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Short Communication

Effects of cloperastine, a non-narcotic antitussive, on the expression of GIRK channels in the brain of methamphetamine-induced hyperactive mice

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ABSTRACT

Objectives: Centrally-acting antitussives with inhibitory effects on G protein-coupled inwardly rectifying potassium (GIRK) channels have been shown to also inhibit methamphetamine-induced hyperactivity in mice. In this study, we examined if cloperastine, which is the most potent inhibitor of the GIRK channels among antitussives, is sensitive to the expression levels of GIRK channels in the brain of methamphetamine-treated mice.

Materials and Methods: The brain tissues have been removed and the total RNA has been extracted from tissues. The mRNA levels were evaluated using semiquantitative reverse transcription-polymerase chain reaction.

Results: The concentration levels of the mRNA of GIRK channels within the ventral midbrain of methamphetamine-treated mice increased as compared with that in control and cloperastine reduced an upregulation in GIRK2, one of the subunits of the GIRK channels, by the injection of methamphetamine.

Conclusion: These findings suggest that cloperastine might ameliorate hyperactivity by inhibiting the GIRK channels in the brain.

Keywords: Antitussives, G protein-coupled inwardly rectifying potassium channels, Hyperactivity, Methamphetamine, Ventral midbrain

INTRODUCTION

Previously, we have reported that centrally-acting antitussives (CAAs), like cloperastine, exhibit inhibitory effects on G protein-coupled inwardly rectifying potassium (GIRK) channel-activated currents and alleviate not only persistent cough but also intractable brain disease symptoms in rats and mice. For example, CAAs have been reported to improve cerebral infarction-associated urinary disorders among rodents.[1] Moreover, the drug markedly lowers the immobility time in the forced swimming test among both adrenocorticotropic hormone-treated and normal rodents,[2,3] alluding to an antidepressant effect of the medication. In addition, mice who received the antitussives tend to have lower anxiety levels, based on their reduced performance (using number of marbles buried) in a marble-burying test,[4] pointing out that the medication may exhibit anti-anxiety properties. Furthermore, a chronic administration of cloperastine has been reported to improve learning and memory disorders caused by endocrine disruptors such as diethylstilbestrol.[5] Overall, these

observations imply that antitussives, such as cloperastine, may improve disrupted brain conditions induced by several diseases or environmental toxins.

Hyperactive behaviours are symptoms of a severe developmental illness. For instance, attention deficit hyperactivity disorder is currently defined as a developmental disorder, in which all clinical criteria manifest as behavioural changes. Hyperactivity, impulsivity and inattention are currently considered the primary clinical symptoms (Diagnostic and statistical manual of mental disorders: DSM-5; American Psychiatric Association; 2013). Our previous study suggested that CAAs, such as cloperastine, ameliorated methamphetamine-induced hyperactivity (MIH). In addition, there was a significant correlation between the ameliorative effects of antitussives on MIH and the blockade of GIRK channel currents.[6]

This study investigated whether the blockade of brain GIRK channels was involved in the effects of CAAs on MIH in mice, as the first step toward the understanding of action mechanisms of CAAs on hyperactivity in mice.

MATERIALS AND METHODS

Subjects and housing

Forty-eight male ddY mice (SLC, Shizuoka, Japan) were used for this study. They were kept in standard cages (33.8 long × 22.5 wide × 14.0 cm high) with bedding of paper chips in the animal centre of the Graduate School of Pharmaceutical Sciences of Kumamoto University. A 12:12-h light-to-darkness cycle was continued throughout the experiments, with lights switched on at 08:00–20:00, and the temperature was maintained at 22°C ± 2°C. Standard mouse food and tap water were made freely available to the mice. The mice were processed based on recommendations made by the Japanese Pharmacological Society. All experiments were approved by the Animal Experiment Committee at Kumamoto University. Reference no of the ethics approval of our study was AA17-189, and its date of approval was December 21, 2005.

Drugs

Cloperastine hydrochloride was bought from Sigma-Aldrich Japan (Tokyo, Japan). Methamphetamine hydrochloride was purchased from Dainippon Sumitomo Pharma (Osaka, Japan). The drugs were administered to the animals as indicated in the figure legends, and the doses were estimated using the respective free base.

Methamphetamine-induced hyperactive mice

We purchased 4-week-old male mice and performed handling for 1–2 weeks. Methamphetamine was administered subcutaneously (s.c.) at 0.5- or 2.0-mg/kg body weight.

Semiquantitative reverse transcription-polymerase chain reaction

The brain tissues were excised and the frontal cortex (FC), dorsal hippocampus (DH), striatum (ST) and ventral midbrain (VM) were quickly dissected and immersed in liquid nitrogen and stored at −80°C for later use. Total RNA was extracted using Trizol (Invitrogen, Carlsbad, CA). The amount and quality of RNA were evaluated using their UV absorbance values at 260 nm and agarose gel electrophoresis, respectively. Reverse transcription (RT)-polymerase chain reaction (PCR) was carried out using an RNA PCR Kit Version 3 (Takara Shuzo, Ohtsu, Japan) in accordance with the steps advised by the manufacturers. For RT, total RNA (0.5 μg) was mixed in a 10 μL reaction mixture consisting of 5 mM $MgCl_2$, 1 mM dNTP mixture, 1 U RNase inhibitor, 125 nM oligo dT-adaptor primer and 0.25 U avian myeloblastosis virus reverse transcriptase XL (Life Sciences, Hialeah, FL) in RNA PCR buffer (10 mM Tris-HCl and 50 mM KCl). After producing cDNA on the first strand at 42°C for 60 min, a denaturation step at 99°C for 5 min was carried out. For the PCR, the template (10 μL) underwent amplification in a 50 μL PCR reaction mixture consisting of 200 nM of each PCR-primers for GIRK1, GIRK2, GIRK3, tyrosine hydroxylase (TH), dopamine D_1 receptor (D_1R), dopamine D_2 receptor (D_2R), or β-actin (see Supplementary materials and methods) and 1.25 U Taq polymerase (Takara Shuzo) in PCR buffer. Denaturation was executed at 94°C for 120 s and amplification was performed (1) at 94°C for 60 s and (2) at 56°C (D_1R and D_2R), 58°C (GIRK2), 60°C (GIRK1, GIRK3 and β-actin), 68°C (TH) for 60 s and (3) at 72°C for 120 s in an automated DNA Thermal Cycler (Mastercycler gradient, Eppendorf, Tokyo, Japan). The quantity of template and the number of amplification cycles were preliminarily optimised during the PCR reaction to avoid saturation (GIRK1; FC, DH: 23 cycles; ST: 25 cycles; VM: 30 cycles; GIRK2; FC, DH: 23 cycles; ST, VM: 28 cycles; GIRK3; FC, DH, ST: 25 cycles; VM: 30 cycles; TH; ST: 26 cycles; VM: 28 cycles; D_1R; ST: 25 cycles; VM: 32 cycles; D_2R; ST, VM: 28 cycles; β-actin; FC, DH and ST and VM: 20 cycles). After amplification, the RT-PCR reaction mixture (10 μL) underwent electrophoresis on a 2% agarose gel and was subsequently visualised by ethidium bromide staining using an ultraviolet transilluminator (TCP-15C, M&S Instruments, Osaka, Japan), and quantified by Scion Image beta 4.0.2 (Scion Corporation, USA). The mRNA levels of GIRK1, GIRK2, GIRK3, TH, D_1R and D_2R were then normalised to mRNA β-actin levels and expressed as arbitrary units.

Statistical analysis

The findings are reported as means ± standard error of the mean (SEM). In the case of comparisons between the two groups, statistical significance was assessed using the unpaired two-tailed t-test. For all comparisons, $P < 0.05$ was used as the statistically significant criterion.

RESULTS

Effects of methamphetamine on the expression levels of GIRK channels, TH and dopamine receptors in the brain of normal mice

To ascertain if the ameliorative effects of antitussives on hyperactivity were related to the GIRK channels, we determined the expression levels of the GIRK channels by semiquantitative RT-PCR analysis in some brain regions of methamphetamine-induced hyperactive mice. We then examined the levels of (1) TH, the rate-determining enzyme in dopamine synthesis and (2) GIRK channels in the ST and the VM involved in the nigrostriatal dopamine system. TH mRNA levels were significantly increased in both the ST and the VM by acute injection of methamphetamine at 0.5 and 2.0 mg/kg [Table 1]. In the brain, three subunits of GIRK channel (GIRK1, GIRK2 and GIRK3) have broad and overlapping distributions, while the fourth subunit (GIRK4) occurs mainly in the heart.[7-12] Therefore, we have examined GIRK1, GIRK2 and GIRK3 expression levels, but not GIRK4. Methamphetamine at 0.5 and 2.0 mg/kg significantly increased GIRK2, but not GIRK1 and GIRK3 mRNA in both the ST and the VM [Table 1]. Apart from the above, the levels of mRNA of GIRK1 and GIRK3 were significantly increased in the DH, whereas methamphetamine at 0.5 and 2.0 mg/kg significantly reduced GIRK1 mRNA levels in the FC [Table 1]. In addition, we performed immunohistochemical staining for GIRK2 at 180 min after injection of methamphetamine. In the hippocampus and VM, including the substantia nigra, GIRK2 immunoreactivity was increased in mice injected with methamphetamine compared to controls [Supplementary resources].

Table 1: The expression level of GIRK1-3 subunits, TH and dopamine D_1/D_2 receptors in each part of the brain after methamphetamine injection.

	METH 0.5 (vehicle±METH 0.5 mg/kg)	METH 2.0 (vehicle±METH 2.0 mg/kg)
Frontal cortex		
GIRK 1	85.53±8.23*	69.89±2.39**
GIRK 2	93.76±7.50	84.60±6.37
GIRK 3	102.79±5.57	101.70±2.54
Dorsal hippocampus		
GIRK 1	115.37±4.31**	121.87±4.02**
GIRK 2	93.84±3.74	105.30±3.15
GIRK 3	136.11±7.30**	136.84±6.80**
Striatum		
GIRK 1	151.30±18.48**	127.59±1.32
GIRK 2	158.58±18.66**	138.16±5.72*
GIRK 3	146.54±13.04**	111.94±2.33
TH	117.51±7.01*	122.44±4.53*
D_1R	77.99±4.94*	67.96±4.83**
D_2R	141.38±3.04**	123.26±2.22*
Ventral midbrain		
GIRK 1	121.81±4.94**	128.80±3.10**
GIRK 2	125.97±5.37**	118.18±4.79**
GIRK 3	118.20±3.20**	110.84±5.16
TH	135.98±6.86**	140.76±6.44**
D_1R	94.75±5.89	104.25±10.05
D_2R	136.63±6.96**	121.42±5.25*

% of control (vehicle+vehicle). METH 0.5 and 2.0 indicated the expression in the FC, DH, ST and VM after injection of methamphetamine 0.5 and 2.0 mg/kg, s.c., respectively. The brain was removed at 40 min after injection of methamphetamine. Mean±SEM of 5 to 6 mice. *P<0.05, **P<0.01 versus control (vehicle+vehicle) group. METH: Methamphetamine; TH: Tyrosine hydroxylase; D_1R: Dopamine D_1 receptors; D_2R: Dopamine D_2 receptors; GIRK: G protein-coupled inwardly rectifying potassium

In this study, our findings suggest that methamphetamine activated the nigrostriatal system and GIRK2. It was known that GIRK channels were coupled to the dopamine D_2 receptors, but not the dopamine D_1 receptors. Therefore, we also examined dopamine receptors mRNA levels to determine, whether the action of methamphetamine was associated with the GIRK channels coupled with dopamine receptors. Dopamine D_2 receptor mRNA levels were increased by methamphetamine in both the ST and the VM. In contrast, methamphetamine at 0.5 and 2.0 mg/kg significantly reduced the dopamine D_1 receptor mRNA levels in the ST [Table 1].

Moreover, we examined the time-course of the expression levels of the mRNA of both GIRK2 subunits and dopamine receptors after methamphetamine injection. GIRK2 mRNA levels had increased significantly at 40 min but decreased at 180 min after methamphetamine injection. On the other hand, dopamine D_2 receptors mRNA levels were both significantly increased at 40 and 180 min after methamphetamine injection compared to the control [Figure 1].

Effects of centrally-acting non-narcotic antitussive cloperastine on the expression levels of GIRK2 subunits and dopamine D_2 receptors in the VM of methamphetamine-induced hyperactive mice

Finally, we evaluated the effects of cloperastine on the concentration of GIRK2 subunits and dopamine D_2 receptors in the VM, which is involved in the origin of the dopaminergic cell bodies, of methamphetamine-induced hyperactive mice. First, cloperastine at a dose of 20 mg/kg was injected and 10 min thereafter, methamphetamine was injected. Subsequently, 40 min after methamphetamine injection, GIRK2 mRNA levels were significantly reduced in the VM by subcutaneous injection of cloperastine administered at 20 mg/kg dose. However, dopamine D_2 receptors mRNA levels did not change [Figure 2]. In addition, 180 min after methamphetamine injection, the levels of the mRNA of GIRK2 subunits and dopamine D_2 receptors did not change

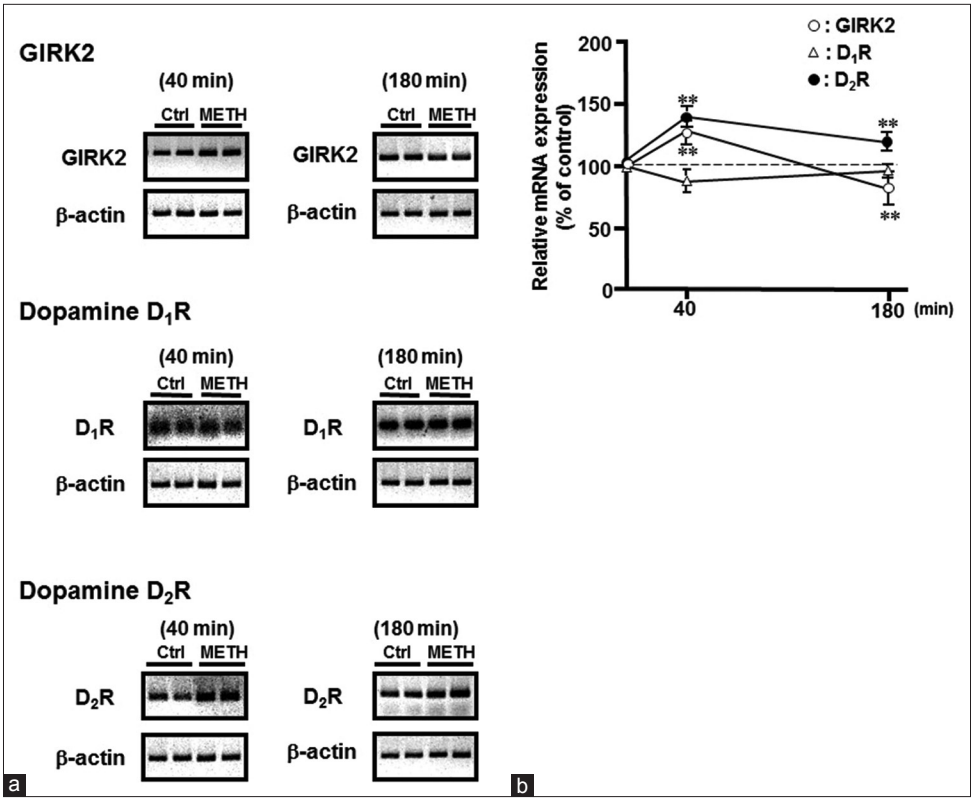

Figure 1: Relative mRNA expression of G protein-coupled inwardly rectifying potassium channel 2 (GIRK2) subunits and dopamine receptors in the ventral midbrain after methamphetamine injection. (a) Semiquantitative reverse transcription-polymerase chain reaction analysis of GIRK2 subunits, dopamine D_1 receptors and dopamine D_2 receptors in the ventral midbrain. Samples were obtained from mice s.c. injected with saline (Ctrl) or 0.5-mg/kg methamphetamine. Expression of β-actin was also analysed in the same sample, as a housekeeping gene. The brain was removed at 40 min (left) or 180 min (right) after injection of methamphetamine. (b) Relative expression levels of each mRNA in the ventral midbrain. The optical density of each mRNA was normalised to that of corresponding β-actin. Mean ± SEM of 5 to 6 mice. $^{**}P < 0.01$ versus 0 min group. Ctrl: Control, METH: Methamphetamine, D_1R: Dopamine D_1 receptors, D_2R: Dopamine D_2 receptors.

by subcutaneous injection of cloperastine using a 20 mg/kg dose (data not shown).

DISCUSSION

Our previous research reported that non-narcotic antitussives blocked GIRK channel currents coupled to various receptors, such as 5-HT_{1A}, dopamine D_2, noradrenaline α_2, $GABA_B$ and delta-opioid.[13-15] Furthermore, we have shown that non-narcotic antitussives decreased MIH at effective antitussive doses and found that there is a correlation between the suppression of hyperactivity and the inhibition of GIRK channel currents.[6] Activation of GPCR-mediated GIRK channels stabilises the expression of neurons through the hyperpolarisation induced by outward currents of K^+. Therefore, some investigators including us have postulated that the inhibition of GIRK channels should stimulate neurons, facilitating the expression of neurotransmitters.[15-18] In fact, non-narcotic antitussives such as cloperastine and tipepidine have been reported to increase levels of neurotransmitters and neurotrophic factors such as dopamine and BDNF.[5,19] In this study, it was suggested that cloperastine inhibited the expression levels of GIRK channels in the region containing the nucleus of origin in dopamine. It was found that the administration of methamphetamine upregulated the expression levels of GIRK2 subunits and dopamine D_2 receptors. However, the administration of cloperastine inhibited the expression levels of GIRK2 subunits, but not those of dopamine D_2 receptors, 40 min after methamphetamine injection. Therefore, it was suggested that cloperastine may selectively affect GIRK channels in the brain. Although not shown in the data, the expression level of GIRK2 subunits and dopamine D_2 receptors did not change at 180 min after methamphetamine injection, suggesting that the action of cloperastine may be transient. We have previously reported that cloperastine

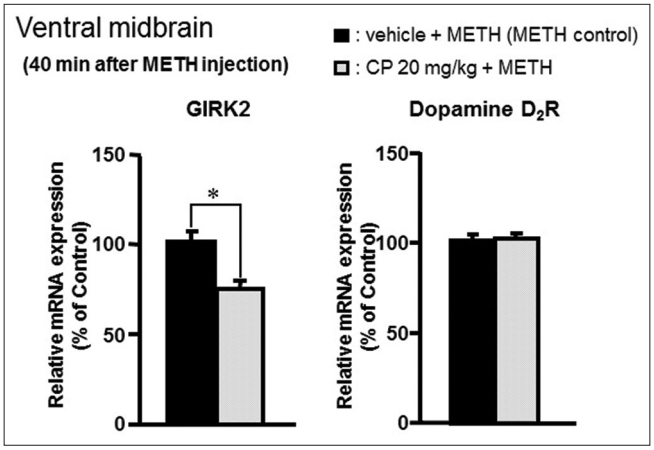

Figure 2: Effects of cloperastine on the expression of G protein-coupled inwardly rectifying potassium channel 2 (GIRK2) subunits and dopamine D_2 receptors in the ventral midbrain after methamphetamine injection. The brain was removed 40 min after the injection of 0.5-mg/kg methamphetamine, s.c. Relative mRNA expression of GIRK2 subunits was significantly decreased by cloperastine administered at a 20-mg/kg dose, s.c. injection 10 min before the injection of methamphetamine. However, relative mRNA expression of the dopamine D_2 receptors did not change. Mean ± SEM of 3 to 4 mice. *$P < 0.05$ versus methamphetamine control (vehicle + methamphetamine 0.5 mg/kg) group. METH: Methamphetamine; CP: Cloperastine.

inhibited MIH, and the results were indicated at 40 min after methamphetamine injection.[6] Therefore, it is possible that the effects of cloperastine, as observed in this study, could be the mechanism of inhibitory action in MIH.

Furthermore, the present study evaluated the expression levels of GIRK channels in each part of the brain after an acute injection of methamphetamine. As far as we know, there was no previous related study; therefore, we examined reports of changes in mRNA and protein molecules due to the acute injection of methamphetamine. As obtained in the results, there were many reports that mRNA was examined about 1–4 h after treatment with methamphetamine,[20-26] and proteins were examined about 1.5–24 h after treatment with methamphetamine.[27,28] In addition, it was reported that the amount of extracellular dopamine in the ST was maximum at 40 min after an acute injection of 0.5-mg/kg methamphetamine.[29] Therefore, in this study, samples at 40 min and 180 min after the injection of methamphetamine were used for the measurement of the levels of mRNA of GIRK channels by semiquantitative RT-PCR. For the measurement of GIRK channel proteins by immunohistochemistry, samples taken 180 min after methamphetamine injection were used. The results of this study suggest that the acute injection of methamphetamine alters the mRNA expression levels of GIRK channels in the brain. Moreover, the pattern of fluctuation differed by region of the brain. At present, the mechanism is unknown; however, it is generally believed that acute injection of methamphetamine involves the activation of the substantia nigra-striatal pathway that projects from dopamine cells present in the substantia nigra to the ST.[30] In the present study, the expression levels of TH, a rate-limiting enzyme in the dopamine synthesis pathway, and dopamine D_2 receptors coupled to GIRK channels in the ST and the VM were increased by the acute injection of methamphetamine, indicating the pathogenic mechanism of MIH. Furthermore, by comparing changes between GIRK2 subunits and dopamine D_2 receptors after methamphetamine injection, the change in GIRK2 expression levels was transient. Therefore, in this animal model, it is possible that acute injection of methamphetamine increased the expression levels of the GIRK channels in the substantia nigra-striatal pathway, and as a result, the expression levels of the dopamine D_2 receptors coupled to the GIRK channels correspondingly increased.

Obviously, methamphetamine injection has resulted in differences in the expression profiles for striatal dopamine receptors. Reports supporting this finding indicate that mice with genetically altered dopamine D_1 receptor deficiency enhanced their locomotor activity,[31] whereas mice with genetically engineered dopamine D_2 receptor deficiency decreased their locomotor activity.[32] Although the detailed mechanism is not known, it is assumed that the sensitivity of methamphetamine to dopamine receptors may differ in the ST.

CONCLUSION

These findings indicate that MIH in mice involves an increase in GIRK channels coupled to dopamine D_2 receptors. Empirically, it was also suggested that the CAAs, such as cloperastine, may decrease the expression levels of GIRK channels in the brain with the attendant effect of affecting the release of neurotransmitters, such as dopamine, and thus suppress hyperactivity.

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Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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