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The Actions of Fenfluramine and Interaction with 5-HT_3 Receptor-Antagonists to Inhibit Emesis in the Ferret

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Abstract—The racemate and (+)- and (−)-isomers of fenfluramine (5 mg kg^{-1} i.p., 1 h pretreatment) antagonized cisplatin-induced retching and vomiting in the ferret. The intravenous injection of (±)-fenfluramine administered on an established cisplatin-induced emesis antagonized the response within minutes of injection. The administration of a lower dose of (±)-fenfluramine (1·0 mg kg^{-1} i.p., 1 h pretreatment) failed to antagonize cisplatin-induced emesis when administered alone but enhanced the antiemetic effects of metoclopramide and ICS 205-930. This pretreatment with (±)-fenfluramine failed to enhance the antiemetic effects of zacopride. It is considered that an action of the racemate on presynaptic 5-HT/catecholaminergic systems to reduce neurotransmitter release may enhance the action of certain 5-HT_3 receptor antagonists in controlling emesis induced by cisplatin.

Emesis induced by chemotherapeutic agents and radiation treatment in animals is antagonized by 5-HT_3 receptor antagonists and agents that reduce 5-hydroxytryptamine (5-HT) and catecholamine levels in the brain (Alphin et al 1986; Andrews et al 1986; Costall et al 1986, 1987; Miner & Sanger 1986; Miner et al 1986, 1987; Stables et al 1987; Barnes et al 1988a; King et al 1988; Cohen et al 1989), indicating an important role for 5-HT in emesis (see review by Andrews et al 1988). Subsequently, 5-HT_3 receptor antagonists have been shown clinically to reduce or abolish emesis induced by cisplatin and other agents (Cunningham et al 1987; Liebundgut & Lancranjan 1987; Carmichael et al 1989; Kris et al 1989). However, whilst they are clinically of great benefit, there is a less than satisfactory control of emesis in some patients, and it remains possible that the failure of 5-HT_3 receptor antagonists to secure a complete control of emesis in all patients may reflect an incomplete antagonism of 5-HT function. With this in mind, the aim of the present study was to investigate in the ferret whether disruption of 'presynaptic' 5-HT function caused by (±)-fenfluramine, when combined with a disruption of postsynaptic 5-HT function caused by 5-HT_3 receptor antagonists, could achieve a synergistic effect that would control cisplatin-induced emesis. Cisplatin was selected as causing a particularly severe emesis; (±)-fenfluramine was selected rather than reserpine or *p*-chlorophenylalanine (see Barnes et al 1988a) as a safer drug for potential clinical use.

Materials and Methods

Animals

Albino or Fitch male ferrets (0·9–1·7 kg), bred at the University of Bradford, were housed individually at 22 ± 1°C under artificial lighting, with lights on between 07.00 and 21.00 h.

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Induction and measurement of emesis

During the afternoon feeding time (13.40–14.00 h) the ferrets were presented with cat food; water was freely available. After 60–90 min animals were anaesthetized with halothane (N_2O/O_2 carrier) and an incision approximately 2 cm long was made in the skin above one jugular vein and a cannula inserted for the administration of cisplatin (see below) after which the vein was ligated and the wound sealed with cyanoacrylate adhesive. Animals were placed in individual observation cages and began to recover from the anaesthetic within 5 min. After some 10–15 min animals were actively exploring the cages with no overt discomfort from the wound.

In other experiments a cannula was inserted into the jugular vein as described above and exteriorized through the back of the neck. The animals were kept in individual cages and the cannula flushed daily with 0·9% NaCl (saline). Three days after cannulation the ferrets were used without anaesthetic for the intravenous injection of cisplatin and (±)-fenfluramine (see below).

The onset of emesis, characterized by rhythmic abdominal contractions which were associated with the expulsion of liquid or solid material from the gastrointestinal tract (i.e. vomiting) or not associated with the passage of material (i.e. retching), was recorded for each animal. The number of episodes of emesis and the number of vomits and retches during the observation periods were noted. In additon, any overt changes in behaviour were recorded before and during emesis.

Experimental design

In most of the experiments (±)-, (+)- or (−)-fenfluramine was administered i.p. to non-anaesthetized ferrets 60 min before the i.v. injection of cisplatin or its vehicle in the acutely cannulated (anaesthetized) animals. The effect of a combined treatment of (±)-fenfluramine with 5-HT_3 receptor antagonists to antagonize cisplatin-induced emesis was attempted using a dose of (±)-fenfluramine that failed to reduce emesis and threshold antiemetic doses of the metoclopramide, ICS

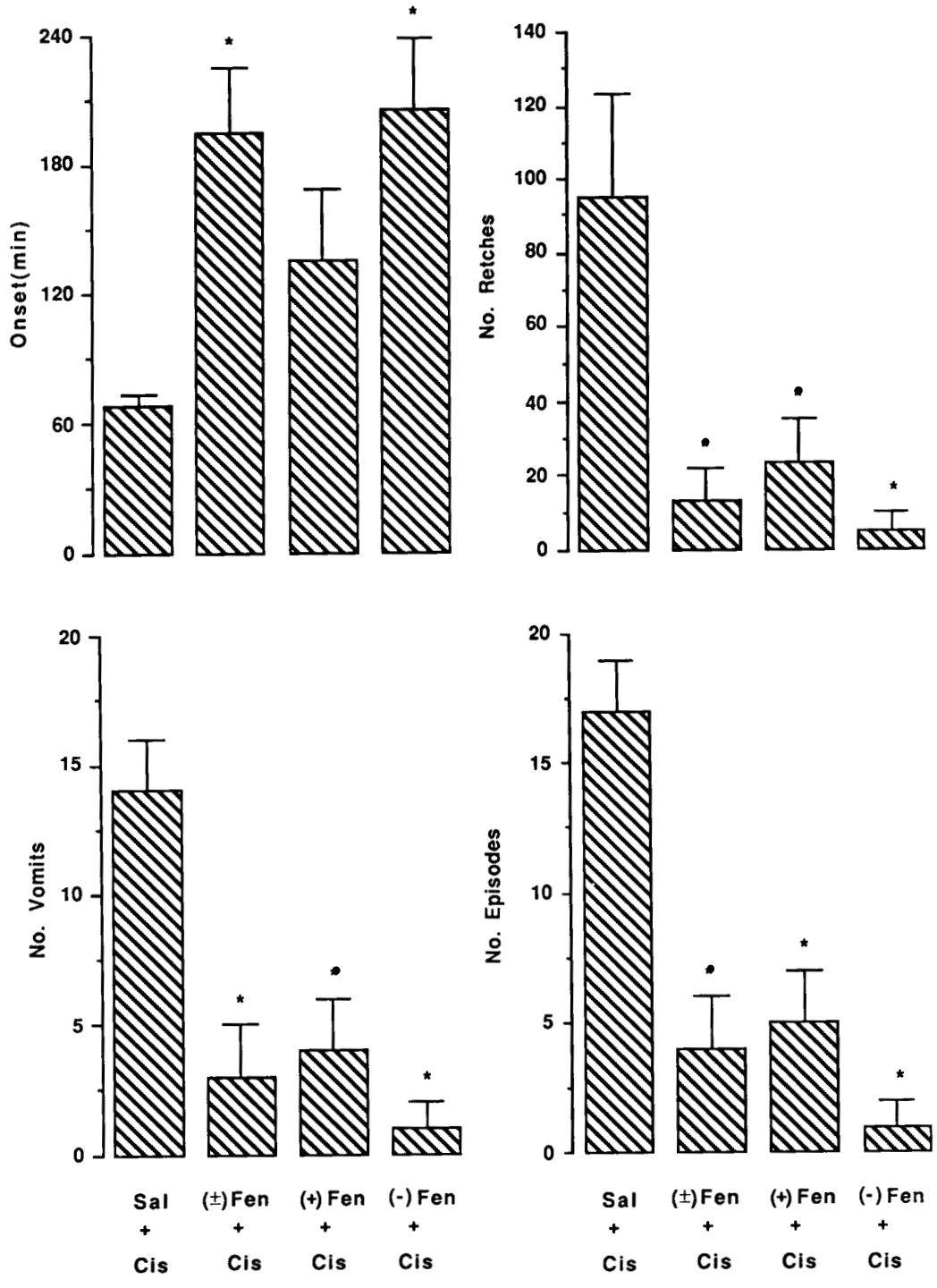

FIG. 1. The effect of (±)-fenfluramine and its isomers on cisplatin-induced emesis in the ferret. Saline (Sal), (±)-fenfluramine ((±)-Fen), (−)-fenfluramine ((−)-Fen) or (+)-fenfluramine ((+)-Fen), (5 mg kg^{-1}) were administered intraperitoneally 1 h before cisplatin (Cis, 10 mg kg^{-1} i.v.). Values are the means ±s.e.m.'s of 4 determinations. Significant differences in the time to onset of emesis, the number of retches, vomits or episodes compared with control values (Sal + Cis) are indicated *$P < 0.05$ (Mann-Whitney U-test). (If an animal failed to either retch or vomit during a 4 h observation period then the time of onset was taken as 240 min.)

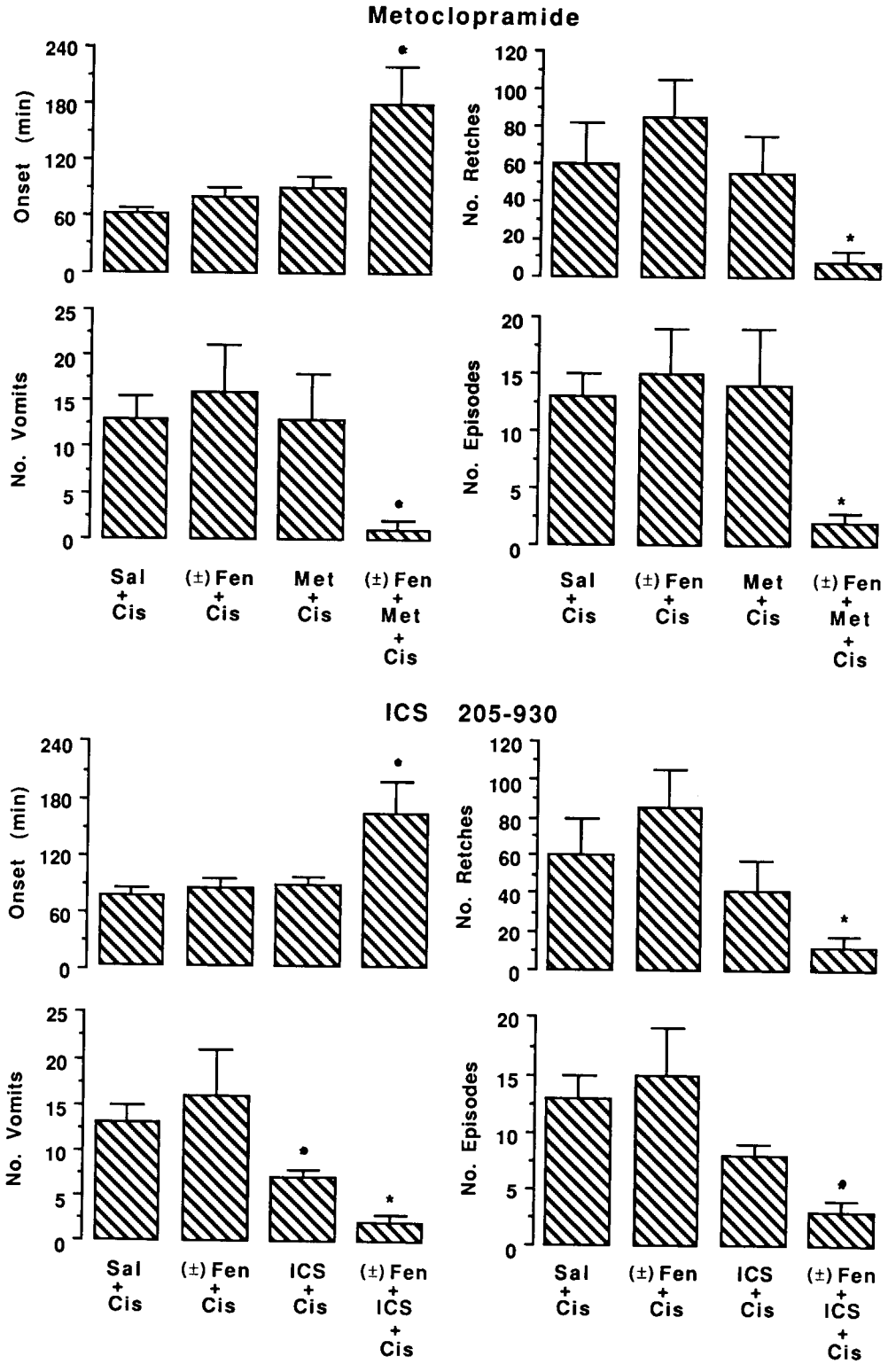

FIG. 2. The ability of (±)-fenfluramine to enhance the actions of metoclopramide and ICS 205-930 in antagonizing cisplatin-induced emesis in the ferret. Some animals received cisplatin (Cis 10 mg kg^{-1} i.v.) after a 1 h pretreatment with saline (Sal 1 mL kg^{-1}), (±)-fenfluramine ((±)Fen 1 mg kg^{-1} i.p.), metoclopramide (Met 1 mg kg^{-1} i.v.) or ICS 205-930 (ICS 0·01 mg kg^{-1}); others received cisplatin after a combined pretreatment with (±)-fenfluramine (1 mg kg^{-1}) administered 1 h before metoclopramide (Met 1 mg kg^{-1}) or ICS 205-930 (0·01 mg kg^{-1}). Values are the means ± s.e.m. of 5 determinations. Significant differences compared with the respective cisplatin control (Sal + Cis) values are indicated *$P < 0·05$ (Mann-Whitney U-test). (If an animal failed to retch or vomit during the 4 h observation period the time of onset was taken as 240 min.)

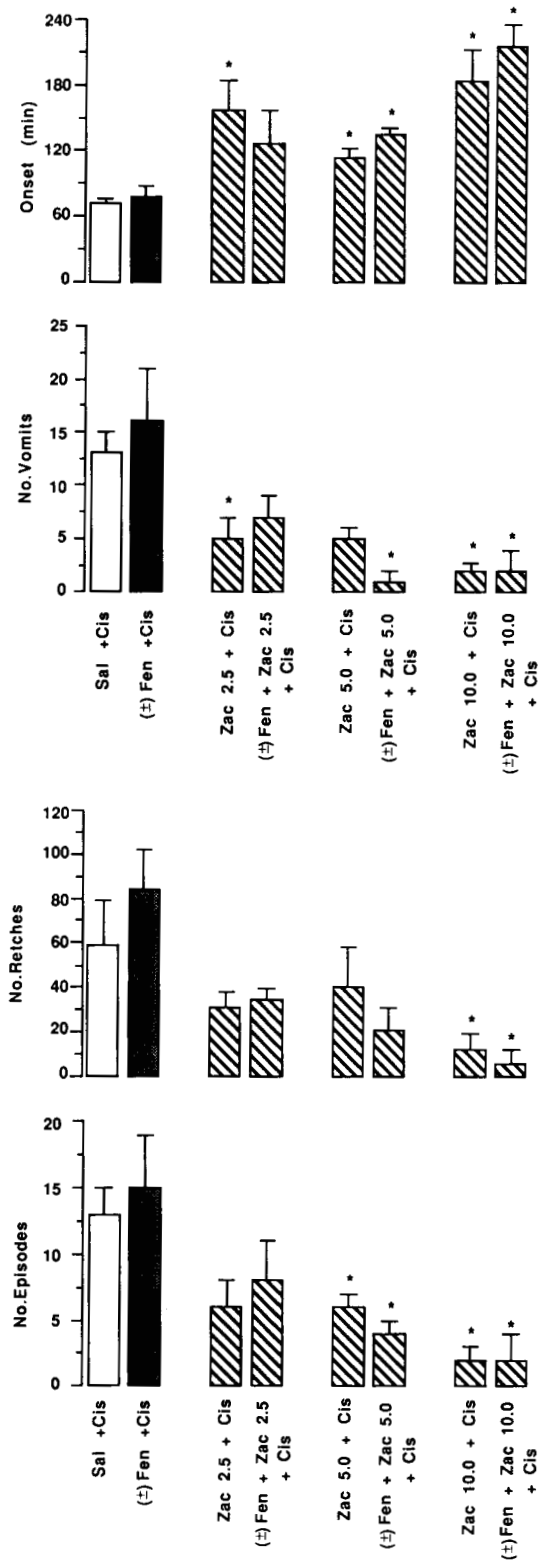

FIG. 3. The ability of (±)-fenfluramine to modify the actions of zacopride in antagonizing cisplatin. Some animals received cisplatin (10 mg kg^{-1} i.v.) after a 1 h pretreatment with saline (Sal 1 mL kg^{-1}) or (±)-fenfluramine ((±)Fen 1·0 mg kg^{-1} i.v.); others received cisplatin after a combined pretreatment with (±)-fenfluramine (1 mg kg^{-1} i.v.) administered 1 h before zacopride (Zac 2·5, 5 or 10 μg kg^{-1} i.v., 1 h pretreatment). Values are the means ± s.e.m. of 5 determinations. Significant differences compared with the respective cisplatin control (Sal + Cis) values are indicated *$P < 0.05$ (Mann-Whitney U test). (If an animal failed to vomit or retch during the observation period then the time of onset was taken as 240 min.)

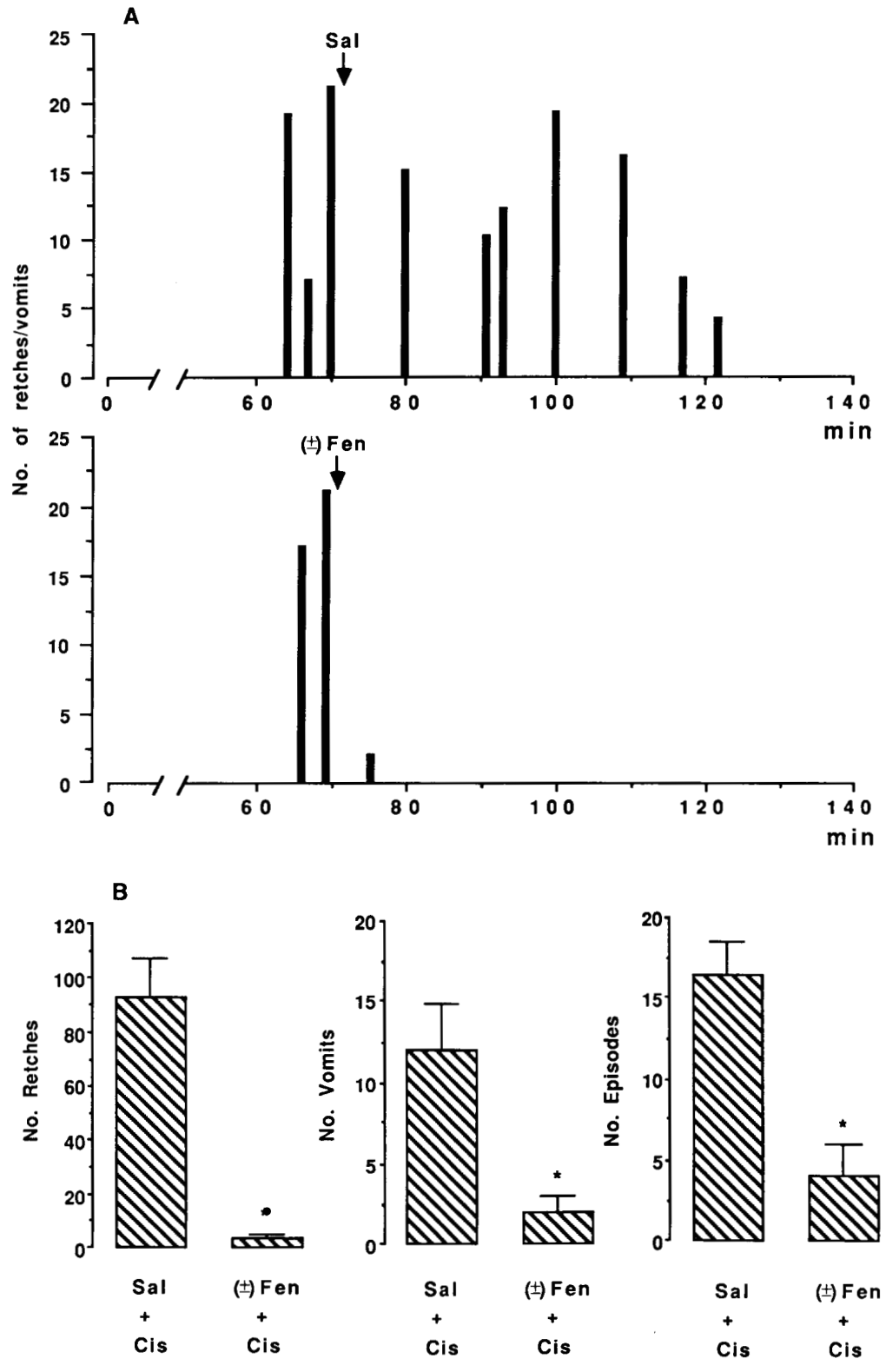

FIG. 4. The effect of (±)-fenfluramine in antagonizing an established emetic response induced by cisplatin (10 mg kg^{-1} i.v.) in the ferret. Saline (Sal) or (±)-fenfluramine ((±)Fen 5 mg kg^{-1} i.v.) was injected via the chronically indwelling venous cannula as soon as the animal had completed its first or second episode of retching and vomiting. A. Example profiles of emesis induced by cisplatin and the effect of treatment with saline or (±)-fenfluramine. B. The antagonism by (±)-fenfluramine of cisplatin-induced emesis in the 4 h period following the injection of (±)-fenfluramine. Values are the means ± s.e.m.s of 5 determinations. Significant differences compared with Sal + Cis are indicated $*P < 0.05$ (Mann-Whitney U test).

205-930 or zacopride. In these experiments, (±)-fenfluramine was administered i.p. 60 min before the i.v. injection of 5-HT$_3$ receptor antagonist followed immediately by the i.v. injection of cisplatin in acutely cannulated ferrets.

In chronically cannulated animals and in the absence of anaesthetic, (±)-fenfluramine was administered i.v. on an established emetic response induced by an i.v. administration of cisplatin 10 mg kg^{-1} injected approximately 60 to 70 min as a pretreatment.

The significance of differences between treatments was assessed using the Mann-Whitney U test.

Drugs

Cisplatin (Lederle) was prepared in 0·9% NaCl (saline) at 70–75°C, followed by gradual cooling to 40–50°C and then immediate administration. Metoclopramide monohydrochloride (Beecham), zacopride HCl (A. H. Robins), ICS 205–930 [3α-tropanyl-1H-indole-3-carboxylic acid ester) (Sandoz), and (±)-, (+)- and (−)-fenfluramine HCl (A. H. Robins) were prepared in distilled water. All drugs were administered in a volume of 1 mL kg^{-1} except cisplatin which was injected at a rate of 1 mL min^{-1} over 10 min. All doses are expressed as the base.

Results

Antagonism by the racemate and isomers of fenfluramine of cisplatin-induced emesis

(±)-Fenfluramine and the (+)- and (−)-isomers (5 mg kg^{-1} i.p., 1 h pretreatments) antagonized the retching and vomiting responses induced by cisplatin (10 mg kg^{-1} i.v.). The time to onset of retching and vomiting was increased, and the number of retches, vomits and episodes of retching and vomiting were decreased by all three treatments. There was a trend for the (+)-isomer to achieve a greater antagonism than either the (−)-isomer or racemate, but this did not reach statistical significance (Fig. 1). The animals treated with (±)- and (+)-fenfluramine appeared sedated, whereas those receiving (−)-fenfluramine could move around the cage if disturbed. Pretreatment with (±)- and (+)-fenfluramine did not appear to delay recovery of the righting reflex induced by the anaesthetic.

The effects of combined treatments of (±)-fenfluramine with metoclopramide, ICS 205-930 or zacopride in antagonizing cisplatin (10 mg kg^{-1} i.v.)-induced emesis

The administration of (±)-fenfluramine (1 mg kg^{-1} i.p.) 1 h before an intravenous injection of cisplatin did not prevent the development of emesis. Metoclopramide (1 mg kg^{-1} i.v.) was chosen as a dose which, given alone, also failed to protect against cisplatin, yet when administered as a combined treatment with (±)-fenfluramine (1 mg kg^{-1} i.v.) prevented emesis in 2 of 5 animals tested and markedly attenuated the emetic response in the remaining ferrets (Fig. 2).

ICS 205-930 (0·01 mg kg^{-1} i.v.) was selected as a threshold dose failing to significantly modify the onset of cisplatin emesis or the number of retches or emetic episodes, although significantly reducing the number of vomits. A combined treatment with ICS 205–930 (0·01 mg kg^{-1} i.v.) plus (±)-fenfluramine (1·0 mg kg^{-1} i.p.) caused a significant decrease in the emetic response to cisplatin; 3 out of 5 animals had only one emetic episode or none; there was a marked reduction in emesis in the remaining animals (Fig. 2).

Zacopride (2·5 and 5·0 μg kg^{-1}) administered intravenously caused a consistent trend to reduce cisplatin-induced emesis. The delay in the onset of emesis achieved significance using both doses, although the reductions in the number of retches, vomits and episodes frequently failed to achieve significance. There was also a trend for (±)-fenfluramine to enhance the antiemetic effects of zacopride 5·0 μg kg^{-1}, but such antagonisms were not significantly different from those observed in animals that had received zacopride alone (Fig. 3).

The ability of (±)-fenfluramine to antagonize an established emetic response induced by cisplatin

Cisplatin (10 mg kg^{-1} i.v.) was administered without the use of anaesthesia via a chronically indwelling cannula positioned in the jugular vein. As soon as the animal had completed its first emetic episode, (±)-fenfluramine (5 mg kg^{-1}) was administered via the cannula as a bolus injection. Within minutes of injection the drug abolished or markedly reduced vomiting and retching in all animals (Fig. 4).

Discussion

We have demonstrated that, like (±)-fenfluramine, its (+)- and (−)-isomers can antagonize cisplatin-induced emesis in the ferret, and that a pretreatment with the racemate enhances the antiemetic potential of metoclopramide and ICS 205-930. In the latter studies the doses of (±)-fenfluramine, metoclopramide and ICS 205-930 selected, when given alone, had little or no effect in antagonising cisplatin-induced emesis. Although metoclopramide has both dopamine and 5-HT$_3$ receptor antagonist properties, ICS 205-930 is a highly selective 5-HT$_3$ receptor antagonist (Richardson et al 1985) and the synergistic interaction between these agents and (±)-fenfluramine probably reflects a more effective disruption of 5-HT neurotransmission. A presynaptic reduction in 5-HT release would contribute to a more effective postsynaptic 5-HT$_3$ receptor blockade, and there is considerable evidence that (±)-fenfluramine can modify the synthesis, storage, release and reuptake of 5-HT (Duhault & Verdavainne 1967; Costa et al 1971; Belin et al 1976; Fuller et al 1978; Steranka & Sanders-Bush 1979); there is no evidence that (±)-fenfluramine has affinity for the 5-HT$_3$ receptor (Barnes, personal communication). However, this interpretation of the interaction between (±)-fenfluramine and the 5-HT$_3$ receptor antagonists in terms of pre- and postsynaptic actions on the 5-HT system may be too simplistic.

(±)-Fenfluramine was used as an acute treatment and there is no evidence that it or its isomers at the doses used can cause a significant depletion of 5-HT within 1 or 2 h (Invernizzi et al 1986). Furthermore, the rapidity of action of (±)-fenfluramine in antagonizing within minutes of injection an established emetic response to cisplatin indicates a rapid and incisive antagonistic effect. Again, it is difficult to envisage that the inhibition of 5-HT synthesis could significantly contribute to such an effect. Also, the two isomers of fenfluramine appeared equipotent in inhibiting cisplatin-induced emesis, whereas (+)-fenfluramine is slightly more potent than (−)-fenfluramine in depleting cerebral 5-HT (Invernizzi et al 1986). Furthermore, the racemate and isomers also influence catecholamine function, particularly

in the area postrema (Invernizzi et al 1986; Barnes et al 1988b). Such data indicate that the antimetic effects of (±)-fenfluramine might relate to an inhibition of 5-HT or catecholamine release, or inhibition of neurotransmitter function in other unspecified systems.

It remains an interesting observation that pretreatment with (±)-fenfluramine failed to consistently enhance the antiemetic effects of the 5-HT_3 receptor antagonist zacopride (Smith et al 1988; Cohen et al 1989). Zacopride is an extremely potent antiemetic agent (Smith et al 1986, 1989; Cohen et al 1989), and at an estimated threshold dose of 5 $\mu g\ kg^{-1}$ caused a reduction of cisplatin-induced emesis which was enhanced by pretreatment with (±)-fenfluramine. However, zacopride alone was more effective than anticipated, and the enhancement by (±)-fenfluramine failed to achieve significance. Therefore a smaller dose (2·5 $\mu g\ kg^{-1}$) was used and found to reduce emesis to the same extent as the larger dose, but (±)-fenfluramine failed to increase the antiemetic effect. The data indicate that a 5-HT_3 receptor antagonism may not be the essential prerequisite for the synergism between (±)-fenfluramine and metoclopramide or ICS 205-930 in inhibiting emesis. Alternatively, the failure of (±)-fenfluramine to enhance the antiemetic action of zacopride might relate to the affinity of zacopride for other 5-HT receptors. Thus the gastrointestinal prokinetic effects of the substituted benzamides, which may influence an antiemetic potential, may be mediated via a non-classical 5-HT receptor designated 5-HT_4 (Dumuis et al 1989a). Zacopride has an agonist action at the 5-HT_4 receptor whereas ICS 205-930 is an antagonist (Dumuis et al 1989b). The significance of these findings to the present study is not clear but deserving of further study.

The precise site(s) of action of (±)-fenfluramine and the 5-HT_3 receptor antagonists in inhibiting emesis is not known, and may involve peripheral and/or central site(s) (see review by Andrews et al 1988; Barnes et al 1988a). The location of 5-HT and a high density of 5-HT_3 recognition sites in the area postrema may indicate a central site of action (Barnes et al 1988a, b; Higgins et al 1989). The chemoreceptor trigger zone located within the area postrema contributes importantly to the emetic reflex (Borison et al 1984) although it is uncertain whether (±)-fenfluramine can exert additional influence at other sites within the emetic circuits. The recent demonstration that the racemate can also antagonize the emesis induced by apomorphine, lisuride and ipecacuanha indicates the potential breadth of antiemetic activity (Costall et al 1989).

In summary, (±)-fenfluramine has been shown to enhance the effects of metoclopramide and ICS 205-930 in inhibiting cisplatin-induced emesis in a ferret model. Further analyses of the sites and mechanisms of interactions between (±)-fenfluramine and 5-HT_3 receptor antagonists may contribute to an understanding of the systems mediating emesis, and the development of additional therapeutic strategies for the treatment of drug and radiation induced emesis.

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References

Alphin, R. S., Smith, W. L., Jackson, C. B., Droppleman, D. A., Sancilio, L. F. (1986) Zacopride (AHR11190B): A unique and potent gastrointestinal prokinetic and anti-emetic agent in laboratory animals. Dig. Dis. Sci. 31: 4825

Andrews, P. L. R., Hawthorn, J., Sanger, G. J. (1986) The effect of abdominal visceral nerve lesions and a novel 5HT-M receptor antagonist on cytotoxic and radiation induced emesis in the ferret. J. Physiol. 382: 47P

Andrews, P. L. R., Rapeport, W. G., Sanger, G. J. (1988) Neuropharmacology of emesis induced by anti-cancer therapy. Trends Pharmacol. Sci. 9: 334–341

Barnes, J. M., Barnes, N. M., Costall, B., Naylor, R. J., Tattersall, F. D. (1988a) Reserpine, parachlorophenylalanine and fenfluramine antagonise cisplatin-induced emesis in the ferret. Neuropharmacology 27: 783–789

Barnes, N. M., Costall, B., Naylor, R. J., Tattersall, F. D. (1988b) Identification of 5-HT_3 recognition sites in the ferret area postrema. J. Pharm. Pharmacol. 40: 586–588

Belin, M.-F., Kouyoumdhan, J.-C., Bandakdjian, J., Duhault, J., Gonnard, P. (1976) Effects of fenfluramine on accumulation of 5-hydroxytryptamine and other neurotransmitters into synaptosomes of rat brain. Neuropharmacology 15: 613–617

Borison, H. L., Borison, R., McCarthy, L. E. (1984) Role of the area postrema in vomiting and related functions. Fed. Proc. 43: 2955–2958

Carmichael, J., Cantwell, B. M. J., Edwards, C. M., Zussman, B. D., Thompson, S., Rapeport, W. G., Harris, A. L. (1989) A pharmacokinetic study of granisetron (BRL 43694A), a selective 5-HT_3 receptor antagonist: correlation with anti-emetic response. Cancer Chem. Pharmacol. 24: 45–49

Cohen, M. L., Bloomquist, W., Gidda, J. S., Lacefield, W. (1989) Comparison of the 5-HT_3 receptor antagonist properties of ICS 205-930, GR38032F and zacopride. J. Pharmacol. Exp. Ther. 248: 197–202

Costa, E., Groppetti, A., Revuelta, A. (1971) Action of fenfluramine on monoamine storage of the rat tissue. Br. J. Pharmacol. 41: 57–64

Costall, B., Domeney, A. M., Naylor, R. J., Tattersall, F. D. (1986) 5-hydroxytryptamine M-receptor antagonism to prevent cisplatin-induced emesis. Neuropharmacology 25: 959–961

Costall, B., Domeney, A. M., Naylor, R. J., Tattersall, D. F. (1987) Emesis induced by cisplatin in the ferret as a model for the detection of antiemetic drugs. Ibid. 26: 1321–1326

Costall, B., Naylor, R. J., Rudd, J. A., Tattersall, F. D. (1989) Fluphenazine, ICS205-930 and dl-fenfluramine differentially antagonise drug induced emesis in the ferret. Ibid. In press

Cunningham, D., Pople, A., Ford, H. T., Hawthorn, J., Gazet, J.-C., Challoner, R. (1987) Prevention of emesis in patients receiving cytotoxic drugs by GR38032F, a selective 5-HT_3 receptor antagonist. Lancet i: 1461–1462

Duhault, J. Verdavainne, C. (1967) Modification du taux de serotonine cerebral chez le rat par iles trifluoromethylphenyl-2-ethyl-aminopropane fenfluramine 7682. Archs. Int. Pharmacodyn. Ther. 170: 276–286

Dumuis, A., Bouhelal, R., Sebben, M., Cory, R., Bockaert, J. (1989a) A nonclassical 5-hydroxytryptamine receptor positively coupled with adenylate cyclase in the central nervous system. Molec. Pharmacol. 34: 880–887

Dumuis, A., Sebben, M., Bockaert, J. (1989b) The gastrointestinal prokinetic benzamide derivatives are agonists at the non-classical 5-HT receptor (5-HT_4) positively coupled to adenylate cyclase in neurons. Naunyn-Schmiedeberg's Arch. Pharmacol. 340: 403–410

Fuller, R. W., Snoddy, H. D., Hemrick, S. K. (1978) Effects of fenfluramine and norfenfluramine on brain serotonin metabolism in rats. Proc. Soc. Exp. Biol. Med. 157: 202–205

Higgins, G. A., Kilpatrick, G. J., Bunce, K. T., Jones, B. J., Tyers, M. B. (1989) 5-HT_3 receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. Br. J. Pharmacol. 97: 247–255

Invernizzi, R., Berettera, C., Garattini, S., Samanin, R., (1986) D- and l-isomers of fenfluramine differ markedly in their interaction

with brain serotonin and catecholamines in the rat. Eur. J. Pharmacol. 120: 9–15

King, G., Landauer, V., Kessler, D., Davis, E. (1988) Zacopride, a 5-HT$_3$ antagonist, modifies emetic and behavioural responses to radiation in the ferret. FASEB 2: A325

Kris, M. G., Gralla, R. J., Clark, R. A., Tyson, L. B. (1989) Phase II trials of the serotonin antagonist GR38032F for the control of vomiting caused by cisplatin. J. Natl. Cancer Inst. 81: 42–46

Liebundgut, U., Lancranjan, I. (1987) First results with ICS 205-930 (5-HT$_3$ receptor antagonist) in prevention of chemotherapy-induced emesis. Lancet i: 1198

Miner, W. D., Sanger, J. J. (1986) Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. Br. J. Pharmacol. 88: 497–499

Miner, W. D., Sanger, G. J., Turner, D. H. (1986) Comparison of the effect of BRL24924, metoclopramide and domperidone on cisplatin-induced emesis in the ferret. Ibid. 88: 374P

Miner, W. D., Sanger, G. J., Turner, D. H. (1987) Evidence that 5-hydroxy-tryptamine$_3$ receptors mediate cytotoxic drug and radiation-evoked emesis. Br. J. Cancer 56: 159–162

Richardson, B. P., Engel, G., Donatsch, P., Stadler, P. A. (1985) Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs. Nature 316: 126–131

Smith, W. L., Jackson, C. B., Proakis, A. G., Leonard, C. A., Munson, H. R., Alphin, R. S. (1986) Zacopride (AHR11190B): a unique and potent inhibitor of cancer chemotherapy-induced emesis in dogs. Proc. Am. Soc. Clin. Oncology 5: 260

Smith, W. L., Sancilio, L. F., Naylor, R. J., Owera-Atepo, J. B., Lambert, L. (1988) Zacopride: a potent 5-HT$_3$ antagonist. J. Pharm. Pharmacol. 40: 301–302

Smith, W. L., Alphin, R. S., Jackson, C. B., Sancilio, L. F. (1989) The antiemetic profile of zacopride. Ibid. 41: 101–105

Steranka, L. R., Sanders-Bush, E. (1979) Long term effects of fenfluramine on central serotonergic mechanisms. Neuropharmacology 18: 895–903

Stables, R., Andrews, P. L. R., Bailey, H. E., Gunning, S. J., Hawthorn, J., Naylor, R. J., Tyers, M. B. (1987) Antiemetic properties of the 5-HT$_3$ receptor antagonist, GR38032F. Cancer Treatment Rev. 14: 333–336