F. Artigas

# Serotonin receptors: role in depression

Department of Neurochemistry and Neuropahrmacology
Institut d'Investigacions Biomèdiques de Barcelona
CSIC-IDIBAPS
Barcelona (Spain)

Regardless of chemical structure, pharmacokinetic properties and molecular or cellular target in the brain, all antidepressant drugs need to be administered for weeks to produce a significant clinical improvement (e.g., 50% reduction of severity). This lag is considered to be necessary for certain brain adaptive processes to occur, which are the neurobiological substrate of the clinical improvement[1-4]. However, a number of observations indicate that more rapid and efficaciious antidepressant treatments are possible. Hence, the tricyclic drug clomipramine appears to have greater efficacy/speed than the selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SSRIs)[5]. Also, some non-standard treatments such as sleep deprivation or electroconvulsive therapy (ECT) exert their effects more rapidly than drugs blocking the reuptake of 5-HT and/or noradrenaline (NA), which represent >90% of all treatments. Moreover, high frequency frequency stimulation of Broadman area 25 (cingulate) produces an immediate symptom relief in treatment-resistant depressive patients[6]. Altogether, these observations suggest that antidepressant treatments have not yet reached their upper limit of speed and efficacy and that further developments are based on the use of new brain targets.

## USE OF 5-HT AUTORECEPTOR ANTAGONISTS

Serotonergic neurons are endowed with two sets of autoreceptors, located in the somatodendritic level in the midbrain raphé nuclei (5-$HT_{1A}$) and in 5-HT axons (5-$HT_{1B}$/1D) in projection areas (fig. 1). The activation of 5-HT1A autoreceptors by 5-HT or selective agonists suppresses cell firing and impulse-dependent 5-HT release whereas 5-$HT_{1B}$ receptors control 5-HT synthesis and release at terminal level. The increase of extracellular 5-HT produced by reuptake blockade activates 5-$HT_{1A}$ receptors in the midbrain raphé, suppressing cell firing and terminal release[3,7], an effect that attenuates the extracellular 5-HT increase produced by reuptake blockade. 5-$HT_{1B}$ autoreceptors exert a similar negative feedback at local level (fig. 1). Following repeated administration of SSRIs, 5-$HT_{1A}$ receptors desensitize, which enables 5-HT neurons to recover cell firing[2] and leads to an increase of extracellular 5-HT, to a level higher than seen after single treatment[8]. The blockade of these negative feedback mechanisms with 5-$HT_{1A}$ and/or 5-$HT_{1B}$ receptor antagonists potentiates the 5-HT increase produced by SSRIs and therefore might serve to accelerate the clinical effects of SSRIs (for review, see[3,9]).

The lack of selective 5-$HT_{1A}$ receptor antagonists available for human use, dictated that this strategy be investigated using the β-adrenoceptor/5-$HT_{1A}$ (partial) antagonist pindolol[10,11]. The results of 15 placebo-controlled clinical trials and several open-label studies using pindolol have been reported. A meta-analysis has indicated that pindolol significantly hastens the effect of SSRIs within the first two weeks of treatment[11].

The above studies open the way to the development of dual action drugs (e.g., SSRI + 5-$HT_{1A}$ receptor antagonist) and of add-on strategies based on the addition of autoreceptor antagonists to SSRIs/SNRIs.

## POSSIBLE ROLE OF POSTSYNAPTIC 5-$HT_{2A/2C}$ RECEPTORS IN THE AUGMENTATION OF ANTIDEPRESSANT RESPONSE

Several open-label and double blind placebo-controlled studies show that some antidepressants (e.g. mirtazapine and mianserin) and atypical antipsychotics may augment the clinical response to SSRIs in treatment-resistant patients (see[12] for review). Often, these responses have been observed shortly after administration of these drugs, which suggests that addition of the second drug induces rapid antidepressant changes. One common characteristic of mirtazapine, mianserin and the atypical antipsychotics is their ability to occupy 5-$HT_{2A}$ receptors at the doses used. Histo-

Correspondence:
Francesc Artigas
Department of Neurochemistry and Neuropahrmacology
Institut d'Investigacions Biomèdiques de Barcelona
CSIC-IDIBAPS
Barcelona (Spain)
E-mail: fapnqi@iibb.csic.es

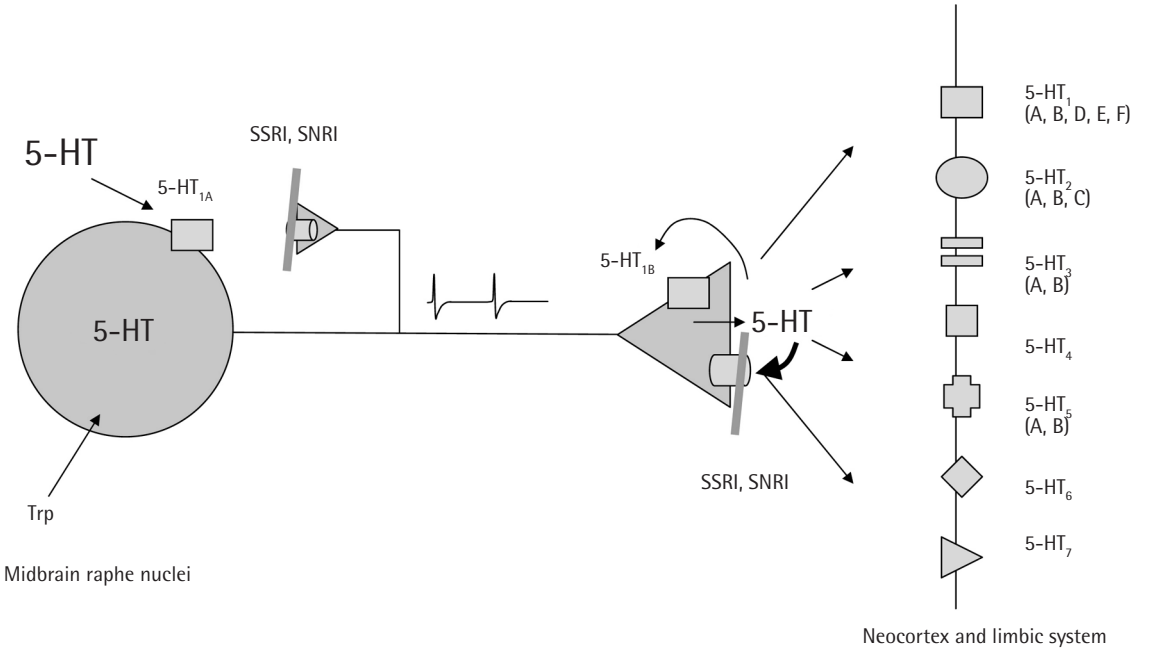


**Figura 1** *Schematic representation of the action of antidepressants on 5-HT neurons. SSRIs and SNRIs inhibit 5-HT reuptake and increase the serotonergic tone on postsynaptic 5-HT receptors located in forebrain, where the therapeutic effect of an increased 5-HT function is supposed to occur. However, 5-HT reuptake inhibition takes also place in the midbrain, where cell bodies of 5-HT neurons are located. Hence, SSRIs and SNIRs produce a very large increase in extracellular 5-HT in the raphe nuclei, which activates 5-HT$_{1A}$ autoreceptors and reduces the activity of 5-HT neurons and the terminal release of 5-HT, thus opposing to the 5-HT enhancing effects in areas in forebrain. The simultaneous blockade of this negative feed-back with 5-HT$_{1A}$ receptor antagonists markedly enhances the pharmacological effects of 5-HT reuptake inhibitors (see refs. 3, 9 for review).*

logical techniques reveal the presence of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors in cortical areas of human brain[13]. It is controversial to speculate whether depressive symptoms may be associated with changes in the cortical density of 5-HT$_{2A}$ receptors. Also, conflicting results have been reported after antidepressant treatments since SSRI appear to increase [and tricyclic drugs to decrease ligand binding to the 5-HT$_{2A}$ receptor. Likewise, many antidepressants down-regulate 5-HT$_{2A}$ receptors after repeated treatment. Altogether, we would suggest that this supports a role for 5-HT$_{2A}$ receptors in antidepressant drug action. The selective blockade of these receptors, by acute administration of M100907, augments the antidepressant effect of SSRIs in the DRL 72-s schedule, a task related to prefrontal cortex function. This effect does not involve a presynaptic potentiation of the 5-HT release produced by the SSRI, which suggests that the improvement in executive functions arises from the blockade of postsynaptic 5-HT$_{2A}$ receptors[14].

The 5-HT$_{2C}$ receptor also warrants consideration in the development of novel antidepressant therapies. Using the technique of in vivo microdialysis it has been reported that 5-HT2C receptor-selective antagonists (SB 242084 and RS 102221), potentiate the elevation in extracellular 5-HT concentration elicited by SSRIs. These observations are in accordance with the fact that fluoxetine increases cortical extracellular 5-HT levels more in 5-HT$_{2C}$ receptor knockout than in wild-type mice[15].

Enhancement of central 5-HT system function has been associated with antidepressant action, as indicated by the widespread use of SSRIs. In addition, dysfunction in the catecholamine systems (noradrenaline and dopamine) is likely to have some role in the etiology of depression. Hence, the combination of atypical antipsychotic agents synergistically potentiated the effect of fluoxetine on the cortical extracellular concentrations of catecholamines, an effect that may also contribute to the aforementioned effects of these drugs in clinical trials.

Overall, the above observations suggest that there is ample room for the development of new antidepressant drugs based on the 5-HT system, targeting either presynaptic inhibitory autoreceptors or postsynaptic excitatory 5-HT receptors in addition to 5-HT reuptake blockade.

## REFERENCES

1. Caldecott-Hazard S. Clinical and biochemical aspects of depressive disorders: II. Transmitter/Receptor theories. Synapse 1991; 9:251-301.

2. Blier P, de Montigny C. Current advances and trends in the treatment of depression. Trends Pharmacol Sci 1994;15: 220-6.
3. Artigas F. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT1A antagonists. Trends Neurosci 1996;19:378-83.
4. Nestler EJ. Neurobiology of depression. Neuron 2002;34:13-25.
5. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disorders 1990;18:289-99.
6. Mayberg H. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45:651-60.
7. Adell A, Artigas F. Differential effects of clomipramine given locally or systemically on extracellular 5-hydroxytryptamine in raphe nuclei and frontal cortex. An *in vivo* microdialysis study. Naunyn-Schmiedeberg's Arch Pharmacol 1991;343: 237-44.
8. Bel N, Artigas F. Chronic treatment with fluvoxamine increases extracellular serotonin in frontal cortex but not in raphe nuclei. Synapse 1993;15:243-5.
9. Artigas F.How does pindolol improve antidepressant action? Trends Pharmacol Sci 2001;22:224-8.
10. Artigas F. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch Gen Psychiatry 1994;51:248-51.
11. Ballesteros J, Callado LF. Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. J Affect Disorders 2004;79:137-47.
12. Marek GJ. Synergistic action of 5-HT2A antagonists and selective serotonin reuptake inhibitors in neuropsychiatric disorders. Neuropsychopharmacology 2003;28:402-12.
13. Pazos A. et al. Serotonin receptors in the human brain-IV. Autoradiographic mapping of serotonin-2 receptors. Neuroscience 1987;21:123-39.
14. Marek. The selective 5-HT2A receptor antagonist M100907 enhances antidepressant-like behavioral effects of the SSRI fluoxetine. Neuropsychopharmacology 2005;30:2205-15.
15. Cremers TIFH. Inactivation of 5-HT2C receptors potentiates consequences of serotonin reuptake blockade. Neuropsychopharmacology 2004;29:1782-9.