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Short communication

Synergistic neurochemical and behavioral effects of fluoxetine and 5-HT_{1A} receptor antagonists

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Abstract

We studied the ability of WAY 100635 {*N*-[4-(2-methoxyphenyl)-1-piperazinyl]-*N*-(2-pyridinyl) cyclo-hexanecarboxamide}, 0.5 mg/kg, i.v. and (−)-5-Me-8-OH-DPAT {(−)-5-methyl-8-hydroxy-2-(di-*n*-propylamino)tetralin}, 3 mg/kg, i.v. two selective 5-HT_{1A} receptor antagonists, to potentiate: (1) the enhancement of extracellular 5-HT levels ([5-HT_{ext}]) induced by a single administration of 5 mg/kg i.p. fluoxetine using in vivo microdialysis in the ventral hippocampus of conscious rats, (2) the decrease in food intake induced by this antidepressant drug in food-deprived rats. The effects of fluoxetine were significantly potentiated, by 30–40%, by WAY 100635 as well as by (−)-5-Me-8-OH-DPAT in the two sets of experiments. Thus, fluoxetine increased [5-HT_{ext}] in serotonergic nerve terminal areas and consequently, induced hypophagia, both effects being limited by indirect activation of somatodendritic 5-HT_{1A} autoreceptors.

Keywords: Fluoxetine; WAY 100635; (−)-5-Me-8-OH-DPAT ((−)-5-methyl-8-hydroxy-2-(di-*n*-propylamino)tetralin); Microdialysis; Food intake; 5-HT_{1A} receptor

1. Introduction

The effects of selective serotonin reuptake inhibitors, such as fluoxetine, on presynaptic somatodendritic 5-HT_{1A} receptors have been extensively studied over the last years. At low doses and after acute peripheral administration, these antidepressant drugs slightly increase the extracellular levels of endogenous serotonin (5-hydroxytryptamine, 5-HT) at serotoninergic nerve terminals as measured by in vivo microdialysis in rats. We and others recently demonstrated that this neurochemical effect of fluoxetine is limited in serotoninergic nerve terminal regions such as the frontal cortex and ventral hippocampus compared to that measured in the raphe nuclei region where cell bodies of these neurons are found (Malagié et al., 1995; Gartside et al., 1995). Thus, it is assumed that, by blocking the selective 5-HT transporter located on the membrane cell bodies of 5-HT neurons, selective serotonin reuptake inhibitors mainly increase extracellular 5-HT levels ([5-HT_{ext}]) around cell bodies, which in turn activate somatodendritic 5-HT_{1A} autoreceptors highly abundant in the raphe nuclei. This leads to inhibition of the firing of 5-HT neurons (Gartside et al., 1995) and to the subsequent decrease in 5-HT release in nerve terminal forebrain regions (Auerbach et al., 1995). When the somatodendritic 5-HT_{1A} autoreceptors are blocked by selective antagonists, the inhibition of 5-HT neuronal activity is prevented and the effect of selective serotonin reuptake inhibitors on [5-HT_{ext}] in various regions of forebrain is facilitated. Indeed, it has been shown that pretreatment with the highly selective 5-HT_{1A} receptor antagonist, WAY 100635 (*N*-[4-(2-methoxyphenyl)-1-piperazinyl]-*N*-(2-pyridinyl) cyclo-hexanecarboxamide), or with (−)-pindolol can potentiate the effects of acute systemic administration of selective serotonin reuptake inhibitors such as paroxetine (Gartside

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et al., 1995), fluoxetine (Malagié et al., 1996) or citalopram (Hjorth, 1996) on [5-HT_{ext}] in various rat brain regions. It is thus tempting to presume that potentiation of the selective serotonin reuptake inhibitor-induced increases in [5-HT_{ext}] in forebrain regions may reinforce the postsynaptic effects of such drugs. However, little is known about the subsequent effects of endogenous 5-HT after the combined treatment with a selective serotonin reuptake inhibitor and a 5-HT_{1A} autoreceptor antagonist on postsynaptic receptors.

It is well established that fluoxetine induces anorexia in rats (Wong et al., 1988), although the postsynaptic 5-HT receptor subtype(s) involved in this effect is not clearly identified. Earlier work suggested that direct activation of 5-HT_{2C} receptors could explain part of the hypophagic response to another indirect serotoninergic agonist, dexfenfluramine, but not that to fluoxetine (Curzon et al., 1997; Clifton and Lee, 1997). The direct binding of fluoxetine and its major active metabolite, norfluoxetine, to 5-HT_{2A} and 5-HT_{2C} receptor subtypes was not significant in rats (Stanford, 1996). Furthermore, since these drugs act as indirect serotoninergic agonists, all 5-HT receptor subtypes may potentially mediate their hypophagic effect in rats. However, the hypophagic response of rats to systemic administration of fluoxetine does not appear to depend solely on increased availability of 5-HT in the synaptic cleft (Caccia et al., 1992). An additional, unknown mechanism has been proposed to complete this effect (Lightowler et al., 1996). Furthermore, a large body of evidence suggests that stimulation by the standard 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), of 5-HT_{1A} autoreceptors located in the midbrain raphe nuclei induces hyperphagia in satiated rats (Hutson et al., 1986; O'Connell and Curzon, 1996). However, the functional assessment of the role of central 5-HT_{1A} receptors in the fluoxetine-induced hypophagia in rats has been delayed because of the lack of availability of 5-HT_{1A} receptor antagonists.

The present study was thus designed to determine the involvement of the pre- and postsynaptic 5-HT_{1A} receptor subtype in the hypophagic effect of fluoxetine. We further investigated the effects of selective serotonin reuptake inhibitor treatment on [5-HT_{ext}] in the rat ventral hippocampus when combined with highly selective 5-HT_{1A} receptor antagonists such as WAY 100635 (Forster et al., 1995) or a novel agent, (−)-5-methyl-8-hydroxy-2-(di-*n*-propylamino)tetralin, (−)-5-Me-8-OH-DPAT (Trillat et al., 1998) that has been recently characterized in our laboratory. Second, we investigated the extent to which 5-HT_{1A} receptor blockade could potentiate the hypophagic response of rats to fluoxetine. We used a low dosage of fluoxetine (5 mg/kg) administered intraperitoneally to rats, to avoid abnormal sedative and motor side-effects of the drug, leading to a decrease in feeding that could be misinterpreted as a selective enhancement of satiety in rats under our experimental conditions.

2. Materials and methods

2.1. Animals

Microdialysis and food intake studies were carried out in male Sprague–Dawley rats (200–300 g, Charles River, France). Animals were allowed to have free access to food and water and were housed singly for the experiments.

2.2. Drugs and treatment

The following drugs and chemicals were used in this study: WAY 100635 (*N*-[4-(2-methoxyphenyl)-1-piperazinyl]-*N*-(2-pyridinyl) cyclo-hexanecarboxamide, 3HCl), from Wyeth Research (Maidenhead, UK), (−)-5-methyl-8-Hydroxy-2-(di-*n*-propylamino)tetralin, HBr, (−)-5-Me-8-OH-DPAT was synthetized by Drs. Mathé-Allainmat and Langlois, CNRS BIOCIS URA 1843 (Châtenay-Malabry, France) and fluoxetine hydrochloride was purchased from Alchymars (Milan, Italy).

2.3. Surgery and microdialysis procedure

Concentric dialysis probes were made of polyacrilonitril fibers (Hospal AN69, France) and constructed as described previously (Malagié et al., 1996). The size of the dialysis membranes was 4 mm long × 0.30 mm OD. The probes were tested for in vitro recovery of 5-HT on the day before use to verify that recoveries were within a desired range of efficacy (around 20% for 5-HT). The animals were anaesthetized with chloral hydrate (400 mg/kg i.p.) and placed in a stereotaxic frame. The rats were implanted with a probe in the left ventral hippocampus according to the following coordinates (in millimeters), from bregma and top of the skull (Paxinos and Watson, 1986): A—4.8, L—4.8, V—7.5. The probe was cemented in place. The animals were allowed to recover from the surgery for approximately 20 h, and the probe was then continuously perfused with an artificial cerebrospinal fluid (composition in mM: NaCl 147, KCl 3.5, $CaCl_2$ 1.0, $MgCl_2$ 1.2, NaH_2PO_4 1.0, $NaHCO_3$ 25.0, pH 7.4 ± 0.2) at a flow rate of 1.3 μl/min, using a CMA/100 pump (Carnegie Medicine, Stockholm, Sweden). At the end of each experiment, the brain was removed, fixed in NaCl (0.9%)/paraformaldehyde solution (30%), cut on a Leitz cryomicrotome, and the placement of microdialysis probes was verified on serial coronal sections. Only data obtained from rats with properly implanted probes were included in the results. During the surgery for probe implantation, a jugular vein was cannulated with polyethylene tubing, for intravenous administration of drugs.

2.4. Chromatographic analysis

Dialysate samples were collected every 15 min in Eppendorf tubes and were immediately analyzed for 5-HT by

high performance liquid chromatography (HPLC), using an LC-4B amperometric detector (Bioanalytical System), as previously described (Malagié et al., 1996). The limit of sensitivity was about 0.5–1 fmol/sample for 5-HT. Usually four to five fractions were collected for each rat to reliably determine basal 5-HT levels (means ± S.E.M) before peripheral administration of the drugs.

2.5. Food intake experiments

Twenty days before the experiments, the animals were placed on a light–dark schedule (lights on: 0400–1600) in our animal facility. Three days before the test for food intake, the rats were lightly anaesthetized and a jugular vein was cannulated with polyethylene tubing for intravenous administration of drugs. The animals were allowed to recover for 3 days by placing them in individual cages in which the behavioral test was conducted. The rats were food deprived for 24 h, while water was available ad libitum. The food intake experiment was performed for three consecutive days, thus all the different treatments were administered on the same day. Vehicle and drug-treated animals were tested concurrently. At 1600, i.e., the start of the dark period, they received the first injection. Each rat was provided with a known, weighed amount of lab chow and intake was measured by weighing the remainder 1, 2, 3 and 4 h and 24 h after the fluoxetine injection.

2.6. Drug administration

Each animal received a first intraperitoneal (i.p.) injection of either saline or fluoxetine (5 mg kg^{-1} (2 ml of water)$^{-1}$) followed by a second intravenous (i.v.) injection, 1 h later, of either saline or WAY 100635 (0.5 mg kg^{-1} (1 ml of water)$^{-1}$) or (−)-5-Me-8-OH-DPAT (3 mg kg^{-1} (1 ml of water)$^{-1}$). Drug doses are expressed as the salt.

2.7. Data analysis

All the statistical analyses were performed with the computer software Statview 4.02 (Abacus concepts, Berkeley, CA, USA). Significance was set at $P < 0.05$. Data from microdialysis experiments (not corrected for in vitro recovery) were expressed as percentages of the basal value (means ± S.E.M.). To compare [5-HT_{ext}] to the respective basal value in each group of treated animals, statistical analysis was carried out with a one-way analysis of variance (ANOVA) for repeated measures on the time, followed by Fisher Protected Least Significant Difference (PLSD) post-hoc test. Further, using percentage data, net changes in dialysate 5-HT were determined by calculating the area under the curve (AUC) for the 0- to 180-min period. Statistical comparisons of these AUCs were made by applying a one-way ANOVA followed by PLSD post-hoc test. The data from food intake experiments were analyzed by one-way ANOVA followed by a Fisher PLSD post-hoc test.

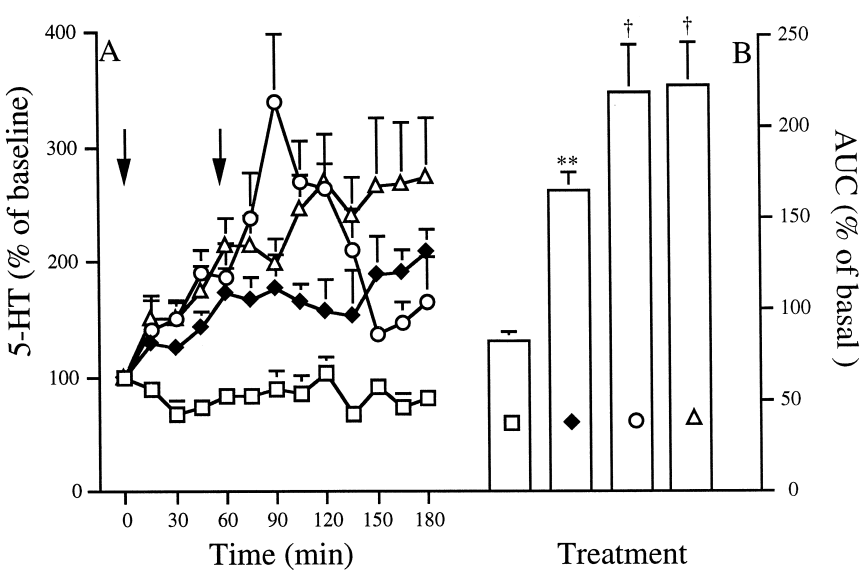

Fig. 1. Effect of the co-administration of (−)-5-Me-8-OH-DPAT (3 mg/kg) or WAY 100635 (0.5 mg/kg) with fluoxetine (5 mg/kg) on extracellular 5-HT in rat ventral hippocampal dialysates. Data are presented as (A) 5-HT concentration expressed as the % of 5-HT baseline and (B) as the area under the curve, AUC (% of 5-HT, 0–180 min). Values are means ± S.E.M. for five to six animals per treatment group. First arrow denotes intraperitoneal administration of vehicle or fluoxetine, the second denotes intravenous administration of vehicle, (−)-5-Me-8-OH-DPAT or WAY 100635. ∗∗ $P < 0.01$ one-way ANOVA followed by Fisher PLSD multiple comparison test vs. NaCl–NaCl group. $^{\dagger}P < 0.05$ one-way ANOVA followed by Fisher PLSD multiple comparison test vs. fluoxetine–NaCl group. NaCl–NaCl (□), Fluoxetine–NaCl (◆), Fluoxetine–(−)-5-Me-8-OH-DPAT (○), Fluoxetine–WAY 100635 (△).

3. Results

3.1. Effect of the co-administration of WAY 100635 or (−)-5-Me-8-OH-DPAT with fluoxetine on extracellular 5-HT levels in rat ventral hippocampus

Basal hippocampal [5-HT_{ext}] (means ± S.E.M. in fmol/20 μl) from animals receiving a combination of fluoxetine (5 mg/kg, i.p.) either with (−)-5-Me-8-OH-DPAT: 3.3 ± 0.8 ($n = 7$) or with WAY 100635: 3.0 ± 0.7 ($n = 6$) did not differ significantly from the values for animals receiving fluoxetine alone: 2.9 ± 0.2 ($n = 6$). Administration of either (−)-5-Me-8-OH-DPAT (3 mg/kg, i.v.) or WAY 100635 (0.5 mg/kg, i.v.) alone did not induce changes in [5-HT_{ext}] in the ventral hippocampus (AUC values (% of basal 5-HT): 105 ± 12, 98 ± 11, respectively). In contrast, during the first hour following fluoxetine administration, [5-HT_{ext}] in the ventral hippocampus was similarly increased in the three groups of rats examined, the resulting levels being approximately twice their respective baseline values (Fig. 1A). Systemic administration of WAY 100635 (0.5 mg/kg, i.v.) or (−)-5-Me-8-OH-DPAT (3 mg/kg, i.v.) in animals pretreated with fluoxetine (5 mg/kg, i.p.) induced a statistically significant enhancement of the fluoxetine-induced increase in [5-HT_{ext}] as compared to control rats treated with fluoxetine and subsequently with saline (Fig. 1A). Thus, AUC values measured for the 0- to 180-min period in the [fluoxetine + WAY 100635]- or [fluoxetine + (−)-5-Me-8-OH-DPAT]-treated groups were significantly higher than in groups receiving fluoxetine alone ($P < 0.05$, Fig. 1B).

3.2. Effect of the co-administration of WAY 100635 or (−)-5-Me-8-OH-DPAT with fluoxetine on food intake

Fluoxetine (5 mg/kg, i.p., $n = 11$) decreased food intake (Fig. 2A) from the first to the 24th hour following its administration, statistical significance ($P < 0.05$) being reached at various times (1, 4 and 24 h) after fluoxetine injection. At these three time points, food intake was decreased by 2.8 g, 4.1 g and 6.3 g, respectively, when compared to that of the saline group ($n = 12$). Neither WAY 100635 (0.1 mg/kg) nor (−)-5-Me-8-OH-DPAT (3 mg/kg) had any effect on food intake on their own (Fig. 2B). In contrast, the combined administration of fluoxetine with either WAY 100635 ($n = 7$) or (−)-5-Me-8-OH-DPAT ($n = 5$) decreased food intake (Fig. 2A) more than in the group of rats given fluoxetine alone. Thus, the combined treatment with fluoxetine and WAY 100635 significantly decreased food intake, when compared to that in the fluoxetine group, by 3.9 g ($P < 0.05$), 3.7 g ($P < 0.05$) and 5.0 g ($P < 0.01$) at 2, 3 and 4 h after fluoxetine injection, respectively. The combination of fluoxetine with (−)-5-Me-8-OH-DPAT significantly ($P < 0.05$) decreased food intake, when compared to that in the fluoxetine alone group by 4.2 g, 5.0 g at 3 and 4 h after fluoxetine injection, respectively.

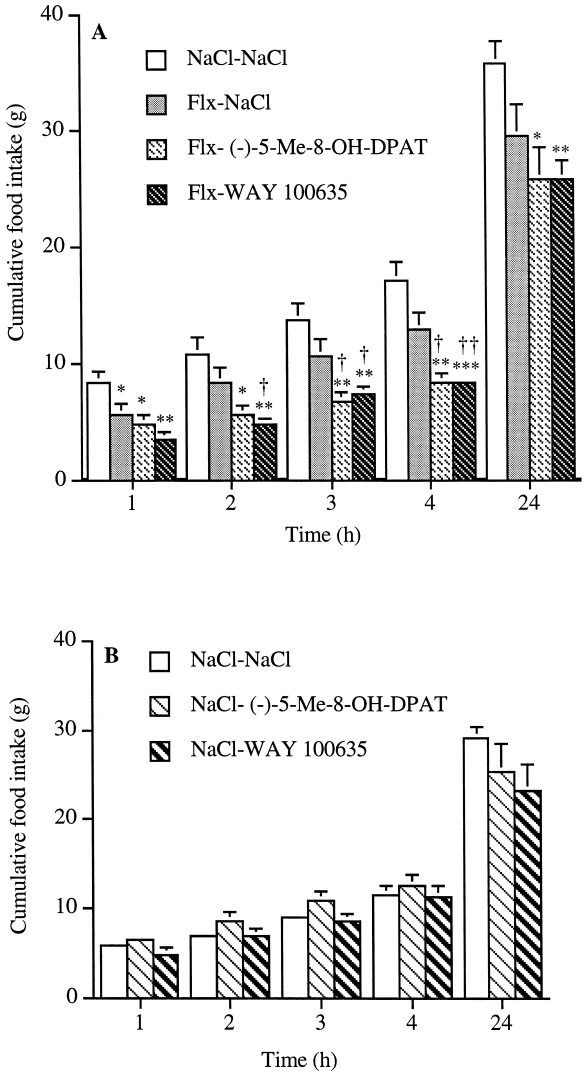

Fig. 2. (A) Effect of fluoxetine and of the co-administration of fluoxetine with (−)-5-Me-8-OH-DPAT or WAY 100635 and (B) effect of (−)-5-Me-8-OH-DPAT or WAY 100635 alone on food intake. The 24-h food-deprived rats were treated with saline or fluoxetine (5 mg/kg) i.p. 1 h before saline, (−)-5-Me-8-OH-DPAT (3 mg/kg) or WAY 100635 (0.5 mg/kg) i.v. administration. Each point is the mean ± S.E.M. for 5 to 12 animals per treatment. $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$ vs. NaCl–NaCl group; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ vs. fluoxetine–NaCl group (one-way ANOVA followed by Fisher PLSD multiple comparison test).

4. Discussion

We observed that the injection of 5 mg/kg, i.p. fluoxetine alone induced a slight increase in [5-HT_{ext}] in the rat ventral hippocampus, while the same dose of fluoxetine co-administered with either WAY 100635 (0.5 mg/kg, i.v.) or (−)-5-Me-8-OH-DPAT (3 mg/kg, i.v.) caused a greater increase in [5-HT_{ext}]. The potentiation of fluoxetine's effect on [5-HT_{ext}] in the ventral hippocampus by

WAY 100635 or (−)-5-Me-8-OH-DPAT is likely the consequence of the interaction of these latter drugs with somatodendritic 5-HT_{1A} autoreceptors located in the raphe nuclei, the activation of which is known to exert an inhibitory feedback control on the released 5-HT. Indeed, it has been shown that this latter region has one of the highest densities of 5-HT_{1A} receptors in rats (Hrdina et al., 1990). Furthermore, the local application of 5-HT_{1A} receptors antagonists into the dorsal raphe nucleus by 'reverse' dialysis also potentiated the effects of selective serotonin reuptake inhibitor on [5-HT_{ext}] in serotoninergic nerve terminal areas such as the hippocampus (Romero and Artigas, 1997).

There is only slight evidence suggesting that fluoxetine and other selective serotonin reuptake inhibitors, by increasing [5-HT_{ext}], can cause functional postsynaptic receptor activation, leading to increased 5-HT neurotransmission in the rat central nervous system. The functional effects include decreased muricidal aggression (Molina et al., 1987), decreased food intake and altered food preference (Goudie et al., 1976), increased plasma corticosterone levels (Fuller et al., 1996), decreased rapid-eye-movement (REM) sleep (Slater et al., 1978) as well as anticonvulsant effects in epilepsy models in rats (Dailey et al., 1992). We have now found that the blockade of the 5-HT_{1A} receptors either by WAY 100635 (0.5 mg/kg, i.v.) or by (−)-5-Me-8-OH-DPAT (3 mg/kg, i.v.), neither drug having any intrinsic activity on food intake, potentiated the fluoxetine (5 mg/kg, i.p.)-induced hypophagia in rats. Thus, our data suggest that somatodendritic 5-HT_{1A} autoreceptors, by regulating synaptic 5-HT levels, may play a key role in the fluoxetine-induced hypophagia. In agreement with our findings, a recent study has shown that blockade of these 5-HT_{1A} autoreceptors could enhance the ability of fluoxetine to decrease the consumption of sweetened condensed milk in mice (Li et al., 1998). In contrast, other authors did not find any evidence of this potentiation, using (+)WAY 100135 in rats (Ciccocioppo et al., 1997). However, the fact that this drug, which has been shown to have weak 5-HT_{1A} receptor agonist properties (Fornal et al., 1996), was administered to genetically selected alcohol-preferring rats, i.e., a particular experimental model, might explain the differences observed. In agreement with our hypothesis, it has been shown that the systemic administration of low 8-OH-DPAT doses increases food intake in satiated rats (Dourish et al., 1985). The involvement of this 5-HT_{1A} receptor subtype located within the midbrain raphe nuclei in the hyperphagia has been confirmed by results of studies using local intraraphe injection of 8-OH-DPAT (Hutson et al., 1986; O'Connell and Curzon, 1996). Thus, 8-OH-DPAT activates raphe somatodendritic 5-HT_{1A} autoreceptors, leading to inhibition of 5-HT neuronal activity and reduced endogenous 5-HT release in forebrain nerve terminal areas. Together, these results suggest that indirect activation of somatodendritic 5-HT_{1A} autoreceptors by fluoxetine may limit the hypophagic action of this selective serotonin reuptake inhibitor, thus stressing the possible advantage of blocking somatodendritic 5-HT_{1A} autoreceptors to enhance the hypophagic action (and possibly other behavioral effects) of fluoxetine.

It has already been demonstrated that co-administration of fluoxetine and WAY 100635 potentiated the fluoxetine-induced activation of the pituitary–adrenocortical axis in rats (Fuller et al., 1996). However, further studies using local application of (−)-5-Me-8-OH-DPAT or WAY 100635 in the dorsal raphe nucleus combined with an acute systemic injection of fluoxetine are required to convincingly demonstrate that this effect likely involved pre- rather than postsynaptic 5-HT_{1A} receptors since the two selective 5-HT_{1A} receptor antagonists used in the present study were systemically administered.

Previously, we have demonstrated, using multiple probe implantations in the same rat, that marked changes in [5-HT_{ext}] occur at the same time in various forebrain regions such as the ventral hippocampus, frontal cortex and raphe nuclei following a single fluoxetine injection (Malagié et al., 1995). Systemic administration of an acute dose of fluoxetine also increases [5-HT_{ext}] in dialysates of the lateral hypothalamus (Perry and Fuller, 1993). It is likely that this latter effect could explain at least partially the hypophagic response to fluoxetine we observed in rats, since various hypothalamic nuclei densely innervated by 5-HT nerve terminals have been found to be involved in the control of food intake (Slater et al., 1978; Wurtman and Wurtman, 1990). Nonetheless, we cannot rule out the possibility that other brain areas as well as other neurotransmitter systems also participated to this response measured here in food-deprived rats. By combining a 5-HT_{1A} receptor antagonist with fluoxetine, presynaptic somatodendritic 5-HT_{1A} receptors are blocked and a greater increase in [5-HT_{ext}] not only in hypothalamic nuclei (Dreshfield et al., 1996), but also in other brain regions, becomes possible. It has also been demonstrated that acute systemic administration of fluoxetine can affect the activity of dopaminergic neurons in a region-specific manner: the extracellular dopamine level was found to be increased in the frontal cortex (Gobert et al., 1997) and decreased in the nucleus accumbens and striatum (Ichikawa and Meltzer, 1995). Based on the observation that an increase in hypothalamic 5-HT was accompanied by a decrease in dopamine in the nucleus accumbens (Hoebel et al., 1991), the authors suggest that the central mechanism leading to fluoxetine-induced hypophagia in rats may involve mesolimbic dopaminergic projections to the nucleus accumbens. Thus, it cannot be ruled out that the hypophagic effect of fluoxetine in rats may involve interactions between brain serotoninergic and dopaminergic systems as reflected by fluoxetine-induced changes in [5-HT_{ext}] and extracellular dopamine levels.

This work supports a role of endogenous 5-HT probably among other neurotransmitters and, via an inhibitory effect on 5-HT release, the importance of somatodendritic 5-HT_{1A}

autoreceptors in the hypophagic effect of selective serotonin reuptake inhibitors.

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