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Differential action of domperidone to modify emesis and behaviour induced by apomorphine in the ferret

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Abstract

The action of domperidone (1 mg/kg, i.p.) on spontaneous behaviour and the emesis and behavioural change induced by apomorphine (0.25 mg/kg, s.c.) were studied in the ferret. Domperidone was inactive to modify spontaneous behaviour but apomorphine-induced emesis and increased locomotor activity (distance travelled and velocity of movement; $P<0.05$); the emesis, but not the modification of locomotor activity was antagonized significantly ($P<0.01$) by domperidone. However, apomorphine did not modify significantly other behavioural measures (i.e. lip licking, rearing, burrowing, backward walking, curling-up activity, or defecatory frequency; $P>0.05$). The action of apomorphine to modify behaviour and its interaction with domperidone in this species is discussed in relation to animal models of nausea.

Keywords: Apomorphine; Domperidone; Nausea; Emesis; Dopamine

1. Introduction

The ferret is frequently used in anti-emetic research and has been integral to the discovery of the anti-emetic action of the 5-hydroxytryptamine$_3$ (5-HT$_3$; e.g. ondansetron and granisetron) and tachykinin NK$_1$ receptor antagonists (e.g. aprepitant) (see Andrews and Rudd, 2004; Naylor and Rudd, 1996). However, it is considered relatively straightforward to assess if a compound has an activity to reduce retching and emesis, but more problematic to determine a reduction of nausea, since animals are unable to communicate directly their emotional status (Fox, 1992).

A number of investigations using emetic treatments (e.g. cisplatin, radiation) and ferrets have suggested that several drug-induced behaviours may be analogous to nausea (e.g. increases in the incidence of 'lip licking', 'backward walking' and 'burrowing', or decreases in locomotor activity (Bermudez et al., 1988; King and Landauer, 1990); some investigators have collated and/or transformed the behaviours into a point system, to assess the effectiveness of anti-emetic agents (Gonsalves et al., 1996; Hawthorn and Cunningham, 1990).

Unfortunately, a potential weakness with most of the studies conducted to date in the ferret is that the action of anti-emetic drugs has not been thoroughly investigated alone for their capacity to modify normal behaviour, before progressing to evaluate their action on emetogen-induced behavioural changes. We recently addressed this by carefully evaluating the normal repertoire of the ferret before anti-emetic or emetic challenge (Lau et al., 2004). Using this approach, we observed a differential action of the tackykinin NK$_1$ receptor antagonist, CP-99,994 ((+)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine), to paradoxically reduce lip licking and spontaneous locomotor activity, whilst ondansetron was inactive. Further, we were not able to demonstrate specific changes in behaviour induced by cisplatin (apart from emesis). We concluded that none of the behaviours that we measured could be used as an index of 'nausea behaviour' (Lau et al., 2004).

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We considered that cisplatin may have a complicated mechanism (direct and/or indirect?) to induce emesis that potentially involves activation of abdominal vagal afferents and the area postrema and associated nuclei in the brain (Andrews et al., 1988; Naylor and Rudd, 1996); there may also be non-specific effects, or toxicity (e.g. on neurones, see Scott et al., 1995), that could complicate a meaningful interpretation of data. In the present studies, therefore, we chose to investigate the behavioural consequences of apomorphine, an emetogen considered to act directly at the area postrema via dopamine receptors (Andrews et al., 2001, 1990; Higgins et al., 1989); a dose of 0.25 mg/kg, s.c. was selected based on our previous studies showing a robust emetic response (Costal et al., 1990). Domperidone was studied as an agent known to prevent nausea and emesis in man induced by dopamine receptor agonists (Barone, 1999; Muguet et al., 1995), with the advantage that it does not easily penetrate the blood brain barrier to cause undesirable side effects (Niemegeers, 1982; Wauquier et al., 1981); the dose of 1 mg/kg, i.p. used in the present studies was extrapolated from our preliminary studies showing inhibition of apomorphine-induced emesis in the ferret (Rudd, unpublished data) and others showing activity against apomorphine in the dog (Niemegeers et al., 1980; Niemegeers, 1982).

2. Methods

2.1. Animals

Castrated male ferrets weighing between 1.0–2.5 kg were used. They were obtained from a reputable breeder in New Zealand and were housed in a temperature-controlled room (24±1 °C) in the Laboratory Animal Services Centre, The Chinese University of Hong Kong. Artificial lighting was provided between 0600 and 1800 h, with humidity being maintained at 50±5%. Water and dry pelleted cat chow (Feline Diet 5003, PMI® Feeds, St. Louis, USA) was available ad libitum. All experiments were conducted under the licence provided by the Government of the Hong Kong SAR and the Animal Research Ethics Committee, The Chinese University of Hong Kong.

2.2. Behavioural observation

Ferrets were transferred to opaque Perspex observation chambers (50 × 50 × 50 cm) illuminated to 15±1 Lux. The image of each animal was captured by an overhead camera (Panasonic WV-CP460/P; Panasonic, Yokahoma, Japan) and the analog–video signal was converted to digital by a frame grabber and calculations of movement made using EthoVision Color Pro software (Version 2.3; Noldus Information Technology, Costerweg, Netherlands) running on a personal computer. Using this approach it was possible to determine the spontaneous movement (total distance travelled and velocity) of each animal. Other behaviours were recorded manually and included episodes of retching and/or vomiting, lip licking, burrowing, rearing, curling-up, backward walking, and defecation. The experiment started when the animals were introduced into the observation chamber. However, in order to reduce artifacts that might be induced by exposing the animals to a novel environment, the ferrets were first allowed to habituate in a Perspex box (50 × 50 × 50 cm), that was identical to the experiment observation chamber. This was done for 2 h periods on 3 consecutive days, prior to the start of the experiment. On the day of the experiment, animals were also allowed a 30 min habituation period in the Perspex box before drug administration, where behavioural data were collected (see below).

2.3. Administration of drugs

Domperidone (1 mg/kg; Sigma-Aldrich, St. Louis, USA), or its vehicle (0.5 ml/kg dimethylsulphoxide; Sigma-Aldrich, St. Louis, USA), was administered intraperitoneally at time=0 ($t=0$). Animal behaviour was then recorded for 30 min before the subcutaneous injection of apomorphine hydrochloride (0.25 mg/kg; Sigma-Aldrich, St. Louis, USA), or vehicle (0.5 ml/kg, 0.01% (w/v) sodium metabisulphite; Riedel-de Haën, Germany). Animals were then observed further for 60 min. Doses are expressed as the free base.

2.4. Data analysis

Prior to the investigation, we had collected behavioural data from 72 normal ferrets (Rudd, unpublished data). Analysis of this historical data, and data from the habituation period of the present studies, was done using the Kolmogorov–Smirnov test (GraphPad Prism version 4.0, GraphPad Software, San Diego, California, USA). This was necessary to determine which behaviours were not Gaussian, and in such cases, subsequent non-parametric statistical methods were used when testing hypotheses. Thus, for spontaneous locomotor activity, the distance travelled and velocity data were analyzed using a Students *t*-test (GraphPad Prism version 4.0, GraphPad Software, San Diego, California, USA), or one-way analysis of variance (ANOVA) followed by pre-planned contrasts of specified means (SuperANOVA version 1.11, Abacus Concepts Inc., Berkeley, California, USA); the distance travelled data were Log_{10} transformed prior to the analysis. The total lip licking, curling-up, burrowing, backward walking, rearing and defecatory episodes and latency data were analyzed using a Mann Whitney *U* test, or Kruskal–Wallis test followed by a Dunn's multiple comparison test (GraphPad Prism version 4.0, GraphPad Software, San Diego, California, USA). When an animal failed to retch or vomit, a latency value equal to the test

period observation time (i.e. 60 min) was used to perform the statistical analysis. The retching+vomiting data were only analyzed during the test period (i.e. following apomorphine, or vehicle) and differences between treatment groups were assessed by a one-way ANOVA followed by pre-planned contrasts of specified means (SuperANOVA version 1.11, Abacus Concepts Inc., Berkeley, California, USA). A potential correlation of behaviours to each other was investigated using a Pearson or Spearman's analysis, as appropriate (GraphPad Prism version 4.0, GraphPad Software, San Diego, California, USA). The observer and person responsible for analyzing the data were blind to the treatments. Results are expressed as the mean±S.E.M. unless otherwise stated. In all cases, differences between treatment groups were considered significant when $P<0.05$.

3. Results

3.1. Basal activity of the ferrets during the habituation period

The data from all the 24 animals used in the study were collated together to provide a profile of the normal repertoire of the ferret under laboratory conditions. During the 30 min habituation period, animals travelled 60.0±4.0 m with a velocity of 3.3±0.2 cm/s and exhibited 1.4±0.3 episodes of backward walking (14 out of 24 animals had at least 1 episode), 2.5±1.5 episodes of burrowing (all animals exhibited at least 2 episodes), and 14.1±1.6 episodes of vertical rears (all animals exhibited at least 4 episodes). There was approximately 1.7±0.3 episodes where they curled-up (at least 17 out of 24 animals had 1 episode or more) and the ferrets also exhibited 8.5±1.4 episodes of lip licking (all animals had at least 2 or more episodes) and 0.1±0.1 episodes of defecation (only 3 out of 24 animals had 1 episode). No retching or vomiting was observed during the habituation period ($n=24$). The distance travelled by the animals was only positively correlated to their velocity of movement ($r=0.98$, $P<0.0001$) and there was also a positive relationship between lip licking behaviour and rearing activity ($r=0.47$, $P<0.05$); there was no relationship between the other behaviours ($P>0.05$).

3.2. Effect of domperidone and/or apomorphine on ferret behaviour

The control animals were generally less active during this period compared to the initial habituation period (e.g. the distance travelled and number of vertical rears recorded appeared to be reduced by 31% and 51%, respectively; see Table 1). Domperidone failed to modify the behaviour of the ferret recorded prior to apomorphine administration ($P>0.05$; see Table 1), and the administration of domperidone, or vehicle, was not associated with retching or vomiting ($n=12$). However, there was no correlation between lip licking and rearing activity (as reported above) during the pretreatment period in the dimethylsulphoxide ($P>0.05$) or domperidone ($P>0.05$) treated animals, whereas distance travelled was still highly correlated to velocity in both treatment groups (dimethylsulphoxide treated: $r=0.97$, $P<0.0001$; domperidone treated: $r=0.98$, $P<0.0001$).

Table 1
Effect of domperidone on the behavioural repertoire of the ferret

Parameter	Vehicle	Incidence (%)	Domperidone	Incidence (%)
Distance (m)	41.2±4.8	NA	38.7±4.6	NA
Velocity (cm/s)	2.3±0.3	NA	2.2±0.3	NA
Lip licking	6.3±1.6	83.3	4.3±1.4	66.7
Backward walking	4.5±1.5	66.7	0.9±0.4	66.7
Burrows	0.1±0.1	8.3	0.9±0.9	16.7
Rears	6.9±3.4	50.0	8.1±3.9	83.8
Curl-ups	0.9±0.3	50.0	0.8±0.4	41.7
Defecations	0.2±0.1	16.7	0.7±0.2	58.3

Data represent the mean±S.E.M. of 12 observations. There were no significant differences between the animals scheduled to receive vehicle (dimethylsulphoxide, 0.5 ml/kg) or domperidone (1 mg/kg, i.p.) ($P>0.05$, Students t test, or Mann Whitney U test, as appropriate).

Apomorphine increased significantly locomotor activity and the velocity of motion of the animals by 139.5% ($P<0.05$) and 139.1% ($P<0.01$) respectively, without affecting significantly burrowing, rearing, backward walking, defecatory activity, lip licking, or curling-up activity ($P>0.05$; Fig. 1). It is interesting that apomorphine appeared to increase the lip licking, backward walking and rearing activity in 3 out of 6 animals. However, when the animals were ranked according to their responsiveness, there was no apparent relationship between the data (i.e. the animal with the highest lip licking activity was not ranked highest for backward walking or rearing; also see below). Apomorphine also induced approximately 40 retches+vomits following a latency of approximately 2 min (Fig. 1). Domperidone was active to antagonize significantly the apomorphine-induced retching+vomiting response ($P<0.01$; protecting 4 out of 6 animals and delaying the onset of emesis, $P<0.05$), but had no action to modify the apomorphine-induced change in locomotor (distance travelled and velocity of movement) activity ($P>0.05$). In the animals that had received apomorphine alone, there was no correlation of retching+vomiting activity with the distance travelled, velocity of movement, lip licking activity, backward walking, burrowing, rearing, curling-up activity, or defecatory frequency ($P>0.05$, $n=6$).

4. Discussion

The basal activity of the animals in the present study was fairly consistent with our previous studies that examined the consequence of cisplatin treatment and its interaction with ondansetron and CP-99,994 (Lau et al., 2004). However, in the present studies we examined the behaviour in more detail, revealing a correlation between the distance travelled of the animal with its velocity, and a correlation between rearing and lip licking activity; a retrospective analysis of data from our previous studies (Lau et al., 2004) also showed these correlations. Whilst a correlation between distance travelled and velocity was expected, the correlation between rearing and lip licking was not and remains unexplained. However, in the subsequent 'drug pretreatment' period, lip licking was not correlated to rearing activity. It is possible, therefore, that dimethylsulphoxide

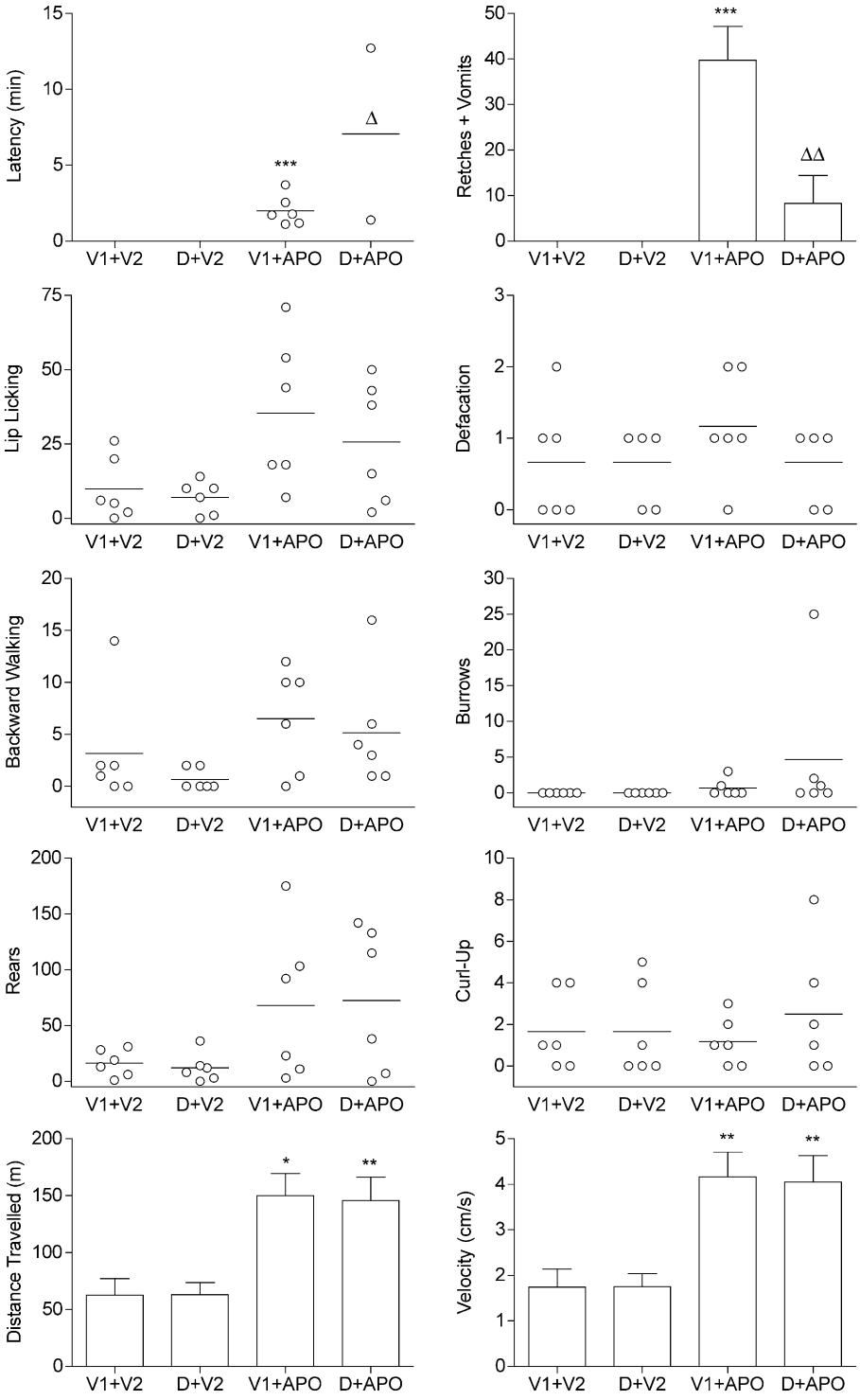

Fig. 1. Behavioural repertoire of the ferret following treatment with domperidone and/or apomorphine. Domperidone (D: 1 mg/kg, i.p.), or vehicle (V1: dimethylsulphoxide, 0.5 ml/kg, i.p.), was administered 30 min prior to the injection of apomorphine (APO: 0.25 mg/kg, s.c.) or vehicle (V2: 0.01% (w/v) sodium metabisulphite, 0.5 ml/kg, s.c.). Data were collected for 60 min post-apomorphine or V2 administration and results represent the mean ± S.E.M. of 6 determinations. Significant differences relative to V1 + V2 treated animals are indicated as $^{*}P<0.05$ $^{**}P<0.01$, or $^{***}P<0.001$; significant differences relative to V1 + Apo treated animals are indicated as $^{\Delta}P<0.05$, or $^{\Delta\Delta}P<0.01$ (one-way ANOVA followed by pre-planed contrasts of specified means, or Kruskal–Wallis test followed by Dunn's multiple comparison tests, as appropriate).

has actions in its own right to uncouple this relationship. Certainly, dimethylsulphoxide is a useful agent to solubilize drugs, but it is not inert, and has a plethora of effects (e.g. analgesic, anti-inflammatory actions and a capacity to cause vasodilation and neuromuscular block; Swanson, 1985) that may be envisaged to disrupt behaviour.

Our studies clearly demonstrated the ability of apomorphine to induce emesis and increase spontaneous locomotor including distance travelled and velocity of movement; the latter two behaviours were highly correlated and were not uncoupled by domperidone. Domperidone antagonized apomorphine-induced retching and emesis, which is consistent with previous reports (Miner et al., 1987). The differential profile of domperidone is probably explained by its distribution characteristics and by the relative sites of action of apomorphine to modify behaviour and induce emesis. Thus, apomorphine probably penetrates the blood brain barrier to the limbic system and activates dopamine receptors (D_1 and D_2) to increase locomotor activity (Mittleman et al., 1993; Van Ree et al., 1989), with a concurrent activation of dopamine (D_2) receptors in the area postrema to induce emesis (see above for references). The apomorphine-induced increase in locomotor activity was resistant to domperidone because this dopamine receptor antagonist only poorly penetrates the blood brain barrier (Ferretti et al., 1983). However, domperidone is able to antagonize emesis, since the area postrema has a leaky blood brain barrier permitting its access. Indeed, previous studies in the dog have shown that doses of domperidone that prevent apomorphine-induced emesis are approximately 300 times lower than required to prevent apomorphine-induced stereotypy, whilst brain penetrant dopamine receptor antagonists, such as metoclopramide, are approximately equipotent (Niemegeers, 1982; Niemegeers et al., 1980). Indeed Gylys et al. (1988) briefly mentions without quantifying the data that metoclopramide (used at anti-emetic doses) prevents apomorphine-induced-stereotypy (head and upper body motion) in ferrets.

In our previous studies, cisplatin did not modify behaviour (including backward walking, or burrowing; see below), apart from inducing emesis, although there was a trend for a reduction of locomotor activity. A general reduction of locomotor activity in the ferret during emesis has been reported following treatment with radiation (King and Landauer, 1990), whilst in other studies, specific locomotor behaviours such as backward walking and burrowing are reported to be increased after cisplatin (Bermudez et al., 1988), and following an emetic dose of loperamide, lip licking and wet dog shake behaviour are increased (Zaman et al., 2000). From the literature, and our studies, it seems that different stimuli may have a common ability to provoke retching and emesis, but their action on other behaviours may be diverse, probably because they affect other systems which are not necessarily directly related to nausea and/or emesis control.

It should be noted that whilst our studies clearly revealed the action of apomorphine to induce emesis in the ferret and to produce an increase in generalized locomotor activity, we did not detect significant increases in other behaviours such as lip licking and backward walking. This is may be because of variability in the individual animal data. For example, in some animals, apomorphine appeared to induce increases in behaviours, whilst having no apparent action in others. It is not known if increasing the number of animals used would have revealed significant changes, but we considered this inappropriate given that the group size was more than sufficient to detect changes in emetic patterns. Moreover, it is also important to note that the behaviours that we measured were all expressed as part of the normal behavioural repertoire of the ferret, and we did not see the expression of a 'novel' behaviour in response to treatment with apomorphine. Certainly, none of the behaviours that we measured were correlated to retching and emesis (see above), but we must still be cautious since it is possible that retching and emesis are not directly related to nausea status, since nausea and emesis can occur independently of each other, or could have different control mechanisms (Andrews and Rudd, 2004; Del Favero et al., 1992; Reid et al., 2000).

In conclusion, the emetic and anti-emetic action of drugs in animals is relatively easy to assess. However, assessing nausea by relying solely on behavioural changes remains a significant challenge. Further studies are required to understand the mechanisms controlling nausea and its detection to facilitate a more rational approach to anti-emetic drug discovery.

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