Shotgun proteomics analysis of protein responding to methamphetamine addiction in rat cerebellum

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Background : *Methamphetamine (METH) is an addictive psychostimulant drug that induces damages several regions of the brain, including the cerebellum. METH can induce some proteins changes in synaptic neurotransmission and signal transduction underlying the mechanism of drug addiction in several brain regions such as the striatum, hippocampus and nucleus accumbens. Nevertheless, few studies have examined the effects of METH in the cerebellum.*

Objective : *The aim of the current study was to investigate changes in the synaptic neurotransmission and signal transduction protein expression in rat cerebellum following METH exposure using proteomics technique.*

Methods : *Male Sprague-Dawley rats were treated with an escalating dose-METH binge and saline in control group for 15 days. Three samples from each group were pooled and proteins were extracted from the cerebellar tissues. The proteomics, liquid chromatography-tandem mass spectrometry (LC-MS/MS) was then performed to identify the protein associated with the METH-induced drug addiction.*

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Results　　**:**　*In the cerebellar samples, it was found that nine proteins were altered and mapped to synaptic transmission and signal transduction. In METH group, seven proteins were identified, including excitatory amino acid transporter 1, synaptotagmin-7, shisa-6, thioredoxin-related transmembrane protein 4, serine/ threonine-protein kinase SIK1, plexin-B3, calbindin, were found upregulation while two down-regulated proteins including cAMP-specific 3',5'-cyclic phosphodiesterase 4D and neuronal acetylcholine receptor subunit alpha-10 were observed.*

Conclusion　**:**　*The alteration of synaptic transmission and signal transduction proteins was found in the cerebellum following METH exposure. The results of this study provide evidence to support disturbance of protein expression in cerebellum in METH addiction.*

Keywords　**:**　*Methamphetamine, drug addiction, cerebellum, proteomics.*

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เหตุผลของการทำวิจัย : *เมทแอมเฟตามีน เป็นยาเสพติดที่ออกฤทธิ์กระตุ้นระบบประสาทส่วนกลาง ซึ่งมีรายงานถึงการเหนี่ยวนำสมองในหลายบริเวณได้รับความเสียหายรวมทั้งสมองส่วนซีรีเบลลัม ทั้งยังส่งผลให้เกิดการเปลี่ยนแปลงของโปรตีนในกระบวนการ synaptic transmission และ signal transduction ภายใต้กลไกการติดยาเสพติดในสมองหลายบริเวณ เช่น striatum, hippocampus และ nucleus accumbens อย่างไรก็ตามรายงานการศึกษาถึงผลกระทบของเมทแอมเฟตามีนต่อสมองส่วนซีรีเบลลัมยังมีไม่มาก*

วัตถุประสงค์ : *เพื่อศึกษาถึงการเปลี่ยนแปลงของโปรตีนในกระบวนการ synaptic transmission และ signal transduction ในสมองหนูส่วนซีรีเบลลัมภายหลังจากได้รับเมทแอมเฟตามีน โดยใช้เทคนิคทางโปรตีโอมิกส์*

วิธีการทำวิจัย : *ทำการเหนี่ยวนำหนูแรทเพศผู้สายพันธุ์ Sprague-Dawley ให้เกิดการเสพติดโดยได้รับเมทแอมเฟตามีนแบบ Escalating dose-Binge และในกลุ่มควบคุมได้รับสารละลายน้ำเกลือเป็นระยะเวลา 15 วัน จากนั้นนำสมองส่วนซีรีเบลลัมในแต่ละกลุ่ม (n = 3) มารวมกันและทำการสกัดโปรตีนเพื่อที่จะศึกษาระบุชนิดโปรตีนที่เกี่ยวข้องกับกลไกการติดยาเสพติดเมทแอมเฟตามีนด้วยเทคนิค liquid chromatography-tandem mass spectrometry (LC-MS/MS)*

ผลการศึกษา : *พบว่าหลังจากหนูได้รับเมทแอมเฟตามีน มีการเปลี่ยนแปลงของโปรตีนในสมองหนูส่วนซีรีเบลลัมทั้งสิ้น 9 ชนิด ที่ถูกจัดอยู่ในกลุ่ม synaptic transmission และ signal transduction โดยพบโปรตีน 7 ชนิดที่โปรแกรม MultiExperiment Viewer (MeV) ทำนายว่ามีการแสดงออกมากขึ้น ได้แก่ excitatory amino acid transporter 1, synaptotagmin-7, shisa-6, thioredoxin-related transmembrane protein 4, serine/threonine-protein kinase SIK1, plexin-B3 และ calbindin ในขณะที่โปรตีนอีก 2 ชนิด ได้แก่ cAMP-specific 3',5'-cyclic phosphodiesterase 4D และ neuronal acetylcholine receptor subunit alpha-10 มีการแสดงออกลดลง*

สรุป : *โปรตีนในกลุ่ม synaptic transmission และ signal transduction ถูกพบว่ามีการเปลี่ยนแปลงในสมองหนูส่วนซีรีเบลลัมหลังจากได้รับ เมทแอมเฟตามีน ซึ่งผลจากการศึกษาวิจัยในครั้งนี้เป็นการสนับสนุน และเพิ่มเติมข้อมูลในส่วนของโปรตีนที่มีการแสดงออกอย่างผิดปกติ ในสมองส่วนซีรีเบลลัมในโมเดลของสัตว์ทดลองที่มีการติดยาเสพติด เมทแอมเฟตามีน*

คำสำคัญ : *เมทแอมเฟตามีน, การติดยาเสพติด, ซีรีเบลลัม, โปรตีโอมิกส์.*

Methamphetamine (METH), an amphetamine derivative, is a psychostimulant drug with potent effects on the central nervous system (CNS). [1] The abuse of the drugs, including METH, can induce changes of mood and feeling, leading to addiction. [2, 3] Drug addiction, also called drug dependence, is characterized by compulsive drug-seeking and drug use leading to impairments of the brain. [4] Previous studies indicated abnormalities of several brain areas such as the frontal cortex, hippocampus and amygdala underlying the processes of addiction. [5, 6] Apart from these brain areas, increasing evidences suggests that the cerebellum is also involved in drug-related behavioral alterations. [7, 8] Cerebellum is a brain region that plays important roles in control and coordination of movements. In addition, the neuroimaging studies showed the association of cerebellum with cocaine and alcohol related addictive behaviors. [7, 9] A previous study investigated an increasing of tyrosine hydroxylase protein, the rate-limiting enzyme of catecholamine biosynthesis, in mice cerebellar cortex after METH administration suggesting an involvement with motor function alteration. [10] Moreover, the repeated METH exposure can induce an impairment of biological functions in rat cerebellum. [11] Nowadays, the mechanism of drug addiction involved with cerebellar function abnormalities has been drawn attention and needed to be elucidated. There are several evidences that indicates the role of neurotransmission systems in addiction processes. [12, 13] METH induces disruption of dopamine transporter functions leading to abnormal dopaminergic neurotransmission. [12, 14] Furthermore, glutamatergic neurotransmission has been found to be disrupted after METH and amphetamine administration including an alteration of glutamate receptor protein, mRNA, and gene expression. [15, 16] Several studies have pointed out to the role of GABAergic neurotransmission in drug addiction by disrupting gamma-aminobutyric acid (GABA) receptors, GABA transporters and calcium binding proteins (neuronal marker). [17, 18] However, the molecular mechanisms underlying the processes of METH addiction in the cerebellum remains unclear. Recently, the proteomics has been employed to evaluate the differential expression of proteins and functional outputs of a biological system in drug addiction such as oxidative stress response, protein modification and degradation, synaptic function and neurotransmission. [19] Proteomics analysis revealed the effects of METH sensitized rats including synaptic regulation, protein phosphatase signaling, mitochondrial function and alterations to the inhibitory GABAergic network in the prefrontal cortex. [6] Moreover, the proteome study in rat cortex indicated alteration of protein after acute METH exposure. [20] Therefore, the proteomic approach was employed in this study to investigate the differential protein expression in rat cerebellum associated with METH addiction, an escalating dose-binge (ED-Binge) treatment suggesting a similar effect to human METH addiction profile. [21]

Methods

Animals

Male Sprague-Dawley rats (200 - 250 g) were obtained from the National Laboratory Animal Center, Mahidol University, Nakorn Pathom, Thailand. The animals were housed in cages and maintained at $24 \pm 1^\circ$C under a 12-h light/dark cycle with free

access to food and water. Before drug administration, all animals were habituated for 5 days. All animal procedures were carried out in compliance with Mahidol University Code of Practice the National Institutes of Health (USA) Guidelines for treatment of laboratory animals. The experimental protocol for this study was approved by the Animals Research Committee of Naresuan University, Thailand.

Methamphetamine administration

D-Methamphetamine hydrochloride (Alletch, palatine & DC, IL, USA) was used for the experiment with permission from the Thai Ministry of Public Health. METH was dissolved in saline. The animals were divided into two groups: control group and escalating dose METH binge (ED-METH Binge) group. The rats in the former group were intraperitoneally injected (i.p.) with saline whereas the latter, with increasing doses of METH following previous studies. [18, 21] As for the control group, the rats were injected i.p. with saline for 15 days. ED-METH Binge rats were received three injections per day at 3-h intervals of gradually increasing doses of METH from 0.1 mg/kg to 4.0 mg/kg for 2 weeks. The last day, ED-METH Binge rats received four injections per day at 2-h intervals of 6.0 mg/kg METH. The rats were sacrificed by cervical dislocation at 24 h after the last injection. The brains were removed and cerebellums dissected and stored at -80°C for further processing.

Protein extraction

Cerebellar tissues were homogenized [18] in 5 mM Tris-HCl containing 20 mM NaCl, pH 8.0 and homogenate was then centrifuged for 10 min at 14,000 × g. The pellet was collected and homogenized again in lysis buffer containing 50 mM Tris-HCl, 0.15 M NaCl, 0.1% SDS, 0.25% sodium deoxycholate, and 1% protease inhibitor cocktail (P8340, Sigma-Aldrich). Protein concentrations in the tissue lysates was measured by the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL., USA).

Protein digestion

Protein samples of each group were pooled (n = 3) for LC-MS/MS analysis. A total of 5 ตg of protein samples were reduced with 10 mm dithiothreitol in 10 mM ammonium bicarbonate and incubated at 56°C for 1 h, followed by the alkylation with 30 mM iodoacetamide 10 mM ammonium bicarbonate incubation at room temperature in the dark box for 1 h. To perform in-solution digestion, the proteins were digested with 50 ng trypsin in 10 mM ammonium bicarbonate, and incubated overnight at 37°C.

LC-MS/MS and protein identification

The tryptic peptides were purified with ZipTip pipette tips (Merck Millipore, Darmstadt, Germany).The purified peptides were eluted with 70% acetonitrile, 0.1% formic acid solution. The elute peptides were dried and resuspended in 0.1% formic acid. The solution was centrifuged at 10,000 rpm for 10 min and transferred to vial tubes. The resuspended peptide was injected three times to LC-MS/MS. The quantification of protein from rat cerebellums was analyzed by DeCyder MS Differential Analysis software (GE Healthcare) and submitted to database search using the Mascot program. The data was searched against the NCBI database for protein identification.

Results

A total of 1,595 proteins were identified by a mascot search of the *Rattus* database. The proteins expression of control and ED-METH Binge groups were compared as shown in Venn's diagram (Figure 1). The results demonstrated possible relations of protein expression in both groups. A total of 1,262 expressed proteins were presented in at least one sample in each of the two sample groups. A total of 141 expressed proteins were found only in control group and 192 expressed proteins were found only in ED-METH Binge group.

The expressed proteins were classified by the PANTHER (Protein Analysis through Evolutionary Relationships) software. The expressed proteins are listed following the protein categories including biological processes, cellular components, and molecular functions (Figure 2). The identified proteins according to the biological processes, cellular components and molecular functions were classed into 11, 7 and 8 classes respectively. In addition, most of the identified proteins in the biological processes are involved in cellular process (28.70%; control and 29.10%, METH). High percentages of identified proteins in the molecular functions were shown in catalytic activity (40.00%; control and 40.30; METH) and binding (36.10%; control and 34.20%; METH) classes. Furthermore, the identified proteins in the cellular components showed a higher percentage in both classes such as cell part (35.30%; control and 36.50%; METH) and organelle (27.50%; control and 27.70%; METH).

The identified proteins in the cellular process were focused underlying the biological process functions to control molecular activities. A sub-class of the cellular processes is mostly mapped to cellular communication that contains both of subtypes including cell-cell signaling (synaptic transmission) and signal transduction. The protein in those subtypes are included the neuronal acetylcholine receptor subunit alpha-10, excitatory amino acid transporter 1, synaptotagmin-7, cAMP-specific 3',5'-cyclic
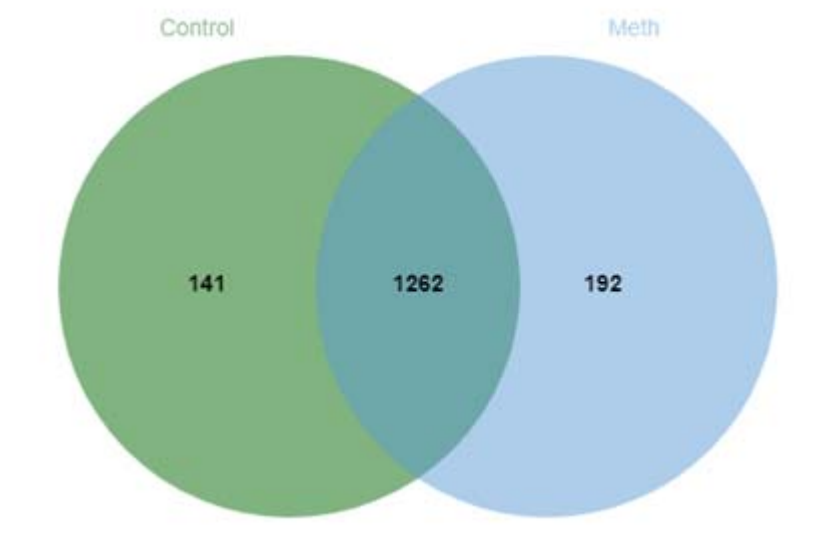

Figure 1. Venn diagram of protein expression with different intensity between control and METH of rat cerebellum.
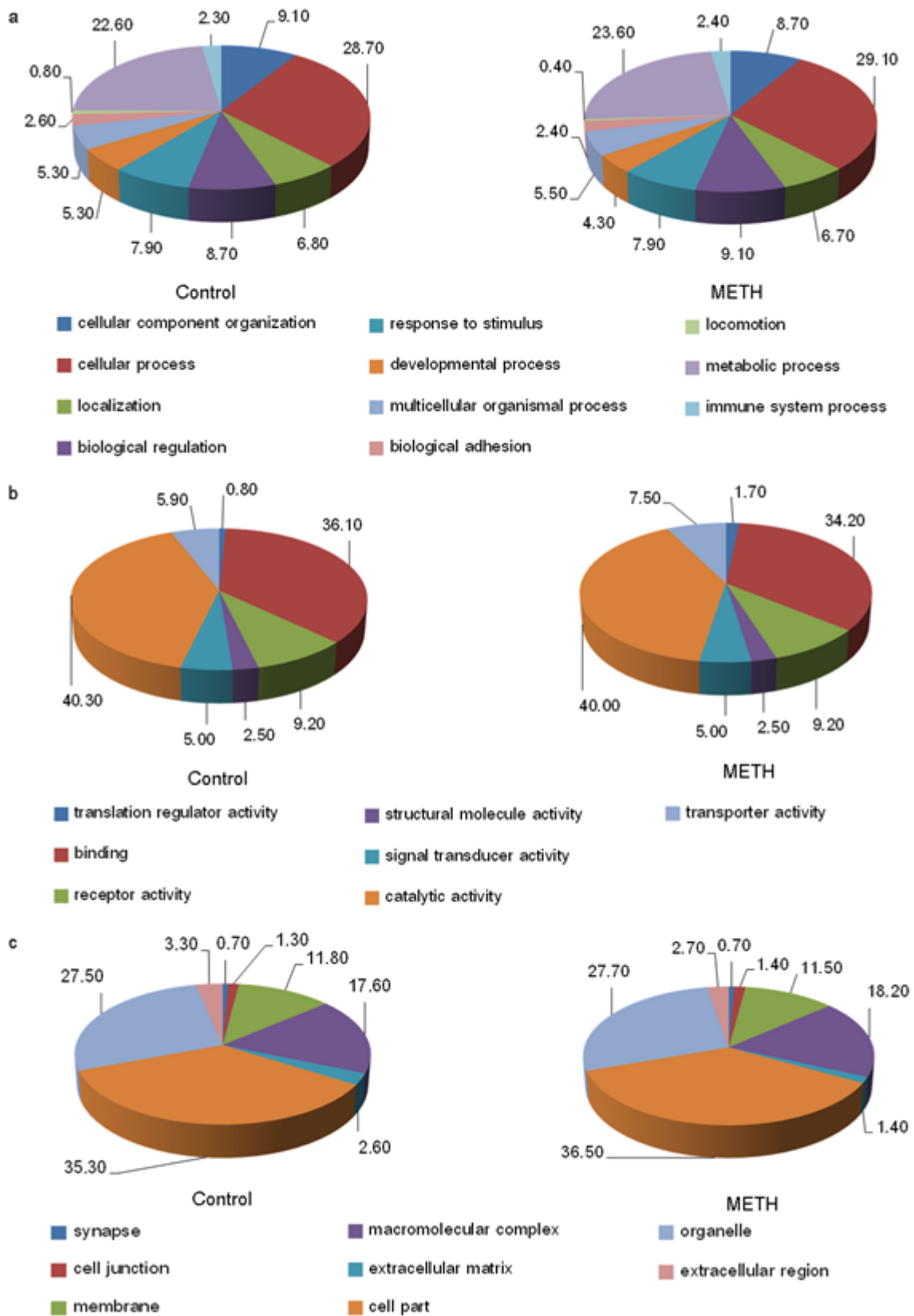
Figure 2. Percentage of proteins in biological process (a), molecular function (b) and cellular component (c) in control and METH groups.

phosphodiesterase 4D, thioredoxin domain containing 13, plexin-B3, protein shisa-6, serine/threonine-protein kinase SIK1, and calbindin mapped to calcium ion homeostasis (subtype of cellular process). An expression pattern of these proteins were analysed by MultiExperiment Viewer (MeV, Version 4.9) software as shown in Figure 3. Quantitative proteins is marked using a color scale from low to high (green, dark, and red, respectively). The differentially expressed proteins are presented between control and ED-METH Binge groups. A value of protein expression ratio between ED-METH Binge and control groups are presented in Table 1. These proteins were grouped according to majority of biological processes (cellular process) which derived from the PANTHER software. Furthermore, these proteins are linked to molecular functions and cellular components (localization). Seven proteins were up-regulated including excitatory amino acid transporter 1 (EAAT1), synaptotagmin-7 (Syt7), protein shisa-6, thioredoxin-related transmembrane protein 4 (TMX4), serine/ threonine-protein kinase SIK1 (SIK1), plexin-B3 (PLXNB3), and calbindin, while 2 proteins were down-regulated including cAMP-specific 3',5'-cyclic phosphodiesterase 4D (PDE4D) and neuronal acetylcholine receptor subunit alpha-10 (nAChRα10).

Discussion

The present study revealed that ED-METH Binge administration produced the alteration of protein expression in rat cerebellums. All the nine proteins showed the majority of proteins mapped to synaptic transmissions and signal transduction groups. Seven of these proteins were up-regulated after METH exposure while 2 proteins were down-regulated. The results are consistent with previous reports which abnormalities of synaptic transmission found in METH administration, especially glutamatergic [16] and GABAergic [17] neurotransmission. In addition, an up-regulation of proteins associated with glutamatergic neurotransmission including glial glutamate transporter EAAT1 and shisa-6 proteins, has been observed in this study. Previous studies also reported an up-regulation of neuronal glutamate transporter EAAT3 protein in the hippocampus [22] and glial glutamate transporter EAAT2 in striatum [23] following METH exposure. Furthermore, METH induced glutamate release was observed in several brain regions, such as hippocampus [24], nucleus accumbens [25] and striatum. [26] Thus, increased expression of EAAT1 protein in this study may be a compensatory of the EAAT1 (glial glutamate transporter) to maintain extracellular glutamate levels which are induced by
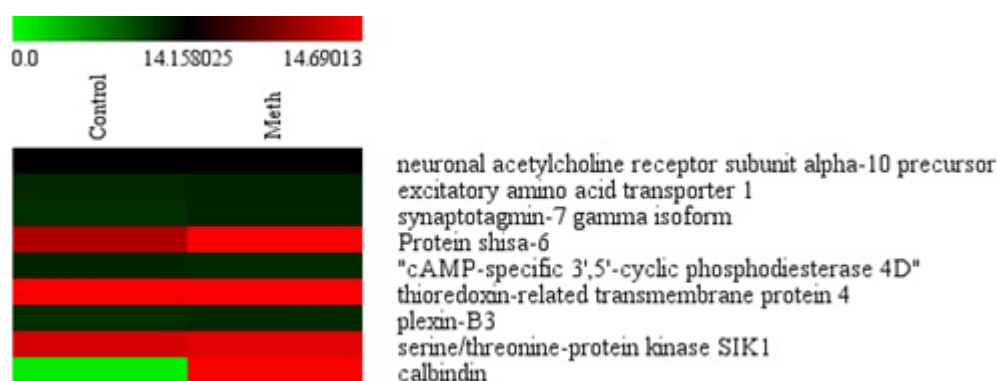

Figure 3. Heat map of differentially expressed proteins between control and METH-treated rats.

Table 1. Relative ratio of proteins alteration after METH exposure.

Protein name	Biological process	Molecular function	Localization	ER
neuronal acetylcholine receptor subunit alpha-10	- neuromuscular synaptic transmission	- ligand-gated ion channel activity	Cell membrane	0.999
excitatory amino acid transporter 1	- signal transduction - synaptic transmission	- transporter activity - calcium ion binding	Unknown	1.021
synaptotagmin-7	- synaptic transmission - synaptic vesicle exocytosis	- protein binding	Unknown	1.057
protein shisa-6	- response to stimulus - synaptic transmission - cell surface receptor signaling pathway	- glutamate receptor activity - ligand-gated ion channel activity	Cell membrane	1.011
cAMP-specific 3',5'-cyclic phos-phodiesterase 4D	- signal transduction	Unknown	Unknown	0.984
thioredoxin-related transmembrane protein 4	- intracellular signal transduction	Unknown	Unknown	1.104
serine/threonine-protein kinase SIK1	- intracellular signal transduction	- protein kinase activity	Cytoplasm, Nucleus	1.002
plexin-B3	- Cell surface receptor signaling pathway	- receptor activity - signal transducer activity	Cell membrane	1.018
calbindin	- cellular calcium ion - homeostasis cellular process	- calcium ion binding	Cytoplasm, Nucleus	N/A

Notation: ER; expression ratio between Meth and control, >1; protein is up-regulated in Meth, <1; protein is down-regulated in Meth. N/A; Proteins found only in Meth group.

METH exposure.[27] Moreover, shisa-6 protein was found to be up-regulated in METH treated rats in this study. It is possible that an up-regulation of shiha-6 proteins would be mediated mechanism to protect synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor from desensitization on repeated synaptic activity[28] in METH addiction. Surprisingly, five proteins comprised of calbindin, Syt7, SIK1, TMX4 and PLXNB3 were found up-regulation in this study. Calbindin (a calcium

binding protein) has been shown differentially changes by an up-regulation of mRNA encoding for calbindin protein in rat prefrontal cortex after METH sensitization underlying an involvement of GABAergic neurotransmission in METH addiction. [29] Syt7, a calcium sensor that is required for facilitation at several central synapses, was presented an up-regulation of mRNA expression after acute and chronic METH treatment of rat brains. [30] SIK1, a protein that regulates active sodium transport through a calcium-dependent process, was found to induce protein expression after cocaine exposure. [31] TMX4 is a type I transmembrane protein. It has not previously been reported in drug addiction related brain disorder. However, mutation in the TMX3 gene has been linked with Huntington's disease, a neurodegenerative disorder. [32] Although, PLXNB3 protein, a main receptor for semaphorin, has not been linked to a process of addiction, semaphorin was shown the mutation by disrupting limbic and cortical connectivity of neurodevelopmental psychopathology models. [33] A down-regulation of two proteins in this study comprises of nAChRα10 and PDE4D. Nicotinic acetylcholine receptor (nAChR) subtypes $\alpha(4)\beta(2)$ and $\alpha7$ are mediated synaptic neurotransmission and plasticity in cerebellum that are important for alcohol and alcohol addictions. [34] A previous study reported the contribution of alpha7 nicotinic acetylcholine receptor or nAChR$\alpha7$ to the pathogenesis of neurocognitive disorders. [35] PDE4D, a subtype of cyclic nucleotide phosphordiesterase (PDEs), is implicated in the regulation of alcohol consumption [36] and neuropsychiatric disorders. [37] Our results provide evidence to support abnormal functions of synaptic transmission and signal transduction in cerebellum of METH addiction model.

Conclusion

In summary, ED-METH Binge exposure resulted in the changes of protein expression mapped to synaptic neurotransmission and signal transduction. These protein alterations in this study are initially investigate for the pattern of protein which may be related to addiction. Consequently, further studies of proteins mapped to these groups are needed to confirm the results from proteomics analysis and to understand the mechanisms underlying synaptic transmission and signal transduction dysfunction in drug addiction.

Acknowledgement

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