Region and gender specific neurochemical alterations and sleep deprivation in major depressive episodes

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Introduction

Major depression associated with changes in GABAergic and glutamatergic neurotransmission (1-3) can be rapidly treated by total sleep deprivation (TSD). However, its mode of action has not been resolved. Recently we demonstrated reduced unresolved levels of glutamate and glutamine (GLX) in patients with depression compared to healthy controls (4), and an increase in GLX and glutamine in healthy subjects after TSD (5). The latter has been also demonstrated in parallel with clinical recovery from depression. We now were interested to examine if changes in GLX might also be related to the therapeutic effect of sleep deprivation. Furthermore we were interested in assessing if specific clinical characteristics which have been demonstrated to differentiate the pathophysiology of patients (2, 6-9) are related to the effect of therapeutic sleep deprivation.

Material and Methods

Thirteen patients (8 men, 5 women, mean ± SD age 47.5 ± 11.8 years (31-66 years)), with major depression rated by the 21 item Hamilton Depression Rating Scale (HAMD) were examined by means of proton magnetic resonance spectroscopy at 1.5 T (Signa Horizon EchoSpeed (n=11, 8 male and 3 female) and Signa EchoSpeed Plus Excite II (n=4, 2 male and 2 female), GE Medical Systems, Milwaukee, Wisc., USA) before and after 24 hours of sleep deprivation using a highly standardized acquisition technique (probe-p) and a PRESS sequence (TR/TE=2000 or 4000 /35 ms 128 averages). Two anatomical areas, i.e. dorsolateral prefrontal cortex (DLPFC, voxel size around 5.8ml) and parieto-occipital cortex (POC, voxel size around 17.5 ml) were studied with TR=4000ms for the latter. Concentrations of total creatine (Cr), choline-containing compounds (Cho), myo-inositol (mI), N-acetylaspartate (NAA), unresolved (Glx) an resolved glutamine (Gln) were estimated using LCModel software, and expressed as institutional units. To clinically differentiate the patients, gender and the presence or absence of characteristics which are related to melancholic depression (early morning awakening, appetite and weight loss) and defined as vegetative melancholia (VM, 8), were used. ANCOVA was performed to investigate GLX changes as the main variable of interest, whereas other metabolite estimates were tested on an exploratory basis. For between group analysis, non parametric tests for metabolite ratios was deployed to avoid confounds from varying voxel composition. Significance was considered if $p < 0.05$.

Results

Sleep deprivation led to an increase in GLX (4.35 ±0.87 at baseline vs. 4.99 ±0.88 after TSD; $F = 8.47$, $p = 0.023$, $n = 8$) in the frontal cortex of male, but not female patients. Frontal GLN estimates despite considerable fitting uncertainties showed an increase in male patients (0.85 ±0.60 at baseline vs. 1.79 ±0.64 after TSD; $F = 39.09$, $p = 0.001$, $n = 8$) and similarly in patients with VM (0.78 ±0.60 at baseline vs. 1.50 ±0.76 after TSD; $F = 11.25$, $p = 0.010$, $n = 9$). Finally total creatine (2.80 ±0 40 at baseline vs. 3.11 ±0.34 after TDS, $F = 7.18$; $p = 0.032$) and choline-containing compounds (0.72 ± 0.11 at baseline vs. 0.77 ±0.12 after TDS, $F = 7.52$, $p = 0.029$) increased marginally in the whole population.
Moreover, prefrontal GLX/Cr ratios were significantly lower at baseline in MDE patients showing a therapeutic response (defined as 50% decrease of Hamilton score) compared with nonresponders (1.44 ±0.08 , 1.89 ±0.31, $p = 0.01$).
In the parieto-occipital cortex no changes could be revealed.

Conclusion

The study is limited by methodological constraints affecting the accuracy of the estimates for GLX and in particular GLN using 1D proton MRS at 1.5T. Nevertheless, we provide moderate support for the clinical separation of patients on the basis of gender and vegetative features. As melancholic features and male gender are related to an increased hypothalamo-pituitary-adrenal (HPA) axis activity it can be assumed that patients with an increased HPA axis activity are those who show the most pronounced biological changes after sleep deprivation. Furthermore, regional neurochemical alterations may provide a biologic marker to predict the therapeutic response to TSD in depressed patients. Larger studies at higher field strengths are required to confirm these findings and to research whether GLX levels at baseline reflect specific clinical phenotypes or independently predict the therapeutic response to TSD.

References

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