Cortical GABA and glutamate changes in Posttraumatic Stress Disorder

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Introduction:

Exposure to war events and civilian trauma are associated with a high risk of mental health problems, known as Post Traumatic Stress Disorder (PTSD). Long-lasting dysfunction in glutamatergic and GABA-ergic neurotransmission and related cytotoxic cell death has been postulated to be associated with the clinical symptomatology of PTSD. However, cortical gamma-amino butyric acid (GABA) and Glutamate (Glu) concentrations, which can be measured with proton magnetic resonance spectroscopy (1 H MRS), are unknown in PTSD patients. The goal of this study was to quantitate cortical levels of GABA, Glu, and N-acetylaspartate (NAA: a neuronal marker) in military personnel and civilians with PTSD and to assess correlations between these metabolites and measures of PTSD symptomatology. We hypothesized that relative to PTSD negative controls, NAA and GABA levels are lower and Glu levels higher in the anterior cingulate cortex (ACC), posterior occipital cortex (POC) and the medial temporal lobe (TEMP) of PTSD patients.

Methods:

Twenty-seven PTSD patients (35± 11 years) and 17 trauma exposed non-PTSD individuals (37 ± 12 years) were scanned on a 4 Tesla Bruker Research System, equipped with an 8-channel transmit-receive radio frequency head coil. Participants were American veterans of any war and civilians. Eleven of the patients and 7 of the controls were re-scanned after three months to assess possible changes in the levels of the metabolites with time. Six of the 11 were being treated with cognitive behavioral therapy. 3D T1-weighted and 2D T2-weighted images were acquired andused to aid MRS volume-of-interest placements and tissue segmentation. Single volume MRS data were acquired from the ACC, POC and TEMP, with the volumes placed to include as much cortical gray matter as possible. Signals from NAA, creatine- (Cr) and choline-containing compounds (Cho), myo-Inositol (ml), and Glu were acquired with a STEAM sequence (TR/TE/TM = 1800/15/12 ms) . GABA was acquired with a modified J-editing sequence at TE = 68 ms. MR spectra were processed with an in-house program and SITOOLS and IDL version 6.0. The T1-weighted images were segmented into gray matter, white matter and cerebrospinal fluid (CSF) and used to estimate tissue and CSF contributions to MRS voxels. Metabolite concentrations were then calculated from metabolite peak area values together with the tissue contributions and individualized system calibration parameters. Clinician administered PTSD scores (CAPS) were obtained via interviews. PTSD symptomatology was assessed with a self-report rating scale (PTSD Checklist, PCL). Sleep quality was assessed with the Insomnia Severity Index (ISI). Alcohol consumption and cigarette smoking variables were also obtained from participants through structured interviews to be used as possible covariates in the analyses of metabolite concentrations.

Results:

In ACC at the first assessment point (AP1), NAA was lower in PTSD patients compared to controls ($p = 0.008$), but GABA and Glu levels were not significantly different between PTSD patients and controls. In the POC, GABA was lower in PTSD patients compared to controls ($p = 0.04$), but there were no significant NAA or Glu differences between the groups. In the TEMP voxel, GABA was lower ($p = 0.04$) and Glu higher ($p = 0.05$) in PTSD patients than in controls. However, there were no significant NAA differences between PTSD patients and controls.

Comparing AP2 metabolites levels with AP1 levels, NAA ($p = 0.03$) and Glu ($p = 0.02$) each decreased significantly in PTSD in TEMP and tended to decrease in ACC (NAA: $p = 0.09$, Glu: $p =0.07$). However, there were no significant longitudinal changes of GABA in TEMP and ACC and no significant changes in any of the metabolites in POC.

In all voxel locations and among PTSD patients, Glu concentrations strongly correlated with the corresponding NAA concentrations (all $r > 0.6$, $p < 0.001$). In ACC, NAA and Glu concentrations correlated inversely with arousal (all $r < -0.43$, $p < 0.04$). In POC, GABA concentration correlated inversely with the insomnia severity index (ISI), whereas Glu concentrations correlated positively with ISI ($r > 0.49$, $p < 0.02$). PCL scores did not correlate significantly with any of the metabolite levels in any voxel. Finally, although PTSD patients drank more alcoholic drinks over their lifetime (37 ± 40 vs. 11 ± 13 drinks/month), this did not significantly affect the metabolite levels.

Discussion:

As hypothesized, GABA levels were reduced in the POC and TEMP of PTSD patients compared to trauma-exposed non-PTSD individuals and Glu was higher in TEMP of PTSD patients vs. controls. Regional metabolite concentrations correlated with PTSD symptomatology, suggesting functional and clinical significances of these metabolite concentrations. Regional cortical GABA reductions and Glu elevations suggest disturbances of GABAergic tone in PTSD, perhaps with neurotransmitter involvement. Lower cortical GABA is consistent with findings in panic disorder and with reports of low plasma GABA in those vulnerable to PTSD. Although PTSD symptomatology did not worsen over 3 months in patients, cortical NAA and Glu continued to decrease. signalling ongoing neuronal injury. We replicated suggestions of neuronal injury (i.e., reduced NAA) in ACC of PTSD patients reported previously and newly detected changes in glutamatergic and GABA-ergic tone in PTSD patients.

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