Proton MR spectroscopy at 3 Tesla in brain of lithium-treated euthymic bipolar patients: increased glutamate concentration in the left hippocampus

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Introduction

While lithium is accepted as the most widely used mood-stabilizer in the treatment of bipolar disorders, and even discussed as a candidate drug against Alzheimer's disease, the mechanism of its action remains largely speculative. Considering the narrow therapeutic window and the possible neurotoxicity of lithium (Li) overdose, insight into the mode of action of the drug appears highly desirable. In pertinent studies using proton MRS contradictory observations have been made regarding the influence of chronic Li on brain metabolites. Remarkable findings have been increased NAA [1,2] and decreased glutamate + glutamine [3] concentrations in different cortical brain regions of Li treated patients. Moreover, Li treatment of rats has lowered glutamate in their whole brain extracts [4]. As Li has been shown to exert neuroprotective effects in vitro and to stimulate neurogenesis in the hippocampus [5] we performed an MRS examination of this region in the brain of chronically treated bipolar patients and healthy controls, with special emphasis on the neurotransmitter glutamate (Glu). Serum Li concentration was determined as a measure for brain Li because they are known to be positively correlated [6].

Methods

Twenty patients (age 36-68 y, 9 m) were studied, meeting the DSM-IV criteria for bipolar disorder and having been medicated for 3-27 years with Li. Nineteen age, gender and education matched healthy controls were also examined. Measurements were carried out with a 3-Tesla-scanner (MEDSPEC 30/100, Bruker Medical) using a quadrature head coil. Following T_1-weighted imaging of the whole brain at a resolution of 1 x 1 x 1.5 mm^3, MR spectra were acquired using PRESS (T_R = 3 s, T_E = 80 ms; n = 128) from two symmetrical brain voxels (2 x 3 x 2 cm^3) including the left and right hippocampi. The pulse sequence was optimized for Glu detection with minor glutamine contamination [7]. Metabolite quantification relied on a time domain-frequency domain program package [7] involving automatic retrospective frequency drift correction. Choline-containing compounds (tCho), total creatine (tCr), NAA, Glu, and glutamine resonances were fitted, including phantom spectra for the latter three and prior knowledge for frequency, linewidth and phase. Segmentation of brain voxels was performed using SPM. Li concentration in patient serum was assayed enzymatically.

Results and Discussion

The only significant difference in concentrations in the two populations examined was that the Glu level in the left hippocampus voxel in patients was higher than that in the right one (11.0 ± 1.9 vs. 9.5 ± 1.4 mM, p = 0.008) (fig. 1). Moreover, in patients the concentration of Glu in the left, but not right, hippocampus voxel was positively correlated with Li concentration in serum (fig. 2), which was confirmed for the amplitude ratios Glu/tCr and Glu/water (p = 0.027). No such relationships were found for other metabolite levels. Specifically, the recent findings of elevated NAA concentration [1,2] could not be reproduced. On the other hand, we confirmed earlier studies that Li may not alter tCho levels in the temporal lobe of chronically treated bipolar patients [8]. As a marginal finding the csf fraction in both voxels studied was observed to increase with age in patients significantly (p < 0.02) and in controls with a trend only (p ~ 0.1).

The most noteworthy observation of an elevation of Glu and its positive correlation with Li on chronic Li therapy supports earlier in vitro findings that the drug may amplify Glu release and inhibit synaptosomal Glu uptake [9]. However, also contradicting results have been communicated suggesting a trend in the opposite direction [3], albeit for patients with therapeutic periods of less than 4 months, compared to up to 27 years for our cohort. Clearly, the relationship between the level of the drug in blood and brain and that of neurotransmitters in brain warrants further investigation, possibly using direct Li spectroscopy.

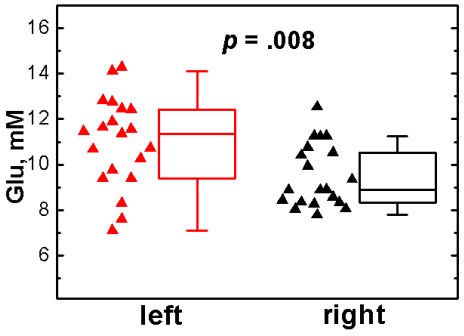

Fig. 1. Glu concentration in the left and right hippocampus voxels of patients.

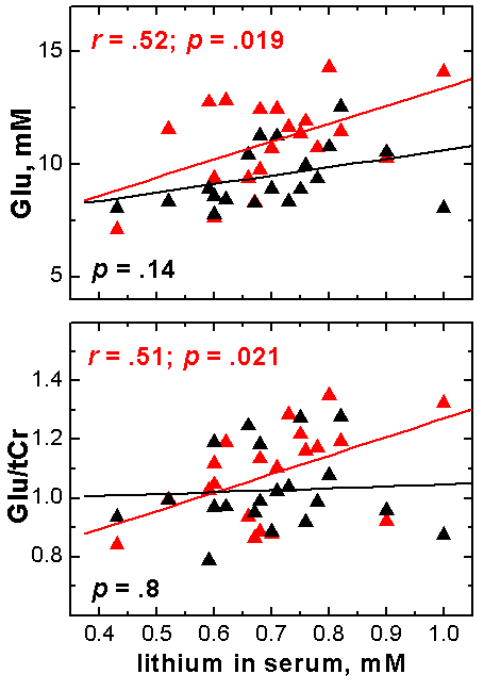

Fig. 2. Relationship of Glu concentration and Glu/tCr for the **left** and **right** hippocampus voxels with serum Li in patients.

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