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 (Li_2CO_3) 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 Li_2CO_3 on human embryonic kidney (HEK293) cells. XTT assays revealed that increasingly higher Li_2CO_3 doses induced greater decreases in cell viability ($p<0.001$). Li_2CO_3 was shown by the β-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 Li_2CO_3 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 Li_2CO_3 administration resulted in DNA condensation ($p<0.001$). Then the potential mitigating effects of aspirin in combination with Li_2CO_3 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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