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Suppression of Food Intake in Rats by Fluoxetine: Comparison of Enantiomers and Effects of Serotonin Antagonists

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WONG, D. T., L. R. REID AND P. G. THRELKELD. *Suppression of food intake in rats by fluoxetine: Comparison of enantiomers and effects of serotonin antagonists.* PHARMACOL BIOCHEM BEHAV 31(2) 475–479, 1988.—R- and S-enantiomers of fluoxetine lowered food intake in meal-fed rats and in 2-deoxyglucose-induced hyperphagic rats. In both feeding paradigms, the S-enantiomer was slightly more potent. The potency of the two enantiomers of fluoxetine in producing anorectic effects paralleled their potency as inhibitors of 5-hdyroxytryptamine (5HT) uptake in vivo. Both enantiomers were selective inhibitors of 5HT uptake in vitro and showed only weak affinity for 5HT-1, 5HT-1A and 5HT-2 receptors or for other receptors in rat brain. The anorectic effect of fluoxetine in meal-fed rats was not reversed by either centrally or peripherally acting 5HT-2 receptor antagonists (ritanserin, LY53857, xylamidine, BW 501C67) or a nonspecific 5HT receptor antagonist, metergoline. However, the serotonergic mechanism involved in the anorexic effect of fluoxetine is discussed.

Enantiomers Fluoxetine Anorectic Serotonin Receptor Antagonists

INCREASING evidence shows that 5HT in the central nervous system plays an inhibitory role in the control of feeding behaviors (3,27). Pharmacologic agents that increase the intrasynaptic availability of 5HT lead to the suppression of food consumption. Drugs that release 5HT, including fenfluramine and p-chloroamphetamine, lower food consumption (18,22). Inhibition of presynaptic reuptake of 5HT by fluoxetine lowered food intake in meal-fed rats (12, 20, 21), in deprived or 2-deoxyglucose-induced hyperphagic rats (6) and in meal-fed lean and obese mice (35). The anorectic effects of the 5HT precursor amino acid L-5-hydroxytryptophan (L-5HTP) were potentiated and prolonged by coadministration with fluoxetine (12). The combined administration of fluoxetine and L-5HTP suppressed consumption of sweetened milk, while fluoxetine alone was ineffective (10). The R- and S-enantiomers of fluoxetine inhibited 5HT uptake with equal potency and selectivity in vitro and in vivo (30). In the present studies, we compared the anorectic effects of the two enantiomers of fluoxetine and also attempted to antagonize the anorectic effects of fluoxetine with antagonists acting on the peripheral and central 5HT receptors.

METHOD

Male Sprague-Dawley rats (2.5 months old) weighing 300 g were meal-fed 6 hr (9 a.m. to 3 p.m.) daily for a training period of eight days. One of the two enantiomers was intraperitoneally injected at specified doses to groups of five or six rats 1/2–1 hr before feeding. Total food intake was recorded by weighing the pellets and spillage at the beginning and the end of the indicated periods of time. In the hyperphagic model, nondeprived rats were treated with 2-deoxyglucose at 600 or 750 mg/kg, and fluoxetine or one of its enantiomers was administered at specified doses 1/2 hr before feeding. Food intake was recorded at the end of 1, 2, 3 or 4 hr. Statistical analysis was conducted by the method of Student's *t*-test to compare means of saline-treated and drug-treated groups. A probability of <0.05 was regarded as significant.

Uptake of monoamines was assayed as previously described (30). Rats (110–150 g) were killed by decapitation. Brain was immediately removed and cerebral cortex was dissected. Cerebral cortex was homogenized in 9 volumes of a medium containing 0.32 M sucrose and 10 mM glucose. Crude synaptosomal preparations were isolated after differential centrifugation at 1000×g for 10 min and 17,000×g for 28 min. Cortical synaptosomes (equivalent to 1 mg of protein) were incubated at 37°C for 5 min in 1 ml of Krebs bicarbonate medium containing also 10 mM glucose, 0.1 mM iproniazid, 1 mM ascorbic acid, 0.17 mM EDTA, 50 nM ^{3}H-5HT and 100 nM ^{14}C-NE (norepinephrine).

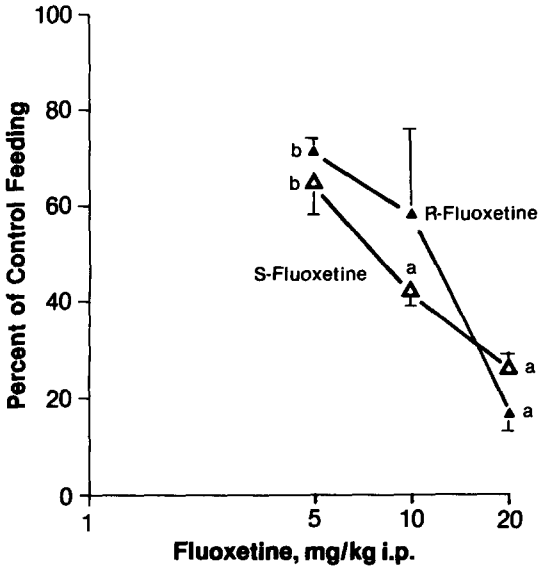

FIG. 1. Reduction of food intake in meal-fed rats by R- and S-fluoxetine. Groups of 6 rats were treated with R-fluoxetine (▲) or S-fluoxetine (△) at 5, 10 and 20 mg/kg IP 30 min prior to food access. Saline-treated group was used as control. Food intake was recorded after 1 hr of food access and reported as percent of control (saline-treated group ate 3.1±0.3 g/100 g body weight), with bars indicating standard errors of the means. Statistical analysis was conducted by the method of Student's *t*-test to compare the means of saline-treated and drug-treated groups. $^{a}p<0.005$; $^{b}p<0.025$.

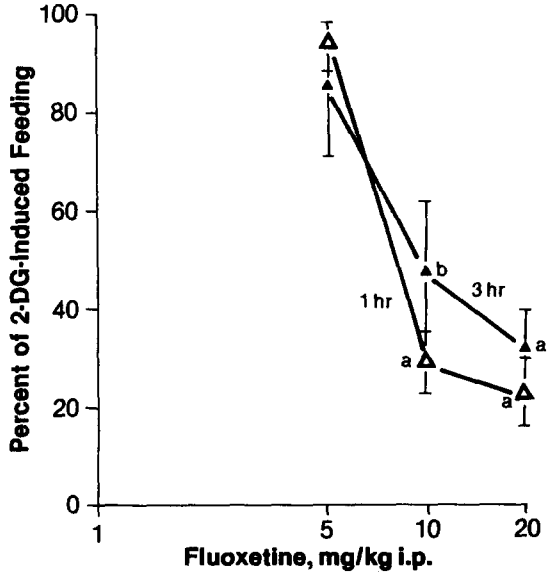

FIG. 3. Reduction of food intake in 2-deoxyglucose-treated rats by fluoxetine during 1 and 3 hr of feeding. Groups of 6 rats were treated with 2-deoxyglucose (600 mg/kg IP) and fluoxetine at 5, 10 or 20 mg/kg SC 30 min prior to food access. Food intake was recorded after 1 hr (▲) and 3 hr (△), with 2-deoxyglucose- (2-DG) and saline-treated group consuming the accumulated amounts of 2.3±0.2 and 2.9±0.2 g/100 g body weight, respectively, while the saline-treated group ate the accumulated amounts of 0.4 and 0.5 g/100 g body weight, respectively. Statistical analysis was conducted as described in Fig. 1. $^{a}p<0.001$; $^{b}p<0.025$.

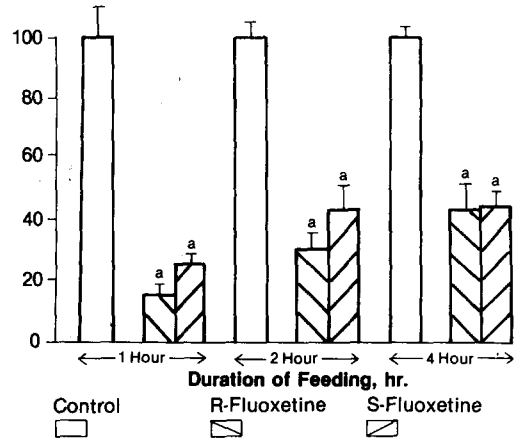

FIG. 2. Duration of reduced feeding after administration of R- and S-fluoxetine in meal-fed rats. Groups of 6 rats were treated with R-fluoxetine or S-fluoxetine at 20 mg/kg IP as described in Fig. 1. Food intake was recorded after 1, 2 and 4 hr of food access, with the saline-treated rats as control consuming the accumulated amounts of 3.1±0.3, 3.9±0.2 and 6.6±0.2 g/100 g body weight, respectively. Statistical analysis was as described in Fig. 1. $^{a}p<0.005$.

Radioligand binding to various receptors was conducted as described previously (24,31). Cortical membranes were used for binding of ^{3}H-5HT to 5HT-1 receptors; ^{3}H-8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) to 5HT-1A receptors; ^{3}H-ketanserin to 5HT-2 receptors; ^{3}H-WB4101, ^{3}H-clonidine and ^{3}H-dihydroalprendol to alpha-1, alpha-2 and beta-adrenergic (Adr) receptors; ^{3}H-quinuclidinyl benzilate (QNB) to muscarinic-acetylcholine (Ach) receptors; and ^{3}H-pyrilamine to histamine-1 receptor. Striatal membranes were used for binding of ^{3}H-apomorphine and ^{3}H-spiperone to dopamine-2 receptors.

Fluoxetine and its two enantiomers were kindly provided by Dr. B. G. Jackson, Eli Lilly and Company (Indianapolis, IN). The R- and S-enantiomers are levorotatory and dextrorotatory in methanol, respectively (D. W. Robertson, personal communication). Radioactive materials were purchased from New England Nuclear (Boston, MA).

RESULTS

R-Fluoxetine and S-fluoxetine hydrochloride at 5, 10 and 20 mg/kg IP dose-dependently reduced food intake in meal-fed rats with about equal potency, although only S-fluoxetine at 10 mg/kg IP lowered feeding significantly (Fig. 1). Significant reduction to 16% and 26% of control feeding resulted from the administration of R-fluoxetine and S-fluoxetine, respectively, at 20 mg/kg IP within 1 hr of food access ($p<0.005$, Student's *t*-test). The anorectic effects of both enantiomers persisted during 2 and 4 hr of feeding ($p<0.005$), although they were not as pronounced as observed in 1 hr of feeding (Fig. 2).

Rats treated with 2-deoxyglucose consumed 6- to 7-fold more food than the control, nondeprived rats at 1 and 3 hr of recording of food consumption. Fluoxetine at 10 ($p<0.025$ at 1 hr; $p<0.001$ at 3 hr) and 20 ($p<0.001$ at 1 and 3 hr) mg/kg IP lowered food intake significantly during both periods (Fig. 3). The two enantiomers of fluoxetine at 10 mg/kg IP were about equally potent in the suppression of feeding in

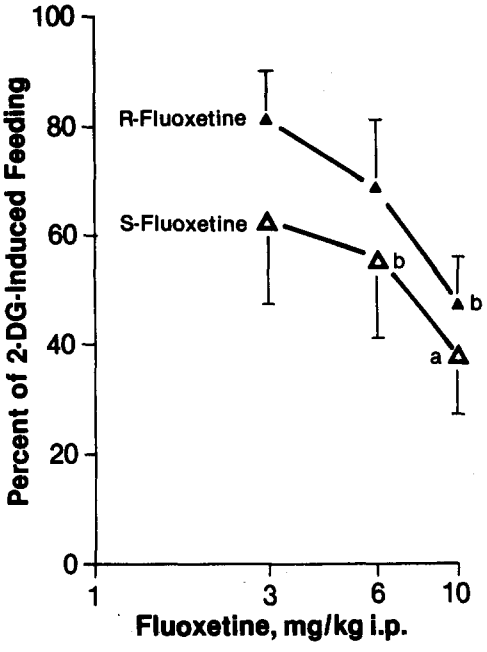

FIG. 4. Reduction of food intake in 2-deoxyglucose-treated hyperphagic rats by R- and S-fluoxetine. Groups of 5 rats were treated with 2-deoxyglucose (2-DG) at 750 mg/kg IP and R-fluoxetine (▲) or S-fluoxetine (△) at 3, 6 or 10 mg/kg IP 30 min prior to food access. Food intake was recorded after 3 hr of food access, with the 2-DG-saline-treated group eating 5.4±0.6 g/100 g body weight. Statistical analysis was conducted as described in Fig. 1. $^{a}p<0.005$; $^{b}p<0.05$.

TABLE 1

EFFECTS OF SEROTONIN ANTAGONISTS ON FLUOXETINE-INDUCED SUPPRESSION OF FEEDING IN MEAL-FED RATS

Compound	mg/kg	Cumulative Food Intake 1 Hour g/100 g Body Weight	Cumulative Food Intake 6 Hours g/100 g Body Weight
Control		2.43 ± 0.16	6.39 ± 0.34
Fluoxetine	10	0.52 ± 0.06*	3.48 ± 0.19†
Xylamidine	5	2.28 ± 0.15	6.29 ± 0.17
Fluoxetine	10	0.65 ± 0.09*	3.92 ± 0.15‡
+ xylamidine	5		
BW 501C67	5	1.55 ± 0.05‡	4.22 ± 0.2‡
Fluoxetine	10	0.26 ± 0.18*	2.76 ± 0.25*
+ BW 501C67	5		
Metergoline	5	1.36 ± 0.16†	5.29 ± 0.49†
Fluoxetine	10	0.31 ± 0.08†	3.77 ± 0.23*
+ metergoline	5		

Groups of six meal-fed rats were treated with xylamidine, BW 501C67 or metergoline at 5 mg/kg IP 1 hr before administration of fluoxetine at 10 mg/kg IP. Food intake was recorded at 1 and 6 hr after food access and presented as means ± S.E. with statistically significant difference between drug and saline-treated groups, as indicated: *$p<0.001$; †$p<0.005$; ‡$p<0.05$.

TABLE 2

EFFECT OF RITANSERIN OR LY53857 ON FLUOXETINE-INDUCED SUPPRESSION OF FOOD INTAKE IN MEAL-FED RATS

Compound	mg/kg	Cumulative Food Intake 1 Hour g/100 g Body Weight	Cumulative Food Intake 6 Hours g/100 g Body Weight
1. Control		1.97 ± 0.26	6.01 ± 0.21
Ritanserin	0.2	1.60 ± 0.16	5.21 ± 0.43
Fluoxetine	10	1.01 ± 0.21‡	4.34 ± 0.28†
Fluoxetine	10	1.06 ± 0.43	3.80 ± 0.60‡
+ ritanserin	0.2		
2. Control		3.15 ± 0.20	8.27 ± 0.44
Fluoxetine	20	0.98 ± 0.26*	3.98 ± 0.40*
LY53857	10	2.60 ± 0.08‡	6.77 ± 0.28§
Fluoxetine	20	1.11 ± 0.41†	3.61 ± 0.32*
+ LY53857	1		
Fluoxetine	20	1.26 ± 0.43†	3.68 ± 0.63*
+ LY53857	10		

Groups of six meal-fed rats were treated with 1) ritanserin (0.2 mg/kg IP) 15 min or 2) LY53857 (1 or 10 mg/kg IP) 20 min before fluoxetine at doses as indicated. Feeding was initiated 1/2 hr later and was recorded as means ± S.E. with statistically significant differences, as indicated: *$p<0.001$; †$p<0.005$; ‡$p<0.025$; §$p<0.05$.

the 2-deoxyglucose-treated rats (S-fluoxetine, $p<0.005$; R-fluoxetine, $p<0.05$), although only the S-enantiomer lowered food intake significantly at 6 mg/kg IP ($p<0.05$) (Fig. 4).

In our attempt to further understand the involvement of the serotonergic mechanism in the suppression of food intake by fluoxetine, we examined possible antagonism with the centrally or peripherally acting 5HT antagonists. Pretreatment with two peripherally acting 5HT-2 receptor antagonists, xylamidine (16) and BW 501C67 (9), at 5 mg/kg IP failed to reverse the suppression of food intake by fluoxetine in meal-fed rats during 1 and 6 hr ($p<0.001$ and $p<0.005$, respectively) of food access (Table 1), while BW 501C67 itself exerted an intermediate anorectic effect ($p<0.05$). Neither the centrally acting antagonist (9) of multiple 5HT receptors, metergoline at 5 mg/kg (Table 1), nor the antagonists specific for central 5HT-2 receptors (ritanserin at 0.2 mg/kg and LY53857 at 1 or 10 mg/kg) (Table 2), antagonized the reduction of food intake by fluoxetine treatment, while metergoline or LY53857 at 10 mg/kg ($p<0.005$) alone also lowered food intake.

Both enantiomers of fluoxetine were equally effective and selective inhibitors of 5HT uptake in vitro (Table 3) and behaved as competitive inhibitors of the 5HT uptake carrier in synaptosomal preparations (30). S- and R-enantiomers of fluoxetine were 27 and 10 times weaker, respectively, as inhibitors of NE uptake. Similar to the findings with the racemate (26,31), the two enantiomers were weak inhibitors of 5HT-1 and 5HT-2 receptors labeled by ^{3}H-5HT and ^{3}H-ketanserin, respectively. At 5000 nM concentration, neither enantiomer of fluoxetine inhibited ^{3}H-8-OH-DPAT binding to 5HT-1A receptors, which upon activation by 8-OH-DPAT and other agonists could lead to increase of food intake in rats (7,8). High concentrations of the enantiomers were also required to inhibit binding of radioligands to the other receptors: ^{3}H-WB4101, ^{3}H-clonidine and ^{3}H-dihydroalprenolol to

TABLE 3

INHIBITION OF MONOAMINE UPTAKE AND RADIOLIGAND BINDING TO RECEPTORS BY TWO ENANTIOMERS OF FLUOXETINE

Assay	S-Fluoxetine	R-Fluoxetine
	IC_{50}, nM	
5HT uptake	61.5 ± 1.5	99.5 ± 10.5
NE uptake	1700 ± 300	1025 ± 25
^{3}H-5HT (5HT-1)	(10000; 31)	(10000; 18)
^{3}H-8-OH-DPAT (5HT-1A)	(5000; 0)	(5000; 0)
^{3}H-Ketanserin (5HT-2)	4500	1620
^{3}H-WB4101 (Alpha-1-Adr)	17000	9000
^{3}H-Clonidine (Alpha-2-Adr)	9100	8000
^{3}H-Dihydroalprenolol (Beta-Adr)	9000	10000
^{3}H-Apomorphine (Dopamine-1,2)	(10000; 44)	9100
^{3}H-Spiperone (Dopamine-2)	8600	7000
^{3}H-QNB (Muscarinic-ACh)	2200	3600
^{3}H-Pyrilamine (Histamine-1)	9000	2000

Values within parentheses indicate the concentration of drug tested and the percent inhibition that resulted.

alpha-1, alpha-2 and beta-adrenergic receptors, respectively; ^{3}H-apomorphine and ^{3}H-spiperone to dopamine-2 receptors; ^{3}H-QNB to muscarinic-acetylcholine receptors and ^{3}H-pyrilamine to histamine-1 receptors.

DISCUSSION

Being potent and selective inhibitors of 5HT uptake, R- and S-enantiomers of fluoxetine suppressed feeding by a mechanism(s) consistent with the involvement of serotonergic neurons in control of food intake by rodents (3, 4, 27). Inhibiting 5HT reuptake by fluoxetine in vivo would lead to greater synaptic availability of the endogenous transmitter (32,34). Consistent with this interpretation, fluoxetine administered centrally to the paraventricular nucleus (PVN) of hypothalamus produced a profound suppression of food intake induced by an injection of norepinephrine to PVN in rats (27).

Food intake in meal-fed rats is suppressed by the two enantiomers of fluoxetine in a dose-dependent fashion, and with comparable potency. The doses of the two enantiomers are in the same dose range required to block 5HT reuptake in vivo (30) and agree with their equal potency in vitro and in vivo as inhibitors of 5HT uptake.

Hyperphagia induced by 2-deoxyglucose is also dose-dependently reversed by fluoxetine, as previously reported by Carruba *et al.* (6). Both enantiomers of fluoxetine are effective, with the S-enantiomers being slightly more potent. The duration of the effect of fluoxetine in the reversal of 2-deoxyglucose-induced feeding appears to persist up to 3 hours. The potency of fluoxetine to suppress feeding in meal-fed rats diminishes after the first hour of food access, although inhibition of 5HT uptake in vivo lasted up to 24 hr (29). A number of humoral factors, including opioid peptides in CNS, are known to influence feeding (14). Serotonergic agents, including fluoxetine (5,23), have been shown to stimulate release of opioid peptides which may gradually negate the inhibitory control of feeding by 5HT in a time-dependent manner since opiates are known to stimulate feeding (14,15).

Pretreatment with the peripherally acting 5HT-2 receptor antagonists (xylamidine and BW 501C67) at 5 mg/kg IP did not reverse the anorectic effects of fluoxetine, although the two antagonists at much lower doses have been shown to antagonize the cardiovascular effects of 5HT (9). The two antagonists of the central 5HT-2 receptors, LY53857 and ritanserin, at doses of 5 mg/kg were also ineffective, while they blocked the central effect of quipazine at lower doses (9). These data suggested that neither peripheral nor central 5HT-2 receptors are involved in the suppression of feeding by fluoxetine.

Pretreatment with metergoline, a nonspecific 5HT antagonist, at a dose of 5 mg/kg, well above the doses that have been shown to block some serotonergic responses (9,16), failed to block the anorectic effect of fluoxetine. Metergoline, however, does not antagonize all central serotonmergic responses (1, 2, 13), including the elevation of corticosterone in serum by a 5HT-1A receptor agonist, LY165163 (11), although metergoline has been shown to have an affinity for 5HT-1A receptors in vitro (24). The failure of metergoline to antagonize the suppression of food intake by fluoxetine, therefore should not be taken as evidence that the anorectic effects are not mediated through 5HT receptors, which are activated by an increase of 5HT availability upon inhibition of 5HT reuptake by fluoxetine.

Neither enantiomer of fluoxetine exerts direct effects of 5HT-1, 5HT-2 or other neural receptors (17,31). Chronic administration of fluoxetine, however, has caused a down-regulation of 5HT-1 receptors, but no other receptors (28,34). Since down-regulation of 5HT-1 receptors did not accompany tolerance to the anorectic effects of fluoxetine during chronic administration (34,35), the adaptive change of 5HT-1 receptors is a consequence of a sustained activation by an increase in intrasynaptic availability of 5HT.

Recently, 5HT-1 receptors have been resolved by radioligand binding techniques into 5HT-1A, -1B and -1C subtypes (19,25). Activation of 5HT-1A receptors by specific agonists (8-OH-DPAT, ipsapirone and LY165163) would stimulate feeding (8, 32, 33). Thus, 5HT-1A receptors are not likely to mediate the anorectic effects of fluoxetine. Other 5HT-1 receptor subtypes (B and C) and unidentified 5HT receptors might be involved in the suppression of food intake by fluoxetine. It has been proposed that 5HT-1B receptors might mediate the anorectic effects of the 5HT agonists RU24969 and quipazine (8). The availability of specific antagonists may resolve which receptors mediate the inhibitory role of 5HT in the control of feeding.

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