Effects of sustained (±)pindolol administration on serotonin neurotransmission in rats

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Objective: Given reports that (±)pindolol, a β-adrenergic-5-HT₁A/1B receptor antagonist, accelerates the onset of the therapeutic effect of certain antidepressant drugs in major depression, the aim of this study was to assess the effect of sustained (±)pindolol administration on the sensitivity of pre- and postsynaptic 5-HT₁A receptors, terminal 5-HT₁A autoreceptors and on overall 5-HT neurotransmission. Design: Prospective animal study. Animals: Sprague-Dawley rats. Outcome measures: Modifications of the sensitivity of somatodendritic and postsynaptic 5-HT₁A receptors using in vivo electrophysiological paradigms in animals treated with vehicle or (±)pindolol (20 mg/kg/day, subcutaneously) through osmotic minipumps for 2 weeks. Results: (±)Pindolol attenuated the suppressant effect of the 5-HT autoreceptor agonist lysergic acid diethylamide (LSD) on the firing activity of 5-HT neurons, suggesting that (±)pindolol antagonized somatodendritic 5-HT₁A autoreceptors in the dorsal raphe nucleus. However, following a 2-day washout period, the suppressant effect of LSD was still attenuated, indicating rather a desensitization of 5-HT₁A autoreceptors had occurred. In the CA3 region of the dorsal hippocampus, (±)pindolol treatment did not modify the responsiveness of postsynaptic 5-HT₁A receptors to microiontophoretic applications of 5-HT. Moreover, such a treatment modified neither the effectiveness of the electrical stimulation of 5-HT fibers nor the function of terminal 5-HT₁A autoreceptors. Finally, the administration of the selective 5-HT₁A receptor antagonist WAY 100635 (100 μg/kg, intravenously) did not increase the firing activity of dorsal hippocampus CA1 pyramidal neurons in rats treated with (±)pindolol, thus failing to reveal the enhanced tonic activation of postsynaptic 5-HT₁A receptors associated with major classes of antidepressant treatments. Conclusion: Prolonged administration of (±)pindolol by itself is not sufficient to enhance overall 5-HT neurotransmission; pindolol should therefore not be endowed with intrinsic antidepressant activity. Although pindolol is capable of antagonizing the 5-HT₁A autoreceptor upon the initiation of a 5-HT reuptake-blocker treatment, it also induces a desensitization of this 5-HT₁A autoreceptor, which could explain why patients do not relapse upon its discontinuation when they continue taking a 5-HT reuptake blocker.

Objectif : Des études cliniques ont récemment démontré que le (±)pindolol, un antagoniste des récepteurs β-adrenergic/5-HT₁A/1B, accélérait la réponse thérapeutique de certains médicaments antidépresseurs chez des patients atteints de dépression majeure. Le but de la présente étude était d’évaluer les effets d’une administration prolongée de (±)pindolol sur la sensibilité des récepteurs pré et postsynaptiques 5-HT₁A...
Introduction

Although the pathophysiology of major depression has not been elucidated, there is a growing body of evidence that supports the involvement of the serotonergic (5-HT) system in the therapeutic effect of antidepressant treatments. Various classes of antidepressant treatments enhance 5-HT neurotransmission with a time course that is consistent with their delayed therapeutic effect. This would be mediated via different mechanisms such as postsynaptic sensitization to 5-HT, desensitization of the somatodendritic or terminal 5-HT autoreceptors, or both, or a desensitization of α2-adrenergic heteroreceptors located on 5-HT terminals.

A novel strategy to accelerate the antidepressant response of medications acting on 5-HT neurons is to combine the aryalkylamine (±)pindolol, a β-adrenergic–5-HT1A/B receptor antagonist, with a selective serotonin reuptake inhibitor (SSRI), a monoamine oxidase inhibitor (MAOI) or a 5-HT1A receptor agonist from the beginning of a treatment to obtain a more rapid onset of antidepressant action. Although negative results have been reported by one group, there are now 7 placebo-controlled studies showing that this approach can result in a rapid onset of action and, in some cases, a greater efficacy in treating major depression. Accordingly, preclinical studies have shown that (±)pindolol can potentiate the enhancing effect of SSRIs on extracellular 5-HT concentration by preventing the activation of somatodendritic 5-HT1A autoreceptors. Paradoxically, however, the active enantiomer, (−)pindolol, possesses some partial agonist activity at human 5-HT1A receptors, and it has been shown that its intravenous administration can decrease the firing activity of dorsal raphe 5-HT neurons in freely-moving cats and anesthetised rats. These results appear incompatible with a potentiation of extracellular 5-HT levels in postsynaptic structures resulting from 5-HT1A autoreceptor blockade by pindolol when given in combination with SSRIs. Nevertheless, a biphasic effect of pindolol on the firing activity of 5-HT neurons has been reported recently. At low doses, (±)pindolol acts as a somatodendritic 5-HT1A autoreceptor antagonist, but at a higher dose, it decreases the firing rate of 5-HT neurons, in part by attenuating the tonic excitatory input from noradrenergic neurons to 5-HT neurons.

To mimic as much as possible the clinical condition in which pindolol has been given 3 times daily in double-blind trials, we treated rats with (±)pindolol for 2 weeks and used in vivo electrophysiological paradigms in the rat dorsal raphe and dorsal hippocampus to assess the effect of sustained treatment with a constant infusion of (±)pindolol on the sensitivity of pre- and postsynaptic 5-HT1A receptors and terminal 5-HT1B autoreceptors and on overall 5-HT neurotransmission.
Methods

Male Sprague-Dawley rats (Charles River Laboratories, St-Constant, Que.) weighing 250 to 300 g were kept under standard laboratory conditions (12-hour light–dark cycle with free access to food and water). Groups of 12 to 22 rats were treated for 2 weeks with (±)pindolol (20 mg/kg/day) or vehicle (saline), delivered by osmotic minipumps (ALZA, Palo Alto, Calif.) inserted subcutaneously. The rats were tested with the minipumps in place, and some were also tested after a 2-day washout period to allow for drug elimination. Animals were anesthetized with chloral hydrate (400 mg/kg, given intraperitoneally) for recordings, and supplemental doses were given to maintain constant anaesthesia and to prevent any nociceptive reaction to a tail pinch.

Drugs

(±)Pindolol, WAY 100635 ((N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexancarboxamide trihydroxychloride), 8-OH-DPAT, quisqualic acid and prazosin (see Fig. 1) were purchased from Research Biochemicals (Natick, Mass.), methiothepin maleate from Hoffmann-La Roche Ltd (Etobicoke, Ont.) and lysergic acid diethylamide (LSD) from Health Canada (Ottawa, Ont.). The concentrations and doses used were chosen on the basis of previous successful experiments carried out in our and other laboratories.

Extracellular recordings of dorsal raphe 5-HT neurons

Extracellular recordings were performed with single-barrelled glass micropipettes preloaded with fibreglass filaments to facilitate filling. The tip was broken back to 2–4 µm and filled with a 2 M NaCl solution. Rats were placed in a stereotaxic frame and a burr hole was drilled on the midline 1 mm anterior to lambda. Dorsal raphe 5-HT neurons were encountered over a distance of 1 mm, starting immediately below the ventral border of the Sylvius aqueduct. These neurons were identified using the criteria of Aghajanian (i.e., slow [0.5–2.5 Hz] and regular firing rate and long-duration [0.8–1.2 ms] positive action potentials). For the controls and 2-week treated rats, the responsiveness of 5-HT neurons was assessed using an intravenous injection of LSD (10 µg/kg) and of 8-OH-DPAT (5 µg/kg). In both the dorsal raphe nucleus and the dorsal hippocampus, the change of firing activity was assessed by calculating the mean of firing rate of neurons from about 1 to 2 minutes before the intravenous administration of the drugs and a mean after, until a plateau was reached. A percentage change was then calculated.

Recordings from CA3 dorsal hippocampus pyramidal neurons

Recording and microiontophoresis were performed with 5-barrelled glass micropipettes broken back to 8–12 µm under microscopic control (ASI Instruments, Warren, Mich.). The central barrel, used for extracellular unitary recordings, was filled with a 2 M NaCl solution. The side barrels contained the following solutions: 5-HT creatinine sulphate (2 mM in 200 mM NaCl, pH 4), quisqualate (1.5 mM in 200 mM NaCl, pH 8) and 2 M NaCl used for automatic current balancing. Rats were mounted in a stereotaxic apparatus, and the microelectrodes were lowered into the CA3 region of the dorsal hippocampus (4.2 mm lateral and 4.2 mm anterior to lambda). Pyramidal neurons were identified by their large amplitude (0.5–1.2 mV) and long-duration (0.8–1.2 ms) simple spikes that alternated with complex spike discharges. Since most hippocampal pyramidal neurons are not spontaneously active under chloral hydrate anaesthesia, a leak or a small ejection current of quisqualate (+1 nA to –4 nA) was used to activate them within their physiological firing range (10–15 Hz). Neuronal responsiveness to the microiontophoretic application of 5-HT was assessed by determining the number of spikes suppressed per nanoampere of ejection current. The duration of the microiontophoretic application of the agonist was 50 seconds, and the same ejection current was used before and after the intravenous injection of the selective 5-HT1A receptor antagonist WAY 100635 (100 µg/kg). Finally, to assess the degree to which postsynaptic 5-HT1A receptor activation was inhibiting CA3 pyramidal neuron firing activity, the ejection current of quisqualate was reduced to about 5 Hz to lower the firing rate, and WAY 100635 (100 µg/kg) was injected intravenously. Disinhibition would best be determined if the neuron was not already firing at high rate.

Electrical activation of afferent 5-HT fibers to the hippocampus

A bipolar electrode (NE-110; David Kopf, Tujunga, Calif.) was implanted on the midline with a 10° back-
ward angle in the ventromedial tegmentum to stimulate the raphe 5-HT fibres (1 mm anterior to lambda and 8.3 mm below the cortical surface). A stimulator (S8800; Grass Instruments, Quincy, Mass.) delivered 200 square pulses of 0.5 ms at a frequency of 1 Hz and an intensity of 300 µA. The stimulation pulses and the firing activity of the hippocampal neuron recorded were fed to an IBM-PC computer equipped with a Tecmar interface, and peristimulus time histograms were generated to determine the duration of suppression of firing activity of the CA3 pyramidal neuron, measured as absolute silence value (SIL) in milliseconds. This value was obtained by dividing the total number of events suppressed following the stimulation by the mean frequency of firing of the recorded neuron. The CA3 region of the hippocampus receives extensive innervation from 5-HT neurons of the dorsal and median raphe nuclei. This brief suppressant effect (about 50 ms with a stimulation of 300 µA), resulting from the electrical stimulation of the ascending 5-HT pathway, is due to the release of 5-HT for each impulse applied to the 5-HT axons and is mediated by postsynaptic 5-HT1A receptors. Thus, for the CA3 pyramidal neurons tested in control rats, the effect of the stimulation of the ascending 5-HT pathway was first determined before and after an intraperitoneal injection of (±)pindolol (20 mg/kg) and then after an intravenous injection of the 5-HT autoreceptor antagonist methiothepin (1 mg/kg). To determine the possible changes of the responsiveness of the terminal 5-HT autoreceptors, in each group, 2 series of stimulations (1 Hz and 5 Hz) were carried out while recording the same neuron, since it has previously been demonstrated in vitro and in vivo that the activation of terminal 5-HT autoreceptors decreases the release of 5-HT, and this reduction is enhanced by increasing the frequency of the stimulation.

Results

Effect of sustained administration of (±)pindolol on firing activity of dorsal raphe 5-HT neuron

It has been demonstrated that 5-HT neuron firing activity is dependent on the activation of somatodendritic 5-HT1A autoreceptors. Accordingly, and as illustrated in Fig. 1A, the intravenous administration of the 5-HT autoreceptor agonist LSD (10 µg/kg, given intravenously) suppressed the firing activity of dorsal raphe 5-HT neurons, and this suppressant effect was reversed by the selective 5-HT1A receptor antagonist WAY 100635 (100 µg/kg, intravenously). A 2-week treatment with (±)pindolol (20 mg/kg/day, given subcutaneously) sig-

Fig. 1: Integrated firing rate histograms of dorsal raphe 5-HT neurons showing their response to lysergic acid diethylamide (LSD; 10 µg/kg), WAY 100635 and prazosin in control rats (A), rats treated with (±)pindolol (20 mg/kg subcutaneously) for 14 days (B), and rats treated (±)pindolol for 14 days followed by a 2-day washout period (C). The α1-adrenoceptor antagonist prazosin was used to suppress 5-HT neuron firing activity through the blockade of this excitatory noradrenergic receptor. The degree of suppression of the firing of 5-HT neurons by LSD (% and standard errors of the means [SEM]) in controls and rats treated with (±)pindolol is summarized in D. The numbers within the histograms indicate the number of neurons or rats tested for each treatment (*p < 0.05; unpaired Student’s t-test).
significantly attenuated (by 70%) the suppressant effect of LSD (Figs. 1B and 1D). Moreover, in rats treated for 14 days with (±)-pindolol followed by a 2-day washout period, the suppressant effect of a dose of LSD (10 µg/kg, intravenously, n = 7) was still attenuated by 80% (Figs. 1C and 1D), indicating a desensitization of somatodendritic 5-HT$_{1A}$ autoreceptors. In contrast, the 2-week treatment with (±)-pindolol did not modify the suppressant effect of the more selective 5-HT$_{1A}$ receptor agonist 8-OH-DPAT, as was previously observed with its acute administration. Both in control (n = 6) and treated rats (n = 5), the intravenous administration of 5 µg/kg of 8-OH-PAT completely suppressed 5-HT neuronal firing, and this was reversed by the subsequent intravenous administration of 100 µg/kg of WAY 100635 (data not shown).

**Effect of sustained administration of (±)-pindolol on CA$_3$ dorsal hippocampus pyramidal neuron responsiveness to 5-HT**

The microiontophoretic application of 5-HT onto rat dorsal hippocampus pyramidal neurons suppresses firing activity, and this effect is mediated by postsynaptic 5-HT$_{1A}$ receptors. Both CA$_3$ pyramidal neurons tested in this study, 5-HT (10 nA) markedly reduced firing...
activity (Figs. 2A and 2B). This suppressant effect did not alter the shape of the action potentials. As illustrated in Fig. 2C, long-term treatment with (±)pindolol did not modify the suppressant effect of microiontophoretically applied 5-HT (number of spikes suppressed per nanoampere of 5-HT: controls, 114 (standard error of the mean [SEM] 6), n = 15; (±)pindolol-treated rats, 104 [SEM 5], n = 14). WAY 100635 (100 µg/kg, intravenously) had an antagonistic effect on the responsiveness of postsynaptic 5-HT1A receptors, and the significant reduction of the suppressant effect of 5-HT was similar for both controls and rats treated with (±)pindolol (by 73% and 72% respectively; Fig. 2C). Finally, WAY 100635 (100 µg/kg, intravenously) did not modify the quisqualate-activated firing activity of CA3 pyramidal neurons in control rats or in (±)pindolol-treated rats (t = 1.07, p = 0.3; Fig. 2D).

**Electrical stimulation of afferent 5-HT fibers to the hippocampus**

To determine whether treatment with (±)pindolol could modulate the in vivo release of 5-HT (per electrical impulse reaching 5-HT terminals), its capacity to modify the duration of the firing suppression produced by the electrical activation of the ascending 5-HT pathway was examined. As illustrated in Fig. 3B, long-term (±)pindolol treatment (20 mg/kg, subcutaneously for 14 days) did not modify the effectiveness of the stimulation of the 5-HT pathway (SIL value in controls, 41 [SEM 3] ms and in (±)pindolol-treated rats, 43 [SEM 4] ms; t = 0.37, p > 0.7). The responsiveness of terminal 5-HT autoreceptors was evaluated by increasing the frequency of the stimulation from 1 Hz to 5 Hz. In control rats, 5-Hz stimulations were 37% less effective than 1-Hz stimulations (Figs. 3A and 3B). The decremental effect obtained by increasing the frequency from 1 Hz to 5 Hz was similar in rats treated with (±)pindolol and that observed in the controls (41%), indicating the function of terminal 5-HT autoreceptors was unaltered by pindolol treatment (Fig. 3B).

To ensure that the 5-HT1A antagonistic property of (±)pindolol was detectable in the present paradigm, the daily amount of the drug infused over a 24-hour period was injected intraperitoneally in a single bolus. The SIL value after (±)pindolol administration was increased by 16% (t = 3.56, p < 0.05, Figs. 4B and 4D), and the decremental effect of the 5-HT pathway stimulation was also no longer present (Fig. 4D), confirming a blockade of

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**Fig. 3:** (A) Peristimulus time histograms illustrating the effect of the electrical stimulation of the ascending 5-HT pathway at the level of the ventromedial tegmentum on the firing activity of dorsal hippocampus CA3 pyramidal neurons at 1 Hz (upper) and 5 Hz (lower) in a control rat. Note the reduction of the absolute silence value (SIL) in milliseconds, which represents the duration of suppression of firing, by increasing frequency. (B) Effect of (±)pindolol treatment on the efficacy of stimulating the ascending 5-HT pathway and of an increase in frequency from 1 to 5 Hz (*p < 0.05, paired Student’s t-test). The responsiveness of terminal 5-HT autoreceptors in rats treated with (±)pindolol was not significantly different than that of control rats. The numbers within the histograms indicate the number of neurons tested.
the terminal 5-HT₁₅ autoreceptor by (±)pindolol when administered acutely. However, the subsequent intravenous injection of the 5-HT autoreceptor antagonist methiothepin (1 mg/kg) further increased, by 36%, the duration of firing suppression induced by the electrical stimulation of the ascending 5-HT pathway at 1 Hz ($t = 2.9, p < 0.05$, Figs. 4C and 4D).

**Discussion**

The sustained administration of (±)pindolol for 2 weeks prevented the suppressant effect of the 5-HT autoreceptor agonist LSD, suggesting that (±)pindolol antagonizes somatodendritic 5-HT₁₅ autoreceptors in the dorsal raphe nucleus. However, following a 2-day washout period, the suppressant effect of LSD was still attenuated, indicating rather a desensitization of somatodendritic 5-HT₁₅ autoreceptors. Accordingly, there is some evidence suggesting that (±)pindolol may act as a partial 5-HT₁₅ autoreceptor agonist.¹⁸

Pindolol interacts with 5-HT₁₅ receptors with nanomolar affinity ($K_i = 8 \text{nM in recombinant human 5-HT₁₅ receptors using (–)pindolol and } K_i = 13 \text{nM in rat hippocampal membranes using (±)pindolol}^{36–38}$ and prevents some biological responses mediated via 5-HT₁₅ receptor activation.³³–³⁵ One peculiar characteristic found with this ligand is its preferential activity at the presynaptic 5-HT₁₅ receptor. In vitro, it has been reported that 1 μM (±)pindolol antagonizes the inhibitory effect of gepirone on the firing activity of rat dorsal raphe 5-HT neurons.³⁶ In vivo, it has been also shown that a 2-day treatment with (–)pindolol (15 mg/kg/day, subcutaneously) prevents the inhibitory effect of LSD on rat dorsal raphe 5-HT neuronal activity, as well as the reduction of firing activity observed after a 2-day treatment with the SSRI paroxetine, thus supporting its antagonistic property for dorsal raphe somatodendritic 5-HT₁₅ autoreceptors.¹⁴ However, whether (–)pindolol was given using the latter regimen or administered acutely, it did not antagonize postsynaptic 5-HT₁₅ receptors mediating the suppression of extracellularly recorded firing of dorsal hippocampus CA₁–CA₃ pyramidal neurons,³⁷ further suggesting the existence of pharmacologically distinct subpopulations of 5-HT₁₅ receptors.²⁹,³⁷,³⁸ Nevertheless, in vitro, antagonistic activity of (±)pindolol for postsynaptic 5-HT₁₅ receptors on CA₁–CA₃ pyramidal neurons has been reported,³⁹ and in vivo (±)pindolol (0.1–1.0 mg/kg, intravenously) fails to antagonize the suppressant effect of 8-OH-DPAT (10
µg/kg, intravenously) on the firing activity of dorsal raphe 5-HT neurons in freely moving cats.

In an attempt to untangle these discrepancies, both LSD and 8-OH-DPAT were used in an earlier study to determine the contribution of somatodendritic 5-HT1A autoreceptors and of 5-HT1A receptors located on a long-feedback loop originating from the forebrain in modifying 5-HT neuronal firing in the rat dorsal raphe nucleus. The intravenous administration of 200 µg/kg (±)pindolol, a dose which does not modify 5-HT neuronal firing rate, prevented only the suppressant effect of LSD on the firing activity of 5-HT neurons. As initially proposed, the difference between the effects of systemic injection of LSD and 8-OH-DPAT on 5-HT neuron firing activity can be explained by the existence of a negative feedback loop — the intravenous administration of 8-OH-DPAT at low doses would activate postsynaptic 5-HT1A receptors located on neurons in the medial prefrontal cortex, which exert a negative feedback influence on dorsal raphe 5-HT neurons. (±)Pindolol would thus be unable to antagonize the effect of 8-OH-DPAT on 5-HT neurons, most likely because (±)pindolol may not block this postsynaptic 5-HT1A receptor as the 5-HT1A receptors present on pyramidal neurons in the dorsal hippocampus (Fig. 2). However, both (±)pindolol and WAY 100635 antagonized the suppressant effect of the autoreceptor agonist LSD on the firing activity of dorsal raphe 5-HT neurons because both antagonists are effective on the somatodendritic 5-HT1A autoreceptor.

In the CA3 region of the dorsal hippocampus, a 2-week treatment with (±)pindolol (20 mg/kg/day) did not modify the responsiveness of postsynaptic 5-HT1A receptors to the microiontophoretic application of 5-HT, indicating that the sensitivity of these receptors remains unchanged following such a treatment. Hence, this observation provides yet an additional line of evidence for differential properties of pre- and postsynaptic 5-HT1A receptors. For instance, in contrast to their capacity to desensitize the 5-HT1A autoreceptors in the dorsal raphe, it has been shown that the long-term treatment with 5-HT1A receptor agonists or with SSRIs does not alter the responsiveness of 5-HT1A receptors located on CA3 pyramidal neurons. With respect to radioligand binding studies examining the density of 5-HT1A receptor sites, long-term treatments with the 5-HT1A receptor agonists tandospirone or gepirone do not change the density of hippocampal 5-HT1A sites but do affect receptor density in the frontal cortex.

Among the 5-HT1A receptor antagonists available, WAY 100635 is the most potent and selective antagonist acting at both pre- and postsynaptic 5-HT1A receptors. In contrast to (±)pindolol, WAY 100635 (100 µg/kg, intravenously) significantly antagonized the suppressant effect of 5-HT microiontophoretically applied onto CA3 pyramidal neurons, thus showing its capacity to block 5-HT1A receptors on the cell body of CA3 pyramidal neurons. In the hippocampus, however, it has been shown that 5-HT terminals are almost exclusively located in apposition to the dendritic tree of pyramidal neurons and that the endogenous 5-HT, released by the electrical stimulation of the ascending 5-HT pathway, activates these intrasynaptic 5-HT1A receptors on dendrites of hippocampus pyramidal neurons. It is important to emphasize here that pindolol fails to prevent the activation of both the intrasynaptic 5-HT1A receptors present on pyramidal neurons, whereas WAY 10635 appears to antagonize only extrasynaptic 5-HT1A receptors.

In contrast to results obtained with SSRIs, a 2-week treatment with (±)pindolol did not modify the effectiveness of electrical stimulation of 5-HT afferents to the dorsal hippocampus and did not modify the function of terminal 5-HT autoreceptors (as indicated by the lack of effect in the 1 Hz–5 Hz stimulation paradigm; Fig. 3). This is surprising because (±)pindolol is endowed with antagonistic activity at the 5-HT1B autoreceptor. Nonetheless, when (±)pindolol was acutely administered intraperitoneally at a dose of 20 mg/kg, it significantly increased the effectiveness of the electrical stimulation and prevented the decremental effect of the 5-HT pathway stimulation (Fig. 4B). The fact that the subsequent administration of the terminal 5-HT autoreceptor antagonist methiothepin further prolonged the duration of firing suppression suggests that the terminal 5-HT1B autoreceptors were not completely antagonized by the acute dose of (±)pindolol. Consequently, (±)pindolol appears to be, at best, a weak 5-HT1A autoreceptor antagonist. Nevertheless, when considering the net effect of pindolol on extracellular levels of 5-HT in microdialysis studies, there are striking discrepancies. Indeed, it was reported that pindolol, administered by itself, locally or systemically, either decreases, enhances or has no effect on 5-HT levels in several brain structures (e.g., frontal cortex, hippocampus, raphe nuclei or striatum) of rats and cats. The difference between the acute and chronic administration of (±)pindolol in the blockade of terminal 5-HT1B autoreceptor activation (Fig. 3 and Fig. 4) highlights the crucial importance of the treatment regimen. The critical role of the concen-
tration of (±)-pindolol is also emphasized by recent studies using different models in humans (e.g., body temperature and cortisol levels) showing that an oral dose of 30 mg of (±)-pindolol acts as a weak 5-HT$_{1A}$ receptor agonist but also prevents the full effect of subsequent administration of potent 5-HT$_{1A}$ agonists.

In this study, we did not observe any disinhibition of the firing activity of CA$_1$ pyramidal neurons in rats treated with (+)-pindolol for 14 days. These negative results stand in contrast with previous data showing that repeated electroconvulsive shock or chronic treatment with antidepressant drugs, such as the tricyclic antidepressant imipramine, the SSRI paroxetine, the selective and reversible MAO-A inhibitor befloxatone, the $\alpha_2$-adrenergic antagonist mirtazapine, the 5-HT$_{1A}$ receptor agonist gepirone or the dual 5-HT–noradrenergic reuptake blocker venlafaxine, enhanced the tonic activation of postsynaptic 5-HT$_{1A}$ receptors in the dorsal hippocampus, as evidenced by a clear disinhibition produced by WAY 100635 injection. A lack of antidepressant activity of pindolol when given by itself might thus be predicted on the basis that it did not produce any WAY 100635-induced disinhibition, as was the case in rats treated for 3 weeks with the neuroleptic chlorpromazine, or in rats receiving only 1 electroconvulsive shock, or having a lithium diet for 3 days — 3 treatment modalities devoid of antidepressant effect. At best, pindolol on its own could provide some preventive effect in depression, as indicated by a marked reduction in the number of disability pensions due to major affective disorders.

In conclusion, it appears that (±)-pindolol is not only capable of antagonizing the 5-HT$_{1A}$ autoreceptor but also of inducing its desensitization. The former effect would thus contribute to accelerate the antidepressant response to SSRIs by preventing the initial decrease in 5-HT neuron firing activity and thereby increasing 5-HT neurotransmission more rapidly. The latter effect could account for the lack of relapse of the depressive syndrome when patients discontinue (±)-pindolol and continue with their SSRI treatment regimen. Finally, the observation that (±)-pindolol did not alter overall 5-HT neurotransmission implies that this drug may not be endowed with intrinsic antidepressant activity.

Acknowledgements

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