Identifying and Mitigating Renal Toxicity of Lithium on Bipolar Disorder Using HEK293 Cells

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Lithium, the first-line treatment for bipolar disorder (BD), reportedly causes chronic kidney disease (CKD) in at least 20% of patients. To manage BD, physicians prescribe lithium carbonate (Li2CO3) at dosages that depend on symptom severity and produce blood serum levels of 0.4-1.2 mM. As lithium effects at the cellular level are largely unknown, an improved understanding of lithium-induced nephrotoxicity may help to prevent the development of CKD. This study aimed to quantify the effects of low, average, and high therapeutic dosages (0.6, 1.0, 1.2 mM) of Li2CO3 on human embryonic kidney (HEK293) cells. XTT assays revealed that increasingly higher Li2CO3 doses induced greater decreases in cell viability ($p<0.001$). Li2CO3 was shown by the ß-galactosidase senescence and Lysotracker green DND-26 assays to cause cellular senescence ($p<0.001$) and lysosomal damage ($p<0.001$), respectively. Using the scratch-wound assay, we demonstrated that Li2CO3 inhibited cell migration ($p<0.001$); cell cycle analysis found the greatest decrease of cell viability in the G2/M phase ($p<0.001$). The Hoechst 33342 DNA stain showed that Li2CO3 administration resulted in DNA condensation ($p<0.001$). Then the potential mitigating effects of aspirin in combination with Li2CO3 was investigated, as regular aspirin use by individuals with CKD has been associated with slower progression of the disease. The study found that 200-360 mg of aspirin increased cell viability, eliminated lysosomal damage, and stimulated cell migration ($p<0.001$). Furthermore, when tested alone, aspirin did not adversely affect HEK293 cells. These results suggest that aspirin supplementation for bipolar disorder patients on lithium therapy may significantly reduce nephrogenic toxicity.

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