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European Journal of Pharmacology 544 (2006) 153 – 159
www.elsevier.com/locate/ejphar

Differential action of anti-emetic drugs on defecation and emesis induced by prostaglandin E_2 in the ferret

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Received 28 March 2006; received in revised form 14 June 2006; accepted 19 June 2006
Available online 27 June 2006

Abstract

In the present studies we investigated the mechanism of action of prostaglandin E_2 (1 mg/kg, i.p.) to induce emesis and defecation and/or tenesmus in the ferret. The emesis was antagonized significantly ($P<0.05$) by ondansetron (0.3 and 1 mg/kg, i.p.) and (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine hydrochloride (CP-99,994; 10 mg/kg, i.p.), but neither compound reduced defecations and/or tenesmus, with ondansetron (0.3 mg/kg) actually producing a slight increase ($P<0.05$). Droperidol (1 and 3 mg/kg), metoclopramide (0.3 and 3 mg/kg), domperidone (0.3 and 3 mg/kg), promethazine (0.3 and 3 mg/kg) and scopolamine (0.3 and 3 mg/kg) failed to reduce prostaglandin E_2 induced emesis. However, droperidol (1 and 3 mg/kg) and scopolamine (0.3 and 3 mg/kg) reduced significantly the defecatory and/or tenesmus response ($P<0.05$). Bilateral abdominal vagotomy was ineffective to reduce emesis and defecations and/or tenesmus. The data suggests that 5-HT_3 receptor and NK_1 tachykinin receptor antagonists could be useful in the clinic to prevent emesis but not defecations induced by prostaglandin E_2.

Keywords: Prostanoid; Emesis; Defecation; Ferret; NK_1; 5-HT_3

1. Introduction

Prostaglandins are well known to have a wide range of biological actions encompassing those viewed as protective or detrimental (Narumiya et al., 1999; Negishi et al., 1995). There are several clinical indications for synthetic prostaglandins ranging from treatment of cardiovascular diseases to the treatment of dyspepsia associated with non-steroidal anti-inflammatory drugs, but their use may be associated with side effects including a disturbed gastrointestinal function (Bianchi Porro and Parente, 1989; Grant and Goa, 1992; Reiter et al., 2002). Certainly, the use of prostaglandins E_2 and $F_{2\alpha}$ or their analogues for obstetric purposes is often associated with the side effects of nausea, emesis and diarrhoea (Lauersen and Wilson, 1977; Nelson and Bryans, 1976; Schaff et al., 1995; Thavarasah and Almohdzar, 1986). The diarrhoea can be effectively treated using opioids such as loperamide (Karim and Adaikan, 1977; Lange et al., 1977). However, attempts to control the emetic side effect rely mainly on the use of dopamine receptor antagonists such as droperidol, prochlorperazine and chlorpromazine (see Fahmy, 1981; Lippes and Hurd, 1975). Unfortunately, the use of brain penetrating dopamine receptor antagonists is sometimes associated with other side effects which impact on the patient (Montastruc et al., 1994; Niemegeers, 1982).

Recently, we focused on the potential involvement of prostanoids in mechanisms controlling emesis and diarrhoea in the ferret (Kan et al., 2002). There are five major types of prostanoid receptors (DP, EP, FP, IP and TP; Coleman et al., 1994; Narumiya et al., 1999), but only DP, EP and TP receptor agonists induced emesis, with EP and FP receptors agonists causing an increased frequency of defecation (Kan et al., 2002). We also demonstrated that DP, EP and TP receptor agonists depolarized the isolated ferret vagus nerve preparation (Kan et al., 2004), providing a potential mechanism to mediate emesis and/or defecation.

It is notable that other classes of anti-emetic drug such as the 5-hydroxytryptamine$_3$ (5-HT_3) and tachykinin NK_1 receptor antagonists have not been investigated for a capacity to prevent prostanoid-induced emesis and/or diarhhoea in man. In the present studies, therefore, we decided to use the ferret to determine

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0014-2999/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2006.06.034

an optimal anti-emetic treatment for prostaglandin E_2-induced emesis and to simultaneously determine an action on defecatory frequency. We used droperidol, metoclopramide and domperidone as representative dopamine receptor antagonists (Dahlof and Hargreaves, 1998), promethazine as a representative histamine H_1 receptor antagonist (Dahlof and Hargreaves, 1998), and ondansetron as a representative 5-HT_3 receptor antagonist (Butler et al., 1988). We selected (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenlypiperidine (CP-99,994), as a tachykinin NK_1 receptor antagonist with broad inhibitory anti-emetic actions in the ferret (Bountra et al., 1993). Scopolamine was used as an anti-emetic agent known to reduce defecatory frequency (Stewart et al., 1994); loperamide was not selected to reduce defecatory frequency because it is emetic in the ferret (Bhandari et al., 1992). To compliment the studies, we examined if bilateral abdominal vagotomy could differentially modify the action of prostaglandin E_2 to induce emesis and defecation.

2. Methods and materials

2.1. Animals

Castrated male ferrets (1–2 kg) were obtained from a reputable breeder in New Zealand. Prior to the experiments, they were housed in a temperature-controlled room at 24±1 °C under artificial lighting, with lights on between 0600 h and 1800 h. They were allowed free access to water and pelleted cat chow (Feline Diet 5003, PMI® Feeds, St. Louis, U.S.A.). All experiments were conducted under license from the Government of the Hong Kong SAR and endorsement of the Animal Research Ethics Committee, The Chinese University of Hong Kong.

2.2. Bilateral vagotomy

The surgical techniques to lesion the vagi have been described previously (Bhandari et al., 1992). Briefly, the animals were anaesthetized with ketamine (35 mg/kg, i.m.) and xylazine (2 mg/kg, i.m.) and the ventral abdominal surface shaved from the costal margin to the inguinal ligament. The skin was subsequently sterilized with 0.5% chlorhexidine in 70% (v/v) alcohol. A midline 6–8 cm laparotomy incision was then made and the ventral and dorsal trunks running along the oesophagus were located by blunt dissection and at least 0.5 cm of each nerve removed (the serosa of the oesophagus was slightly incised to facilitate the procedure). Braided silk suture (2/0, Mersilk, Ethicon, Ltd., U.K.) was used to ligate the cut ends of the vagi. The abdominal contents were moistened with sterile saline and the peritoneum and skin layers closed separately with 2/0 braided silk sutures using interrupted stitches. Skin incisions were sprayed with antibiotic aerosol (Tribiotic Spray®, Riker Laboratories, U.K.) and then silicone wound dressing (Opsite®, Smith and Nephew, U.K.). Butorphanol (0.1 mg/kg, s.c.) was used as a pre- (immediately before) and post- (×2, 4 h apart) operative analgesic. Sham operations were performed using similar procedures except that the nerves were not lesioned. All animals were allowed 7 days to recover from the surgery. All animals were challenged with copper sulphate pentahydrate (50 mg/kg, i.g.) 48 h post-prostaglandin E_2 administration to confirm the success of surgery (see below).

2.3. Measurement of emesis and defecation

On the day of experiment, the animals were transferred to individual cages where they were allowed 30 min to adapt before being presented with approximately 100 g of commercially available cat food (Whiskas®, Effem Foods Pty. Ltd., Woodonga, Australia). Anti-emetic drugs, or respective vehicles were administered subcutaneously 30 min prior to the administration of prostaglandin E_2 [1 mg/kg (Kan et al., 2002)]. A trained observer that was blind to the treatment groups recorded animal behaviour for 90 min. Episodes of emesis were 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). Two consecutive episodes of retching and/or vomiting were considered separate when an animal changed its location in the observation cage or when the interval between retches and/or vomits exceeded 5 s. An episode of defecation was characterized as a series of lower abdominal contractions and expulsion of solid or liquid faecal matter from the anus. Episodes of tenesmus were characterized as non-productive lower abdominal contractions and only tenesmus involving spasm of the anal sphincter was recorded to differentiate between potential non-productive attempts of the animals to micturate. The animals had raised tails during episodes of defecation and tenesmus and consecutive episodes were considered separate when an animal changed its location in the observation cage.

2.4. Formulation of drugs

A stock solution of prostaglandin E_2 (Cayman Chemical Co., U.S.A.) was prepared in absolute ethanol (20 mg/ml) for storage at −20 °C. Immediately prior to the experiments, it was diluted with distilled water. Domperidone (Sigma-Aldrich, St. Louis, U.S.A.) and droperidol (Sigma-Aldrich, St. Louis, U.S.A.) were freshly dissolved in 100% dimethylsulphoxide (Sigma-Aldrich, St. Louis, U.S.A.). Metoclopramide hydrochloride (Sigma-Aldrich, St. Louis, U.S.A.), scopolamine hydrochloride (Sigma-Aldrich, St. Louis, U.S.A.), promethazine hydrochloride (Sigma-Aldrich, St. Louis, U.S.A.), (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenlypiperidine hydrochloride (CP-99,994; Pfizer Inc., Groton, U.S.A.), and copper sulphate pentahydrate, were dissolved in distilled water. Ondansetron hydrochloride dihydrate (GlaxoSmithKline, Barnard Castle, U.K.) was formulated in saline (0.9% w/v). Drug doses (excepting copper sulphate pentahydrate) are indicated as the free acid or base. All drugs were administered in a volume of 0.5 ml/kg and had matching vehicle controls.

2.5. Statistical analysis

In each animal, the following parameters were recorded: (1) latency to first retch or vomit, (2) latency to the first episode of defecation or tenesmus, (3) number of episodes of retches and/or vomits and (4) sum of the number of episodes of defecation and tenesmus. The significance of differences between episode data was assessed by one-way analysis of variance (ANOVA) followed