Neuroprotective effects of antidepressant and mood stabilizing drugs

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Recent animal studies have led us to reconsider the mechanism of action of antidepressant and mood stabilizing drugs. Whereas effects on neurotransmitter systems and intracellular signalling pathways continue to amass, studies now suggest that these drugs may act to prevent neuronal damage and cell loss that may occur in the brain of patients with mood disorders. Animal studies suggest that antidepressant and mood stabilizing drugs are neuroprotective and may also lead to neurogenesis in selected brain regions. Although the mechanisms through which neuroprotection occurs and the experimental conditions differ for these 2 classes of drugs, the net effects are clearly relevant to the pathophysiology of mood disorders.

In rat hippocampus and cerebral cortex, long-term treatment with a range of antidepressants, including tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and electroconvulsive shock, increases the expression of several target genes including brain-derived neurotrophic factor (BDNF).[1,2] In addition, infusion of BDNF blocks depressive-like behaviours in rats. Conversely, stress, which is important in the pathogenesis of depression, can decrease the expression of BDNF in key brain regions. Treatment with antidepressants has been found to enhance neurogenesis in the dentate gyrus region of rat hippocampus, and this may be linked to an increase in the expression of BDNF.[3] One study found that long-term lithium treatment also increased neurogenesis in mouse hippocampus.[4] A compelling series of studies has shown that long-term treatment with lithium and anticonvulsants such as divalproex sodium increases the expression of several other neuroprotective factors.[5–9] Treatment with these mood stabilizing drugs protects primary neuronal cultured cells and stable neuronal cell lines from excitotoxicity and a large number of other pharmacologic insults. Some evidence even suggests that lithium may protect against ischemic changes in rat brain.[10] Although the targets of mood stabilizers may be different from those of antidepressants and the data to support the potential neuroprotective effects of these classes of drugs have only recently been reported, the results emanating from a number of laboratories in North America and Europe are remarkably consistent.

How relevant are these results from animal studies for the clinical management of patients with mood disorders? Clinicians are justifiably cautious when prescribing psychotropic drugs to patients with compromised central nervous system (CNS) function for risk of toxicity. Indeed, prescribing lithium to patients with CNS dysfunction has long been avoided because of a clear worsening of neurologic symptoms in patients with pre-existing neurologic disease. Fears that psychotropic drugs cause "brain damage" are commonplace in patients and have presented a therapeutic challenge for psychiatrists. Several mood stabilizing drugs have the risk of serious CNS teratogenicity, including neural tube defects, when taken by pregnant women, and most should be avoided during pregnancy and breast-feeding.[11,12] These clinical guidelines, which are

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well accepted and based on substantial clinical experience and data, must be considered when evaluating the recent animal data demonstrating the neuroprotective effects of antidepressant and mood stabilizing drugs.

There are increasing reports of cell loss, both neuronal and glial, in key cerebral cortex regions and layers in patients with major depression and bipolar disorder.[13–16] The changes are often subtle, limited to key regions and cortical layers and detected only by careful nonbiased stereologic cell-counting techniques. Changes in the size of key regions such as the hippocampus and amygdala have also been reported in patients with mood disorders,[17–20] and these cellular and volumetric changes may be related to the persistent cognitive deficits that appear resistant to treatment in these patients. Additional evidence obtained from the examination of brain tissue of patients with mood disorders supports the proposed targets of these drugs. For example, as measured in postmortem tissue of depressed patients, antidepressants may increase the levels of BDNF in hippocampus.[21] As well, lithium treatment may lead to small but potentially relevant increases in gray matter volume in patients with bipolar disorder.[22]

Enthusiasm and excitement about the neuroprotective effects of these psychotropic drugs is warranted, but more evidence is needed before clinicians can use this data to influence practice. Neither antidepressants nor mood stabilizers can reverse pre-existing brain lesions or treat neurodegenerative diseases. In the same manner, patients do not experience enhanced memory after treatment with either class of drugs. Studies designed to measure neuroprotective effects of these commonly prescribed drugs in patients with psychiatric disorders, with careful measurement of CNS function and structure, are needed to assess the impact these data will have in clinical psychiatry.

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