ACS Chemical Neuroscience

Editorial

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Current Hypotheses of Lithium's Mechanism of Action as a Neuropsychiatric Medication

Ten years ago, in collaboration with a colleague, I was a Guest Editor of a *Clinical Neuroscience Research* special issue "Lithium and Mood Stabilizers: Mechanism of Action". I now thought that the time is ripe for an updated special issue dealing with lithium, the smallest metal ion on earth, an amazing drug. All the reviews except one (originating from Chuang's group) are written by other group authors than those who took part in the previous special issue. In a similar manner, the content of the present reviews is mostly different from that in the previous special issue. The present special issue encompasses potential beneficial effects of lithium beyond mood disorders and possible mechanisms of action beyond inhibition of inositol monophosphatase and glycogen synthase kinase (GSK)3β.

Forlenza et al. deal with neuroprotective effects of lithium and their implication for the treatment of neurodegenerative disorders. They comprehensively summarize converging lines of evidence derived from preclinical and clinical studies which support the concept of lithium being protective against chronic degeneration of the central nervous system (CNS). However, in an additional contribution by this group, they present their own [18F]FDG-PET results showing that long-term (4 years) subtherapeutic (0.25−0.5 mequiv/L) lithium treatment reduces cerebellar and hippocampal glucose metabolism of non-demented old adults, not accompanied by clinical toxicity signs.

Along a similar line, Leeds et al. from Chuang's group, in a scholarly written review, provide compelling evidence suggestive of a new avenue for lithium—intervention in traumatic brain injury. Smith and Liu summarize results of multiple studies in mouse and fruit fly models of fragile X syndrome (FXS) showing reversal effects of lithium treatment on behavioral, physiological, cellular, and molecular phenotypes. They also refer to a pilot clinical trial of 2 months of lithium treatment of adult FXS patients with positive results.

Two learned reviews comprehensively present evidence for two previously less elaborated hypotheses of lithium's therapeutic mechanism in bipolar disorder. Nassar and Azab review others and their own data pointing out that lithium has anti-inflammatory effects that may contribute to its therapeutic efficacy. The summarized reports found both anti- and pro-inflammatory effects. Nassar and Azab discuss this controversy and conclude that utilization of a variety of model systems in the different studies prevents drawing an unequivocal conclusion regarding the effect of lithium on specific inflammatory mediators.

Rapoport reviews his group's extensive studies reported in numerous publications suggesting that lithium and other mood stabilizing drugs target brain arachidonic acid (AA) cascade. Based on evidence in unanesthetized rats chronically administered with lithium, or carbamazepine, or valproate or lamotrigine, the review evaluates the hypothesis that mood stabilization is mediated via dampening brain AA metabolism.

Motoi et al. deal with lithium-induced regulation of autophagy, via the drug's effect either on mTOR-independent inositol metabolism or on the mTOR/GSK3β cascade and its possible implications in mood stabilization as well as in neurodegenerative disorders.

Last but not least, Rybakowski excellently summarizes clinical and genetic findings related to the extent of response of bipolar patients to lithium treatment and the possible mechanisms underlying response versus nonresponse.

This special issue of *ACS Chemical Neuroscience* reflects the paradigm shift in lithium research at two levels: (i) with regard to the drug's mechanism of action, from specific enzymes' inhibition to the effect on cellular processes such as inflammation, mitochondrial function, and autophagy; (ii) at the disease level, from bipolar disorder, per se, to mood and neurodegenerative disorders.

It is obviously inevitable that there will be some overlap among the reviews. We have not made an effort to eliminate overlaps because we believe that each paper offers its own important and unique point of view, and because we wanted each paper to be fully self-contained. This way, readers may select to read particular papers without necessarily having to read others.

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Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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