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Transient increases of histamine H_1 and H_2 receptor mRNA levels in the rat striatum after the chronic administration of methamphetamine

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Abstract: In our previous studies, we found that behavioral sensitization evoked by repeated administration of methamphetamine (METH) was suppressed by the activation of the histaminergic neuron system in the brain. In continuation of these studies, we measured the levels of H_1 and H_2 receptor mRNAs in the rat striatum by semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR). Seven days after the 21 consecutive administrations of METH (4 mg/kg, i.p.), the levels of both H_1 and H_2 receptor mRNAs in the rat striatum increased significantly. But 1 day and 14 days after the last administration, there were no significant changes in levels of either H_1 or H_2 receptor mRNA in the rat striatum. These transient increases of H_1 and H_2 receptor mRNA may have some relation to chronic METH abuse and its withdrawal.

Key Words: Methamphetamine; H_1 receptor; H_2 receptor; Semi-quantitative RT-PCR; Rat striatum.

Running Title: Histamine H1 and H2 receptor mRNA and methamphetamine.

A biogenic amine, histamine (HA), is widely distributed in the mammalian brain and has recently been suggested to be a neurotransmitter or neuromodulator[10, 11, 20]. Cell bodies of HA neurons are localized in the tuberomammillary nucleus in the posterior hypothalamic region, while their varicose fibers are found in almost all regions of the brain. The HA neuron system has been shown to be involved in diverse brain functions and behaviors through H_1, H_2, and H_3 receptors, such as arousal, sleep-wake cycle, appetite control, seizure, learning and memory, aggressive behaviors, emotion, and so on[10, 11, 13, 20].

It is well known that methamphetamine (METH) facilitates the release of dopamine via especially acting on a dopamine transporter, and induces increases of locomotor activity and stereotyped behavior[14, 15]. Repeated administration of METH causes a progressive and lasting augmentation of locomotion and stereotyped behavior called behavioral sensitization[14, 15].

With respect to relationship between METH and the HA neuron system, there were several reports that HA agonists inhibited METH-induced locomotor hyperactivity and stereotyped behavior in rodents, whereas HA antagonists potentiated METH-induced reinforcing effects and stereotyped behavior[5, 6]. Both H_1 and H_2 antagonists can potently increase DA levels in the neostriatum and nucleus accumbens of rats [1, 17]. In addition, acute administration of

METH increases the release of HA in the rat striatum via dopamine D_2 receptors [4]. Recently, our behavioral pharmacological study suggested that the HA neuron system had an inhibitory effect on the development of METH-induced behavioral sensitization through H1 and H2 receptors[5]. Moreover, after the METH-induced behavioral sensitization is formed, the release of HA and the HDC activity increases in the rat striatum [3, 4]. However there is no neurochemical report on changes of H_1 and H_2 receptors after the development of METH-induced behavioral sensitization is accomplished. In this study, we measured changes of H_1 and H_2 receptor mRNA levels in rat striatum after chronic administrations of METH by the semi-quantitative RT-PCR, because the striatum has close relationship with METH-induced stereotyped behavior and acute and chronic administrations of METH increase HA release in the rat striatum [4]. Male Wistar rats weighing 220-240g at the beginning of experiments were group-housed (four rats per cage) with free access to food and water in a room maintained at 22±2℃ and 65±5% humidity under a 12-h light/12-h dark cycle (lights on at 6:00 a.m.).

In treatment of METH, rats were injected intraperitoneally (i.p.) with saline [0.9% (wt/vol) NaCl] (1 ml/kg) or METH (4 mg/kg) once daily for 21 consecutive days. METH (Dainippon, Japan) was dissolved in saline.

Rats were decapitated 1, 7 and 14 days after the last intraperitoneal injection of saline or METH. Total RNAs was prepared from the striatums using acid guanidium phenol chloroform extraction (ISOGEN, Wako, Japan). Total RNAs were treated by DNaseI to exclude contamination of genomic DNA as follows. Fifty to 100 μg of total RNA were digested using 120-160 units DNaseI (Takara, Japan) in a solution containing 100 mM $MgCl_2$, 10 mM dithiothreitol, 25-100 units ribonuclease inhibitor (Wako, Japan) in a total volume of 200 μl at 37 ℃ for 60 min. Then, we confirmed that there is no genomic DNA contamination by performing PCR with total RNAs as templates and H_1, H_2 and GAPDH primers at 40 cycles.

First strand complementary DNA (cDNA) mixture was made by random priming from RNA samples containing 4 μg total RNA by using Superscript II system (GIBCO BRL, Bethesda) and the procedures recommended by the manufacturer. All PCR reactions were carried out in a total volume of 30 μl of solution containing 10 μl of cDNA mixture, 0.75 unit of AmpliTaq Gold polymerase (Perkin Elmer, New Jersey), 0.2 mM dNTP mixture, and 1 μM specific sets of H_1, H_2 and GAPDH primers[2, 12, 18] (H_1 receptor: sense primer, 5'CTGGTGGTGGTTCTCAGTAGTATC, positions 88-111; antisense primer, 5'-CAGCATAAGCAAAGTGGGGAGGTA-3', positions 598-621; H_2 receptor: sense primer, 5'-AATGGCACAGTTCATTCCTGCT-3', positions

10-31; antisense primer, 5'-ATCCGTTTGGCCTGCTCCCTGGCAA-3', positions 620-644; GAPDH: sense primer, 5'-ACTGTGGATGGCCCCTCTGGAAA, positions 583-605; antisense primer 5'-AGGTTTCTCCAGGCGGCATGTCA-3', positions 758-780). Cycling conditions are 9 min of pre-PCR incubation at 95 ℃, 1 min of denaturation at 94 ℃, 1 min of annealing at 60 ℃ (H_1 and GAPDH) or 65 ℃ (H_2), and 1 min of extension at 72 ℃ for 17-40 cycles at 2-cycle intervals. Then products were electrophoresed on a 2 % agarose gel containing ethidium bromide. Quantitations of PCR products were carried out as described by Nakayama et al.[9]. The intensity of the ethidium bromide luminescence was recorded using CCD image sensor FOTODYNE FOTO/Analyst Archiver Eclipse system (FOTODYNE, Wisconsin) and analyzed by computer software 1-D Basic (Advanced American Biotechnology, California). Reaction cycle-PCR product yield curves of each reaction were plotted on semilogarithmic graphs. From the graphs, we decided the numbers of cycles that each clone could exponentially be amplified. As an internal control, we also measured the rat GAPDH mRNA in the same manner. Data were analyzed by one way ANOVA, followed by Duncan's test. In all cases, p values less than 0.05 were considered statistically significant.

When PCR with H_1 primers were performed for 17-40 cycles at 2-cycle intervals, the amount of products increased exponentially with each cycle until cycle 33. To compare the levels of H_1 mRNA, we performed PCR at cycle 30-32. As shown in Figs. 1 and 2, 7 days after the last administration of 21 consecutive administrations, the level of H_1 receptor mRNA in the rat striatum increased significantly. On the other hand, 1 day and 14 days after the last administration, there were no significant changes of H_1 mRNA level in the rat striatum, being lower than that 7 days after the last administration.

When PCR with H_2 primers were performed for 17-40 cycles at 2-cycle intervals, the amount of products increased exponentially with each cycle until cycle 31. To compare the levels of H_2 mRNA quantitatively, we performed PCR at cycle 28-30. As similarly as H_1 receptors, Fig. 1 and 3 show that the mRNA level of H_2 receptor in the rat striatum increased significantly 7 days after the last administration, whereas there were no significant changes of H_2 receptor mRNA level in the rat striatum 1 day and 14 days after the last administration.

The H_1 receptor is moderately expressed in the striatum [8]. On the other hand, the H_2 receptor mRNA is abundant in the basal ganglia [19]. Nevertheless, the amount of total RNA isolated from the rat striatum is

relatively small, semi-quantitative RT-PCR was more useful for detecting the H_1 and H_2 mRNA than Northern blot[9].

In this study, we measured the mRNA levels of histamine receptors 1, 7, and 14 days after the last administration, because the HA content increased immediately after the chronic administrations of METH[3], and the release of HA increased 7days after the last administration[4], and behavioral responsiveness persists for at least several weeks[14]. We found that 7 days after the chronic administrations of METH for 21 consecutive days, both H_1 and H_2 receptor mRNA levels increased significantly, but one day and 14 days after the last administration, there were not significant changes in either H_1 or H_2 receptor mRNA level. Thus, these increases at the day 7 were transient, and the levels of H_1 and H_2 receptor mRNAs returned to almost the same levels as those of control group by the 14 days after the last administration of METH. Chronic administration of METH increased HA levels, HA release and HDC activity in the rat striatum [3, 4]. Because these consecutive increases of HA release and HDC activity in the rat striatum are abolished by the cessation of METH treatment, it seems likely that mRNA levels of H_1 and H_2 receptors are subjected to the up-regulation.

We have recently reported that pretreatment with a precursor of HA, L-His, inhibited the development of METH-induced behavioral sensitization, whereas

pretreatment with an inhibitor of HA synthesis, α-fluoromethylhistidine, an H_1 antagonist pyrilamine or an H_2 antagonist zolantidine enhanced it [5]. H_1 antagonists have an addictive effect in combination use with opioids [16]. For example, in USA, the H_1 antagonist tripelennamine has been used illicitly in combination with pentazocine by many heroin addicts known as “T’s and blues”[7, 10]. Thus, the HA neuron system has an inhibitory effect on the development of psychostimulant abuse through H_1 and H_2 receptors. It is well-known that the behavioral sensitization which remains for long time after the drug administration is completed shows the vulnerability for relapse of psychostimulant abuse and psychostimulant-induced psychosis. However, increases of H_1 and H_2 receptor mRNA levels during the lasting period of METH-induced behavioral sensitization are transient, and are consistent with a period of METH withdrawal. Thus, our results in this study may be related to withdrawal state of chronic psychostimulant abuse rather than maintenance of behavioral sensitization or psychostimulant abuse itself.

In conclusion, our study shows that after the chronic administration of METH, levels of H_1 and H_2 receptor mRNA in the rat striatum are increased transiently, and the increase may have some relation to withdrawal state of chronic psychostimulant abuse.

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Figure 2

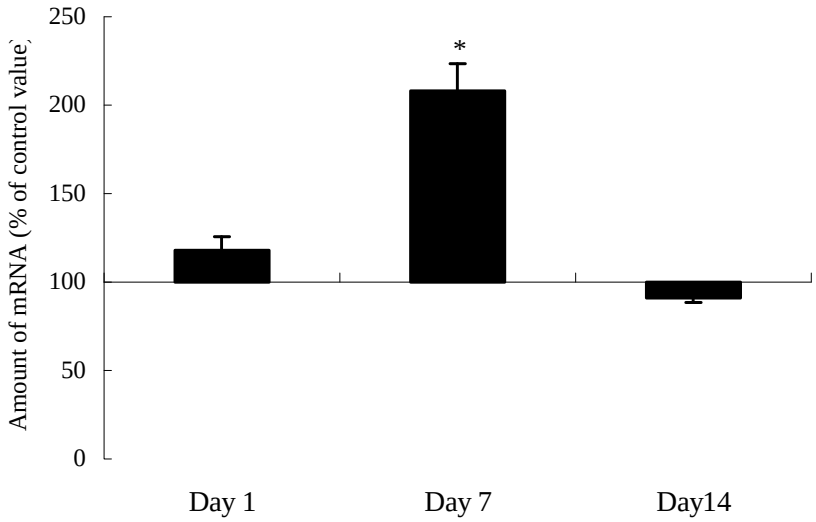
250
200
150
100
50
0
Amount of mRNA (% of control value)
*
Day 1
Day 7
Day14

Figure 3

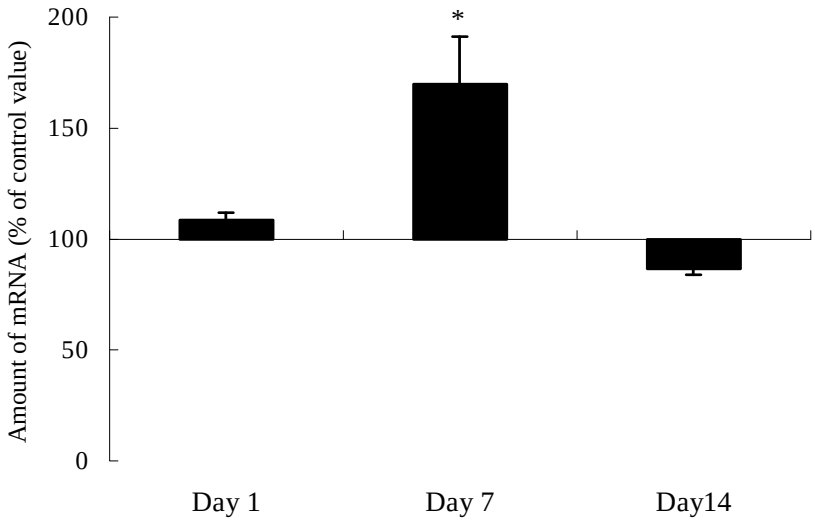
200
150
100
50
0
Amount of mRNA (% of control value)
*
Day 1
Day 7
Day14

Figure legends

Fig. 1. H1 and H2 receptor mRNA expressions in the rat striatum 7days after the last administration of saline or METH captured by the CCD image sensor. Rats were injected intraperitoneally with saline [0.9% (wt/vol) NaCl (1 ml/kg)] as control or METH (4 mg/kg) once daily for 21 consecutive days, and decapitated 7 days after the last injection, and measured mRNA level by semi-quantitative RT-PCR. The GAPDH gene was used as internal control for evaluation of the amount of cDNA synthesized.

Fig. 2. Effect of chronic administration of METH on mRNA levels of H_1 receptor in the rat striatum. Rats were injected intraperitoneally with saline [0.9% (wt/vol) NaCl (1 ml/kg)] or METH (4 mg/kg) once daily for 21 consecutive days, and decapitated 1 (n = 7), 7 (n = 6) and 14 (n=8) days after the last injection, and measured the H_1 receptor mRNA level by semi-quantitative RT-PCR. The average value of saline injected group is taken as 100%. Results are mean values, and their standard errors are shown as vertical bars. Statistical analysis was performed by means of ANOVA (* $p < 0.05$).

Fig. 3. Effect of chronic administration of METH on mRNA levels of H_2 receptor in the rat striatum. Rats were injected intraperitoneally with saline

[0.9% (wt/vol) NaCl (1 ml/kg)] or METH (4 mg/kg) once daily for 21 consecutive days, and decapitated 1 (n = 7), 7 (n = 6) and 14 (n=8) days after the last injection, and measured the H_2 receptor mRNA level by semi-quantitative RT-PCR. The average value of saline injected group is taken as 100%. Results are mean values, and their standard errors are shown as vertical bars. Statistical analysis was performed by means of ANOVA (* $p < 0.05$).

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