Research Article

Proteomic analysis of cell-cell signaling alteration in rat frontal cortex following methamphetamine exposure

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Abstract

Methamphetamine (METH) is an addictive psychostimulant with potent effects on the central nervous system (CNS). Prolonged use of METH can impair brain structures and functions, especially the frontal cortex, a key brain involved in behavioral and cognitive functions. Moreover, METH has been reported change a number of proteins in neurotransmitter systems as well as proteins related to synaptic functions. Therefore, the objective of this study was to use the proteomic approach to investigate the differential expression of proteins related to synaptic function, including cell-cell signaling, in frontal cortex after METH administration. 20 male Sprague-Dawley rats were divided into 2 groups of control and METH; the rats were treated with saline and escalating binge dose of METH (0.1 to 4 mg/kg of METH (3 times /day), for 14 days and binge dose, 6 mg/kg (4 times /day) at day 15), respectively. The proteins in rat frontal cortex were investigated by proteomics technique. The results showed that there were 1,312 differentially expressed proteins in the frontal cortex of control and METH rats. Fifty-eight proteins were grouped in cell-cell signaling proteins. Thirty-six proteins were down-regulated and twenty-two proteins were up-regulated following METH administration. Furthermore, METH-interacted cell signaling proteins were mostly involved in neurotransmitter systems, 10 proteins in glutamatergic system, including 5 proteins in GABAergic system and 6 proteins in acetylcholine system. The results suggested that METH administration affects changes of proteins related in cell-cell signaling of the brain. These effects may implicate in METH-induced neurotoxicity. Studying in the differentially expressed protein by proteomic approach provides potential proteins related to METH-induced neurotoxicity.

Keywords: Methamphetamine, Frontal cortex, Cell-cell signaling, Proteomics

Introduction

Methamphetamine (METH) is an amphetamine derivative. It is a highly addictive psychostimulant drug which has potent effects on the central nervous system (CNS). Long-term and high frequency of METH abuse can induce psychiatric symptoms such as euphoria, paranoia, hallucinations, delusions and psychomotor deficits [1, 2]. Additionally, much evidence has reported that METH has the effects on changed neurotransmitter systems such as dopamine, glutamate, and gamma-aminobutyric acid (GABA). It has been reported to damage neurons in several brain areas leading to brain dysfunctions [3].

The mesocorticolimbic pathway is a pathway involving in reward and drugs addiction [4]. This pathway is the projection of dopaminergic fibers connecting from the ventral tegmental area (VTA) to the nucleus accumbens, the amygdala, the hippocampus, and the frontal cortex [4]. The frontal cortex is a part of this pathway which has been reported in association with cognitive impairment and hyper-locomotor activity after METH exposure [5]. Recently, the mechanism of drug-induced behavioural abnormalities remains unclear. However, METH-induced dysregulations of neurotransmitter systems and alterations of addiction-related proteins in the frontal cortex are implicated in drug addiction and drug-induced psychosis [6, 7]. Exposure of METH can disturb the synaptic transmission by changing the distribution of receptors and proteins related to synaptic functions. Previous studies have reported that the effects of METH are related to dysregulation of chemical synapses, such as dopamine, glutamate and GABA [8, 9, 10]. In addition, the effects of METH on neuronal mechanisms for chemical exchange between pre- and post-synaptic neurons have been reported, including synaptic vesicle trafficking protein [7]. Taken together, as neurotransmission and protein changes can conduct the behavioral abnormalities of METH addiction, identification of the protein expression in the brain, especially cell-cell signaling (synaptic transmission) proteins, is then crucial for understanding the comprehensive molecular mechanism of METH addiction. Proteomics is a comprehensive approach to examine the protein expression profile such as identification, quantitation and characterization of the differentially expressed proteins [11].

The proteomic analysis has been performed to evaluate the effects of drug addiction on differential expression of proteins and functional biological process such as cell signaling, oxidative stress, and apoptosis [7]. Several studies have demonstrated the association of METH and amphetamine exposures with differential expressions of proteins involving in oxidative stress, apoptosis, inflammation, and mitochondrial metabolism [12, 13, 14]. Moreover, the proteomic study has revealed the effect of a single dose of METH administration relating biological system of cell-cell signaling [15]. Therefore, the present study has hypothesized that gradually increased doses of METH (escalating binge doses, which mimic a pattern of METH abuse in human, may affect alterations of proteins related to cell-cell signaling function. The objective of this study was to investigate the differential expression of cell-cell signaling proteins in the frontal cortex of METH-treated rats by using the proteomic approach.

Material and Method

Animal and METH administration

Male Sprague-Dawley rats weighing 280-350 g were obtained from National Laboratory Animal Center of Mahidol University, Thailand. The animals were maintained under conditions of controlled temperature (22°± 1°C) and 12-hour light and dark cycle, with given access to food and water. The experimental protocol for this study was approved by the Naresuan University Animal Care and Use Committee, Thailand, project number NU-AE590304. The protocols were adapted from Segal et al., 2003 and Veerasakul et al., 2016 [16, 17]. Briefly, the rats were divided into 2 groups (n=10 per group) including control and METH groups. The rats in the control group were injected intraperitoneally (i.p.) with 0.9% saline 2.0 ml/kg (3 times /day) for 15 days. In the METH group, rats were injected i.p. with escalating-binge dose d-Methamphetamine HCl (Lipomed AG, Arlesheim, Switzerland) with the permission of the Ministry of Public Health. The rats were injected a gradually increasing dose from 0.1 to 4 mg/kg of d-Methamphetamine HCl (3 times /day), for 14 days and a binge dose, 6 mg/kg (4 times /day) at day 15. After the end of administration, rats were sacrificed by cervical dislocation after anaesthetized by CO_2 and brains were removed. The frontal cortex was dissected and kept at -80 °C until assay.

The frontal cortex tissues were homogenized in 5 mM Tris-HCl containing 20 mM NaCl, pH 8.0. After that, the homogenate was centrifuged at 14,000 rpm for 10 minutes at 4°C. The pellet was collected and dissolved in lysis buffer (50 mM Tris-HCl, 0.15 M NaCl, 0.1% SDS, 0.25% sodium deoxycholate, and 1% protease inhibitor cocktail, P8340, Sigma-Aldrich), and was then incubated for 60 minutes on ice. Protein concentrations were measured by the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL., USA) and stored at -20°C.

Protein digestion

Protein samples were pooled into control or METH groups for LCMS/MS [18]. Briefly, equal amount (µg) of individual proteins (n=3) were pooled, based on protein concentration. A total of protein sample was 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 in 10 mM ammonium bicarbonate incubation at room temperature 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 digested peptide solutions were analyzed with Impact II UHR-TOF MS System (Bruker Daltonics Ltd., Germany) coupled to a nanoLC system: UltiMate 3000 LC System (Thermo Fisher Scientific, USA). Peptides were separated on a nanocolumn (PepSwift monolithic column 100 µm i.d. x 50 mm). Eluent A was 0.1% formic acid and eluent B was 80% acetonitrile in water containing 0.1% formic acid. Peptide separation was achieved with a linear gradient from 10% to 45% B for 8.5 min at a flow rate of 1 µL/min, including a regeneration step at 90% B and an equilibration step at 1% B, one run took 20 min. Peptide fragment mass spectra was acquired in data-dependent AutoMS mode with selecting most abundant precursor ions in 3 second cycle for fragmentation. The mass range of the MS scan was set to extend from 150 to 2200 m/z. The MS/MS data was submitted for a database search using the Mascot software (Matrix Science, London, UK, [19].

Bioinformatics tools

The data were searched against the NCBI database for protein identification. The maximum values of each group were used to determine the presence or absence of each identified protein. The Uniprot retrieve/ID mapping tool (http://www.uniprot.org) was used to create file for protein identifications, which was uploaded into PANTHER (http://www.pantherdb.org/) to classify the Gene ontology annotation including molecular function, biological process, and protein class [20]. The identified proteins and METH were submitted to STITCH version 5.0 to search for understanding cellular functions and interactions between proteins and small molecules in METH addiction [21].

Results

Protein identification

The results of protein expressions in the control and METH groups are shown in **figure 1**. A total of 5,101 proteins expressions were identified in two groups of study. There were 2,495 expressed proteins observed in both control and METH groups. A total of 1,401 proteins were only expressed in the control and 1,205 proteins were only expressed in METH. In 2,495 co-proteins expressions, the results identified 1,312 differentially expressed proteins in both control and METH groups. 558 proteins (43%) were found up-regulation and a down-regulation of 754 proteins (57%) were observed.

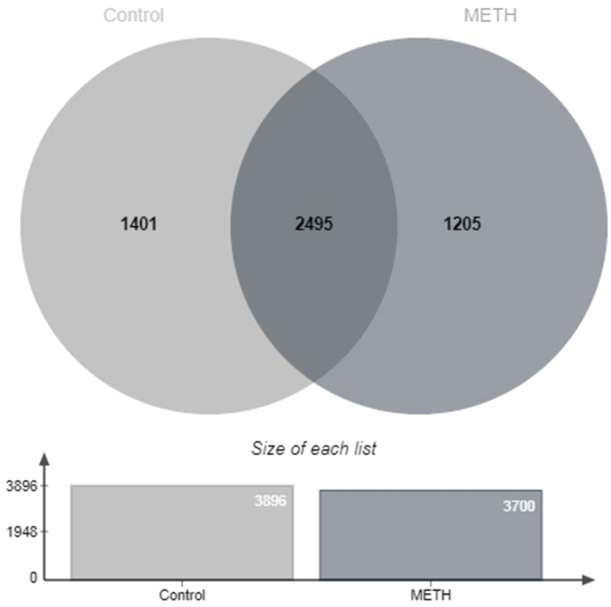

Figure 1: Venn diagram showing the number of differentially expressed proteins in frontal cortex of control and METH-administered rats.

Ontology of identified proteins

Uniprot and Pantherdb softwares were used to classify the expressed proteins into protein categories. The protein categories include biological processes, molecular functions and cellular components. The distributions of 1,312 differentially expressed proteins on gene ontology terms are displayed in **figure 2**. The results showed that METH responsive proteins are involved in many biological processes, molecular functions and cellular components. In biological processes, the cellular process (25%), the metabolic process (15%) and the biological regulation (15%) were altered after METH exposure **(Figure 2A).**

The major proteins in molecular functions associated with binding (38%) and catalytic activity (34%) were differentially expressed in METH exposure **(Figure 2B)**. In the cellular component classification **(Figure 2C)**, the protein changes were involved in the cell (37%) and organelle (23%).

In signaling functions-related proteins, 7% of differentially expressed proteins were found in the signaling class of the biological process **(Figure 2A)**. A total of 58 proteins changes were observed in cell-cell signaling subclass **(Table 1)**. The expression levels of these cell-cell signaling proteins are shown in the Heatmap **(Figure 3A)**, in which 36 proteins were down-regulated and 22 proteins were up-regulated following METH administration. Furthermore, the results from STITCH analysis showed the interactions between 58 cell-cell signaling proteins and METH. The METH-interacted proteins were mostly involved in neurotransmitter systems including 10 proteins in glutamatergic system, 5 proteins in GABAergic system and 6 proteins in acetylcholine system **(Figure 3B)**.

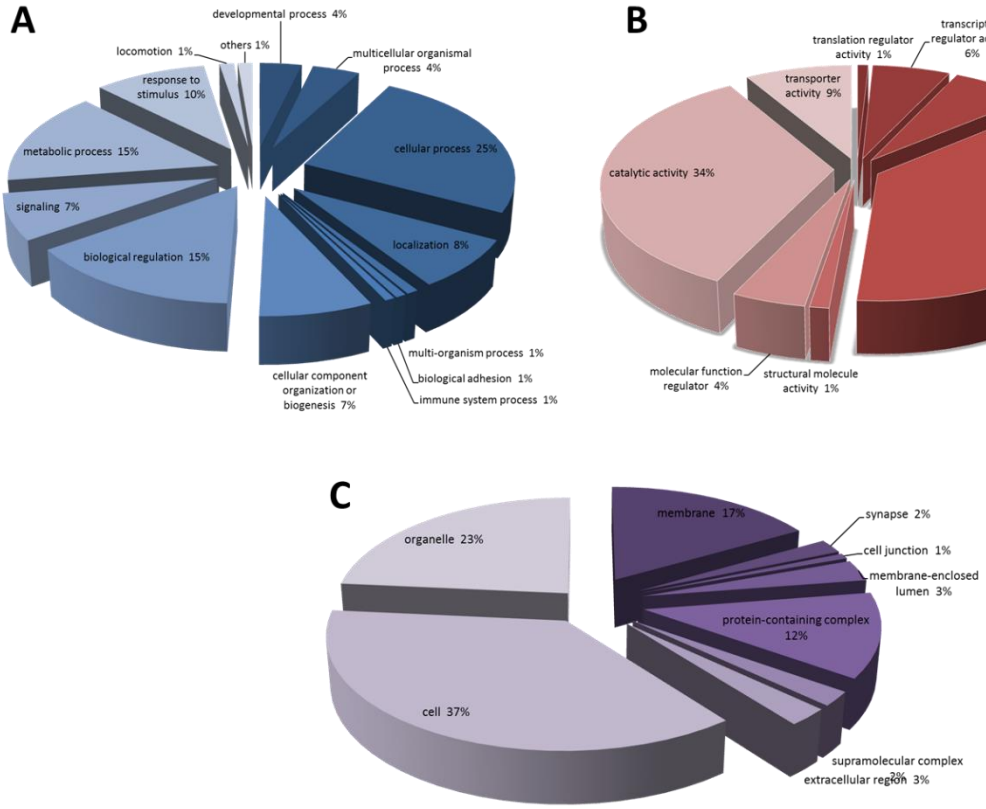

Figure 2: Distribution of Gene Ontology (GO) terms in Biological process (A), Molecular function (B) and Cellular component, (C) of 1,312 differentially expressed proteins after METH addiction.

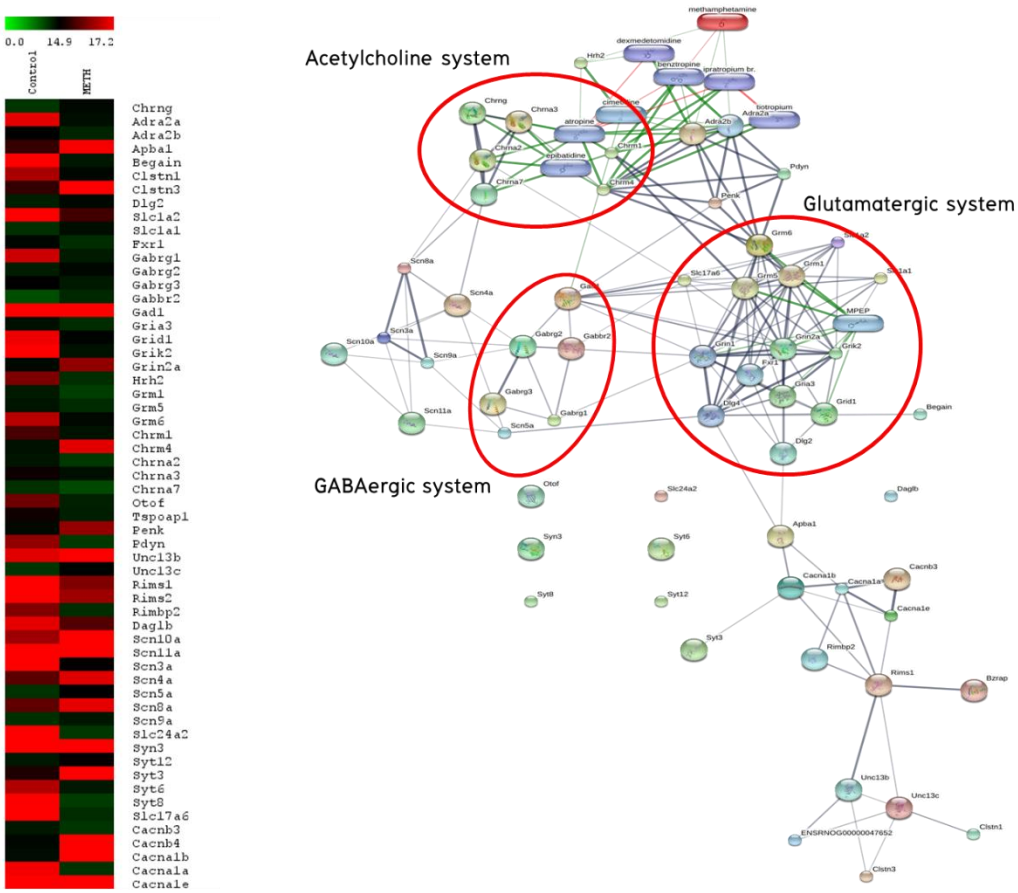

Figure 3: The heatmap from MultiExperiment Viewer (MEV) version 4.6.1 showing the levels of 58 proteins expression in control and METH groups. Green, black and red colors represent proteins with low, average and high levels of expression, respectively (A). An online STITCH 5.0 database predicted the interactions between METH and cell-cell signaling proteins involving in neurotransmitter systems. Modes of action are shown in different color lines (B).

Table 1 Identification of 58 cell-cell signaling proteins observed in METH and control

Uniprot number	Protein name	Gene name	Mr [kDa]
P18916	Acetylcholine receptor subunit gamma	Chrng	58.62
P22909	Alpha-2A adrenergic receptor	Adra2a	48.94
P19328	Alpha-2B adrenergic receptor	Adra2b	50.37
O35430	Amyloid-beta A4 precursor protein-binding family A member 1	Apba1	92.65
O88881	Brain-enriched guanylate kinase-associated protein	Begain	66.99
Q6Q0N0	Calsyntenin-1	Clstn1	106.26
Q8R553	Calsyntenin-3	Clstn3	105.94
Q63622	Disks large homolog 2	Dlg2	94.93
P31596	Excitatory amino acid transporter 2, EAAT2	Slc1a2	62.11
P51907	Excitatory amino acid transporter 3, EAAT3	Slc1a1	56.77
Q5XI81	Fragile X mental retardation syndrome-related protein 1	Fxr1	63.95
P23574	Gamma-aminobutyric acid receptor subunit gamma-1, GABAγ1R	Gabrg1	53.55
P18508	Gamma-aminobutyric acid receptor subunit gamma-2, GABAγ2R	Gabrg2	54.08
P28473	Gamma-aminobutyric acid receptor subunit gamma-3, GABAγ3R	Gabrg3	54.29
O88871	Gamma-aminobutyric acid type B receptor subunit 2, $GABA_BR2$	Gabbr2	105.75
P18088	Glutamate decarboxylase 1	Gad1	66.64
P19492	Glutamate receptor 3, AMPA3	Gria3	100.37

Uniprot number	Protein name	Gene name	Mr [kDa]
Q62640	Glutamate receptor ionotropic, delta-1	Grid1	112.12
P42260	Glutamate receptor ionotropic, kainate 2	Grik2	102.47
Q00959	Glutamate receptor ionotropic, NMDA 2A	Grin2a	165.47
P25102	Histamine H2 receptor	Hrh2	40.25
P23385	Metabotropic glutamate receptor 1, mGluR1	Grm1	133.23
P31424	Metabotropic glutamate receptor 5, mGluR5	Grm5	131.88
P35349	Metabotropic glutamate receptor 6, mGluR1	Grm6	95.09
P08482	Muscarinic acetylcholine receptor M1, M_1 mAChR	Chrm1	51.37
P08485	Muscarinic acetylcholine receptor M4, M_4 mAChR	Chrm4	52.81
P12389	Neuronal acetylcholine receptor subunit alpha-2, α7-nAChR	Chrna2	58.61
P04757	Neuronal acetylcholine receptor subunit alpha-3, α7-nAChR	Chrna3	57.00
Q05941	Neuronal acetylcholine receptor subunit alpha-7, α7-nAChR	Chrna7	56.50
Q9ERC5	Otoferlin	Otof	226.34
Q9JIR0	Peripheral-type benzodiazepine receptor-associated protein 1	Tspoap1	200.20
P04094	Proenkephalin-A	Penk	30.93
P06300	Proenkephalin-B	Pdyn	28.08
Q62769	Protein unc-13 homolog B	Unc13b	184.06
Q62770	Protein unc-13 homolog C	Unc13c	249.13
Q9JIR4	Regulating synaptic membrane exocytosis protein 1	Rims1	179.65
Q9JIS1	Regulating synaptic membrane exocytosis protein 2	Rims2	175.91
Q9JIR1	RIMS-binding protein 2	Rimbp2	115.61
P0C1S9	Sn1-specific diacylglycerol lipase beta	Daglb	73.77
Q62968	Sodium channel protein type 10 subunit alpha	Scn10a	219.73
O88457	Sodium channel protein type 11 subunit alpha	Scn11a	201.84
P08104	Sodium channel protein type 3 subunit alpha	Scn3a	221.38
P15390	Sodium channel protein type 4 subunit alpha	Scn4a	208.86
P15389	Sodium channel protein type 5 subunit alpha	Scn5a	227.36
O88420	Sodium channel protein type 8 subunit alpha	Scn8a	225.16
O08562	Sodium channel protein type 9 subunit alpha	Scn9a	226.04
O54701	Sodium/potassium/calcium exchanger 2	Slc24a2	74.66
O70441	Synapsin-3	Syn3	63.35
P97610	Synaptotagmin-12	Syt12	46.61
P40748	Synaptotagmin-3	Syt3	63.31
Q62746	Synaptotagmin-6	Syt6	57.18
Q925B4	Synaptotagmin-8	Syt8	43.98
Q9JI12	Vesicular glutamate transporter 2	Slc17a6	64.58
P54287	Voltage-dependent L-type calcium channel subunit beta-3	Cacnb3	54.56
D4A055	Voltage-dependent L-type calcium channel subunit beta-4	Cacnb4	57.96
Q02294	Voltage-dependent N-type calcium channel subunit alpha-1B	Cacna1b	262.25
P54282	Voltage-dependent P/Q-type calcium channel subunit alpha-1A	Cacna1a	251.52
Q07652	Voltage-dependent R-type calcium channel subunit alpha-1E	Cacna1e	252.11

Discussion

In the present study, the proteomic analysis demonstrated the differentially expressed proteins in the rat frontal cortex relating to METH addiction. 1,312 differentially expressed proteins were identified in control and METH groups. These proteins were distributed in many important biological processes, including the cellular process, metabolic process and biological regulation. However, proteins identified in cell-cell signaling are specifically represented to the neuronal function changes in METH addiction [15]. In this study, 58 proteins were detected in cell-cell signaling and most of them were involved in the neurotransmitter systems. Numerous studies have reported that METH exposure can damage

neuronal functions in the brain through the several mechanisms including neurotransmitter systems. The network connecting the identified proteins to METH implies the role of neurotransmitter related with METH addiction.

Based on the results of the protein interaction study, METH was associated with glutamate, GABA, and acetylcholine neurotransmitter systems. The glutamatergic system, a major excitatory neurotransmitter in the brain, plays an essential role to mediate locomotor actions of psychomotor stimulants, including METH [9]. In this study, at least 10 proteins in the glutamatergic system showed interaction with METH. Those proteins may be implicated in neurotoxicity of METH. METH has been reported to induce glutamate release in extracellular through the vesicular glutamate transporter (vGluT). High levels of extracellular glutamate can induce a high stimulation of the glutamate receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor (AMPA), N-methyl-D-aspartate glutamate receptor (NMDA) and metabotropic glutamate receptor (mGluR) leading to the neurotoxicity [22, 23]. Moreover, maintenance of the extracellular glutamate below excitotoxicity levels is performed by the reuptake of glutamate transporter (excitatory amino acid transporters; EAATs) [24]. Interestingly, our previous studies have shown the change of EAAT3 expression in the frontal cortex [23] and the genetic variation of GRIA3 (rs502434) gene, encodes for AMPA3 receptor [25], which are associated with METH addiction. The striatal vGluT2 was also altered by METH administration [26]. Moreover, another consistent with our finding, an alteration of group I mGluR (including mGluR1 and mGluR5) is implicated in METH addiction. Repeated administrations of amphetamine have been reported to increase mGlu1 and decrease mGlu5 expression in the rat striatum [27]. Taken together, changes in expression levels in those 10 proteins strongly represent the responses of the glutamatergic system to METH addiction.

In the same way, the present study found differentially expressed proteins in the GABAergic system which is an inhibitory neurotransmitter system in the brain. GABA is synthesized from glutamate by the glutamic acid decarboxylase (GAD). It is stored in vesicles and secreted to synaptic cleft. The system is activated by extracellular GABA binding to gamma-aminobutyric acid receptors (GABAR). The activation of GABAergic system plays a critical role in brain reward [28]. In this study, at least 5 proteins in GABAergic system showed interaction with METH, including GABAγ1R, GABAγ2R, GABAγ3R, GABABR2 and GAD67. Several reports have revealed the deficits of the GABAergic system in METH addiction. Reductions of GAD67 mRNA and protein expressions have been observed in schizophrenic patients [29, 30]. METH-induced psychosis can develop positive symptoms of schizophrenia [31]. Decreases in GAD67 may also initiate a decrease in GABA concentrations. In addition, genetic polymorphism of GAD67 was associated with METH psychosis [10, 32]. Furthermore, the present study found alterations of GABA receptors in METH addiction, especially GABABR2. The GABABR is a G-protein-coupled receptor which modulates the release of various neurotransmitters such as noradrenaline, serotonin, and somatostatin. However, the stimulation of GABABR has been reported to induce the inhibition of glutamate release [33]. The alterations of both GAD67 and GABABR2 proteins have also supported evidence that METH can induce a decrease in GABA concentration [34].

Another neurotransmitter system which are found to be involved in METH addiction is the cholinergic system. Acetylcholine plays an essential role in cognitive function, including learning, thinking, reasoning, remembering, problem solving, decision making, and attention. The alterations of acetylcholine and its receptors have been suggested in the cognitive impairments following METH exposure [35]. Six acetylcholine receptor proteins were altered after METH addiction. There are 2 types of acetylcholine receptors (AChRs), muscarinic receptor (mAChR) and nicotinic receptor (nAChR). The muscarinic receptor is a G-protein-coupled receptor (mAChR), which is located in both pre- and post-synaptic neurons throughout the brain. It therefore produces various consequences for brain activities [36]. Previous studies in addiction have shown an increase in the M1 mAChR in the hippocampus after METH exposure, and the stimulation of M1/M4 mAChR can decrease cocaine seeking behaviour in mice [37, 38]. In addition, a change of nAChR was also found in this study. Interestingly, the stimulation of nAChR modulates the GABA, glutamate, dopamine, serotonin, norepinephrine and acetylcholine transmission [36]. The key subtype of this effect is the α7-nAChR, which has been reported to be involved in nicotine mediated glutamate release in the rat hippocampus [39]. Moreover, decreased α7-nAChRs mediates to increase tobacco consumption in schizophrenia [40]. The M1 mAChR, M4 mAChR and α7-nAChRs were also found in the present study. Therefore, the alteration of acetylcholine system is related with METH addiction.

Proteomic analysis was very useful for measuring the alterations of cell signaling processes in the rat frontal cortex after METH exposure. The technique can initially demonstrate the networks of the proteins which are specific targets of METH-induced neurotoxicity. These results are valuable for the further study which is to investigate the expression levels of genes and proteins in cell-cell signaling function after METH administration. Studying in gene and protein expression levels may be an alternative study for better understanding the characteristic of METH addiction. In addition, the activation or inhibition of the target proteins may be an alternative approach to provide more information on the mechanisms of METH addiction. It may accurately reflect addiction in human.

In conclusion, the proteomic approach provides the potential proteins related to METH exposure in which METH affects cell-cell signaling proteins, highlighting in the glutamatergic, GABAergic and cholinergic systems. These effects may implicate in the mechanisms of METH-induced neurotoxicity.

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