ROLE OF THE 5-HT2A RECEPTOR IN THE MECHANISM OF ACTION OF ANTIDEPRESSANT DRUGS: A TRANSLATIONAL HUMAN-MOUSE STUDY

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Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for the treatment of major depression. However, 50% of depressive patients do not respond adequately to these medications. Although evidence incriminates the overactivation of the 5-HT1A autoreceptor in this poor response [1], others serotonergic receptors could be recruited to modulate the therapeutic activity of SSRIs [2]. In agreement with this hypothesis, growing arguments suggest that variants at gene encoding the 5-HT2A receptor are associated with antidepressants responses [3] but the results of pharmacogenetic studies in human are still matter of debate.

The purpose of this translational study was to determine the effects of 5-HT2A receptor inactivation on the electrophysiological, neurochemical and behavioral activity of SSRIs in mice. On the other hand, this work evaluated the impact of two putatively functional single nucleotide polymorphisms of the 5-HT2A receptor gene (rs6313 and rs6314) [3] on SSRIs responses in depressed patients from the French cohort METADAP. In particular, we studied the percentage of responders and the improvement of their depression scores from various relevant scales.

In wild-type 5-HT1A+/+ mice, the acute administration of the SSRIs escitalopram or fluoxetine decreased the firing rate of dorsal raphe (DR) 5-HT neurons, while the administration of the selective 5-HT1A receptor antagonist WAY100635 reversed this effect. Remarkably, the electrophysiological response induced by both SSRIs persisted in 5-HT1A−/− mice pretreated with WAY100635 or in 5-HT1A+/− mice thereby demonstrating the involvement of another serotonergic receptor type in the inhibitory activity. The observation that the 5-HT2A receptor antagonist MDL100907 also reversed escitalopram-induced decrease in DR 5-HT neuronal activity indicates that the simultaneous blockade of 5-HT1A and 5-HT2A receptors is required to prevent the acute inhibitory effects of SSRIs upon the serotonergic system. It also suggests that the activity of SSRIs might be enhanced in 5-HT2A−/− mice after chronic treatment. However, the genetic inactivation of the 5-HT2A receptor significantly attenuated the ability of repeated administration of escitalopram or fluoxetine to increase the firing rate of DR 5-HT neurons and reduced their antidepressant-like effects in the tail suspension test or the novelty suppressed feeding paradigm. Finally, the enhancement of adult hippocampal neurogenesis induced by prolonged administration of SSRIs was blunted in 5-HT2A−/− mice.

In depressed patients, rs6313 and rs6314 genetic variants were not associated with SSRIs response. We extended this observation to the fact that separately analyzed neither escitalopram nor fluoxetine responses were altered for the rs6313. In marked contrast, a trend toward a lower percentage of improvement of depression score was detected after escitalopram treatment in homozygous individuals for the C allele of the rs6314 (p=0.06).

Altogether, these preclinical and clinical data indicate that a functional variant of the 5-HT2A receptor gene may be associated with a poor SSRIs response resulting, at least in part, from an impairment of serotonergic neurotransmission. Although this study has to be completed by determining the consequence of the C allele on the function/expression of the 5-HT2A receptor in the human brain, these results could be of particular importance to select appropriate antidepressant treatment according to the patients’ genotype.
