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Action of metyrapone and tetracosactrin to modify cisplatin-induced acute and delayed emesis in the ferret

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Abstract

Cisplatin 5 mg/kg, i.p., induced an acute (day 1) and delayed (days 2 and 3) emetic response in the ferret that was used to investigate the potential anti-emetic activity of metyrapone and tetracosactrin and their potential interaction. The 11β-hydroxylase enzymes inhibitor metyrapone 10–30 mg/kg, i.p., dose dependently potentiated the acute cisplatin-induce retching + vomiting response by up to 219% at the highest dose ($P<0.001$) but failed to affect significantly delayed emesis ($P>0.05$). The adrenocorticotropic hormone (ACTH) mimetic tetracosactrin 0.1 mg/kg, i.m., antagonised significantly the acute and delayed emetic response by 98% ($P<0.01$) and 75% ($P<0.001$), respectively. The anti-emetic action of tetracosactrin on acute but not delayed emesis was prevented by combination with metyrapone 10 mg/kg, i.p. Tetracosactrin 0.1 mg/kg, i.m., failed to modify apomorphine (0.25 mg/kg, s.c.)-induced emesis. The potential anti-emetic mechanism of action of metyrapone and tetracosactrin to modulate emesis is discussed.

Keywords: Emesis; Cisplatin; ACTH (adrenocorticotropic hormone); Metyrapone

1. Introduction

Cisplatin based chemotherapy is often associated with severe nausea and vomiting. Glucocorticoids such as dexamethasone are usually combined with other anti-emetic drugs (e.g. 5-hydroxytryptamine receptor antagonists or metoclopramide) to reduce the acute (first 24 h) and delayed (several days post chemotherapy) emetic response that may occur (Gralla et al., 1999). The anti-emetic mechanism of the glucocorticoids probably relates to an ability to mimic the action of endogenous cortisol but the precise mechanism of action is unknown (Sam et al., 2001).

An alternative approach to using glucocorticoids to control emesis may be to use adrenocorticotropic hormone (ACTH) or its analogues to facilitate the synthesis and secretion of cortisol from the adrenal cortex (Imura, 1987; Schwyzer, 1977). Indeed, studies have shown that ACTH improves the control of cisplatin-induced acute and delayed emesis when used alone or combined with other anti-emetics in man (Colbert et al., 1983; Culine et al., 1989; Passalacqua et al., 1992, 1997). An ability of ACTH to increase plasma cortisol levels, via 11β-hydroxylase, may contribute to the anti-emetic action, since plasma cortisol levels are inversely related to the development of chemotherapy-induced acute nausea and vomiting (Hursti et al., 1993). However, no studies have directly investigated the role of 11β-hydroxylase in the development of chemotherapy-induced acute and delayed emesis or in the anti-emetic mechanism of action of ACTH.

In the present studies, therefore, we investigate the potential of the ACTH mimetic, tetracosactrin (ACTH-(1-24); Weaver, 1978), to modify cisplatin-induced acute and delayed emesis in the ferret. We have previously shown that cisplatin-induced acute and delayed emesis in the ferret is particularly sensitive to glucocorticoids (Sam et al., 2001). Tetracosactrin was also investigated for its potential to modify apomorphine-induced emesis. This study was conducted to provide information relevant to the specificity of tetracosactrin to affect the vomiting reflex; dexamethasone is inactive to reduce apomorphine-induced emesis (Rudd et al., 1996). Metyrapone a well-known 11 β-hydroxylase enzyme inhibitor (Lambert et al., 1986; Meikle

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et al., 1975), was also investigated for its potential to modify cisplatin-induced emesis and for its potential interaction with tetracosactrin on the cisplatin-induced emetic response.

2. Methods

2.1. Animals

Castrated male ferrets (0.8–1.8 kg) were obtained from a reputable breeder in New Zealand and were housed communally at 22 ± 1 °C under artificial lighting, with lights on between 07:00 and 21:00 h. They were fed a dry pellet diet (Laboratory Feline Diet 5003, PMI Nutrition, St. Louis, MO, USA); water was available ad libitum. 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. Induction and measurement of emesis

Animals were transferred to individual observation cages and allowed at least 48 h to adapt to the new environment. On the day of the experiment (at 10:30 h) they were presented with 100 g of commercially available cat food (Whiskas®, Effem Foods, Woodonga, Australia). At 11:00 h the ferrets were removed from their observation cages and injected with tetracosactrin (0.1 mg/kg, i.m.), metyrapone (10–30 mg/kg, i.p.) or their respective vehicles 4 h prior the administration of cisplatin 5 mg/kg, i.p. ($t = 0$). Tetracosactrin or vehicle was then injected 8 h post cisplatin administration and then at regular 12 h intervals. Further administrations of metyrapone or vehicle were made immediately following cisplatin injection and then at 8 h intervals for the duration of the experiment. In another experiment (following the above dosing schedules), combination of injections of tetracosactrin (0.1 mg/kg, i.m.) and metyrapone (10 mg/kg, i.p.) were made to assess a potential interaction to modify cisplatin (5 mg/kg, i.p.)-induced acute and delayed emesis; vehicle combinations were administered as appropriate. Food (Laboratory Feline Diet 5003, PMI Nutrition) and water were available ad libitum for the duration of the experiments involving cisplatin.

The potential of a 5-h pretreatment of tetracosactrin 0.1 mg/kg, i.m., to modify apomorphine (0.25 mg/kg, s.c)-induced emesis was also investigated ($n = 4–5$). Cat food was made available 30 min prior to the administration of apomorphine. Metyrapone 10–30 mg/kg, i.p., was also administered, alone at 8 h intervals, for 3 days, to assess a potential to induce emesis.

Animal behaviour was recorded remotely using a closed circuit video recording system and analysed at the end of the experiments. Emesis was characterised 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 the animal changed its location in the observation cage, or when the interval between retches and/or vomits exceeded 5 s. At the end of the observation period, the animals were killed by an overdose of barbiturate (pentobarbital sodium 80 mg/kg, i.p.).

2.3. Statistical analysis

In animals receiving cisplatin, the latency to retch or vomit and/or the total number of retches, vomits and episodes was calculated in each 1-h period for the duration of the experiment. In animals receiving apomorphine, the latency to retch or vomit and the total numbers of retches and vomits were recorded during a 30-min observation period. The significance of difference between treatments was assessed by an unpaired Student's *t*-test or one-way analysis of variance (ANOVA) followed by a either a Dunnett's or Bonferroni's multiple comparison test, as appropriate (Graphpad Prism® version 3.0a, Graphpad Software, San Diego, CA, USA). Differences were considered significant when $P < 0.05$.

2.4. Drugs used

Cisplatin was purchased as a sterile saline solution at a concentration of 1 mg/ml (David Bull Laboratories, Victoria, Australia). Tetracosactrin was in the form of tetracosactide hexaacetate (N.V. Organon, Oss, Holland) and was formulated in 0.96% benzyl alcohol in saline (0.9% w/v) and administered in a volume of 0.1 ml/kg. Metyrapone (Biomol Research Laboratories, Plymouth Meeting, PA, USA) was formulated in saline (0.9% w/v) and administered in a volume of 1–2 ml/kg. Apomorphine hydrochloride (Sigma, St. Louis, MO, USA) was dissolved in 0.01% sodium metabisulphite (Riedel-DeHaën, Germany) and administered in a volume of 0.5 ml/kg. Doses are expressed as the free base.

3. Results

3.1. Effect of metyrapone alone and on cisplatin-induced emesis

Metyrapone 10–30 mg/kg, i.p. administered every 8 h, was investigated for a potential to induce emesis ($n = 3$). Only two out of three animals receiving metyrapone 30 mg/kg exhibited emesis. One of the animals had one episode of 11 retches and one vomit that occurred 2.3 h after the first injection. The other animal had 25 episodes comprising 222 retches and 17 vomits following a latency of 3.5 h but the

emetic response was confined to the initial 8-h period. None of the animals receiving metyrapone 10 mg/kg retched or vomited ($n = 3$) and all animals survived the 72 h observation period.

In vehicle treated animals, cisplatin induced a retching and/or vomiting response following a latency of 6.5 ± 1.5 h and comprised 78.8 ± 17.1 retches + vomits during the 0–24 h period and 507.2 ± 70.5 retches + vomits during the 24–72 h period. The regimen of metyrapone 30 mg/kg and cisplatin was toxic in three out of seven animals (animals died on day 3) and only data for the surviving animals were analysed. Metyrapone did not affect significantly ($P > 0.05$) the latency of cisplatin to induce emesis but did potentiate significantly the retching + vomiting occurring during the 0–24 h period by 219.0% at 30 mg/kg ($P < 0.05$; see Fig. 1). Metyrapone failed to affect significantly ($P > 0.05$) the retching + vomiting response occurring during the 24–72 h period, although a 47.8% reduction was observed at 30 mg/kg in the surviving animals (Fig. 1).

3.2. Effect of tetracosactrin alone and in combination with metyrapone on cisplatin-induced emesis

In vehicle treated animals, cisplatin induced a retching and/or vomiting response following a latency of 7.4 ± 2.3 h and comprised 179.5 ± 51.7 retches + vomits during the 0–24 h period and 366.2 ± 52.6 retches + vomits during the 24–72 h period. Tetracosactrin at 0.1 mg/kg prevented emesis in two out of six animals and delayed significantly the onset of cisplatin-induced emesis in the responding animals ($P < 0.01$) and also significantly delayed emesis compared to animals that received a combination of tetracosactrin 0.1 mg/kg and metyrapone 10 mg/kg ($P < 0.01$; Fig. 2). Tetracosactrin also significantly reduced the retching + vomiting response induced by cisplatin during the 0–24 h and 24–72 h period by 97.8% ($P < 0.001$) and 75.3% ($P < 0.01$), respectively (see Fig. 2).

The combination of tetracosactrin 0.1 mg/kg with metyrapone 10 mg/kg was ineffective to reduce cisplatin-induced retching + vomiting during the 0–24 h period but did reduce emesis occurring during the 24–72 h period by 64.6% ($P < 0.01$; Fig. 2).

3.3. Effect of tetracosactrin on apomorphine-induced emesis

A 5-h pretreatment of tetracosactrin 0.1 mg/kg, i.m., failed to modify apomorphine-induced retching + vomiting (controls 41.0 ± 4.6, tetracosactrin treated animals 26.0 ± 7.5; $P < 0.05$) or the onset of retching and/or vomiting (controls 3.5 ± 1.0 min, tetracosactrin treated animals

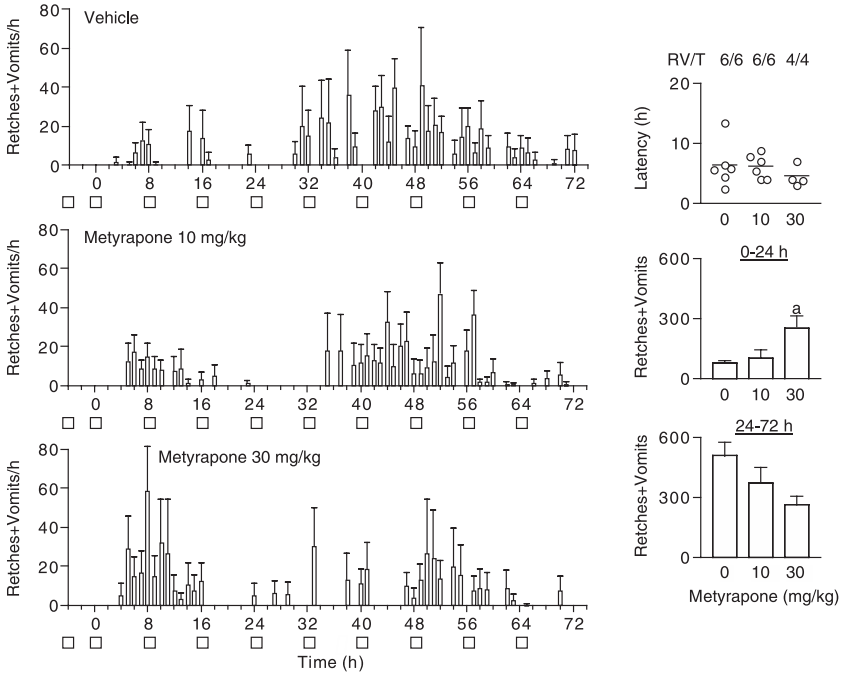

Fig. 1. The effect of vehicle (saline 2 ml/kg, i.p.) or metyrapone 10–30 mg/kg, i.p. on the profile of retching + vomiting in the ferret induced by a single injection of cisplatin, 5 mg/kg. The first administration of metyrapone or vehicle was 4 h prior to cisplatin. Further administrations of metyrapone or vehicle were made immediately following cisplatin injection and then at 8 h intervals for the duration of the experiment (metyrapone or vehicle administration is indicated as open squares). Results represent the mean ± S.E.M. of the total numbers of retches + vomits occurring during 1, 0–24 and 24–72 h periods. The number of animals retching and/or vomiting out of the number of animals tested (RV/T) is also shown. Individual latencies to the first episode of retching and/or vomiting are shown as open circles (horizontal lines on the latency plot represent the mean latencies of the respective treatment groups). Significant differences relative to the respective vehicle treated animals are indicated as $^{a}P < 0.001$ (one-way ANOVA followed by a Dunnett's multiple comparison test).

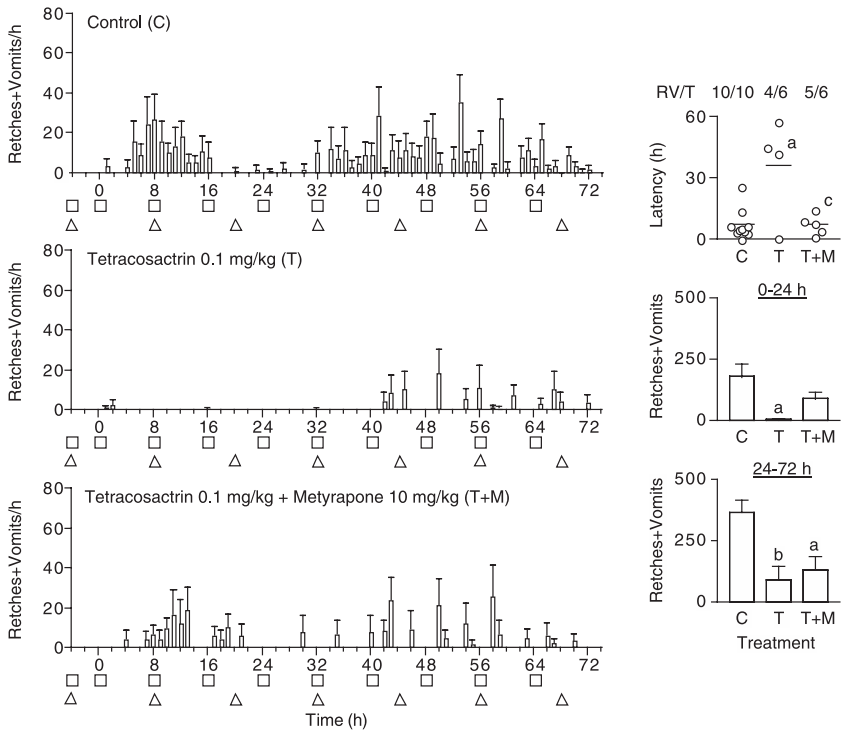

Fig. 2. The effect of vehicle (0.95% benzyl alcohol in saline, 0.1 ml/kg, i.m. + saline 1 ml/kg, i.p.; C) tetracosactrin 0.1 mg/kg, i.m. (T) or tetracosactrin 0.1 mg/kg, i.m. + metyrapone 10 mg/kg, i.p. (T + M) on the profile of retching + vomiting in the ferret induced by a single injection of cisplatin, 5 mg/kg. The first administration of tetracosactrin and/or metyrapone or the respective vehicle treatments was administered 4 h prior to cisplatin. Tetracosactide or vehicle was then injected 8 h post cisplatin administration and then at regular 12 intervals. Further administrations of metyrapone or vehicle were made immediately following cisplatin injection and then at 8 h intervals for the duration of the experiment. Tetracosactrin or vehicle administration is indicated as open triangles, metyrapone or vehicle administration is indicated as open squares. Results represent the mean ± S.E.M. of the total numbers of retches + vomits occurring during 1, 0–24 and 24–72 h periods. The number of animals retching and/or vomiting out of the number of animals tested (RV/T) is also shown. Individual latencies to the first episode of retching and/or vomiting are shown as open circles (horizontal lines on the latency plot represent the mean latencies of the respective treatment groups). Significant differences relative to the respective vehicle treated animals are indicated as $^{a}P<0.05$, $^{b}P<0.001$, significant differences relative to tetracosactrin treated animals is indicated as $^{c}P<0.01$ (one-way ANOVA followed by a Bonferroni's multiple comparison test).

5.9 ± 0.6 min; $P<0.05$). Tetracosactide did not induced emesis during the pretreatment period.

4. Discussion

In man, plasma cortisol levels are inversely related to the development of cisplatin-induced acute emesis (see Introduction). The present studies therefore tested the hypothesis that tetracosactrin, a drug well known to elevate plasma cortisol levels, would reduce emesis and that metyrapone, a drug treatment known to reduce plasma cortisol levels, would potentiate emesis. This hypothesis was essentially confirmed for cisplatin-induced acute emesis. However, the action of the drugs on cisplatin-induced delayed emesis appears more complex and the hypothesis was not supported. The major findings of the study are discussed below.

One of the major findings of the present studies was the impressive anti-emetic action of tetracosactrin to antagonise cisplatin-induced emesis at doses above those producing long lasting (>6 h) elevations of plasma cortisol (ranging from 89% to 410%) in the ferret (Garibaldi et al., 1988; Rosenthal et al., 1993). The anti-emetic action was evident during both the acute and delayed phases and reflects the known activity of the drug in man (see Introduction). The anti-emetic action was selective in that tetracosactrin was ineffective to reduce apomorphine-induced emesis, an emetic challenge also resistant to dexamethasone treatment (Rudd et al., 1996). However, this was expected since apomorphine-induced emesis is rapid in onset and not likely to involve components of the inflammatory cascade.

If tetracosactrin antagonises cisplatin-induced acute emesis by elevating cortisol levels we expected that inhibiting cortisol synthesis would exacerbate the vomiting response. Indeed, metyrapone alone at high doses (30 mg/kg) was transiently emetic and we also observed a potentiation of the initial cisplatin-induced acute retching and vomiting response was seen with metyrapone. It is possible, therefore, that the apparent potentiation of cisplatin-induced emesis is the result of the variable

intrinsic activity of metyrapone. Nevertheless, the apparent potentiation of acute emesis by metyrapone was seen at doses known to reduce plasma cortisol levels in other species and may be reasonably attributed to an inhibition of the 11β-hydroxylase enzyme (Girard et al., 1986; Setchell et al., 1975; Szeberenyi and Garattini, 1969). Unfortunately, we were unable to measure plasma cortisol levels during the present investigations because chronically cannulated animals do not tolerate cisplatin treatment and rapidly deteriorate (Rudd, unpublished data), precluding a meaningful assessment of biochemical and behavioural data.

Since tetracosactrin and glucocorticoids are active to reduce cisplatin-induced delayed emesis, we expected that metyrapone would produce a potentiation of the delayed emetic response. However, metyrapone did not potentiate emesis occurring during the 24–72 h period: if anything a reduction in emesis was observed (although not statistically significant). The failure of metyrapone to potentiate delayed emesis is difficult to explain, even though 30 mg/kg is reported to reduce plasma cortisol levels by at least 60% in other species (e.g. rhesus monkey); the reduction persists longer than 6 h and is evident 2 h after administration (Setchell et al., 1975). In addition, metyrapone alone was not toxic, but cisplatin combined with metyrapone at the high dose of 30 mg/kg was fatal in three out of seven animals. Unfortunately, the mechanism of the interaction between cisplatin and metyrapone to cause toxicity is unknown.

To further investigate the mechanism of tetracosactrin to inhibit emesis we used, metyrapone at 10 mg/kg, three times per day, a treatment that was not emetic alone and that was also inactive to potentiate significantly the retching and vomiting response induced by cisplatin. Yet metyrapone at the repeated dose of 10 mg/kg was effective to reduce the anti-emetic action of tetracosactrin during the acute phase of cisplatin-induced emesis. The data may indicate the importance of the 11β-hydroxylase enzyme and possibly cortisol in the anti-emetic action of tetracosactrin during acute emesis. In contrast, however, metyrapone failed to affect the anti-emetic action of tetracosactrin to reduce delayed emesis.

An examination of the literature reveals that cisplatin itself actually impairs steroid synthesis, but that the inhibitory action is slow in onset (i.e. 2 days) (Maines, 1990; Vacca and Preziosi, 1984). If cisplatin suppresses cortisol secretion in the ferret model, metyrapone may not be expected to impact much on delayed emesis, since the secretion of cortisol may be already impaired. Therefore, it is possible that tetracosactrin antagonises cisplatin-induced delayed emesis via mechanisms not directly involved in the facilitation of cortisol synthesis.

Perhaps an important consideration that may be pertinent to the potential anti-emetic action of tetracosactrin could be its metabolism to biologically active fragments (Reith and Neidle, 1981). Indeed, ACTH fragments (e.g. ACTH-(4-9)) and melanocyte stimulating hormone (a hormone structurally similar to some ACTH fragments) have neuroprotective actions against cisplatin (Gispen et al., 1992; Hol et al., 1995; Windebank et al., 1994). ACTH fragments also reduce plasma free radical levels via cortisol independent mechanisms (Guarini et al., 1996); such actions may be relevant to a capacity to antagonise cisplatin-induced emesis (Torii et al., 1993). Certainly, an ability of ACTH to modulate central neurotransmitter and other mediator levels such as corticotrophin releasing factor or vasopressin is well known (Donovan, 1978; Estienne et al., 1997; Koenig, 1989). Whilst vasopressin is implicated in the emetic reflex, a recent study found that the vasopressin V_{1a} receptor antagonist, (2*S*)1-[(2*R* 3*S*)-5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxybenzene-sulfonyl)-3-hydroxy-2,3-dihydro-1H-indole-2-carbonyl]-pyrrolidine-2-carboxamide (SR49059), was inactive to prevent cisplatin-induced emesis in the piglet (Grélot et al., 2001). No studies have directly examined the potential of corticotrophin releasing hormone to induce emesis, but both ACTH and glucocorticoids can decrease corticotrophin releasing hormone levels (Castro and Moreira, 1996; Holmes et al., 1985) and this may be relevant to their anti-emetic mechanism of action and requires further investigation. Certainly, such mechanisms may operate independently from steroid synthesis.

In conclusion, the studies have revealed an important difference in the mechanisms involved in acute and delayed emesis induced by cisplatin in the ferret and the impressive anti-emetic action of tetracosactrin. The anti-emetic action of tetracosactrin may initially involve an ability to increase cortisol synthesis that subsequently functions to antagonise cisplatin-induced acute emesis. However, the action of tetracosactrin to antagonise cisplatin-induced delayed emesis may be complex and partially independent of mechanisms involved in cortisol synthesis. Apomorphine-induced emesis was not affected by tetracosactrin indicating the action probably does not reflect a general suppression of the emetic reflex. Further studies are required to elucidate the anti-emetic action of tetracosactrin and should include measurements of cortisol function at selected time points during acute and delayed emesis. Tetracosactrin may have advantages over the use of glucocorticoids in the clinic where a longer duration of anti-emetic action is required without suppressing adrenal function.

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