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Effect of lithium and ebselen, a novel inhibitor of inositol monophosphatase, on molecular markers of neuronal plasticity in the mouse

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The mood stabilizer and antidepressant agent lithium inhibits inositol monophosphatase (IMPase) to attenuate phosphoinositide signalling [1]. When administered repeatedly lithium also activates genes linked to increased neuronal plasticity [2], an effect that is common to antidepressants and may be critical to their therapeutic actions [3]. In a recent 'reprofiling' study, we identified ebselen as a potent IMPase inhibitor [4] and found that the drug 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 (n=8/group) were injected (i.p.) twice daily for 2 weeks with vehicle or ebselen (5 mg/kg).In a second study mice (n=8-13/group) were injected (i.p.) twice daily for two weeks with saline 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^{o}C). Coronal sections (12 µm) were cryostat-cut, and processed for *in situ* hybridization using ^{35}S-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. Mean±S.E.M values are reported.

Compared to vehicle-injected controls, repeated administration of lithium caused a statistically significant increase in mRNA abundance of each of BDNF(dentate gyrus: veh 100±3, lithium 127±9), Arc (CA3: veh 100±9, lithium 146±6), VGluT1 (piriform cortex: veh 100±3, lithium 113±5) and Shank1B (caudate putamen: veh 100±3, lithium 131±3) across a variety of cortical and subcortical regions. Interestingly, repeated administration of ebselen also significantly increased mRNA of BDNF (dentate gyrus: veh 100±6, ebs 127±9), Arc (CA3: veh 100±8, ebs 137±9), VGluT1 (piriform cortex: veh 100±7, ebs 131±6) and Shank1B (caudate putamen: veh 100±5, ebs 134±13), 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.

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