

Effect of ebselen, a putative lithium mimetic, on central 5-HT_{2C} receptor function in the mouse

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Inhibition of inositol monophosphatase (IMPase) and decreased phosphoinositide (PI) signalling may underlie lithium's antidepressant action (Berridge et al., 1989). Ebselen was recently identified through drug reprofiling as a potent IMPase inhibitor (Singh et al., 2009). The 5-HT_{2C} receptor is G_q linked to the PI cycle and a mediator of antidepressant effects. Here we investigated the effect of ebselen on molecular and behavioural effects of the 5-HT_{2C} receptor agonist Ro 60-0175 in mice.

For behavioural studies, mice (male C57BL/6, 20-25 g), were injected i.p. with vehicle or ebselen and 1 h later injected with Ro 60-0175. Locomotion was measured using activity meters. For molecular studies, mice were injected with vehicle or ebselen followed 1 h or 4h later by Ro 60-0175. Brains were removed 1 h after agonist injection. Regional brain abundance of mRNA of the activity-dependent genes *c-fos* and *Arc* was measured in frozen tissue sections by *in situ* hybridization using ³⁵S-dATP labelled oligonucleotides. Autoradiograms were quantified by densitometry. Data were analysed statistically using one way ANOVA with post hoc LSD (n=6 per group). Mean ± SEM values are given.

Ro 60-0175 (2, 3 or 6 mg/kg) dose-dependently decreased locomotion. This effect was not blocked by ebselen (10 mg/kg). However ebselen decreased locomotion when injected alone. Ro 60-0175 (2, 3 or 6 mg/kg) dose-dependently increased *c-fos* and *Arc* mRNA in specific cortical areas, whereas ebselen alone (10 mg/kg) did not affect either gene. However, 1 h pretreatment with ebselen significantly (p<0.05) attenuated the increase in *Arc* mRNA induced by Ro 60-0175 (cingulate cortex vehicle 130±16, Ro 213±18, ebselen 167±17 nCi/g; somatosensory cortex vehicle 123±15, Ro 243±19, ebselen 181±13 nCi/g). Ebselen also reduced the Ro 60-0175-evoked increase in *c-fos* mRNA (somatosensory cortex vehicle 486±55, Ro 667±64, ebselen 472±41 nCi/g). Pretreatment with ebselen for 4 h also reduced Ro 60-0175 induced gene expression.

The current data indicate that ebselen attenuates central 5-HT_{2C} receptor function in the mouse, as assessed by *c-fos* and *Arc* expression in cerebral cortex. This result is consistent with our previous finding that ebselen attenuates function of the 5-HT_{2A} receptor (Antoniadou et al., 2011), which is also G_q coupled to the PI cycle. Together these findings support the hypothesis that ebselen attenuates 5-HT₂ receptor function through IMPase inhibition and suggest that like lithium, the drug may have antidepressant properties.

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Berridge, MJ, Downes, CP & Hanley, MR 1989, *Neural and developmental actions of lithium: a unifying hypothesis*. Cell, 59, 411-419.

Singh, N, Vasudevan, S, Thomas, J, et al 2010, *Inositol monophosphatase: drug target or false alarm*. European Neuropsychopharmacology, 20, pp.S166-S166

Antoniadou, I, Arsiwala, T, Serres, F, et al 2011, Effect of ebselen, a putative lithium-mimetic on central 5HT_{2A} receptor function in the mouse. BPS meeting 2011