The Impact of Ebselen Administration on Brain myo-Inositol Concentration

Uzay E Emir[1], Nisha Singh[2,3], Ann Sharpley[3], Charles Masaki[3], Sridhar Vasudevan[2], Peter Jezzard[1], Phil Cowen[3], and Grant Churchill[2]

[1]*University of Oxford, FMRIB Centre, Oxford, Oxfordshire, United Kingdom,* [2]*University of Oxford, Department of Pharmacology, Oxford, Oxfordshire, United Kingdom,* [3]*University of Oxford, Department of Psychiatry, Oxford, Oxfordshire, United Kingdom*

Introduction

Bipolar disorder (BPD) is a relatively common psychiatric disorder for which lithium is the gold standard of treatment. However, lithium has a very narrow therapeutic index, and a number of side-effects which require careful monitoring of plasma levels of the drug (1). Amongst its other side effects, lithium is an inhibitor of the enzyme inositol mono-phosphatase (IMPase) (2), leading to marked decreases in brain *myo*-inositol (*myo*-Ins) levels (3). Therefore the development of drugs mimicking the therapeutic profile of lithium but without its serious adverse effects is essential for safer treatment of BPD. Recently, it has been reported that ebselen, a drug developed for its antioxidant and inflammatory properties, inhibits IMPase and lowers *myo*-Ins levels in mouse brain tissue (4). Since *myo*-Ins is one of the most abundant metabolites visible on ^{1}H-MRS at 3T, we attempted to use ^{1}H-MRS to establish if ebselen alters brain *myo*-Ins levels and/or other brain neurochemicals in humans, versus placebo control.

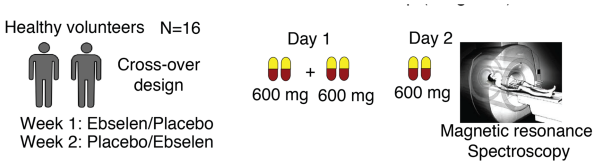

Figure 1 Study design: two MRS scans were conducted, separated by 7-14 days, with either administration of ebselen or placebo, as appropriate.

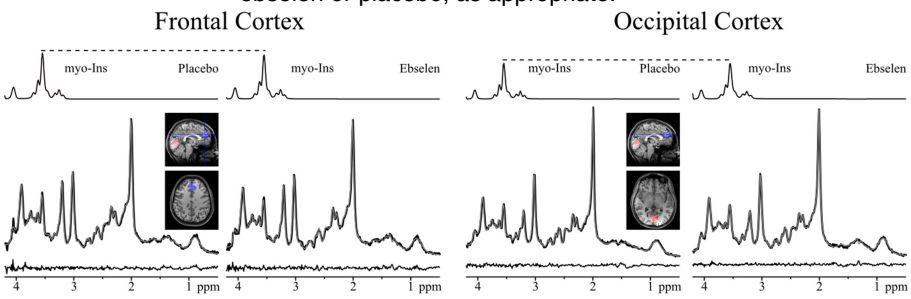

Figure 2 LCModel fitting of spectra acquired from two voxel for ebselen and placebo conditions

	Frontal Cortex		Occipital Cortex	
	Placebo	Ebselen	Placebo	Ebselen
SNR	40.9±8.4	44.2±7.6	53.6±10.4	54.7±7.3
Linewidth(Hz)	6.5±1.4	6.2±1.9	4.5±0.6	4.4±0.5
CSF Fraction	0.25±0.04	0.25±0.04	0.14±0.04	0.14±0.04
CRLB of myo-Ins (%)	3.10±0.7	3.5±0.6	3.5±0.7	3.5±0.6

Table 1 Spectral quality

Methods

16 healthy volunteers (18-40 years) were studied in a double-blind, cross-over design with ebselen and placebo in identical capsules. Spectra were measured from two 8ml voxels (Fig. 1, one in the frontal and the other in the occipital cortices) at 3T (Siemens Tim Trio) with body coil excitation and a 32-channel receive array. The semi-LASER sequence (TE = 28 ms, TR = 5 s, NEX = 64) was used for localization (5). First- and second-order shims were adjusted using GRESHIM (6). Metabolites were quantified with LCModel (7) using the unsuppressed water signal as a reference. Concentrations were corrected for the individual cerebrospinal fluid (CSF) fraction within the ^{1}H MRS voxel using tissue segmented MPRAGE images. Two-tailed paired t-tests were performed to determine whether the measured metabolite levels differed between administration of placebo and administration of ebselen.

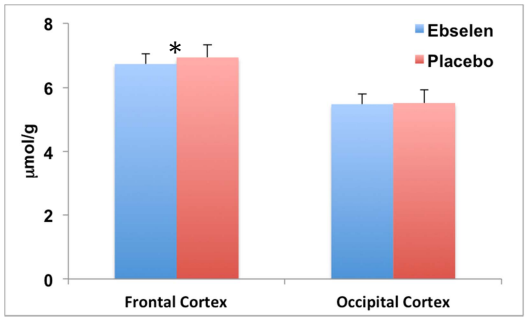

Figure 3 *myo*-Ins concentrations for both ebselen and placebo conditions in frontal and occipital cortices

Results and Discussion

Figure 2 shows representative spectra obtained from two VOIs in both the ebselen and placebo conditions. Artifact free spectra with good SNR, spectral resolution and excellent water suppression were obtained in both brain regions. Also, the linewidth and SNR values estimated by LCModel were similar between the placebo and ebselen conditions in both VOIs ($p>0.05$, Table 1). The consistent CSF fraction among placebo and ebselen conditions attested to the accuracy of the VOI positioning. This excellent repeatability and spectral quality allowed detection of an effect of ebselen on *myo*-Ins in the frontal cortex VOI (Fig. 3). Compared to the placebo subjects, ebselen-administered subjects exhibited significantly decreased *myo*-Ins in frontal cortex (ebselen vs placebo, 6.73 ± 0.32 vs 6.93 ± 0.40 µmol/g, $p=0.02$), but not in occipital cortex (ebselen vs placebo, 5.47 ± 0.31 vs 5.51 ± 0.40 µmol/g, $p=0.68$). In agreement with the previous animal study, showing IMPase inhibition by ebselen, we have successfully demonstrated a decrease in the concentration of *myo*-Ins following ebselen administration in the frontal cortex of healthy human volunteers. These positive results may not only lead to subsequent clinical trials in patients with BPD but also demonstrate how MRS continues to play an ever-increasing role in drug discovery studies.

References

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