Central mechanisms of acute lithium toxicity: do accumulating data offer a new approach in treatment?

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Editorial

Lithium, a simple cationic alkali metal is still the drug of choice in the treatment of bipolar disorder for more than 6 decades. In fact, it has been in medical use since the middle of 19th century, first as an anti-gout and later as a psychoactive agent to treat miscellaneous disorders including bipolar disorder [1]. Shortly after 1950s, lithium became a milestone in the treatment of bipolar disorder. Moreover, this progress was important not only for patients with such a devastating disease but also for patients with other mental disorders. Remarkably, the successful therapy with lithium in bipolar disorder has shown that pharmacotherapy may rescue patients with mental disorders. In recent years, accumulating data indicate that lithium has neuroprotective effects [2] and thus, this knowledge may extend its use in the near future.

Unfortunately, this promising treatment potential of lithium was overshadowed by its narrow therapeutic index. Occurrence of toxicity even at therapeutic levels, despite checking lithium blood levels at regular intervals [3,4], increased the concern of physician.

Clinical manifestations of lithium toxicity have many faces and the mechanism of injury on each system is not completely known [5]. Approaching to acute lithium toxicity is based on general treatment principles of drug poisonings and it is mainly supportive care. Currently, a known antidote does not exist. It has been reported that neurological deficits may occur as a sequelae of acute lithium toxicity [4,6,7]. The expansion of our understanding in the mechanism of lithium toxicity may also open a new avenue to find a candidate molecule, which may prevent such sequelae and improve the clinical outcome of lithium poisoning.

It has been well-known that lithium has many effects on biological systems. It affects both signal tranduction pathways and various neurotransmitters. However, the specific mechanism of therapeutic effect of lithium remain elusive and, still not known whether it is the same mechanism by which the lithium exerts its toxic effects.

Experimental modelling of the therapeutic effects of lithium have some limitations. In addition, different dose, exposure time, administration way and species used in experiments may lead discrepancy in the available data. Therefore, obtained results from various studies are controversial. Besides, *in vitro*, *in vivo* or *ex vivo* nature of studies should be taken into consideration when interpreting the reports. It is striking that there are a few studies on acute toxicity of lithium among experimental studies. Furthermore, clinical studies on lithium seem not to be designed to investigate specific mechanisms of lithium effects but rather to clarify the biological basis of bipolar disorder. However, such studies also contribute to elucidate lithium's mechanisms of action and may help to find new therapeutics for bipolar disorder.

The consequences of the experimental findings have not always been found integrative to each other. It has been aimed to ameliorate the overdose toxicity of lithium in a mouse model by administering forskolin and inositol regarding lithium actions had been detected but they were not found effective [8]. However, the any obtained negative result of previous research activities are very valuable and they should be appreciated for further studies without losing enthusiasm.

Except the widely known hypothesis about the mechanism of lithium effects that it reduces inositol by inhibiting inositol monophosphatase and inositol polyphosphate-1-phosphatase [9], other reported molecular targets for lithium effects, were glycogen synthase kinase-3β [10,11] and akt/β-arrestin-2 [12]. Hypotheses about possible mechanisms of lithium effects related to neurotransmitter systems, were mainly cholinergic [13], glutamatergic [14,15] and serotonergic [16,17].

In Jope's review [18] the author concluded that lithium's multiple sites of action, to adjust the balance, may be necessary regarding the complex neurobiology of bipolar disorder. Later, Shaldubina et al. [19] suggested that the acute inhibition of glutamate uptake of lithium may be related to lithium's toxicity since it has been found on a dose-dependent manner with maximal effect at the highest dose. On the other hand, a toxic dose of lithium has been determined to reduce glutamate levels long-lasting in frontal cortex dialysate of rats [20]. Consistent with this report, our study [21] provided stunning findings which may result from the action of lithium on glutamatergic and/or nitrergic systems during its acute toxicity in rats. The recent data seem to underpin more about the involvement of glutamatergic and/or nitrergic systems in both therapeutic and/or toxic effects of lithium [22-25]. Taken together all these findings with Jope's suggestion [18] of ballancing effect of lithium in complex neurobiology of bipolar disorder, nitric oxide may be the adjusting molecule. If so, augmented pharmacological action on glutamatergic and/or nitrergic systems may be the specific mechanism of acute toxicity of lithium.

In conclusion, the accumulating data seem inadequate to offer a new treatment approach in acute lithium toxicity. However, it may provide strong background for the future studies in which the nitric oxide would be considered as one of the key molecules.

Also future clinical studies on the mechanism of lithium effect, would be extremely valuable and very welcome. Neuroimaging methods have been found promising to extend our knowledge of lithium's mechanism of action [26]. Or better still, translational research, with its "from bench to bedside and back again" spectrum, may provide valuable impact in this complex field.

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