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Role of 5-HT_{1A} Receptors in the Effects of Acute and Chronic Fluoxetine on Extracellular Serotonin in the Frontal Cortex

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INVERNIZZI, R., M. BRAMANTE AND R. SAMANIN. *Role of 5-HT_{1A} receptors in the effects of acute and chronic fluoxetine on extracellular serotonin in the frontal cortex.* PHARMACOL BIOCHEM BEHAV **54**(1) 143-147, 1996.- Fluoxetine 10 mg/kg IP significantly increased the extracellular concentrations of serotonin (5-HT) in the frontal cortex as assessed by in vivo microdialysis. This effect was significantly potentiated when 0.3 mg/kg SC WAY-100635, a 5-HT_{1A} receptor antagonist, was administered 30 min before. WAY-100635 by itself had no effect on extracellular 5-HT. Twenty-four hours after chronic fluoxetine schedule (10 mg/kg/day IP × 14 days), basal extracellular 5-HT concentrations in the frontal cortex were higher than those of animals that had received the vehicle chronically. At 24 h after the last dose, a challenge dose of fluoxetine (10 mg/kg IP) raised extracellular 5-HT similarly in chronically vehicle or fluoxetine treated rats. At this same interval 25 μg/kg SC 8-OH-DPAT, a 5-HT_{1A} receptor agonist, significantly reduced extracellular 5-HT only in the frontal cortex of rats treated chronically with the vehicle. Examining basal extracellular 5-HT, the effect of a challenge dose of fluoxetine and the effect of 25 μg/kg 8-OH-DPAT after 96 h washout, no differences were found between chronically fluoxetine and vehicle-treated rats. The results confirm that the ability of fluoxetine to stimulate 5-HT_{1A} autoreceptors through an increase of endogenous 5-HT attenuates its effect on cortical dialysate 5-HT. Chronic fluoxetine increased the basal concentrations of extracellular 5-HT only when a substantial amount of its metabolite was present in the brain and during the desensitization of presynaptic 5-HT_{1A} autoreceptors (24 h after the last dose). These effects, in fact, disappeared after 96 h washout. The continuous presence of the drug may, therefore, be necessary to maintain extracellular 5-HT at concentrations high enough to produce a therapeutic effect.

Serotonin Fluoxetine 5-HT_{1A} autoreceptors WAY-100635 Frontal cortex Intracerebral microdialysis Rat

ACUTE treatment with selective serotonin (5-HT) reuptake inhibitors (SSRI) such as clomipramine, fluvoxamine, sertraline, and citalopram raises the extracellular concentrations of 5-HT in the cell body region (dorsal raphe, DR) with little or no effect on dialysate 5-HT in the frontal cortex (1,2,16,17). A nonselective 5-HT receptor antagonist, methiothepin, infused through the dialysis probe in the DR, significantly increased the effect of citalopram and sertraline on extracellular concentrations of 5-HT in the frontal cortex of rats (16,17). Because 5-HT_{1A} receptor density is particularly high in the DR (23), it was suggested that the effect of SSRI on extracellular 5-HT in the frontal cortex is attenuated by their simultaneous ability to activate somatodendritic 5-HT_{1A} receptors through an increase of endogenous 5-HT in the DR (17). The rapid improvement seen recently in some depressed patients after cotreatment with SSRI and (−)pindolol, a β-adrenoceptor antagonist that blocks 5-HT_{1A} receptors, suggests that the therapeutic action of SSRI can be hastened by combining them with a 5-HT_{1A} receptor antagonist (1).

However, it has still to be proved that selective blockade of 5-HT_{1A} receptors facilitates the effect of SSRI on extracellular 5-HT in terminal regions. This is particularly important because the DR contains not only 5-HT_{1A} binding sites but also 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C} receptors (24,27), for which methiothepin has high affinity (15).

The recent availability of a potent, selective and silent receptor antagonist at 5-HT_{1A} receptors, WAY-100635 (6), prompted us to examine whether this compound facilitated the effect of fluoxetine on dialysate 5-HT in the frontal cortex.

Repeated treatment with fluvoxamine or citalopram raises cortical extracellular 5-HT more than a single injection and, at least for citalopram, this effect was associated with desensitization of somatodendritic 5-HT_{1A} receptors assessed by the ability of a 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propyl-

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amino)tetralin (8-OH-DPAT) to reduce extracellular 5-HT (18). Under different experimental procedures other authors have found no changes in the sensitivity of 5-HT_{1A} receptors after chronic treatment with citalopram (14) or fluvoxamine (3). Rutter et al. (26) found extracellular 5-HT rose more in rat diencephalon, and 5-HT_{1A} receptors were desensitized 24 h after the last dose of a repeated schedule with fluoxetine (10 mg/kg/day IP × 14 days). Similar results were reported by Kreiss and Lucki (20).

Extracellular 5-HT concentrations in the frontal cortex were reduced 24 h after a 3-day treatment with 15–30 mg/kg fluoxetine (9). This effect, however, could be due to toxic effects of these doses of fluoxetine (9), although differences in length of treatment or brain region examined could contribute.

A second point addressed in the present study was whether chronic treatment with fluoxetine, similar to that used by Rutter et al. (26), had a greater effect on cortical 5-HT than a single injection and whether any such facilitation was associated with desensitization of presynaptic 5-HT_{1A} receptors. Because interpretation of results 24 h after the last dose of a repeated fluoxetine schedule is complicated by the fact that norfluoxetine, an active metabolite of fluoxetine, presumably reaches substantial levels in the rat brain (4), in the present study we measured extracellular 5-HT in the frontal cortex and the effect of 8-OH-DPAT 24 and 96 h after the last injection. This allowed us to assess the effects of chronic fluoxetine in the absence of the drug and its metabolite in the rat brain and to establish the time course of the changes in extracellular 5-HT and 5-HT_{1A} receptor sensitivity after chronic treatment.

ABBREVIATIONS

5-HT, serotonin; WAY-100635, N-[2-[4-(2-methoxyphenyl)-1-piperazynil]ethyl]-N-(2-Pyridinyl)cyclohexanecarboxamide; DR, dorsal raphe; SSRI, selective serotonin reuptake inhibitors; aCSF, artificial cerebrospinal fluid; ANOVA, analysis of variance.

METHOD

Animals

Male Sprague-Dawley rats (CD-COBS, Charles River, Italy), weighing about 300 g, were housed under standard laboratory conditions. Procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national and international laws and policies (EEC Council Directive 86/609, OJ L 358,1, Dec. 12, 1987; NIH Guide for the Care and Use of Laboratory animals, NIH Publication No. 85-23, 1985).

Dialysis

Dialysis was performed in awake rats as previously described (17). A horizontal dialysis probe made of Cuprophan (Sorin Biomedica, Italy) was covered with epoxy glue except for a central zone 8 mm long, and implanted into the frontal cortex at the following stereotaxic coordinates from the interaural line: AP, 7.2; H, 8.2 according to the Paxinos and Watson atlas (22). Probes were positioned with the help of bilateral marks on the probe. To prevent clogging, a thin fishing line (0.08 mm outer diameter) was inserted into the lumen. The probe was perfused with artificial cerebrospinal fluid (aCSF; composition in mM: NaCl, 145; KCl, 3; $CaCl_2$ dihydrate, 1.26; $MgCl_2$ hexahydrate, 1; buffered at pH 7.4 with 2 mM sodium phosphate buffer; flow rate, 2 μl/min) starting 20–24 h after surgery. Perfusate was collected every 20 min, except for the two samples after WAY-100635 injection that were collected every 15 min, and immediately assayed.

In vitro recovery of 5-HT measured at room temperature by dipping the dialysis probe into vials containing 10 pg/μl 5-HT and collecting three consecutive 20 min fractions, was 31.8 ± 1.1% (n = 3).

Analytical Procedure

Samples of perfusate were assayed by high-performance liquid chromatography with electrochemical detection. A reverse phase column (Supelcosil LC-18 DB, 150 × 4.6 mm, 3 μm packing, Supelco, Bellefonte, PA) in combination with a mobile phase containing 6.5 g/l sodium acetate tryhydrate, 1.95 g/l citric acid, 100 μl/l tryethylamine, 37 mg/l disodium EDTA, and 50 ml/l acetonitrile, pH 5.0–5.1 was used to separate 5-HT. Elution time of 5-HT was 6.00 min. A coulometric detector (Coulochem II, ESA, Bedford, MA) equipped with a two electrodes high sensitivity cell (mod. 5011) was used to oxidize 5-HT. Potential setting was +60 mV (E1) and +200 mV (E2). The output signal from E2 was used to detect 5-HT. The limit of detection for 5-HT was about 0.3 pg/sample with a signal-to-noise ratio of 2. A stable output of 5-HT was typically reached 3–4 h after the beginning of perfusion. Tetrodotoxin (1 μM in the perfusion fluid) reduced extracellular 5-HT in the frontal cortex by 70–80%.

Histology

At the end of the experiment rats were deeply anesthetized and killed by decapitation; their brains were removed, frozen, and sliced (40 μm). Data were included in the results if no signs of nonspecific tissue damage were seen and the probes were positioned in the region of the frontal cortex included between ±0.5 mm AP and ±0.3 mm H of the coordinates.

Drugs

Fluoxetine (10 mg/kg) (Eli-Lilly, Indianapolis, IN) dissolved in sterile distilled water was injected intraperitoneally (IP) once daily for 14 days (n = 16). Controls were given an equal volume of water (n = 12). A challenge dose of 10 mg/kg fluoxetine was injected 24 or 96 h after the last of this series of injections. In the same rats, a challenge dose of 25 μg/kg 8-OH-DPAT (RBI), dissolved in saline, was injected subcutaneously 2 h after the fluoxetine challenge. Body weight was recorded daily.

In one experiment the effect of fluoxetine on extracellular 5-HT was examined in rats injected 30 min before with 0.3 mg/kg SC WAY-100635 (synthesized by Pharmacia, Milan, Italy; n = 6) or saline (n = 3).

Statistics

Basal extracellular concentrations of 5-HT are defined as the mean of three consecutive samples before drug treatment, not differing by more than 10%.

To compare the values at each time after drug treatment with baseline, the data were analyzed by one-way ANOVA for repeated measures, followed by Dunnett's test. The effect of challenge with fluoxetine or 8-OH-DPAT in rats given the drug or saline chronically was analyzed by two-way ANOVA (Split-plot) with treatment (tr) as between-subject factor and time (t) as within-subject factor.

RESULTS

The dose of 10 mg/kg fluoxetine significantly raised extracellular 5-HT in the frontal cortex to 120% of baseline values at 2 h (Fig. 1). This effect was significant from 60 to 180 min. The increase of extracellular 5-HT induced by fluoxetine was significantly potentiated (+205%) in rats given 0.3 mg/kg WAY-100635 30 min before, $F_{tr}(1, 7) = 0.51$, $p > 0.05$; $F_t(11, 77) = 20.16$, $p < 0.05$; $F_{tr} \times t(11, 77) = 2.71$, $p < 0.05$. In this group the effect was significant starting from 20 min after injection to the end of the observation period. WAY-100635 by itself had no significant effect on extracellular 5-HT (data not shown).

Chronic fluoxetine caused a significantly lower increase in body weight than in vehicle treated rats (respectively 264 ± 2 and 289 ± 4 g after 2 weeks of treatment with fluoxetine ($n = 16$) and water ($n = 12$); $p < 0.05$, Tukey's test).

Twenty-four hours after the last fluoxetine injection basal concentrations of extracellular 5-HT were significantly higher (+115%) than in rats receiving water for 14 days (Fig. 2). By 96 h there was no longer any real difference (Fig. 2).

At 24 h after the last dose of the chronic schedule the fluoxetine challenge dose (10 mg/kg) raised extracellular 5-HT by 66% (at peak) in rats repeatedly given water and the effect was significant from 20 to 120 min. In rats given the drug for 14 days the increase of extracellular 5-HT tended to be lower (36% at peak) than in rats receiving saline but the difference between the two groups was not significant, $F_{tr}(1, 11) = 14.75$, $p < 0.05$; $F_t(6, 66) = 8.39$, $p < 0.05$; $F_{tr} \times t(6, 66) = 1.96$, $p > 0.05$. In these rats extracellular 5-HT was significantly higher than baseline 20, 40, 80, and 100 min after fluoxetine. In rats given water for 14 days, 25 μg/kg 8-OH-DPAT 2 h after the fluoxetine challenge significantly reduced extracellular 5-HT in the frontal cortex; this dose had no such effect in rats given fluoxetine for 14 days (Table 1).

Basal extracellular 5-HT and the effect of a challenge dose of fluoxetine after 96 h washout showed no difference in rats given water or drug (Fig. 2), $F_{tr}(10, 9) = 0.00$, $p > 0.05$; $F_t(6, 54) = 13.97$, $p < 0.05$; $F_{tr \times t}(6, 54) = 0.91$, $p > 0.05$.

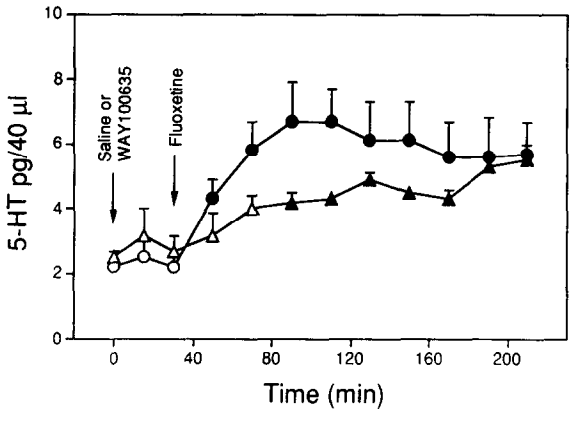

FIG. 1. Effect of WAY-100635 on fluoxetine-induced rise of extracellular 5-HT in the rat frontal cortex. An arrow indicates the time of injection of WAY-100635 and fluoxetine. Saline (Δ) or WAY-100635 (0.3 mg/kg; ○) was administered 30 min before 10 mg/kg fluoxetine IP. Mean ± SEM of three to six rats. Solid symbols indicate a significant difference ($p < 0.05$) from baseline (Dunnett's test).

8-OH-DPAT reduced extracellular 5-HT to the same extent in rats given water or fluoxetine for 14 days (Table 1).

DISCUSSION

A single IP injection of 10 mg/kg fluoxetine significantly raised the extracellular concentrations of 5-HT by 120% over baseline values. This increase is smaller than in other brain regions after the same dose (25), confirming that the frontal cortex is relatively resistant to changes in basal 5-HT concentrations after acute treatment with SSRI (8). At 0.3 mg/kg, WAY-100635 did not modify extracellular 5-HT but significantly enhanced the effect of fluoxetine (by 205% at the peak). Similar results were recently reported by combining WAY-100635 with paroxetine (10).

Together with studies showing that two 5-HT_{1A} receptor antagonists, (S)-UH-301 and (+)WAY-100135, facilitated the ability of citalopram to increase extracellular 5-HT in the ventral hippocampus (12,13), the present results confirm that the ability of SSRI to stimulate 5-HT_{1A} receptors through an increase of endogenous 5-HT attenuates their effect on cortical dialysate 5-HT (12,13). That presynaptic 5-HT_{1A} receptors in the raphe area are involved is indicated by the fact that local blockade of 5-HT_{1A} receptors in the ventral hippocampus did not modify the effect of citalopram on dialysate 5-HT (12) and 0.1–1 μg/0.5 μl WAY-100635 in the DR markedly increased the effect of 10 mg/kg citalopram on extracellular 5-HT in the frontal cortex (unpublished results).

The fact that the 5-HT_{1A} receptor antagonist by itself had no effect confirms previous neurochemical studies showing it had no effect on extracellular 5-HT in the ventral hippocampus (11) and further suggests that somatodendritic 5-HT_{1A} receptors are not tonically activated by endogenous levels of 5-HT. Accordingly, the firing rate of 5-HT cells in the DR is not changed by intravenous WAY-100635 (6), although it has been shown that WAY-100635 does increase the firing of 5-HT neurons in awake cats (7).

Daily treatment with 10 mg/kg fluoxetine for 14 days slightly but significantly reduced the body weight of rats that otherwise appeared healthy and without gross behavioral changes. This effect is likely to be the consequence of reduced food intake throughout the treatment period, as recently shown with fluoxetine 6 mg/kg daily for 3 weeks (21). Whether changes in body weight and extracellular 5-HT are related is not known.

Twenty-four hours after the last injection basal levels of extracellular 5-HT in rats given chronic fluoxetine were significantly higher than controls. This is in line with the effect in the diencephalon (26). Although in Rutter's and the present study 25 μg/kg 8-OH-DPAT significantly lowered extracellular 5-HT concentrations only in rats chronically treated with the vehicle, indicating desensitization of presynaptic 5-HT_{1A} receptors in fluoxetine-treated animals, it is not likely that this was responsible for the higher basal 5-HT levels in fluoxetine-treated animals. In fact, the lack of effect of the 5-HT_{1A} receptor antagonist clearly suggests that 5-HT_{1A} receptors are not tonically activated and, in fact, chronic treatment with citalopram (10 mg/kg twice daily for 14 days) caused desensitization of 5-HT_{1A} receptors, with no effect on basal extracellular 5-HT in the frontal cortex 24 h after the last injection (18).

Electrophysiological studies, however, suggest that desensitization of presynaptic receptors, although not affecting basal 5-HT synaptic concentrations, may facilitate the postsynaptic actions of stimulating the serotoninergic pathways (5).

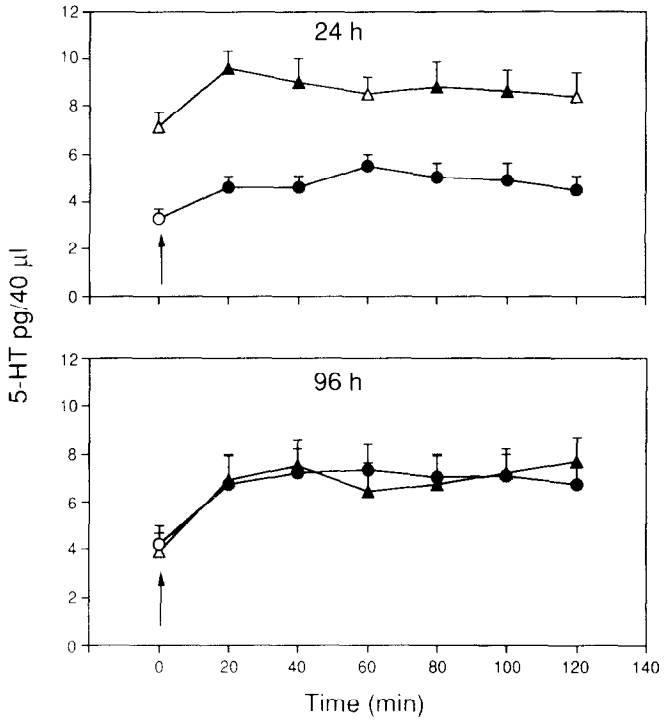

FIG. 2. Extracellular 5-HT in the frontal cortex of rats given water (○) or 10 mg/kg fluoxetine (Δ) once daily for 14 days 24 and 96 h after the last injection. The arrow indicates the time of injection of 10 mg/kg fluoxetine. Mean ± SEM of five to seven rats. Solid symbols indicate a significant difference ($p < 0.05$) from baseline (Dunnett's test).

The different effects 24 h after repeated treatment with citalopram and fluoxetine probably reflect the different kinetics of the two drugs. Only traces of citalopram or its metabolites are found in the rat brain under the treatment conditions we used earlier (18), whereas there was a considerable amount of norfluoxetine (7.1 ± 1.4 µg/g tissue) in the brain of rats under the conditions used by Rutter and in the present study. These are in the range of the levels reported to block 5-HT uptake (4) and, therefore, are presumably responsible for the higher extracellular 5-HT in chronically fluoxetine-treated animals. Desensitization of presynaptic 5-HT_{1A} receptors, although not by itself influencing basal 5-HT concentrations, very likely increases the effect of norfluoxetine on dialysate 5-HT. The fact that 5-HT uptake is blocked by norfluoxetine 24 h after the last fluoxetine injection may explain why the challenge dose of fluoxetine had little (present study) or no effect (Rutter's experiments) on extracellular 5-HT in fluoxetine-treated animals, whereas its effect was enhanced in animals treated chronically with citalopram (18).

To examine the effect of chronic treatment with fluoxetine in the absence of norfluoxetine in the rat brain and gain information on the time course of the changes in 5-HT_{1A} receptor sensitivity, we studied extracellular 5-HT levels and the effect of fluoxetine and 8-OH-DPAT 96 h after the last fluoxetine injection, when the metabolite was no longer measurable in the rat brain. Basal extracellular 5-HT levels and the effects of a challenge dose of fluoxetine or 8-OH-DPAT were the same in chronically vehicle- or fluoxetine-treated animals. It seems,

TABLE 1

EFFECT OF 8-OH-DPAT ON EXTRACELLULAR 5-HT (pg/40 µl) IN RATS GIVEN WATER OR 10 mg/kg FLUOXETINE ONCE DAILY FOR 14 DAYS

	Washout			
	24 h		96 h	
	Basal	40 min After 8-OH-DPAT	Basal	40 min After 8-OH-DPAT
Water	4.5 ± 0.6	3.4 ± 0.6*	6.7 ± 4.2	4.9 ± 0.7*
Fluoxetine	8.4 ± 1.0	7.9 ± 0.8	7.7 ± 1.0	6.0 ± 1.1*

*$p < 0.05$ vs. basal values.

therefore, that the change in 5-HT_{1A} receptor sensitivity is relatively short lasting, at least in the present conditions.

In conclusion, the present study has confirmed that selective blockade of 5-HT_{1A} receptors facilitates the effect of SSRI on synaptic 5-HT in terminal regions of the brain. In view of the report that the combination of (−)pindolol with SSRI hastens their therapeutic effect (1), it would be of interest to assess whether a clinical improvement can be obtained by administering a selective 5-HT_{1A} receptor antagonist with SSRI. Chronic treatment with SSRI desensitizes presynaptic 5-HT_{1A} receptors and this is one mechanism explaining why the effect on cortical extracellular 5-HT is greater after chronic treatment. The continuous presence of the drug, however, may be necessary to maintain extracellular 5-HT at high enough concentrations to produce a therapeutic effect. A recent study has shown that the same repeated treatment with citalopram that facilitated the drug effect in the frontal cortex (18) did not modify the effect of a challenge dose of citalopram on dialysate 5-HT in the dorsal hippocampus (19). In addition, desensitization of 5-HT_{1A} receptors apparently did not occur in these conditions (19). Further studies are necessary to clarify the extent to which the type of drug, the length of treatment, and the brain region examined influence the effects of chronic treatment with SSRI on brain 5-HT dynamics.

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