Editorial: Future Trends in the Development of New Antidepressant Drugs

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Major depression is a severe psychiatric disorder with very high prevalence and socioeconomic effect. In spite of the intensive research carried out, the biological substrate of this disease is still poorly understood. The monoaminergic theory has been for many years the most strongly established hypotheses: in line with this, almost all antidepressant drugs currently used act by interacting with monoaminergic neurotransmission. However, these drugs present serious limitations, including lack of efficacy and delayed onset of action. Recent data indicate that depression might be also associated with modifications involving cell proliferation and plasticity in some brain limbic areas. These results are leading to the identification of new pharmacological targets for the treatment of depressive disorders. This volume analyzes the most interesting recent findings in this field, suggesting new trends for the development of new and better antidepressants. The first review analyzes the contribution of the use of genetically modified mice to the analysis of the pathophysiological mechanisms underlying depressive disorders. The use of these novel genetic tools, generated with selective deletions in genes related to emotional behavior, has allowed a better understanding of the role of the different neurobiological pathways in depressive and affective disorders. Genetic modifications of monoaminergic, peptidergic and endocannabinoid systems, together with those affecting the hypothalamic-pituitary-adrenal axis, are discussed in detail. Albert and Fiori focus on the 5-HT_{1A} receptor subtype as a critical target in the mediation of the effects of most antidepressant drugs. This elegant review analyzes the relevance of the transcriptional regulation of this 5-HT receptor subtype and the existence of association with polymorphisms of the HTR1A promoter in susceptibility to depression. The possibility of targeting specific transcription factors involved in 5-HT_{1A} receptor regulation in order to improve major depression through the increase of 5-HT neurotransmission is discussed in detail. Vidal et al. review the possible role of 5-HT₄ receptors in the pathogenesis of depression, especially from the point of view of the search for fast-acting antidepressant strategies. In addition to the known regulation of this receptor subtype by antidepressants, the authors discuss the experimental data showing that the short term administration of partial agonists of this receptor induces a number of behavioral, neurochemical and neuroplastic responses similar to those observed after chronic treatment with classical antidepressants. The fourth review analyzes in detail the neurogenic hypothesis of depression, one of the key elements of the recent theories involving neuroplasticity mechanisms in affective disorders. The authors review all the information available on this issue, critically discussing the role of adult hippocampal neurogenesis in the responses induced by antidepressants. The need for further studies that could clarify the contribution of decreased neurogenesis to the onset of depression is also analyzed. The authors address the question of whether new antidepressant strategies should be based solely on increasing neurogenesis.

New hypotheses on the pathogenesis of mood disorders have been proposed in the recent years, on the basis of the existence of brain neuroplastic alterations. Valdizán et al. review the role of several signaling pathways involved in synaptic plasticity in the mediation of antidepressant responses. They include the Wnt-catenin system, neurotrophic factors (i.e. BDNF) and the mTOR pathway. In addition to reinforce the role of neuroplasticity in major depression, the authors discuss the pros and cons of the possible development of specific drugs addressed to these molecular targets. The excellent review of Hillard and Liu addresses the role of the endocannabinoid system in depressive disorders. Evidences include that deficient CB1 receptor-mediated signaling results in symptoms that mimic those observed in depressive disorders, and that the activity of the endocannabinoid neurotransmission is modified by chronic antidepressants. The authors propose that the activation of this system could be a target for the development of new therapeutic approaches, mainly through the inhibition of the key enzyme fatty acid amide hydrolase. Anderson and Maes review the role of immune-inflammatory and oxidative stress pathways in the biological substrate of depressive disorders. The association of these pathways with autoimmune responses in depression could be mediated by neurodegeneration, apoptosis and reduced plasticity. In this regard, the authors analyze the interest in studying the possible efficacy of compounds such as melatonin, PDE4 inhibitors, statins and other antioxidants, among others, in the treatment and prevention of the progression of affective disease. Novel therapeutic strategies for the treatment of depression are being developed. Bortolozzi et al. review some of these promising approaches, still at an experimental level. The use of deep brain stimulation (DBS) of cingulate cortex, the experimental data supporting the rapid antidepressant action of the non-competitive NMDA receptor antagonist ketamine, and the possibilities of knocking-down the expression of genes involved in depression by means of RNAi strategies are analyzed. The authors discuss the promising antidepressant responses induced by siRNA inactivation of the serotonin transporter (SERT) or the 5-HT_{1A} receptor.