J. Pharm. Pharmacol. 1998, 50: 1387–1392
Received June 1, 1998
Accepted July 29, 1998

Effects of Fluoxetine and Norfluoxetine on 5-Hydroxytryptamine Metabolism in Blood Platelets and Brain after Administration to Rats

ROLAND BOURDEAUX, DIDIER DESOR*, PAUL R. LEHR*, CHAFIQUE YOUNOS† AND BERNARD CAPOLAGHI

*Laboratoire de Biochimie, CHR Metz-Thionville, 57100 Thionville, *Laboratoire de Biologie et Physiologie du Comportement, URA CNRS 1293, Université Henri Poincaré, Nancy I, 54000 Nancy, and † Centre de Sciences de l'Environnement, Université de Metz, 57000 Metz, France*

Abstract

The effects of intraperitoneal administration of fluoxetine (2·5, 5, 10 or 20 mg kg^{-1}) and norfluoxetine (10 mg kg^{-1}) on 5-hydroxytryptamine (5-HT) and 5-hydroxyindole-3-acetic acid (5-HIAA) metabolism were examined in the blood platelets and brain of rats killed 3 h after a single dose. Several experiments were performed to evaluate the effect of norfluoxetine.

Plasma 5-HT concentrations decreased significantly (48%) compared with control group results 3 h after administration of a single dose of fluoxetine (10 or 20 mg kg^{-1}). Similar plasma 5-HT levels, $0{\cdot}54 \pm 0{\cdot}04$ and $0{\cdot}56 \pm 0{\cdot}09$ mg L^{-1}, respectively, were observed after administration of 10 mg kg^{-1} fluoxetine or norfluoxetine. In the same way 5-HIAA levels in whole brain were similar, $0{\cdot}36 \pm 0{\cdot}03$ and $0{\cdot}34 \pm 0{\cdot}01$ $\mu g\, g^{-1}$, respectively, after administration of fluoxetine or norfluoxetine. There was a good correlation between plasma and brain levels of fluoxetine (0·962) and norfluoxetine (0·957).

The results suggest that fluoxetine and norfluoxetine lead to reduced levels of 5-HT in platelets and of 5-HIAA in the brain. Like the parent drug, norfluoxetine is a potent and selective inhibitor of 5-HT uptake.

Fluoxetine is an antidepressant which facilitates 5-hydroxytryptaminergic transmission by inhibition of neuronal re-uptake of 5-hydroxytryptamine (5-HT). Its biochemical and pharmacological profiles have been studied extensively in animals (for reviews see Benfield et al 1986, Schmidt et al 1988 and Wong et al 1995).

The purpose of this study was to evaluate the effect of norfluoxetine on 5-HT in plasma (platelets) and on 5-HT and 5-hydroxyindole-3-acetic acid (5-HIAA, the main metabolite of 5-HT) in the whole brain of rats. In preliminary studies the role of norfluoxetine in the inhibition of 5-HT uptake was examined after administration of fluoxetine to rats (for review see Wong et al 1995) but not after norfluoxetine administration.

We have previously measured levels of 5-HT and 5-HIAA in control groups after intraperitoneal administration of fluoxetine at different doses to follow the ratio norfluoxetine/fluoxetine. To evaluate the effect of norfluoxetine, two experiments were performed. One in which only norfluoxetine was injected and one in which fluoxetine was injected after the administration of proadifen, which blocks fluoxetine demethylation.

Studies of fluoxetine and norfluoxetine in rats might enable understanding of their mechanism of action and facilitate extrapolation of the biochemical and pharmacological findings to man.

Correspondence: B. Capolaghi, Laboratoire de Biochimie, CHR Metz-Thionville, 57100 Thionville, France.

Materials and Methods

Drugs

Fluoxetine hydrochloride and norfluoxetine hydrochloride were kindly provided by Lilly (France). Fluphenazine dichlorhydrate was kindly provided by Squibb (France). 5-Hydroxytryptamine, creatinine sulphate, N^{ω}-methyl-5-hydroxytryptamine oxalate, 5-hydroxyindole-3-acetic acid, 5-hydroxyindole-2-carboxylic acid and proadifen hydrochloride (SK&F 525A) were purchased from

Sigma. Other chemicals and reagents were of HPLC or analytical grade of purity.

Animals

Experiments were performed on adult male Wistar rats (Iffa Credo, L'Arbresle, France), 295 ± 25 g (mean ± s.d.). The animals were housed in wire-mesh cages in an air-conditioned room maintained at a relatively constant temperature (21 ± 1°C) and with a 12-h light–dark cycle. Water and standard diet (food pellets; Extra Labo, Provins, France) were freely available.

The rats were given single intraperitoneal injections of fluoxetine hydrochloride dissolved in water at doses of 0, 2·5, 5, 10 or 20 mg kg^{-1}. In another experiment rats received an intraperitoneal injection of proadifen (40 mg kg^{-1}) 1 h before intraperitoneal administration of fluoxetine (20 mg kg^{-1}). Other rats received intraperitoneal norfluoxetine (10 mg kg^{-1}). The rats were killed by decapitation under light ether anaesthesia, to facilitate blood flow, 3 h after administration of fluoxetine or norfluoxetine. Blood from each rat was immediately drawn into two tubes containing 0·15% Na_2EDTA. The first tube, used for the analysis of 5-HT in platelet-rich plasma, was immediately centrifuged at 150 *g* for 15 min; the platelet-rich plasma (PRP) was aspirated and stored at −20°C before determination of 5-HT. The second tube was centrifuged at 3500 *g* for 5 min and the plasma stored at −20°C before determination of fluoxetine and norfluoxetine. The whole brains (with cerebellum) were rapidly removed, frozen on dry ice, and stored at −20°C. On the day of analysis they were thawed and weighed.

Plasma 5-HT assay

Platelet-rich plasma (PRP) was prepared by centrifugation at 150 *g* for 15 min at room temperature. After addition of *N*-methyl-5-hydroxytryptamine as internal standard, 5-HT was extracted from PRP at pH 10·0 (borate buffer, 0·2 M) with dichloromethane-*n*-butanol, 75 : 25 (v/v) then back-extracted with HCl (0·01 M). Samples were analysed by reversed-phase HPLC on a 250 mm × 4·6 mm Capcell RP18 column, 5 μm particle size (Interchim, France); compounds were eluted isocratically with ammonium acetate (0·2 M)–acetonitrile, 92 : 8, as mobile phase and detected amperometrically (+0·5 V). The recovery of 5-HT from plasma samples reached 92% and the calibration curve was linear over the range 0·1–5 mg L^{-1}. The estimated coefficients of variation (CV) of peak height for within-day and between-day analyses (pools of PRP) were 2·1 and 1·8%, respectively.

Plasma fluoxetine

The drug and its metabolite were extracted with hexane–isoamyl alcohol, 98 : 2 (v/v) from alkaline plasma (NaOH, 4 M), then back-extracted with HCl (0·01 M). The compounds were determined by reversed-phase HPLC on a 125 mm × 4 mm i.d. Superspher RP8 column, 4 μm particle size (Merck); compounds were eluted with $K_2HPO_4.3H_2O$, 0·012 M adjusted to pH 3·0 with 2 M H_3PO_4–acetonitrile, 43 : 57, as mobile phase and detected by means of a UV-detector operated at 226 nm. Calibration curves were linear over the 10–800 μg L^{-1} range for both fluoxetine and norfluoxetine. CV over ten days were 2·2 and 1·6%, respectively, for fluoxetine and norfluoxetine at 100 μg L^{-1}. There was no interference from common psychoactive drugs.

Whole brain

The concentrations of fluoxetine, norfluoxetine, 5-HT and 5-HIAA in whole brain were determined by the method of Caccia et al (1990) with some modification—1 M formic acid was replaced by 0·02 M HCl. The whole brain was homogenized in cold acetone–0·02 M HCl, 85 : 15 (v/v), after addition of the internal standards–*N*-methyl-5-HT (5 mg L^{-1}) for 5-HT, 5-hydroxyindole-2-carboxylic acid (5 mg L^{-1}) for 5-HIAA, and fluphenazine (100 mg L^{-1}) for fluoxetine and norfluoxetine. The mixture was centrifuged at 3000 *g* for 15 min at room temperature. The supernatant (10 mL) was shaken twice with *n*-heptane–chloroform, 9 : 1 (v/v), and centrifuged (3000 *g* for 15 min). The organic layer was discarded and three samples of the aqueous phase (3 × 1 mL) were used for extraction. The extraction procedures for 5-HT (first sample) and the drugs fluoxetine and norfluoxetine (second sample) were similar to those used for plasma.

5-HIAA (third sample) was extracted with dichloromethane–2-propanol, 9 : 1 (v/v). The aqueous phase was discarded, the organic layer evaporated to dryness, and the extract obtained dissolved in mobile phase (200 μL). The final solution was injected on to the HPLC column (150 mm × 4 mm i.d. RP18, 5 μm particle size) protected with a Brownlee–Newguard precolumn (4 cm, 5 μm). A 0·05 M KH_2PO_4 solution adjusted to pH 3·0 with 2 M H_3PO_4 containing 4% ethanol was used as mobile phase. Elution of the compounds from the column was performed at 40°C at a flow rate of 1·5 mL min^{-1}, amperometric detection was performed at +0·7 V.

Statistics

Analysis of the data was performed by analysis of variance (single factor, repeated measures) for

overall comparisons and Fisher's protected least significant difference (PLSD) test for multiple comparisons. Student's *t*-test was used to compare results from the experimental groups with those from their respective controls. The null hypothesis was rejected at the 5% significance level ($P < 0.05$).

Results

The effect of fluoxetine and norfluoxetine on the levels of 5-HT and 5-HIAA in plasma and rat brain are shown in Table 1. Three hours after administration of a single dose of fluoxetine (10 or 20 mg kg^{-1}) plasma 5-HT concentrations were significantly lower (48%) than for the control group. Lower doses (2·5 or 5 mg kg^{-1}) had no effect. There were no significant differences between 5-HT levels in the whole brains of the four groups of rats treated with fluoxetine and the control group. The lowest dose of fluoxetine eliciting significant depression of brain levels of 5-HIAA was 5 mg kg^{-1}.

The reductions of plasma 5-HT concentrations and of levels of 5-HIAA in whole brain were similar after administration of fluoxetine or norfluoxetine at 10 mg kg^{-1}. In contrast, the reduction in brain 5-HT level was significantly greater ($P < 0.05$, Student's *t*-test) after treatment with norfluoxetine (10 mg kg^{-1}) than after treatment with fluoxetine (10 mg kg^{-1}).

Pretreatment of the rats with proadifen (40 mg kg^{-1}) to block microsomal drug metabolism (or fluoxetine demethylation) did not alter plasma and brain 5-HT values obtained after administration of fluoxetine (20 mg kg^{-1}) alone. Levels of 5-HIAA in the brain differed significantly ($P < 0.05$, Student's *t*-test) after this treatment.

Plasma and brain levels of fluoxetine and norfluoxetine after intraperitoneal administration of fluoxetine or norfluoxetine to rats are shown in Tables 2 and 3. Plasma fluoxetine levels increased linearly with dose ($y = 21.763x - 66.010$, $r^2 = 0.969$) whereas levels of the metabolite norfluoxetine in plasma increased exponentially ($y = 101.144\ln x - 73.270$, $r^2 = 0.952$). The mean metabolite-to-parent drug ratio decreased with increasing fluoxetine dose; the percentage of norfluoxetine also decreased because of the greater proportion of fluoxetine formed in the plasma.

Fluoxetine levels in the brain increased linearly with the dose ($y = 1.269x - 2.221$, $r^2 = 0.994$) but, as for plasma norfluoxetine, metabolite levels increased exponentially with increasing dose ($y = 4.272\ln x - 1.083$, $r^2 = 0.958$). The level of norfluoxetine in plasma after administration of norfluoxetine (10 mg kg^{-1}) did not differ significantly from the sum fluoxetine + norfluoxetine obtained after a single dose of fluoxetine (10 mg kg^{-1}); in contrast, these values differ significantly in the brain ($P < 0.0001$, Student's *t*-test).

After treatment of the rats with proadifen, the sum of fluoxetine + norfluoxetine in plasma and brain differed significantly ($P < 0.05$) for the values obtained after administration of fluoxetine only (20 mg kg^{-1}), although the ratio fluoxetine/norfluoxetine and the percentage norfluoxetine in plasma and brain did not differ significantly.

Linear regression plots were obtained for the relationships between the concentrations of fluoxetine in plasma and brain (Figure 1, $y = 0.056x + 1.883$, $r^2 = 0.962$) and between the concentrations of norfluoxetine in plasma and brain (Figure 2, $y = 0.041x + 2.144$, $r^2 = 0.957$).

Discussion

In this study intraperitoneal doses were limited to 20 mg kg^{-1} because of the high general toxicity of the compounds. In preliminary studies when rats received doses of fluoxetine greater than 20 mg kg^{-1} day^{-1} the animals suffered and most

Table 1. Effect of fluoxetine and norfluoxetine on the levels of indolamines in plasma and rat brain.

Treatment and dose (mg kg^{-1})	n	Platelet-rich plasma 5-HT (mg L^{-1})	Whole brain 5-HT (μg g^{-1} wet weight)	5-HIAA (μg g^{-1} wet weight)
Control: (0)	8	1·03 ± 0·17	0·39 ± 0·03	0·47 ± 0·04
Fluoxetine (2·5)	5	1·04 ± 0·08	0·36 ± 0·01	0·45 ± 0·03
Fluoxetine (5)	5	0·93 ± 0·10	0·40 ± 0·03	0·41 ± 0·02*
Fluoxetine (10)	6	0·54 ± 0·04*	0·38 ± 0·03	0·36 ± 0·03*
Fluoxetine (20)	5	0·51 ± 0·02*	0·36 ± 0·04	0·28 ± 0·04*
Proadifen: (40) + FL: (20)	5	0·46 ± 0·02*	0·34 ± 0·01*	0·33 ± 0·02*
Norfluoxetine (10)	6	0·56 ± 0·09*	0·34 ± 0·02*	0·34 ± 0·01*

Drugs were administered intraperitoneally. Values are means ± s.e.m.; n is the number of rats. 5-HT—5-hydroxytryptamine; 5-HIAA—5-hydroxyindole-3-acetic acid. Statistical analysis was performed by Fisher's PLSD test; *$P < 0.05$, significantly different from control result.

Table 2. Concentrations ($\mu g\,L^{-1}$) of fluoxetine and norfluoxetine in plasma after intraperitoneal administration to rats.

Treatment and dose ($mg\,kg^{-1}$)	n	Norfluoxetine	Fluoxetine	Norfluoxetine + fluoxetine	Norfluoxetine/ fluoxetine	% Norfluoxetine
Fluoxetine (2·5)	5	31·0 ± 4·5	11 ± 1·2	44·0 ± 2·1	2·84 ± 0·47	0·70 ± 0.09
Fluoxetine (5)	5	65·4 ± 3·05	38·8 ± 1·6	104·2 ± 4·4	1·69 ± 0·05	0·63 ± 0·01
Fluoxetine (10)	6	170·8 ± 14·8	123·7 ± 19·0	294·5 ± 30·0	1·40 ± 0·18	0·58 ± 0·03
Fluoxetine (20)	5	228·8 ± 13·3	384·2 ± 28·6	613·0 ± 37·3	0·60 ± 0·04	0·37 ± 0·01
Proadifen (40) + fluoxetine (20)	5	118·8 ± 12·6	549·4 ± 23·6	668·2 ± 25·8	0·21 ± 0·03	0·18 ± 0·02
Norfluoxetine (10)	6	280·5 ± 12·1				

Values are means ± s.e.m.; n is the number of rats.

Table 3. Brain concentrations ($\mu g\,g^{-1}$ wet weight) of fluoxetine and norfluoxetine after intraperitoneal administration to rats.

Treatment and dose ($mg\,kg^{-1}$)	n	Norfluoxetine	Fluoxetine	Norfluoxetine + fluoxetine	Norfluoxetine/ fluoxetine	% Norfluoxetine
Fluoxetine (2·5)	5	2·80 ± 0·16	1·18 ± 0·15	3·98 ± 0·30	2·32 ± 0·16	0·71 ± 0·03
Fluoxetine (5)	5	5·38 ± 0·33	3·62 ± 0·47	9·00 ± 0·60	1·48 ± 0·16	0·60 ± 0·03
Fluoxetine (10)	6	9·52 ± 0·52	10·77 ± 0·73	20·29 ± 0·86	0·88 ± 0·07	0·47 ± 0·02
Fluoxetine (20)	5	11·24 ± 0·75	23·08 ± 0·93	34·32 ± 1·64	0·49 ± 0·02	0·33 ± 0·01
Proadifen (40) + fluoxetine (20)	5	4·30 ± 0·35	26·76 ± 1·65	31·06 ± 1·48	0·16 ± 0·02	0·14 ± 0·02
Norfluoxetine (10)	6	24·63 ± 0·95				

Values are means ± s.e.m.; n is the number of rats.

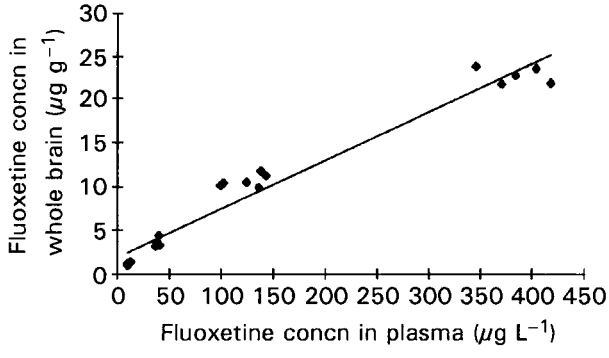

Figure 1. Relationship between the concentrations of fluoxetine in plasma and whole brain. Regression equation $y = 0{\cdot}056x + 1{\cdot}883$ ($r^2 = 0{\cdot}962$).

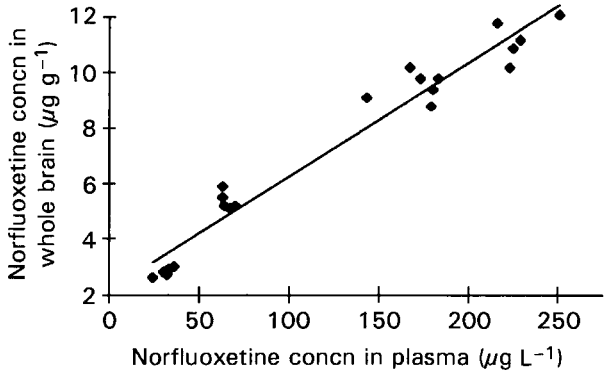

Figure 2. Relationship between the concentrations of norfluoxetine in plasma and whole brain. Regression equation $y = 0{\cdot}041x + 2{\cdot}144$ ($r^2 = 0{\cdot}957$).

died within minutes of intraperitoneal injection (Caccia et al 1990; Sarkissian et al 1990; Trouvin et al 1993).

The rats were killed by decapitation 3 h after drug injection, because greater effects of fluoxetine ($10\,mg\,kg^{-1}$) were observed between 2 and 4 h both after a single dose and after repeated administration (Fuller et al 1974; Wong et al 1974; Ross & Renyi 1977; Caccia et al 1990; Fuller & Snoddy 1991).

Our results obtained from control groups (Table 1) are in accordance with those reported by other authors for plasma 5-HT (Mais et al 1981; Ross et al 1981; Martin & Aldegunde 1989; Celada et al 1992), brain 5-HT (Growdon 1977; Keshavan et al 1981; Ross et al 1981; Berezsenyi et al 1983; Oka et al 1984) and brain 5-HIAA (Fuller et al 1974; Messing et al 1976; Growdon 1977; Keshavan et al 1981; Ross et al 1981; Berezsenyi et al 1983).

The significant decrease of platelet 5-HT concentration elicited by injection of fluoxetine (10 mg) was because of inhibition of the 5-HT reuptake pump in blood platelets. Although intraperitoneal injection of fluoxetine at various doses had no effect on the 5-HT concentration in rat brain, the brain level of 5-HIAA was reduced after injection of fluoxetine (Fuller et al 1975; Ross & Renyi 1977; Ross et al 1981). The dose-dependent reduction of brain 5-HIAA levels with no change in 5-HT concentrations after administration of fluoxetine suggested that turnover of 5-HT was reduced by fluoxetine (Fuller et al 1974).

The reduction of platelet 5-HT concentration was similar after administration of fluoxetine or norfluoxetine at 10 mg kg^{-1}; after this treatment plasma concentrations of norfluoxetine (280·5 $\mu g\,L^{-1}$) and fluoxetine + norfluoxetine (294·5 $\mu g\,L^{-1}$) were similar (Table 2). In the brain the concentrations were significantly different (24·63 and 20·29 $\mu g\,g^{-1}$ for norfluoxetine and norfluoxetine + fluoxetine respectively; Table 3). This observation could explain the greater reduction in brain 5-HT after treatment with norfluoxetine than after treatment with fluoxetine. Identical concentrations of brain 5-HIAA were observed 3 h after intraperitoneal injection of 10 mg fluoxetine or norfluoxetine. However, 5 h after intraperitoneal injection, the level of 5-HIAA was significantly higher after administration of fluoxetine (10 mg kg^{-1}) than after the same dose of norfluoxetine (Fuller & Snoddy 1991).

Pretreatment of the rats with proadifen did not modify the plasma and brain 5-HT values obtained after administration of fluoxetine (20 mg) alone. Brain 5-HIAA concentrations alone differed significantly after the two treatments; this might be explained by the differences between the norfluoxetine + fluoxetine values (34·32 and 31·06 $\mu g\,g^{-1}$ for fluoxetine and for proadifen + fluoxetine, respectively). Elsewhere this experiment reflects metabolic blockage by proadifen: R (ratio norfluoxetine/fluoxetine) = 0·21 and R = 0·16 instead of 0·60 and 0·49 for plasma and brain, respectively.

These results suggest that norfluoxetine makes a major contribution to inhibition of 5-HT uptake after administration of fluoxetine; both compounds were also similarly potent at reducing brain 5-HIAA. Correlations between fluoxetine and norfluoxetine levels according to the dose showed that fluoxetine was rapidly demethylated in liver. However, the norfluoxetine concentration after intraperitoneal injection of fluoxetine (20 mg kg^{-1}) indicated slight metabolism saturation, which might explain the exponential dependence of norfluoxetine level on dose. This result could certainly be the result of the liver first-pass effect.

The similar decreases of the ratio norfluoxetine/fluoxetine in plasma and brain with increasing doses could be explained by concomitant saturation of hepatic clearance. Good relationships were obtained between plasma and brain levels for fluoxetine (0·962) and norfluoxetine (0·957). Fluoxetine and its metabolite norfluoxetine easily cross the haemoencephalic barrier because of their liposolubility.

In conclusion, these results support the notion that treatment with fluoxetine and norfluoxetine induces reduced levels in platelet 5-HT and brain 5-HIAA, which might reflect reduced uptake; the demethylated metabolite of fluoxetine is as potent as the parent drug itself as an inhibitor of 5-HT uptake.

References

Benfield, P., Heel, R. C., Lewis, S. P. (1986) Fluoxetine, a review of its pharmacologic and pharmacokinetics properties and therapeutic efficacy in depressive illness. Drugs 32: 481–508

Berezsenyi, P., Alateo, E., Valzelli, L. (1983) Fluoxetine activity on muricidal aggression induced in rats by *p*-chlorophenylalanine. Aggressive Behav. 9: 333–338

Caccia, S., Cappi, M., Fracasso, C., Garattini, S. (1990) Influence of dose and route of administration on the kinetics of fluoxetine and its metabolite norfluoxetine in the rat. Psychopharmacology 100: 509–514

Celada, P., Dolera, M., Alvarez, E., Artigas, F. (1992) Effects of acute and chronic treatment with fluvoxamine on extracellular and platelet serotonin in the blood of major depressive patients. Relationship to clinical improvement. J. Affect. Disord. 25: 243–250

Fuller, R. W., Snoddy, H. D. (1991) Role of norfluoxetine in the inhibition of desipramine metabolism and in the inhibition of serotonin uptake after fluoxetine administration to rats. Res. Commun. Chem. Pathol. Pharmacol. 73: 31–40

Fuller, R. W., Perry, K. W., Molloy, B. B. (1974) Effect of an uptake inhibitor on serotonin metabolism in rat brain: studies with 3-(*p*-trifluoromethylphenoxy)*N*-methyl-3-phenylpropylamine (Lilly 110140). Life Sci. 15: 1161–1171

Fuller, R. W., Snoddy, H. D., Molloy, B. B. (1975) Potentiation of the L-5-hydroxytryptophan-induced elevation of plasma corticosterone levels in rats by a specific inhibitor of serotonin uptake. Res. Commun. Chem. Path. Pharmacol. 10: 193–196

Growdon, J. H. (1977) Postural changes, tremor, and myoclonus in the rat immediately following injections of *p*-chloramphetamine. Neurology 27: 1074–1077

Keshavan, H. J. H., Gurbani, N. K., Dandiya, P. C. (1981) Effects of fluoxetine on a specific serotonergic syndrome in rats. Ind. J. Med. Res. 73: 653–657

Mais, D. E., Lahr, P. D., Bosin, T. R. (1981) Determination of serotonin, its precursors, metabolites and [^{3}H]serotonin in lung by high-performance liquid chromatography with fluorescence detection. J. Chromatogr. B. 225: 27–35

Martin, F., Aldegunde, M. (1989) Simple HPLC with electrochemical detection for the determination of indolamines in tissue and plasma. J. Chromatogr. B. 491: 221–225

Messing, R. B., Fisher, L. A., Phebus, L., Lytle, L. D. (1976) Interaction of diet and drugs in the regulation of brain 5-hydroxyindoles and the response to painful electric shock. Life Sci. 18: 707–714

Oka, K., Kojima, K., Togari, A., Nagatsu, T. (1984) An integrated scheme for the simultaneous determination of biogenic amines, precursor amino acids, and related metabolites by liquid chromatography with electrochemical detection. J. Chromatogr. B. 308: 43–53

Ross, S. B., Renyi, A. L. (1977) Inhibition of the neuronal uptake of 5-hydroxytryptamine and noradrenaline in rat brain by (*Z*)- and (*E*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl) allylamines and their secondary analogues. Neuropharmacology 16: 57–63

Ross, S. B., Hall, H., Renyi, A. L., Westerlund, D. (1981) Effects of zimelidine on serotonergic and noradrenergic neurons after repeated administration in the rat. Psychopharmacology 72: 219–225

Sarkissian, C. F., Wurtman, R. J., Morse, A. N., Gleason, R. (1990) Effects of fluoxetine or D-fenfluramine on serotonin release from, and levels in, rats frontal cortex. Brain Res. 529: 294–301

Schmidt, M. J., Fuller, R. W., Wong, D. T. (1988) La fluoxétine, un inhibiteur hautement sélectif de la recapture de la sérotonine; revue des études pré-cliniques. Br. J. Psychiatry 153 (Suppl. 3): 43–50

Trouvin, J. H., Gardier, A. M., Chanut, E., Pages, N., Jacquot, C. (1993) Time course of brain serotonin metabolism after cessation of long-term fluoxetine treatment in the rat. Life Sci. 52: 187–192

Wong, D. T., Horng, J. S., Bymaster, F. P., Hauser, K. L., Molloy, B. B. (1974) A selective inhibitor of serotonin uptake: Lilly 110140, 3-(*p*-trifluorométhylphénoxy)-*N*-méthyl-3-phénylpropylamine. Life Sci. 15: 471–479

Wong, D. T., Bymaster, F. P., Engleman, E. A. (1995) Prozac (Fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: twenty years since its first publication. Life Sci. 57: 411–441