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# Fenfluramine antagonizes the stimulation of food intake induced by the putative 5-hydroxytryptamine$_{1A}$ agonist, isapirone, in non-fasted rats

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Isapirone, a 5-hydroxytryptamine$_{1A}$ receptor agonist, stimulated food intake in non-fasted rats in a dose-dependent manner (1, 3 and 10 mg kg$^{-1}$ s.c.). Fenfluramine, an antiobesity agent and a 5-HT releaser, at 3 and 10 mg kg$^{-1}$ s.c. antagonized the isapirone-induced (3 mg kg$^{-1}$ s.c.) feeding. These results are consistent with the known inhibitory role of 5-HT in the control of food intake in rats.

Isapirone (TVX Q 7821) has been shown to be a potent anxiolytic and antiaggressive agent (Traber et al 1984) when tested in animal models of anxiety. Unlike the classical anxiolytics, isapirone does not have affinity for the benzodiazepine/γ-aminobutyric acid receptor complex (Traber et al 1984; Dompert et al 1985). Radioreceptor binding studies with [$^3$H]isapirone, [$^3$H]5-hydroxytryptamine (5-HT) and [$^3$H]8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) showed that isapirone binds to 5-HT$_{1A}$ receptors in brain membranes and slices (Dompert et al 1985; Glaser et al 1985; Smith & Peroutka 1986). Unlike 8-OH-DPAT, another non-benzodiazepine anxiolytic agent, isapirone at doses up to 80 mg kg$^{-1}$ (Spencer et al 1984; Smith & Peroutka 1986) produces minimal evidence for the presence of 5-HT behavioural syndrome, which is characteristic of postsynaptic 5-HT receptor stimulation (Hjorth et al 1982). It is a common belief (Blundell 1977; Blundell & Hill 1985) that 5-HT plays an inhibitory role in the control of feeding behaviour in which, for example, the antiobesity agent, fenfluramine, a releaser of 5-HT, decreases food intake and the 5-HT antagonist, cyproheptadine, increases food intake (Samanin et al 1980; Baxter et al 1970). Nevertheless, 8-OH-DPAT, a 5-HT$_{1A}$ receptor agonist, has been reported to stimulate food intake in freely feeding rats (Dourish et al 1985). In these preliminary studies, we also observed the stimulation of food intake with an acute administration of isapirone (Dourish et al 1986), which was antagonized by fenfluramine.

## *Methods*

Thirty-six male Sprague-Dawley rats (240–290 g, Harlan Industries, Cumberland, IN, USA) were housed, with free access to Purina Chow pellets and water, in a room with 12 h dark/light cycle (lights on at 0600h) at 23 °C. On the day of the experiment, rats were randomly divided into six groups (6 rats per group) and caged individually. Isapirone (0·03, 0·1, 1, 3 or 10 mg kg$^{-1}$ s.c.) or saline was administered to rats at 1130h (0·5 h before food access). Food intake during the first hour of feeding was recorded by weighing the food pellets and spillage at the beginning and the end of the period.

In a separate experiment, rats were administered saline or fenfluramine (a racemate) at 3 or 10 mg kg$^{-1}$ s.c. Isapirone was injected at a dose of 3 mg kg$^{-1}$ s.c. 0·5 h later to half of the saline-treated and all of the fenfluramine-treated groups (6 rats per group). Feeding began immediately, and the amount of food consumed at the end of 1 h was recorded.

## *Results and discussion*

Isapirone (Fig. 1), at doses of 1, 3 and 10 mg kg$^{-1}$, significantly stimulated food intake in rats by 137, 240 and 190% above control level ($P < 0·05$, $< 0·001$ and $< 0·025$, respectively, according to Student's *t*-test). In the second experiment, isapirone at 3 mg kg$^{-1}$ s.c.

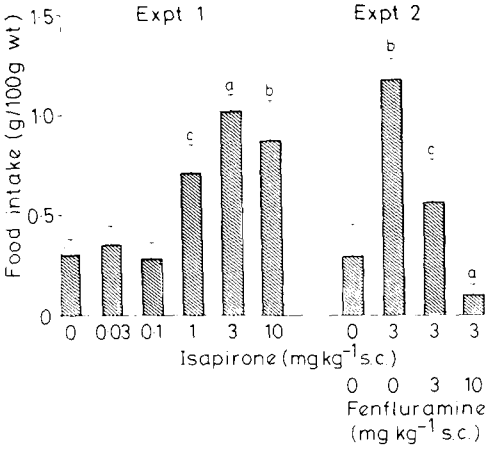


FIG. 1. Dose-dependent stimulation of food intake by isapirone (Expt 1) and reversal by fenfluramine (Expt 2) in rats. Groups of 6 rats were treated with isapirone at the doses indicated to control and fenfluramine-treated rats. Each bar represents the mean (± s.e.) intake for 6 rats during a 1 h test. Significant difference between the treated groups and the corresponding control-saline groups were determined by Student's *t*-test. (a, $P < 0·001$; b, $P < 0·025$; c, $P < 0·05$).

* Correspondence.

stimulated food intake by 322% above the saline-treated control group ($P < 0.005$). Pretreatment with fenfluramine at 3 and 10 mg $kg^{-1}$ reduced food intake to one-third of the isapirone-stimulated feeding ($P < 0.05$) and to below control level ($P < 0.001$), respectively.

The dose-dependent stimulation of food intake by isapirone observed here resembles the increase in feeding induced by another $5HT_{1A}$ agonist, 8-OH-DPAT (Dourish et al 1985), except that 8-OH-DPAT inhibited feeding at high doses (Dourish et al 1985, 1986). The two compounds exhibit comparable potencies. The present studies represent the first demonstration of the ability of fenfluramine, an antiobesity agent and a 5-HT releaser, to reverse the stimulation of food intake by a $5\text{-}HT_{1A}$ agonist. Apparently, 5-HT released into the synapse by fenfluramine prevents the response to the administration of isapirone. An alternative method to increase synaptic availability of 5-HT by a selective inhibitor of 5-HT reuptake, including fluoxetine, sertraline and indalpine, is also effective (unpublished data). These observations are consistent with the idea that the $5\text{-}HT_{1A}$ agonists might stimulate the 5-HT autoreceptors (Hjorth et al 1982; Carlsson et al 1985), resulting in a decrease of 5-HT release. Indeed, based on intracellular recording studies, dorsal raphe 5-HT neurons are highly responsive to isapirone (Sprouse & Aghajanian 1985). However, the present studies cannot rule out a 5-HT antagonist action of isapirone as an explanation for its stimulation of feeding. The findings that fenfluramine, a 5-HT releaser, antagonizes hyperphagia induced by the $5\text{-}HT_{1A}$ agonist isapirone, are also consistent with an inhibitory role of 5-HT in the control of food intake (Blundell & Hill 1985).

Salbutamol, an agonist at $\beta_2$-adrenoceptors and a known anorectic agent (Borsini et al 1982), also reversed isapirone-induced feeding (unpublished observation). The anorectic effect of salbutamol in meal-fed rats was considered to be mediated centrally by $\beta_2$-adrenoceptors, which might also be involved in the attenuation of hyperphagia induced by the $5\text{-}HT_{1A}$ agonist isapirone. Indeed, $\beta_2$-adrenoceptors can mediate an increase of tremor intensity induced by 5-hydroxytryptophan in rats (Hallberg 1986), and salbutamol is also known to stimulate 5-HT turnover in several rat brain areas (Waldmeier 1981; Erdö et al 1982).

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