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ORIGINAL INVESTIGATION

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Chronic treatment with fluvoxamine by osmotic minipumps fails to induce persistent functional changes in central 5-HT_{1A} and 5-HT_{1B} receptors, as measured by in vivo microdialysis in dorsal hippocampus of conscious rats

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Abstract This study investigated the alterations of the 5-HT_{1A} and 5-HT_{1B} autoreceptor function following chronic treatment with fluvoxamine using osmotic minipumps. The 5-HT_{1A} and 5-HT_{1B} autoreceptor function were studied using microdialysis in the dorsal hippocampus. The effect of the 5-HT_{1A} receptor agonist 8-OH-DPAT (0.3 mg/kg, SC) and the 5-HT_{1B} receptor agonist RU-24969 (100 nM through the dialysis probe for 30 min) on 5-HT release was compared with rats chronically treated with saline. 8-OH-DPAT decreased 5-HT release to 55% and 60% of baseline, while RU-24969 decreased 5-HT release to 66% and 70% of baseline value in the saline and fluvoxamine group, respectively. In both cases, differences between the saline and fluvoxamine groups were not statistically significant. Plasma levels of fluvoxamine after 21 days of treatment ranged from 3 to 5 ng/ml. Fluvoxamine concentration in rat brain during treatment was estimated between 100 and 200 nM, which approximates to the IC_{50} value of fluvoxamine on the 5-HT transporter in synaptosomes and is 50 times higher than the K_d value for the 5-HT reuptake site. In conclusion, no evidence was found for changes in 5-$HT_{1A,B}$ receptor function using 8-OH-DPAT and RU-24969 as probes after continuous treatment with fluvoxamine by means of osmotic minipumps.

Key words Microdialysis · Dorsal hippocampus 5-HT_{1A} and 5-HT_{1B} receptors · Chronic treatment Fluvoxamine · Rat

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Introduction

Selective serotonin reuptake inhibitors (SSRIs) constitute a novel class of drugs for which clinical efficacy has been established in depression as well as in certain types of anxiety disorders, including panic disorder, social phobia and obsessive compulsive disorder (Westenberg and den Boer 1993, 1994). Although serotonin (5-HT) reuptake is impeded without delay, the clinical effects of SSRIs in these psychiatric domains are fully expressed after several weeks of treatment only. The latency to the beneficial clinical effects has been attributed to adaptive changes brought about by long term treatment. In this regard, most electrophysiological studies have shown that chronic administration of SSRIs enhances the effectiveness of 5-HT synaptic transmission in the rat hippocampus (Chaput et al. 1988). Desensitization of the somatodendritic 5-HT_{1A} autoreceptors and/or modification of the terminal release-controlling 5-HT_{1B} autoreceptors in rodents (or 5-HT_{1D} autoreceptors in man) would account for some of these effects. Thus, electrophysiological studies reveal that chronic treatment with SSRIs may produce this effect by attenuating the negative feedback exerted by the terminal 5-HT_{1B} autoreceptors on 5-HT release (Chaput et al. 1991). Desensitization of the 5-HT_{1A} autoreceptors in the raphe nuclei, that control the firing of the 5-HT neurons, has also been found to occur after repeated administration of SSRIs (Chaput et al. 1986). The desensitization of the terminal 5-HT autoreceptors has also been deduced from in vivo and in vitro neurochemical studies. Thus, administration of citalopram to rats for 21 days, followed by a washout of 24 h, resulted in an augmented stimulation-induced release of 5-HT from hypothalamic slices, suggesting a down regulation of the 5-HT_{1B} autoreceptor (Moret and Briley 1990). Treatment with fluoxetine (20 mg/kg, IP) for 3 days resulted also in an increased 5-HT release as measured

by microdialysis (Malagie et al. 1992). Similarly, Bel and Artigas (1993) have reported that chronic treatment with low doses of fluvoxamine (1 mg/kg per day) increases the basal 5-HT levels in frontal cortex in vivo as compared to saline treatment. This finding suggests that adaptive changes had occurred at the presynaptic level. Autoradiographic studies have shown that prolonged treatment with SSRIs may reduce the number of 5-HT_{1A} binding sites in the dorsal raphe nucleus (Welner et al. 1989). In keeping with these electrophysiological and neurochemical findings, Griebel et al. (1994) recently reported that acute and chronic administrations of SSRIs have differential effects on emotional responses in animal models of anxiety. Using two animal models of anxiety, they found that acute treatment with SSRIs produces an anxiogenic-like behavior, whereas these effects were no longer produced or even reversed after chronic treatment. This biphasic behavioral profile is in keeping with data from clinical studies, where improvement in patients with panic disorder is usually preceded by a worsening of anxiety symptoms during the first week of treatment (Westenberg and den Boer 1993).

These data converge to suggest that a weakening of the negative feedback control of 5-HT neurons is implicated in the pharmacological activity of SSRIs in man. At variance with this notion, however, Sleight et al. (1989) were not able to measure a desensitization of cortical 5-HT_{1B} autoreceptors after chronic treatment with amitriptyline, a mixed 5-HT and noradrenaline (NA) reuptake inhibitor. In addition, no significant changes were found in the density of the 5-HT_{1B} receptors in rat frontal cortex following chronic treatment with the tricyclic antidepressant chlorimipramine, a potent 5-HT reuptake blocker (Montero et al. 1991).

An issue ignored in most studies is the drug disposition. By and large, animal studies do not consider the difference in pharmacokinetics between species. The plasma half-life of most SSRIs, is approximately 10 times shorter in rodents as compared to man. Therefore, plasma steady state levels of fluvoxamine and other SSRIs in rodents will not be attained at a dosage regime of once or twice daily. To mimic the drug disposition in man, where fluctuations in drug levels are small, continuous infusion is a requirement.

The purpose of the present work was to study the effects of chronic subcutaneous infusion with the SSRI, fluvoxamine, on the sensitivity of the release controlling 5-HT_{1A} and 5-HT_{1B} autoreceptors in the rat. The sensitivity of these receptors was tested by measuring the effects of the 5-HT_{1A} agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), and the 5-HT_{1B} agonist, RU-24969, on 5-HT output in dorsal hippocampus using in vivo microdialysis (Sharp et al 1989a, b; Bosker et al. 1994). In addition, fluvoxamine plasma and brain concentrations were measured following acute and chronic treatment.

Materials and methods

Animals

Male Wistar rats (GDL, Utrecht, Netherlands) weighing 160–210 g were housed three per cage under standard conditions (22–24°C: 12/12-h light/dark cycle, food and water and libitum) at least 3 days until implantation of the osmotic minipumps. After implantation the rats were housed separately and were weighed every morning except the weekends.

Chronic administration

For drug treatment osmotic minipumps (Alzet, model 2ML4) were used. The pumps were filled with fluvoxamine (20 mg/ml in saline) or vehicle. Filling was performed under aseptic conditions. The pumps were calibrated by the manufacturer to deliver 2.5 µl per h during 28 days. Pumps were implanted in the dorsal subcutaneous tissue under anaesthesia with diazepam (IP 2.5 mg/kg) and hypnorm (IM 5 mg/kg). Pumps were wiped with isopropanol, quickly dried and inserted. The wound was stitched and disinfected with betadine. The mean daily dose of the drug at the outset of the study was 6.7 mg/kg. In vitro experiments revealed that the fluvoxamine preparation was sufficiently stable at 38°C. The proper delivery of fluvoxamine was verified by measuring plasma drug levels every 4 days in two control rats provided with a permanent catheter in the jugular vein and by measuring the remaining amount of drug in the minipumps after their removal after 21 days in all other animals. In addition, blood samples were taken from the tail in all animals before removal of the minipumps for the determination of fluvoxamine. The mean brain concentration of fluvoxamine in rats chronically treated with fluvoxamine was determined in three control animals.

Surgery

After 21 days rats were anaesthetized with chloral hydrate (400 mg/kg, IP). Blood was taken from a tail artery and the minipump was removed. A catheter for the subcutaneous administration of 8-OH-DPAT and a microdialysis probe were implanted. The microdialysis probes were of the concentric type (AN 69 Filtral 16, Hospal, Uden, Netherlands; Santiago and Westerink 1990) and were stereotaxically positioned into the dorsal hippocampus using the following coordinates (tooth bar set at +5 mm): A, 4 mm, L, 2.9 mm, V, 4.1 mm, from bregma and dura surface (according to Paxinos and Watson 1982). Exposed tip length was 2 mm (ID: 220 µm, OD: 310 µm). The probe and the catheter inlet were fixed to the skull with dental cement. Rats were allowed to recover from surgery for 2 days.

Microdialysis experiment

Experiments with 8-OH-DPAT and RU-24969 were performed 2 and 3 days after surgery, respectively. During microdialysis, probes were perfused with Ringer (147 mM NaCl, 4 mM KCl, 2.3 mM $CaCl_2$) containing 10 µM fluvoxamine, using a Harvard micro infusion pump (Harvard, USA) at a constant flow rate of 1.5 µl/min. Tubing (Carnegie, Sweden) was connected through a homemade liquid swivel with a syringe mounted on the infusion pump. Following 90 min equilibration time, 15-min samples were collected in vials containing 7.50 µl 0.10 M acetic acid. 8-OH-DPAT (0.30 mg/kg, SC) was given through a subcutaneous catheter after collection of four basal fractions. RU-24969 (100 nM) was added to the perfusion fluid for 30 min after collection of four basal fractions. Samples were mixed and immediately frozen (−80°C).

Analytical procedure

Analysis of 5-HT was performed by HPLC with electrochemical detection. Briefly, 20-µl samples were injected into HPLC (LKB, Woerden, Netherlands) equipped with a 10-cm reversed phase column (Hypersil RP-18, 3 µm, 2.0 mm, Shandon) and an electrochemical detector (ANTEC Leyden B. V., Leiden, Netherlands) at a potential setting of 600 mV versus an Ag/AgCl reference electrode. A column oven (LKB, Woerden, Netherlands) set at 40°C was used for both column and electrochemical detector. The mobile phase consisted of 5 g/l $(NH_4)_2SO_4$, 50 mg/l heptane sulphonic acid sodium salt, 500 mg/l EDTA, 4% methanol, 30 µl/l triethylamine, adjusted to pH 4.65 with acetic acid. Flow rate was 0.4 ml/min. Detection limit for 5-HT was 0.5 fmol/20-µl sample (S/N 2). Analysis of fluvoxamine was carried out with HPLC and fluorimetric detection after precolumn derivatization with fluorescamine. In short, fluvoxamine was extracted from plasma using CH_2Cl_2. After aspiration of the solvent with N_2, the residue was taken up in 0.05 M phosphate buffer pH 8 and acetone 1.5:1 (v/v) and derivatized with fluorescamine. A 100-µl sample was injected into a high performance liquid chromatograph (LKB, Woerden, Netherlands) equipped with a 25-cm reversed phase column (Supelcosil RP-8; 5 µm, 4.6 mm, Supelco) at 40°C and a fluorescence detector (Applied Biosystems 980, excitation filter: 380 nm, emission filter: 470 nm). The mobile phase consisted of 0.05 M phosphate buffer pH 7.5 and methanol, 40:60 (v/v). To assay brain fluvoxamine levels, tissue was homogenized in 0.1 M NaOH, extracted with CH_2Cl_2 and analyzed as described above. The detection limit for fluvoxamine was 3 pmol/injection

Histology

Following termination of each experiment, animals were anaesthetized with chloral hydrate and the probes were flushed with a $FeCl_3$ solution, H_2O and a $K_4Fe(CN)_6$ solution successively, which results in a green-blue staining of the tissue surrounding the probe tip. Subsequently, the animals were decapitated, brains were removed, fixated in a 5% formaldehyde solution, frozen and cut in 150 µm slices. The position of the probes was verified microscopically by the track of the probe through the brain and the green-blue staining of the tissue surrounding the probe tip. Data were discarded if the dialysis probes were not in the vicinity of the region aimed at.

Statistics

The mean 5-HT concentration of three baseline samples immediately before the administration of drugs was taken as 100%. All subsequent samples were expressed as percentage of the baseline value. Data were analyzed statistically by multivariate analyses of variance (MANOVA) with repeated measures on sample. This analysis allows to asses mean group and mean time effects and time by group interaction. Subsequently, data were broken down by group to detect time effects in the two groups separately.

Data are reported statically significant when the probability value was less than 5%.

Chemicals

All reagents were from Merck (Darmstadt, Germany) except heptane sulphonic acid sodium salt (Kodak, USA) and methanol (Riedel-de Haën, Germany). 5-HT and fluorescamine were from Sigma (St. Louis, Mo. USA). Fluvoxamine, 8-OH-DPAT and RU-24969 were from Duphar (Weesp, Netherlands), Research Biochemical Inc. (USA) and Roussel UCLAF, respectively. AN 69 filtral 16 was kindly donated by Hospal (Uden, Netherlands).

Results

Microdialysis in dorsal hippocampus of chronically treated rats

Subcutaneous injection of 8-OH-DPAT

The mean baseline level of 5-HT in the saline group was 2.73 ± 0.24 pg/15 min (mean ± SEM, $n = 9$). Upon injection of 0.3 mg/kg 8-OH-DPAT, a significant decrease in the extracellular 5-HT levels was seen. The mean 5-HT concentration in the dialysate dropped to 55% of baseline ($F = 7.15$, $P < 0.0001$). The maximum decrease was attained 30 min after the injection, while 5-HT levels returned to baseline within 90 min (Fig. 1).

In the fluvoxamine group the mean baseline level of 5-HT was 2.21 ± 0.14 pg/15 min ($n = 8$). Administration of 8-OH-DPAT decreased 5-HT levels to 60% of baseline ($F = 4.46$, $P < 0.0001$). Statistical analysis of the two treatment conditions did not reveal a significant time by group interaction nor a mean group difference.

Local administration of RU-24969

The mean baseline 5-HT level in the saline group was 2.45 ± 0.20 pg/15 min ($n = 6$). Administration of 100 nM RU-24969 through the probe resulted in a small but persistent (150 min) decrease of 5-HT levels in the dialysate. The maximum decrease amounted to 34% of baseline value ($F = 1.98$, $P < 0.03$). The maximal effect was reached 45 min after the start of the administration (Fig. 2). In the fluvoxamine group the mean baseline level was 2.73 ± 0.27 pg 15 min ($n = 8$).

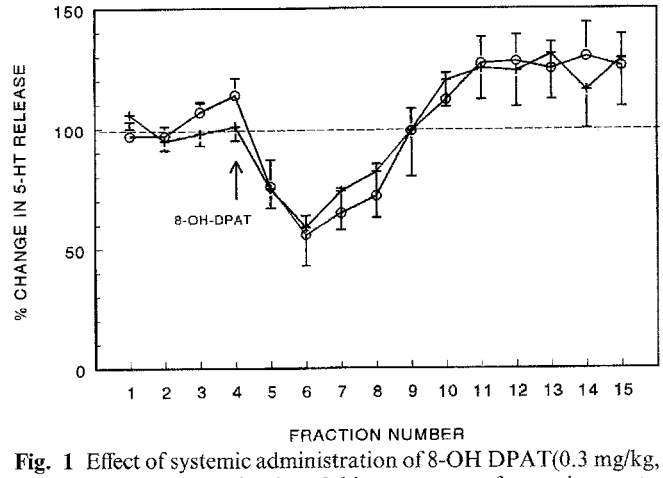

Fig. 1 Effect of systemic administration of 8-OH DPAT(0.3 mg/kg, SC) on 5-HT release in dorsal hippocampus of conscious rats, chronically treated with either fluvoxamine (+) or saline (—○—)

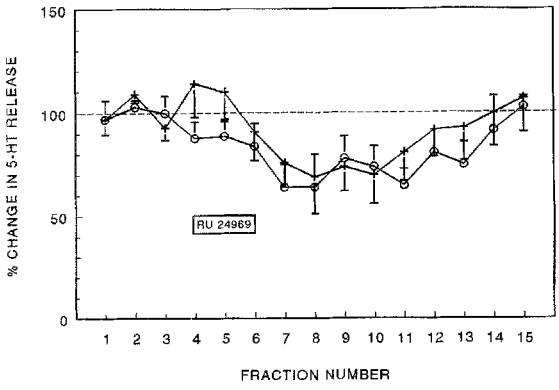

Fig. 2 Effect of 100 nM RU-24969, administered through the microdialysis probe for 30 min, on 5-HT release in dorsal hippocampus of conscious rats, chronically treated with either fluvoxamine (+) or saline (—O—)

Upon administration of RU-24969 a statistically significant decrease of 30% was obtained ($F = 2.12$, $P < 0.02$), which was obtained 60 min after the start of the administration (Fig. 2). No significant mean group and time by group effects were obtained.

Effect of chronic fluvoxamine treatment on body weight

Body weights of saline (186 ± 3.7 g, $n = 12$) and fluvoxamine (177 ± 3.1 g, $n = 14$) groups were slightly different at the outset of the study. The change in body weight during the study was not statistically significant between the treatment conditions.

Fluvoxamine levels

Measurement of the residual fluvoxamine after removal of the minipumps showed that $77.4 \pm 4.5\%$ (mean $\pm$ SEM, $n = 8$) of the fluvoxamine was delivered during treatment, which is in fair agreement with the declaration of the manufacturer. Plasma fluvoxamine levels in two control rats with a cannula declined from 10 and 9 ng ml (day 7), through 4 and 4 ng/ml (day 14), to 4 and 3 ng/ml (day 21). Mean plasma fluvoxamine levels in all other animals treated with fluvoxamine ($n = 9$) prior to removal of the minipumps amounted 4 ng/ml, which is in excellent agreement with the value observed in the two control rats. Brain fluvoxamine levels ranged from 100 to 200 nM.

Discussion

It is generally assumed that the beneficial effects of SSRIs and other antidepressants in depression and anxiety disorders are related to desensitization of the release controlling autoreceptors brought about by chronic treatment with these compounds. The main finding of the present study is that chronic treatment with fluvoxamine, a potent and selective 5-HT reuptake inhibitor, does not affect the sensitivity of the 5-HT_{1A} and 5-HT_{1B} autoreceptors.

Various studies have shown that the release of 5-HT from nerve terminal is under inhibitory control of 5-HT_{1A} receptors in the cell body region (Blier and de Montigny 1987; Sprouse and Aghajanian 1987; Sotelo et al. 1990). Systematic administration and injection into the cell body region of 8-OH-DPAT, a 5-HT_{1A} receptor agonist, reduce the 5-HT output in the hippocampus (Sharp et al. 1989c; Bonvento et al. 1992), whereas administration through the microdialysis probe into the hippocampus has no effect (Sharp et al. 1989b). The release of 5-HT in the terminal region of rodents is controlled by release inhibiting 5-HT_{1B} autoreceptors located on 5-HT neurons in the terminal region (Sharp et al. 1989a). Administration of RU-24969, a 5-HT_{1B} agonist, into the terminal region decreases the extracellular 5-HT levels. We found that treatment with fluvoxamine for 21 days had no effect on either the 8-OH-DPAT or the RU-24969 induced decreases in 5-HT output in rat hippocampus. The finding suggests that, under the conditions used in this study, the sensitivity of the samatodendritic 5-HT_{1A} autoreceptors to 8-OH-DPAT and the sensitivity of the 5-HT_{1B} autoreceptors to RU-24969 was unchanged. The present study, does not support therefore the theory that the beneficial effects of SSRIs result from adaptive changes in the release controlling 5-HT autoreceptors. Our findings agree with the microdialysis studies of Sleight et al. (1989), who were unable to show a desensitization of cortical 5-HT_{1B} autoreceptors after chronic treatment with amitriptyline. Our findings are at variance with a microdialysis study by Malagie et al. (1992), who reported a desensitization of 5-HT_{1A} and/or 5-HT_{1B} autoreceptors after administration of fluoxetine for 3 days. In both studies the drug was administered by means of IP injection once a day. Using continuous administration of fluvoxamine by means of osmotic minipumps, Bel and Artigas (1993) reported an increase in the extracellular 5-HT concentration in the frontal cortex of rats, suggesting an augmented output of the 5-HT system. Based on the finding that an acute challenge with fluvoxamine did not further increase the cortical 5-HT levels, indicating that the uptake was blocked completely, they suggested that repeated administration of fluvoxamine had desensitized the 5-HT transporter. However, the sensitivity of the 5-HT_{1A} and 5-HT_{1B} autoreceptors, which may have contributed to this phenomenon, were not assessed. Moreover, the increased cortical 5-HT release could also be explained by a change in 5-HT synthesis. To explain the discrepancy with the electrophysiological study by Chaput et al. (1988), differences in treatment regimes and drug properties

should be allowed for. A parsimonious explanation would be that electrophysiology is superior to biochemical methods in detecting local adaptive changes. This is corroborated by a chronic study by Schechter et al. (1990), who presented evidence for a desensitization of 5-HT_{1A} autoreceptors using an electrophysiological approach, while biochemical data, including 5-HT_{1A} receptor binding studies, 5-HT synthesis and metabolism, failed to show alterations. Several other factors may also have confounded our results. First, in the present study fluvoxamine was delivered by osmotic minipumps, resulting in relatively low but steady state plasma drug levels as opposed to IP administration, where much higher but also largely fluctuating plasma drug levels are obtained. Moreover, repeated IP administration of fluvoxamine may cause severe damage of the abdominal cavity (Solvay Duphar, data on file), and requires repeated handling of the animals, which by itself may have an effect on 5-HT output. The plasma steady state levels of fluvoxamine attained by osmotic minipumps, although lower as opposed to the peak values obtained after IP injections, did approximate the in vitro IC50 value of fluvoxamine for the 5-HT transporter, as determined by Solvay Duphar (150 nM; Solvay Duphar, data on file). Others have also reported somewhat higher IC50 values (500 nM) for fluvoxamine (Leonard 1992). On the other hand, Bel and Artigas (1993), who used minipumps delivering even smaller amounts of fluvoxamine (1 mg/kg per day) found that an additional IP dose of fluvoxamine did not further increase the 5-HT output, suggesting that the dose used in the present study was sufficient to completely block 5-HT reuptake in vivo. Moreover, Lesch et al. (1993) have shown a decrease in 5-HT transporter mRNA after 21 days of continuous administration of fluoxetine (2.5 mg/kg per day), which has the same ex vivo potency as fluvoxamine (Leonard 1992). Secondly, the probes to asses 5-HT_{1A} and 5-HT_{1B} receptor functions used in this study are not selective. Therefore, we cannot exclude that more complex feedback mechanisms have obscured functional changes. Thirdly, the microdialysis experiments in the present study were performed 2 and 3 days after removal of the minipumps. Rapid restoration of receptor sensitivity cannot be fully excluded. Finally, it is possible that various brain regions respond differentially to chronic treatment with SSRIs (Pandey et al. 1991).

In conclusion, we found no evidence for a persistent functional change of 5-HT_{1A} and 5-HT_{1B} autoreceptors after chronic treatment with fluvoxamine in rat hippocampus as measured by the response to systemic administration of 8-OH-DPAT and local application of RU-24969.

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