Subchronic Administration of Ketamine Decreases the mRNA Expression of Serine Racemase in Rat Brain

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The behavioral impairment produced by ketamine represents a pharmacological model for some aspects of schizophrenia such as positive, negative, and cognitive symptoms. Despite the multiple properties of ketamine, the main mechanism for its psychomimetic and anesthetic effect involves NMDA receptor system. Present study examined whether subchronic administration of ketamine at the subanesthetic doses (50 mg/kg) induces changes of behavior analogous to those observed in schizophrenia and the gene expressions of the enzymes for D-serine, an endogenous co-agonist for the NMDA-glycine site, in rat brain. Administration of ketamine daily for 14 consecutive days increased stereotyped behavior, ataxia and locomotion. The levels of serine racemase mRNAs in forebrain areas significantly decreased after subchronic administration of ketamine. In contrast, subchronic ketamine administration produced a significant increase in the mRNA expression of D-amino acid oxidase in the midbrain. These findings suggest that there is a relationship between the gene expression of the D-serine-related enzymes and the blockade of the NMDA receptors.

Key words: NMDA receptor, D-serine, serine racemase

INTRODUCTION

Ketamine, a dissociative anesthetics and noncompetitive antagonist of the N-methyl-D-aspartate (NMDA)-type glutamate receptor, induces positive, negative, and cognitive schizophrenia-like symptoms in healthy humans and exacerbates these psychotic symptoms in schizophrenic patients at subanethsetic doses [4, 6, 7, 16, 17]. In rodents, the blockade of the NMDA receptors by phencyclidine (PCP) and dizocilpine (MK-801) produces behaviors analogous to those observed in schizophrenia, including increased locomotion, stereotyped behaviors, ataxia, cognitive deficits, and impaired social interactions [4, 6, 16, 17]. Due to these characteristics, psychoses induced by the blockage of the NMDA receptors are regarded as a valid pharmacological model of schizophrenia [4, 6, 7, 16, 17]. These observations, together with the fact that NMDA receptor knockdown mice exhibit behavioral abnormalities, including increased locomotion, stereotyped behaviors closely resemble those seen in the PCP- or MK-801-treated mice [28], provide the basis for the hypothesis that the hypofunction of the NMDA receptors is implicated in the pathophysiology of schizophrenia [4, 6, 16, 17].

D-Serine has been proposed as an endogenous co-agonist for the NMDA-glycine site in the mammalian brain [11, 12, 29]. Serine racemase (Srr) that catalyzes the direct formation of D-serine from L-serine has been purified and cloned from the mammalian brain [23, 38, 39]. Growing evidence has indicated that the distributional profile of Srr corresponds well with those of the endogenous D-serine and NMDA receptors with the highest level in the forebrain and the lowest level in the hindbrain [11, 38, 40]. In contrast, D-amino acid oxidase (DAO), which catalyzes the oxidative deamination of neutral D-amino acids, occurs in the hindbrain with the higher levels in the cerebellum and pons-medulla, decreasing levels in the midbrain and with low levels in the cortex and hippocampus [15, 22, 31, 41], and has been cloned from several mammalian species [8, 9]. Because D-serine and Srr are concentrated in the forebrain [11, 12, 38, 40], the regional distribution of DAO in the brain inversely correlates with both those of D-serine and Srr [11, 31, 38, 40, 41]. Administration of D-serine improves the negative, positive and cognitive symptoms of schizophrenic patients [37] and blocks the PCP- and MK-801-induced hyperactivity, stereotyped behavior and ataxia in rats [3, 35]. We have shown that single administration of ketamine (50 mg/kg) produced significant transient elevation in the levels of Srr and DAO mRNA in all the brain areas [34].

Several lines of evidence have revealed glutamatergic hypofunction in frontal cortical area of schizophrenic patients [27, 36]. Similar results providing a decrease in glutamate binding were obtained in subchronically ketamine-treated rats [1]. To further obtain insight into the relationship between the gene expression of the D-serine-related enzymes and schizophrenia-related behavior by the blockade of the NMDA receptors, we have investigated the effects of subchronic administration of ketamine at subanesthetic dose on the expression of Srr and DAO mRNAs in brain of rats.

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MATERIALS AND METHODS

Animal

The present animal experiments were performed in strict accordance with the guidelines of Tokai University, and were approved by the Animal Investigation Committee of the university. Male Wistar rats (Clea Japan Inc., Tokyo, Japan) weighing 180−200g at postnatal week 7 were used in this study. The rats were group-housed in laboratory cages and kept in a temperature-controlled room (23 ± 2°C) with a 12h light/dark cycle (light on: 07:00) with food and water provided *ad libitum*. Ketamine was purchased from the Daiichi Sankyo Co., Ltd. (Tokyo, Japan).

Ketamine administration

Ketamine was dissolved in physiological saline and then intraperitoneally administered (50 mg/kg) once-daily for 14 consecutive days. This dose was found to increase the mRNA expression of Srr and DAO after single injection [34]. The control animals received only saline (1 ml/kg/day).

The animal behavior

The behavioral effects of ketamine were evaluated based on the methods of previous our study [13] with slight modification. On the fourteenth day (Day 14) following administration of ketamine (50 mg/kg) or saline (1 ml/kg/day) daily, the rats were individually placed into 37 × 24 × 30 cm high plastic cages divided into quadrants by lines on the floor and allowed to acclimate for at least 30 min before the testing began. The test sessions were also videotaped. Behavioral tests were performed between 10 a.m. and 4 p.m.

The stereotyped behaviors were assessed by counting the number of turning, weaving, and head bobbing. Turning was measured by counting turn around every 5 min over 60 min. Weaving and head bobbing were measured by counting its neck wave right and left, and go up and down every 5 min over 60 min. The cumulative behavioral rating for each animal was determined as the summation of each 5 min score over 60 min. The intensity of the stereotypy was scored on a scale of 0−4 where 0 = absent; 1 = equivocal; 2 = present (moderate rate of sniffing, head-weaving); 3 = intense (moderate rate of turning, sniffing, head-weaving); 4 = intense and continuous (continuous turning, sniffing, head-weaving).

Ataxia was assessed by counting the number of fall over four all feet (falling) every 5 min over 60 min. The intensity of the ataxia was scored on a scale of 0-3 where 0 = absent; 1 = equivocal; 2 = present (awkward-jerky movements, moderate rate of falling while side while moving about); 3 = intense (frequent falling on back and/or side while moving about).

Locomotor activities (counts) of the rats were measured every 5 min for 60 min with an animal activity meter. Locomotor activity was also assessed by counting the number of line-crossing (crossing).

Real time quantitative reverse transcriptase-polymerase chain reaction (RT-PCR)

Following administration of ketamine or saline for 14 days, the rats were stunned and decapitated 4h after the last administration. The total RNA was extracted by a method similar to the one described by Chomczynski and Sacchi [2]. The gene expression of the Srr and DAO was determined by real-time PCR using the glyceraldehyde 3-phosphate dehydrogenase (GAPDH; accession number NM017008) gene as an internal control and primers specific for Srr (accession number NM013761) and DAO (accession number NM053626) mRNAs. The upstream primers were CCT GCA GTG ATA GCT GGA CA (Srr), CCC TTT CTG GAA AAG CAC AG (DAO), and GTG GAC CTC ATG GCC TAC AT (GAPDH); the downstream primers were AAG CCA ATG CTG GAT TTG AC (Srr), CTC CTC TCA CCA CCT CTT CG (DAO), and TGT GAG GGA GAT GCT CAG TG (GAPDH). The cDNA was amplified by real-time PCR using the DyNAmo SYBR green qPCR Kit (Finnzymes, Espoo, Finland) on the DNA Engine Opticon 2 System (MJ Research, Inc., MA, USA) running 35 cycles of the following protocol: 10 min predenaturation at 95˚C, 15 sec denaturation at 95˚C, 20 sec at 58˚C for Srr, 60 ˚C for DAO or 62˚C for GAPDH, followed by a 20 sec extension at 72˚C. The PCR products were separated by an Agilent 2100 Bioanalyzer (Agilent Technologies; Palo Alto, CA, USA), which utilizes chip-based nucleic acid separation technology. DNA 1000 Lab Chips (Agilent Technologies) were loaded with the samples as recommended by the manufacture. Furthermore, the identification of the amplified PCR products of the Srr, DAO and GAPDH cDNAs were determined by the dye terminator cycle sequencing.

Statistical analysis

These results are given as means with standard error of mean (S. E. M.) of the data. A statistical evaluation was carried out using computer software (Prism, version 5.0, GraphPad Software, San Diego, CA) for comparison across the experimental conditions. Statistical comparisons were performed using Mann-Whitney U-test or two-way repeated analysis of variance (ANOVA) test followed by Bonferroni post-hoc test. A value of $P < 0.05$ was considered as reaching statistical significance.

RESULTS

The animal behavior

Fig. 1 shows the time course of effects of ketamine on turning counts for 60 min after administration of ketamine (50 mg/kg) or saline on Day 14. Ketamine produced severe stereotyped behavior such as turning, weaving, and head bobbing as shown in Fig. **1A,** 1B and 1C, respectively. Two-way repeated ANOVA revealed a significant effect of treatment ($F(1, 110) = 21.43$; $P = 0.0009$), time ($F(11, 110) = 6.472$; **$P < 0.0001$),** interaction ($F(11, 110) = 1.440$; $P = 0.1652$) on turning (Fig. 1A); treatment ($F(1, 110) = 55.12$; $P < 0.0001$), time ($F(11, 110) = 3.284$; $P = 0.0006$), interaction ($F(11, 110) = 3.186$; $P = 0.0008$) on weaving (Fig. 1B), treatment ($F(1, 110) = 226.0$; $P < 0.0001$), time ($F(11, 110) = 5.087$; $P < 0.0001$), interaction ($F(11, 110) = 1.939$; $P = 0.0417$) (Fig. 1C). Fig. 2 shows the cumulative stereotyped behaviors such as turning (Fig. 2A), weaving (Fig. 2B), head bobbing (Fig. 2C), and the cumulative stereotyped score (Fig. 2D) for 60 min after admin-

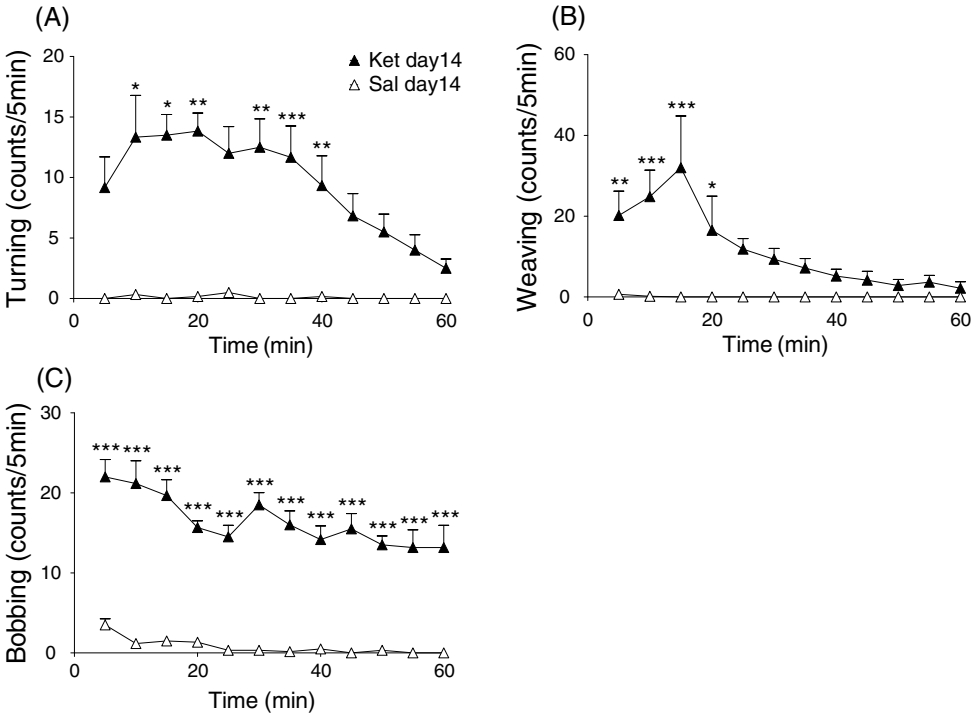

Fig. 1 Time course of changes in the turning (A) weaving (B) and head bobbing (C) in rats received daily injections of either ketamine (50 mg/kg/day) or saline (1 ml/kg/day) for 14 days. The number of turning, weaving and bobbing were taken every 5 min over 60 min after ketamine or saline administration. The results are means with S. E. M. of data from six rats. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ as compared with saline-treated group. Statistical evaluations were carried out using the two-way repeated ANOVA followed by Bonferroni post-hoc test.

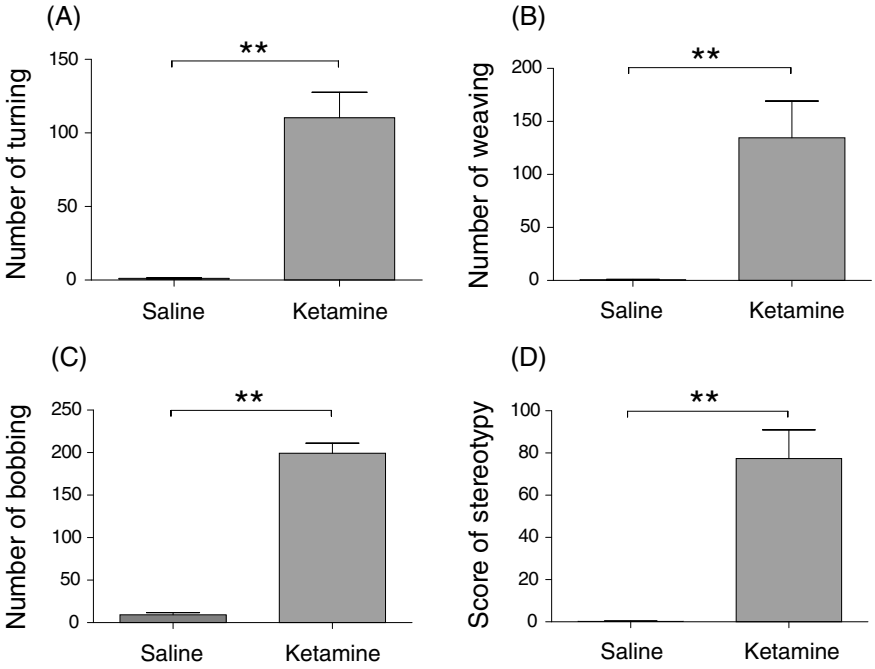

Fig. 2 Effect of ketamine (10 mg/kg/day) on cumulative stereotyped behaviors such as turning (A), weaving (B), head bobbing (C), and the cumulative stereotyped score (D) for 60 min after ketamine or saline. The behavioral ratings for the numbers and scores were taken every 5 min over 60 min after ketamine administration. The results are means with S. E. M. of data from six rats. Statistical evaluations were carried out using the Mann-Whitney U test. $^{**}P < 0.01$ as compared with saline-treated group.

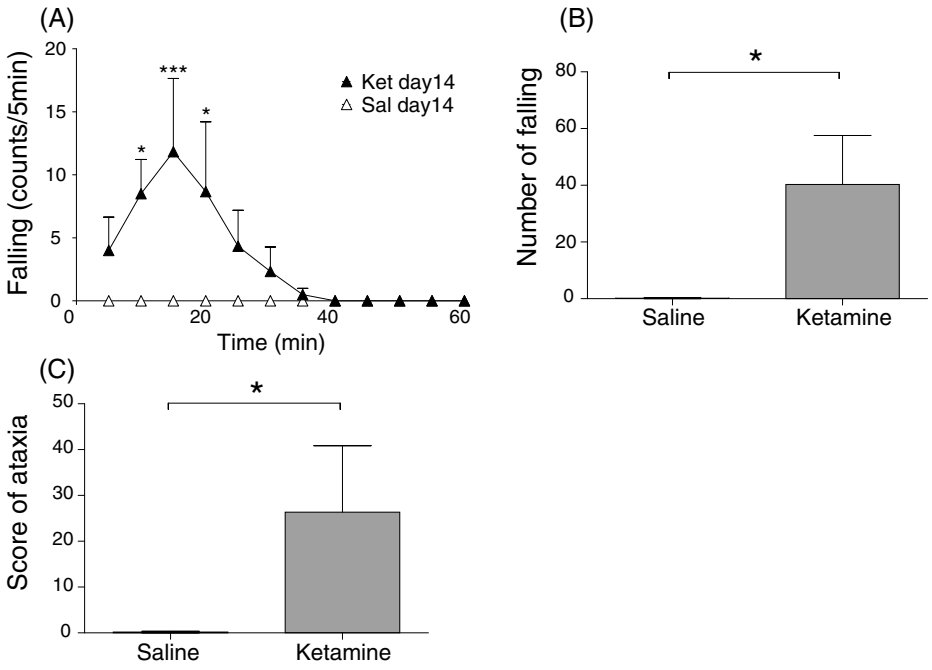

Fig. 3 Time course of changes in the falling in rats administrated with either ketamine (50 mg/kg/day) or saline (1 ml/kg/day) (A), the cumulative number of falling (B), and the cumulative stereotypy scores (C) for 60 min after ketamine or saline. The number of falling was taken every 5 min over 60 min after ketamine or saline administration. The cumulative stereotypy scores (C) were taken for 60 min after ketamine administration. The results are means with S. E. M. of data from six rats. Statistical evaluations were carried out using the two-way repeated ANOVA followed by Bonferroni post-hoc test (A) or using Mann-Whitney U test (B) (C). $^{*}P < 0.05$; $^{***}P < 0.001$ as compared with saline-treated group.

istration of ketamine (50 mg/kg) or saline. Mann-Whitney U test indicated that cumulative turning (P = 0.0047), weaving (P = 0.0047), head bobbing counts (P = 0.0022), and the cumulative stereotyped score (P = 0.0037) were significantly higher in ketamine-administrated rats than saline.

Fig. 3A shows the time course of effects of ketamine on number of falling for 60 min after administration of ketamine. Two-way repeated ANOVA revealed a significant effect of treatment ($F(1, 110) = 5.386$; P = 0.0427), time ($F(11, 110) = 2.926$; P = 0.002), interaction ($F(11, 110) = 2.926$; P = 0.002). Fig. 3B shows the cumulative falling counts for 60 min after ketamine or saline. Mann-Whitney U test (P = 0.0167) indicated that cumulative falling counts were significantly higher in ketamine-administrated rats than saline. As shown in Fig. 3C, there were significantly higher ataxia score in ketamine-administrated rats than saline (P = 0.0165).

Fig. 4A shows the time course of effects of ketamine on crossing counts for 60 min after administration of ketamine. Two-way repeated ANOVA revealed a significant effect of treatment ($F(1, 110) = 41.76$; $P < 0.0001$), time ($F(11, 110) = 5.182$; $P < 0.0001$), interaction ($F(11, 110) = 5.452$; $P < 0.0001$). Fig. 4B shows the cumulative crossing counts for 60 min after administration of ketamine or saline. Mann-Whitney U test (P = 0.0022) indicated that cumulative crossing counts was significantly higher in ketamine-administrated rats than saline. As shown in Fig. 4C, there were significantly higher locomotion score in ketamine-administrated rats (P = 0.005).

mRNA expressions of Srr

Fig. 5A shows effect of subchronic administration of ketamine on the mRNA expressions of Srr 4h after last administration. After the subchronic ketamine administration, the expression of Srr mRNA significantly decreased by 40–61% in the four brain areas examined 4h after the administration: striatum (61% decrease, **P = 0.0079), hippocampus (40%, P = 0.0079),** cortex (44%, P = 0.0317), and diencephalon (46%, P = 0.0079) by Mann-Whitney U test.

mRNA expressions of DAO

Fig. 5B shows effect of subchronic administration of ketamine on the mRNA expressions of DAO 4h after last administration. The chronic treatment with ketamine produced a significant enhancement in the levels of DAO mRNA in the midbrain (128%, P = 0.0317) examined 4h after the administration. In contrast, no significant change in the expression of DAO mRNA was found in the striatum, hippocampus, cortex, and diencephalon by Mann-Whitney U test.

DISCUSSION

The present study demonstrated that a significant enhancement of behavioral abnormalities, including stereotyped behaviors, ataxia and increased locomotion, was seen in rats following administration of ketamine at subanesthetic doses (50 mg/kg) for 14 days. These findings correspond well with the previous study that female rats administrated with ketamine (40 mg/kg, twice daily) for 15 days increased behavioral

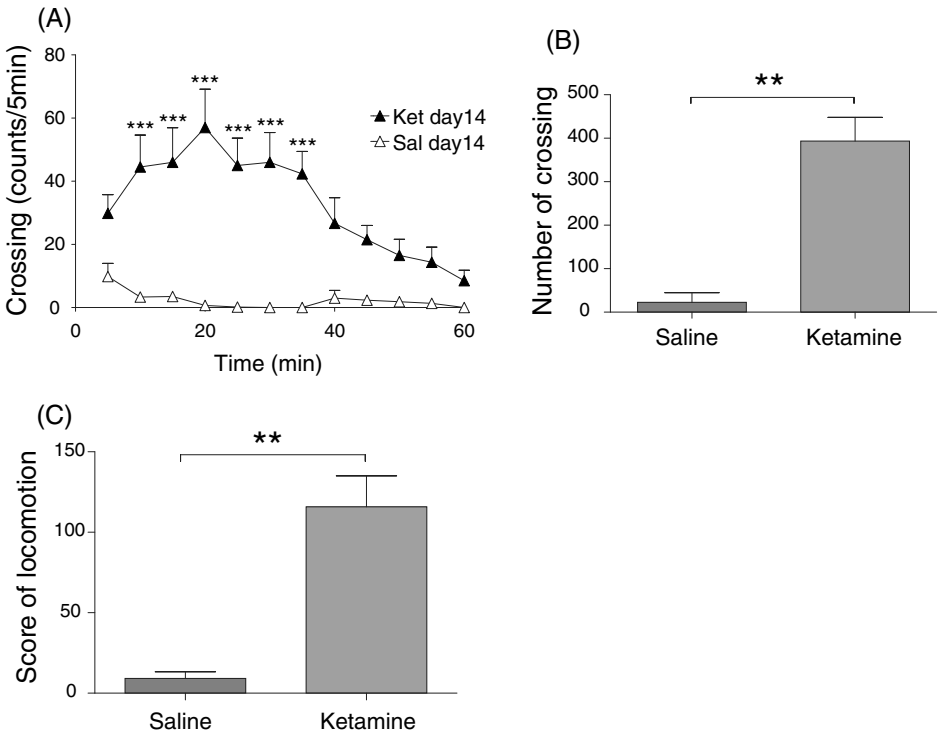

Fig. 4 Time course of changes in the crossing in rats administrated with either ketamine (50 mg/kg/day) or saline (1 ml/kg/day) (A), the cumulative number of crossing (B), and the cumulative locomotion scores (C) for 60 min after ketamine or saline. The number of crossing was taken every 5 min over 60 min after ketamine or saline administration. The cumulative locomotion scores (C) were taken for 60 min after ketamine administration. The results are means with S. E. M. of data from six rats. Statistical evaluations were carried out using the two-way repeated ANOVA followed by Bonferroni post-hoc test (A) or using Mann-Whitney U test (B) (C). $^{**}P < 0.01$; $^{***}P < 0.001$ as compared with saline-treated group.

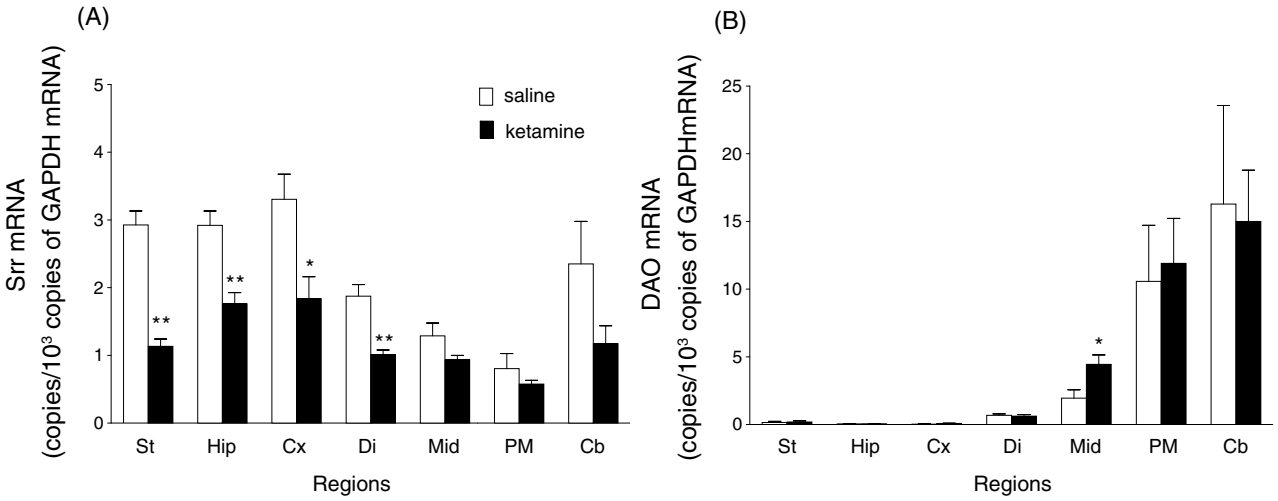

Fig. 5 The levels of the serine racemase (Srr) mRNA (A) and D-amino acid oxidase (DAO) (B) in seven regions of the rat brain. Rats were received daily injections of either ketamine (50 mg/kg/day) or saline (1 ml/kg/day) for 14 days and then sacrified 4h after the last administration. Results are means with S. E. M. of data obtained from five rats. Statistical evaluations were carried out using Mann-Whitney U-test. $^{*}P < 0.05$; $^{**}P < 0.01$ as compared with saline-treated group. St, striatum; Hip, hippocampus; Cx, cortex; Di, diencephalon; Mid, midbrain; PM, pons-medulla; Cb, cerebellum.

abnormalities [26].

Our previous study demonstrated that single administration of ketamine increased Srr mRNA expression in all brain areas [34]. This result is not in agreement with our present study which demonstrated that subchronic administration of ketamine decreased the levels of Srr mRNAs in forebrain areas. The differences in the expression of Srr mRNA between single and subchronic administration of ketamine might be derived from the difference of activity of activator protein-1 (AP-1). A sequence homologous to potential AP-1 binding sites is observed in promoter region of the Srr gene [39]. Keilhoff et al. demonstrated that subchronic administration of ketamine (30 mg/kg, 14 days) decreased AP-1 DNA binding activity [20], supporting our present result. In contrast, several studies demonstrated that single administration of ketamine or MK-801 increased the DNA binding activity of AP-1 [24, 33], supporting our previous result. Further investigations are needed to clarify the mechanisms underlying the opposite expression of Srr mRNA between single and subchronic administration of ketamine.

Our previous study demonstrated that subchronic administration of MK-801 produced a significant increase in the expression of Srr mRNA in most brain areas [14], whereas present study demonstrated that subchronic administration of ketamine significantly decreased expression of Srr mRNA in several regions in rat brain. This discrepancy may be due to differences in affinity and potency to NMDA receptor between two drugs. MK-801 is selective NMDA receptor antagonist and high potency to NMDA receptor, whereas ketamine shows very similar affinity at the NMDA receptor and dopamine D2 receptor with a lower affinity for serotonin 5-HT2 receptor [1, 18]. It is worth recalling that MK-801 fails to cause hypnosis even though it is more potent than ketamine as an NMDA receptor antagonist [5, 21]. While ketamine and MK-801 are presumed to share broadly similar mechanisms of action, e.g. the open-channel blockers for NMDA receptor, there are differences in selectivity against NMDA receptor subunit. Gilmour et al. demonstrated that ketamine is NR2B-subunit preferring antagonist, whereas MK-801 binds both NR2A and NR2B subunits [10]. Further studies are needed to clarify the mechanism underlying the opposite expression of Srr mRNA between subchronic administration of ketamine and MK-801.

A sequence homologous to the cAMP response element is observed in the 5'-flanking region of the human DAO gene [9]. Previous studies have demonstrated that single administration of ketamine caused an enhancement in the expression of the cAMP response element protein in the rat brain [33] and significantly increased DAO mRNA expression in all brain area [34]. These results are not agreed with present study that in only midbrain subchronic administration of ketamine significantly increased DAO mRNA. There are many factors that may be involved in the differential induction of phosphorylated cAMP response element protein in distinct regions of brain: (a) neurotransmitters [19], (b) neurotrophic factors [30], (c) depolarization [32] and (d) intracellular calcium ion concentration [25]. Further study is needed to determine which of these factors may be involved in the region specific expression of DAO mRNA after subchronic administration of ketamine.

The decreased expression of Srr mRNA in forebrain areas and the increased expression of DAO mRNA in midbrain by subchronic administration of ketamine might contribute to the fall in the D-serine level and the NMDA receptor activity. This hypothesis is supported by the fact that administration of D-serine improves the negative, positive and cognitive symptoms of schizophrenia in humans [37] and blocks the PCP- and MK-801-induced hyperactivity, stereotyped behavior and ataxia in rats [3, 35]. The glutamate hypothesis of schizophrenia suggests hypofunction of this neurotransmitter system in frontal cortical area. Several lines of evidence have revealed a lower density of glutamate receptors in brains of schizophrenic patients [27, 36]. The fact about lower density of glutamate receptor was demonstrated in rats administrated with ketamine at the subanesthetic doses (30 mg/kg) daily for 4 weeks [1]. Like the down regulation of glutamatergic receptor, the reduction of Srr mRNA and augmentation of DAO mRNA by subchronic administration of ketamine could at least reflect behaviors analogous to those observed in schizophrenia. To clarify the relation between the abnormal behaviors observed in schizophrenia and D-serine, further investigations should be required to analyze the contents of D-serine and the protein level and activity of Srr and DAO. Because D-serine, which is synthesized by Srr and metabolized by DAO, acts as a potent agonist of the NMDA receptor-associated glycine receptor [40, 41], drugs affecting Srr and/or DAO may offer a new therapeutic approach to diseased related the hyper- and hypofunction of the NMDA receptor-mediated neurotransmission such as epilepsy, stroke, neuronal death, Alzheimer's disease and schizophrenia.

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