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Short communication

# Ketamine enhances the expression of serine racemase and D-amino acid oxidase mRNAs in rat brain

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**Abstract**

We have evaluated the effects of the acute administration of noncompetitive *N*-methyl-D-aspartate receptor antagonist, ketamine, on the expression of serine racemase and D-amino acid oxidase mRNAs in several brain areas of rats. The ketamine administration produced a dose-dependent and transient elevation in the levels of serine racemase and D-amino acid oxidase mRNAs in all the brain areas. These findings suggest that there is a relationship between the gene expression of the D-serine-related enzymes and the blockade of the *N*-methyl-D-aspartate receptors.
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*Keywords:* D-Amino acid oxidase; Anesthetics; Ketamine; NMDA receptor; Schizophrenia; Serine racemase

## 1. Introduction

Dissociative anesthetics, such as phencyclidine (PCP) and ketamine, are noncompetitive antagonists of the *N*-methyl-D-aspartate (NMDA)-type glutamate receptors (Becker et al., 2003; Coyle and Tsai, 2004; Deutsch et al., 1989; Javitt and Zukin, 1991; Johnson and Jones, 1990). These substances induce positive, negative, and cognitive schizophrenia-like symptoms in healthy subjects and exacerbate these psychotic symptoms in schizophrenic patients. In rodents, the blockade of the NMDA receptors by PCP, ketamine and MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine) produces behaviors analogous to those observed in schizophrenia, including hyperlocomotion, stereotyped behaviors, ataxia, cognitive deficits, and impaired social interactions. Due to these characteristics, PCP and ketamine psychoses are regarded as a valid pharmacological model of schizophrenia (Becker et al., 2003; Coyle and Tsai, 2004; Deutsch et al., 1989; Duncan et al., 2001; Javitt and Zukin, 1991; Johnson and Jones, 1990). In fact, the NMDA-glycine receptor agonist D-serine improves the negative, positive and cognitive symptoms of schizophrenic subjects treated with conventional neuroleptics (Tsai et al., 1998) and blocks the PCP- and MK-801-induced hyperactivity, stereotyped behavior and ataxia in rats (Contreras, 1990; Tanii et al., 1994). 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 (Mohn et al., 1999), provide the basis for the hypothesis that the hypofunction of the NMDA receptors is implicated in the pathophysiology of schizophrenia (Coyle and Tsai, 2004; Deutsch et al., 1989; Javitt and Zukin, 1991; Johnson and Jones, 1990).

A variety of evidence has demonstrated that a high level of D-serine occurs in the mammalian brain, although D-amino acids have long been assumed to be unnatural in mammals (Hashimoto and Oka, 1997; Hashimoto et al., 1993a,b, 1995; Schell et al., 1995). D-Serine is confined to the forebrain where the NMDA receptors exist (Hashimoto and Oka, 1997; Hashimoto et al., 1993b; Schell et al., 1995). In vivo microdialysis studies have demonstrated that the extracellular

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level of D-serine parallels or is higher than that of glycine in the prefrontal cortex and striatum, respectively (Hashimoto et al., 1995). Because D-serine acts as an obligatory co-agonist of the NMDA-glycine receptors (Hashimoto and Oka, 1997; Matsui et al., 1995), D-serine has been proposed as an endogenous co-agonist for the NMDA-glycine site in the mammalian brain (Hashimoto and Oka, 1997; Hashimoto et al., 1993b).

Serine racemase that catalyzes the direct formation of D-serine from L-serine has been cloned from the mammalian brain (Konno, 2003; Wolosker et al., 1999). Growing evidence has indicated that the distributional profile of serine racemase 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 (Hashimoto et al., 1993b; Wolosker et al., 1999; Yoshikawa et al., 2004a). 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 (Horiike et al., 1994; Schell et al., 1995; Yoshikawa et al., 2004b), and has been cloned from several mammalian species (Fukui and Miyake, 1992). Recently, a new human gene, *G72*, on 13q34 that interacts with the gene for DAO on 12q24, was identified (Chumakov et al., 2002). Although both of these genes have been associated with schizophrenia (Chumakov et al., 2002; Harrison and Weinberger, 2005), there is little information available regarding the relationship between DAO and schizophrenia except for genetic evidence. We have recently revealed that mice lacking DAO activity exhibit a marked reduction in stereotypy and ataxia produced by the NMDA receptor antagonist MK-801, suggesting that the elevated D-serine in the brain of DAO-deficient mice could antagonize the MK-801-induced stereotypy and ataxia (Hashimoto et al., 1993a, 2005).

We have also shown that a significant elevation in the gene expression of serine racemase and DAO is observed in the brain 1 and 4 h after the acute administration of MK-801 (0.4 mg/kg), respectively (Yoshikawa et al., 2004a,b). To gain further insight into the relationship between the gene expression of D-serine-related enzymes and the NMDA receptor antagonism, we have investigated the acute effects of ketamine on the expression of serine racemase and DAO mRNAs in several brain areas of rats.

## 2. Materials and methods

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 at 7 weeks postnatal were used in this study. Ketamine (50 mg/kg) was dissolved in physiological saline and then intraperitoneally injected. The control animals received only saline. In the time-dependency experiment of ketamine (50 mg/kg), the rats were stunned and decapitated 2, 4 or 8 h after the administration. In the dose dependency experiment of ketamine (20, 50 or 100 mg/kg), the rats were stunned and decapitated 4 h after the administration. The gene expression of the serine racemase and DAO was determined by real-time polymerase chain reaction (PCR) using the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene as an internal control and primers for serine racemase and DAO mRNAs as previously described (Yoshikawa et al., 2004a,b). Briefly, 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). The PCR products were separated by an Agilent 2100 Bioanalyzer (Agilent Technologies; Palo Alto, CA, USA), which utilizes chip-based nucleic acid separation technology. The identification of the amplified PCR products of the serine racemase, DAO and GAPDH cDNAs were determined by the dye terminator cycle sequencing. These results are given as means±S.E.M. of the data. A statistical evaluation was carried out using one-way analysis of variance followed by Dunnett's test. A $P$-value $<0.05$ was considered statistically significant.

## 3. Results

Ketamine (50 mg/kg) induced a characteristic behavioral response consisting of staggered locomotion, sniffing, head-weaving, turning and falling within 5 min after the injection. This behavior persisted for 20–30 min. Fig. 1A shows the time course of changes in the levels of the serine racemase mRNA after the ketamine administration. Following this administration, the levels transiently increased and peaked at 4 h, and then

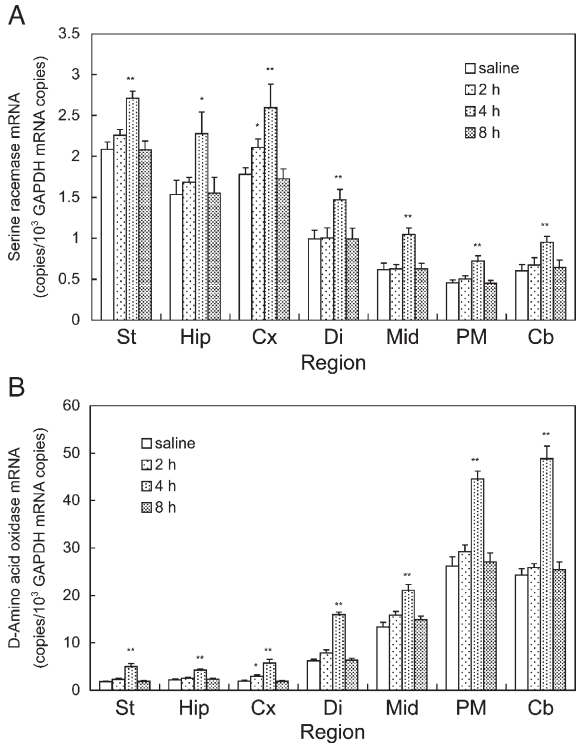


Fig. 1. Time course of changes in the gene expression of serine racemase (A) and D-amino acid oxidase (B) in several brain areas of rats after the systemic administration of ketamine (50 mg/kg). Results are means±S.E.M. of data obtained from five rats. *$P<0.05$, **$P<0.01$ as compared with saline-treated group. St, striatum; Hip, hippocampus; Cx, cortex; Di, diencephalon; Mid, midbrain; PM, pons-medulla; Cb, cerebellum.

decreased to the control levels. The levels increased by 30–70% in the seven brain areas examined: striatum (30% increase), hippocampus (48%), cortex (46%), diencephalon (48%), midbrain (70%), pons-medulla (60%), and cerebellum (59%). As shown in Fig. 1B, the ketamine administration produced a transient elevation in the expression of the DAO mRNA in all the brain areas. Following the administration, the levels transiently increased and peaked at 4 h in the seven brain areas examined: striatum (169% increase), hippocampus (95%), cortex (198%), diencephalon (156%), midbrain (57%), pons-medulla (70%), and cerebellum (101%). The enhanced levels of DAO mRNA were much higher in the cerebellum and pons-medulla, followed by the midbrain and diencephalon, and were low in the striatum, hippocampus and cortex.

As shown in Fig. 2A, the acute administration of ketamine (20, 50 or 100 mg/kg) caused a dose-dependent increase in the expression of serine racemase mRNA in all the brain areas. Following the administration of ketamine (100 mg/kg), the levels increased by 54–98% in the seven brain areas examined 4 h after the administration: striatum (67% increase), hippocampus (98%), cortex (54%), diencephalon (88%), midbrain (68%), pons-medulla (96%), and cerebellum (91%). As shown in Fig. 2B, the acute treatment of ketamine (20, 50 or 100 mg/kg) produced a dose-dependent elevation in the expression of DAO mRNA in all the brain areas. Following the administration of ketamine (100 mg/kg), the levels increased by 85–348% in the seven brain areas examined 4 h after the administration: striatum (127% increase), hippocampus (178%), cortex (187%), diencephalon (348%), midbrain (85%), pons-medulla (192%), and cerebellum (187%).

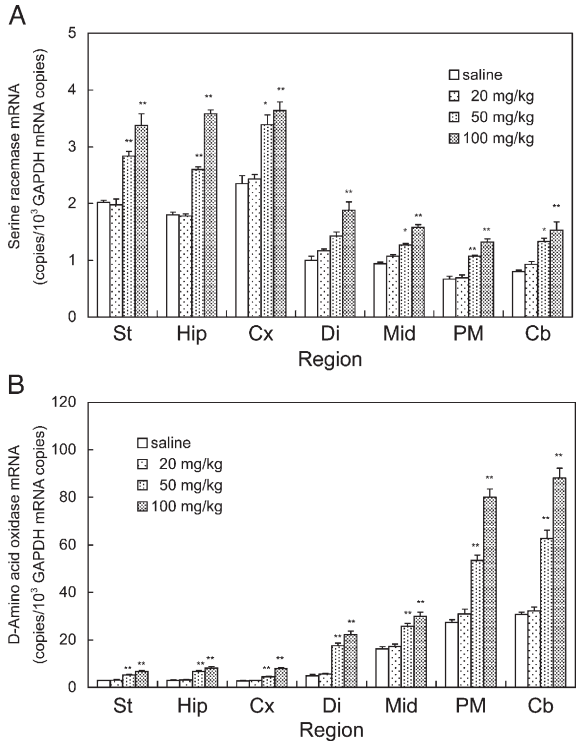


Fig. 2. Effects of increasing doses of ketamine (20, 50 or 100 mg/kg, i.p.) on gene expression of serine racemase (A) and D-amino acid oxidase (B) in several brain areas of rats. Results are means ± S.E.M. of data obtained from five rats. *$P<0.05$, **$P<0.01$ as compared with saline-treated group. St, striatum; Hip, hippocampus; Cx, cortex; Di, diencephalon; Mid, midbrain; PM, pons-medulla; Cb, cerebellum.

## 4. Discussion

The present study demonstrated that the acute administration of ketamine caused a transient and dose-dependent elevation in the expression of serine racemase and DAO mRNAs in all the brain areas. We have recently demonstrated that the systemic administration of MK-801 (0.4 mg/kg) causes the transient elevation of serine racemase and DAO mRNAs in most brain areas of rats (Yoshikawa et al., 2004a,b). These findings, together with the fact that both MK-801 and ketamine are non-competitive NMDA receptor antagonists (Coyle and Tsai, 2004; Deutsch et al., 1989; Javitt and Zukin, 1991; Johnson and Jones, 1990), provide further support for the view that there is an association between the gene expression of the D-serine-related enzymes and the blockade of NMDA receptor function.

In contrast to the expression similarity to MK-801, there are differences in the gene expression of the two enzymes between ketamine and MK-801. First, the levels of serine racemase mRNA peaked at 4 h after the ketamine administration (Fig. 1A), whereas those of serine racemase mRNA peak at 1 h after the MK-801 administration (Yoshikawa et al., 2004a). Second, a dose-dependent elevation in the expression of DAO mRNA was observed after the ketamine administration (Fig. 2B), whereas high doses of MK-801 (0.8 and 1.6 mg/kg) produce a drastic and transient decline in the levels of DAO mRNA (unpublished observations). MK-801 is a selective NMDA receptor antagonist, whereas ketamine has equal affinity for NMDA receptors and the high-affinity state of the dopamine $D_2$ receptor (Kapur and Seeman, 2002). The differences in the gene expression between ketamine and MK-801 might be derived from their selectivity for the NMDA receptors. Further investigations are needed to clarify the mechanisms underlying the gene expression difference of the two enzymes between ketamine and MK-801.

Ketamine administration produced an augmentation in the expression of the serine racemase mRNA in most brain areas. Because the NMDA receptor antagonists have been shown to increase the activator protein-1 (AP-1) DNA binding activity and the expression of the Fos and Jun family members (Kontkanen et al., 2000) and to modulate the AP-1 DNA-binding activity induced by kainate (Kim et al., 1999), the AP-1 complex could play a regulatory role in the gene expression of serine racemase by ketamine. Support for this possibility comes from the fact that the induction of serine racemase by lipopolysaccharide has recently been revealed to be dependent on AP-1 (Wu and Barger, 2004). Recently, Kartvelishvily et al. (in press) have demonstrated that significant amounts of serine racemase and D-serine are present in neurons. Because we have also detected both serine racemase mRNA and protein in the cultured neurons and because both mRNA and protein levels in the neurons are higher than those in the astrocytes (unpublished observations), the upregulation of serine racemase may occur in both neurons and astrocytes after the ketamine administration.

A transient elevation in the levels of DAO mRNA after the ketamine administration was seen in all the brain areas. Because a sequence homologous to the cAMP response element is observed in the 5′-flanking region of the human DAO gene (Fukui and Miyake, 1992), and because NMDA receptor antagonists, such as MK-801 and ketamine, have been shown to induce a variety of immediate early genes and transcription factors via the NMDA receptors (Hughes and Dragunow, 1995; Kontkanen et al., 2000; Storvik et al., 2000), these genes could play an important role in the regulation of the DAO mRNA. Interestingly, the ketamine administration causes an enhancement in the expression of the cAMP response element modulator and inducible cAMP early repressor in the rat brain (Storvik et al., 2000).

The moderate enhancement of serine racemase mRNA in all the brain areas after the ketamine administration (Figs. 1A and 2A) and the absence of DAO activity in the forebrain (Horiike et al., 1994) could contribute to the augmentation of the D-serine level and the NMDA receptor activity in the forebrain. Although NMDA receptor antagonists are neuroprotective when administered in conjugation with NMDA, the pretreatment and chronic administration of the NMDA receptor antagonists has been shown to cause an upregulation of the NMDA receptors and an increase in the NMDA-mediated brain injury (Follesa and Ticku, 1996; McDonald et al., 1990; Williams et al., 1992). Together with the fact that the distribution of the [$^3$H]MK-801 binding sites in the brain coincides well with those of the D-serine content and serine racemase (Hashimoto et al., 1993b; Johnson and Jones, 1990), like the upregulation of the NMDA receptors by the NMDA receptor antagonists (Follesa and Ticku, 1996; McDonald et al., 1990; Williams et al., 1992), the elevated expression of serine racemase by ketamine could be at least in part involved in the activation of the NMDA receptors. Further studies such as Western blot analysis, measurement of D-serine level and chronic ketamine administration are needed to clarify the mechanism underlying the induction of serine racemase and DAO mRNAs by ketamine.

The association between DAO, which metabolizes D-serine, and schizophrenia has recently been reported in French Canadian populations (Chumakov et al., 2002; Harrison and Weinberger, 2005). We have also shown that mutant DAO$^{-/-}$ mice show a drastic diminution of stereotypy and ataxia produced by MK-801, suggesting that the increased D-serine in the brain of mutant DAO$^{-/-}$ mice could antagonize the MK-801-induced stereotypy and ataxia (Hashimoto et al., 1993a, 2005). Because the NMDA receptor antagonists, MK-801 and ketamine, modulate the gene expression of serine racemase and DAO in the brain (present study; Yoshikawa et al., 2004a, b), serine racemase and DAO could play an important role in the regulation of the NMDA receptors via the D-serine metabolism.

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