

Increased Tonic Activation of Rat Forebrain 5-HT_{1A} Receptors by Lithium Addition to Antidepressant Treatments

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The present study was undertaken to determine whether lithium addition to long-term treatment with different classes of antidepressant drugs could induce a greater effect on the serotonin (5-HT) system than the drugs given alone. Because 5-HT_{1A} receptor activation hyperpolarizes and inhibits the firing activity of CA₃ pyramidal neurons in the dorsal hippocampus, the degree of disinhibition produced by the selective 5-HT_{1A} receptor antagonist WAY 100635 was determined using *in vivo* extracellular recordings. In controls, as well as in rats receiving a lithium diet for 3 days, the administration of WAY 100635 (25–100 µg/kg, IV) did not modify the firing activity of dorsal hippocampus CA₃ pyramidal neurons. When the tricyclic antidepressant imipramine (10 mg/kg/day, SC), the monoamine oxidase inhibitor tranylcypromine (2.5 mg/kg/day, SC) and the selective 5-HT reuptake inhibitor paroxetine (10 mg/kg/day, SC) were administered alone for

21 days, a dose of 50 µg/kg of WAY 100635 was needed to increase significantly the firing activity of these neurons. On the other hand, WAY 100635, at a dose of only 25 µg/kg, increased significantly the firing rate of CA₃ pyramidal neurons in rats receiving both a long-term antidepressant treatment and a short-term lithium diet. It is concluded that the addition of lithium to antidepressant treatments produced a greater disinhibition of dorsal hippocampus CA₃ pyramidal neurons than any treatments given alone. The present results support the notion that the addition of lithium to antidepressants may produce a therapeutic response in treatment-resistant depression by enhancing 5-HT neurotransmission. [Neuropsychopharmacology 22:346–356, 2000] © 2000 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

KEY WORDS: Lithium; Imipramine; Tranylcypromine; Paroxetine; WAY 100635, 5-HT_{1A} receptors; Dorsal hippocampus

Although the pathophysiology of major depression is not fully defined, there is a growing body of evidence suggesting the implication of the serotonin (5-HT) system in the therapeutic effect of antidepressant treat-

ments (Heninger and Charney 1987; Price et al. 1990a; Van Praag et al. 1990; Cummings 1993; Blier and de Montigny 1994; Maes and Meltzer 1995). For example, it has been shown that long-term tricyclic antidepressant (TCA) treatment and repeated electroconvulsive shock (ECS) administration lead to enhanced 5-HT neurotransmission via sensitization of the postsynaptic 5-HT_{1A} receptors (de Montigny and Aghajanian 1978; de Montigny 1984; Welner et al. 1989; Nowak and Dulinski 1991; Stockmeier et al. 1992). Long-term treatment with either monoamine oxidase inhibitors (MAOIs) or selective 5-HT reuptake inhibitors (SSRIs) results in a desensitization of the somatodendritic 5-HT_{1A} autoreceptor of 5-HT neurons in the dorsal raphe nucleus, thereby allowing their firing rate to recover in

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the presence of the drugs (Blier et al. 1986; Chaput et al. 1986). In addition, long-term SSRI treatment also desensitizes terminal 5-HT_{1B} autoreceptors; whereas, long-term MAOI treatment desensitizes terminal α_2 -adrenergic heteroreceptors located on 5-HT terminals (Blier and Bouchard 1994; Mongeau et al. 1994). The desensitization of the latter two receptors is thought to contribute to a greater release of 5-HT following SSRI and MAOI administration. Long-term treatment with the antidepressant mirtazapine, an α_2 -adrenoceptor antagonist, increases 5-HT neurotransmission as a result of a sustained increase in the firing activity of 5-HT neurons in the presence of the decreased function of α_2 -adrenergic heteroreceptors located on 5-HT terminals (Hadjjeri et al. 1997). Finally, long-term treatment with 5-HT_{1A} receptor agonists, such as gepirone, desensitizes the 5-HT_{1A} autoreceptor on 5-HT neurons, but not the postsynaptic 5-HT_{1A} receptors located on CA₃ pyramidal neurons (Blier and de Montigny, 1987).

Recently, novel direct evidence of an enhanced 5-HT neurotransmission by antidepressant treatments has been provided (Hadjjeri et al. 1998a). This study showed that long-term treatment with either the TCA imipramine, the SSRI paroxetine, the selective and reversible MAO-A inhibitor biefloxatone, the α_2 -adrenergic antagonist mirtazapine, the 5-HT_{1A} receptor agonist gepirone, as well as repeated ECS administration, enhanced the tonic activation of postsynaptic 5-HT_{1A} receptors in the dorsal hippocampus, as put into evidence by the enhanced disinhibition produced by the acute administration of the selective 5-HT_{1A} receptor antagonist WAY 100635 (Hadjjeri et al. 1998a). Furthermore, no disinhibition was detectable in rats treated for 3 weeks with the neuroleptic chlorpromazine or in rats receiving only one ECS, two treatment modalities devoid of antidepressant effect. Finally, that 5-HT_{1A} receptors mediate the disinhibition induced by WAY 100635 is further supported by the observation that the inactivation of the G_{i/o} proteins by pertussis toxin prevented the disinhibition in rats treated with repeated ECS (Hadjjeri et al. 1998a). Finally, it was recently reported that WAY 100635 inhibits CA1 pyramidal neurons firing activity in naive, but not in 5-HT depleted, freely moving rats (Susuki et al. 1999).

Lithium remains a first-line approach for treatment of acute mania and the prophylactic management of manic-depressive illness (see Lenox et al. 1998, for review). Interestingly, lithium is also a useful augmentation strategy in the treatment of depression (de Montigny et al. 1981; Rouillon and Gorwood 1998). Although the underlying neurobiological mechanism remains as yet not fully defined, there is a considerable body of preclinical evidence reporting an increase in 5-HT neurotransmission following lithium administration (Baptista et al. 1990; Grahame-Smith and Green 1974; Treiser et al. 1981; Blier and de Montigny 1985;

Goodwin et al. 1986; Goodwin 1989; Price et al. 1990b; Sangdeed and Franz 1980; Sharp et al. 1991).

The present study was undertaken to determine whether an association of lithium with various types of antidepressant treatments could act in synergy to enhance 5-HT neurotransmission. Thus, the effects of short-term lithium diet and long-term treatment with the TCA imipramine, the type A and B MAOI tranylcypromine and the SSRI paroxetine, given alone and in combination, were assessed on the degree of activation of postsynaptic 5-HT_{1A} receptors, using an in vivo electrophysiological paradigm in the rat dorsal hippocampus.

METHOD

Animals and Treatments

Male Sprague-Dawley rats (Charles-River, Quebec, Canada) weighing 250–300 g on the day of the experiment were used. The animals were maintained on a 12:12 hours light:dark cycle with free access to food and water. Rats were treated for 21 days with either imipramine (10 mg/kg/day), paroxetine (10 mg/kg/day), or tranylcypromine (2.5 mg/kg/day), using osmotic minipumps (ALZA, Palo Alto, CA, USA) implanted subcutaneously under halothane anesthesia. These drugs were dissolved in a water/ethanol solution (50/50, v/v), and the rats received 0.75 ml of 95% ethanol over a period of 21 days. For each series of experiments, controls were implanted with a minipump filled with the same vehicle as the corresponding treated groups. All the experiments were carried out with the minipumps on board. Rats were fed lithium-containing chow (Ren's Feed & Supplies Ltd, Oakville, ON) for 72 h preceding the electrophysiological experiments. Plasma lithium levels were determined following all experiments by flame emission photometry and ranged from 0.4 to 1.1 mEq/l. None of these treatments altered the normal behavior of the animals in their cages or upon handling. The drug regimens have been chosen on the basis of previous experiments indicating effective doses (de Montigny and Aghajanian 1978; Blier and de Montigny 1985; Goodnough and Baker 1994; Piñeyro et al. 1994).

Electrophysiological Procedures

Rats were anesthetized with chloral hydrate (400 mg/kg, IP) and were mounted in a stereotaxic apparatus. Additional doses (100 mg/kg, IP) were given to maintain the anesthesia along the experiment.

Extracellular Recording and Microiontophoresis from Dorsal Hippocampus CA₃ Pyramidal Neurons. A hole was drilled 4.2 mm lateral and 4.2 mm anterior to

lambda. Extracellular recordings of dorsal hippocampus CA₃ pyramidal neurons and microiontophoretic applications of 5-HT were performed with five-barreled glass micropipettes pulled in the conventional manner to achieve a tip diameter of 10–15 μ m. The central recording barrel was filled with a 2 M NaCl solution saturated with fast green dye. One of the side barrels was filled with quisqualic acid (1.5 mM in 400 mM NaCl, pH 8), because a leak or a small ejection current (+2 to –3 nA) of quisqualate was needed to activate the CA₃ pyramidal neurons within their physiological range, because they are not spontaneously active in anesthetized animals. These neurons were identified according to the criteria of Kandel and Spencer (1961): large amplitude and long duration complex spike discharges. A side-barrel was filled with 5-HT (2 mM in 200 mM NaCl, pH 4). A 10 nA ejection current of 5-HT was used, each ejection period lasting 50 seconds. One barrel was filled with 2 M NaCl and served as an automatic current balance.

To assess the effectiveness of the long-term treatment with paroxetine, the recovery time 50 (RT_{50}) method was used. The RT_{50} value has been shown to be a reliable index of the in vivo activity of the 5-HT reuptake process in the rat hippocampus. This value is obtained by calculating the time in seconds required for the neuron to recover 50% of its initial firing rate at the end of the microiontophoretic application of 5-HT onto the CA₃ pyramidal neuron. Thus, the blockade of the 5-HT transporter by an SSRI reveals a greater RT_{50} value than in controls (Piñeyro et al. 1994). The neuronal responsiveness to 5-HT was assessed using the $I \cdot T_{50}$ method. It is the product of the current (in nA) used to eject 5-HT from the micropipette and the time (in sec) required to obtain a 50% decrease from the baseline of the firing rate of the recorded neuron. The more sensitive a neuron is to 5-HT, the smaller will be the $I \cdot T_{50}$ value, because the number of molecules ejected is proportional to the charge (de Montigny and Aghajanian 1978).

The tonic activation of the postsynaptic 5-HT_{1A} receptors of the dorsal hippocampus CA₃ pyramidal neurons was assessed in the following manner. The firing rate of dorsal hippocampus CA₃ pyramidal neurons was determined before and after systemic injection of the selective 5-HT_{1A} receptor antagonist WAY 100635, via a cannula inserted in a lateral tail vein, in control and treated groups. It is well established that the suppression of the firing activity of CA₃ pyramidal neurons by microiontophoretic applied 5-HT is mediated through the activation of 5-HT_{1A} receptors (Chaput and de Montigny 1988; Blier et al. 1993). Thus, the blockade of these 5-HT_{1A} receptors by WAY100635 will disinhibit the CA₃ hippocampus pyramidal neurons resulting in an increase of their firing activity (Haddjeri et al. 1998a). In this series of experiments, the current of quisqualate was adjusted in order to obtain a firing rate around 4 Hz to allow the detection of enhancements in

firing more readily following administration of WAY 100635. This baseline firing was recorded for at least 2 minutes before the IV injection of WAY 100635. An IV injection of saline preceded the first injection of WAY 100635 to eliminate any effect attributable to the injection by itself. Doses of WAY 100635 (25 μ g/kg, IV) were administered at time intervals of 1 to 2 minutes, and only one neuron was studied in each rat. WAY 100635, administered IV, does not modify the firing rate of 5-HT neurons in the dorsal raphe nucleus of the anesthetized rats but restores 5-HT neuronal firing if it was reduced by 5-HT_{1A} autoreceptor activation (Forster et al. 1995; Gartside et al. 1995; Lejeune and Millan 1998). Therefore, in treated animals, where there would be increased extracellular levels of 5-HT in the raphe region, WAY 100635 would restore 5-HT neuronal firing activity. However, because WAY 100635 was given systemically, it would be simultaneously blocking the effects of 5-HT on postsynaptic neurons, thereby canceling out the effect of WAY 100635 on the somatodendritic autoreceptors. Indeed, if the action of WAY 100635 at the somatodendritic 5-HT_{1A} autoreceptors was influencing the activity of the hippocampal neurons, it would serve to inhibit further their firing due to an increased release of 5-HT into the target area. Thus, it can be assumed that any increment in the firing activity of hippocampus pyramidal neurons would reflect an increased level in the tonic activation of the postsynaptic 5-HT_{1A} receptors and the degree to which WAY 100635 disinhibits this firing would presumably be a direct measure of the tonic level of activation of 5-HT_{1A} receptors on CA₃ pyramidal neurons by extracellular 5-HT. However, because WAY 100635 is injected systemically, it cannot be ruled out that such an effect of this agent could be attributable to its antagonistic action on postsynaptic 5-HT_{1A} receptors projecting to the hippocampus. Nevertheless, an enhanced effect would still be a reflection of an increased 5-HT transmission by the treatments studied.

Statistical Analysis

Results are expressed as the mean \pm SEM. Dunnett's method multiple comparison test following one-way analysis of variance was employed in the RT_{50} and $I \cdot T_{50}$ methods and in the experiments with WAY 100635. The criterion for significance was taken as $p \leq .05$.

Drugs

Paroxetine was provided by SmithKline Beecham (Harlow, UK), imipramine by Ciba-Geigy (Montréal, Canada) and WAY100635 by Wyeth-Ayerst (Princeton, NJ, USA). Tranylcypromine, 5-HT creatinine sulfate and quisqualic acid were purchased from Sigma Chemical Co. (St Louis, MO, USA).

RESULTS

Effects of Long-Term Antidepressant Treatments on the Responsiveness of Dorsal Hippocampus CA₃ Pyramidal Neurons to 5-HT

It has been previously demonstrated that the microiontophoretic application of 5-HT onto rat dorsal hippocampus CA₃ pyramidal neurons produces a suppressant effect on their firing activity via the activation of postsynaptic 5-HT_{1A} receptors (Blier and de Montigny 1987; Chaput and de Montigny 1988). For all CA₃ pyramidal neurons tested, 5-HT (10 nA) induced a reduction of firing activity (Figure 1). This inhibitory effect of 5-HT occurred without any alteration of the action potential shape, thus ruling out current artifact in altering firing pattern. Long-term treatment with tranylcypromine or with paroxetine alone or in combination with a short-term treatment with lithium did not modify the suppressant effect of microiontophoretically applied 5-HT on the firing activity of CA₃ pyramidal neurons. On the other hand, long-term treatment with imipramine alone or in combination with lithium markedly enhanced the responsivity of CA₃ pyramidal neurons to microiontophoretically applied 5-HT: the mean $I \cdot T_{50}$ value for 5-HT was significantly lower in rats treated with imipramine alone or in combination with lithium than in controls or in rats having a short-term lithium diet (Figure 2A).

The mean RT_{50} value for 5-HT was increased by 78% in paroxetine-treated rats and by 57% in rats treated with paroxetine in combination with lithium, because of the blockade of the 5-HT uptake process (Figure 2B). No significant change in the RT_{50} value for 5-HT was observed in the other groups (Figure 2B).

As previously reported (Haddjeri et al. 1998a,b), the intravenous administration of the selective 5-HT_{1A} receptor antagonist WAY 100635 (100 µg/kg) significantly reduced the suppressant effect of 5-HT on CA₃ pyramidal neurons in control rats (Figure 1). WAY 100635 significantly reduced the suppressant effect of 5-HT on the firing activity of CA₃ pyramidal neurons by 73% in controls ($t = 10.38$, $df = 6$, $p < .001$), 71% in lithium-treated rats ($t = 6.72$, $df = 6$, $p < .001$), 80% in imipramine-treated rats ($t = 10$, $df = 5$, $p < .001$) and 76% in rats treated with imipramine followed by a lithium diet ($t = 9.62$, $df = 4$, $p < .001$).

Tonic Activation of the Postsynaptic 5-HT_{1A} Receptors on the Dorsal CA₃ Hippocampus Pyramidal Neurons by Antidepressants

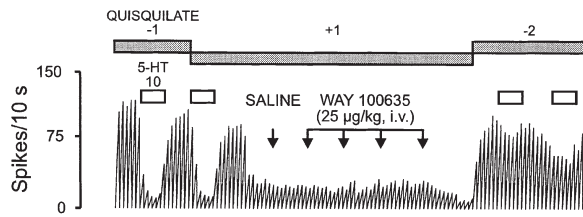
As mentioned in the Materials and Methods section, the dorsal hippocampus CA₃ pyramidal neurons were activated by a leak or a small current of quisqualate. It is important to mention that none of the treatments used

significantly modified the firing activity of the dorsal hippocampus CA₃ pyramidal neurons when compared to controls (-0.1 ± 0.5 nA of quisqualate resulted in a firing activity of 3.8 ± 0.6 Hz, $n = 9$; in rats having received a lithium diet, the application of 0.1 ± 0.6 nA of quisqualate resulted in a firing activity of 4.6 ± 0.7 Hz, $n = 7$; in imipramine-treated rats, 0.2 ± 0.5 nA of quisqualate resulted in a firing activity of 3.5 ± 0.6 Hz, $n = 6$; in rats treated with both imipramine and lithium, -0.3 ± 0.6 nA of quisqualate resulted in a firing activity of 3.6 ± 0.7 Hz, $n = 6$; data not shown for the other groups). This was expected, because the only pretreatment that altered this parameter was the destruction of 5-HT neurons (Blier and de Montigny 1987).

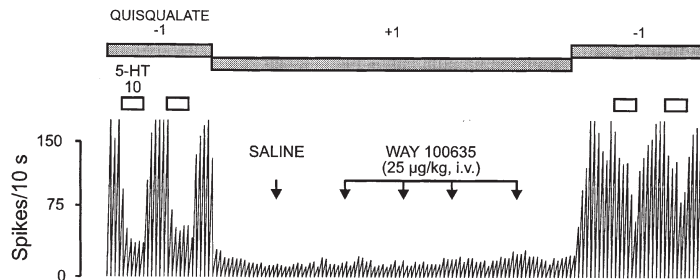
As illustrated in Figure 1, the prior injection of saline did not alter the firing activity of the dorsal hippocampus CA₃ pyramidal neurons in control and treated rats. The IV injection of WAY 100635 also did not modify the firing activity of CA₃ pyramidal neurons in control rats (Figures 1A and 3). In rats having a lithium diet for 3 days, the responsiveness of CA₃ pyramidal neurons to IV injections of WAY 100635 was similar to that of the control rats ($t = -0.2$, $df = 14$, $p = .84$; Figures 1B and 3). On the other hand, in rats treated for 21 days with either tranylcypromine or paroxetine, significant increases in the mean firing rate of CA₃ pyramidal neurons were observed in response to the IV injection of 50 µg/kg of WAY 100635, but not with a dose of 25 µg/kg. This increase was of 37% in rats treated with imipramine ($t = -2.2$, $df = 12$, $p < .05$; Figure 3), of 59% in rats treated with paroxetine ($t = -5.7$, $df = 12$, $p > .05$, Figure 3) and of 80% in rats treated with tranylcypromine ($t = -2.76$, $df = 12$, $p < .05$; Figure 3).

In contrast, in rats treated with imipramine for 21 days in combination with the lithium diet, a dose of only 25 µg/kg (IV) of WAY 100635 increased by 75% the firing activity of hippocampus CA₃ pyramidal neurons (Figure 3); hence, this firing rate was significantly greater than that obtained in controls or in imipramine-treated rats for a dose of 25 µg/kg of WAY 100635 ($t = -5.51$, $df = 13$, $p < .001$; Figure 3). Similarly, in rats treated with tranylcypromine for 21 days in combination with a lithium diet, a dose 25 µg/kg (IV) of WAY 100635 produced a robust increase of 182% of the firing activity of hippocampus CA₃ pyramidal neurons ($t = -5.47$, $df = 13$, $p < .001$; Figure 3); whereas, following the IV injection of a dose 25 µg/kg (IV) of WAY 100635 in rats treated with tranylcypromine alone, the firing rate was not significantly different than in controls ($t = -1.23$, $df = 13$, $p > .24$; Figure 3). Finally, and as previously reported (Besson et al. 1997), in rats treated with paroxetine for 21 days, the IV injection of a dose 25 µg/kg (IV) of WAY 100635 did not affect the firing activity of hippocampus CA₃ pyramidal neurons ($t = -0.41$, $df = 13$, $p > .68$; Figure 3). On the other hand, the same dose of WAY 100635

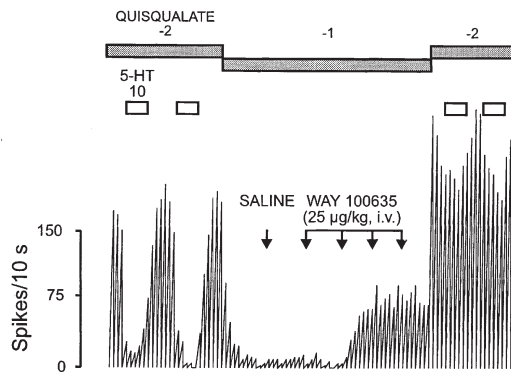
A CONTROL



B LITHIUM DIET (3 days)



C IMIPRAMINE (10 mg/kg/day x 21 days)



D IMIPRAMINE (10 mg/kg/day x 21 days) + LITHIUM DIET (3 days)

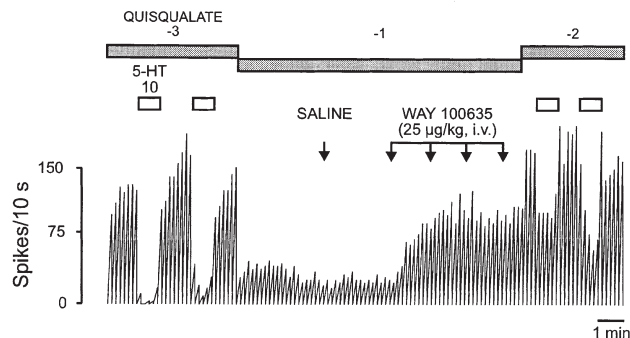


Figure 1. Integrated firing rate histogram of a dorsal hippocampus CA₃ pyramidal neuron, showing its responsiveness to microiontophoretic application of 5-HT in control (A); a rat having received a lithium diet for 3 days (B); a rat treated with imipramine for 21 days (C); and a rat having both a treatment with imipramine and a lithium diet (D). These neurons were activated with a quisqualate ejection current. Horizontal bars indicate the duration of the applications (current given in nanoAmperes). Note the altered effectiveness of 5-HT in suppressing firing activity after administration of WAY 100635 (4 × 0.25 mg/kg, IV) in control rat and treated rats.

increased by 104% the firing activity of hippocampus CA₃ pyramidal neurons in rats treated with paroxetine for 21 days in combination with a lithium diet ($t = -5.06$, $df = 14$, $p < .001$; Figure 3).

DISCUSSION

The main point of interest that emerges from the present electrophysiological experiments is that the en-

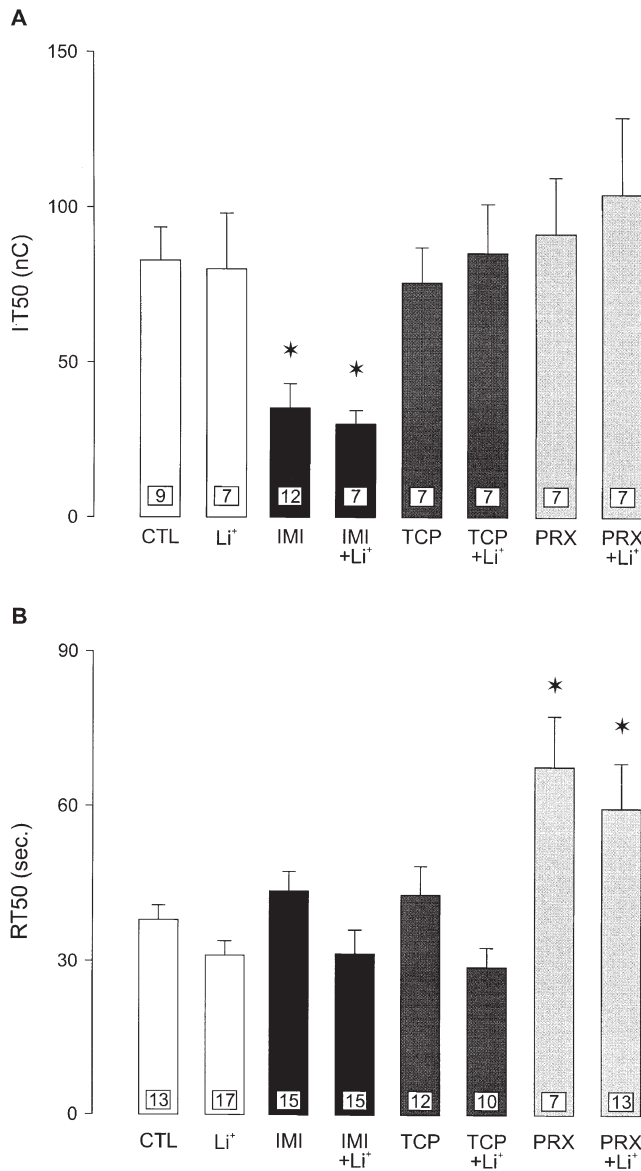


Figure 2. (A) Mean (\pm SEM) $I-T_{50}$ values (see the Method section) in control rats (CTL), rats having a lithium diet (Li^+), rats treated with imipramine for 21 days (10 mg/kg/day, SC, IMI), rats treated with imipramine and having a lithium diet (IMI + Li^+), rats treated with tranylcypromine for 21 days (2.5 mg/kg/day, SC, TCP), rats treated with tranylcypromine and having a lithium diet (TCP + Li^+), rats treated with paroxetine for 21 days (10 mg/kg/day, SC, PRX) and rats treated with paroxetine and having a lithium diet (PRX + Li^+). The number in the columns indicates the number of neurons tested. * $p < .05$ (unpaired Student's t test). (B) Recovery time, expressed as RT_{50} values (means \pm SEM), of dorsal hippocampus CA₃ pyramidal neurons from the microiontophoretic application of 5-HT in control rats (CTL), rats having a lithium diet (Li^+), rats treated with imipramine for 21 days (10 mg/kg/day, SC, IMI), rats treated with imipramine and having a lithium diet (IMI + Li^+), rats treated with tranylcypromine for 21 days (2.5 mg/kg/day, SC, TCP), rats treated with tranylcypromine and having a lithium diet (TCP + Li^+), rats treated with paroxetine for 21

hanced tonic activation of postsynaptic 5-HT_{1A} receptors induced by long-term treatments with imipramine, tranylcypromine, and paroxetine was greater when a lithium diet was added; whereas, lithium alone did not modify this parameter. Hence, it is suggested that lithium addition in treatment-resistant depression might be attributable to a potentiation of 5-HT neurotransmission.

Among the 5-HT_{1A} receptor antagonists available, WAY 100635 is by far the most potent and selective antagonist at both pre- and postsynaptic 5-HT_{1A} receptors (Khawaja et al. 1994; Fletcher et al. 1996). The present results confirm that WAY 100635 is, indeed, an effective antagonist at postsynaptic 5-HT_{1A} receptors, because it reduced the suppressant effect of microiontophoretically applied 5-HT on the firing activity of CA₃ pyramidal neurons (Figure 1). If the tonic activation of postsynaptic 5-HT_{1A} receptors is increased, one could then expect that the blockade of these receptors by WAY100635 would result in an enhancement of the baseline firing activity of CA₃ pyramidal neurons. However, WAY 100635 (25 to 100 μ g/kg, IV) did not produce any disinhibition on dorsal hippocampus CA₃ pyramidal neurons in control rats (Figures 1 and 3). This result indicates the lack of a tonic activation of postsynaptic 5-HT_{1A} receptors in the anesthetized untreated rats. It is also noteworthy that no disinhibition of CA₃ pyramidal neurons was detected following short-term treatments with various antidepressants (Besson et al. 1997). Similarly, in rats receiving a lithium diet for 3 days, WAY 100635 did not induce any significant disinhibition of CA₃ pyramidal neurons. The capacity of WAY 100635 to block the somatodendritic 5-HT_{1A} autoreceptor is not expected to alter its effectiveness in disinhibiting postsynaptic neurons in the paradigm used in the present study. Indeed, any interference of WAY 100635 at the somatodendritic 5-HT_{1A} autoreceptor would dampen this disinhibitory effect at postsynaptic 5-HT_{1A} receptors, because in the presence of an SSRI in freely moving cats (Fornal et al. 1996) and of biefloxatone in anesthetized rats (Haddjeri et al. 1998b), WAY 100635 increases the firing of 5-HT neurons. As described in the Materials and Methods section, the CA₃ pyramidal neurons are activated by quisqualate, hence, it is important to mention that lithium can also affect glutamate neurotransmission. In fact, it has been shown that lithium blocks the uptake of glutamate from cerebral cortex slices of monkey and mouse (Dixon et al. 1994; Dixon and Hokin 1997). Moreover in the

days (10 mg/kg/day, SC, PRX) and rats treated with paroxetine and having a lithium diet (PRX + Li^+). The number in the columns indicates the number of neurons tested. * $P < .05$ significantly different from control group by Dunnett's test following ANOVA.

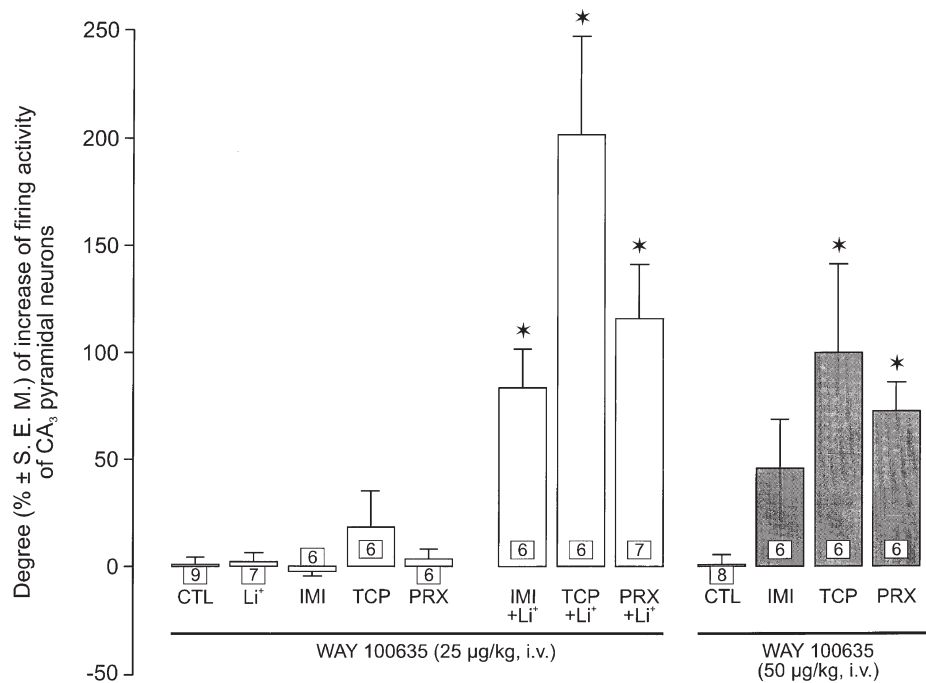


Figure 3. Changes (% \pm S.E.M.) of the firing activity of quisqualate-activated dorsal hippocampus CA₃ pyramidal neurons following intravenous injection of WAY 100635 (25 and 50 μ g/kg) in control rats (CTL), in rats treated with imipramine (IMI), paroxetine (PRX), tranylcypromine (TCP), and in rats treated with both imipramine and lithium (IMI + Li⁺), tranylcypromine and lithium (TCP + Li⁺), or paroxetine and lithium (PRX + Li⁺). One neuron per rat was tested and the number for each column indicates the number of neurons or rats tested. * p < .05 significantly different from control group by Dunnett's test following ANOVA.

mouse, chronic treatment with lithium for 2 weeks up-regulated synaptosomal uptake of glutamate (Dixon and Hokin 1998). Nevertheless, these effects of lithium most likely did not interfere with the present results, because the level of activation of hippocampus neurons induced by quisqualate was not different in any group of rats. Accordingly, it has been recently shown that a short-term lithium treatment (5 days) does not modify the neuronal activity, by assessing the cytochrome oxidase activity, in several brain regions, including the hippocampus (Lambert et al. 1999).

In the present study, WAY100635, at a dose of 50 μ g/kg, induced a significant disinhibition of the firing activity of CA₃ pyramidal neurons in rats treated with tranylcypromine or paroxetine for 21 days. It is suggested that the tonic enhanced activation of postsynaptic 5-HT_{1A} receptors observed after the long-term treatment with paroxetine is accounted for by higher levels of 5-HT in the CA₃ region of the hippocampus, as a result of the recovery of the firing rate of 5-HT neurons associated with the blockade of 5-HT reuptake (Besson et al. 1997; Figure 2B). This assumption is consistent with previous studies showing increased extracellular concentrations of 5-HT in terminal brain areas (frontal cortex, hypothalamus) after long-term SSRI treatment (Bel and Artigas 1992; Rutter et al. 1994), resulting from the desensitization of 5-HT_{1A} and 5-HT_{1B} autoreceptors (Chaput et al. 1986, 1991; Rutter et al. 1994). The enhanced tonic activation of postsynaptic 5-HT_{1A} receptors observed after the long-term treatment with tranylcypromine can also be explained by increased levels of 5-HT in the CA₃ hippocampus resulting, as for other MAOIs, from the recovery of the firing rate of 5-HT

neurons associated with the desensitization of α_2 -adrenergic heteroreceptors located on the terminals of 5-HT neurons (Blier et al. 1986; Ferrer and Artigas 1994; Mongeau et al. 1994). Finally, it is suggested that the enhanced tonic activation of postsynaptic 5-HT_{1A} receptors observed after the long-term imipramine treatment occurred presumably through a sensitization of the postsynaptic 5-HT_{1A} receptors (de Montigny and Aghajanian 1978; Figure 2A). On the other hand, no disinhibition was detectable in rats treated for 3 weeks with the neuroleptic chlorpromazine or in rats receiving only one ECS, two treatment modalities devoid of antidepressant effect (Haddjeri et al. 1998a). However, in the dorsal hippocampus, 5-HT has been also shown to increase neuronal excitability via non-5-HT_{1A} receptors such as 5-HT₂/5-HT₄/5-HT₇ subtypes (Beck 1992; Torres et al. 1996; Beck and Bacon 1998). That 5-HT_{1A} receptors mediate the disinhibition induced by WAY 100635 is further supported by the observation that the inactivation of the G_{i/o} proteins by pertussis toxin prevented the disinhibition in rats treated with repeated ECS (Haddjeri et al. 1998a). However, 5-HT receptors other than those of the 5-HT_{1A} subtype may also be involved in the antidepressant response. Indeed, it has been demonstrated that some postsynaptic 5-HT receptors, other than the 5-HT_{1A} subtype, become sensitized following long-term antidepressant treatments. For example, repeated TCA administration sensitizes postsynaptic 5-HT₂ receptors in the facial motor nucleus and a yet uncharacterized 5-HT receptor subtype in the amygdala (Menkes et al. 1980; Wang and Aghajanian 1980).

Although the mechanism of action of lithium is not yet fully defined, there is, however, a growing body of

evidence suggesting that this agent acts in bipolar disorder by affecting the levels of intracellular second messengers; that is, the activity of adenylate cyclases, the function of G protein, the activity of inositol monophosphatases, and the level or the function of protein kinases (Mørk 1993; Jope and Williams 1994; Manji et al. 1995; Mørk and Geisler 1995; Bitsch Jensen and Mørk 1997; Wang and Friedman 1999). Central 5-HT function has also been shown to be affected by lithium administration, although its effect on the 5-HT system differs according to the duration of treatment and the brain region studied (Goodwin 1989; Price et al. 1990b). Accordingly, it has been shown that acute, but not chronic, lithium administration increases rat brain 5-HT turnover (Grahame-Smith and Green 1974; Minegishi et al. 1981; Karoum et al. 1986). Acute treatment with lithium potentiates the tranylcypromine- plus l-tryptophan-induced 5-HT syndrome in the rat, a syndrome sensitive to stimulation of 5-HT synthesis (Grahame-Smith and Green 1974). Chronic lithium has been shown to increase 5-HT release from rat cortical, hippocampal, and hypothalamic brain slices, possibly resulting from down-regulation of 5-HT autoreceptors (Treiser et al. 1981; Wang and Friedman 1988). Moreover, Hotta and Yamawaki (1988) showed that the inhibitory effect of 5-HT on the KCl- or electrically evoked release of tritiated 5-HT, presumably mediated by presynaptic 5-HT autoreceptors, was attenuated in the hippocampus, but not frontal cortex, after a 3-day lithium treatment, and a significant increase in the release of 5-HT was observed in the hippocampus, but not in the frontal cortex. On the other hand, it has been shown that short-term lithium treatment does not affect dorsal raphe 5-HT neuronal firing rate but augments the endogenous release of 5-HT in the rat dorsal hippocampus induced by the electrical stimulation of the ascending 5-HT pathway, without affecting the sensitivity of terminal 5-HT autoreceptors (Blier and de Montigny 1985; Blier et al. 1987). This enhancing effect of lithium on 5-HT release has been proposed to be attributable to an increased amount of 5-HT released per impulse, because the responsiveness of hippocampal neurons to 5-HT (Figure 1) and to the 5-HT_{1A} receptor agonist 8-OH-DPAT, applied by microiontophoresis, was not modified by the short-term lithium treatment (Blier et al. 1987). Similarly, using microdialysis, the release of 5-HT in the hippocampus, evoked by electrical stimulation of the dorsal raphe nucleus, was markedly enhanced in treated rats with lithium for 3 days, but not 21 days. The same group showed *in vitro* that the depolarization (high potassium)-evoked release of endogenous 5-HT from the hippocampus was increased in lithium-treated rats after 3 days, but not 21 days (Sharp et al. 1991). Moreover, a reduced concentration of 5-HT in rat hippocampal dialysates has been observed after 21 days of treatment with lithium (Sharp et al. 1991). In contrast,

Pei et al. (1995) have shown that long-term (21 days), but not short-term (3 days), lithium treatment enhances the stimulating effect on 5-HT efflux *in vivo* in the rat hippocampus (but not in striatum) induced by the potassium-channel blocking drug 4-aminopyridine. However, this group did not observe any changes in basal outflow of hippocampal 5-HT from lithium-treated rats versus controls (Pei et al. 1995). Taken together, all these experiments clearly show that lithium has the capacity to enhance 5-HT release, but some experimental conditions in laboratory animals may alter this potential.

Only a few preclinical studies have been undertaken to characterize the effects of lithium addition to antidepressant treatment on the 5-HT system. As initially proposed by Newman et al. (1990), Okamoto et al., (1996) have also recently suggested that the therapeutic action of lithium, when added to antidepressants in the treatment of refractory depression, may partly have its basis in a further activation of the 5-HT system. In fact, they showed, *in vitro* in the rat frontal cortex, that the addition of lithium for a short-term (5 days) to a long-term (19 days) period with the TCA clomipramine and the SSRI citalopram potentiated an increase in 5-HIAA level, but not that of 5-HT; whereas, lithium alone had no effect. In addition, they reported that binding parameters of 5-HT_{1A} receptors and 5-HT transporters, using rat cortical membranes, remain unchanged by such treatments; whereas, that of 5-HT₂ receptors were reduced by the clomipramine treatment alone and in combination with lithium. The efficacy of lithium augmentation of the antidepressant response, which is now supported by several placebo-controlled studies (see for review Rouillon and Gorwood 1998), may be at variance with some long-term studies not showing an enhanced 5-HT release. However, short-term lithium addition consistently produces an increase of 5-HT neurotransmission, which may be sufficient to obtain a clinical response. The latter discrepancy may not be so crucial, because it is not yet known how long 5-HT neurotransmission has to be potentiated in order to produce or maintain an antidepressant effect. Indeed, it was observed that some treatment-resistant patients maintained an antidepressant effect even if lithium addition was abruptly stopped immediately after obtaining a therapeutic response (de Montigny et al. 1983).

In summary, the present study showed that lithium addition to antidepressant drugs induced a greater enhancement of the tonic activation of postsynaptic 5-HT_{1A} receptors in rat dorsal hippocampus than any drug given alone. In the light of previous evidence of the key role of the postsynaptic 5-HT_{1A} receptor site in the therapeutic effects of antidepressant drugs (Blier and de Montigny 1994), it can be proposed from the present results that the addition of lithium to antidepressants potentiates the antidepressant response by further enhancing 5-HT neurotransmission.

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