Antiemetic Effects of Morphone on Motion- and Drug-Induced Emesis in Suncus murinus

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Emetic and antiemetic effects of morphine were investigated in Suncus murinus. Subcutaneous (up to 30 mg/kg) or intracerebroventricular administration (50 μg) of morphine failed to cause emesis. However, pretreatment with morphine (s.c.) prevented the emesis induced by nicotine (10 mg/kg, i.p.), copper sulfate (40 mg/kg, p.o.), cisplatin (20 mg/kg, i.p.) and motion stimulus. These results suggest that morphine has only antiemetic potency and may block a common mechanism for the emetic reflex of suncus, because the antiemetic effects of the drug were exerted irrespective of the stimulus.

Key words  emesis; morphine; antiemetic; motion sickness; Suncus

Morphine has been shown to possess biphasic effects on emesis. Its injection induces emesis in dogs and cats. At doses higher than those required to induce emesis, morphine abolishes the own emetic effect and that of nicotine, apomorphine and copper sulfate. These emetic and antiemetic effects of morphine are antagonized by naloxone.

Suncus murinus (a house musk shrew) is a species of insectivore which is considered closer to primates than rodents, lagomorphs or carnivores in the phylogenetic system. We have shown previously that Suncus murinus vomits in response to various emetic drugs and motion stimulus. Suncus murinus is smaller than other experimental animals used for emetic research, and is, therefore, highly suitable for research on motion sickness. The animal is the most sensitive to motion sickness among the experimental mammals that have been studied.

Selve et al. recently, reported that morphine or loperamide causes antiemetic but not emetic effects in Suncus murinus. However, they claimed difficulties in handling the animal and great variation in individual emetic responses. We have frequently experienced that handling of the animal affects emetic responses. Compared to rats or mice, Suncus murinus is sensitive to rough handling and excited animals are generally less sensitive to emetogenic stimuli. Therefore, their results need to be confirmed independently. Furthermore, we have developed a technique for intracerebroventricular injection to Suncus murinus.

In the present study, we investigated emetic effects of systemically or centrally administered morphine in Suncus murinus. Antiemetic effects against motion sickness and various drug (nicotine, copper sulfate, cisplatin)-induced emesis were also studied.

MATERIALS AND METHODS

Experiments were performed on 3 to 6 month-old Suncus murinus of either sex weighing 50–70 g (male) and 30–50 g (female). The animals, originally obtained from the Central Institute for Experimental Animals (Kanagawa), were bred and housed in a temperature controlled room at 24 ± 1°C under a 12 h light/dark cycle with free access to pellet chow and tap water. All experiments were performed between 13:00–18:00.

For injection of substances into the cerebral ventricles, a cannula was inserted stereotaxically into the left lateral ventricle (AP: 9.5, LM: 0.8, DV: 3.4) under anesthesia. Animals were allowed to recover for at least 1 week following the operation. Injection volume for the intracerebroventricular (i.c.v.) administration was 3 μl per animal. The success of i.c.v. injection was confirmed in each animal by postmortem injection of trypan blue solution. The dye diffused instantaneously throughout the ventricles.

When antiemetic effects were studied, morphine or vehicle was injected subcutaneously into the shoulder region of the animals 30 min before application of the emetic stimuli. Emetic stimuli employed were three emetogenic drugs, nicotine (10 mg/kg, i.p.), cisplatin (20 mg/kg, i.p.) and copper sulfate (40 mg/kg, p.o.), and motion. For the experiment on motion sickness, animals were selected for susceptibility to motion sickness at least two weeks before the test of drugs. An interval of more two weeks was allowed to elapse between the two motion tests to avoid any possible habituation to the motion stimulus. When the motion stimulus (amplitude: 40 mm, frequency: 1 Hz, duration: 5 min) was applied, each animal was placed in a transparent cage (W10 × L15 × H12 cm) fixed on a reciprocal shaker (TAITEC R-30 mini; Taiyo Scientific Industrial Co., Ltd., Saitama). After a 10-min acclimation, the motion stimulus was started. The number of vomiting episodes and the latency of the first vomiting were recorded for 5 min (motion) or 120 min (emetogenic drugs).

The compounds except for cisplatin were dissolved in sterile saline. With cisplatin the pH of the saline was adjusted to 4.0 using 0.1 N HCl, and cisplatin was dissolved in this saline by sonication and warming to about 50°C. This solution was cooled to 37°C just prior to administration. Morphine and copper sulfate were administered in a volume of 2 ml/kg, and nicotine and cisplatin in a volume of 10 ml/kg. ID₅₀ values were calculated by Brownlee's up-and-down method.

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RESULTS

Effects of various doses (0.1 to 30 mg/kg, s.c.) of morphine were studied. At the dose of 30 mg/kg morphine induced apparent excitement and increased spontaneous movements. Vocalization and biting of the animal’s own body were often noticed. However, emetic response was not observed during a period of 120 min, nor did the injection of morphine (50, 100 μg/body) into a lateral ventricle did not cause vomiting response (Table 1). To eliminate the possibility that the operation itself affects emetic responses, we used nicotine; both s.c. and i.c.v. injection of this drug induced vomiting. These results are summarized in Table 1.

In investigating the antiemetic effects of morphine, the same emetic stimuli were employed: nicotine, copper sulfate, cisplatin and motion. Pretreatment with morphine (0.02—1.0 mg/kg, s.c.) dose-dependently suppressed emesis caused by all these stimuli (Fig. 1). The ID₅₀ values of morphine against the emesis induced by nicotine, copper sulfate, cisplatin and motion were 0.47, 0.30, 0.60 and 0.12 mg/kg, respectively. These lower doses of morphine did not induce apparent behavioral change.

Nicotine (10 mg/kg, i.p.) elicited vomiting in all animals of the control group with mean latency of 96.4 ± 3.11 s (means ± S.E.M.) and the mean number of vomiting episodes was 11.0 ± 1.64. Nicotine-induced emesis was completely and dose-dependently prevented by treatment with morphine (0.125—1.0 mg/kg, s.c.). Tremors, respiratory excitement and creeping, which lasted for about 60 min, were observed in all animals. Pretreatment of morphine failed to affect these behavioral changes, suggesting that emetic responses are independent of these behaviors.

The mean latency and the number of vomiting episodes for copper sulfate (40 mg/kg, p.o.)-induced emesis of the control group were 3.0 ± 0.32 min and 11.8 ± 0.58 times, respectively. Copper sulfate induced no extraordinary behavior. Morphine (0.11—1.0 mg/kg, s.c.) also blocked emesis caused by copper sulfate.

The administration of cisplatin (20 mg/kg, i.p.) caused emesis in all animals of the control group with mean latency of 32.4 ± 1.63 min, and the number of vomiting episodes was 24.6 ± 1.44. Cisplatin-induced emesis had a

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>No. of suncus vomiting/tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>s.c.</td>
<td>—</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>i.c.v.</td>
<td>—</td>
<td>0/5</td>
</tr>
<tr>
<td>Nicotine</td>
<td>s.c.</td>
<td>10 mg/kg</td>
<td>3/3</td>
</tr>
<tr>
<td></td>
<td>i.c.v.</td>
<td>50 μg/body</td>
<td>4/4</td>
</tr>
<tr>
<td>Morphine</td>
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<td>30 mg/kg</td>
<td>0/5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>i.c.v.</td>
<td>50 μg/body</td>
<td>0/3</td>
</tr>
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<td></td>
<td>100</td>
<td>0/2</td>
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Table 1. Emetic Responses to s.c. and i.c.v. Administration of Several Drugs in Suncus murinus

![Fig. 1](image)  
Fig. 1. Influence of s.c. Injection of Morphine on the Emetis Induced by Nicotine (A: 10 mg/kg, i.p.), Copper Sulfate (B: 40 mg/kg, p.o.), Cisplatin (C: 20 mg/kg, i.p.) and Motion (D) in Suncus  
Morphine was administered 30 min prior to emetic stimuli. Values for the number of vomiting episodes and the period to the first vomit are means ± S.E.M. The ratio of responders indicates the number of vomiting animals/the number of animals tested. The number of animals was 5. *p<0.05, **p<0.01 significantly different from control group (Duncan's multiple range test).
longer latency than other emetic stimuli, and the emesis occurred periodically as reported previously; there was otherwise no remarkable behavioral change in the animals. Morphine (0.36—1.0 mg/kg, s.c.) dose-dependently inhibited cisplatin-induced vomiting also.

The motion stimulus caused emesis in control animals within a few minutes. The mean latency and the number of vomiting episodes were 70.6 ± 19.0 s and 8.4 ± 0.81 times, respectively. Motion-induced emesis was completely and dose-dependently blocked by morphine (0.02—0.5 mg/kg, s.c.).

**DISCUSSION**

The variability of opioid-mediated emesis has long been studied using laboratory animals like dogs, cats or ferrets. There is fairly general agreement that morphine is emetic in low doses and is antiemetic in high doses. These effects of morphine are antagonized by naloxone, indicating that they are mediated by opioid receptors. Selve et al. also showed that the antiemetic effect of morphine is blocked by naloxone in *S. m. marinus*.

In the present study, however, morphine did not cause emesis in *S. m. marinus*, confirming the previous report by Selve et al. We employed a wider dose range of 0.02 to 30 mg/kg. At a dose as high as 30 mg/kg, ordinary vocalization and biting behavior was observed; however, at doses below 5 mg/kg the animals behaved quite normally. Salivation and scrubbing the floor with the jaw were unusual signs preceding vomiting, but this behavior was not observed, suggesting that morphine did not induce nausea either. Direct i.c.v. injection of morphine also failed to evoke emesis. Therefore, it is clear that an emetic response to morphine is lacking in *S. m. marinus*.

Wang and Glaviano found that morphine failed to evoke emesis in area postrema ablated dogs. Similarly, Costello and Borison reported that ablation of the area postrema eliminated the emetic effect of morphine in cats. They also showed that the antiemetic effect of morphine was not abolished by ablation of the area postrema. These results suggest that morphine elicits emesis by stimulating the chemoreceptor trigger zone (CTZ) of the area postrema, whereas the antiemetic effect is through inhibition of the vomiting center.

One conceivable explanation for the lack of emetogenic potency of morphine in *S. m. marinus* is the functional and structural difference of the area postrema, or CTZ. The presence of species variations in emetic responses is well documented. Apomorphine is thought to cause emesis by stimulating of dopamine receptors in this area. The lack of apomorphine-induced emesis in *S. m. marinus* may indicate different distribution of receptors in the area postrema. *Solex anguillatus* is also insensitive to apomorphine in terms of vomiting. However, more selective D₁ and D₂ receptor agonists caused emesis in *S. m. marinus*, suggesting that, besides stimulating dopamine receptors, apomorphine has an additional effect of masking emetogenic action. It is still possible that density or subtype distribution of opioid receptors in the CTZ of *S. m. marinus* is different from to other animal models. Opiate δ-receptors are believed to mediate the emetic effect of opioids, and μ- and/or κ-receptors mediate their antiemetic effect. Further experiments using drugs more specific to the receptor subtype are necessary.

In the present study, we showed that morphine is a potent general antiemetic. The drug completely blocked four emetic stimuli thought to be mediated via different mechanisms: nicotine acts both on the central and peripheral nervous systems; copper sulfate is believed to stimulate the mucous membrane of the stomach; cisplatin mainly stimulates serotonergic 5-HT₂ receptors located on the vagus afferents; the vestibule and semicircular canals participate in motion-induced emesis. Therefore, these results suggest that the antiemetic effect of morphine is caused by an action on a common neural pathway(s) of the emetic reflex in the central nervous system, such as the so-called “vomiting center”. The vomiting center is considered to be a function of a number of separate effector nuclei: the nucleus tractus solitarius, the reticular formation and the dorsal vagal motor nucleus. Since opioid μ-receptors are densely located in these areas, the antiemetic potency of morphine may reflect the action at the μ-receptor in the systems.

We have shown previously that serotonergic 5-HT₁A and 5-HT₂ receptor agonists completely block emetic responses caused by various stimuli, and more recently it was shown that blockade of tachykinin NK₁ receptor prevents emetic responses in various animal models including *S. m. marinus*. Therefore, clarification of the contributions of these opiate, serotonin and tachykinin receptors in emetic reflex pathways is of interest.

In conclusion, the results here suggest that morphine is a potent and general antiemetic agent with a wide spectrum to suppress motion- and drug-induced emesis, and that *S. m. marinus* is a good pharmacological model for the analysis of the opiate receptor-mediated anti-emetic reflex.

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