Lithium induces clearance of protease resistant prion protein in prion-infected cells by induction of autophagy.

Abstract:
Lithium is used for several decades to treat manic-depressive illness (bipolar affective disorder). Recently, it was found that lithium induces autophagy, thereby promoting the clearance of mutant huntingtin and alpha-synucleins in experimental systems. We show here for the first time that lithium significantly reduces the amount of pathological prion protein (PrP(Sc)) in prion-infected neuronal and non-neuronal cultured cells by inducing autophagy. Treatment of prion-infected cells with 3-methyladenine, a potent inhibitor of autophagy, counteracted the anti-prion effect of lithium, demonstrating that induction of autophagy mediates degradation of PrP(Sc). Co-treatment with lithium and rapamycin, a drug widely used to induce autophagy, had an additive effect on PrP(Sc) clearance compared to treatment with either drug alone. In addition, we provide evidence that the ability to reduce PrP(Sc) and to induce autophagy is common for diverse lithium compounds, not only for the drug lithium chloride, usually administered in clinical therapy. Furthermore, we show here that besides reduction of PrP(Sc)-aggregates, lithium-induced autophagy also slightly reduces the levels of cellular prion protein. Limiting the substrate available for conversion of cellular prion protein into PrP(Sc) may provide an additional mechanism for reduction of PrP(Sc) by lithium-induced autophagy.