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Short communication

Improved efficacy of fluoxetine in increasing hippocampal 5-hydroxytryptamine outflow in 5-HT_{1B} receptor knock-out mice

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Abstract

To test for the contribution of the 5-HT_{1B} receptor subtype in mediating the effects of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), we used intracerebral in vivo microdialysis in awake, freely moving 5-HT_{1B} receptor knock-out mice. We show that a single systemic administration of fluoxetine (1, 5 or 10 mg/kg, i.p.) increased extracellular serotonin levels $[5\text{-HT}]_{ext}$ in the ventral hippocampus and frontal cortex of wild-type and mutant mice. However, in the ventral hippocampus, fluoxetine, at the three doses studied, induced a larger increase in $[5\text{-HT}]_{ext}$ in knock-out than in wild-type mice. In the frontal cortex, the effect of fluoxetine did not differ between the two genotypes. The region-dependent response to fluoxetine described here in mutants confirms data we recently reported for another SSRI, paroxetine. These data suggest that 5-HT_{1B} autoreceptors limit the effects of selective serotonin reuptake inhibitors on dialysate 5-HT levels at serotonergic nerve terminals located mainly in the ventral hippocampus. Alternative mechanisms, e.g., changes in 5-HT transporter and/or 5-HT_{1A} receptor density in 5-HT_{1B} receptor knock-out mice could also explain these findings.

Keywords: Antidepressant drug, 5-HT_{1B} autoreceptor; Microdialysis, intracerebral; Knock-out mouse; Fluoxetine; 5-HT (5-hydroxytryptamine, serotonin) reuptake inhibitor, selective

1. Introduction

The main hypothesis regarding pathogenesis of major depression involves a deficiency in the brain serotonergic function. In support of this hypothesis, selective serotonin reuptake inhibitors (SSRI), by blocking the transporter of serotonin (5-hydroxytryptamine, 5-HT), increase its synaptic availability, thus improving the central serotonergic neurotransmission. However, activation of somatodendritic 5-HT_{1A} and nerve terminal 5-HT_{1B} autoreceptors by endogenous 5-HT seems to limit the therapeutic efficacy of these antidepressant drugs following their acute administration (Gardier et al., 1996). The 5-HT_{1B} receptor localized in the central nervous system on presynaptic nerve terminals of serotonergic neurons are called autoreceptors because they are involved in a local inhibitory control of 5-HT release (Engel et al., 1986; Maura et al., 1986; Göthert et al., 1987; Piñeyro et al., 1995; Trillat et al., 1997).

We recently used intracerebral in vivo microdialysis to investigate the contribution of 5-HT_{1B} autoreceptors in mediating the effects of a selective serotonin reuptake inhibitor, paroxetine (Malagié et al., 2001). Experiments were performed in awake, freely moving mice lacking 5-HT_{1B} receptors (5-HT_{1B} knock-out; Saudou et al., 1994). We demonstrated that a single systemic administration of paroxetine induced a larger increase in extracellular serotonin levels $[5\text{-HT}]_{ext}$ in the ventral hippocampus of 5-HT_{1B} receptor knock out than that observed in wild-type mice. In the frontal cortex, the effect of paroxetine was larger in mutants than in wild-type mice at the 1 mg/kg dose, but not at 5 mg/kg. These results were confirmed by using a receptor antagonist strategy in wild-type mice showing that the blockade of 5-HT_{1B} receptor with the mixed 5-$HT_{1B/1D}$ receptor antagonist (*N*-[4-methoxy-3-(4-methylpiperazin-1-

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yl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide) GR 127935, potentiated the effect of paroxetine on $[5\text{-HT}]_{ext}$ in the ventral hippocampus, but not in the frontal cortex. These data demonstrate that the activation of 5-HT_{1B} autoreceptors by endogenous 5-HT limit the effects of paroxetine on dialysate 5-HT levels particularly in the hippocampus. To know whether this property could be extended to other molecules, we compared here the effects of a single systemic administration of another selective serotonin reuptake inhibitor, fluoxetine (1, 5 or 10 mg/kg, i.p.) on $[5\text{-HT}]_{ext}$ in 5-HT_{1B} selective serotonin reuptake inhibitor versus wild-type mice using the same experimental conditions than those we previously used for paroxetine.

2. Materials and methods

2.1. Drugs

Fluoxetine hydrochloride (1, 5 and 10 mg/kg; Alchymars, Italy) was dissolved in water in a volume of 10 ml/kg and administered intraperitoneally (i.p.). The animals were habituated to intraperitoneal injection before injection of the drugs or saline solution.

2.2. Animals

The founders of the wild-type and mutant colonies used in the present study were the product of heterozygous matings made at the animal facility of Columbia University. These founders were shipped to France and their offspring were bred and reared in independent colonies. Wild type and 5-HT_{1B} receptor knock-out mice were male mice, 9–11 weeks old, obtained from a pure 129/Sv genetic background. Group-housed mice were kept in standard cages on a 12-h light/12-h dark cycle with light onset at 7 h. The mice were tested between 10:00 and 16:00 during the light phase. Only mice with probes confined to either the ventral hippocampus or the frontal cortex were used for subsequent data analysis.

2.3. Microdialysis

Concentric dialysis probes were made of cuprophan fibers and constructed as described previously (Malagié et

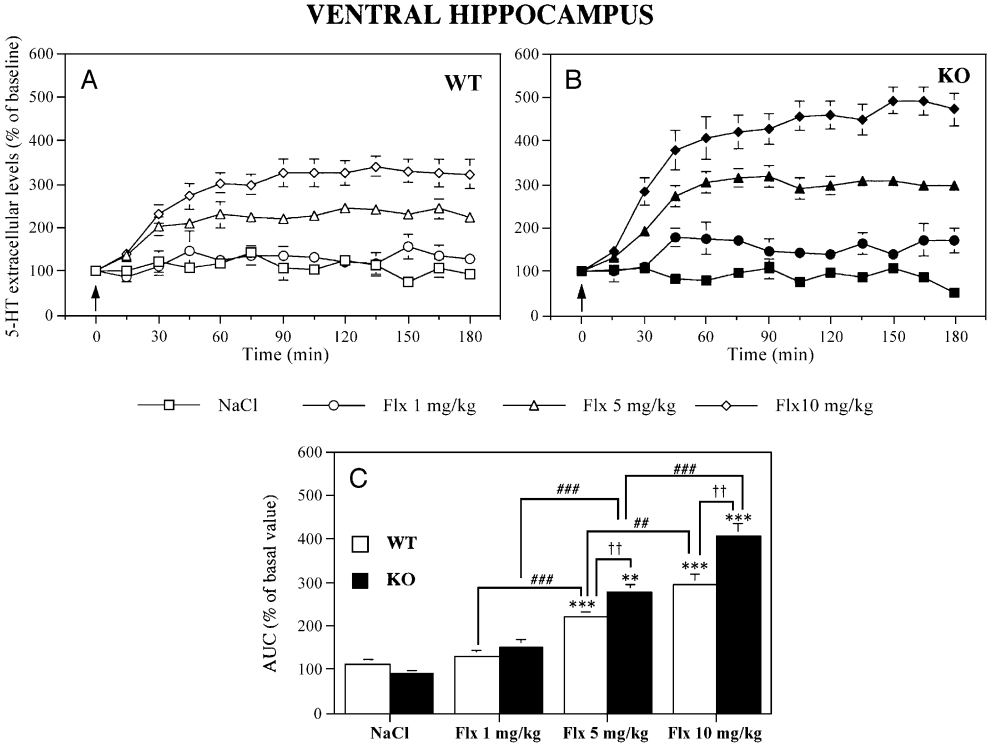

Fig. 1. Effects of fluoxetine on extracellular 5-HT levels in the ventral hippocampus of wild-type (WT) and 5-HT_{1B} receptor knock-out (KO) mice. Data are means ± S.E.M. of extracellular 5-HT levels expressed as percentages of baseline in wild-type (white symbols, A) and KO (black symbols, B) mice following exposure to saline (□ or ■), fluoxetine 1 mg/kg (○ or ●), 5 mg/kg (△ or ▲) and 10 mg/kg (◇ or ♦), respectively ($n = 5–9$ determinations per group). Drugs were administered i.p. at t_0 (black arrow). Basal values (in fmol/20 μl): 2.65 ± 0.32 ($n = 31$) and 2.2 ± 0.14 ($n = 29$) in the ventral hippocampus of wild-type and KO mice, respectively. (C) Area under the curve (AUC; mean ± S.E.M.) values calculated for the amount of 5-HT outflow collected during the 0–180 min post-treatment period are expressed as percentage of basal values. ** $P < 0.01$ and *** $P < 0.001$ relative to the corresponding control group; †† $P < 0.01$ relative to wild-type; ## $P < 0.01$ and ### $P < 0.001$ relative to the corresponding fluoxetine-treated group.

al., 2001). All probes present an active length of 1.6 and 2 mm for the frontal cortex and ventral hippocampus, respectively (× 0.30 mm OD). Animals were anaesthetized with chloral hydrate (400 mg/kg, i.p.) and were implanted with two probes, cemented in place, one in the right frontal cortex and the other in the left ventral hippocampus, according to a mouse brain atlas (Franklin and Paxinos, 1997) [coordinates: from bregma (in mm), frontal cortex, $A = +2.0$, $L = +1.2$, $V = -1.6$; ventral hippocampus, $A = -2.8$, $L = -3.0$, $V = -4.0$ (A, anterior; L, lateral; and V, ventral)]. The animals were allowed to recover from the surgery overnight. The next day, ≈ 20 h after surgery, the probes were continuously perfused with an artificial cerebrospinal fluid (composition in mM: NaCl 147, KCl 3.5, $CaCl_2$ 1.26, $MgCl_2$ 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 Medicin, Stockholm, Sweden). Dialysate samples were collected every 15 min in small Eppendorf tubes and were analyzed for 5-HT by a high-performance liquid chromatography apparatus (XL-ODS, 4.6 × 7.0 mm, particle size 3 μm; Beckman) coupled to an amperometric detector (1049A, Hewlett-Packard, Les Ulis, France) as previously described (Malagié et al., 2001). Usually four fractions were collected to obtain basal values (means ± S.E.M.) before peripheral administration of the drugs. The limit of sensitivity for 5-HT was ≈ 0.5 fmol/sample (signal-to-noise ratio = 2).

2.4. Data analysis and statistics

Data (mean ± S.E.M.) in Figs. 1 and 2 were standardized by transforming dialysate 5-HT concentrations into percentages of baseline values based on averages of the first four fractions uncorrected for in vitro probe recovery. Groups of wild-type ($n = 32$) and mutant ($n = 29$) mice were exposed to saline or fluoxetine. Area under the curve (AUC; mean ± S.E.M.) values calculated for the amount of 5-HT outflow collected during the 0–180 min period from the ventral hippocampus and frontal cortex are expressed as percentage of basal values. Statistical analyses were performed using the computer software StatView 4.02 (Abacus Concepts, Berkley, CA, USA). For each brain structure, a two-way analysis of variance (ANOVA) on AUC values was performed, with the drug treatment (saline, fluoxetine 1, 5 or 10 mg/kg) and the mouse genotype (wild-type or knock-out) as main factors. The significance level was set at $P < 0.05$.

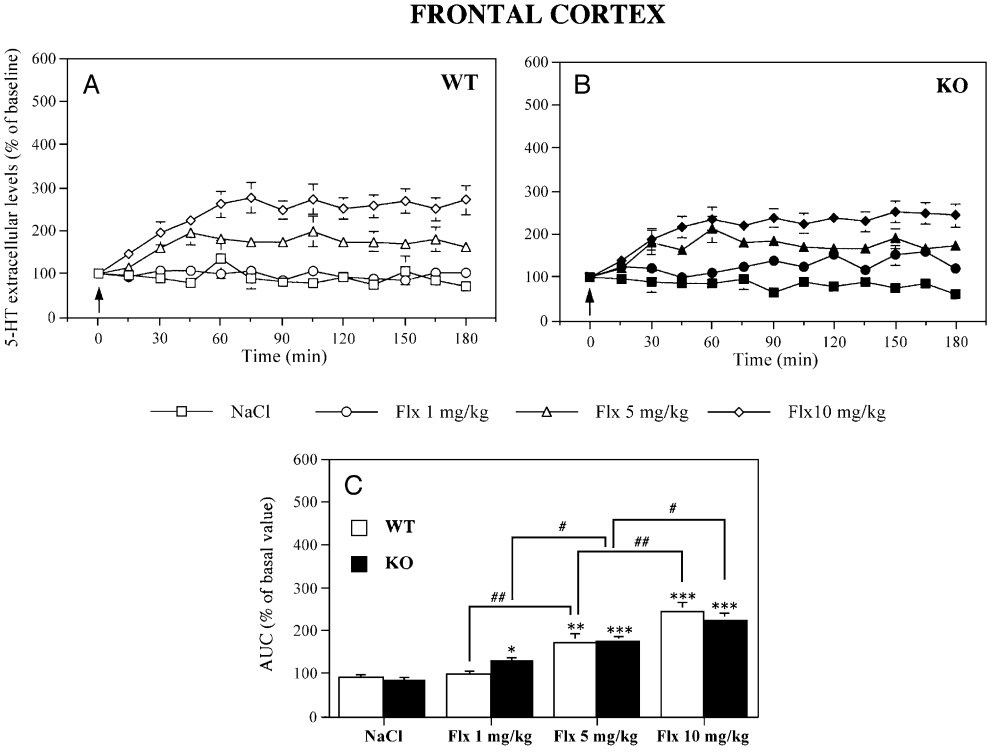

Fig. 2. Effects of fluoxetine on extracellular 5-HT levels in the frontal cortex of wild-type (WT) and 5-HT receptor knock-out (KO) mice. Data are means ± S.E.M. of extracellular 5-HT levels expressed as percentages of baseline in wild-type (white symbols, A) and KO (black symbols, B) mice following exposure to saline (□ or ■), fluoxetine 1 mg/kg (○ or ●), 5 mg/kg (△ or ▲) and 10 mg/kg (◇ or ♦), respectively ($n = 6–9$ determinations per group). Drugs were administered i.p. at t_0 (black arrow). Basal values (in fmol/20 μl): 4.1 ± 0.4 ($n = 29$) and 4.05 ± 0.44 ($n = 28$) in the ventral hippocampus of wild-type and KO mice, respectively. (C) Area under the curve (AUC; mean ± S.E.M.) values calculated for the amount of 5-HT outflow collected during the 0–180 min post-treatment period are expressed as percentage of basal values. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ relative to the corresponding control group; # $P < 0.05$ and ## $P < 0.01$ relative to the corresponding fluoxetine-treated group.

3. Results

Basal extracellular levels of 5-HT did not differ significantly between the two strains of mice [mean ± S.E.M. of the various groups of mice studied, in fmol/20 μl, n = number of determinations per group: 2.65 ± 0.32 (n = 31) and 2.2 ± 0.14 (n = 29) in the ventral hippocampus of wild-type and knock-out mice, respectively, and 4.1 ± 0.4 (n = 29) and 4.05 ± 0.44 (n = 28) in the frontal cortex of wild-type and knock-out mice, respectively]. A single systemic administration of fluoxetine (1, 5 or 10 mg/kg, i.p.), dose-dependently increased $[5\text{-HT}]_{ext}$ in the two brain regions studied in wild-type and 5-HT_{1B} receptor knock-out mice. However, in the ventral hippocampus, fluoxetine at the two doses studied induced a larger increase in $[5\text{-HT}]_{ext}$ in 5-HT_{1B} receptor knock-out than in wild-type mice (Fig. 1A–C). A two-way ANOVA (genotype × treatment) on AUC values revealed significant genotype factor [$F(1,53) = 9.50$, $P < 0.01$], treatment factor [$F(3,53) = 65.26$, $P < 0.001$] and a significant interaction [$F(3,53) = 3.86$, $P = 0.05$]. The effect in mutants was significantly greater than in wild-type mice for the intermediate and the highest fluoxetine doses studied (††$P < 0.01$). In the frontal cortex, a two-way ANOVA (genotype × treatment) on AUC values revealed a significant treatment factor [$F(3,53) = 30.16$, $P < 0.001$], but no significant genotype factor [$F(1,53) = 0.006$, $P = 0.94$], and no interaction [$F(3,53) = 0.81$, $P = 0.49$] (Fig. 2A–C). Thus, in the frontal cortex, fluoxetine-induced increases in $[5\text{-HT}]_{ext}$ were similar in wild-type and knock-out mice at the three doses studied. Fluoxetine induced a region-dependent effect, the largest increase in dialysate 5-HT being observed in the ventral hippocampus of mutant mice.

4. Discussion

A systemic administration of a single dose of fluoxetine (1–10 mg/kg), increased [5-HT_{ext}] values in the two brain regions studied in both mice' genotypes. The results obtained in wild-type mice confirm the dose-dependent effect we have previously found following the systemic administration of a single dose of either fluoxetine in rats (Malagié et al., 1995) or paroxetine in mice (Malagié et al., 2001). Furthermore, in the ventral hippocampus, fluoxetine induced a larger increase in $[5\text{-HT}]_{ext}$ in 5-HT_{1B} receptor knock-out than in wild-type mice. In the frontal cortex, the effect of fluoxetine on $[5\text{-HT}]_{ext}$ was similar in both genotypes. We found a similar phenomenon with paroxetine (Malagié et al., 2001), although it was less pronounced than for fluoxetine. Taken together, these results demonstrate that terminal 5-HT_{1B} autoreceptors limit the effects of selective serotonin reuptake inhibitors on [5-HT_{ext}], in the ventral hippocampus, while these autoreceptors do not appear to play a prominent role in regulating the amount of dialysate 5-HT at serotonergic nerve terminals located in the frontal cortex.

This phenotypic difference in response to fluoxetine was mainly observed in the ventral hippocampus, a brain region preferentially innervated by the median raphe nucleus, while there was no phenotypic effect observed in the frontal cortex, a brain region preferentially innervated by the dorsal raphe nucleus (Jacobs and Azmitia, 1992). Since it is known that somatodendritic 5-HT_{1A} receptors exert a relatively greater negative feedback control over the dorsal raphe nucleus compared to the median raphe nucleus (see Hjorth et al., 2000 for a review), our data suggest that terminal 5-HT_{1B} autoreceptors play a more prominent role in regulating the activity of the median raphe nucleus versus dorsal raphe nucleus projection system. It is thus conceivable to propose that combining a selective serotonin reuptake inhibitor with a 5-HT_{1A} receptor antagonist may improve the efficacy of the selective serotonin reuptake inhibitor in the dorsal raphe nucleus-innervated brain areas such as the frontal cortex, striatum and globus pallidus, while co-administration of a selective serotonin reuptake inhibitor with a 5-HT_{1B} receptor antagonist may improve the efficacy of the selective serotonin reuptake inhibitor in the median raphe nucleus-innervated brain areas such as the ventral hippocampus, hypothalamus and medial septum. It is now very important to identify which one of these brain regions is implicated in the etiology of depression and/or plays a predominant role in the mediation of the therapeutic effects of selective serotonin reuptake inhibitors. If two non-overlapping and perhaps functionally distinct brain 5-HT systems may exist, then a tri-therapy combining (a selective serotonin reuptake inhibitor + a 5-HT_{1A} receptor antagonist + a 5-HT_{1B} receptor antagonist) could help to increase further the extracellular levels of 5-HT in a very large number of brain regions. However, the resulting activation of postsynaptic 5-HT receptors by endogenous 5-HT may explain the therapeutic efficacy of these antidepressant drugs. The answer to the following question "which of the fifteen known 5-HT receptor subtypes mediate this therapeutic effect?" is still a matter of a very important debate.

Another key question regarding constitutive knock-out animals, and here with mice lacking the 5-HT_{1B} receptor subtype (5-HT_{1B} receptor knock-out), deals with adaptive compensatory changes that may have occurred in the functional activity of somatodendritic 5-HT_{1A} receptors during the development of these mutants. We have not tested this hypothesis in detail by using microdialysis or behavioral tests in our laboratory, but several studies have already been reported. Thus, results of a ligand binding study using [^{3}H]8-hydroxy-2-(di-*N*-propylamino)tetralin ([^{3}H]8-OH-DPAT) indicated that the number of 5-HT_{1A} receptors is the same in mutant and WT mice (unpublished data-Saudou et al., 1994). In vitro/in vivo studies have already evaluated the *functional activity* of 5-HT_{1A} receptors in 5-HT_{1B} receptor knock-out mice, and homogenous results have been obtained: it has been found that 5-HT_{1A} receptors do not adapt in 5-HT_{1B} receptor knock-out mice (Ase et al., 2001). In addition, in these mutants, no changes in the spontaneous

firing of the raphe 5-HT neurons, or in the potency of the 5-HT_{1A} receptor agonist, 8-OH-DPAT, to inhibit these cells have been found (Evrard et al., 1999). By contrast, in our laboratory, we recently assayed for decrease in body temperature induced by an acute subcutaneous injection of 8-OH-DPAT (Gardier et al., 2001). We found a higher efficacy of 8-OH-DPAT in inducing hypothermia in 5-HT_{1B} receptor knock-out compared to wild-type mice suggesting that an adaptive thermoregulatory process involving the functional activity of somatodendritic 5-HT_{1A} receptors is indeed altered in mutant mice lacking 5-HT_{1B} receptors. The development of regional compensations after genetic deletion of 5-HT_{1B} receptors has been suggested in a recent microdialysis study showing a *decreased sensitivity* of 5-HT_{1A} receptors in the ventral hippocampus in 5-HT_{1B} receptor knock-out mice (Knobelman et al., 2001). The authors suggest a potential desensitization of 5-HT_{1A} receptors in the median raphe nucleus of 5-HT_{1B} receptor knock-out mice. Altogether, whether or not compensatory changes in the efficacy of 5-HT_{1A} receptors would have occurred in 5-HT_{1B} receptor knock-out mice must be further investigated by using additional neurochemical or functional tests.

Previous data suggested interactions between the plasma membrane 5-HT transporter (5-HTT) and 5-HT_{1B} receptors (Daws et al., 2000). 5-HTT is up- or down-regulated in 5-HT_{1B} receptor knock-out mice depending on the brain region studied (Ase et al., 2001). For example, the density of [^{3}H]citalopram binding was *decreased* in parts of the basal ganglia and thalamus of these mutants. The reduced number of uptake sites might contribute to enhance 5-HT neurotransmission in these brain regions under physiological conditions. By contrast, the density of 5-HTT was *increased* in the ventral hippocampus of 5-HT_{1B} receptor knock-out mice. This latter change was correlated with a 5-HT hyperinnervation in this brain region of mutants: this regional selectivity of 5-HT hyperinnervation may partly explain our microdialysis data obtained under pharmacological conditions in mutants following administration of paroxetine and fluoxetine. A larger number of uptake sites might be targeted and blocked by a selective serotonin reuptake inhibitor, thus leading to a higher efficacy of a single dose of selective serotonin reuptake inhibitors in increasing extracellular levels of 5-HT in this particular brain area of mutants, when compared to WT mice.

We recently obtained quite different results in our laboratory by using in vivo microdialysis in 5-HT_{1B} receptor knock-out mice. Indeed, we studied the functional status of 5-HTT in vivo by using the *zero net flux method* of quantitative microdialysis (Parsons and Justice, 1994). The extraction fraction of 5-HT (slope of the regression line) provides an in vivo index of 5-HT uptake. Different 5-HT concentrations (0, 5, 10 and 20 nM) were perfused for 30 min through the dialysis probe in the frontal cortex and ventral hippocampus of wild-type and 5-HT_{1B} receptor knock-out mice. In the two brain areas studied, we found that basal extracellular levels of 5-HT (basal levels in fmol/sample) and *E*d did not differ between wild-type and 5-HT_{1B} receptor knock-out mice (data submitted for publication). These results suggest that constitutive deletion of the 5-HT_{1B} receptor is not associated with alteration of 5-HTT. The reason for such discrepancies between our in vivo results and those of quantitative autoradiography/immunocytochemistry obtained in vitro on brain slices by Ase et al. (2001) are currently unknown.

In summary, by using intracerebral in vivo microdialysis in 5-HT_{1B} receptor knock-out mice, we obtained similar results with two selective serotonin reuptake inhibitors, paroxetine and fluoxetine, i.e., an improved efficacy of these drugs in increasing extracellular levels of 5-HT in the ventral hippocampus, but not in the frontal cortex suggesting that 5-HT_{1B} autoreceptors limit the effects of selective serotonin reuptake inhibitors on dialysate 5-HT levels at serotonergic nerve terminals in the ventral hippocampus. The results highlight the crucial need for more selective 5-HT_{1B} receptor antagonists to be tested in human. Such drugs will help us to know whether or not we may expect clinical benefits in depressed patients using a combined administration of a selective serotonin reuptake inhibitor with presynaptic 5-HT_{1B} receptor antagonists (see Hjorth et al., 2000 for a review).

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