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Anorectic Activity of Fluoxetine and Norfluoxetine in Rats: Relationship Between Brain Concentrations and In-vitro Potencies on Monoaminergic Mechanisms

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Abstract—The present study was aimed at establishing the importance of brain monoamine uptake and release mechanisms in the anorectic activity of fluoxetine, relating them to the actual brain concentrations of the parent drug and its metabolite norfluoxetine after anorectic doses in rats. Both compounds showed anorectic activity when administered intraperitoneally, norfluoxetine being slightly more active (ED50 = 22·9 μmol kg^{-1}) than fluoxetine (ED50 = 35·0 μmol kg^{-1}) despite the fact that the metabolite is about ten times less potent than the parent drug in inhibiting 5-hydroxytryptamine (5-HT) uptake. Comparing the brain concentrations of norfluoxetine, in terms of maximum concentrations (C_{max}) and area under the curve (AUC), after the ED50 of fluoxetine or synthetic norfluoxetine, it also appeared that the metabolite plays a major role in the anorectic effect of the parent drug in rats. Brain C_{max} of fluoxetine (48·7 μM) and norfluoxetine (21·7 and 27·3 μM after metabolite and drug, respectively) were several times those blocking 5-HT uptake in-vitro (0·5 μM), making it unlikely that fluoxetine (directly or through its metabolite) reduces food intake by specifically blocking 5-HT neuronal uptake. Brain C_{max} of fluoxetine but particularly norfluoxetine were more compatible with those capable in-vitro of affecting catecholaminergic mechanisms, such as inhibition of dopamine and noradrenaline uptake and enhancement of dopamine release. These results together with recent in-vitro findings that the parent compound and its active metabolite induce tritium release from hippocampal synaptosomes previously loaded with [^{3}H]5-HT suggest that mechanisms other than inhibition of 5-HT uptake are involved in the anorectic action of these compounds in rats.

The increasing evidence that indirect or direct 5-HT-ergic agonists reduce food intake in animals underlines the importance of 5-hydroxytryptamine (5-HT) in the control of mechanisms involved in feeding (Nathan & Rolland 1987; Wong & Fuller 1987; Samanin & Garattini 1990). The fact that some of these drugs may also be effective in the treatment of obesity (Ferguson & Feighner 1987; Freeman 1988) reinforces the interest in animal studies to clarify their mechanism of action. One such agent is the antidepressant fluoxetine (Benfield et al 1986) which has recently proved effective in a number of experimental conditions of hyperphagia (Goudie et al 1976; Reid et al 1984; Carruba et al 1985; Wong et al 1988). Its anorectic effect is believed to result from its ability to enhance 5-HT-ergic transmission, possibly through inhibition of the presynaptic reuptake of 5-HT. Fluoxetine has been shown to only weakly affect noradrenaline and dopamine uptake in-vitro (Wong et al 1974, 1975; Fuller et al 1988) although in another study dopamine uptake in human platelets was significantly inhibited by the drug (Omenn & Smith 1978). However, it is still not clear to what extent the drug affects 5-HT other than by blocking its uptake. In interpreting the effects of fluoxetine in-vivo in animals and man it must be borne in mind that the dealkylated derivative, norfluoxetine, is formed; this metabolite may have neurochemical effects different from those of the parent drug. In the rat, norfluoxetine reaches brain concentrations comparable with or higher than those of fluoxetine, depending on the route, dose and time of administration (Caccia et al 1990). The half-life of norfluoxetine in rats and in man is 2–3 times that of the parent drug (Benfield et al 1986; Caccia et al 1990).

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Considering that studies in this and other laboratories (for review see Samanin & Garattini 1990) have indicated that increased 5-HT release may be a more important mechanism than uptake inhibition for 5-HT-dependent anorexia, and that dopamine in the hypothalamus acts to depress feeding behaviour (Leibowitz & Rossakis 1979), the present studies were designed to examine further the relative importance of brain monoamine uptake and release mechanisms in the anorectic activity of fluoxetine. This was done by relating the in-vitro concentrations of fluoxetine and its metabolite affecting some neurochemical parameters to the actual brain concentrations of the compounds after acute administration of an anorectic ED50 in rats.

Materials and Methods

Animals

Male CD-COBS rats (175–200 g, Charles River, Italy) were housed at constant temperature and relative humidity with fixed 12 h light/dark cycles.

In-vivo studies

All experiments were carried out between 0900 and 1200 h. Fluoxetine hydrochloride and norfluoxetine maleate (E. Lilly, Florence, Italy) were injected intraperitoneally (i.p.), dissolved in 0·9% NaCl (saline) and gum arabic, respectively. In some experiments, animals were trained to eat their daily ration in 4 h (1000–1400 h). On the day of the experiment fluoxetine or norfluoxetine was injected i.p. and 30 min later food was made available. The amount of food eaten during

the next 60 min was measured. The ED50 values were calculated from the data obtained at five dose levels, with five rats per group at each dose, according to the method of De Lean et al (1978).

In a second experiment fluoxetine and norfluoxetine were given to groups of rats at a dose corresponding to their anorectic ED50 and animals were killed by decapitation 5, 30 and 90 min thereafter for determination of drug concentrations and monoamine levels in whole brain and selected brain areas. The brain regions were dissected as described by Glowinski & Iversen (1966).

Fluoxetine and norfluoxetine were extracted from brain homogenates with benzene, after adding nomifensine as an internal standard, derivatized with heptafluobutyric anhydride solution and analysed by electron capture gas liquid chromatography as previously described (Caccia et al 1990). Over the sampling interval the area under the concentration-time curve (AUC) was determined by the trapezoidal rule. The maximum concentration (C_{max}) and the time (t_{max}) of its occurrence were read directly from the concentration-time data for both compounds. Concentrations of 5-HT and its metabolite 5-hydroxyindolacetic acid (5HIAA), noradrenaline (NA), dopamine (DA) and its metabolites dihydroxyphenylacetic acid (dopac) and homovanillic acid (HVA) in brain regions were determined by HPLC as described previously (Achilli et al 1985). The effect of fluoxetine and norfluoxetine on monoamine concentrations was assessed by Dunnett's *t*-test. Probabilities (*P*) less than 0·05 were considered statistically significant.

In-vitro studies

Tissues (cortex, striatum and hippocampus for the uptake of [^{3}H]NA, [^{3}H]DA and [^{3}H]5-HT, respectively) were homogenized in 40 vol of ice-cold 0·32 M sucrose, pH 7·4, using a glass homogenizer with Teflon pestle (average clearance 0·01 to 0·015 cm, 12 full up-and-down strokes in 120 s). Synaptosomes were obtained as previously described by Mennini et al (1987). The homogenate was centrifuged in a Sorvall RC-2B centrifuge at 4°C for 5 min at 1000 *g*. The supernatant was centrifuged at 12000 *g* for 20 min to yield the crude mitochondrial pellet (P2). The final pellet was diluted (20–50 vol of initial weight) with Krebs-Henseleit buffer.

For uptake studies, 0·6 mL samples (final protein concentration 0·5–1 mg mL^{-1}; Peterson 1977), were incubated at 4 or 30°C in a water bath. Drugs (concentration range 100–0·00001 μM) were added during 5 min preincubation at 30°C. Uptake was started by the addition of 50 nM [^{3}H]5-HT, [^{3}H]DA or [^{3}H]NA (sp. act. ID-30 Ci mmol^{-1}) The reaction was stopped 5 min later by adding 1 mL of ice-cold Krebs-Henseleit buffer. Samples were filtered through cellulose nitrate filters (0·65 μm pore size) and washed twice with 2 mL of the buffer. The filters were dissolved in 8 mL of Filter Count and counted for radioactivity in a Beckman LS 7500 liquid scintillation spectrometer with a counting efficiency of 45%.

The difference between ^{3}H accumulated at 30 and 4°C was taken as a measure of the active transport system. Inhibition curves were calculated using the "Allfit" program (De Lean et al 1978) allowing calculation of the concentration reducing uptake by 50% (IC50).

For release experiments, the synaptosomal suspension was added to an equal volume of buffer containing [^{3}H]5-HT, [^{3}H]NA or [^{3}H]DA, final concentration 0·06 μM. After incubation for 15 min at 37°C, the solution was diluted to 80 mL with fresh buffer and 5 mL aliquots were then distributed on 0·65 μm cellulose nitrate filters in a 16-chamber superfusion apparatus (Raiteri et al 1974) thermostated at 37°C. The synaptosomes were stratified on the filters by aspiration from below under moderate vacuum. Superfusion was started (t = 0) at a rate of 0·5 mL min^{-1} and fractions were collected every 2 min. Superfusion was continued until the system was equilibrated (t = 44 min for [^{3}H]5-HT, t = 34 min for [^{3}H]NA and t = 24 min for [^{3}H]DA). Three min later the medium in the chambers was replaced with a new one containing the drugs (3–4 chambers each) which was left for 3 min, then the medium was replaced again with the standard medium and the superfusion and collection of the fractions continued for 10 min.

The filters were then put into scintillation vials and counted for radioactivity, as before, in 8 mL of Atom-light (Packard). The amount of ^{3}H released into each 2 min fraction was calculated as a percentage of the total radioactivity present on the filter at the start of the fraction considered.

The SC20 (drug concentration causing 20% enhancement of monoamine release) was calculated from the cumulative percentage of radioactivity released during 8 min of collection (from t = 48 to t = 56 min).

Results

Table 1 and Fig. 1 illustrate the anorectic properties of fluoxetine and norfluoxetine in the rat. The ED50 calculated by giving different intraperitoneal doses of the drug to overnight-fasted rats used to taking their food ration during a period of 4 h and measuring food consumption within 1 h was 12·0 mg kg^{-1} (35 μmol kg^{-1}) for fluoxetine and 9·5 mg kg^{-1} (22·9 μmol kg^{-1}) for the metabolite.

The anorectic effect of fluoxetine may be related to the brain concentrations of the parent drug and its active metabolite, taking into account the values within 90 min of fluoxetine administration, this being the time over which the anorectic activity was measured. Thus brain concentrations of the parent compound and its active metabolite were measured in another group of rats given the anorectic ED50 of fluoxetine and the results were compared with the findings after an equiactive dose of synthetic norfluoxetine. After fluoxetine, brain concentrations of unchanged drug rose from 12·8 ± 5·0 nmol g^{-1} at 5 min to 32·0 ± 9·8 at 30 and 48·7 ± 6·9 nmol g^{-1} at the end of the food intake period. The metabolite was detected in rat brain within 30 min (7·1 ± 0·3 nmol g^{-1}), achieving concentrations of 27·2 ± 4·5 nmol g^{-1} 90 min after parent drug administration. Brain AUC of fluoxetine and its active metabolite were respectively 50·3 and 19·1 nmol mL^{-1} h, during the 90 min experiment (Table 1).

Brain concentrations of the metabolite after administration of synthetic norfluoxetine (4·6 ± 0·8, 17·0 ± 6·0 and 21·7 ± 6·5 nmol g^{-1}, at 5, 30 and 90 min, respectively) were similar to those after fluoxetine, in terms of C_{max} and AUC (Table 1). It thus appears that norfluoxetine may be very important in the anorectic effect of the parent drug in rats.

The pattern of distribution of unchanged drug and

Table 1. Effect of fluoxetine and norfluoxetine on food intake, maximum brain concentrations and area under the concentration-time curve (AUC).

Compound	ED50 (95% confidence limits) (μmol kg^{-1}, i.p.)	Brain C_{max} (nmol g^{-1})[a]		AUC (nmol g^{-1} h)[b]	
		Fluoxetine	Norfluoxetine	Fluoxetine	Norfluoxetine
Fluoxetine	34·7 (19·8–49·6)	48·7 ± 6·9	27·3 ± 4·7	50·3	19·7
Norfluoxetine	22·9 (17·7–28·1)	—	21·7 ± 6·5	—	24·1

[a] Observed values (mean ± s.d., n = 5); [b] mean area under the curve (calculated up to 90 min).

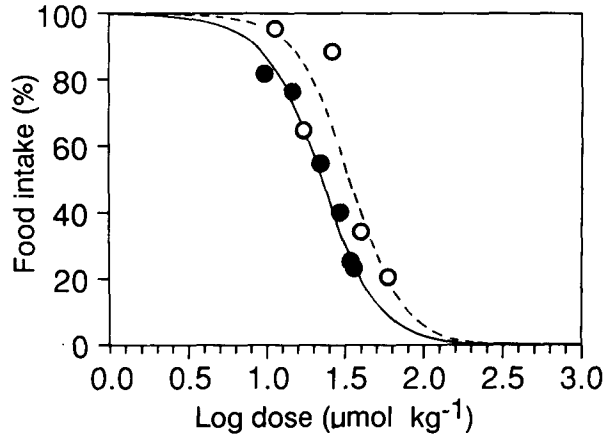

FIG. 1. Plot of the food intake in relation to the dose of fluoxetine (○) and norfluoxetine (●) given to rats. The compounds were given i.p. 30 min before the animals were given food for 1 h. The curves represent the best fit of the experimental points according to De Lean et al (1978).

metabolite in the different regions was similar to that observed for the whole brain, with no preferential distribution of the parent drug or its metabolite in these brain regions 90 min after intraperitoneal injection of the respective anorectic doses. At this time both compounds lowered cortical 5HIAA to a comparable extent without significantly affecting 5-HT concentrations. Neither the drug nor its metabolite had any effect in hippocampus (Table 2) or striatum (data not shown). Cortical and hippocampal noradrenaline and striatal dopamine, HVA and dopac content were not affected 90 min after these doses of fluoxetine and norfluoxetine (data not shown).

Table 3 summarizes the effects of fluoxetine and its metabolite on the uptake (IC50) and release (SC20) of ^{3}H from synaptosomes previously loaded with [^{3}H]5-HT, [^{3}H]NA and [^{3}H]DA. As reported previously (Wong et al 1975) fluoxetine was a powerful inhibitor of 5-HT uptake in-vitro. This effect was specific because approximately 30 and 60 times the concentrations inhibiting 5-HT uptake were necessary to halve noradrenaline dopamine uptake. Norfluoxetine had less effect than the parent drug in inhibiting 5-HT uptake and its selectivity for 5-HT in relation to noradrenaline and dopamine uptake was only 5 and 6 times, respectively. The effect of fluoxetine on release was less specific, affecting not only synaptosomes preloaded with [^{3}H]5-HT, but also [^{3}H]DA though not [^{3}H]NA. The metabolite had slightly less effect than fluoxetine on ^{3}H release from synaptosomes preloaded with [^{3}H]5-HT, but the compounds were equipotent in enhancing ^{3}H release from synaptosomes preloaded with [^{3}H]DA.

Discussion

Fluoxetine has proved effective in a number of experimental conditions of hyperphagia (Goudie et al 1976; Reid et al 1984; Carruba et al 1985; Wong et al 1988), possibly through inhibition of presynaptic neuronal reuptake of 5-HT. However, while it was conceivable that increased availability of 5-HT in the synapse following uptake inhibition resulted in reduced food intake it was still not clear to what extent the drug affected monoaminergic mechanisms other than by blocking 5-HT uptake.

In the present study, this question was considered by comparing the brain concentrations of the parent drug and its active metabolite norfluoxetine after an anorectic ED50 of the two compounds in rats, with their in-vitro activities. These and previous studies show that both compounds are distributed evenly in discrete brain areas of rats; the subcellular distribution was also similar, about 40% of both compounds being available in synaptosomes and mitochondria and in the nuclei fractions and 10% in microsomes and soluble fractions (Caccia et al 1990).

Fluoxetine and norfluoxetine showed dose-dependent anorectic activity in rats, the metabolite being slightly more

Table 2. Drug concentrations and indole content in cortex, hippocampus and striatum after equi-active anorectic ED50 doses of fluoxetine and norfluoxetine to rats.

Compound (mg kg^{-1}, i.p.)	Brain area	Drug concn (nmol g^{-1})		Indole content (% of control)	
		Fluoxetine	Norfluoxetine	5-HT	5HIAA
Fluoxetine (34·7)	Cortex	34·9 ± 1·9	20·6 ± 4·5	96 ± 4	77 ± 2**
	Hippocampus	33·1 ± 2·9	17·7 ± 1·8	107 ± 10	96 ± 5
Norfluoxetine (22·9)	Cortex		19.9 ± 3.2	96 ± 11	80 ± 5**
	Hippocampus		16·7 ± 3·9	105 ± 10	101 ± 7

Each value is the mean ± s.d. of five animals. **$P < 0·07$ vs vehicle.

Table 3. Effect of fluoxetine and norfluoxetine on uptake and release of 5-HT, noradrenaline and dopamine.

Monoaminergic mechanism	Fluoxetine (μM)	Norfluoxetine (μM)
Uptake (IC50)		
5-HT	0·07 ± 0·01	0·5 ± 0·1
Dopamine	4·5 ± 1·4	2·9 ± 0·9
Noradrenaline	2·4 ± 0·4	2·3 ± 0·4
Release (SC20)		
5-HT	6·6	10·6
Dopamine	3·8	3·4
Noradrenaline	> 10	> 10

IC50 ± coefficient of variation were obtained using the Allfit program. SC20 values for release experiments were extrapolated from regression analysis of log concentration-effect curves.

active than the parent compound despite its lower potency and specificity in inhibiting 5-HT uptake in-vitro. Analysis of the brain concentrations of the two compounds within the 90 min experiment further indicated that norfluoxetine was more effective in terms of C_{max} and AUC values required to obtain an equal anorectic effect. Comparing the brain concentrations of norfluoxetine after equiactive doses of the compound it also appeared that the active metabolite most probably plays a major role in the parent drug's anorectic activity in the rat.

Brain concentrations of norfluoxetine, in terms of C_{max}, after fluoxetine or synthetic norfluoxetine (22–27 μM) were 40–50 times those blocking 5-HT uptake in-vitro (0·5 μM). The ratio between brain C_{max} and the in-vitro effect was even higher for fluoxetine (about 700 times), further indicating that the anorectic action in rats is unlikely to be due to its ability to block neuronal 5-HT uptake (directly or through its main metabolite). Consistent with these findings was the inability of fluoxetine and norfluoxetine to reduce food intake at doses below 1 μmol kg^{-1}, or about the minimum effective dose of the two compounds required to affect food intake in our experimental conditions in rats. The 1 μmol kg^{-1} dose results in brain concentrations of 6·1 ± 1·2 and 5·6 ± 1·5 nmol g^{-1} (n = 4) for fluoxetine and metabolite, respectively, at the end of the food intake period, thus more than sufficient to saturate the 5-HT re-uptake mechanism.

Fluoxetine and norfluoxetine have been recently shown to induce ^3H release from hippocampal synaptosomes previously loaded with [^{3}H]5-HT, an effect shared by the well-known anorectic agent (+)-fenfluramine. The drug concentrations active in this model are in the same range as those reached in rat brain after the anorectic ED50, adding another possible mechanism of action to be considered (Gobbi et al 1991). The fluoxetine and norfluoxetine-induced ^3H release, however, is mainly (about 80%) due to [^{3}H]5HIAA, thus differing from the release effect of (+)-fenfluramine, which induces ^3H release comprising 70% unmetabolized 5-HT. Unlike the releasing action of (+)-fenfluramine the action of fluoxetine is not saturable, does not depend on calcium and is not antagonized by the powerful 5-HT uptake inhibitor indalpine (Gobbi et al 1991).

The different mechanisms of the functional effects produced by fluoxetine and (+)-fenfluramine are also indicated by in-vivo neurochemical data. (+)-Fenfluramine at a full anorectic dose (2·5 mg kg^{-1}) reduced 5-HT and 5HIAA content after single or repeated treatment (Garattini et al 1988; Samanin & Garattini 1990) while fluoxetine only lowers 5HIAA after a single dose (Fuller et al 1988, and present results) but reduces both 5-HT and 5HIAA after chronic administration (Hrdina 1987). However, fluoxetine lowered 5HIAA concentrations in the cerebral cortex but had no significant effect in the hippocampus and striatum. Since fluoxetine and its active metabolite appear to be uniformly distributed in brain areas, these results suggest that the in-vivo interaction of fluoxetine on 5-HT metabolism cannot simply be predicted by its ability to inhibit 5-HT uptake.

The anorectic effect of fluoxetine is not reduced by anti-5-HT-ergic drugs (Wong et al 1988), unlike the effect of (+)-fenfluramine for which an involvement of 5-HT has been fully demonstrated (Garattini et al 1988; Nathan & Rolland 1987; Samanin & Garattini 1990). This and the fact that brain concentrations of fluoxetine and norfluoxetine at anorectic doses are consistent with the possibility of an effect on catecholaminergic mechanisms, such as inhibition of dopamine and noradrenaline uptake and enhancement of dopamine release, suggest that some non-5-HT mechanisms may be involved, further complicating any interpretation of the mechanism of action of fluoxetine.

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