

Abstract

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Search for a common mechanism of mood stabilizers.

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BACKGROUND: Manic-depression, or bipolar affective disorder, is a prevalent mental disorder with a global impact. Mood stabilizers have acute and long-term effects and at a minimum are prophylactic for manic or depressive poles without detriment to the other. Lithium has significant effects on mania and depression, but may be augmented or substituted by some antiepileptic drugs. The biochemical basis for mood stabilizer therapies or the molecular origins of bipolar disorder is unknown.

FINDINGS: One approach to this problem is to seek a common target of all mood stabilizers. Lithium directly inhibits two evolutionarily conserved signal transduction pathways. It both suppresses inositol signaling through depletion of intracellular inositol and inhibits glycogen synthase kinase-3 (GSK-3), a multifunctional protein kinase. A number of GSK-3 substrates are involved in neuronal function and organization, and therefore present plausible targets for therapy. Valproic acid (VPA) is an antiepileptic drug with mood-stabilizing properties. It may indirectly reduce GSK-3 activity, and can up-regulate gene expression through inhibition of histone deacetylase. These effects, however, are not conserved between different cell types. VPA also inhibits inositol signaling through an inositol-depletion mechanism. There is no evidence for GSK-3 inhibition by carbamazepine, a second antiepileptic mood stabilizer. In contrast, this drug alters neuronal morphology through an inositol-depletion mechanism as seen with lithium and VPA. Studies on the enzyme prolyl oligopeptidase and the sodium myo-inositol transporter support an inositol-depletion mechanism for mood stabilizer action.

CONCLUSIONS: Despite these intriguing observations, it remains unclear how changes in inositol signaling underlie the origins of bipolar disorder.

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