The mood stabilizer and antidepressant agent lithium inhibits inositol monophosphatase (IMPase) to attenuate phosphoinositide signalling (Berridge et al., 1989). When administered repeatedly lithium also activates genes linked to increased neuronal plasticity (Jacobsen & Mørk, 2004), an effect that is common to antidepressants and may be critical to their therapeutic actions (Sharp, 2012). In a recent ‘reprofiling’ study, we identified ebselen as a potent IMPase inhibitor (Singh et al., 2013). Ebselen has lithium-like effects in various neuropharmacological models in mice. Here we examined the effect of repeated treatment with lithium and ebselen on the expression of a panel of neuronal plasticity genes, specifically brain-derived neurotrophic factor (BDNF), activity-regulated cytoskeleton-associated gene (Arc), vesicular glutamate transporter (VGluT1) and the postsynaptic density scaffold protein, Shank1B.

Adult male C57BL/6 mice (8 per group) were injected (i.p.) twice daily for 2 weeks with vehicle, ebselen (5 mg/kg) or lithium (first dose 10 mmol/kg then 3 mmol/kg). Brains were removed 16 h after the last injection, snap frozen and stored (-80°C). Coronal sections (12 µm) were cryostat-cut, and processed for in situ hybridization using 35S-dATP labelled oligonucleotides complimentary to BDNF, Arc, VGluT1 and Shank1B mRNA. Autoradiograms were quantified for mRNA across a range of forebrain areas using a computerised image analysis system. Data were analysed statistically using Student’s unpaired t-test.

Compared to vehicle-injected controls, repeated administration of lithium caused a statistically significant increase in mRNA abundance of each of BDNF, Arc, VGluT1 and Shank1B across a variety of cortical and subcortical regions. Interestingly, repeated administration of ebselen also increased mRNA expression of BDNF, Arc, VGluT1 and Shank1B, although ebselen did not always increase mRNA in the same regions as lithium. For example, whereas lithium increased Arc mRNA in hippocampus alone, ebselen had this effect in hippocampus and other cortical regions.

In summary, administration of the novel IMPase inhibitor ebselen increased expression of a panel of neuronal plasticity genes in cortical and hippocampal regions in a manner similar (but not identical) to lithium. These results are further evidence that ebselen has lithium-like neuropharmacological effects, and support the testing of this drug in relevant psychiatric patient populations.

This work has been supported by Rosetrees trust and Onassis and Greek Government scholarship.

