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

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Introduction

Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for the treatment of major depression (MDD). However, 50% of depressive patients do not respond adequately to these medications. Although evidence incriminates the overactivation of 5-HT2A autoreceptor in this poor response [1], others serotonin receptors could be recruited by SSRIs to modulate their therapeutic effects [2]. In agreement with this hypothesis, growing arguments suggest that variants at gene encoding for the 5-HT2A receptor are associated with antidepressants response [3] but the results of pharmacogenetic studies in depressed patients are still a matter of debate. The purpose of this translational study was first to determine the effects of 5-HT2A receptor inactivation on the depressive-like symptoms and the electrophysiological, neurochemical and behavioral activity of SSRIs in mice. Secondly, this work evaluated the impact of two putatively functional single nucleotide polymorphisms of the 5-HT2A receptor gene (rs6313 and rs6314) [2] on the severity of MDD in depressed patients.

Results

Preclinical data in non-stressed 5-HT2A receptor WT and Knock-out mice

Impact of 5-HT2A receptor on the regulation of the serotonergic system and the mechanism of action of acute SSRIs administration

Impact of genetic inactivation of 5-HT2A receptor on the antidepressant-like response of long-term SSRIs administration

Preclinical and clinical data in stressed mice and depressed patients displaying 5-HT2A receptor impairment

Conclusion

The present study demonstrates that 5-HT2A receptor in addition to 5-HT1A autoreceptor- plays an important inhibitory action on the serotonergic neuronal activity notably in response to SSRIs. However, the genetic inactivation of 5-HT2A receptor does not favor antidepressant-like activity of SSRIs. Such unexpected data likely result form 5-HT1A autoreceptor hypersensitization in mutants. It seems that a balance between the expression of 5-HT1A and 5-HT2A receptor may exist to maintain an inhibitory feedback control on serotonergic system. Preclinical and clinical data provide converging arguments suggesting that a decrease in 5-HT2AR-mediated transmission may give rise to more severe MDD. These results could be of particular importance to select appropriate antidepressant treatment according to the patients' genotype. Future investigations will examine the association between rs6313 and rs6314 and SSRIs response.

Bibliography


Clinical data highlight an association between rs6313 and depression. An higher Hamilton score is observed in C-carriers of the rs6313.