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1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI) exerts an anorexic action that is blocked by 5-HT_2 antagonists in rats*

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Abstract. Previous literature suggests that the anorexic action of peripherally administered serotonin (5-HT) is mediated by 5-HT_2 receptors. This study, therefore, examined the effect of DOI, a non-indole 5-HT_2 agonist, on deprivation-induced feeding. Rats were first adapted to a schedule in which a milk diet was presented for 6 h daily. Intraperitoneal (IP) administration of DOI (1.0–11.2 μmol/kg) inhibited feeding in a dose-related fashion (ID_{50} = 2.6 μmol/kg). One hour pretreatment with 6.0 μmol/kg of the 5-HT_2 antagonists ketanserin and LY53857 completely reversed the anorexic action of an equimolar dose of DOI. Neither ketanserin nor LY53857, alone, altered baseline feeding. Further testing demonstrated the antagonistic effect of LY53857 (0.047–6.0 μmol/kg, IP) to be dose related, with an ID_{50} of 0.14 μmol/kg. Ten minute pretreatment with 1-(1-naphthyl)-piperazine (1-NP; 2.0 or 4.0 μmol/kg), a mixed-acting agent with 5HT_2 blocking actions, also attenuated the anorexic effect of 6.0 μmol/kg DOI. Unlike ketanserin and LY53857, however, 1-NP did reduce food intake by itself. By contrast with ketanserin, LY53857 and 1-NP, the peripherally-acting 5-HT_2 antagonist xylamidine failed to alter the anorexic effect of DOI. Taken together, these results suggest that central 5-HT_2 receptors are important in the control of ingestive behavior.

Key words: 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane – DOI – 5-HT_2 receptors – LY53857 – 1-(1-naphthyl) piperazine – 1-NP – Ketanserin – Xylamidine – Feeding

A significant amount of evidence has revealed that the peripheral or central administration of serotonergic agonists inhibits feeding in rats (Blundell 1977; Leibowitz and Shor-Posner 1986). Although the receptor subtypes responsible for serotonergic anorexia have not been studied systematically, some workers have suggested a role for central 5-HT_{1b} receptors. This hypothesis derived from studies using agents that gain access to the central nervous system such as RU24969 (Dourish et al. 1986; Bendotti and Samanin 1987), quipazine (Samanin et al. 1977), *m*-chlorophenylpiperazine (Samanin et al. 1979), and 1-(3-trifluoromethylphenyl)piperazine (TFMPP) (Fuller et al. 1981). Other work, however, has demonstrated that the anorexic effect of peripherally administered 5-hydroxytryptamine (5-HT) can be blocked by 5-HT_2 antagonists such as ritanserin (Massi and Marini 1987), ketanserin and LY53857 (Simansky et al. 1987). Notably, this effect of 5-HT on food intake was also antagonized by xylamidine (Clineschmidt et al. 1978; Fletcher and Burton 1986), an antagonist that is thought to block peripheral 5-HT_2 receptors (Fuller et al. 1986) but which fails to penetrate the blood-brain barrier (Copp et al. 1967; Mawson and Whittington 1970).

If, indeed, the anorexic action of 5-HT is mediated by a 5-HT_2 mechanism, then administering a more selective 5-HT_2 agonist should also reduce food intake. 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI) is an agent with a non-indole structure that displayed 100-fold higher affinity for 5-HT_2 than 5-HT_1 sites in binding studies using brain tissue (Shannon et al. 1984). Behaviorally, DOI produced stimulus cues that generalized to 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), which is another agent that activates 5-HT_2 mechanisms (Glennon 1986). Thus, these results by other investigators suggested that DOI would provide a useful probe for exploring the effect of 5-HT_2 stimulation in feeding. The present studies demonstrate that DOI inhibits deprivation-induced consumption of milk in rats. Furthermore, the 5-HT_2 antagonists LY53857 (Cohen et al. 1983b, 1985a), ketanserin (Leysen et al. 1982) and 1-(1-naphthyl)piperazine (1-NP) (Cohen et al. 1983b; Simansky and Schechter 1987) inhibited the anorexic action of DOI whereas xylamidine did not.

Materials and methods

Male Sprague Dawley rats (350–450 g) obtained from AAI Inc. (Boyertown, PA) were used in all experiments. The animals were housed individually in suspended wire mesh cages (41 cm wide × 24 cm deep × 18 cm high) and maintained at an ambient temperature of 22 ± 1° C with a 12-h light photoperiod beginning at 06.00 hours. Experiments were performed in the animals' home cage. A palatable milk diet consisting of one can (300 ml) Gold Cross Mello-ream, 300 ml water, 0.5 ml formaldehyde solution (37% w/v) and 1.0 ml Poly-Vi-Sol^R. Multiple Vitamins with Iron (a gift of Nutritional Division, Bristol Myers, Inc., Evansville, IN) was presented for 6 h each day (11.00–17.00 hours). In order to record the amount of milk consumed, the diet was placed in 100-ml graduated glass drink-

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ing tubes fitted with stainless steel spouts and rubber stoppers (Wahman Manufacturing Co., Timonium, M.D.). Animals were adapted to this schedule for 2 weeks before any studies were initiated. Water was available at all times.

In all experiments, food intake was recorded for 30 min beginning 6 min following the intraperitoneal (IP) administration of DOI or its vehicle (distilled water). Baseline values were obtained the day before testing after injecting the rats IP with distilled water. The rats were then assigned to groups ($n=7$ per group) according to the 30-min intake values recorded. The dose-response curve was determined after administering 1.0, 2.0, 4.0, 8.0, or 11.2 μmol/kg DOI. In experiments using the 5-HT_2 antagonists LY53857, ketanserin or xylamidine, the agents were administered IP 1 h before injecting DOI. In one study, 1-NP was given IP followed 10 min later by the administration of DOI.

The following drugs were used: 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI, MW = 358, Research Biochemicals, Inc., Natick, Mass.), LY53857 (MW = 500, gift of Lilly Research Laboratories, Indianapolis, IN), ketanserin tartrate (MW = 545, gift of Janssen Pharmaceutica Research Laboratories, Piscataway, N.J.), 1-(1-naphthyl)piperazine (1-NP, MW = 249, Research Biochemicals) and xylamidine tosylate (MW = 503, gift of Wellcome Research Laboratories, Beckenham, Kent, UK). All drugs were dissolved in distilled water and administered in a volume of 2.0 ml/kg. Xylamidine tosylate needed to be warmed gently for 15–20 min with constant stirring.

Data analyses were performed by analysis of variance followed by two-tailed Dunnett's tests for comparing the means of treated groups with the values for controls or by Duncan's Multiple Range Test for comparing the means among groups in an experiment (Kirk 1982). The ID_{50} for the DOI dose-response curve was calculated by linear regression of the per cent inhibition of food intake versus the common logarithm of the dose, using the method of least squares. The two-tailed 95% confidence limits for the ID_{50} and the slope were determined by the method of Tallarida and Murray (1981).

Results

DOI administered 6 min before presenting the milk diet inhibited feeding [$F(5,50)=27.92$, $P<0.01$] during the 30-min testing period (Fig. 1). Controls injected with vehicle ingested 22.0 ± 1.1 ml during this interval. Doses of 2.0, 4.0, 8.0 and 11.2 μmol/kg reduced food intake, respectively, by 46, 64, 85 and 96% ($P<0.01$). The dose estimated by regression to inhibit feeding by 50% was 2.6 μmol/kg. Superficial observation during the test interval revealed no behaviors that would overtly impair feeding by the animals given DOI. Importantly, all rats approached and began consuming the diet immediately upon presentation.

In order to examine a role for a 5-HT_2 mechanism, studies were performed using 5-HT_2 antagonists. The probe dose of DOI chosen for the experiments was 6.0 μmol/kg which was approximately twice the ID_{50} for inhibiting food intake. Sixty minute pretreatment with an equimolar dose of LY53857 completely prevented the reduction of food intake produced by DOI (Table 1). In the 30-min test interval, the vehicle + DOI group ingested 17% of the value for controls whereas, in contrast, the LY53857 + DOI group consumed 107% of the control mean. Administration of LY53857 did not alter baseline food intake. A more extensive study showed that the antagonism by LY53857 of DOI-induced anorexia was dose related [$F(9,74)=8.38$, $P<0.01$] (Fig. 2). Rats injected with at least 0.19 μmol/kg LY53857 consumed more milk after DOI than animals pretreated with vehicle before the anorexic agent. Furthermore, the amount of diet ingested by animals given 0.375 μmol/kg or greater was significantly different than the amount consumed by the rats given the two lowest doses, 0.047 and 0.093 μmol/kg ($P<0.01$).

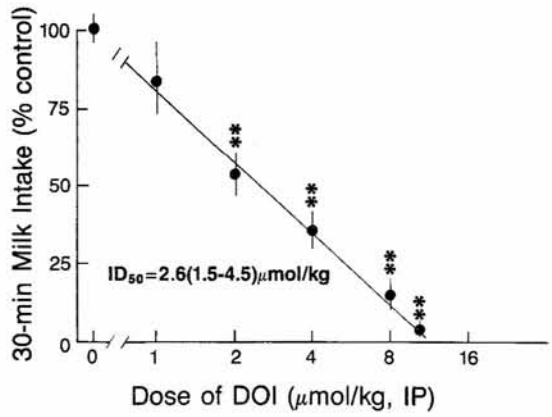

Fig. 1. Dose-response curve for the reduction of milk intake produced by DOI. Volume of milk consumed is expressed as percentage of control (vehicle injection). Data are represented as means ± SEM. *Asterisks* indicate significant difference from vehicle control: $^{**}P<0.01$, two-tailed Dunnett's test

Table 1. Comparison of the abilities of LY53857, ketanserin and xylamidine to antagonize the anorexic effect of DOI

	30-min milk intake (ml) after:	
Pretreatment	Vehicle	DOI
Vehicle	23.0 ± 1.0	3.9 ± 1.4[a]
LY53857	21.4 ± 2.3	24.7 ± 2.1
Vehicle	17.7 ± 2.2	4.1 ± 0.7[a]
Ketanserin	17.6 ± 1.3	16.1 ± 1.4
Vehicle	21.3 ± 1.4	6.3 ± 1.4[b]
Xylamidine	20.3 ± 2.0	5.0 ± 1.5[b]

All values are means ± standard errors based upon seven rats. Three separate experiments were conducted testing the effects of pretreatment with either LY53857, ketanserin or xylamidine. The rats were injected IP first with 6.0 μmol/kg of one of the antagonists or with the distilled water vehicle (2.0 ml/kg) and, 60 min later, with either DOI (6.0 μmol/kg) or vehicle

[a] Significantly different from all other groups within the same experiment: $P<0.01$, Duncan's Multiple Range Test

[b] Significantly different from Vehicle + Vehicle and Xylamidine + Vehicle: $P<0.01$, Duncan's Multiple Range Test

Ketanserin (6.0 μmol/kg) also prevented the reduction of milk intake produced by an equimolar dose of DOI (Table 1). The vehicle + DOI group consumed 23% of the control mean. As in the study using LY53857, the intake of the ketanserin + DOI group did not differ from that of the vehicle + vehicle group. Furthermore, ketanserin did not disrupt feeding by itself.

The reversal of the anorexic effect by the selective 5-HT_2 antagonists LY53857 and ketanserin suggested that DOI was acting through a 5-HT_2 receptor. In order to address

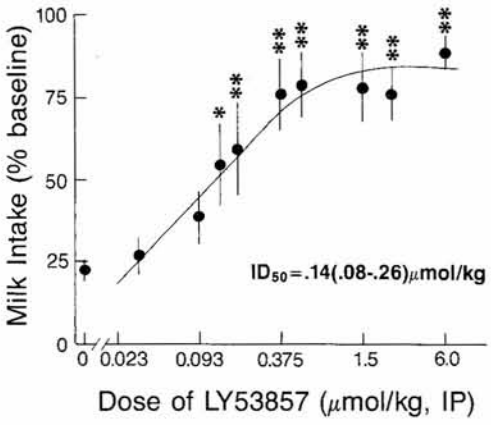

Fig. 2. Dose-response curve for the antagonism by LY53857 of the reduction of milk intake produced by DOI. Milk intake is expressed as percentage of baseline value obtained after vehicle injection on the previous day. Data are represented as means ± SEM. *Asterisks* indicate significant difference from rats that were injected with vehicle (0 dose) before DOI: $*P<0.05$, $**P<0.01$, Duncan's Multiple Range Test

Table 2. Antagonism by 1-NP of the anorexic effect of DOI

	30-min milk intake (ml) after:	
Pretreatment	Vehicle	DOI
Vehicle	17.9 ± 1.7	4.0 ± 1.0[a]
1-NP, 2.0 μmol/kg	14.1 ± 1.0[b]	7.6 ± 0.8[a,c]
Vehicle	16.9 ± 1.6	3.2 ± 0.6[a]
1-NP, 4.0 μmol/kg	12.4 ± 1.5[b]	11.9 ± 1.7[b,d]

All values are means ± standard errors based upon seven rats. Two separate experiments were conducted testing the effects of pretreatment with either 2.0 or 4.0 μmol/kg 1-NP. The rats were injected IP first with one of the doses of 1-NP or with the distilled water vehicle (2.0 ml/kg) and, 10 min later, with either DOI (6.0 μmol/kg) or vehicle. All statistical comparisons were made by Duncan's Multiple Range Test after Analysis of Variance

[a] Significantly different from Vehicle + Vehicle and 1-NP + Vehicle, $P<0.01$

[b] Significantly different from Vehicle + Vehicle, $P<0.05$

[c] Significantly different from Vehicle + DOI, $P<0.05$

[d] Significantly different from Vehicle + DOI, $P<0.01$

the question of whether the anorexic action was mediated by a peripheral or central mechanism, rats were pretreated with the peripherally-acting 5-HT_2 antagonist xylamidine before administration of DOI. The vehicle + DOI and the xylamidine + DOI groups consumed essentially identical volumes of milk (Table 1). Thus, xylamidine did not block the reduction of milk intake produced by an equimolar dose of DOI. Furthermore, xylamidine did not alter feeding when compared to the control baseline.

The 1-arylpiperazine 1-NP was also tested for its ability to block DOI-induced anorexia (Table 2). A dose of 2.0 μmol/kg of 1-NP partially blocked the reduction of milk intake produced by 6.0 μmol/kg DOI ($P<0.05$). In comparison, 4.0 μmol/kg 1-NP reversed the anorexic effect of DOI to a greater degree ($P<0.01$). Notably, rats given this larger dose of 1-NP plus DOI still ate less than the controls injected twice with vehicle. Nonetheless, the reversal of DOI-induced anorexia by 4.0 μmol/kg 1-NP appeared to be maximal under our testing conditions, since rats in the 1-NP + DOI group consumed virtually the same amount of milk as those in the 1-NP + vehicle group. It is important to note that both 2.0 and 4.0 μmol/kg 1-NP produced small anorexic effects. These doses inhibited feeding by 21 and 27%, respectively.

Discussion

This report provides the first direct pharmacological evidence that stimulating central 5-HT_2 receptors inhibits feeding in rats. Previously reported literature has focused on 5-HT_{1b} mechanisms for anorexia produced by serotonergic agonists (Bendotti and Samanin 1987). The present data demonstrate that DOI, a non-indole with putatively selective 5-HT_2 agonist properties (Glennon 1986), inhibits the consumption of milk intake in rats adapted to a restricted feeding schedule. This anorexic action was dose related and occurred without other discernible behavioral changes that might have impaired feeding by the animals. Furthermore, the 5-HT_2 antagonists LY53857, ketanserin, and 1-NP blocked the inhibition of feeding by DOI. LY53857 and ketanserin given at equimolar doses to DOI completely reversed the reduction of food intake without, by themselves, altering feeding. A more extensive study showed that the antagonism by LY53857 was dose related. 1-NP partially antagonized the inhibitory effect of DOI on feeding although the former compound did, by itself, exert a mild anorexic effect.

LY53857, 1-NP and ketanserin are structurally dissimilar drugs that share the ability to antagonize actions of 5-HT at 5-HT_2 receptors. In vitro, the ergoline LY53857 and the 1-arylpiperazine 1-NP also inhibit contractions of the rat fundus elicited by 5-HT (Clineschmidt et al. 1985; Cohen et al. 1985b). Furthermore, DOM, a phenylalkylamine congener of DOI, has been shown to be a weak stimulant of the rat fundus (Standridge et al. 1976). It was possible, therefore, that DOI inhibited feeding by altering stomach motility. However, pharmacological examination of the fundic receptor has revealed that it is not of the 5-HT_2 subtype and is not sensitive to blockade by ketanserin (Leysen and Tollenaere 1982; Clineschmidt et al. 1985; Cohen et al. 1985b). Thus, our data mitigated against a role for the fundus in DOI-induced anorexia because ketanserin completely reversed the inhibition of feeding.

To further address the question of a possible site of action, we performed an experiment with xylamidine. The agents mentioned above act at both peripheral and central sites. In comparison, xylamidine is a 5-HT_2 antagonist (Fuller et al. 1986) which appears not to penetrate the blood brain barrier (Mawson and Whittington 1970). In the present study, 6.0 μmol/kg xylamidine failed to antagonize the decrease in milk intake produced by DOI. In contrast, using this dose, pretreatment interval and testing protocol, xylamidine has been shown to block the anorexic action of peripherally administered 5-HT (Simansky et al. 1987). Thus, the present data are surprising because they suggest that selectively blocking peripheral 5-HT_2 receptors is insufficient for blunting the anorexic effect of DOI. Rather, the results appear to demonstrate that the activation of central 5-HT_2 mechanisms is sufficient for inhibiting feeding.

Although our study characterized the pharmacological mechanism for inhibitory actions of DOI in feeding, the present experiments did not address the behavioral specifici-

ty of the anorexia. It is important to recognize that a variety of drugs have been demonstrated to act via 5-HT_2 receptors to impair ongoing behavior in other paradigms under appetitive control. For example, quipazine and various hallucinogens including DOM, lysergic acid diethylamide (LSD) and mescaline disrupted responding maintained under fixed-ratio schedules employing food pellets as the reinforcer (Dwoskin and Sparber 1983; Mokler et al. 1983, 1985). The 5-HT_2 antagonists, mianserin and pirenperone, blocked the actions of these drugs on operant behavior (Dwoskin and Sparber 1983; Mokler et al. 1985). Although the impairment of responding by quipazine may have involved an anorexic action of this drug (Henck et al. 1985), the disruptive effects of LSD and DOM were attributed to an associational disturbance rather than a direct effect on feeding (Mokler et al. 1985). It is of interest to note, however, that the ED_{50} for the effect of DOM in operant responding (0.84 mg/kg) (Mokler et al. 1985) was virtually identical to the ID_{50} obtained for DOI-induced anorexia in our feeding paradigm (0.93 mg/kg). Our study with DOI, therefore, raises the possibility that hallucinogens disrupt operant responding under food reinforcement by stimulating 5-HT_2 mechanisms involved specifically in the control of ingestive behavior. Conversely, since discriminative conditioning for milk reward may support feeding in our protocol (Simansky et al. 1985), DOI may produce anorexia by impairing a more general behavioral process.

5-HT_2 agonists affect operant behavior by introducing characteristic pauses in responding (Rech and Commissaris 1982). It is conceivable, therefore, that DOI reduced food intake by altering the organization of normal feeding behavior. Undoubtedly, a detailed analysis of the topography of feeding after DOI will yield one piece of important information regarding the behavioral selectivity of the anorexia. We began addressing the issue of behavioral selectivity in a preliminary study examining the effect of DOI on water intake. DOI reduced drinking by rats adapted to a schedule with 6 h daily access to water (unpublished observation). The ID_{50} for this inhibitory effect was 6.6 μmol/kg or 2.6 times greater than that for producing anorexia. Thus, DOI displayed some – though certainly not complete – selectivity in decreasing feeding compared to another consummatory behavior.

An ancillary finding of the present study was the observation that 1-NP, by itself, inhibited feeding despite attenuating the anorexic effect of DOI. These data might be explained if 1-NP had high affinity but poor efficacy at one subclass of 5-HT receptor and therefore acted as a mixed agonist/antagonist. The antagonistic action of 1-NP agreed with previous studies in which this agent displayed high affinity for 5-HT_2 binding sites in brain tissue (Glennon et al. 1986), blocked 5-HT_2-mediated contractions of the rat jugular vein in vitro (Cohen et al. 1983a), prevented head twitches induced by serotonergic agonists in rodents (Simansky and Schechter 1987), and, moreover, antagonized discriminative cues produced by DOM in rats (Glennon et al. 1986). It was unlikely, however, that the anorexic effect of 1-NP revealed 5-HT_2 agonist properties of this drug because 1-NP displayed no intrinsic activity in the rat jugular vein or in the head twitch model. Instead, 1-NP may have reduced feeding by stimulating 5-HT_1 receptors. Notably, 1-NP also displays high affinity for 5-HT_1 binding sites (Glennon et al. 1986), elicits the 5-HT motor syndrome (Simansky and Schechter 1987) associated with central 5-HT_1 stimulation (Lucki et al. 1984; Tricklebank et al. 1985a, b) and produces stimulus cues that generalize to the 5-HT_{1b} agonist, TFMPP, in a drug discrimination paradigm (Glennon et al. 1986). This latter effect is probably the most relevant for the anorexic action of 1-NP, since various other drugs capable of activating 5-HT_{1b} mechanisms decrease food intake in rats (Bendotti and Samanin 1987). Future experiments should explore this possibility by comparing the effects of relatively selective 5-HT_2 antagonists with those of agents that interact with 5-HT_{1b} sites, such as methysergide and pindolol (Hoyer et al. 1985; Peroutka 1986), on the anorexic action of 1-NP. Indeed, analogous studies would also be useful in further specifying whether 5-HT_2 mechanisms solely account for the effect of DOI in feeding.

The results of this study implicate a role for central 5-HT_2 receptors in the control of feeding behavior. It should be recalled, however, that we did not observe orexigenic effects of ketanserin or LY53857. The failure of these drugs to increase feeding agreed with the work of Massi and Marini (1987) who reported that neither acute nor chronic injections of ritanserin, a selective 5-HT_2 antagonist, enhanced food consumption in rats. Similarly, repeatedly administering some antidepressants reduces central 5-HT_2 binding sites (Peroutka and Snyder 1980; Blackshear and Sanders-Bush 1982) despite having no effect on – or decreasing – feeding and body weight in rats (Nobrega and Coscina 1987). Nonetheless, feeding is subject to numerous (redundant) inhibitory influences. One of these other controls may involve 5-HT_1 receptors, since nonselective 5-HT antagonists, such as metergoline, but not ketanserin block the anorexic effect of the 5-HT uptake inhibitor sertraline (Lucki, Kreider and Simansky, submitted for publication). One may speculate that removing only a single brake via 5-HT_2 blockade is insufficient for releasing eating, although exaggerating such a signal with an agonist will suppress food intake. Notably, however, a number of antidepressants reportedly do produce hyperphagia and weight gain in humans (Harris and Harper 1980; Berken et al. 1984). Thus, the methods used to date may have been inappropriate for detecting immediate or long-term effects of diminished 5-HT_2 function on feeding in rats. Resolution of this issue would appear to have implications extending beyond pharmacological concerns. Indeed, in view of evidence that 5-HT_2 stimulation produces such diverse effects as hallucinogenesis (Glennon et al. 1984) and hyperthermia (Gudelsky et al. 1986), the physiological role of these receptors in normal feeding certainly requires additional, careful scrutiny.

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