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Biochemical and Biophysical Research Communications 351 (2006) 300–305
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Methamphetamine induces long-term changes in $GABA_A$ receptor α2 subunit and GAD_{67} expression

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Received 26 September 2006
Available online 16 October 2006

Abstract

The present study investigated whether $GABA_A$ receptor α2 subunit and GAD_{67} are involved in chronic high dose methamphetamine (METH)-induced sensitization and neurotoxicity. The METH sensitization was established in rats by 7-day pump infusion plus daily injection (25 mg/kg/day) and a subsequent 28-day withdrawal period. Behavioral sensitization was assessed by behavioral ratings after challenge with METH (0.5 mg/kg). The neurotoxicity was evaluated by the expression of glial fibrillary acidic protein (GFAP). Western blot assay showed that METH sensitization decreases $GABA_A$ α2 subunit and GAD_{67} protein levels in the nucleus accumbens (NAc) core and shell, and conversely, these proteins were increased in the caudate. An upregulation of GFAP expression was observed in the caudate, but not in the NAc core and shell. These data suggest that inhibition of GABA transmission in the NAc is related to METH behavioral sensitization, whereas activation of GABA transmission in the caudate is associated with METH-induced neurotoxicity.

Keywords: Methamphetamine; GABA; GAD_{67}; GFAP; Glutamate; Dopamine; Sensitization; Neurotoxicity; Nucleus accumbens; Caudate

A growing number of rodent experiments and clinical reports demonstrate that increasing GABAergic tone by activation of $GABA_A$ or $GABA_B$ receptors, or by inhibition of GABA metabolism and reuptake, attenuates the acute reinforcing effects of cocaine, amphetamine, heroin, nicotine, and alcohol [1–3]. The evidence also supports the involvement of GABA transmission in methamphetamine (METH) sensitization and neurotoxicity by regulating dopamine (DA) and glutamate transmission [4–7]. For instance, preclinical and clinical studies reveal that METH-induced alterations in nigrostriatal DA could influence GABAergic and glutamatergic transmission downstream and produce a variety of motor disturbances [4]. Mark et al. [5] have demonstrated that acute high-dose METH increases glutamate release in the striatum through increasing GABA release in the substantia nigra, and in this way mediates long-term DA toxicity in the striatum. However, no studies have demonstrated whether GABA transmission is involved in the sensitization and neurotoxicity induced by the chronic high dose METH.

On the molecular level, the action of GABA is mediated by ionotropic ($GABA_A$) [8] and metabotropic ($GABA_B$) [9] receptors, which are ubiquitously expressed, possibly on every neuron in the central neuron system [10]. Previous studies have revealed that the strength of inhibitory synaptic currents is directly correlated with the number of synaptic $GABA_A$ receptor, therefore, regulation of the expression of $GABA_A$ receptors has profound effects on neural excitability [11]. $GABA_A$ receptors belong to the superfamily of ligand-gate ion channels [8] and form multiple complexes assembled from a family of at least 21 constituent subunits (α1–6, β1–4, γ1–4, δ, ρ1–3, θ, and π)

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doi:10.1016/j.bbrc.2006.10.046

[8,12], which renders their functional analysis technically challenging. However, current progress in immunochemical, pharmacological, and functional analysis of $GABA_A$ receptors suggest that the majority of $GABA_A$ receptors contain a single type of α- and β-subunit variants [13]. The synaptic inhibitory inputs are largely mediated by $GABA_A$ receptors containing the γ2 subunit together with the α1, α2, or α3 subunit and undefined β subunit [14]. The recent studies revealed a haplotypic association of alcohol dependence with the gene encoding the α2 subunit of the $GABA_A$ receptor [15]. Thus, METH-induced alterations in expression of $GABA_A$ α2 subunit could reflect the METH-induced changes in GABA transmission.

Besides expression of $GABA_A$ receptors, GABA release also influences the inhibitory synaptic currents. GABA synthesis is dependent on, and regulated by, the enzyme glutamic acid decarboxylase (GAD) [16]. GAD is present as two isoenzymes, GAD_{65} and GAD_{67}, which are the products of two independently regulated genes [17]. However, the GAD_{67} isoenzyme has a more pronounced effect on brain GABA synthesis than its smaller isoenzyme. For example, brain GABA level is normal in GAD_{65} knockout mice [18], whereas GAD_{67} knockout is lethal and GABA level was reduced in adult heterozygote of GAD_{67} knockout mice, indicating that GAD_{67} is more important in maintaining the GABA levels [19,20]. GAD_{67} expression is regulated by chronic stimulants, such as a seven-day repeated (twice daily) exposure, but not by a single injection of amphetamine [16]. The repeated exposure of amphetamine was followed by a significant decrease in GAD_{67} expression and a reduction in extracellular GABA levels in the rat ventral striatum [16]. Thus, any mechanisms that influence GAD_{67} expression will also affect inhibitory GABA tone. The effect of chronic high dose METH on GAD_{67} expression, subsequent to the regulation of GABA synthesis and release has not been reported. In this study, we investigated changes in $GABA_A$ α2 subunit and GAD_{67} protein levels in the NAc and caudate followed METH sensitization established by the chronic high dose METH regimen.

Materials and methods

Animals. Male Sprague–Dawley rats, initially weighing 300–320 g (Charles River Laboratories), were acclimated to the vivarium on a 12-h light/dark cycle (7 AM to 7 PM). One week later, they were housed in single in plastic cages according to the "Guide for Care and Use of Laboratory Animals".

Methamphetamine treatment. On day one of treatment, the animals were implanted with Alza Osmotic pumps (model 2ML1, Alza Corporation, Palo Alto, CA) filled with (+)-METH hydrochloride (Sigma, St. Louis, MO) to provide 25 mg/kg/day dosing. The pumps were primed by warming in a water bath at 37 °C for 3 h and modified by adding a microdialysis fiber to disperse the drug over a wider surface area. The animals were anesthetized by methoxyflurane inhalation. A 2 cm vertical incision and a large subcutaneous pocket were made. The pump was implanted into this pocket with the delivery portal toward the head. The incision was closed with metal surgical autoclips. METH was injected (s.c.) for 1, 2, 4, 6, 6, and 6 mg/kg/day for 6 days. On day 7, the pumps were removed and the residual amount of METH was measured to make sure the pump worked.

Table 1
Behavioral Rating Scale for stereotyped behaviors[a]

Score	Classification
1	Asleep
2	Almost asleep
3	Inactive
4	Normal alert activity
5	Hyperactive
6	Slow patterned movement
7	Fast patterned movement
8	Restricted movement
9	Intermittent licking stereotypy
10	Constant sniff, Stereotypy

[a] Modified from Ellinwood and Balster [21].

Experimental groups. A group of rats ($n = 10$) received METH pump plus injection for 7 consecutive days (METH group) and then underwent 28 days withdrawal. Another group of rats ($n = 6$) received 7 consecutive days of saline pump plus injection (saline group) also followed by 28 days withdrawal.

Behavioral assessment. Animals were placed in single home cages after minipump surgery. After animals were injected with 0.5 mg/kg METH (i.p.) on the withdrawal day 28, behavior was monitored over the next 1 h. Behavioral rating was taken based on the Ellinwood and Balster [21] rating scale (Table 1). Behavioral ratings were given at 5 min intervals with 20 s observation period for each rat.

Brain dissection and protein extraction. Rats were decapitated 24 h after the behavioral test. Both sides of brain areas (NAc core, NAc shell, and caudate) were dissected and immediately frozen on dry ice. In preparation for Western blot, tissues were homogenized and stored based on previously established protocol [22].

Western blot. The $GABA_A$ α2 subunit antibody (1:1000) was purchased from Chemicon (Temecula, CA). The GAD_{67} antibody (1:1000) and the GFAP antibody (1:500) were purchased from BD Science (San Jose, CA). The Western blot analysis was performed based on the previously established protocol [22]. To control for loading efficiency, the blots for $GABA_A$ α2 subunit, GAD_{67}, and GFAP were stripped and re-probed with α-tubulin (Sigma). The images were scanned with Adobe photoshop (Adobe, San Jose, CA) and quantified with NIH Image J (http://rsb.info.nih.gov). Expression of $GABA_A$ α2 subunit, GAD_{67}, and GFAP proteins were evaluated relative to that for α-tubulin. Background correction values were subtracted from each lane to minimize the variability across membranes.

Data analysis. The behavioral rating data were analyzed by one-way repeated measure ANOVA on ranks with post hoc Dunn's test. The significant level was set at $p < 0.05$ for all comparisons and all post hoc p-values < 0.05 are reported. For the Western blot data, Student's t-test was conducted to determine statistically significant differences between treatment groups.

Results

Chronic high dose METH evokes behavioral sensitization

Behavioral ratings were taken every 5 min. Three baseline ratings were followed by another 60 min of ratings after the METH challenge. The rating scale was based on a modified version of the Ellinwood and Balster [21] behavioral rating scale (Table 1). The behavioral sensitization model has been used extensively in drug abuse. Data were analyzed by repeated one-way ANOVA with post hoc Dunn's test. The METH group exhibited significantly greater METH sensitivity (Fig. 1).

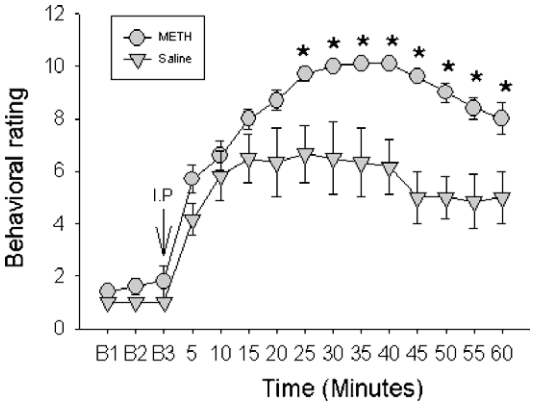

Fig. 1. Methamphetamine evokes behavioral sensitization. Cumulative behavioral rating over 1 h after METH challenge. See Materials and methods section for description of the treatment conditions. B, baseline; arrow indicates the challenge with 0.5 mg/kg METH (i.p.); $^{*}p < 0.05$ METH versus saline group; $N = 6$–10 rats/group.

METH induces divergent changes in GABA$_A$ α2 subunit expression in the NAc and caudate

To investigate whether the expression of $GABA_A$ receptor is regulated by the chronic high dose METH, brain tissues of caudate, nucleus accumbens core, and shell were harvested for Western blot analysis of $GABA_A$ α2 subunit expression 24 h after behavioral testing. As shown in Fig. 2, METH attenuated the expression of $GABA_A$ α2 subunit in the NAc core and shell. In contrast, METH sensitization increased the expression of $GABA_A$ α2 subunit in the caudate. A Student's *t*-test revealed significant decrease in $GABA_A$ α2 subunit expression in the NAc core ($p = 0.005$), and NAc shell ($p = 0.018$) following METH sensitization, and a significant increase in $GABA_A$ α2 subunit expression in the caudate ($p = 0.030$). These results indicate that chronic high dose METH treatment induces differential long-term regulation in expression of $GABA_A$ α2 subunit in the NAc and caudate.

METH induces divergent alterations in GAD$_{67}$ expression in the NAc and caudate

The chronic stimulant-induced reduction of GAD_{67} expression leads to GABA deficit and hyperactivity of midbrain dopamine and glutamate neurons [4,23]. To explore whether METH affects GABA synthesis, we examined the protein expression of GAD_{67} in the caudate, NAc core, and shell. A Student's *t*-test demonstrated significant

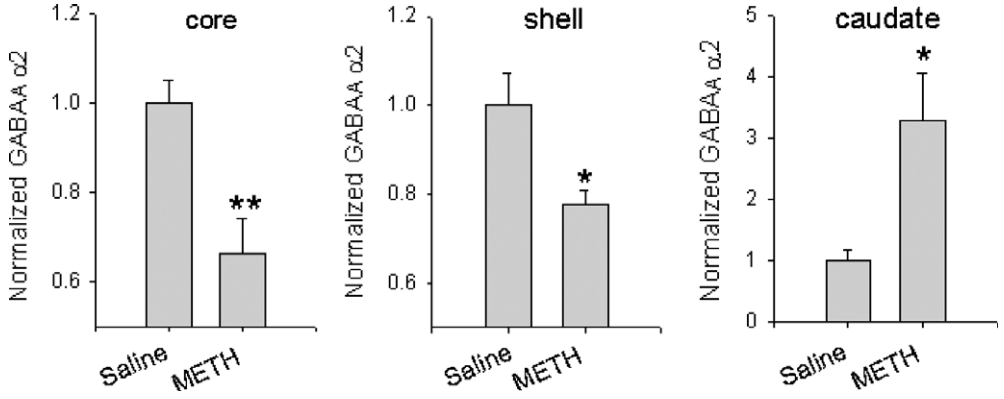

Fig. 2. Expression of $GABA_A$ α2 subunit protein in accumbens and caudate. Blots were scanned and the density under the peaks corresponding to total immunoreactivity of $GABA_A$ α2 and α-tubulin were determined. See Materials and methods for descriptions of the experimental groups. $^{*}p < 0.05$, $^{**}p < 0.01$ METH versus saline group; $N = 6$–8 rats/group.

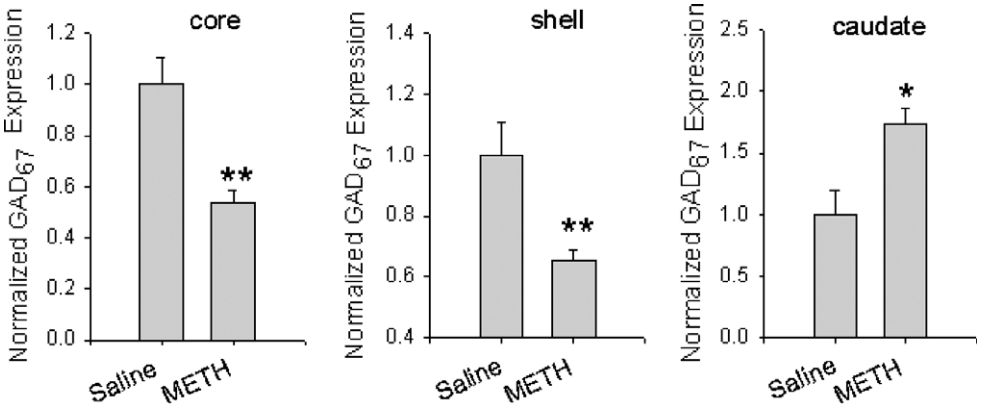

Fig. 3. Expression of enzyme GAD_{67} in accumbens and caudate. The GAD_{67} subunit expression was measured by Western blot assay. $^{*}p < 0.05$, $^{**}p < 0.01$ METH versus saline group; $N = 6$–8 rats/group.

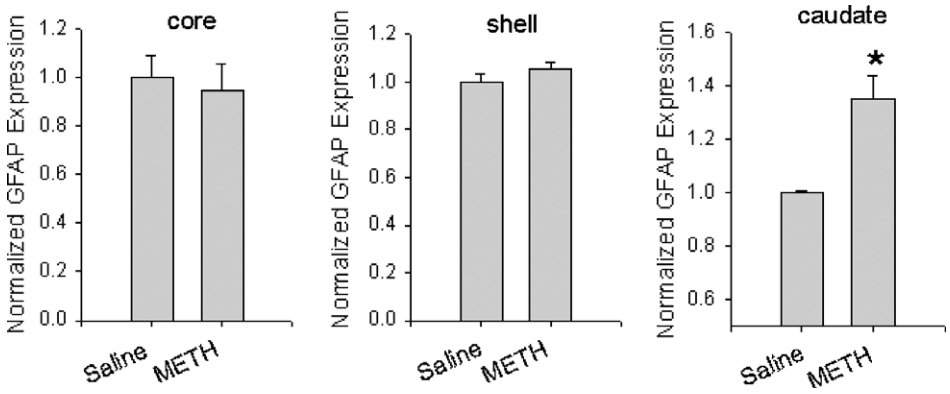

Fig. 4. GFAP expression in accumbens and caudate. The GFAP expression was measured by Western blot assay. $^{*}p < 0.05$ METH versus saline group; $N = 8$–9 rats/group.

reduction in GAD_{67} protein levels in the NAc core ($p < 0.001$) and NAc shell ($p = 0.006$), and significant increase in GAD_{67} protein levels in the caudate ($p = 0.008$). These results indicate that chronic high dose METH produces a divergent long-term regulation of GAD_{67} expression in the NAc and caudate (Fig. 3).

Methamphetamine induces GFAP expression in the caudate, but not in the NAc

To explore whether chronic high dose METH induces long-term neurotoxicity in the striatum, we examined the GFAP protein expression in the caudate, NAc core, and shell. A Student's *t*-test revealed significant increase for GFAP protein in the caudate ($p = 0.02$) in METH sensitized rats. As shown in Fig. 4, no significant difference in GFAP expression was observed in the NAc core and shell between METH sensitized rats and saline control. These data indicate that chronic high dose METH results in long-term (28 days) neurotoxicity in the caudate, but not in the NAc.

Discussion

Previous studies have revealed that the strength of inhibitory synaptic currents is directly correlated with the number of synaptic $GABA_A$ receptors [11]. The expression of GAD_{67} gene directly affects GABA synthesis and subsequently influences membrane GABA receptor stimulation, increasing the strength of inhibitory synaptic currents [16]. Thus, the protein levels of the $GABA_A$ subunit and GAD_{67} directly affect GABA transmission. Our data demonstrated that chronic high dose METH leads to downregulation of $GABA_A$ $\alpha 2$ subunit and GAD_{67} expression in the NAc core and shell, as well as upregulation of $GABA_A$ $\alpha 2$ subunit and GAD_{67} expression in the caudate. This suggests that METH reduces GABA transmission in the NAc and increases GABA transmission in the caudate.

Glial cells are reactive to neurotoxins. For example, various drugs of abuse, such as METH and amphetamine have been revealed to induce glial proliferation and enhancement of GFAP expression [24]. Microglial activation has been revealed to be closely associated with neurotoxicity, but not with other prominent pharmacological effects of METH such as inhibition of DA or 5-HT transporters, stimulation of DA receptors, or hyperthermia [25]. Thus, expression of GFAP can serve as a pharmacologically specific marker for striatal nerve terminal damage resulting from METH treatment [26]. Indeed, our study demonstrated that METH induces GFAP expression in the caudate, but not in the NAc. Our study also demonstrated that chronic high dose METH treatment and 28 days withdrawal induced significant behavioral sensitization. Thus, METH-induced downregulation of GABA transmission in the NAc may be associated with METH behavioral sensitization, while METH-induced upregulation of GABA transmission in the caudate may be related to METH-induced neurotoxicity.

Anatomical and neurochemical data suggest the NAc is an area of functional interaction among the neurotransmitters: glutamate, dopamine, and GABA [27–29]. The NAc receives glutamatergic afferents from limbic areas, such as medial prefrontal cortex (mPFC), hippocampus, and amygdala, and dopaminergic inputs from the ventral tegmental area (VTA). An important feature of these glutamatergic and dopaminergic afferents to the NAc is that they converge on the same dendritic spines of medium-sized spiny GABA projecting neurons without making direct synapses between glutamatergic and dopaminergic neurons [30]. In contrast, the existence of synaptic contacts between glutamatergic terminals and GABAergic neurons in the NAc suggests that the effects of glutamate on GABA are mediated by a direct synaptic interaction. This also implicates that glutamate might exert its effects on dopamine through GABA transmission. The majority of neurons in the NAc are GABAergic, which predominantly project to the VTA and ventral pallidum. These two regions are commonly thought to be involved with rewarding effects and reinforcing properties of most drugs of abuse [31,32]. Thus, the inhibitory GABA tone in the NAc modulates the dopamine and glutamate transmission within the NAc and NAc projection areas. In this study, chronic high dose METH leads to a reduction in NAc

inhibitory GABA tone. Together with the findings that establishment of inhibitory GABA tone can regulate the synaptic plasticity in dopamine neurons of the VTA [33] and glutamate transmission in the mPFC [34], we therefore postulate that downregulation of inhibitory GABA tone in the NAc may mediate METH sensitization through potentiation of dopamine and glutamate transmission in the NAc and NAc projection regions.

At present, some attention has been directed to the effects of high dose METH on the striatonigral pathway [5,35]. For example, Bustamante and colleagues [36] also observed chronic changes after repeated acute METH binges in rats including a decreased release of dopamine and an increased release of glutamate and GABA in both neostriatum and substantia nigra. Kamata and Kameyama [37] reported that 6 days of METH exposure, twice daily, increased striatonigral GABA activity. However, METH-induced alterations in GABA transmission are divergent. Our study demonstrates that expression of $GABA_A$ α2 subunit and GAD_{67} protein was upregulated in the caudate, whereas downregulated in the NAc. Together with the evidence that METH-induced upregulation of GFAP expression (Fig. 4), as well as increased phosphorylated GluR1 and total NR2B subunits levels in the caudate (data not shown), we conclude that the enhancement of GABAergic transmission in the caudate is associated with METH-induced toxicity. The striatum is one of the main sources of GABAergic projections to substantia nigra [38]. We therefore postulate that METH enhances striatonigral GABAergic transmission [39], which in turn activates $GABA_A$ receptors in the substantial nigra [40], leading to a decrease in GABAergic nigrothalamic activity [41], an increase in corticostriatal glutamate release [42], and a consequent long-term depletion of striatal dopamine content, and subsequent induction of neurotoxicity [5].

In conclusion, our data suggest divergent role for GABA transmission in the METH-induced behavioral sensitization and long-term neurotoxicity: METH treatment may enhance GABA transmission and mediate METH-induced striatal neurotoxicity through increased glutamate release in the caudate; METH may reduce NAc inhibitory GABA tone and lead to persistent behavioral changes through regulating the dopamine and glutamate transmission in the NAc and NAc projection areas. These differential alterations of GABA transmission in the NAc and caudate could explain the lack of data to support effectively experimental pharmacotherapy for METH sensitization or reinforcement using GABA receptors agonists. The systemic administration of GABA receptor agonists might affect NAc and other brain regions, subsequently blocking METH sensitization, but aggravating the neurotoxicity in the caudate and other brain regions, which play important roles in the process of neuropsychiatric damage, might counteract the effect. Thus, local upregulation of inhibitory GABA tone in the NAc may be effective in reversing METH sensitization, as well as local downregulation of inhibitory GABA tone in the caudate might reduce METH-induced neurotoxicity.

Acknowledgments

This work was supported by grants from the National Institute of Drug Abuse (DA-10327 and DA-14323 to E.H.E.).

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