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Reply to Regenold

Reply: 'Lithium and Increased Hippocampal Volume: More Tissue or More Water?

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Sir

We thank Dr Regenold for his comments on our data. He raises the interesting question regarding the possibility that lithium alters intracellular water content, and that this may account for our finding that hippocampal volumes were increased following short-term lithium treatment in never-treated patients with bipolar disorder. This is a provocative hypothesis, but unfortunately there is currently little evidence to support it. In fact, Dr Regenold's own study did *not* report increases in hippocampal water volumes in rats that were treated with lithium for either 11 days or 5 weeks (Phatak *et al*, 2006). They measured hippocampal water volumes and found a statistically nonsignificant change in the hippocampus. Their treatment times approximated our assessment intervals and their doses reflected reasonable therapeutic levels. They were able to detect statistically significant differences in frontal cortex, furthermore, suggesting that their doses and duration of treatment were appropriate to alter water content to measurable levels. It is possible that further work from their laboratory and others will determine whether white *vs* grey matter differences in ability to accommodate increases in water content can influence results of the hippocampal findings, but currently this is only an idea.

We like to clarify only one point: it may be worth distinguishing his criticism of the proposed mechanism of neurotrophic effects from the proposed outcome of neuroprotection more explicitly. There are many ways in which treatment with lithium might be neuroprotective, possibly including via modulating cellular hydration as he proposes. Presumably, therefore, Dr Regenold objects primarily to the fact that we discussed data supporting the neurotrophic effects of lithium rather than the discussion of neuroprotection as a more general phenomenon.

FINANCIAL DISCLOSURE

The authors report no financial interests or potential conflicts of interest.

REFERENCE

Phatak P, Shaldivin A, King LS, Shapiro P, Regenold WT (2006). Lithium and inositol: effects on brain water homeostasis in the rat. *Psychopharmacology (Berl)* **186**: 41–47.

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