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Competition between lithium and magnesium ions for the G-protein transducin in the guanosine 5′-diphosphate bound conformation

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Abstract

Li^+ is the most effective drug used to treat bipolar disorder; however, its exact mechanism of action has yet to be elucidated. One hypothesis is that Li^+ competes with Mg^{2+} for the Mg^{2+} binding sites on guanine-nucleotide binding proteins (G-proteins). Using ^7Li T_1 relaxation measurements and fluorescence spectroscopy with the Mg^{2+} fluorophore furaptra, we detected Li^+/Mg^{2+} competition in three preparations: the purified G-protein transducin (G_t), stripped rod outer segment membranes (SROS), and SROS with purified G_t reattached (ROS-T). When purified ROS-T, SROS or transducin were titrated with Li^+ in the presence of fixed amounts of Mg^{2+}, the apparent Li^+ binding constant decreased due to Li^+/Mg^{2+} competition. Whereas for SROS the competition mechanism was monophasic, for G_t, the competition was biphasic, suggesting that in G_t, Li^+/Mg^{2+} competition occurred with different affinities for Mg^{2+} in two types of Mg^{2+} binding sites. Moreover, as $[Li^+]$ increased, the fluorescence excitation spectra of both ROS-T and G_t were blue shifted, indicating an increase in free $[Mg^{2+}]$ compatible with Li^+ displacement of Mg^{2+} from two low affinity Mg^{2+} binding sites of G_t. G_t release from ROS-T membrane was also inhibited by Li^+ addition. In summary, we found evidence of Li^+/Mg^{2+} competition in G_t-containing preparations.

Keywords: Transducin; G-proteins; Lithium; Magnesium; Ionic competition