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LETTER

BIPOLAR DISORDERS WILEY

A tale of (glycogen synthase kinase) three: Lithium, the kidney and coronavirus disease 19

To the Editors,

The long-term use of lithium salts has long been associated with tubular damage and chronic kidney disease development. Nevertheless, there is some interest in the potential role of these drugs in inflammatory pathways regulation including those pathways in the setting of acute kidney injury (AKI).

This therapeutic potential is based on lithium-induced inhibitory phosphorylation of glycogen synthase kinase-3 beta (GSK3b), a protein related to inflammatory response, through many mechanisms, including upregulation of interleukin-6 (IL-6) and tumor necrosis factor(TNF)expression.[1]

Lithium anti-inflammatory action is long known,and the resulting neuroprotective effects is a concept well-established in medical literature. Also, GSK3b inhibition by lithium seems a promising pathway to improve tubular cell regeneration, as shown by a recent study, in which a single dose of lithium inhibited tubular cells apoptosis (through GSK3b phosphorylation) and promoted renal tubules recovery after ischemia-reperfusion AKI and cisplatin-induced AKI.[2]

Even though lithium induced nephropathy is a concern, the incidence of relevant chronic kidney disease is 1.2% and is related to long-term use (10 years or more) and advanced age.[1] Nevertheless, there is an acute side effect of lithium on kidneys, namely nephrogenic diabetes insipidus. This condition is characterized by loss of ability of the kidney to concentrate urine, and may cause electrolytes disturbance, mainly hypernatremia, which can be managed as long as sodium levels are monitored. Therefore, it seems safe to use a single or few doses, as long as we monitor the levels of lithium and other electrolytes.

Of note, AKI is associated with increased mortality rates, especially in the acute care settings. The scientific community has dedicated many efforts in the last years to find a way to prevent AKI or treat it. Until now, only therapeutic alternative continues to be supportive with renal replacement therapy.

One cause of AKI that emerged recently and has called the scientific community attention is Coronavirus Disease 19(COVID-19), caused by SARS-Cov2, which is a health problem that overwhelmed the world in the last months. A putative mechanism for AKI in this context is the direct damage of kidney tubular cells and podocytes due to viral infection. Another mechanism, present in the most severe cases, is the Cytokine Release Syndrome (CRS), which is a well-known cause of renal and pulmonary damage and is characterized by overexpression of IL-6, TNF and Interleukin-10.[3]

As GSK3b upregulates the expression of IL6 and TNF, we can hypothesize that its pharmacologic inhibition, such as that promoted by lithium, could be a way to reduce the inflammatory response that ultimately results in CRS.

Considering the exposure, we propose that bipolar-disorder specialized centers should investigate the death rate, as well as AKI incidence, in COVID-19 affected patients in use of lithium, in comparison to patients using other mood stabilizers. We also propose that it would be interesting to study the effects of lithium in a low or single dose in the most severe cases of COVID-19, as a compassionate therapy.

CONFLICT OF INTEREST

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