Lithium May Have Cardioprotective Potential via the Inhibitory Action on Myocardial Hypertrophy and Mitochondrial Oxidative Stress

Pao-Huan Chen

[1] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[2] Department of Psychiatry, Taipei Medical University Hospital, Taipei, Taiwan
[3] Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Background
Over half a century, lithium has been the gold-standard medication used to treat mood symptoms of bipolar disorder. One of the therapeutic mechanisms of lithium involves regulation of mitochondrial function. In particular, emerging evidence also suggests that lithium may reduce risk of cardiovascular diseases in patients with bipolar disorder. However, it is unclear whether lithium has cardioprotective potentials associated with mitochondrial function in cardiomyocytes.

Aims & Objectives
This study aimed to explore whether lithium attenuated cardiac hypertrophy and mitochondrial oxidative stress in H9c2 cellular model. H9c2 cellular model was employed since *H9c2* cell is a valuable *in vitro* model to study mitochondrial function in cardiomyocytes.

Methods
Angiotensin II 100 nM was given for 24 hours to stimulate hypertrophic changes of H9c2 cells. LiCl was co-administered with angiotensin II 100 nM at concentrations of 1.0 mM (i.e., therapeutic level) or 0.3 mM (i.e., sub-therapeutic level). Cardiac hypertrophy markers, mitochondrial reactive oxygen species, and mitochondrial Ca^{2+} content were measured in H9c2 cells with and without angiotensin II/LiCl treatment using the real-time reverse-transcription polymerase chain reaction (RT-PCR), MitoSox red fluorescence dye, and X-Rhod-1/AM fluorescence dye method, respectively.

Results
Significantly, LiCl at 0.3 mM downregulated mRNA expression levels of brain natriuretic peptide in angiotensin II 100 nM-treated H9c2 cells (0.48-fold, $p < 0.05$). In addition, LiCl at 0.3 mM attenuated mitochondrial reactive oxygen species in H9c2 cells stimulated with angiotensin II 100 nM (0.45-fold, $p < 0.001$). Furthermore, LiCl at 0.3 mM reduced mitochondrial Ca^{2+} overload in H9c2 cells over-activated by angiotensin II 100 nM (0.46-fold, $p < 0.001$).

Discussion & Conclusion
Lithium at sub-therapeutic levels may have cardioprotective potentials via its inhibitory actions on myocardial hypertrophy and mitochondrial oxidative stress. Regulation of mitochondrial Ca^{2+} homeostasis may play a role in the cardioprotective actions of lithium. Future research needs to elucidate the mechanisms for cardioprotective effects of lithium related to the mitochondrial function.