation to motion sickness

Three different groups of animals were challenged with the motion stimulus every 2 days with a total number of 12 trials. All groups received saline on the first trial, and in subsequent trials they were treated with either saline, naloxone 1.0 or 10.0 mg/kg (ip) 30 min prior to the motion stimulus. The three groups of animals that all received saline plus motion stimulus responded similarly with 11.5±2.1, 10.5±2.5 and 8.6±2.5 emetic episodes (Fig. 3).

In the group receiving saline injections prior to the second and subsequent challenges every 2 days, the intensity of emesis was significantly ($P<.01$) reduced to 3.7±1.3 emetic episodes on the second challenge. The onset of emesis was also increased from 100.0+23.4 s in the first trial to 454.0+69.0 s in the second trial ($P<.01$). This reduction in emesis was maintained at a level of approximately 20–25% of the initial trial value for the reminder of the 11 trials (Fig. 3).

In the group receiving 1.0 mg/kg naloxone pretreatment prior to the second and subsequent challenges, there was a trend for an attenuation of the reduction in the intensity of emesis. In the group receiving the higher dose of naloxone (10.0 mg/kg), the attenuation of the reduction in motion stimulus-induced emesis to repeated challenge was significant; the values recorded on the 2nd to the 11th challenge were generally comparable to that recorded on the first challenge. This profile of action was also observed in the latency to onset of emesis (Fig. 3).

On the 12th trial, the naloxone pretreatment was withdrawn from those animals that had received such a pretreatment during the previous 11 trials. These animals then received a saline injection followed by the motion stimulus challenge on the 12th trial; no emesis was recorded from this group (Fig. 3). Conversely, the animals that received the saline injections for 11 trials received a 30-min pretreatment with naloxone before the motion stimulus on the 12th trial. The reduction in emesis afforded by the repeated challenges to motion stimulus was attenuated by the naloxone treatment, the intensity of emesis being comparable to that observed during the first trial (Fig. 3).

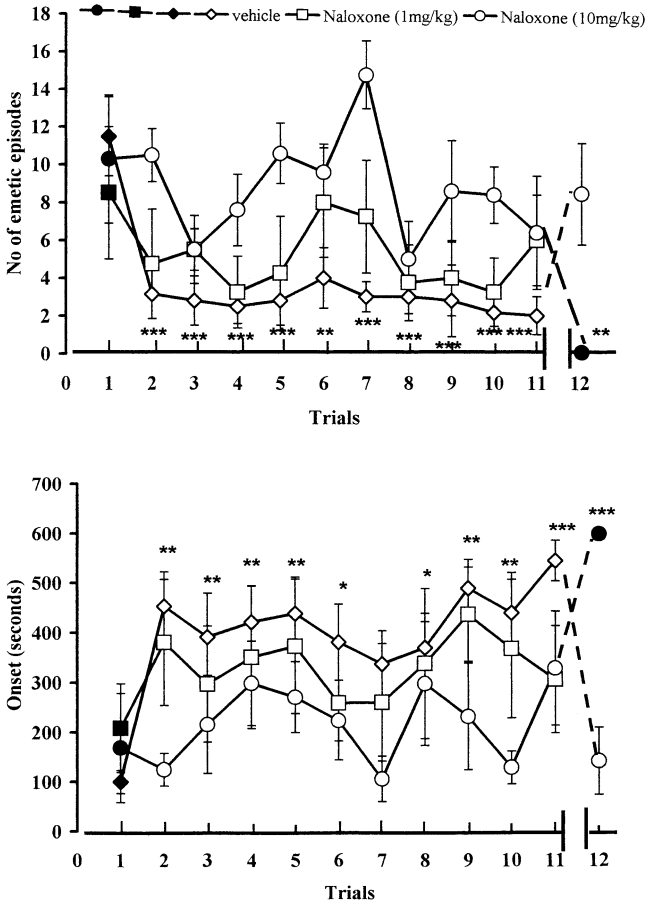

Fig. 3. The effect of naloxone on adaptation to motion sickness in *S. murinus*. In the first trial, all animals received saline 30 min prior to a motion stimulus. On the second and subsequent trials, animals were challenged with either saline, 1.0 or 10.0 mg/kg (ip) naloxone (nal) 30 min prior to a motion stimulus of 1 Hz and 40-mm amplitude of shaking. Experiments were carried out every 2 days with a total number of 11 or 12 trials. On the 12th trial, animals that had previously received naloxone (10.0 mg/kg) were treated with saline, and animals that had received saline were treated with naloxone. The number of emetic episodes and the latency of the onset to the first emetic episode to motion stimuli were measured during a 10-min shaking period on each day of testing. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean±S.E. mean; $n=6$. * $P<.05$, ** $P<.01$ and *** $P<.001$ compared to the vehicle-treated animals in the first trial.

3.5. Effect of morphine on the adaptation to motion sickness

Animals were challenged with the motion stimulus every 2 days for a total number of six trials. All animals initially received saline on the first trial, and in subsequent

trials they were treated with either saline or morphine (0.1 mg/kg, ip) 30 min prior to a motion stimulus. A moderate dose of morphine was chosen to distinguish its inhibitory action from those of desensitisation. Animals that received only saline responded on the first trial with 17.0 ± 2.3 emetic episodes and an onset of 87.4 ± 40.0 s (Fig. 4). On the second trial, the number of emetic episodes was markedly reduced by 67% ($P < .01$) and the intensity of emesis remained at a level of approximately 12–30% of the value recorded during the first trial. This was associated with an increase in the latency of onset ($P < .05$). In the morphine-treated animals, there was a clear trend for the number of emetic episodes to be reduced even further, but such differences did not achieve significant ($P > .05$) or consistent differences to the saline-treated control values (Fig. 4).

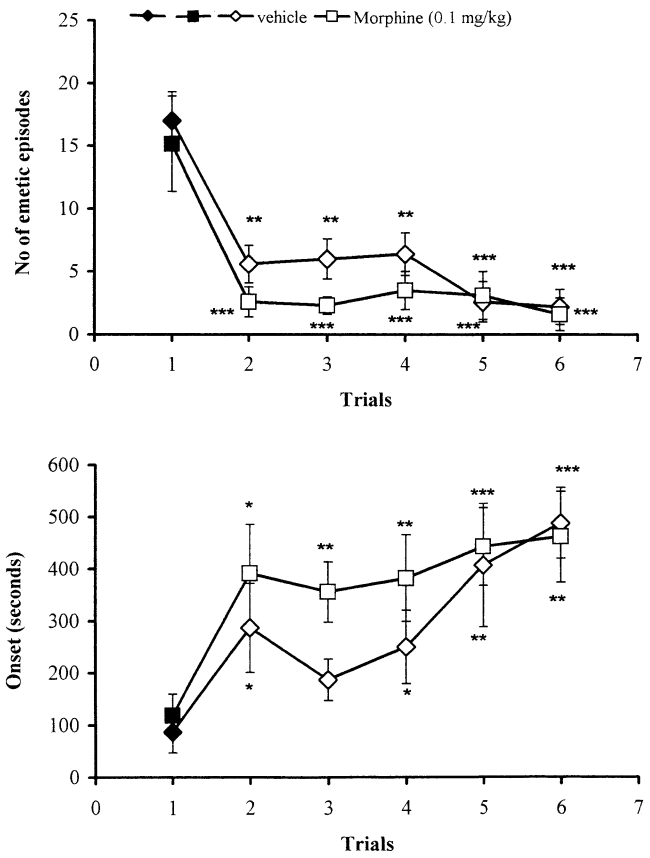

Fig. 4. The effect of morphine on adaptation to motion sickness in *S. murinus*. On the first trial, all animals received saline and subsequently were challenged with a motion stimulus. On the second and subsequent trials, animals were challenged with either saline or morphine (0.1 mg/kg, ip) 30 min prior to the motion stimulus. Experiments were carried out every 2 days with a total number of six trials. The number of emetic episodes and the latency of the onset to the first emetic episode to motion stimuli were measured during a 10-min shaking period on each day of testing at a frequency of 1 Hz with an amplitude of 40-mm movement. If an animal did not develop emesis within 10 min, the latency was considered to be 600 s. Each histogram represents the mean ± S.E. mean; $n = 6$. * $P < .05$, ** $P < .01$ and *** $P < .001$ compared to the vehicle-treated animals in the first trial.

4. Discussion

In the present study, the intensity of retching and vomiting observed in *S. murinus* was comparable to that observed in previous studies (Ueno et al., 1987, 1988; Kaji et al., 1990; Javid and Naylor, 1999) and also to that induced by nicotine, used as a 'control' emetogen that induces a reliable emetic response in *S. murinus* (Rudd and Naylor, 1999; Beleslin and Krstic, 1987). The similarity in the intensity of response to these different stimuli indicates the substantial nature of the motion stimulus response in *S. murinus*.

In the present study, morphine and naloxone were used as tools in an attempt to investigate an opioid receptor involvement in motion sickness and adaptation to the response. Morphine and naloxone were used as an opioid receptor agonist and antagonist, respectively, both compounds having a well-established pharmacology (Strand, 1999; Manzanares et al., 1999). Morphine and related opioid receptor agonists can induce nausea and vomiting in man (Ventafridda, 1984; Watcha and White, 1992) and emesis in the ferret, cat and dog (Barnes et al., 1991; Blancquaert et al., 1986; Costello and Borison, 1977). It was therefore an unusual finding that the administration of morphine to *S. murinus* failed to induce emesis (Selve et al., 1994); this was confirmed in the present study. However, morphine revealed a modest but clear emetic response in all animals when administered as a cotreatment with naloxone.

It is not clear why naloxone should reveal an emetic potential for morphine since they both have high affinity for mu receptors. It seems that naloxone could antagonise or reduce an inhibitory action mediated by morphine at the level of 'vomiting centre'. It is also possible that different opioid receptor subtypes mediate emesis and antiemesis.

In *S. murinus*, naloxone has also revealed the emetic potential to the administration of loperamide in some animals (Selve et al., 1994), and in the ferret is reported to enhance the emetic effects of apomorphine, copper sulphate and s(-)zacopride (Barnes et al., 1991; King and Weatherspoon, 1992). In the cat, a peripheral injection of naloxone also revealed the emetic potential of levorphanol, fentanyl and methadone following their inmtracerebroventricular injection (Costello and Borison, 1977) and exacerbated apomorphine and cytotoxic-induced emesis in man (Rowbotham et al., 1983; Kobrinsky et al., 1988). However, it should be noted that while naloxone does reveal opioid emetogenic potential in *S. murinus*, in the present study, the intensity of response is only some 20% that of a nicotine-induced control response. Similarly, Selve et al (1994) found that only a proportion of animals would display emesis induced by the loperamide/naloxone interaction. These observations indicate that the emetic opioid receptor mechanism may have some sensitivity to naloxone receptor blockade.

The ability to induce emesis may occur within the area postrema (Costello and Borison, 1977; Wang and Glaviano, 1954), whereas the inhibitory effects probably occur downstream in the emetic reflex (Bhargrava et al., 1981). There are

differences between opioid receptor ligands in their affinity for the two sites. For example, fentanyl in the ferret will potently antagonise emesis induced by apomorphine, copper sulphate and cisplatin, and these inhibitory effects are blocked by naloxone (Barnes et al., 1991). Again, the action of levorphanol, fentanyl and methadone to block apomorphine-induced emesis in the cat is inhibited by naloxone (Costello and Borison, 1977). Morphine is also reported to inhibit the emesis induced by apomorphine, nicotine and veratrum in cats (Beleslin et al., 1981; Costello and Borison, 1977) and copper sulphate and *Staphylococcus* enterotoxin in the dog (Blancquaert et al., 1986; Wang and Glaviano, 1954).

In the present study, the antiemetic actions of morphine were extended to the stimulus of movement and confirmed a previous study of Kakimoto et al. (1997) in which motion sickness to an acute challenge in *S. murinus* was completely prevented by a morphine pretreatment. Similar to the drug-induced emetogenic studies, the inhibitory action of morphine on motion sickness was mediated via a naloxone-sensitive mechanism.

In contrast to the drug-induced emesis studies, naloxone treatment alone failed to enhance the emetic effect of an acute challenge to motion sickness. This indicates that unlike a chemically induced emetogenic challenge, the acute challenge with motion sickness in *S. murinus* does not activate an endogenous opioid inhibitory tone to oppose emesis. This may relate to a species difference since naloxone has been shown to enhance the susceptibility to motion sickness in the cat (Crampton and Daunton, 1983) and to enhance the malaise of human subjects exposed to coriolis stimulation in a rotating chair (Allen et al., 1986). In these experiments, the human subjects and, possibly, the animals had previously been exposed to a motion stimulus. This is important since in the present studies, naloxone had a quiet different effect on the consequences to a repeated challenge to motion sickness. A repeated challenge to motion sickness reduced the intensity of the emetic response, which was followed by an increase in the latency of onset of emetic episodes. It has been suggested that a repeated exposure to a stressor increases the levels of endorphins, which may have a role in inhibiting motion sickness by delaying the endpoints to nausea and vomiting (Allen et al., 1986).

Autoradiographic studies have confirmed the existence of opioid binding sites within key structures of the emetic reflex: the area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus nerve, reticular medulla and vestibular nuclei (Barnes et al., 1991; Dashwood et al., 1988; Zanni et al., 1995); however, it is not known where within these structures the enkephalins or endorphins may exert an inhibitory role on emesis. In the rat, enkephalins suppress the increase in the firing rate normally exhibited by medial vestibular nucleus neurones during horizontal rotation or by the application of glutamate (Kawabata et al., 1990). Both of these effects were blocked by naloxone. It has also been reported that medial vestibular nucleus neurones in vitro exhibit an increase in discharge rate in response to the mu and delta opioid receptor agonists morphine and enkephalins, which again were blocked by naloxone (Lin and Carpenter, 1994). It is possible that naloxone may increase the incidence of motion-induced sickness by disinhibiting cell firing in the vestibular nucleus leading to a stimulation of the emetic reflex.

In the present study, naloxone significantly attenuated the decreased emetic response or adaptation to a repeated challenge to a motion stimulus. Briefly, the animals retained their ability to retch and vomit while receiving naloxone. This implicates a role for endogenous opioid(s) and therefore opioid receptors with a protective or adaptive role in the control of motion sickness in *S. murinus*. It remains an interesting observation that the effect of the administration of morphine during the period of repeated challenge to a motion stimulus was inconclusive; the inhibitory effects of morphine could not be distinguished from those of desensitisation.

The hypothesis that endogenous endorphins may be involved in the control of emesis induced by a repeated challenge to motion sickness requires measurement of endocrine changes during motion sickness. This has not been attempted in animals and only limited evidence is available from man. Measurements of growth hormone, cortisol, vasopressin, β-endorphins and other substances have been attempted during chemically induced emesis and also during orbital flight, post flight and during laboratory-induced motion sickness (see Nussey et al., 1988; Kohl, 1987). It has been difficult to dissociate changes induced by stress from those induced by motion sickness (Allen, 1983; Appenzeller et al., 1984). However, Kohl (1987) reported that in subject groups showing a high or low susceptibility to motion sickness, the low-susceptibility group showed demonstrably higher (2–16-fold) levels of β-endorphin (and vasopressin and ACTH) than the high susceptible group.

Finally, in the present study, the lack of an emetic response after withdrawing naloxone in animals that received naloxone and motion stimulus on a repeated basis may suggest a greater sensitivity of the receptors mediating the endogenous opioid inhibitory tone to an additional rise in the level of endogenous opioid inhibitory substances, such as β-endorphin. Indeed, it has been suggested that the sensitivity of receptors increases after a repeated elevation of endorphins (Allen, 1983). Further biochemical experiments are required to compare the levels of endogenous opioid substances before and after the development of adaptation to a motion stimulus.

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