Methamphetamine Regulation of Sulfotransferases in Rat Liver and Brain

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Abstract: Problem statement: Sulfotransferases (SULTs) are important phase II drug metabolizing enzymes. They also regulate the biological activities of various hormones. To the best of our knowledge, psychostimulants regulation of SULTs is basically not studied except one article reported that Methamphetamine (METH) treatment induced rat amygdale rSULT1A1 mRNA 4.3 fold by using microarray method to identify a series of candidate genes after single-dose METH treatment. The psychostimulant METH is used to treat disorders such as attention deficit, narcolepsy and obesity. It is also a highly addictive drug that causes serious social problems. The abuse of this drug leads to the damage of monoaminergic systems in the mammalian brain. It is important to understand how SULT expressions are regulated by psychostimulants. **Approach:** This study was performed to evaluate the effect of METH on SULT gene expressions in rat liver and brain. METH (0, 1, 5, 20 mg kg^{-1} day^{-1}) was used to treat male and female rats for 7 days by oral administration. Rat livers and brains were collected 24 h after the final drug treatment. Western blot and real-time RT-PCR were used to investigate the effect of METH on SULT protein and mRNA expression, respectively, in rat liver and brain. **Results:** Proteins and mRNAs of rSULT1A1, rSULT2A1 and rSULT1E1 were induced in liver and brain of both male and female rats following METH treatment. rSULT1E1 was induced at much higher level compared to that of rSULT1A1 and rSULT2A1. Brain inductions were found to be much higher than those found in liver. **Conclusion:** These data suggest an important role of the central dopaminergic system in the regulation of liver and brain rSULT expressions.

Key words: Sulfotransferase, methamphetamine, psychostimulant, induction, gene regulation

INTRODUCTION

Sulfotransferases (SULTs) are one of the major superfamily of phase II drug metabolizing enzymes (Bojarova and Williams, 2008; Chapman et al., 2004; Gamage et al., 2006; Hempel et al., 2007; Kauffman, 2004; Rath et al., 2004; Runge-Morris and Kocarek, 2005; Wang and James, 2006). They catalyze the sulfation of hydroxyl-containing compounds. The substrates specificities of some SULT are very broad. Most hydroxyl-containing compounds (phenols and alcohols) are substrates for SULT isoforms. The co-substrate for sulfation of all SULTs is adenosine 3'-Phosphate 5'-Phosphosulfate (PAPS). Sulfation is widely observed in various biological processed. Various bio-signaling molecules including hormones such as hydroxysteroid and glucocorticoid, neurotransmitters such as monoamine, peptides and so

on can be sulfated to alter their biological activities. Sulfation usually leads to the inactivation of biological signaling molecules, as the sulfated forms are usually unable to bind to receptors. SULTs also catalyze the sulfation of a wide range of xenobiotics. Sulfation of xenobiotics is mainly associated with detoxification: biotransformation of a relatively hydrophobic xenobiotic into a more water-soluble sulfuric ester that is readily excreted. However, there are numerous important exceptions wherein the formation of chemically reactive sulfuric esters is an essential step in the metabolic pathways leading to carcinogenic responses (Hempel et al., 2007; Gallucci and Mickle, 2006).

Methamphetamine (METH) is one of the well-known psychostimulants. The abuse of this highly addictive drug leads to the long-lasting changes in dopaminergic pathway of Central Nervous System (CNS). METH administration has been shown to

produce long-term decreases in numerous measures of both dopaminergic and serotonergic function such as enzyme activity, monoamine content and monoamine transmitters in experimental animals as well as in human (Quinton and Yamamoto, 2006; Gold *et al.*, 2009; Krasnova and Cadet, 2009; Guilarte *et al.*, 2003; Kish, 2008; Kita *et al.*, 2003; Cadet *et al.*, 2007; Volz *et al.*, 2007; Fleckenstein *et al.*, 2007; Sofuoglu and Sewell, 2009). METH toxicity is frequently reported as a potential model of drug induced Parkinsonism, which is one of the most common movement disorders of the elderly. Chronic or intermittent METH abuse may create temporary or permanent disturbances in the dopaminergic systems of the brain that may predispose individuals to Parkinsonism (Kita *et al.*, 2003; Fisher *et al.*, 2005; Yanai *et al.*, 2005; Tolwani *et al.*, 1999).

SULTs induction by hormones and other endogenous molecules has been relatively well known (Liu and Klaassen, 1996; Duanmu *et al.*, 2001; Dunn and Klaassen, 2000; Klaassen *et al.*, 1998; Runge-Morris, 1998; Runge-Morris *et al.*, 1999; Wu *et al.*, 2001; Runge-Morris and Kocarek, 2005). Xenobiotic induction of SULTs is not well studied. Recent data suggest that SULTs can be induced by xenobiotics, although the mechanisms for xenobiotic induction are less known (Runge-Morris and Kocarek, 2005; 1998; Chen *et al.*, 2008; Maiti and Chen, 2003a; 2003b). Psychostimulants regulation of SULTs is basically not studied. To the best of our knowledge, there is only one report on METH regulation of SULTs, which used microarray method to screen a series of candidate genes after single-dose METH treatment of rats (Niculescu *et al.*, 2000). This report suggested that METH treatment induced rat brain SULT1A1 mRNA 4.3 fold in the amygdale.

Similar to Cytochrome P450 (CYP) enzymes, most SULTs are regulated by hormones that remain under control of the Central Nervous System (CNS). METH treatment is known to cause the change of dopamine in CNS. Dopamine is one of the most important endogenous neurotransmitters as well as an important endogenous substrate of SULTs (Yasuda *et al.*, 2009; Salman *et al.*, 2009; Lu *et al.*, 2005). It has been demonstrated that the expression of CYPs can be regulated by dopamine receptor-linked signaling pathway by changing the hormone (GH, thyroid hormones, glucocorticoids and so on) levels *in vivo* (Wojcikowski, 2004; Wojcikowski *et al.*, 2007; 2008; Konstandi *et al.*, 2008). CNS psychostimulants regulation of the expression of SULTs is not studied. We hypothesize that the effect of METH on monoaminergic systems in the brain may indirectly change the expression of SULTs mediated by the dopamine-related signaling pathway. In this study, we investigated the regulation of rSULT1A1, rSULT2A1 and rSULT1E1 by METH in both rat liver and rat brain.

MATERIALS AND METHODS

Materials: METH was purchased from Sigma-Aldrich (St. Louis, MO). SDS-polyacrylamide gel electrophoresis reagents were obtained from Bio-Rad (Hercules, CA). Western blot chemiluminescence reagent kits (Super Signal West Pico Stable Peroxide and Super Signal West Pico Luminol/Enhancer solutions) were purchased from Pierce Chemical (Rockford, IL). PVDF membranes used for Western blotting analyses were purchased from Millipore Corporation (Bedford, MA). TRI REAGENT for total RNA extraction was purchased from MRC (Cincinnati, OH). M-MLV Reverse Transcriptase was obtained from Promega (Madison, WI). qPCR MasrerMix Plus with SYBR® Green I dNTP was purchased from Eurogentec (San Diego, CA). Antibodies against AST-IV (rSULT1A1) and STa (rSULT2A1) were provided by Dr. Michael W. Duffel (Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa city, IA). An antibody against rSULT1E1 was purchased from Biovision Inc (Boston, MA). Protein assay reagent was purchased from Bio-Rad. All other reagents and chemicals were of the highest analytical grade available.

Animals and drug treatment: Male and Female Sprague-Dawley rats (Harlan, Indianapolis, IN), 10-11 weeks old and 200-300 g body weight were used in this investigation. Rats were housed in a temperature- and humidity-controlled room and supplied with rodent chow and water for at least 1 week before use. Rats of both sexes were divided into 4 groups with four in each. METH was dissolved in sterile saline and administrated by gavage at 1, 5 and 20 mg kg^{-1} day^{-1} for 7 days. The corresponding group of control rats of either gender received only sterile saline. The rats were sacrificed 24 h after the final drug treatment. Livers and whole brains were collected, washed with sterile, ice-cold NaCl (0.9%, w/v) solution and snap-frozen. Samples were stored at -80°C until use.

Cytosol preparation: Both liver and brain tissues were homogenized in 50 mM Tris buffer containing 0.25 M sucrose, 3 mM β-mercaptoethanol and 0.02% (v/v) Tween-20, pH 7.4. All homogenates were centrifuged at 100,000 g for 1 h at 4°C. Cytosol aliquots were collected and preserved at -80°C for Western blot.

Western blot analysis: Cytosol protein from liver (10 μg) and brain (50 μg) was used in a 12% polyacrylamide gel in an electrophoresis system (Novex, San Diego, CA). After running at 200 V, the protein bands were transferred overnight at 35 V onto a PVDF membrane. Membranes were blocked for 1 h by 5% (w/v) nonfat dry milk in Tris-Buffered Saline (TBS). For both liver and brain cytosol proteins, membranes were incubated with either rabbit anti-rat AST-IV (rSULT1A1), or rabbit anti-rat STa (rSULT2A1) or mouse anti-rat SULT1E1 (1:1000) overnight in TBST (50 mM Tris, pH 7.5, 150 mM NaCl and 0.05% (v/v) Tween 20) containing 5% (w/v) nonfat dry milk on a shaker at 4°C After incubation, all membranes were washed with TBST for 3×10 min and incubated in secondary antibody (Horseradish peroxidase-conjugated Immuno-Pure goat anti-rabbit IgG (H+L) for rSULT1A1 and rSULT2A1, Horseradish peroxidase-conjugated Immuno-Pure goat anti-mouse IgG(H+L) for rSULT1E1) at 1:8000 dilutions in the same buffer for at least 1 h. The membranes were washed with TBST for 3×10 min. Fluorescent band were developed with 3 mL of substrate containing the same volume of each Super Signal West Pico Luminol Enhancer solution and Super Signal West Pico Stable Peroxidase solution at room temperature for 5 min. The fluorescence image was obtained using VersaDoc IMAGING SYSTEM 5000MP (BIO-RAD, Hercules, CA). The densitometric quantification of protein bands was obtained using Quantity One 4.6.5 software of VersaDoc imaging system.

Quantitative real-time PCR: Total RNA was extracted from liver using TRI REAGENT from MRC according to supplier's guidelines. The concentration and purity of the extracted RNA were checked spectrophotometrically by measuring 260/280 absorption ratios. M-MLV Reverse Transcriptase (Promega) with 1 μg of total RNA was used to synthesize cDNA and 1 μL of reverse-transcribed product served as the template in polymerase chain reactions. Real-time PCR was performed using the qPCR MasrerMix Plus with SYBR® Green I kit (EUROGENTEC) following the manufacturer's instruction. Primers were designed with Primer Express as follow: rActin-F320:5'-AGGCCCCTCTGAACCCTAAG-3', rActin-R435: 5'-AGAGGCATACAGGGACAACACA-3', GI NM_031144; rSULT1A1-F530: 5'-AGCTGAGACACACTCACCCTGTT-3', rSULT1A1-R651: 5'-ATCCACAGTCTCCTCGGGTAGA-3', GI. L19998; rSULT2A1-F496: 5'-ATCCGTGCCTGGCTGTCTAT-3', rSULT2A1-R642:

5'-GAGGACCAAATCCAGCTCATCT-3'. GI M33329; rSULT1E1- F432: 5'-GGT GGC TGG TCA TCC AAA TC-3', rSULT1E1-R557: 5'-CGT GGA CTC TTT CCC TTT TCC-3', GI BC088157

Real-time PCR was performed on an 7500 Fast Real-Time PCR System. (Applied Biosystems, Foster City, CA). Initially, regular PCR products were purified with GENECLEAN Turbo (Qbiogene, Carlsbad, CA) for constructing standard curves ($10-10^8$ copies). A standard curve was plotted with the Threshold Cycle (CT) Vs the logarithmic value of the gene copy number. The gene copy number of unknown samples was generated directly from the standard curve by the software Sequence Detector 1.7. At least two duplications were run for each standard or unknown sample. All gene copy numbers were normalized to rat β-Actin mRNA.

Data analysis: One-way ANOVA followed by the Dunnett's test was used to calculate the statistical significance of the difference between the control group means and methamphetamine treatment group means. In all cases, *: $p<0.05$ was considered significant; **: $p<0.01$ was considered very significant. Data presented in the figures are means Standard Deviation (±SD) of the data collected separately from at least three individual animals.

RESULTS

METH regulation of rSULT1A1, rSULT2A1 and rSULT1E1 in rat liver: In female liver, Western blot data showed that rat SULT1A1 (rSULT1A1, AST-IV) protein expression increased by about 44, 35 and 47%, respectively, after 1, 5, 20 mg kg^{-1} day^{-1} METH treatment for 7 days (Fig. 1A). Those increases were statistically significant. Rat SULT 2A1 (rSULT2A1, STa) in female rat liver increased 27% in protein level with the middle dose treatment of METH (Fig. 1A). METH induced female rat SULT1E1 (rSULT1E1, EST) protein level in liver 2.4-, 4.7- and 3.5-fold, respectively, in response to the three dose treatment (Fig. 1A). In male liver, rSULT1A1 protein expression was induced by about 77, 66 and 32% respectively at low, middle and high doses treatment of METH (Fig. 1B). In male rat liver, rSULT2A1 protein expression was not significantly changed, although rSULT2A1 was decrease 40% at the high dose treatment, this was not statistically significant. In male rat liver, rSULT1E1 protein expression was significantly induced at the low and medium dosed, while it was significantly suppressed at the high dose.
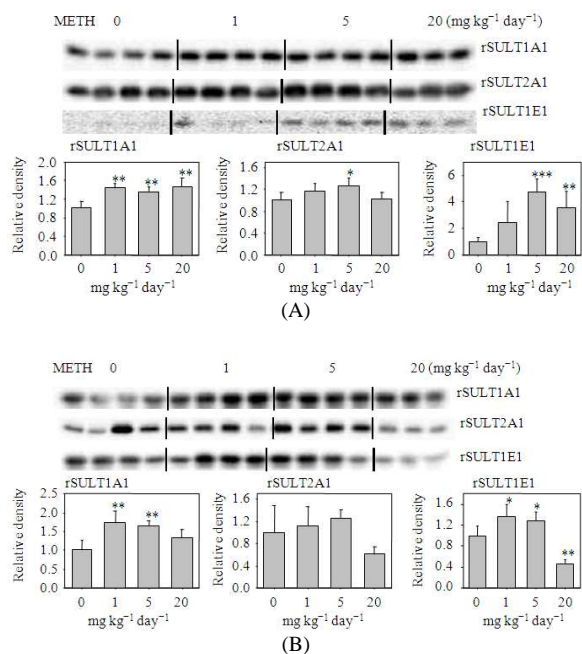
Fig. 1: Representative Western blot and densitometric analysis of rSULT1A1, rSULT2A1 rSULT1E1 in liver of (A) female and (B) male rats treated 1 week with varying doses of METH. Values were divided by the smallest densitometric value of the blot. The division factors are plotted and expressed as relative densities. *: $p<0.05$; **: $p<0.01$ and ***: $p<0.001$

Real-time PCR data demonstrated that the effect of METH treatment on the mRNA expressions of the three SULT isoforms (Fig. 2) was in good agreement with that of protein expressions (Fig. 1). This applies to all three doses treatment to all the three isoforms of SULT. This suggests that the regulation of METH on SULT expression is on the gene transcription level.

METH regulation of rSULT1A1, rSULT2A1 and rSULT1E1 in rat brain: The Western blot results and the densitometric analysis (Fig. 3A) suggested that rSULT1A1, rSULT2A1 and rSULT1E1 protein in female rat brain is significantly induced by the treatment of METH in the dose range between 1-20 mg kg^{-1} day^{-1}. The corresponding protein expression of rSULT1A1 increased by about 70%, 80% and 70%; of rSULT2A1 increased by 113%, 131% and 90% and of rSULT1E1 increased by about 4.7-, 2.6-and 1.2-fold respectively, after 1, 5, 20 mg kg^{-1} day^{-1} METH treatment (Fig. 3A). The induction of female rat brain rSULTs was much greater than that found in female rat liver.
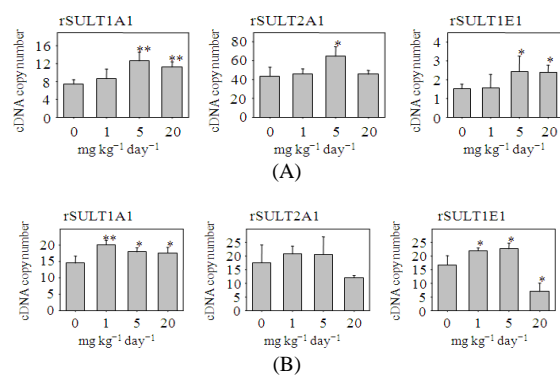

Fig. 2: rSULT1A1, rSULT2A1 and rSULT1E1 mRNA expression in livers of (A) female and (B) male rats treated 1 week with varying doses of METH. Rat β-actin was used as control for real-time PCR. Relative copy number of rSULT1A1, rSULT2A1 and rSULT1E1 mRNA were standardized by using rat β-actin mRNA. Induction fold was calculated by dividing the copy number of rSULT mRNA in METH-treated rats by the copy number of corresponding rSULT mRNA in control rats. *: $p<0.05$ and **: $p<0.01$
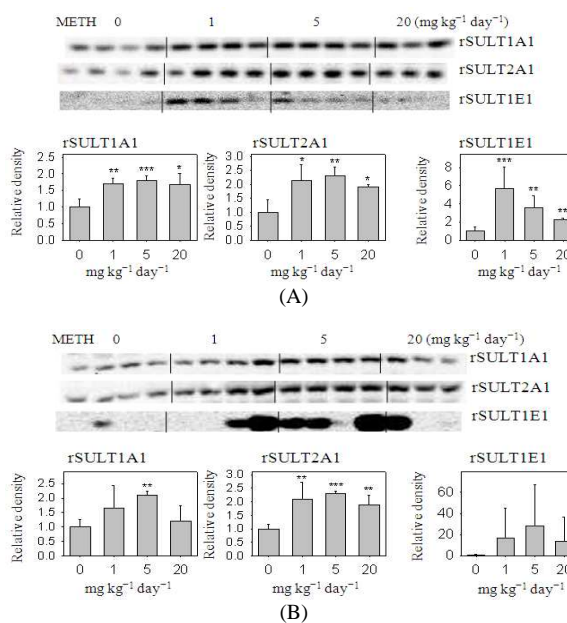

Fig. 3: Representative Western blot and densitometric analysis of rSULT1A1, rSULT2A1 and rSULT1E1 in the brain of (A) female and (B) male rats treated 1 week with varying doses of METH. Values were divided by the smallest densitometric value of the blot. The division factors are plotted and expressed as relative densities. *: $p<0.05$; **: $p<0.01$ and ***: $p<0.001$

In male rat brain, rSULT1A1 protein level increased by about 66, 110 and 19%, respectively, in response to the treatment of 1, 5, 20 mg $kg^{-1} day^{-1}$. The induction of rSULT1A1 was not statistically significant in low and high doses treatment. rSULT2A1 protein expression was found dramatically induced in male rat brain (Fig. 3B). rSULT2A1 protein level increased by about 109, 132 and 88%, respectively, in response to the three dose treatment. rSULT1E1 protein level in male rat brain was induced at a very high level, increased up to about 16-, 27-, 13-fold, respectively, after 1, 5, 20 mg kg^{-1} day^{-1} METH treatment. The induction of male rat brain SULT1E1 was not statistically significant due to huge variation between individuals. The induction of male rat brain rSULT1A1, rSULT2A1 and rSULT1E1 was much greater than that found in male rat liver.

DISCUSSION

SULTs catalyze the sulfation of xenobiotics and different biosignaling molecules including hydroxysteroid hormones, thyroid hormones, glucocorticoid hormones, neurotransmitters, bile acids, heparan and so on. Some isoforms of SULTs, e.g., SULT1A1, have very broad substrate specificity and play important roles in xenobiotics detoxification. Other SULTs, e.g., SULT1E1, have high specificity for only endogenous substrates. Although some SULT isoforms have been isolated and characterized, the biological functions of SULTs remain largely unknown. Studies on cytosolic SULTs have been mainly focused on drug metabolism and detoxification. We believe that SULTs are not only important for xenobiotic detoxification but also play important biological roles in the regulation of the activities of various biosignaling molecules and their functions. The malfunction of SULTs will therefore lead to diseases.

METH is a psychostimulant used to treat several disorders, including attention deficit, narcolepsy and obesity (Cadet *et al*., 2007; Fleckenstein *et al*., 2007). Over use of this drug causes drug dependence and addiction and cause serious social problems. We are interested to investigate the roles that SULTs play under physiological and various pathological conditions and to understand the importance of SULTs for general human health. METH is known to cause hormone level changes *in vivo*, we are interested to understand how METH regulate SULTs in the drug detoxifying tissue rat liver and in the center of the nervous system rat brain. SULT1A1 is the major phenol-sulfating SULT and has very broad substrate specificity. It not only sulfates simple xenobiotic phenols with high activity but also sulfates many endogenous phenolic compounds, including various hormones and neurotransmitters. SULT1A1 is also widely distributed in different tissues. SULT2A1 mainly catalyzes the sulfation of alcohol compounds; it is also the major enzyme to catalyze the sulfation of hydroxysteroids, especially for DHEA. SULT1E1 is specific for the sulfation of estrogens; it is also the major enzyme to catalyze the sulfation of thyroid hormones (Wu *et al*., 2008; Santini *et al*., 1993). In this study, these three isoforms were selected for the investigation of METH effect in rat liver and brain.

Our experimental results suggested that the simple phenol SULT, rSULT1A1 (it also catalyzes the sulfation of neurotransmitters) is induced by METH treatment in both rat liver and brain. The hydroxysteroid SULT, rSULT2A1, is somewhat less inducible by METH. The estrogen and thyroid SULT, rSULT1E1, is very sensitive to the treatment of METH. In general, the effect of METH on rat brain SULTs is much higher than that of rat liver.

Genes encoding different SULT isoforms expression can be regulated through endogenous hormones (growth hormone, sex hormones, thyroid hormones, glucocorticoids) and immune system (cytokines) in different ways and at various levels, being also tissue-dependent (Liu and Klaassen, 1996; Duanmu *et al*., 2001; Dunn and Klaassen, 2000; Klaassen *et al*., 1998; Runge-Morris, 1998; Runge-Morris *et al*., 1999; Wu *et al*., 2001; Runge-Morris and Kocarek, 2005; Chen *et al*., 2008; Maiti and Chen, 2003a; 2003b). Glucocorticoid-inducible rat hepatic SULT1A1 gene transcription occurs through a Glucocorticoid Receptor (GR)-mediated mechanism, a low dose of a synthetic glucocorticoid, can have physiologically significant effects attributable to the increased expression of SULT1A1 (Runge-Morris and Kocarek, 2005). Glucocorticoids have been known as important regulatory factors in the control of rat hepatic SULT2A enzyme activity (Fang *et al*., 2005a). The expression of rodent and human hepatic SULT2A is regulated by the Pregnane X Receptor (PXR) (Liu and Klaassen, 1996; Runge-Morris and Kocarek, 2005; Fang *et al*., 2005a; 2005b; Duanmu *et al*., 2002). Dexamethasone administration produced significant increases in rat hepatic SULT2A mRNA and protein contents, relative to control (Fang *et al*., 2005a). Treatment of human hepatocyte cultures with PXR-activating concentrations of dexamethasone and rifampicin both produced concentration-dependent increases in human SULT2A1 mRNA and protein contents (Fang *et al*., 2005a; 2005b; Duanmu *et al*., 2002). In addition, more and more recent data suggest

that hepatic SULT gene expression is regulated by the same transcription factor networks that also control the expression of the Cytochrome P450s (CYP), such as the Aryl hydrocarbon (Ah) receptor and members of the nuclear receptor superfamily, such as PXR, CAR and PPARα, although the co-regulation between the SULT and CYP gene families doesn't always occur in a coordinate direction (Runge-Morris, 1998; Runge-Morris and Kocarek, 2005; Jain *et al*., 2008).

Endogenous hormones including glucocorticoids and cytokines are under CNS control. METH is a CNS stimulant which has been shown to produce long-term changes in numerous measures of both dopaminergic and serotonergic function such as enzyme activity, dopamine content and monoamine transmitters (Quinton and Yamamoto, 2006; Gold *et al*., 2009; Krasnova and Cadet, 2009; Guilarte *et al*., 2003; Kish, 2008; Kita *et al*., 2003; Cadet *et al*., 2007; Volz *et al*., 2007; Fleckenstein *et al*., 2007; Sofuoglu and Sewell, 2009). METH increase synaptic levels of the monoamines Dopamine (DA), serotonin and Norepinephrine (NE) (Sofuoglu and Sewell, 2009). It has been demonstrated that dopaminergic system can regulate CYP isoenzymes expression in liver by altering levels of pituitary hormones and cytokine (Wojcikowski, 2004; Wojcikowski *et al*., 2007; 2008; Konstandi *et al*., 2008). Psychostimulant amphetamine has been shown to cause a large increase in corticosterone concentration leading to a substantial rise in CYP3A activity and protein level by activating PXR (Wojcikowski *et al*., 2008). Being one of important endogenous glucocorticoids, corticosterone may regulate SULT1A1 and SULT2A1 by acting on GR and PXR respectively, in the similar way as to dexamethasone. As the analog of amphetamine, METH is also an important member of the family of phenethylamines. METH has similar chemical structure to amphetamine and they have same pharmacology action mechanism. So it is highly possible that METH administration may change the corticosterone concentration *in vivo* and regulate rSULTs through GR or PXR. Our results shows that rSULT1A1, rSULT2A1 and rSULT1E1 were induced in liver and brain of both male and female rats following METH treatment at low and middle doses treatment for 7 days. At these doses range treatment, the induction of rSULTs by METH may be mediated through the dopamine-related signaling pathway. METH changes the dopamine content in brain and caused increase in corticosterone (and or other hormones) concentration leading to a substantial rise in SULTs expression by activating PXR or GR. It is known that 4-Hydroxymethamphetamine (4-OH-METH) is one of the main metabolites of

METH and 4-OH-METH is the substrate of SULT1A1. The induction of CYP3A and SULTs will enhance the detoxification of METH.

CONCLUSION

Our data suggest that the central dopaminergic system may play an important role in the regulation of liver and brain rSULTs. This influence of brain dopaminergic system on the rSULTs can have physiological and toxicological significance, since rSULTs are important for drug detoxification and endogenous biosignaling molecules regulation.

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