Archival Report

Biological Psychiatry: CNNI

Myo-inositol, Glutamate, and Glutamine in the Prefrontal Cortex, Hippocampus, and Amygdala in Major Depression

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ABSTRACT

BACKGROUND: The brains of patients with depression exhibit many changes in various regions. Recently, proton magnetic resonance spectroscopy has been used to measure brain metabolites, using saturation bands to shape the volume of interest. Our a priori hypothesis was that myo-inositol and glutamate were downregulated in the hippocampus and amygdala in depression.

METHODS: We measured brain metabolites from the medial prefrontal cortex, hippocampus, and amygdala of 22 drug-naïve, first-episode patients with major depressive disorder and 27 healthy control subjects using 3T proton magnetic resonance spectroscopy.

RESULTS: Compared with healthy control subjects, patients showed statistically significant reductions in myo-inositol levels in all three regions and reductions in glutamate levels in the medial prefrontal cortex. Furthermore, we found significant decreases in the ratios of glutamate to creatine plus phosphocreatine in the medial prefrontal cortex and amygdala. Additionally, the ratios of glutamine to creatine plus phosphocreatine were also decreased in all three regions examined, although not all the participants presented reliable data. Finally, glutamate levels in the medial prefrontal cortex and amygdala have significant correlations with executive function and those in the hippocampus with memory function. Hippocampal myo-inositol was significantly related to blood cortisol.

CONCLUSIONS: Our findings indicated abnormal myo-inositol, glutamate, and glutamine levels in the brains of major depressive disorder patients.

Keywords: Amygdala, Depression, Glutamate, Glutamine, Hippocampus, Myo-inositol

http://dx.doi.org/10.1016/j.bpsc.2016.11.006

The mechanisms underlying depression remain elusive. Various studies have indicated that the medial prefrontal cortex—including the anterior cingulate cortex—hippocampus, and amygdala are candidates regions for depression pathology. Medial prefrontal cortex, hippocampus, and amygdala are connected via neuronal circuits that serve working memory, learning, and contextual processing. Patients with depression show deficits in neurocognitive functions, including executive function and working memory (1) and learning and memory (2). Amygdala-hippocampus interaction is integral to memory and stress processes (3). Thus, the hippocampus could provide contextual information that informs the inhibitory control of the medial prefrontal cortex over the amygdala (4,5). While sadness caused by the recall of unhappy memories induced increased blood flow in the medial prefrontal cortex (6), patients with depression showed blunted cingulate activation during the Stroop interference task (7).

The pathophysiology of depression is thought to involve the hypothalamic-pituitary-adrenal axis, through direct and feedback interactions [reviewed by Pariante and Lightman (8)]. Major depressive disorder has been associated with hypercortisolism, where cortisol targets the hippocampus through glucocorticoid receptors. Smaller hippocampal volumes have been reported in major depressive disorder, and this has been attributed to hippocampal atrophy, caused by glucocorticoid neurotoxicity (9). On the other hand, some previous studies showed amygdala hypertrophy in patients with the first episode of major depression (10). Amygdala hyperactivity has also been reported in patients with depression (11). A previous study reported that chronic stress-induced hippocampal dendritic atrophy had a relationship with impaired learning and memory (12). It is of note that administering repeated stress to rats resulted in dendritic atrophy in the hippocampus (13) but growth in the amygdala (14). Supporting this, repeated stress decreased brain-derived neurotrophic factor expression in the hippocampus, while increasing it in the amygdala (15). Conversely, the hypothalamus, which is activated directly by stress, is affected negatively by hippocampal and positively by amygdala signaling (16). Therefore, it is likely that the hippocampus and amygdala are contrasting systems in major depressive disorder.

Previous studies reported increases in blood cortisol, dehydroepiandrosterone sulfate (DHEA-S), and cortisol-DHEA ratios in depression (17,18). Cognitive impairment in depression

was associated with salivary cortisol (19). Thus, stress-related hormones might be useful markers for evaluating patient function. In healthy control subjects, acute hydrocortisone administration impaired memory performance, whereas hydrocortisone had no effects on memory in patients with major depressive disorder (20). Acute administration of hydrocortisone decreased prefrontal and hippocampal activation detected by functional magnetic resonance imaging during declarative memory retrieval (21). The role of glucocorticoids in depression remains unknown.

Magnetic resonance spectroscopy (MRS) studies demonstrate that patients with depression show attenuated glutamate plus glutamine (Glx) in the anterior cingulate (22–24), hippocampus (25), and amygdala (26), although negative data have also been reported for the anterior cingulate (27,28) and hippocampus (29). It is likely that this decrease reflects attenuated levels of glutamate and/or glutamine in major depression.

Owing to increases in magnetic field strengths such as 3 or 4T, proton (^{1}H) spectra can be acquired from a smaller volume of interest (VOI), with fewer scan numbers than before, resulting in a reduction of typically large standard deviation (SD) of values. We previously showed comparable glutamine values with a small SD of 22% in the medial prefrontal cortex, using a large volume of 18.5 cm^3 at 3T (30). Although it is difficult to obtain MRS data from the hippocampus and amygdala owing to a lack of local field homogeneity and flow artifacts, reliable results from the amygdala are possible to obtain using new techniques with saturation bands for shimming (31). Using 3T MRS and saturation bands, we obtained acceptable measures of glutamine from hippocampus and amygdala using a volume of 8 to 9.5 cm^3.

Based on the existing literature, we tested the following hypotheses: 1) levels of myo-inositol would be decreased in the hippocampus and amygdala in depression, and 2) levels of glutamate would be decreased in the hippocampus and amygdala in depression. Here we examined metabolites in the medial prefrontal cortex, hippocampus, and amygdala of drug-naïve, first-episode patients with major depressive disorder and a healthy comparison group, using 3T ^{1}H-MRS and saturation bands. Additionally, we examined the relationship between brain metabolites with neurocognitive function and blood stress-related hormones.

METHODS AND MATERIALS

Subjects

The participants consisted of 22 patients with depression and 27 sex- and age-matched control subjects. Inclusion criteria required patients with major depressive disorder to be drug naïve and within their first episode. All patients were recruited from the outpatient clinic of Teikyo University Chiba Medical Center, met the DSM-IV criteria for major depressive disorder (first episode), and had no other psychiatric disorders. Other criteria for exclusion were history of head trauma, seizures, or other neurological disorders, mental retardation, or alcohol and substance abuse. Patient scores were required to be 14 or more on the 17-item Hamilton Depression Rating Scale (HDRS). Characteristics of the subjects are shown in Table 1.

Table 1. Characteristics and Clinical Severity of Participants

Characteristics	Control (n = 27)	Depression (n = 22)	p (uncorrected)
Sex, Male/Female	18/9	17/5	.461[a]
Age, Years	36.8 ± 8.4	40.9 ± 2.4	.145
Education, Years	15.7 ± 1.1	13.8 ± 2.1	<.001[b]
Estimated IQ[c]	103.6 ± 10.5	102.1 ± 13.7	.668
HDRS-17		21.5 ± 3.9	
Cortisol, pg/dL	11.8 ± 3.8	15.5 ± 5.0	.006[d]
DHEA-S, μg/dL	246 ± 111	305 ± 113	.075
Cortisol/DHEA-S × 100	5.54 ± 2.89	6.26 ± 4.67	.511
Verbal Fluency, Letter	31.7 ± 8.2	30.0 ± 11.1	.531
Verbal Fluency, Category	47.2 ± 8.4	42.8 ± 9.3	.088
Stroop C	18.0 ± 3.9	21.1 ± 6.1	.036[e]
Stroop D	12.1 ± 2.2	12.8 ± 2.6	.296
Stroop, C-D	5.9 ± 3.7	8.1 ± 4.3	.062[f]
TMT A	24.0 ± 7.5	29.4 ± 6.8	.011[e]
TMT B	57.0 ± 16.7	77.6 ± 35.6	.005[d]
RAVLT, Total, Learning	51.6 ± 8.6	46.8 ± 9.5	.068[f]
RAVLT, Maximum	12.8 ± 1.5	12.2 ± 2.2	.234
RAVLT, Retention, Memory	11.0 ± 2.6	10.1 ± 3.0	.267
VPAT	18.7 ± 3.8	16.8 ± 4.1	.121

Values are mean ± SD.

HDRS-17, 17-item Hamilton Depression Rating Scale; DHEA-S, dehydroepiandrosterone sulfate; RAVLT, Rey Auditory Verbal Learning Test; TMT A and B, Trail Making Test parts A and B; VPAT, Verbal Paired Associates Test.

[a]Chi-square test.

[b]$p < .001$ when compared with normal control subjects.

[c]Short form of Wechsler Adult Intelligence Scale III.

[d]$p < .01$ when compared with normal control subjects.

[e]$p < .05$ when compared with normal control subjects.

[f]$p < .07$, a trend for change without significance.

IQ scores were estimated from the scales of information, comprehension, vocabulary, and picture arrangement subtests using the short version of the Wechsler Adult Intelligence Scale III (32).

This research was approved by the ethics committee of Teikyo University Chiba Medical Center (ethical committee approval no. 12-060-2) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained after the procedures had been fully explained to each participant.

^{1}H-MRS Methods

^{1}H-MRS data were acquired from all subjects using a Discovery MR750 (GE, Milwaukee, WI), operated at 3T. ^{1}H nuclear magnetic resonance used a 12-channel head coil. The VOI location was chosen under the guidance of T2-weighted image pulses (repetition time 5 seconds, echo time 98 ms, slice thickness 3 mm) and T1-weighted image pulses (repetition time 2 seconds, echo time 25 ms, slice thickness 5 mm) for the cubic voxel to include the medial prefrontal cortex (20 × 20 × 20 mm), right hippocampus (17 × 20 × 28 mm), and right amygdala (20 × 20 × 20 mm) (Figure 1). In general, the