Developing antidepressant and antimanic treatment strategies involving modulation of neuroplasticity

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Traditionally, development of antidepressant and antimanic treatment strategies has focused on biogenic amines, especially on 5-HT and noradrenaline. Over the last 10 years, much work aimed at the development of small molecule, non-peptidergic compounds acting at neuropeptidergic G-protein coupled receptors (GPCRs), in particular in relation to stress systems. One of the most recent approaches focuses on neuroplastic processes as it is becoming increasingly clear that intracellular pathways involved in the modulation of neurogenesis and synaptogenesis are important targets for the discovery of novel drugs to treat affective disorders.
Three strategic approaches will be discussed: (i) development of compounds acting at classical, GPCR-related targets that affect neuroplastic processes via activation of downstream intracellular signaling cascades, (ii) development of compounds that interact with receptors for neurotrophic factors, and (iii) intracellular targets suggested to be involved in the therapeutic effects of mood stabilizers, such as lithium. The first group of compounds involves a variety of different mechanisms, including compounds acting at biogenic amines and more recently developed small molecules acting at neuropeptidergic systems. The second group focuses on receptors for neurotrophins such as brain derived neurotrophic factor (BDNF), including the low affinity growth factor receptor p75. The last group centers around intracellular targets such as inositol monophosphatases or glycogen synthase kinase 3β (GSK3β).

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