Chronic administration of methamphetamine increases the mRNA expression of diazepam binding inhibitor in rat brain

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Anxiety is one of the common features of withdrawal syndrome caused by abuse-inducing drugs such as methamphetamine (MAP). The neural pathways associated with anxiety are established within the network sustained by diencephalon, cerebral cortex, cerebellum and hippocampus. Diazepam binding inhibitor (DBI), a peptide consisting of 87 amino acids, serves as an inverse agonist for the type A receptor of the gamma-aminobutyric acid ($GABA_A$ receptor) with endogenous anxiogenic potential. We examined the effect of chronic administration of MAP on the mRNA expression of DBI and DBI-related proteins, such as alpha 2 subunit of $GABA_A$ receptor (GABA-α2), peripheral-type benzodiazepine receptor (PBR), and pituitary adenylate cyclase-activating polypeptide (PACAP) in seven regions (diencephalon, cerebral cortex, cerebellum, striatum, hippocampus, midbrain, and pons-medulla) of the rat brain. The mRNA expression of DBI increased significantly in all areas of the brain, especially diencephalon, after chronic administration of MAP. The mRNA expression of PBR, GABA-α2 and PACAP increased significantly in all areas of the brain, especially cerebral cortex, after chronic administration of MAP. These results suggest that anxiety is associated with the mRNA expression of DBI as well as DBI-related genes.

Key words; methamphetamine, diazepam binding inhibitor, anxiety

INTRODUCTION

Anxiety disorders are widespread, with lifetime prevalence rates ranging between 13.6% and 28.8% in Western countries [19]. Anxiety is one of the common symptoms in patients suffering from dependence and withdrawal symptoms of drug abuse. Methamphetamine (MAP) is one of the common abuse-inducing drugs which cause dependence and withdrawal syndrome such as anxiety. Diazepam binding inhibitor (DBI) mRNA increased in the cerebral cortex of mice and rats showing dependency on morphine [13, 17], ethanol [12] and nicotine [14] in relation to anxiety. DBI, an approximately 10 kDa polypeptide, distributed in both the central and peripheral nervous system [1, 2, 8, 27], was initially isolated from the rat brain by monitoring its ability to displace diazepam from the benzodiazepine recognition site located on the extracellular domain of the type A receptor for the gamma-aminobutyric acid ($GABA_A$ receptor) [10], defined as an inverse agonist for $GABA_A$ receptor [11]. The alpha2 subunit (GABA-α2) of $GABA_A$ receptor has a benzodiazepine binding site (benzodiazepine receptor) and mediates the anxiolytic action of the benzodiazepines [15]. Injection of DBI into the lateral ventricle induced anxiety [4, 11, 27] and an elevation in the levels of DBI in the brain induced behavioral changes, including anxiety [7, 11, 24]. These results obtained from behavioral and pharmacological studies confirm the anxiogenic property of DBI.

DBI, in addition to the inverse agonist for benzodiazepine receptor, is an endogenous agonist for the peripheral-type benzodiazepine receptors (PBR) to stimulate steroid synthesis in the mitochondria [22]. PBR are abundant in peripheral tissues as well as in the astrocytes in the brain and are located primarily on the mitochondrial membranes [3, 9, 16, 22]. The binding of PBR ligands leads to the formation of the neurosteroids such as pregnenolone which can activate the benzodiazepine receptor [5], assumingly inducing anxiolysis.

In vitro study has shown that cultured astrocytes of rat contain and release substantial amount of DBI and that the secretion of DBI is cAMP dependent [18]. Pituitary adenylate cyclase-activating polypeptide (PACAP) stimulates cAMP formation in cultured astrocytes [28]. PACAP dose-dependently increases the mRNA expression of DBI and stimulates DBI release through activation for the receptor of pituitary adenylate cyclase-activating polypeptide (PAC1-R) in astrocytes [18].

To elucidate how DBI is regulated by PACAP and contributes to the subsequent events resulting in anxiety in central nervous system, we examined the mRNA expression of DBI and PACAP in the several regions of the rat brain after chronic administration of MAP

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using the real time quantitative reverse transcriptase-polymerase chain reaction (RT-PCR). Furthermore, to evaluate the action of GABA-α2 and PBR exerting on the distinct functions for anxiety, we have examined the mRNA expression of each receptor.

MATERIALS AND METHODS

Animals and materials

The present animal experiments were performed in strict accordance with the guidelines of Tokai University, and were approved by the Animal Experimentation Committee of Tokai University. Male Wistar rats (Clea Japan, Tokyo, Japan) weighing 200 to 250 g were group-housed in laboratory cages and kept in a temperature-controlled room (23 ±2°C) with a 12 h light / dark cycle (light on: 7:00) with food and water freely available. SUPERSCRIPT First-Strand Synthesis System for RT-PCR containing reverse transcriptase (RTase)(Superscript II, RNase H-), dithiothreitol (DTT), oligo (dT)12-18 primer, deoxynucleosidetriphosphate (dNTP), RNase H, DNase I and RNase inhibitor were purchased from Invitrogen (San Diego, CA). SV Total RNA Isolation System and PCR Master Mix were from Promega (Madison, WI). DyNAmo SYBER green qPCR Kit were from Finnzymes (Espoo, Finland), DNA 1000 Lab Chips Kit (Agilent Technologies; Palo Alto, CA) were from Takara Bio Co. (Tokyo, Japan). PCR primers were synthesized by Sigma Genosys Japan (Tokyo, Japan). All other chemicals and reagents were purchased from Wako Chemical Co. (Tokyo, Japan) unless otherwise noted.

Chronic treatment of MAP

Rats were intraperitoneally injected with MAP (5mg/kg) twice daily (10 a.m. and 6 p.m. around the clock) for 14 days. Sixteen hours after the last injection, rats were decapitated and the brain was removed to be divided into the seven regions; striatum, hippocampus, cerebral cortex, diencephalon, midbrain, pons-medulla, and cerebellum.

Real time quantitative RT-PCR

The total RNA was extracted by a method similar to the one described previously [30]. Total RNA (0.5 μg) was incubated with 200 units of the reverse transcriptase in a buffer containing 50 mM Tris-HCl (pH 8.3), 40 mM KCl, 2.5 mM $MgCl_2$, 10 mM DTT, 0.5 mM of each dNTP, and 0.5 μg oligo $(dT)_{12\text{-}18}$ primer in the final volume of 20 μl. The mixture was incubated at 42ºC for 50 min, and the reaction was stopped by heating at 70ºC for 15 min. The RNA was removed by adding 2 units of the ribonuclease H to facilitate the synthesis of double stranded cDNA. The mRNA expression was determined using the glyceraldehydes 3-phosphate dehydrogenase (GAPDH) (GenBank accession number NM_017008) gene as an internal control and primers specific for DBI mRNA (accession number NM_031853) (upper primer, ACG CTC TGG AAC TTG ATT GC; lower primer, CAG TTG GCT GAG TCT TGA GG; product size, 138 base pairs), PBR mRNA (NM_012515) (upper primer, ACA CTG GTC AGC TGG CTC TGA A; lower primer, CAG GCC AGG TAA GGA TAC AGC AA; product size, 175 base pairs), GABA-α2 mRNA (ENSRNOT00000003197) (upper primer, TGC TCC TGA TGG CTC TAG GT; lower primer, TGA GCT GTC ATT ACC GTG TAT TC; product size, 105 base pairs) and PACAP mRNA (NM_016989) (upper primer, TGT CCG CCA GGA AGT ACC; lower primer, CCG AGT GGC GTT TGG TAA; product size, 105 base pairs). The cDNA was amplified by the real-time quantitative PCR using the DyNAmo SYBER green qPCR Kit (Finnzymes; Espoo, Finland) on the DNA Engine Opticon 2 System (Bio-Rad Laboratories; Hercules, CA, USA) running 40 cycles of the following protocol: 10 min predenaturation at 95ºC, 15 sec annealing at 62ºC for DBI and 61ºC for PBR, GABA-α2, PACAP and GAPDH, followed by a 20 sec extension at 72ºC. The PCR products were separated by an Agilent 2100 Bioanalyzer (Agilent Technologies; Palo Alto, CA, USA) which utilizes chip-based nucleic acid separation technology. Furthermore, the identification of the amplified PCR products of the DBI, PBR, GABA-α2, PACAP and GAPDH cDNAs were determined by the dye terminator cycle sequencing.

Statistical analysis

These results are given as mean with standard error of mean (S.E.M.). A statistical analysis was conducted using a computer software (SPSS 15.0.1, SPSS Inc., Chicago, IL; Prism, version 4.0c, GraphPad Software, San Diego, CA) for comparison across the experimental conditions. Statistical comparisons were performed using the Mann Whitney U test or the Kruskal-Wallis H test followed by Dunn's multiple comparison test. The level of statistical significance was set at $P<0.05$.

RESULTS

The mRNA expression of DBI in the rat brain after chronic administration of MAP

The mRNA expression of DBI demonstrated a widespread distribution in the rat brain (Fig. 1). Fig. 1 shows the changes in the mRNA expression of the DBI after chronic treatment with MAP (5 mg/kg). Following chronic administration of MAP, the mRNA expression of the DBI in the brain areas, especially striatum, cortex, diencephalon, midbrain, and pons-medulla, increased. The levels increased by 17%-344% in the seven brain areas examined 16 h after the last administration: striatum (20% increase), hippocampus (31%), cortex (23%), diencephalon (344%), midbrain (17%), pons-medulla (33%), and cerebellum (33%).

The mRNA expression of PBR in the rat brain after chronic administration of MAP

The mRNA expression of PBR demonstrated a widespread distribution in the rat brain (Fig. 2). Kruskal-Wallis analysis, however, indicated significant differences among the regions of the rat brain. Fig. 2 shows the changes in the mRNA expression of PBR after chronic treatment with MAP (5 mg/kg). Following chronic administration of MAP, the mRNA expression of the PBR in the brain increased except diencephalon. The levels increased by 29%-68% in the seven brain areas examined 16 h after the last administration: striatum (49% increase), hippocampus (39%), cortex (68%), diencephalon (-26%), midbrain (32%), pons-

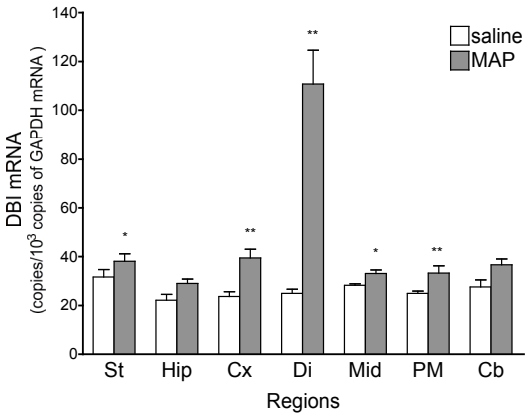

Fig. 1. The mRNA expression of diazepam binding inhibitor (DBI) in seven regions of the rat brain. The mRNA levels of DBI were measured by real-time quantitative RT-PCR. Significantly different from the values of a group treated with saline by Mann-Whitney U test; *p<0.05, **p<0.01. St, striatum (saline, n=6; MAP, n=6); Hip, hippocampus (n=6; n=6); Cx, cortex (n=6; n=6); Di, diencephalon (n=6; n=5); Mid, midbrain (n=6; n=6); PM, pons-medulla (n=6; n=6); Cb, cerebellum (n=6; n=6).

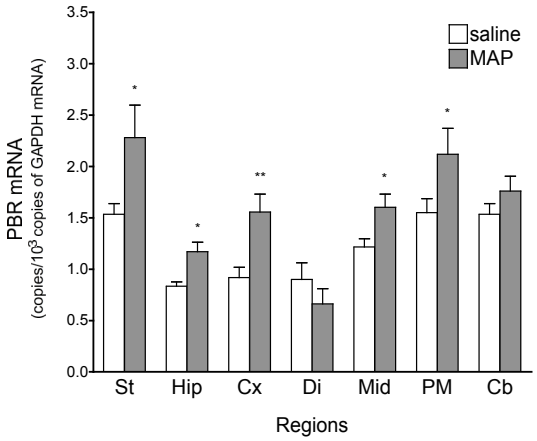

Fig. 2. The mRNA expression of peripheral-type benzodiazepine receptor (PBR) in seven regions of the rat brain. The mRNA levels of PBR were measured by real-time quantitative RT-PCR. Significantly different from the values of a group treated with saline by Mann-Whitney U test; *p<0.05, **p<0.01. St, striatum (saline, n=6; MAP, n=6); Hip, hippocampus (n=6; n=6); Cx, cortex (n=6; n=6); Di, diencephalon (n=6; n=6); Mid, midbrain (n=6; n=6); PM, pons-medulla (n=6; n=6); Cb, cerebellum (n=6; n=6).

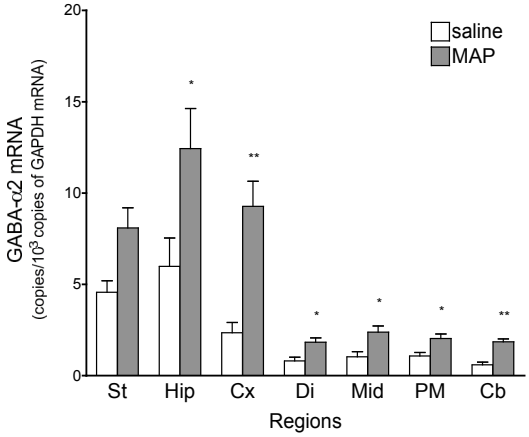

Fig. 3. The mRNA expression of a2 subunit of $GABA_A$ receptor (GABA-α2) in seven regions of the rat brain. The mRNA levels of GABA-α2 were measured by real-time quantitative RT-PCR. Significantly different from the values of a group treated with saline by Mann-Whitney U test; *p<0.05, **p<0.01. St, striatum (saline, n=6; MAP, n=6); Hip, hippocampus (n=5; n=6); Cx, cortex (n=6; n=5); Di, diencephalon (n=6; n=6); Mid, midbrain (n=6; n=6); PM, pons-medulla (n=6; n=6); Cb, cerebellum (n=6; n=6).

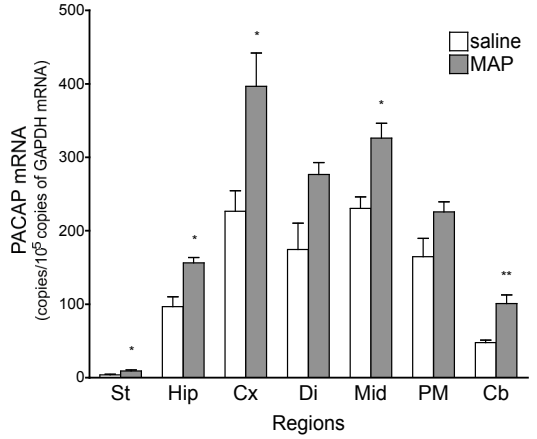

Fig. 4. The mRNA expression of pituitary adenylate cyclase-activating polypeptide (PACAP) in seven regions of the rat brain. The mRNA levels of PACAP were measured by real-time quantitative RT-PCR. Significantly different from the values of a group treated with saline by Mann-Whitney U test; *p<0.05, **p<0.01. St, striatum (saline, n=5; MAP, n=6); Hip, hippocampus (n=6; n=6); Cx, cortex (n=6; n=5); Di, diencephalon (n=6; n=6); Mid, midbrain (n=6; n=6); PM, pons-medulla (n=6; n=6); Cb, cerebellum (n=5; n=6).

medulla (37%), and cerebellum (29%).

The mRNA expression of GABA-α2 in the rat brain after chronic administration of MAP

The mRNA expression of GABA-α2 demonstrated a widespread distribution in the rat brain (Fig. 3). Kruskal-Wallis analysis, however, indicated significant differences among the regions of the rat brain. The high levels of GABA-α2 mRNA were detected in the striatum, hippocampus and cortex where approximately 7.5, 10 and 4 times of cerebellum, respectively. Fig. 3 shows the changes in the mRNA expression of the GABA-α2 after chronic treatment with MAP (5 mg/kg). Following chronic administration of MAP, the mRNA expression of the GABA-α2 in the brain increased. The levels increased by 77%–296% in the seven brain areas examined 16 h after the last administration: striatum (77% increase), hippocampus (108%), cortex (296%), diencephalon (89%), midbrain (131%), pons-medulla (89%), and cerebellum (211%).

The mRNA expression of PACAP in the rat brain after chronic administration of MAP

The mRNA expression of PACAP demonstrated a widespread distribution in the rat brain (Fig. 4). Kruskal-Wallis analysis, however, indicated significant

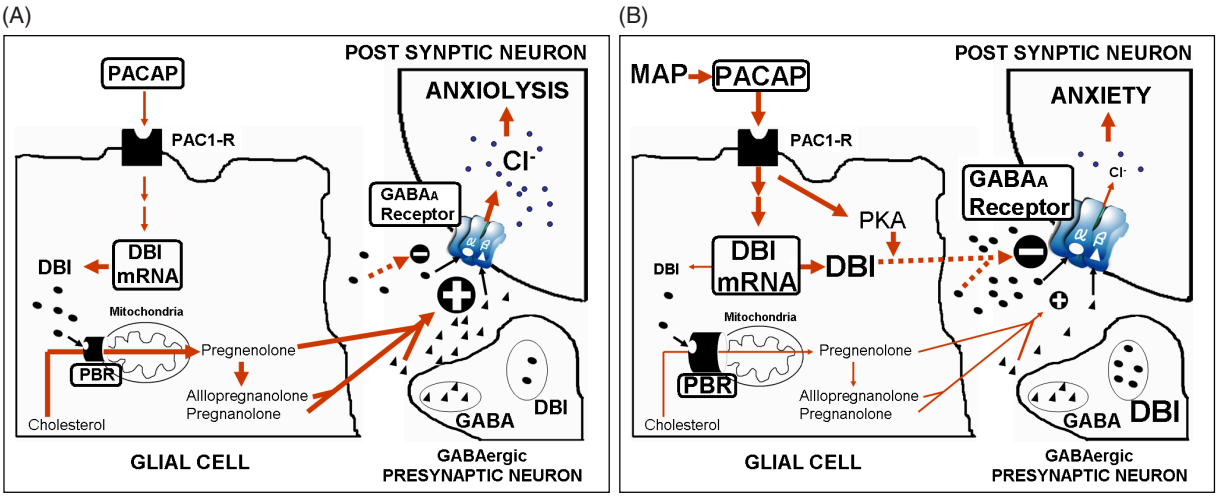

Fig. 5. The pathways of action of DBI in CNS showing the modulation of GABAergic function and anxiety. (A), physiological status; (B), after chronic administration of MAP. DBI, diazepam binding inhibitor; MAP, methamphetamine; PACAP, pituitary adenylate cyclase-activating polypeptide; PAC1-R, PACAP receptor; PBR, peripheral-type benzodiazepine receptor.

differences among the regions of the rat brain. The high levels of the mRNA expression of PACAP were detected in the hippocampus, cortex, diencephalon, midbrain, pons-medulla and cortex where approximately 27, 64, 50, 65 and 45 times of striatum, respectively. Fig. 4 shows the changes in the mRNA expression of PACAP after chronic treatment with MAP (5 mg/kg). Following chronic administration of MAP, the mRNA expression of PACAP in the brain increased. The levels increased by 37%-244% in the seven brain areas examined 16 h after the last administration: striatum (144% increase), hippocampus (62%), cortex (75%), diencephalon (58%), midbrain (42%), pons-medulla (37%), and cerebellum (112%).

DISCUSSION

The present study for first time demonstrated that chronic administration of MAP increased the mRNA expression of DBI in all areas of the brain, especially cerebral cortex and diencephalon. These results agree with the previous studies which demonstrated that the mRNA expression of DBI increases in the cerebral cortex of mice and rats showing dependency on morphine [13, 17], ethanol [12] and nicotine [14]. The increase of the mRNA expression of DBI 16 h after chronic administration of MAP may be related to anxiety. Several lines of evidences support this possibility. First, up-regulation of the mRNA expression of DBI may increase the peptides level of DBI after chronic administration of MAP, because the peptide level of DBI is regulated at the transcriptional level [7]. Second, the administration of DBI into brain induced anxiety [4, 11, 27], and an elevation in the level of DBI in brain induced anxiety [7, 11, 24]. Third, the half-life of DBI is more than 3 h [21]. Fourth, the rats treated with amphetamine, close structural homologue of MAP, for 6 days exhibited a transient reduction of the locomotor activity 24 h after the last administration of amphetamine, which is considered as a sign of anxiety [25].

The neural pathways associated with anxiety are established within the network sustained by diencephalon, cerebral cortex, hippocampus and cerebellum [6, 20]. The diencephalon have a high density of benzodiazepine receptors, which are known to facilitate GABA transmission [6]. The regions where chronic administration of MAP increased the mRNA expression of DBI, especially diencephalon and cerebral cortex, are correlated to the neural pathways responsible for anxiety.

The present study suggested that chronic administration of MAP increase the peptide level of DBI in the synaptic cleft through increase of the mRNA expression of PACAP in astrocytes, inducing anxiety via $GABA_A$ receptor. Several lines of facts supported that. First, the sequence homologous to cAMP response element is found in the 5'-flanking region of the PACAP gene [29]. Second, chronic administration of amphetamine causes phosphorylation of the cAMP response element binding protein (CREB) and the induction of downstream CREB-regulated gene [26]. Third, the increase of the peptide level of PACAP upregulates the mRNA expression of DBI through the activation of PAC1-R located in the astrocytes [18]. Fourth, the increase of the peptide level of PACAP enhances the release of DBI from the cultured astrocytes of rat into conditioned media through activation of the adenylyl cyclase / protein kinase A (PKA) pathway [18], which can increase DBI in the synaptic cleft.

In contrast, DBI causes anxiolysis via the effect of PBR in mitochondria of astrocytes on the synthesis of neurosteroids such as allopregnanolone and pregnanolone which activates $GABA_A$ receptor [23]. Based on that, the release of DBI into the synaptic cleft from astrocytes through the activation of PKA by PACAP results in the reduction of DBI in astrocytes, which can induce the decrease of neurosteroidogenesis in the astrocytes, hence anxiogenesis ultimately. The increase of the mRNA expression of PBR could be induced for the compensation for the decrease of DBI binding to PBR.

The mechanisms underlying the interactions between the neuronal and the glial DBI remain yet to be determined. However, the present and previous

observations suggest that chronic administration of MAP increase the levels of DBI in both the neurons and the astrocytes, and then may induce anxiety via the $GABA_A$ receptor. The increase of mRNA level of GABA-α2 is assumingly due to the pharmacological upregulation to improve the sensitivity of PBR in the astrocytes and the signal transduction in the neurons, respectively.

In conclusion, the mRNA expression of DBI, PBR, GABA-α2 and PACAP increased in all areas of the brain, especially diencephalon and cerebral cortex, after chronic administration of MAP. These results indicated that anxiety is associated with the mRNA expression of DBI as well as DBI-related genes. Our findings contribute to an understanding of the chemical mechanism of anxiety disorder. Upon the present study, further investigations should be required to determine the mRNA expression of DBI in mice and the exact localization of DBI at the cellular and tissue level after chronic administration of MAP using in situ hybridization and immunohistochemistry technique.

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