Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 477 (2003) 247–251
www.elsevier.com/locate/ejphar

Action of prostanoids on the emetic reflex of *Suncus murinus* (the house musk shrew)

Kelvin K.W. Kan, Robert L. Jones, Man-P. Ngan, John A. Rudd*

Department of Pharmacology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China

Received 5 August 2003; accepted 12 August 2003

Abstract

Several prostanoids were investigated for a potential to induce emesis in *Suncus murinus*. The TP receptor agonist 11α,9α-epoxymethano-15*S*-hydroxyprosta-5*Z*,13*E*-dienoic acid (U46619) induced emesis at doses as low as 3 μg/kg, i.p. but the DP receptor agonist 5-(6-Carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin (BW245C) was approximately 1000 times less potent. The emetic action of U46619 (300 μg/kg, i.p.) was antagonized significantly by the TP receptor antagonist, vapiprost ($P < 0.05$). EP (prostaglandin E_2, 17-phenyl-ω-trinor prostaglandin E_2, misoprostol and sulprostone), FP (prostaglandin $F_{2\alpha}$ and fluprostenol) and IP (iloprost and cicaprost) receptor agonists failed to induce consistent emesis at doses up to 300–1000 μg/kg, i.p. Fluprostenol reduced nicotine (5 mg/kg, s.c.)-but not copper sulphate (120 mg/kg, intragastric)-induced emesis; the other inconsistently emetic prostanoids were inactive to modify drug-induced emesis. The results indicate an involvement of TP and possibly DP and FP receptors in the emetic reflex of *S. murinus*.

Keywords: Emesis; Emetic; Anti-emetic; Prostanoid; (*Suncus murinus*)

1. Introduction

The rank order of inhibitory potency of glucocorticoids to antagonize cisplatin-induced emesis in the ferret may suggest that inflammatory mediators, or components of the immune system, are involved in the emetic reflex (Sam et al., 2001). One such group of mediators could be the prostaglandins, given the reported anti-emetic activity of cyclo-oxygenase inhibitors against chemotherapy/radiotherapy treatment (Carpenter et al., 1986; Girod et al., 2002). Certainly, the use of prostaglandin E_2 and prostaglandin $F_{2\alpha}$ and their analogues is associated with emesis (Lauersen and Wilson, 1977; Ylikorkala and Jarvinen, 1975) and prostaglandins may also be involved in the emesis induced by bacterial infection (Jett et al., 1990), ethanol ingestion (Kaivola et al., 1983) and changes in metabolism (Sato et al., 1988).

There are five major types of prostanoid receptor (EP, DP, FP, IP and TP; see Coleman et al., 1994). Our recent studies in the ferret indicate that EP, DP, and TP prostanoid receptors are involved in the emetic reflex, although a subtle role for IP receptors could not be discounted (Kan et al., 2002). These receptors may represent new targets for anti-emetic drug development and further studies appear warranted.

In the present studies, therefore, we have used *Suncus murinus* to investigate the emetic potential of a range of prostanoid receptor agonists. 5-(6-Carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin (BW245C) was used as an agonist with selectivity for DP receptors. Prostaglandin E_2 activates the four EP receptor subtypes, while several of its analogues show some selectivity: 17-phenyl-ω-trinor prostaglandin E_2 ($EP_1 > EP_3 > EP_4 > EP_2$), misoprostol ($EP_3 = EP_2 > EP_4 > EP_1$) and sulprostone ($EP_3 > EP_1 \gg EP_2 = EP_4$). Prostaglandin $F_{2\alpha}$ and fluprostenol were used as FP receptor selective agonists and iloprost and cicaprost were used as relatively selective IP receptor agonists (see Abramovitz et al., 2000; Coleman et al., 1994; Kiriyama et al., 1997 for prostanoid receptor specificity data). To complete the investigation, 11α,9α-epoxymethano-15*S*-hydroxy-prosta-5*Z*,13*E*-dienoic acid (U46619) was selected as a potent agonist for TP receptors (Coleman et al., 1994). All prostanoids were initially tested for their ability to induce emesis. However, the prostanoids that failed to induce emesis, or that inconsistently induced emesis, were subse-

* Corresponding author. Tel.: +852-2609-6789; fax: +852-2603-5139.
E-mail address: jar@cuhk.edu.hk (J.A. Rudd).

0014-2999/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2003.08.020

quently tested for their effect on nicotine- and copper sulphate-induced emesis. Vapiprost was also employed in the studies as a selective TP prostanoid receptor antagonist (Lumley et al., 1989).

2. Methods and materials

2.1. Animals

The experiments were performed on male or female *S. murinus* (30–80 g), bred at the Chinese University of Hong Kong. They were maintained in temperature-controlled room at 24 ± 1 C under artificial lighting, with lights on between 0700 and 1730 h. Artificial humidity was maintained at 50 ± 5%. Animals were allowed free access to water and pelleted cat chow (Feline Diet 5003, PMI® Feeds, St. Louis, USA). All experiments were conducted under licence from the Government of the Hong Kong SAR and the Animal Research Ethics Committee, The Chinese University of Hong Kong. No animal was used more than once.

2.2. Induction and measurement of emesis

On the day of experiment, the animals were transferred to clear Perspex observation chambers (21 × 14 × 13 cm) for the assessment of emetic behaviour. They were allowed 30 min to adapt before being injected intraperitoneally with prostanoids or their respective vehicles. The animals were then observed for 60 min. In another experiment, vapiprost (0.3 and 3 mg/kg) was administered subcutaneously 30 min prior to U46619 (300 μg/kg, i.p.). Prostanoids that were not consistently emetic (where ≤ 50% of animals responded) were subsequently tested for a potential to modulate nicotine (5 mg/kg, s.c.)- and copper sulphate (120 mg/kg, intragastric)-induced emesis. In these experiments, the prostanoid or respective vehicle was injected intraperitoneally 30 min prior to the administration of the emetogen. The animals were then observed for a further 60 min. An episode of emesis was characterized by rhythmic abdominal contractions that were either associated with the oral expulsion of solid or liquid material from the gastrointestinal tract (i.e. vomiting) or not associated with the passage of material (i.e. retching movements). An episode of retching and/or vomiting was considered separate when an animal changed its location in the observation chamber, or when the interval between retches and/or vomits exceeded 2 s.

2.3. Formulation of drugs

5-(6-Carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin (BW245C; Cayman Chemical, USA) was freshly dissolved in 10% ethanol. Stocks of prostaglandin E_2 (20 mg/ml; Cayman Chemical), misoprostol (20 mg/ml; Cayman Chemical), sulprostone (20 mg/ml; Schering Aktiengesellschaft, Germany), fluprostenol (10 mg/ml; Cayman Chemical), iloprost (10 mg/ml; Schering Aktiengesellschaft) and 11α,9α-epoxymethano-15*S*-hydroxy-prosta-5*Z*,13*E*-dienoic acid (U46619; 1 mg/ml; Cayman Chemical) were prepared in absolute ethanol for storage at −20 °C. Immediately prior to the experiments, the stocks were diluted using distilled water to provide the desired top doses. Prostaglandin $F_{2\alpha}$ (Cayman Chemical), cicaprost clathrate (Schering Aktiengesellschaft), vapiprost hydrochloride (GlaxoSmithKline, UK), nicotine ditartrate (Sigma-Aldrich, St. Louis, USA) and copper sulphate pentahydrate (Riedel-DeHaën, Germany) were dissolved in distilled water. Drug doses (excepting copper sulphate pentahydrate) are indicated as the free acid or base.

2.4. Statistical analysis

In each animal, the following parameters were recorded: (1) the latency to first retch/vomit and (2) the number of episodes of retches and/or vomits. The significance of difference between treatments was assessed either by a one-way analysis of variance (ANOVA) followed by a Fisher's Protected Least Significant Difference (PLSD) test

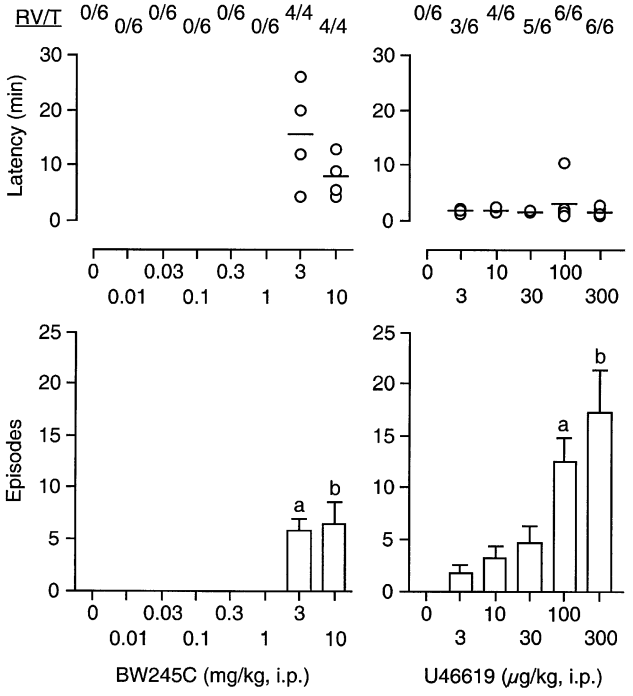

Fig. 1. Emetic activity of BW245C and U46619 in *S. murinus*. Individual latencies to the first episode of retching and/or vomiting are shown as open circles (horizontal lines represent the mean latencies of the respective treatment group). The mean ± S.E.M. of the total number of episodes of retching and/or vomiting and the number of animals retching and/or vomiting out of the number of animals tested (RV/T) is also shown. Significant differences relative to the respective vehicle treated animals are indicated as $^{a}P < 0.01$, $^{b}P < 0.001$ (One-way ANOVA followed by a Fisher's PLSD test).

(Statsview®, Abacus Concepts, USA). Differences were considered significant when $P < 0.05$.

3. Results

3.1. Emetic action of prostanoids

U46619 induced emesis in 50% of animals at doses as low as 3 μg/kg. However, emesis was seen in all animals at 100 and 300 μg/kg, with the highest dose inducing 17.2 ± 4.1 episodes ($P < 0.001$) following a latency of 1.6 ± 0.3 min. BW245C was about 1000 times less potent than U46619 (comparisons made at threshold doses) with 3 and 10 mg/kg inducing 5.8 ± 1.3 ($P < 0.01$) and 6.5 ± 2.1 ($P < 0.001$) episodes following latencies of 15.6 ± 4.8 and 7.9 ± 1.9 min, respectively (see Fig. 1). Prostaglandin E_2, 17-phenyl-ω-trinor prostaglandin E_2, misoprostol, sulprostone, prostaglandin $F_{2\alpha}$, fluprostenol, cicaprost and iloprost were either weakly emetic or failed to induce consistent emesis at doses up to 1000 μg/kg (see Table 1).

Table 1
The action of weak/inconsistent emetic prostanoids on drug-induced emesis

Prostanoid	Doses (μg/kg)	Latency (min)	Emetic activity of prostanoid	Nicotine-induced emesis	$CuSO_4.5H_2O$-induced emesis
PGE_2	0	–	0.0 ± 0.0 (0/4)	14.0 ± 3.1 (6/6)	14.7 ± 3.4 (6/6)
	30	–	0.0 ± 0.0 (0/4)	15.8 ± 2.9 (5/5)	13.7 ± 2.0 (6/6)
	100	–	0.0 ± 0.0 (0/4)	16.8 ± 1.4 (6/6)	12.0 ± 2.6 (5/5)
	300	–	0.0 ± 0.0 (0/4)	15.2 ± 2.1 (5/5)	13.8 ± 2.7 (5/5)
	1000	–	0.0 ± 0.0 (0/4)	NT	NT
17-Phenyl-	0	–	0.0 ± 0.0 (0/4)	27.8 ± 3.0 (5/5)	18.2 ± 2.9 (5/5)
ω-Trinor	30	NT	NT	25.8 ± 4.0 (5/5)	9.5 ± 2.4 (6/6)
PGE_2	100	–	0.0 ± 0.0 (0/4)	25.2 ± 2.0 (6/6)	14.5 ± 4.4 (6/6)
	300	–	0.0 ± 0.0 (0/4)	23.5 ± 2.1 (6/6)	10.8 ± 2.7 (4/4)
	1000	–	0.0 ± 0.0 (0/4)	NT	NT
Misoprostol	0	–	0.0 ± 0.0 (0/4)	21.0 ± 3.5 (6/6)	20.0 ± 3.3 (6/6)
	10	–	0.0 ± 0.0 (0/4)	NT	NT
	30	–	0.0 ± 0.0 (0/4)	14.5 ± 3.5 (6/6)	18.6 ± 3.3 (5/5)
	100	–	0.0 ± 0.0 (0/4)	19.3 ± 2.2 (6/6)	10.8 ± 2.6 (5/5)
	300	41.2	1.3 ± 1.3 (1/4)	19.2 ± 1.5 (6/6)	24.2 ± 3.8 (6/6)
	1000	1.6	5.3 ± 5.3 (1/4)	NT	NT
Sulprostone	0	–	0.0 ± 0.0 (0/4)	23.3 ± 2.8 (6/6)	18.8 ± 3.6 (5/5)
	30	NT	NT	21.8 ± 2.8 (6/6)	16.6 ± 3.8 (5/5)
	100	–	0.0 ± 0.0 (0/4)	21.0 ± 3.1 (6/6)	14.0 ± 4.6 (5/5)
	300	–	0.0 ± 0.0 (0/4)	21.5 ± 1.7 (6/6)	18.5 ± 3.7 (4/4)
	1000	2.6	0.5 ± 0.5 (1/4)	NT	NT
$PGF_{2\alpha}$	0	–	0.0 ± 0.0 (0/4)	25.3 ± 5.9 (6/6)	20.0 ± 5.7 (6/6)
	30	–	0.0 ± 0.0 (0/4)	29.8 ± 3.8 (6/6)	12.8 ± 1.5 (6/6)
	100	2.0	0.5 ± 0.5 (1/4)	21.8 ± 4.6 (6/6)	8.3 ± 1.7 (6/6)
	300	–	0.0 ± 0.0 (0/4)	24.0 ± 3.9 (6/6)	10.0 ± 0.6 (6/6)
	1000	3.6	0.5 ± 0.3 (2/4)	NT	NT
Fluprostenol	0	–	0.0 ± 0.0 (0/4)	19.3 ± 2.2 (6/6)	11.3 ± 2.0 (6/6)
	30	–	0.0 ± 0.0 (0/4)	19.2 ± 2.9 (6/6)	9.6 ± 1.3 (5/5)
	100	–	0.0 ± 0.0 (0/4)	10.8 ± 2.8 (5/5)	6.7 ± 2.4 (6/6)
	300	–	0.0 ± 0.0 (0/4)	7.7 ± 1.7[a] (6/6)	9.0 ± 3.1 (5/5)
	1000	–	0.0 ± 0.0 (0/4)	NT	NT
Iloprost	0	–	0.0 ± 0.0 (0/4)	15.3 ± 2.8 (9/9)	12.2 ± 2.8 (5/5)
	30	–	0.0 ± 0.0 (0/4)	20.4 ± 3.3 (9/9)	17.0 ± 4.1 (5/5)
	100	–	0.0 ± 0.0 (0/4)	19.1 ± 1.9 (8/8)	15.6 ± 2.5 (5/5)
	300	–	0.0 ± 0.0 (0/4)	18.3 ± 2.7 (9/9)	16.8 ± 2.1 (6/6)
	1000	–	0.0 ± 0.0 (0/4)	NT	NT
Cicaprost	0	–	0.0 ± 0.0 (0/6)	21.0 ± 2.5 (3/3)	13.3 ± 2.9 (6/6)
	30	–	0.0 ± 0.0 (0/6)	19.3 ± 2.9 (3/3)	12.5 ± 4.5 (6/6)
	100	–	0.0 ± 0.0 (0/6)	23.3 ± 0.9 (3/3)	18.8 ± 4.3 (6/6)
	300	–	0.0 ± 0.0 (0/6)	16.7 ± 0.1 (3/3)	15.0 ± 3.4 (6/6)

The experiments involving the initial testing of prostanoids for emetic activity were conducted in different animals form those used to determine their action on drug-induced emesis. In the latter experiments (see the table above), the prostanoids or their respective vehicles were injected intraperitoneally 30 min prior to the administration of nicotine (5 mg/kg, s.c.) or copper sulphate (120 mg/kg, intragastric). Latency data are expressed as the mean time (min) of only the animals that had episodes; all other represent the mean ± S.E.M. Fractions in parenthesis represent the number of animals retching and/or vomiting out of the number of animals in the tested. 'NT' indicates 'not tested'. Significant differences relative to the respective vehicle treated animals are indicated as [a]$P < 0.05$ (One-way ANOVA followed by a Fisher's PLSD test.). None of the prostanoids affected significantly the latency to onset of nicotine- or copper sulphate-induced emesis ($P > 0.05$, data not shown).

3.2. Action of vapiprost on U46619-induced emesis

U46619 at 300 μg/kg induced emesis following a latency of 1.5 ± 0.2 min and comprised 5.2 ± 1.3 episodes (seven out of nine animals responded). Vapiprost 0.3 mg/kg delayed U46619-induced emesis by approximately 1 min and reduced the number of emetic episodes by 44% ($P>0.05$; only three out of seven animals responded). A higher dose of vapiprost, 3 mg/kg, prevented emesis in seven out of seven animals ($P<0.01$).

3.3. Action of non-emetic/weakly emetic prostanoids on nicotine-(5 mg/kg, s.c.) and copper sulphate (120 mg/kg, intragastric)-induced emesis

In the preliminary studies, prostaglandin E_2, 17-phenyl-ω-trinor prostaglandin E_2, misoprostol, sulprostone, prostaglandin $F_{2\alpha}$, fluprostenol, cicaprost and iloprost failed to induce dose-related or consistent emesis. They were therefore investigated for a potential to modify drug-induced emesis. Nicotine was selected as an emetogen with a mechanism potentially involving the area postrema (Beleslin and Krstic, 1987) and copper sulphate as an emetogen with a mechanism potentially involving the vagus and/or splanchnic nerves (Wang and Borison, 1952). However, in these studies, only fluprostenol significantly modified nicotine (5 mg/kg, s.c.)-induced emesis, producing an approximate 60% reduction in the number of episodes at 300 μg/kg ($P<0.05$; Table 1). None of the prostanoids tested affected significantly copper sulphate (120 mg/kg, intragastric)-induced emesis ($P>0.05$; Table 1) or the latency of nicotine (pooled mean latency: 4.2 ± 0.3 min, $n=9$) or copper sulphate (pooled mean latency: 2.6 ± 0.2 min, $n=45$) to induce emesis.

4. Discussion

The present studies are the first to investigate systematically the emetic action of prostanoids in *S. murinus*. One of the major findings was the potent activity of U46619 to induce emesis and the anti-emetic activity of vapiprost suggests an involvement of TP receptors. Indeed, U46619 is one of the most potent drugs ever reported to induce emesis in this species, suggesting that TP receptors may play an important role in the emetic reflex. Antagonists at TP receptors may be useful to treat emesis in circumstances where prostaglandins are suspected to be elevated (see Introduction). The findings are in agreement with our previous studies in the ferret that concluded that TP receptors may represent a novel site for anti-emetic drug development (e.g. for the treatment of chemotherapy-induced emesis, or the emesis induced by bacterial infection or ethanol ingestion; see Kan et al., 2002). Unfortunately, however, the mechanism of action of U46619 to induce emesis is currently unknown but the rapid onset of emesis (generally <2 min) following intraperitoneal administration) tentatively suggests a peripheral action.

Our previous studies in the ferret using agonists also implicated a role of DP, EP and possibly IP receptors in the emetic reflex (Kan et al., 2002). However, in *S. murinus*, none of the EP (Prostaglandin E_2, 17-phenyl-ω-trinor prostaglandin E_2, misoprostol or sulprostone), FP (prostaglandin $F_{2\alpha}$ and fluprostenol) or IP (iloprost and cicaprost) receptor agonists tested could reliably induce emetic responses. Indeed, apart from U46619, only the DP receptor agonist BW245C was capable of consistently inducing emesis, but this was only seen at relatively high doses (>1 mg/kg). Moreover, BW245C appeared 1000 times less potent than U46619 to induce emesis in *S. murinus*, but is only 19 times less potent than U46619 in the ferret (Kan et al., 2002). Taken together, it is possible that the emetic action of BW245C is via other prostanoid receptors: these could be TP receptors, since BW245C is approximately 370 times less active than U46619 at human recombinant TP receptors (Abramovitz et al., 2000). Alternatively, BW245C may be a weak agonist at *S. murinus* DP receptors, DP receptors may be absent, or the emetic action is via non-prostanoid receptor mechanisms. Further characterization of the action of BW245C on *S. murinus* tissues is required to fully elucidate the mechanisms involved.

We were initially cautious in rejecting a role for EP, FP and IP in the emetic reflex of *S. murinus* from data showing low/absent emetic activity. This is because there is evidence in the literature of the potent anti-emetic action of agonists on other receptor systems: e.g. μ-opioid and 5-HT_{1A} receptor agonists are anti-emetic in *S. murinus* (Okada et al., 1994; Rudd et al., 1999a). Further, there is also evidence that non-emetic prostanoids (or prostanoids with low emetic potential) can potentiate drug-induced emesis (Kan et al., 2002). However, none of the EP or IP receptor agonists tested affected nicotine- or copper sulphate-induced emesis (these emetics have been characterized previously in our laboratory; Rudd et al., 1999b) to lead us to believe that they are not generally involved in the emetic reflex when activated by these stimuli. However, it is still possible that prostanoid receptors are involved in other causes of emesis that were not tested in the present studies. Unfortunately, the situation regarding FP receptors is less clear since prostaglandin $F_{2\alpha}$ was inactive to modulate emesis but fluprostenol antagonized the emetic response induced by nicotine. This may indicate a subtle role of FP receptors in the emetic reflex (specifically related to pathways activated by nicotine) of *S. murinus*, a situation different from the ferret where fluprostenol is inactive against other emetic stimuli (Kan et al., 2002). Unfortunately, the mechanism of action of fluprostenol to antagonize nicotine-induced emesis is unknown, but it is unlikely to involve a direct block of nicotinic receptors. It is also unknown if fluprostenol has potential to antagonize emesis to other centrally active emetic stimuli or why prostaglandin $F_{2\alpha}$ failed to affect

emesis; however, we are unable to rule out the possibility that prostaglandin $F_{2\alpha}$ is rapidly metabolised.

Our studies have mainly focussed on the action of prostanoids to affect the vomiting reflex, but it is perhaps pertinent to mention two other observations made during the course of the investigations that we consider important. Firstly, DP receptor agonists are sedative (Kan et al., 2002; Onoe et al., 1988), but no sedative action was seen with BW245C in *S. murinus* (Kan, unpublished observations). Secondly, EP and FP receptor agonists potently induce defecation in the ferret (Kan et al., 2002), but they appeared inactive in *S. murinus* (Kan, unpublished observations). The significance of these observations is not entirely clear, but we believe they may indicate that further important differences exist between the general role of prostanoids in *S. murinus* and other species. It remains to be seen if the inactivity of EP and FP receptor agonists to induce emesis is related to their inability to increase the frequency of defecation in *S. murinus*.

In conclusion, U46619 was revealed as a potent emetic agent with a mechanism of action involving TP receptors. It is possible that a model of U46619-induced emesis may have a utility to rapidly screen for the in vivo pharmacological activity of TP receptor antagonists, as anti-emetics, or for use in other areas of therapeutics. The DP receptor agonist BW245C was a weak emetic agent, but further studies are required to clarify the mechanisms of action. However, the ability of fluprostenol to antagonize nicotine-induced emesis may indicate a subtle role of FP receptors in the emetic reflex (this also requires further clarification) of this species as both prostaglandin $F_{2\alpha}$ and fluprostenol were inactive to induce emesis when used alone. Conversely, EP and IP receptors do not appear to be involved in the emetic reflex of *S. murinus*. Further studies are required to elucidate the general role of prostanoids and their receptors in *S. murinus*.

Acknowledgements

The research was partially supported by the Research Grants Council of Hong Kong (CUHK 98.1.54). We are grateful to Dr. M. Schirner (Schering Aktiengesellschaft) for the gifts of iloprost, cicaprost and sulprostone and to Dr. K.T. Bunce (GlaxoSmithKline for organising the generous gift of vapiprost.

References

Abramovitz, M., Adam, M., Boie, Y., Carriere, M., Denis, D., Godbout, C., Lamontagne, S., Rochette, C., Sawyer, N., Tremblay, N.M., Belley, M., Gallant, M., Dufresne, C., Gareau, Y., Ruel, R., Juteau, H., Labelle, M., Ouimet, N., Metters, K.M., 2000. The utilization of recombinant prostanoid receptors to determine the affinities and selectivities of prostaglandins and related analogs. Biochim. Biophys. Acta 1483, 285–293.

Beleslin, D.B., Krstic, S.K., 1987. Further studies on nicotine-induced emesis: nicotinic mediation in area postrema. Physiol. Behav. 39, 681–686.

Carpenter, D.O., Briggs, D.B., Knox, A.P., Strominger, N.L., 1986. Radiation-induced emesis in the dog: effects of lesions and drugs. Radiat. Res. 108, 307–316.

Coleman, R.A., Smith, W.L., Narumiya, S., 1994. International Union of Pharmacology. Classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. Pharmacol. Rev. 46, 205–229.

Girod, V., Dapzol, J., Bouvier, M., Grélot, L., 2002. The COX inhibitors indomethacin and meloxicam exhibit anti-emetic activity against cisplatin-induced emesis in piglets. Neuropharmacology 42, 428–436.

Jett, M., Brinkley, W., Neill, R., Gemski, P., Hunt, R., 1990. *Staphylococcus aureus* enterotoxin B challenge of monkeys: correlation of plasma levels of arachidonic acid cascade products with occurrence of illness. Infect. Immun. 58, 3494–3499.

Kaivola, S., Parantainen, J., Osterman, T., Timonen, H., 1983. Hangover headache and prostaglandins: prophylactic treatment with tolfenamic acid. Cephalalgia 3, 31–36.

Kan, K.K.W., Jones, R.L., Ngan, M.P., Rudd, J.A., 2002. Action of prostanoids to induce emesis and defecation in the ferret. Eur. J. Pharmacol. 453, 299–308.

Kiriyama, M., Ushikubi, F., Kobayashi, T., Hirata, M., Sugimoto, Y., Narumiya, S., 1997. Ligand binding specificities of the eight types and subtypes of the mouse prostanoid receptors expressed in Chinese hamster ovary cells. Br. J. Pharmacol. 122, 217–224.

Lauersen, N.H., Wilson, K.H., 1977. The effects of intramuscular injections of 15(*S*)-15-methyl prostaglandin F2alpha in failed abortions. Fertil. Steril. 28, 1044–1047.

Lumley, P., White, B.P., Humphrey, P.P., 1989. GR32191, a highly potent and specific thromboxane A_2 receptor blocking drug on platelets and vascular and airways smooth muscle in vitro. Br. J. Pharmacol. 97, 783–794.

Okada, F., Torii, Y., Saito, H., Matsuki, N., 1994. Antiemetic effects of serotonergic 5-HT_{1A}-receptor agonists in *Suncus murinus*. Jpn. J. Pharmacol. 64, 109–114.

Onoe, H., Ueno, R., Fujita, I., Nishino, H., Oomura, Y., Hayaishi, O., 1988. Prostaglandin D_2, a cerebral sleep-inducing substance in monkeys. Proc. Natl. Acad. Sci. 85, 4082–4086.

Rudd, J.A., Cheng, C.H., Naylor, R.J., Ngan, M.P., Wai, M.K., 1999a. Modulation of emesis by fentanyl and opioid receptor antagonists in *Suncus murinus* (house musk shrew). Eur. J. Pharmacol. 374, 77–84.

Rudd, J.A., Ngan, M.P., Wai, M.K., 1999b. Inhibition of emesis by tachykinin NK_1 receptor antagonists in *Suncus murinus* (house musk shrew). Eur. J. Pharmacol. 366, 243–252.

Sam, T.S.W., Chan, S.W., Rudd, J.A., Yeung, J.H., 2001. Action of glucocorticoids to antagonise cisplatin-induced acute and delayed emesis in the ferret. Eur. J. Pharmacol. 417, 231–237.

Sato, T., Igarashi, N., Minami, S., Okabe, T., Hashimoto, H., Hasui, M., Kato, E., 1988. Recurrent attacks of vomiting, hypertension and psychotic depression: a syndrome of periodic catecholamine and prostaglandin discharge. Acta Endocrinol. 117, 189–197.

Wang, S.C., Borison, H.L., 1952. A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides. Gastroenterology 22, 1–12.

Ylikorkala, O., Jarvinen, P.A., 1975. Induction of abortion with intra-amniotic or intra-muscular 15(*S*)-15-methyl-prostaglandin F2alpha. Prostaglandins 10, 423–434.