If you ever suffered from depression or have been close to someone whose depression resists amelioration by available antidepressant treatments, you do appreciate the importance of the continuing efforts of academic and industrial research toward the development of new antidepressant drugs. As a result of the serendipitous finding in the 1950s that indicated antidepressant activity of iproniazid, a drug later found to act as a monoamine oxidase inhibitor, most of the currently prescribed antidepressants target neurons that utilize monoaminergic neurotransmitters. However, current antidepressant drugs have two main drawbacks: they take several weeks of treatment until their beneficial effects manifest and these treatments are not very effective acutely or following long-term administration in patients suffering from more chronic forms of depression.

Based on the neuropharmacological mechanisms of current antidepressant drugs, their clinical utility is consistent with the traditional neurochemical conceptualization of depression, suggesting that the disorder is due to neurotransmitter imbalances. However, traditional hypotheses have recently been challenged based on converging evidence from studies in animals and humans that highlighted alterations in neuronal connectivity as underlying causes of mood disorders (Castren, 2005).

This ‘network’ hypothesis of depression focuses on the finding that morphological shrinkage, including reduced hippocampal volume, dendritic and synaptic atrophy, and reduced adult neurogenesis, are observed in the ‘depressed’ brain. Moreover, evidence indicates that antidepressant treatments reverse such morphological processes, and that the timing of such reversal coincides with the emergence of therapeutic efficiency. If perturbations in neuronal networks underlie depression, molecules implicated in neural remodeling mechanisms therefore may constitute promising new pharmacological targets. One such target is the neural cell adhesion molecule (NCAM), based in part on its key roles in neurogenesis, synapse formation and stabilization, and on its interactions with cytoskeletal components and neurotrophic factors. A model for the involvement of NCAM in depression was recently described (Sandi & Bisaz, 2007). This model conceptualizes evidence showing bidirectional regulation of NCAM levels by manipulations that produce depression-like symptoms in rodent and antidepressant treatment, respectively. Furthermore, evidence showing altered NCAM levels in patients with mood disorders informed this model. This model led to two main predictions: (1) a deficiency in NCAM levels is a risk factor for developing depression; and (2) stimulation of the NCAM binding site situated on the fibroblast growth factor receptor 1 (FGFR1) should counteract depression.

Both predictions were tested by the experiments described in Aonurm-Helm et al. (2008). Collectively, their results indicate that that NCAM knockout mice exhibit behavioral symptoms of depression and attenuated hippocampal neurogenesis. Furthermore, they demonstrated that the behavioral phenotype was reversed by treatment with conventional antidepressant drugs. Finally, and perhaps representing the most striking result of this study, the behavioral symptoms and reduced levels of neurogenesis were attenuated by systemic administration of a peptide, termed FGL, that stimulates the NCAM binding site on the FGFR1.

These results provide the first experimental evidence for an antidepressant effect resulting from targeting the NCAM-FGFR1 signaling pathway. They also corroborate previous results from studies in humans that implicated fibroblast growth factor (FGF) systems in depression and the effects of antidepressant treatment (Evans et al., 2004). Thus, the results by Aonurm-Helm et al. underscore the potential therapeutic significance of a novel pharmacological target. Future research first needs to substantiate the therapeutic efficacy of this new approach in animal models of depression and, second, to determine whether treatments acting at this new target are therapeutically advantageous when compared with traditional antidepressant drugs.

References


