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# Evidence that blockade of post-synaptic 5-$HT_1$ receptors elicits feeding in satiated rats

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**Abstract.** The effects of nine central 5-HT antagonists on food intake in free feeding male rats were examined. The 5-$HT_2$ antagonists ritanserin and ketanserin and the selective 5-$HT_3$ antagonists ICS 205–930 and MDL 72222 had no effect on food intake. In contrast, the non-selective 5-HT antagonists metergoline, methiothepin, mesulergine, mianserin and methysergide (all of which have high affinity for various 5-$HT_1$ receptor subtypes), dose-dependently increased food intake during a 4-h daytime test. Furthermore, metergoline dose dependently increased food intake over a 24-h period. Suprisingly, mesulergine decreased food intake over a 24-h period at the same doses that increased daytime food intake. This may indicate that the increase in daytime feeding produced by mesulergine is a non-specific response. Although the antagonists used have varying degrees of selectivity for 5-HT receptor subtypes, the pattern of results suggests that postsynaptic 5-$HT_1$ receptors (possibly of the 5-$HT_{1C}$ type) play an important role in the control of feeding in rats.

**Key words:** Feeding – 5-HT antagonists – 5-$HT_1$ receptors – 5-$HT_{1C}$ receptors – Rat

In general, the results of drug studies have indicated that enhancing central 5-hydroxytryptamine (5-HT) transmission decreases food intake (see Blundell 1977 for a review). Thus, 5-HT releasers such as *para*-chloroamphetamine and fenfluramine (Owen 1963; Rowland and Carlton 1986), 5-HT uptake inhibitors like zimelidine and fluoxetine (Goudie et al. 1976; Simpson et al. 1981; Reid et al. 1984) and 5-HT agonists such as quipazine, 1-(3-chlorophenyl) piperazine (mCPP), RU 24969 and MK-212 (Clineschmidt et al. 1977; Samanin et al. 1979; Dourish et al. 1986; Kennett et al. 1987) all decrease food intake. In contrast, decreasing 5-HT transmission by 5,7-dihydroxytryptamine lesions of 5-HT neurones or *para*-chlorophenylalanine-induced 5-HT depletion has been reported to increase feeding, albeit not in all studies (Saller and Stricker 1976; Blundell 1977; Coscina 1978; Hoebel et al. 1978; Dourish et al. 1986). Therefore, it has been proposed that endogenous 5-HT has a tonic inhibitory role in the control of feeding behaviour (Blundell 1977).

From the aforementioned hypothesis, it would be predicted that blockade of the action of endogenous 5-HT on its receptor by a 5-HT antagonist should increase food intake. To date, however, there is very limited evidence of hyperphagia induced by 5-HT antagonists in animals or man (see Garattini et al. 1986 for a review). Thus, in a few studies, the non-selective 5-HT antagonists methysergide, pizotifen and cyproheptadine have been claimed to increase food intake in rats and cats (Baxter et al. 1970; Blundell and Leshem 1974; Weischer and Opitz 1979). Similarly, in humans, cyproheptadine, methysergide, mianserin and metergoline have occasionally been reported to increase appetite (Graham 1967; Pawlowski 1975; Silverstone and Schuyler 1975; Hopman 1980; Silverstone and Goodall 1986). The need for a systematic evaluation of the effects of 5-HT antagonists on feeding behaviour is now appropriate because of the recent discovery of multiple receptors for 5-HT in both the peripheral and central nervous systems. Functional receptors for 5-HT have been classified into three types designated 5-$HT_1$-like, 5-$HT_2$ and 5-$HT_3$ (Bradley et al. 1986). On the basis of ligand binding studies, 5-$HT_1$ receptors have been subdivided into 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1C}$ and 5-$HT_{1D}$ subtypes (Pedigo et al. 1981; Pazos et al. 1984; Heuring and Peroutka 1987). There is now evidence for the existence of 5-$HT_1$, 5-$HT_2$ and 5-$HT_3$ receptors in the brain (Peroutka and Snyder 1979; Kilpatrick et al. 1987) and selective antagonists for 5-$HT_2$ receptors (Leysen 1985) and for 5-$HT_3$ receptors (Fozard 1984; Richardson et al. 1985) have been described. However, to date, a selective 5-$HT_1$ antagonist has not been identified.

The present study examined the effects of nine 5-HT antagonists, with varying degrees of selectivity for 5-$HT_1$, 5-$HT_2$ and 5-$HT_3$ receptors, on food intake in free feeding rats. The aims of the study were twofold: first, to establish whether postsynaptic 5-HT receptor blockade reliably increases food intake in rats; second, if 5-HT receptor antagonists increase feeding, to establish which receptor subtype mediates this effect.

## Materials and methods

*Animals.* Male Sprague-Dawley rats (350 ± 50 g, Bantin and Kingman Ltd, UK) were used. The animals were housed in individual cages (40 × 24 × 40 cm) in a room with a 12-h light:dark cycle, (lights on 07.00 hours) for at least 7 days prior to experiments. Temperature was kept constant at 22 ± 1° C. Food pellets (mouse and rat diet, Bantin and Kingman Ltd, UK) and tap water were available ad lib.

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All testing was conducted during the light phase of the cycle, between 10 a.m. and 3 p.m.

*Apparatus and procedure.* Testing was conducted in the individual home cage. Rats were randomly assigned to treatment groups and injected subcutaneously in the nape of the neck with drug or vehicle ($n \geq$ eight animals in each treatment group). A weighed amount of food was placed in the hopper and the weight consumed, including spillage, was measured 4 and 24-h after injection, to an accuracy of 0.1 g.

*Drugs.* Methiothepin maleate (Hoffman La Roche, Basle, Switzerland), methysergide maleate, mesulergine HCl, ICS 205–930 methane sulphonate (all from Sandoz, Basle, Switzerland), mianserin HCl (RBI, Wayland, MA, USA) MDL 72222 methane sulphonate (Merrell Dow, Strasbourg, France) and ketanserin tartrate (Janssen, Beerse, Belgium) were dissolved by gentle warming in 0.9% NaCl. Metergoline base (Farmitalia, Milan, Italy) was dissolved in 50 µl 1 M glacial acetic acid, made to volume in warm 0.9% NaCl and bought to pH 4.5–5.0 with 1 M NaOH. Ritanserin base (Janssen, Beerse, Belgium) was dissolved in a 20% dimethyl sulphoxide (DMSO)/80% propylene glycol mixture. All drugs were injected in a volume of 1 ml/kg, except for metergoline (5 ml/kg). NaCl (0.9%) was used as a control for all drugs except for metergoline, where 0.9% NaCl was adjusted to pH 4.5–5.0 with 1 M glacial acetic acid and ritanserin where vehicle-treated animals received a mixture of 20% DMSO/80% propylene glycol.

*Statistical analysis.* Data were analysed by analysis of variance and comparisons between drug treatments and control being made using Dunnett's multiple range test. A probability level of $<0.05$ was regarded as significant.

## Results

### *Effects of the non-selective 5-HT antagonists, metergoline, methysergide, methiothepin, mesulergine and mianserin, on food intake*

Food intake during the 4-h test was significantly increased by 3.0 and 10.0 mg/kg metergoline [$F(4,75)=18.75$, $P<0.0001$], 3.0 and 10.0 mg/kg methysergide [$F(4,74)=9.84$, $P<0.001$], 0.03 and 0.1 mg/kg methiothepin [$F(4,75)=2.07$, $P<0.05$], 1.0 and 3.0 mg/kg mesulergine [$F(6,85)=4.39$, $P<0.001$] and 1.0, 3.0 and 10.0 mg/kg mianserin [$F(4,111)=4.63$, $P<0.002$] (see Table 1). The highest dose of methiothepin used (0.3 mg/kg) did not significantly increase feeding perhaps because of sedation. In addition, metergoline dose dependently increased 24-h food intake [$F(4,75)=8.2$, $P<0.0001$] (see Fig. 1).

Surprisingly, 1.0 and 3.0 mg/kg mesulergine (doses which increased 4-h food intake, see Table 1) significantly decreased 24-h food intake [$F(6,85)=6.48$, $P<0.001$] (see Fig. 2). None of the other drugs had any effect on 24-h food intake.

### *Effects of the 5-HT$_2$ antagonists, ritanserin and ketanserin, and of the 5-HT$_3$ antagonists, MDL 72222 and ICS 205–930, on food intake*

The 5-HT$_2$ antagonists ritanserin at doses of 0.1–3.0 mg/kg [$F(4,55)=1.3$, ns] and ketanserin at doses of 0.001–10.0 mg/kg [$F(4,35)=0.66$, ns] had no effect on 4-h food intake. Similarly, the 5-HT$_3$ antagonists MDL 72222 at doses of 0.001–10.0 mg/kg [$F(5,42)=1.69$, ns] and ICS 205–930 at doses of 0.001–10.0 mg/kg [$F(5,42)=1.1$, ns] had no effect

**Table 1.** Effects of the non-selective 5-HT antagonists metergoline, methysergide, methiothepin, mesulergine and mianserin on food intake in free feeding rats during a 4-h daytime test

| Drug | Dose (mg/kg) | Food intake (g/4 h) |
|---|---|---|
| Metergoline | vehicle | 2.1±0.4 |
| | 0.3 | 2.0±0.5 |
| | 1.0 | 3.2±0.5 |
| | 3.0 | 3.6±0.5* |
| | 10.0 | 6.8±0.5** |
| Methysergide | vehicle | 1.3±0.3 |
| | 0.3 | 1.8±0.3 |
| | 1.0 | 1.6±0.3 |
| | 3.0 | 2.8±0.3** |
| | 10.0 | 4.0±0.5** |
| Methiothepin | vehicle | 1.8±0.3 |
| | 0.01 | 1.6±0.4 |
| | 0.03 | 3.0±0.4* |
| | 0.1 | 3.4±0.4* |
| | 0.3 | 2.7±0.4 |
| Mesulergine | vehicle | 1.1±0.3 |
| | 0.01 | 1.5±0.4 |
| | 0.03 | 1.6±0.5 |
| | 0.1 | 2.5±0.4 |
| | 0.3 | 1.9±0.5 |
| | 1.0 | 3.4±0.9** |
| | 3.0 | 4.3±0.6** |
| Mianserin | vehicle | 1.8±0.2 |
| | 0.3 | 1.9±0.4 |
| | 1.0 | 2.8±0.4* |
| | 3.0 | 3.2±0.4** |
| | 10.0 | 3.5±0.4** |

Data are mean±SEM ($n \geq 8$ per group). Significant differences between drug and vehicle treatments were determined by Dunnett's multiple range test following ANOVA: * $P<0.05$; ** $P<0.01$

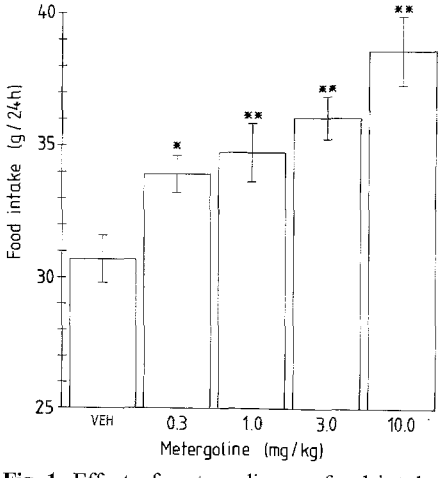


**Fig. 1.** Effect of metergoline on food intake during a 24-h period in free feeding rats. Data are mean±SEM of at least eight animals per treatment group. Significant differences between drug treatments and control were determined by Dunnett's multiple range test: * $P<0.05$; ** $P<0.01$

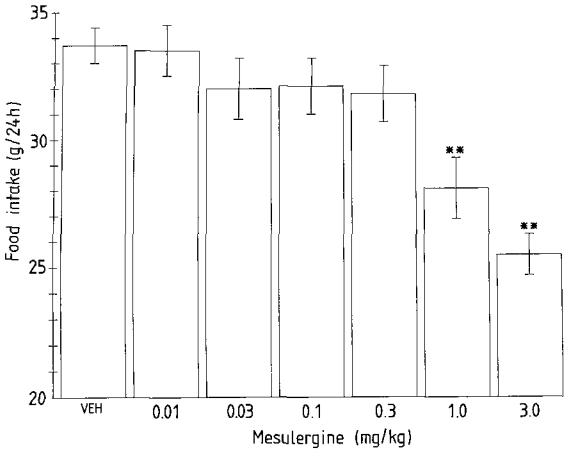


**Fig. 2.** Effect of mesulergine on food intake during a 24-h period in free feeding rats. Data are mean ± SEM of at least eight animals per treatment group. Other details are as described in Fig. 1

on daytime feeding. None of these drugs had any effect on 24-h food intake.

## Discussion

The results show that the 5-HT antagonists metergoline, methiothepin, methysergide, mesulergine and mianserin dose-dependently increase food intake in rats during a 4-h daytime test. Although a considerable body of data suggests that enhanced brain serotonergic activity inhibits feeding (Blundell 1977) there is little previous evidence that 5-HT antagonists increase food intake in animals (see Introduction). However, the present demonstration that five non-selective 5-HT antagonists (metergoline, methysergide, methiothepin, mesulergine and mianserin) increase feeding in rats is consistent with reports that methysergide, mianserin and metergoline increase food intake in man (see Introduction). Therefore, these data provide strong support for the hypothesis that endogenous 5-HT has an inhibitory role in the control of feeding (Blundell 1977).

Metergoline was the only antagonist to increase food intake during a 24-h period. The long lasting hyperphagic action of metergoline may be explained by its very long half-life, since in peripheral models it blocks the effects of 5-HT for 24–48 h (Beretta et al. 1965).

Mesulergine at doses of 1.0 and 3.0 mg/kg increased daytime feeding but decreased 24-h food intake at the same doses. This apparently paradoxical action may be explained by the lack of selectivity of the drug for 5-HT receptors. Mesulergine was originally synthesised as an antiparkinsonian agent and is a potent dopamine agonist (Enz 1981; Jellinger 1982). Recently, we have observed that another dopamine agonist PHNO ((+)-4-propyl-9-hydroxynaphthoxazine) increases the consumption of food pellets but decreases the intake of a liquid diet during a 4-h daytime test (Martin-Iverson and Dourish 1988). We believe that the increased consumption of food pellets observed after PHNO injection may be due to the induction of a non-specific gnawing response, whereas the decrease in liquid diet intake may be due to a direct effect on dopaminergic feeding mechanisms (Martin-Iverson and Dourish 1988). Indeed, it is well established that most dopamine agonists cause anorexia in animals (see review by Sugrue 1987). A similar dopaminergic mechanism could account for the effects of mesulergine observed in the present study, such that the initial effect of the drug is to elicit gnawing and eating of food pellets which is succeeded by an anorectic effect over 24 h. Alternatively, an initial blockade of 5-HT receptors by mesulergine may elicit feeding during a 4-h period, whereas a long latency and long duration dopamine agonist action could decrease feeding over a 24-h period. A study of the effects of mesulergine on the consumption of liquid diets may help to resolve this issue.

The other four antagonists that increased food intake are also not completely selective for 5-HT receptors. Thus, metergoline binds with nanomolar affinity to $\alpha_1$-adrenoceptors and to dopamine receptors (Spano et al. 1978; Leysen et al. 1981). Methiothepin and mianserin have nanomolar affinity for $\alpha_1$- and $\alpha_2$-adrenoceptors and $H_1$ histamine receptors (Leysen et al. 1981; Peroutka and Snyder 1981). Furthermore, methiothepin has nanomolar affinity and methysergide micromolar affinity for dopamine receptors (Leysen et al. 1981). However, metergoline, methysergide and methiothepin are unlikely to cause hyperphagia by dopamine receptor blockade as selective dopamine antagonists decrease food intake, under similar conditions (Zis and Fibiger 1975). Similarly, specific blockade of $\alpha_1$-adrenoceptors by prazosin has no effect on food intake in rats (M.L. Clark and A. Fletcher, unpublished observations). Methiothepin and mianserin do not appear to increase feeding by an action at $H_1$ histamine receptors, as ketanserin (which is also a potent displacer of $H_1$ histamine receptor binding, Leysen et al. 1981) had no effect on food intake. Finally an inhibitory action at $\alpha_2$-adrenoceptors is unlikely to account for mianserin or methiothepin-induced hyperphagia as the selective $\alpha_2$-antagonist idazoxan does not effect food intake in free feeding rats (Hutson et al. 1988a).

The second major finding of the present study is that hyperphagia induced by 5-HT antagonists appears to be mediated by 5-$HT_1$ receptors. All of the five antagonists that increased food intake have appreciable affinity for various 5-$HT_1$ recognition sites in ligand binding studies (Peroutka and Snyder 1979; Leysen et al. 1981; Pazos et al. 1984; Hoyer et al. 1985). Furthermore, methiothepin and methysergide have been used to characterize 5-$HT_1$-like receptors in functional assays in vitro (Bradley et al. 1986). In contrast, the selective 5-$HT_2$ antagonists ketanserin and ritanserin (Leysen 1985) and the selective 5-$HT_3$ antagonists MDL 72222 (Fozard 1984) and ICS 205–930 (Richardson et al. 1985), at doses sufficient to block these respective receptor types, had no significant effect on food intake.

The lack of effect of ketanserin and ritanserin on free feeding is consistent with previous results (Kennett et al. 1987; Massi and Marini 1987; Hewson et al. 1988). It appears that brain 5-$HT_2$ receptors are not involved in feeding as ritanserin has no effect on hypophagia induced by hypothalamic 5-HT infusion (Massi and Marini 1987). In contrast, hypophagia induced by IP injection of 5-HT and fenfluramine is blocked by ritanserin and ketanserin, respectively (Massi and Marini 1987; Hewson et al. 1988), suggesting an involvement of peripheral 5-$HT_2$ receptors in feeding.

The inability of 5-$HT_3$ receptor antagonists to reliably increase feeding was somewhat surprising in view of reports that 5-$HT_3$ receptor antagonists increase gastric emptying in guinea pigs (Buchheit et al. 1985; Costall et al. 1987). Thus, increased gastric emptying has been shown to be a major determinant of hyperphagia induced by lesions of

the ventromedial hypothalamus in rats (Duggan and Booth 1986). At the highest doses of the 5-$HT_3$ antagonists employed there was a (non-significant) trend towards increased intake. Possibly, 5-$HT_3$ receptors may not have a tonic inhibitory role in feeding but could influence food intake when feeding has been initiated by other factors. Thus, it would be interesting to examine the effects of 5-$HT_3$ antagonists on feeding induced by food deprivation or the availability of a palatable diet.

5-$HT_1$ receptors are thought to comprise four distinct subtypes (see Introduction). At present, however, selective antagonists for 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1C}$ and 5-$HT_{1D}$ receptors do not exist. Nevertheless, the pattern of results suggests that 5-$HT_{1C}$ receptors may mediate the hyperphagic response observed in the present study. Thus, all five antagonists that increased feeding are more potent inhibitors of binding to 5-$HT_{1C}$ receptors ($IC_{50} < 20$ nM in all cases) than to any other 5-$HT_1$ receptor subtype (Pazos et al. 1984; Heuring and Peroutka 1987). Further, the results of a recent study in which mianserin, mesulergine and cyproheptadine (which also has high affinity for 5-$HT_{1C}$ binding sites) increased feeding in rats during a 20-min test in a novel environment are also consistent with this proposal (Kennett and Curzon 1988).

It seems clear that the feeding response induced by 5-HT antagonists is due to post-synaptic rather than pre-synaptic 5-$HT_1$ receptor blockade. Blockade of 5-HT autoreceptors increases 5-HT synthesis and release (Chaput et al. 1986). Increased 5-HT release is known to decrease food intake (e.g. fenfluramine decreases feeding via this mechanism; see Introduction) and this effect is opposite to the hyperphagia observed after 5-HT antagonist treatment in the present study.

It appears likely that the 5-$HT_1$ receptors which mediate 5-HT antagonist-induced hyperphagia may be located on hypothalamic neurones. Thus, infusion of 5-HT, the 5-HT releaser norfenfluramine, and the 5-HT agonists RU 24969 and TFMPP into the hypothalamus decreases food intake in rats (Shor-Posner et al. 1986; Hutson et al. 1988b). Since autoradiographic studies have identified a high density of 5-$HT_{1C}$ binding sites in the ventromedial hypothalamus (Pazos et al. 1987), it is possible that this region may play an important role in mediating 5-HT antagonist-induced feeding.

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