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Original Article

Metabolite Alternations in the Dopamine Circuit Associated with Methamphetamine-Related Psychotic Symptoms: A Proton Magnetic Resonance Spectroscopy Study

Javad Sheikhi Koohsar[1], Fariborz Faeghi[1], Raheleh Rafaiee[2], Mohammad Niroumand Sarvandani[3], Sadegh Masjoodi[4], Hamid Kalalian Moghaddam[5*]

Abstract

Objective: Chronic METH use results in neurodegenerative alternations in the human brain. The present study aimed to assess the long-term METH impact on brain metabolite concentrations in cases meeting the DSM-5 criteria regarding METH use.

Method: We recruited 42 METH users meeting the DSM-5 criteria and 21 healthy controls. Psychotic signs were measured using the Positive and Negative Syndrome Scale (PANSS). Proton magnetic resonance spectroscopy (1HMRS) evaluating Myo-inositol (MI), Choline (Cho), Glutamine plus Glutamate (Glx), N-acetyl aspartate (NAA), and Creatine (Cre) were obtained in the dopaminergic pathway (Frontal Cortex, Substantia nigra, Ventral Tegmental Area (VTA), Nucleus Accumbens (NAc), Hippocampus, Striatum,) the subjects. All participants collected urine specimens for 24 hours to measure presence of specific metabolites including METH metabolite level, 5-Hydroxy indoleacetic acid metabolite (for serotonin level monitoring), and metanephrine metabolite (for dopamine level monitoring).

Results: Dopamine and Serotonin increased in the METH group ($P < 0.001$). METH caused an increase in the Cre ($P < 0.001$) and a decline in the Glx ($P < 0.001$), NAA ($P = 0.008$), and MI ($P < 0.001$) metabolite concentrations of dopamine circuits in METH users in comparison with healthy subjects. We found no change in Cho metabolite concentration. Psychological data and the neurometabolite concentrations in the studied area of the brain were significantly correlated.

Conclusion: There is an association between METH use and active neurodegeneration in the dopamine circuit, and it causes serious mental illness. 1HMRS can detect patient's deterioration and progression of disease as well as follow-up management in patients with METH use disorder.

Key words: *Brain; Dopamine; Magnetic Resonance Spectroscopy; Methamphetamine; Serotonin; Substance-Related Disorders*

1. Department of Medical Imaging, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Neuroscience, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
3. Student Research Committee, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.
4. Institute for Cognitive and Brain Sciences, Shahid Beheshti University, Tehran, Iran.
5. Department of Physiology, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.

***Corresponding Author:**
Address: Department of Physiology, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran, Postal Code: 7394736147.
Tel: 98-23 32395054, Fax: 98-23 32395009, Email: h.kalalian@shmu.ac.ir

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Methamphetamine (METH) use can cause compulsive consumption and craving despite its severe adverse effects (1). METH use disorders, following opioid use disorders, are responsible for a major part of the global burden of drug use. According to the United Nations report in 2020, about 27 million people worldwide (0.5% of the adult population) are estimated to have used amphetamine-type stimulants in the past year. The past-year use of METH in Asia is at a similar level (0.5 per cent) to the world average (2). The past-year prevalence of METH use in Iran is estimated around 0.4% of the population aged 15–64 (3). Evidence suggest that METH causes the greatest global health concern. Its usage is associated with psychotic symptoms and morphological and neurochemical dysfunctions affecting several brain areas (4, 5). METH-induced psychiatric signs are anxiety, irritability, psychosis, and changes in mood. In METH psychosis, positive psychotic symptoms (paranoid delusions and hallucinations) are much more commonly reported compared to negative symptoms (poverty of speech, psychomotor retardation, and a flattened affect) (6).

METH stimulates the nigrostriatal pathways, mesocortical circuit, and the mesolimbic which have been associated with the reward system (7). METH can cause alternation in dopaminergic, serotonergic, and noradrenergic systems by stimulating secretion of monoamines, inhibiting monoamine reuptake, inactivating presynaptic vesicular monoamine transporter 2, and a reduction in the effectiveness of monoamine metabolic enzymes (8, 9). However, METH effects in the human brain on glutamate and glutamine (Glx), and key neurometabolites such as N-acetylaspartate (NAA), myo-inositol (MI), choline (Cho), and creatine (Cre) are poorly understood. Changes in these neurometabolites could be informative regarding the mechanism of action of METH drugs and their dependence potential in humans. NAA is a neuronal marker and reflects neuronal integrity, viability, and number (10). Cre may be a marker of brain energy metabolism (11). Glx is a marker of cognitive function (12). Cho serves as a marker for enhanced membrane turnover, cell growth and cell division, or inflammation, and increased Cho has been associated with gliosis and membrane breakdown (13). MI is generally considered a marker for gliosis (14). Significant long-term alternation of neurometabolites found in METH consumers is linked to psychomotor defect (15).

Neurochemical alternations in human METH consumers were detected using proton magnetic resonance spectroscopy (1HMRS) that is capable of quantifying different neurometabolites in the millimolar levels range in targeted brain regions (16). 1HMRS has demonstrated neurometabolites disturbances in brain tissue in METH use including NAA, Cre, Glx, Cho, and MI (17-22). Most of the 1HMRS studies focused on cingulate (19, 23-25), basal ganglia (26), frontal cortex (22, 27-29) with less evidence in the dopaminergic circuit including Nucleus Accumbemce (NAc), Ventral Tegmental Area (VTA), Substantia nigra, Hippocampus, Prefrontal Cortex (PFC), and Striatum. Although numerous studies have examined the METH-induced alternation of neurometabolites, few have investigated the association of alternation of neurometabolites with psychological symptoms. This study was performed to expand the prior investigations of neurometabolites in patients with METH use disorder. Both 1HMRS and psychological tests were performed in METH users and healthy controls. The aim of this study was to first assess neurometabolites alternation as neuronal integrity and glial markers (NAA, Cre, Glx, Cho, MI) in targeted brain regions as reward circuit. In addition, the study aimed to determine correlates of neurometabolites with neuropsychiatric symptoms in METH user subjects and healthy controls with 1HMRS.

Materials and Methods

Participants

This study was designed and performed in February, 2019 in Shahroud, Iran. Two groups were studied: 42 METH abusing subjects and 21 non-substance-abusing control subjects. The subjects signed the written informed consent before entering this research. Inclusion criteria were (i) age 18–50 yr; (ii) lifetime diagnosis of DSM-5 METH use, according to the Structured Clinical Interview for DSM-5; (iii) no use of medications or herbal medicine affecting the brain. Exclusion criteria were (i) drug use except for METH (not for nicotine and caffeine) for the past year; (ii) current or past non–drug-related psychiatric disorders; (iii) current or past significant medical, neurological disorder or trauma affecting the CNS (cerebrovascular or seizure disease); (iv) severe hepatic, respiratory, renal, endocrine disease, AIDS or loss of consciousness lasting 30 min or more; and (v) metal implant or any other contraindications to MR scanning.

METH users were selected from outpatient drug use camps. All patients were interviewed by a psychiatrist and a neurologist, considering the inclusion and exclusion criteria. The control group was selected from the local community and was homogenous with the METH group (not for METH use background). To detect the current use of METH, urine screening was conducted: urine analysis at the baseline interview and before the MRS scan. All participants were current METH user. Then, all participants collected urine specimens for 24 hours to measure presence of specific metabolites including METH metabolite level, 5-Hydroxy indoleacetic acid metabolite (for serotonin level monitoring), and metanephrine metabolite (for dopamine level monitoring).

Positive and Negative Syndrome Scale (PANSS)

Psychotic symptoms were assessed with the full 30-item PANSS, which has been used previously validated in the

Persian population (30). Analysis of the PANSS Data was done based on the standard three factors and the five-factor models. Regarding five-factor models, the items on the PANSS were categorized into the factors as follows followed by summing: negative (N1, N2, N3, N4, N6, G7, G13, and G16), positive (items P1, P3, P5, P6, G9, and G12), anxiety/depression (G1, G2, G3, G4, and G6), disorganization (P2, N5, N7, G5, G10, G11, and G15), excitement (P4, P7, G8, and G14) dimensions (31).

Proton Magnetic Resonance Spectroscopy Data

1HMRS imaging as the MRS multivoxel version as well as prescriptive structural MRI were obtained in a session. 1HMRS spectra of reward pathway (PFC, Hippocampus, VTA, Substantia nigra, NAc, Striatum) was conducted on 1.5T Siemens (Avanto, Imamhosein Hospital, Shahroud University of Medical Sciences, Iran) with standard head coil (18 channel) and the subsequent criterion: T1 image parameters with ms parameters (TE = 1.53.3.21.4.89.6.57ms, TR = 1500) (FOV = 256mm) (FA = 7), 160 cut, with 10min scan time, and sectional thickness about 1mm. Then 3D CSI imaging with the following criteria: TR = 1500, TE = 270 and, VOI = 100.50.80, FOV = 160.160.160, NEX = 2, 15 mm sectional thickness. CHESS automatic pulse twice with 2TE and 2VOIs showed in 15min. Analysis was performed with the console Siemens syngo software and measuring the curvature of the NAA, Cre, Cho, Glx, MI with 2VOIs (left and right five brain regions) with 2 TE short and high and after achieving the corresponding curve. The spectrum of neurometabolites were sent to the neuroradiologist.

Magnetic Resonance Post-processing

1HMRS imaging spectra were obtained by the spectroscopic evaluation software (syngosimens) and levels of neurometabolites were obtained in the brain areas by statistical analysis (Note: Glx concentration due to limited field strength (1.5 T) was low SNR).

Statistical analysis

SPSS 20 was used to analyze data using a Student's t-test to compare the means of the metabolites in METH consumers and controls. The correlation between the metabolites and each clinical parameter, such as duration of METH usage, PANSS score, and Subscale of PANSS were assessed by Pearson's correlation coefficient at $P < 0.05$. The metabolites were calculated in the reward pathway (PFC, Hippocampus, VTA, Substantia nigra, NAc, Striatum). For error avoidance, repeated-measures ANOVA was applied for repeated values of the right and left hemispheres.

Ethical Approval

The research was approved by the local Ethics Committee of Shahroud University of Medical Sciences and has been performed under the ethical standards of the Declaration of Helsinki (Ethical code: IR. SHMU.1397.132). The present study was completed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health research established by ministry of Health and Medical Education and Ministry of Science, Research and Technology, Iran. All the participants provided their informed written consent for participation in the present study.

Results

No significant difference was found regarding age, sex, handedness, and socioeconomic status between the 42 METH users (34 men, 8 women; 38.04 ± 8.03 yr) and 21 healthy control subjects (14 men, 7 women; 38.42 ± 10.87 yr). The METH consumers used crystalline METH via inhalational and intravenous routes. They had used the drug for 4±3 years. The mean daily estimated METH use was 0.5 grams.

Table 1 demonstrated significant differences in the total concentration of Dopamine, Serotonin (in urine), NAA, Cre, Glx, and MI brain metabolites in the studied areas of the brain between METH users and Healthy controls, while two groups showed no significant differences in Cho. Mean (±SD) scores of total PANSS in the METH user group was 79.66±57.93.

Table 2 showed changes in amounts of NAA, Cre, Glx, and MI metabolites that were significantly correlated (negatively) with the PANSS total score and psychiatric disorders. Nonetheless, the PANSS total score and the Cho measure were not correlated. Furthermore, there is a significant association between the changes in metabolism of MI, and NAA, Cre, and Glx metabolites.

Table 3 showed that there was significant reduction in NAA metabolite levels in the METH group correlated with psychotic symptoms (Positive subscale in PANSS test) in the studied areas compared to the controls. Changes in Cho and Glx metabolism and psychological symptoms were associated.

Table 4 showed there was a negative correlation between NAA changes with duration of use and METH dosage. Changes in the amount of Cho, Glx, and MI with dose and duration of METH use have a positive correlation. Our findings showed there was no significant correlation between Cre and duration of consumption and METH dosage.

Table 1. Comparison of Total Metabolite Values in METH Users and the Healthy Control Group

Metabolites (ppm, Mean ± SD)	METH Users (n = 42)	Healthy Controls (n = 21)	Sig.
Dopamine	4.21±1.25	2.38±0.8	<0.001*
Serotonin	3.75±1.38	1.9±0.69	<0.001*
NAA	22.24±5.6	26.14±4.6	0.008 *
Cre	12.02±3.1	7.78±1.4	<0.001*
Cho	9.6±3.2	9.7±2.11	0.89
Glx	2.5±1.43	4.6±1.1	<0.001*
MI	2.59±1.33	4.9±1.29	<0.001*

* Significantly different from controls, Abbreviations: METH, Methamphetamine; ppm, parts per million; NAA, N-acetyl aspartate; Cho, Choline; Cre, Creatine; MI, Myo-inositol; Glx, Glutamine plus Glutamate; PANSS; Positive and Negative Syndrome Scale.

Table 2. Pearson r Correlations between Total PANSS Score and Neurometabolite Measures for the METH User Group (n = 42)

	PANSS	NAA	Cre	Cho	Glx	MI
PANSS	1					
NAA	r = -0.39 p = 0.002*	1				
Cre	r = -0.57 p < 0.001*	r = -0.14 p = 0.25	1			
Cho	r = -0.05 p = 0.7	r = 0.04 p = 0.72	r = 0.07 p = 0.58	1		
Glx	r = -0.55 p < 0.001*	r = 0.09 p = 0.48	r = -0.27 p = 0.03*	r = -0.05 p = 0.68	1	
MI	r = -0.59 p < 0.001*	r = 0.26 p = 0.04*	r = -0.32 p = 0.01*	r = 0.03 p = 0.82	r = 0.57 p < 0.001*	1

Abbreviations: METH, Methamphetamine; NAA, N-acetyl aspartate; Cho, Choline; Cre, Creatine; MI, Myo-inositol; Glx, Glutamine plus Glutamate; PANSS; Positive and Negative Syndrome Scale.

Table 3. Pearson r Correlations between Subscale PANSS Scores and Total Neurometabolite Values for the METH User Group (n = 42)

	Positive subscale	Negative subscale	Disorganization subscale	Excitement subscale	Anxiety/depression subscale	Total
Dopamine	r = -0.07 p = 0.67	r = -0.12 p = 0.44	r = -0.16 p = 0.32	r = -0.17 p = 0.29	r = -0.19 p = 0.23	r = 0.13 p = 0.41
Serotonin	r = 0.23 p = 0.14	r = -0.09 p = 0.54	r = 0.005 p = 0.97	r = 0.05 p = 0.75	r = -0.18 p = 0.28	r = 0.14 p = 0.38
NAA	r = -0.31 p = 0.04*	r = 0.07 p = 0.65	r = -0.03 p = 0.85	r = 0.04 p = 0.77	r = 0.06 p = 0.71	r = -0.2 p = 0.18
Cre	r = -.08 p = 0.58	r = -0.06 p = 0.7	r = -0.04 p = 0.98	r = -0.006 p = 0.97	r = -0.12 p = 0.43	r = 0.03 p = 0.86
Cho	r = 0.05 p = 0.76	r = 0.37 p = 0.01*	r = 0.24 p = 0.12	r = 0.4 p = 0.008*	r = 0.19 p = 0.22	r = -0.05 p = 0.75
Glx	r = 0.47 p = 0.002*	r = 0.19 p = 0.22	r = 0.08 p = 0.62	r = 0.06 p = 0.72	r = -0.09 p = 0.56	r = 0.19 p = 0.22
MI	r = 0.21 p = 0.18	r = 0.01 p = 0.93	r = -0.11 p = 0.49	r = -0.1 p = 0.52	r = -0.03 p = 0.85	r = 0.14 p = 0.37

* Significantly different from controls, Abbreviations: METH, Methamphetamine; NAA, N-acetyl aspartate; Cho, Choline; Cre, Creatine; Glx, Glutamine; MI, Myo-inositol plus Glutamate; PANSS; Positive and Negative Syndrome Scale.

Table 4. Pearson r Correlations between Dose of METH and Time of Use with Neurometabolite Values for the METH User Group (n = 42)

	NAA	Cho	Cr	Glx	MI
Dose of METH	r = -0.421 p < 0.007*	r = 0.482 p < 0.002*	r = 0.121 p < 0.458	r = 0.681 p < 0.0001*	r = 0.569 p < 0.0001*
Duration of Use	r = -0.415 p < 0.008*	r = 0.351 p < 0.026*	r = 0.164 p < 0.313	r = 0.571 p < 0.0001*	r = 0.392 p < 0.012*

* Significantly different from controls, Abbreviations: METH, Methamphetamine; NAA, N-acetyl aspartate; Cho, Choline; Cre, Creatine; MI, Myo-inositol; Glx, Glutamine plus Glutamate.

Discussion

We evaluated long-term METH use impact on brain metabolite concentration in cases who met the DSM-5 criteria regarding METH addiction. Our results showed that subsequent to consumption of METH and continuation of use, neurodegradation extended over various areas of the brain, especially serotonergic and dopaminergic (reward-related circuitry). The major findings obtained from the present study are as follows: (1) METH induced an increase in Dopamine and Serotonin (in urine sample); (2) METH caused elevation in Cre and a reduction in the NAA, Glx, and MI metabolite concentrations of dopamine circuits (PFC, VTA, NAc, Striatum, Substantia nigra, Hippocampus) in METH users compared to control subjects: (3) We found no change in Cho metabolite concentration; (4) A significant correlation was detected between psychological values and neurometabolite concentrations in the studied area of the brain.

Difference in brain metabolites between METH consumers and normal cases has been widely compared through 1HMRS. The associated brain areas were PFC (27, 28), anterior cingulate cortices (ACC) (24, 25), hippocampus, amygdala (32), and basal ganglia (26). The key role of the reward circuit and the mesocorticolimbic circuit in drug use has been demonstrated in literature. However, the 1HMRS assessment of all mentioned brain regions together has obtained less attention.

Our findings, in line with previous studies, showed decreased NAA metabolite concentration in the METH user group (19, 33). Finding abnormally low NAA in the METH users is consistent with the pattern associated with neuronal loss or damage (34). Related psychological findings have also been reported in other studies (29, 35). Another consistent finding was a decrease of Glx in the studied area (27). The effect of METH is associated with dopamine and serotonin as well as other neurotransmitters, including glutamate (36, 37). The decreased Glx may be due to the loss of glutamatergic neurons.

Inconsistent findings include Cre, MI, and Cho levels (5, 16, 19, 38). Our obtained finding was decreased MI which may indicate reduced glial density or function in response to prolonged METH use. However, METH-induced neurotoxicity associated with decreased glial reactivity remains currently unknown (39). We did not detect a significant difference in the Cho level and significantly increased Cre level in METH users than the control group. This inconsistency in some metabolite levels may be due to differences in dosage and duration of METH use (40). Chronic users of METH show elevated levels of Glx, MI, and Cho, and reduced levels of NAA and Cre compared to healthy controls in a variety of cortical regions (18-20, 22, 26, 41, 42). METH-induced psychiatric signs are common, including irritability, anxiety, psychosis, and mood abnormalities (15).

According to previous research, those with chronic METH psychosis and no use of METH, had psychotic symptoms (43). There were no differences in delusion patterns between cases with schizophrenia and chronic psychosis due to METH and auditory hallucinations were the most common type of hallucination (44). Our results also show that there was decline in concentration of NAA and elevation in Glx metabolites consistent with enhancement in positive symptoms (hallucinations, delusions) in METH users. Another study found persistent METH psychosis as well as schizophrenia with same severity and rate, and the two groups obtained significantly higher PANSS scores compared with cases with acute METH psychosis (44). Based on the PANSS scale scores in the current research, it was found that the severity and frequencies of positive symptoms were significantly associated with neurometabolite concentrations than negative manifestations. Negative manifestations, like flat affect, apathy, social isolation, poverty of speech, loss of drive, and anhedonia were found in cases with psychosis due to METH. However, in the present research, no significant association was observed between these symptoms and other variables.

Present findings showed that in the METH group, neurometabolite concentrations were significantly correlated with psychotic symptoms. In the present research, the total PANSS score significantly correlated with abnormal concentration of NAA, Cre, Glx, and MI. Moreover, positive symptoms significantly correlated with lower NAA and high Glx. Also, negative symptoms and excitement correlated with Cho. The present results add to the growing body of literature indicating abnormalities in neurometabolites in particular brain regions correlated with psychiatric symptoms. Liemburg *et al.* (2016) performed a 1HMRS study and showed that the chronicity of schizophrenia was related to decreased

levels of Glx and NAA in PFC (45). In contrast with our results, Callicott *et al.* (2000) reported lower prefrontal NAA predicted more severe negative symptoms in patients with schizophrenia (46). Patients with untreated psychosis display significant increase in total Cho in the left anterior cingulate and left thalamus (47) and there is correlation between high Cho concentrations in the caudate nucleus in schizophrenic patients (48). Rothermundt *et al.* (2007) reported schizophrenic patients showed high myo-inositol concentrations (49).

Suggestions for future studies

Both detailed research using resting-state functional connectivity and studies utilizing a task such as cue-associated craving need to extend and deepen our knowledge of the neurobiological bases of drug abuse. Future studies by researchers are suggested to perform more detailed research on brain microstructural abnormalities of METH users with single-voxel spectroscopy and fiber-tract sites of the reward system. They are also recommended to study functional connectivity in the neurocircuitry of the brain in METH users through diffusion tensor imaging (DTI).

Limitation

In terms of study limitations, first, due to the difficulty of access to METH users, the sample size was small and second, sample finding was resolved by assistance of peer user friends.

Conclusion

METH consumption correlates with reduced neuronal integrity and viability, particularly in dopamine pathways (PFC, VTA, Striatum, NAc, Substantia nigra, Hippocampus). There is an association between METH addiction and active neurodegeneration in the dopamine circuit, and it causes serious mental illness. 1HMRS can detect patient's deterioration and progression of disease as well as follow-up management in patients with METH use disorder.

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Conflict of Interest

None.

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