Both Metabotropic Glutamate I and II Receptors Mediate Augmentation of Dopamine Release From the Striatum in Methamphetamine-Sensitized Rats

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ABSTRACT—The role of metabotropic glutamate receptor (mGluR) on dopamine overflow from the striatum was studied in methamphetamine (MAP)-sensitized rats. The increase of dopamine release by MAP was significantly inhibited by perfusion of a mGluR antagonist (S)-4-carboxy-3-hydroxyphenylglycine. The perfused mGluR agonist 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid enhanced the dopamine level. The enhancement was significantly attenuated by co-perfusion of a mGluR group I antagonist (S)-4-carboxy-3-hydroxyphenylglycine or a mGluR group II antagonist R,S-α-methyl-4-tetrazolylphenylglycine. These suggest that both mGluR group I and II mediate augmentation of dopamine release in MAP-sensitized rats.

Keywords: Methamphetamine sensitization, Metabotropic glutamate receptor, Dopamine

The mechanism of behavioral sensitization to amphetamine (AMP) or methamphetamine (MAP) have focused on possible alterations in the dopamine system. But the potential role of glutamate receptors has only recently been assessed. Glutamate receptors (GluRs) are categorized into two groups, ionotropic receptors (iGluRs) and metabotropic receptors (mGluRs). iGluRs are known to mediate the majority of conventional fast excitatory transmission in the central nervous system. Recently, we demonstrated that long-term enhancement of striatal dopamine release occurred after activation of NMDARs and AMPARs (1).

On the other hand, mGluRs are known to be coupled to alterations in cAMP formation, phosphatidylinositol (PI) turnover and activation of phospholipase D. mGluRs are involved in a family of G-protein-coupled receptors that activate second messenger systems. They are categorized into three groups. Group I (mGluRs 1 and 5) couples to phospholipase C and increases synaptic transmission via IP3/diacylglycerol production. Group II (mGluRs 2 and 3) and III (mGluRs 4, 6, 7 and 8) decreases synaptic transmission by the suppression of cAMP production. It was reported that not only iGluRs but also mGluRs play important roles in the synaptic plasticities such as long-term potentiation (LTP) (2) and long-term depression (3). However, little is known about the role of mGluR in AMP- and/or MAP-induced sensitization. We have reported that a mGluR agonist 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) enhances dopamine release and induces stereotyped behavior, and that the enhancement of dopamine level and the stereotyped behavior are attenuated by co-perfusion of a mGluR antagonist R,S-α-methyl-4-carboxyphenylglycine (4, 5). Therefore, the purpose of the present study is to investigate the role of the mGluR subtype on dopamine release in the striatum in MAP-sensitized rats.

The animals used in this experiment were male rats of the Wistar strain (Kuroda Animal Co., Fukuoka), weighing between 300 – 400 g. The rats were housed under a constant temperature (23 ± 2°C) and a 12-h light/dark cycle (light period: 07.00 – 19.00 h). The rats were allowed free access to food and water throughout the experiment. The rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and were fixed on a stereotaxic instrument. A guide cannula (0.5-mm outer diameter, AG-8; Eicom Co., Kyoto) was placed just above the striatum (0.7 mm anterior to the bregma, 2.6 mm lateral to the midline, 3.2 mm ventral to the surface of the skull measured at the bregma), according to the brain atlas of Paxinos and Watson.

After at least a 2-day recovery period, rats were injected with saline or MAP (Dainippon Pharmaceuticals Ltd., Osaka). Saline (SAL) or MAP (1.0 mg/kg, i.p.) was administered every 3 days with a total of 5 injections. After 7-day withdrawal, rats were used for the microdialysis studies.

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We used this schedule because significant augmentation of locomotor activity is constantly and stably induced in this one (6).

Brain microdialysis was carried out in unanesthetized, freely moving rats. A concentric dialysis probe (3.0-mm active membrane length and 0.2-mm outer diameter, A-L-8-03; Eicom Co.) was inserted into the striatum through the guide cannula so that the tip of the probe was located at 6.2 mm ventral to the skull surface. During the dialysis experiment, the probe was connected to an infusion pump (EP-60, Eicom Co.) and was perfused with Ringer solution (147 mM NaCl, 4 mM KCl, 2.3 mM CaCl₂) at a rate of 2.0 µl/min. Perfusate samples collected at 20-min intervals (40 µl) were directly injected into HPLC-ECD system for quantification of dopamine. The HPLC-ECD consisted of a pump (EP-10, Eicom Co.) coupled to a reversed-phase column (5 µm, 4.6 × 150 mm, Developil ODS-HG-5; Nomura Chemical Co., Ltd., Aichi) and an ECD (ECD-100, Eicom Co.). A graphite working electrode (WE-3G, Eicom Co.) was set at +0.60 V against the Ag/AgCl reference electrode. The mobile phase was composed of 36.8 mM citric acid, 52.6 mM sodium acetate, 0.6 mM sodium 1-octanesulphonate, 14 µM EDTA and 11% methanol. The flow rate was 1.0 ml/min.

We used 0.1 mM mGluR agonist (1S,3R)-1-amino-cyclopentane-trans-1,3-dicarboxylic acid (1S,3R-ACPD), 0.5 mM mGluR antagonist R.S-α-methyl-4-carboxyphenylglycine (MCPG), 0.1 mM mGluR Group I agonist R,S-3,5-dihydroxyphenylglycine (DHPG), 0.1 mM mGluR Group I antagonist/Group II agonist, S-4-carboxy-3-hydroxyphenylglycine (4C3HPG) and 0.1 mM mGluR Group II antagonist R.S-α-methyl-4-tetrazolylphenylglycine (MTPG) (Tocris Cookson, Ltd., Bristol, U.K.). The drugs were dissolved in distilled water. First, after the basal dopamine level was stabilized (at least 2 h after the probe insertion), Ringer solution with or without MCPG (5 × 10⁻⁴ M) was applied directly into the striatum through the microdialysis probe, and MAP (0.5 mg/kg, i.p.) was challenged. Then, dopamine release was measured for up to 3 h. Next, drugs were applied directly into the striatum through the microdialysis probe during a 20-min period, and then dopamine release was measured for up to 3 h.

Data were expressed as a percentage of the baseline levels, and significance was analyzed with a repeated measures analysis of variance (ANOVA). If the interaction within each group was shown, significant differences between means were determined by a one-way ANOVA followed by Dunnett’s test. The baseline value of the extracellular concentration of dopamine in dialysates from the striatum was 17.7 ± 1.0 pg/20 min (mean ± S.E.M., n = 24) in SAL-treated rats. The value was not different from that in MAP-sensitized rats (17.8 ± 0.7 pg/20 min, n = 27). Therefore, the basal dopamine release in each group was set as 100%.

Figure 1. Time course of dopamine release from the striatum after methamphetamine (MAP, 0.5 mg/kg, i.p.) challenge with or without application of R.S-α-methyl-4-carboxyphenylglycine (MCPG, 5 × 10⁻⁴ M) into the striatum in freely moving rats. Saline or MAP (1.0 mg/kg, i.p.) was administered every 3 days with a total of 5 injections. After 7-day withdrawal, rats were used for microdialysis studies. Each point is the mean ± S.E.M. of the basal dopamine level. The number of animals used is indicated in parentheses. The significance of differences was determined by means of repeated measure ANOVA followed by Bonferroni/Dunn test. *P<0.05, **P<0.01, SAL vs MAP; 7P<0.05, 77P<0.01, MAP vs MCPG. SAL, saline-treated group; MAP, MAP-treated group; MAP-MCPG, application of MCPG in MAP-treated group.
effects continue through 120 min. The enhancement of dopamine release by 1S,3R-ACPD was significantly attenuated by the co-application of 4C3HPG or MTPG in MAP-sensitized rats (4C3HPG: 60, 80, 100 and 120 min, \( P < 0.05 \); MTPG: 100 and 120 min, \( P < 0.05 \)). 1S,3R-ACPD induced stereotyped behavior such as grooming, chewing, face washing, and so on. The stereotyped behavior was also diminished by the application of 4C3HPG or MTPG. Single application of DHPG (10\(^{-3}\) M) or 4C3HPG (10\(^{-5}\) M) did not have any effect on dopamine level in MAP-sensitized rats (data not shown).

The striatum receives two main afferent pathways; namely, dopaminergic and glutamatergic inputs from the substantia nigra and the cortex, respectively. Recently, we demonstrated that long-term enhancement of striatal dopamine release was maintained after the activation of NMDAR and AMPAR (1). Although mGluRs were present in the striatum with widely varying relative densities and cellular patterns, it is little known whether mGluR-dependent mechanism is involved in Glu-stimulated dopamine release. In the nucleus accumbens, it was reported that microdialysis application of mGluR agonist 1S,3R-ACPD caused an increase of dopamine release with a high concentration (1 mM) (7), but small decrease with a low concentration (0.1 mM). We reported that 1S,3R-ACPD-induced dopamine release is significantly enhanced in MAP-sensitized rats (4). Moreover, in our previous report, the activation of mGluRs caused an augmentation of dopamine release from the MAP-sensitized striatal slices (5). Trans-ACPD, racemic mixture of 1S,3R- and 1R,3S-isomers, possesses a selective agonistic effect on mGluRs that are coupled to adenylate cyclase. However, 0.1 mM trans-ACPD could stimulate the inositol phosphate accumulation in the striatal neurons (8), due to the activation of phospholipase C. On the other hand, 1S,3R-ACPD is reported to inhibit the stimulation of cyclic AMP synthesis by forskolin and to stimulate brain phosphoinositide hydrolysis, although these effects are blocked by co-administration with \( R,S\)-MCPG (9). These reports have suggested that 1S,3R-ACPD activates various type of mGluRs, and then activation of mGluRs may affect dopamine release through the modification of the formation of second messengers (10). The present results support these reports including our previous ones, and the role of mGluR was more clearly shown.

On the other hand, Kim and Vezina (11) reported that \( R,S\)-MCPG produces hyperlocomotion in AMP pre-exposed rats. They also mentioned that the effect of \( R,S\)-MCPG depends on the dose used in AMP-induced locomotion (12). The dose used in our experiment was relatively high. The discrepancy of the result might be induced by the dose of \( R,S\)-MCPG used or the difference of the injection cite. Moreover, mGluRs are known to play important roles in the central nervous system plasticities such as LTP in the hippocampus (2) and long-term depression in the cerebellum (13) and striatum (3). Thus long-term changes in striatal synaptic function may require the activation of mGluRs. Therefore, it is suggested that
mGluRs may have a facilitatory role in the expression process of MAP-induced sensitization. Neither a group I mGluR agonist DHPG nor a group II mGluR agonist 4C3HPG potentiated dopamine release from the striatum in MAP-sensitized rats (data not shown). The augmentation of dopamine release in the striatum by 15,3R-ACPD was significantly inhibited by co-application with 4C3HPG or MTPG. Group I mGluRs are known to increase synaptic transmission through IP3 (14). On the other hand, group II mGluRs inhibit synaptic transmission through the inhibition of cAMP production (14). However, it is reported that both receptors have synergistic effects on inositol phospholipid hydrolysis in the hippocampus. Moreover, group II mGluRs increase cAMP production induced by the activation of G-protein coupled receptors. Cartmell et al. (15) described that a group II mGluR agonist blocks AMP-induced ambulations and rearing. However, this experiment was described for the acute effect of MAP. In MAP-sensitized rats, functional change may be induced on the neural mechanism. So, a different effect might be caused by this functional change. Then, the drugs were injected into the nucleus accumbens in this experiment. The region of the application might cause a different effect. Taken together, the augmentation of dopamine release in the striatum may be induced by synergistic action of both receptors. In summary, both group I and group II mGluRs mediate augmentation of dopamine release from the striatum in MAP-sensitized rats.

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