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Original research article

Alteration in plasma and striatal levels of D-serine after D-serine administration with or without nicergoline: An *in vivo* microdialysis study

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Abstract

Aims: D-Serine (D-Ser), a co-agonist of *N*-methyl-D-aspartate receptor (NMDAR), is effective for treating schizophrenia. The present study investigated changes in plasma and striatal D-Ser levels in Sprague-Dawley (SD) rats after intraperitoneal D-Ser administration alone or together with nicergoline (Nic), a commercial cerebral ameliorating drug, using *in vivo* microdialysis (MD) to explore the function of Nic.

Main methods: Phosphate-buffered saline (PBS) or Nic (0, 1.0, or 3.0 mg/kg) followed by D-Ser (5.0, 10.0, 20.0, and 50.0 mg/kg for PBS or 20.0 mg/kg for Nic) was administered intraperitoneally to male SD rats, and the profiles of D-Ser levels in plasma and striatal MD samples were examined by high-performance liquid chromatography (HPLC) with fluorescence detection. The area under the curve (AUC) for the MD and plasma samples was also calculated and statistically compared among groups.

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Key findings: AUC values of D-Ser increased in a D-Ser dose-dependent manner in plasma samples, while a proportional increase in the AUC values of striatal MD samples was only observed in D-Ser doses up to 20 mg/kg. The Nic co-administered group showed a significant increase in the AUC of plasma D-Ser in a Nic dose-dependent manner, but the AUC in striatal D-Ser significantly decreased with increasing Nic doses suggesting that Nic may prevent excess D-Ser from penetrating the central nervous system (CNS).
Significance: Nic may prevent an excessive distribution of exogenous D-Ser, such as that from a dietary origin, into the CNS by suppressing excitatory neurotransmission through NMDAR.

Keywords: Pharmaceutical science, Neuroscience

1. Introduction

D-Serine (D-Ser), a co-agonist of the *N*-methyl-D-aspartate receptor (NMDAR), is essential for the excitatory neurotransmission of glutamatergic neurons, but an excess of D-Ser may exacerbate neuropathy during cerebral ischemia by activating NMDAR, which is a sub-type of glutamate receptor. The NMDAR contains a ligand-gated ion channel, mediates rapid neurotransmission, and plays important roles in brain function such as in excitatory neurotransmission, synaptic plasticity, learning, and memory. In addition, the NMDAR has binding sites for L-glutamate and glycine, both essential for its activation, and D-Ser can bind to the glycine-binding site as a co-agonist to modulate and enhance the activation of NMDAR exerted by glutamate [1, 2].

Choi et al. [3] reported that overexcitation of NMDAR may cause excessive Ca^{2+} influx and induce cerebral ischemia, neurodegenerative disease, and neuronal cell death in various neurological disorders. Decreasing D-Ser levels in the central nervous system (CNS) may effectively prevent overexcitation of NMDAR. However, D-Ser is biosynthesized *in vivo* by serine racemase expressed in several tissues [4] and contained in some foods [5, 6, 7, 8] and fermented drinks [9] and can thus be ingested as part of the daily diet. Exogenous D-Ser, such as that from diet, may be distributed into the CNS *via* circulating blood. Therefore, exploring the relationship between D-Ser blood levels and the distribution of D-Ser within the CNS is essential.

Dialysis sampling of extracellular fluids through the blood-brain barrier is possible in living experimental animals; hence, brain microdialysis (MD) is a useful technique to investigate penetration of a compound from the periphery into the CNS. Nicergoline (Nic) is a commercial CNS-active drug prescribed for cerebral amelioration to patients with cerebrovascular disorders [10]. In the present study, we investigated the time-course profiles of D-Ser in rat plasma and striatal MD samples after the administration of several dosages of D-Ser. Thereafter,

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co-administration of Nic with D-Ser was assessed. The Nic dose-dependent alterations of D-Ser in striatum and plasma in addition to dopamine (DA) concentrations were also investigated using MD followed by high-performance liquid chromatography (HPLC).

2. Materials and methods

2.1. Animal welfare and ethical statement

All experiments conducted for this study were approved by the Animal Care Committee, Toho University (15-54-165).

2.2. Chemicals

Nicergoline was purchased from Tokyo Chemical Industry Co. Ltd. (Tokyo, Japan). Methanol and trifluoroacetic acid were obtained from Wako Pure Chemicals (Osaka, Japan). D-Ser and CH_3CN were purchased from Kanto Kagaku Kogyo Co. Ltd. (Tokyo, Japan). Phosphate-buffered saline (PBS) (Dulbecco's PBS (−) "*Nissui*") was obtained from Nissui Pharmaceutical Co., Ltd. (Tokyo, Japan). The H_2O used in the present study was purified by a Millipore purification system (Nihon Millipore K.K., Tokyo, Japan).

2.3. Nic administration and blood collection

Male Sprague-Dawley rats (6–7 weeks old) were purchased from Charles River Japan (Kanagawa, Japan) and housed for at least one week in a temperature-controlled and humidity-controlled room before starting the experiments.

Blood (approximately 0.2 mL) was drawn from the left jugular vein while the rats were under light anesthesia with diethylether just before Nic (0, 1.0, or 3.0 mg/kg in PBS) was administered intraperitoneally (*i.p.*) ($n = 6, 5, 5$, respectively). Thirty minutes later, blood was collected again before the *i.p.* administration of D-Ser (20.0 mg/kg in PBS). In the group that did not receive Nic, PBS (1.0 mL/kg), followed by D-Ser (5.0, 10.0, 20.0, or 50.0 mg/kg; $n = 3, 3, 6, 3$, respectively) was administered. In the group that did not receive D-Ser, Nic (0, 1.0, or 3.0 mg/kg; $n = 3, 2, 2$, respectively), followed by PBS (1.0 mL/kg) was administered. Blood samples were then collected at 15, 30, 60, 120, 180, and 240 min after the administration of D-Ser and centrifuged at 3 000 × g for 15 min at 4 °C to obtain the plasma supernatant, which was then transferred to another tube and stored at −80 °C until analysis.

2.4. Microdialysis

Surgical implantation of an MD guide cannula (Bioanalytical Systems [BAS*i*], West Lafayette, IN) into the striatum of the rats (anteroposterior, +1.0; lateral,

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−2.0 from bregma; ventral, +3.6 from dura) was performed in accordance with previously published methods [11, 12].

MD samples (~30 μL each) were collected every 30 min under ice cooling and immediately stored at −80 °C until analysis. The first three samples, collected over 90 min, were used as baseline samples. After collecting the third MD sample fraction, rats received *i.p.* injections of Nic (0, 1.0, or 3.0 mg/kg) (n = 5, 4, 4, respectively) at time 0, followed by D-Ser (20.0 mg/kg) 30 min after Nic administration. In the group that did not receive Nic, PBS (1.0 mL/kg) was *i.p.* administered at time 0, and D-Ser (5.0, 10.0, 20.0, or 50.0 mg/kg in PBS; n = 3, 5, 5, 6, respectively) was administered 30 min after the *i.p.* administration of PBS. In the group that did not receive D-Ser, Nic (0, 1.0, or 3.0 mg/kg; n = 6, 2, 2, respectively) was *i.p.* administered at time 0, and PBS (1.0 mL/kg) was administered 30 min after the *i.p.* administration of Nic. Sample collection was carried out until 210 min after Nic administration.

For the *in vitro* study, Ringer's solution was perfused at 1.0 μL/min into the MD probe, which was inserted into test solutions containing D-Ser (100, 400, or 1 000 μM) in PBS. In all test conditions, three MD samples were collected every 30 min.

2.5. Determination of D-Ser and DA

Plasma (10 μL) or striatal MD samples (5 μL) were subjected to fluorescence derivatization using 4-fluoro-7-nitro-2,1,3-benzoxadiazole (NBD-F) as previously described [13] with minor modifications. D-Ser concentrations in plasma or MD samples were then determined using HPLC with fluorescence detection as previously reported [11]. The concentration of DA in the MD samples was also determined using HPLC as previously described [14].

2.6. Statistical analyses

Plasma D-Ser concentrations were compared among study groups using a one-way analysis of variance (ANOVA) followed by Bonferroni corrections; a $p < 0.05$ was considered statistically significant. The area under the curve (AUC) for D-Ser (0–240 min) was calculated using the trapezoidal method, and Bonferroni's corrections were performed to identify significant differences among groups.

Changes in the concentrations of striatal D-Ser are expressed as percentages in relation to baseline concentrations. The average concentration of the first three samples was defined as 100%, and the variance of each subsequent concentration is presented as a percentage (mean ± the standard error of the mean). At each time point, a repeated-measures two-way ANOVA followed by Tukey's tests were performed to compare differences among groups; a $p < 0.05$ was considered

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significant. The AUC for D-Ser (0–210 min) was also calculated, and Bonferroni's corrections were applied as described above.

3. Results

3.1. AUC of D-Ser in plasma and striatum

The AUC values of D-Ser in plasma samples increased linearly in a dose-dependent manner (Fig. 1a). However, D-Ser AUC values in MD samples increased linearly with increasing D-Ser doses up to 20.0 mg/kg, but only slightly increased with doses of 20.0 to 50.0 mg/kg (Fig. 1b).

3.2. *In vitro* recovery test

The concentration of D-Ser in MD samples was determined for the standard D-Ser solutions (concentrations of 100, 400, and 1 000 μM D-Ser) (Fig. 2). In the standard D-Ser solution, the D-Ser concentration in the collected MD samples was 31.2 ± 2.36, 133 ± 2.54, and 408 ± 20.8 μM, respectively. In addition, D-Ser recovery in all test conditions ranged from 31.2 to 40.9%.

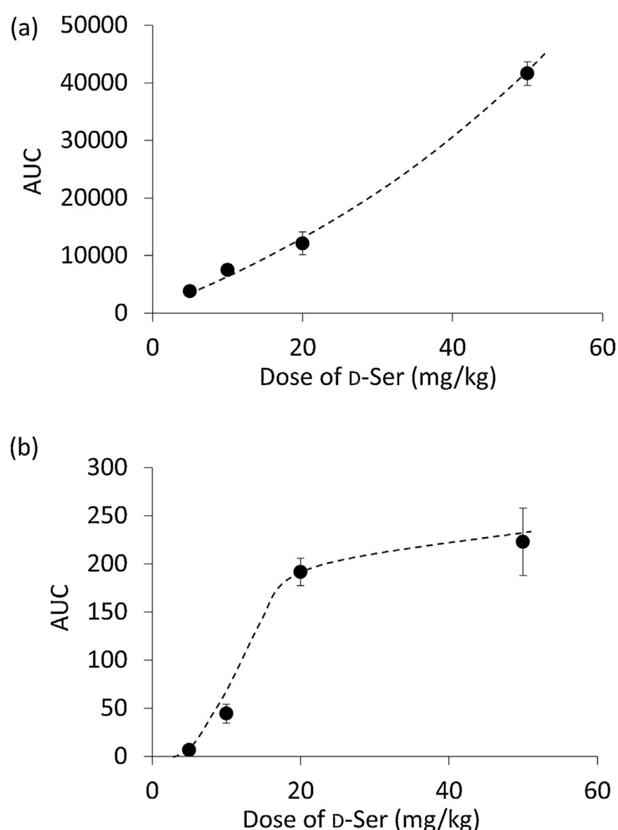

Fig. 1. Area under the D-Ser concentration-time curve (AUC) in plasma (a) and striatal microdialysis (MD) (b) samples. Dots and bars indicate means and standard errors, respectively.

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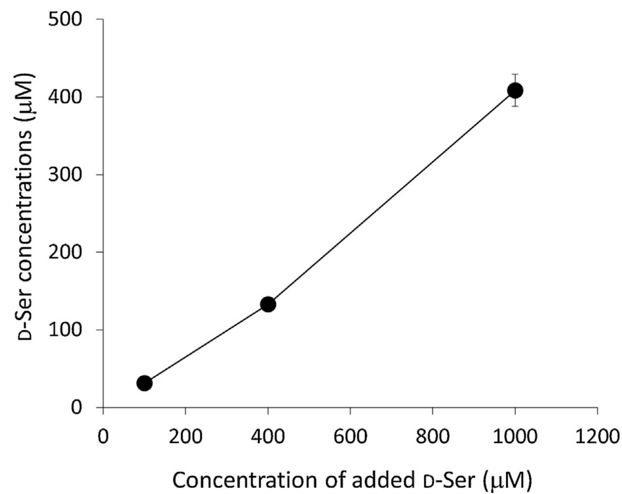

Fig. 2. D-Ser concentration in collected microdialysis (MD) samples in an *in vitro* recovery test. Test solutions contained D-Ser (100, 400, or 1000 μM) in PBS.

3.3. Changes in plasma D-Ser after the administration of Nic followed by D-Ser

The concentration of D-Ser in rat plasma after pre-treatment with Nic (0, 1.0, or 3.0 mg/kg) followed by D-Ser (20.0 mg/kg) significantly increased in the groups that received Nic at 15 and 30 min after *i.p.* administration of D-Ser ($p < 0.05$; Fig. 3a). Maximum plasma D-Ser concentration (C_{max}) in these groups appeared within 15 min after D-Ser injection and gradually decreased to the baseline level by the end of the experiment (*i.e.*, 240 min). In the Nic-administered groups, D-Ser concentrations decreased to a level similar to that of the control group 60 min after D-Ser *i.p.* administration. In the control groups without administration of D-Ser, few changes were observed in D-Ser levels regardless of the Nic dose. The AUC of the group treated with 1.0 mg/kg Nic was similar to that of the control, but the AUC of the group treated with 3.0 mg/kg Nic was significantly larger (Fig. 3b).

3.4. Changes in striatal D-Ser and DA after administration of Nic followed by D-Ser

The levels of D-Ser in rat striatum after administration of Nic (1.0. or 3.0 mg/kg) showed no remarkable decrease compared with those of the untreated (PBS + PBS) group (Fig. 4a). Significant decreases in striatal D-Ser levels were observed depending on the *i.p.* dose of Nic administered to individual rats (Fig. 4a). In the control groups without administration of D-Ser, there were no significant changes in D-Ser levels. AUC values also decreased in a Nic dose-dependent manner with the AUCs of the Nic-treated groups (1.0 and 3.0 mg/kg) being significantly smaller than that of the control group (Fig. 4b). Regarding the neurotransmitter DA, only

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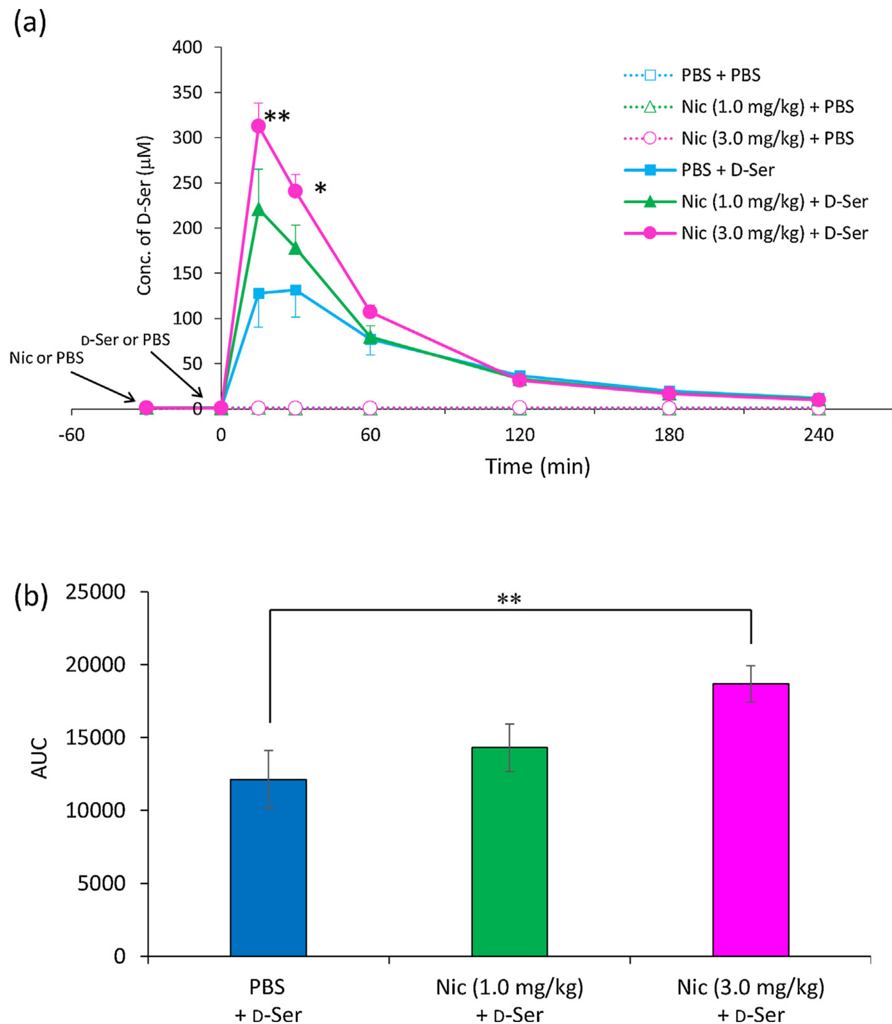

Fig. 3. (a) Comparison of time-course profiles of D-Ser in rat plasma following intraperitoneal administration of Nic (0, 1.0, or 3.0 mg/kg, $n = 6, 5, 5$, respectively) followed by D-Ser (20.0 mg/kg) with control groups [Nic (0, 1.0, or 3.0 mg/kg, $n = 3, 2, 2$) without D-Ser]. The arrows indicate the time of Nic (−30 min) and D-Ser (0 min) administration, respectively. *$p < 0.05$ and **$p < 0.01$ for Nic (3.0 mg/kg) + D-Ser *vs*. PBS + D-Ser. (b) The respective areas under the plasma D-Ser concentration-time curves (AUC) from 0 to 240 min. **$p < 0.01$ for Nic (3.0 mg/kg) + D-Ser *vs*. PBS + D-Ser.

slight changes in its concentration in MD samples from Nic-treated groups were observed (Fig. 5).

4. Discussion

Several lines of evidence have suggested that D-Ser is a key compound modulating the functions of NMDAR related with some CNS disorders. In the field of neuropsychiatric disorders, the hypofunction of the NMDAR is one of the hypotheses explaining schizophrenia, which is a severe mental disorder characterized by positive symptoms (hallucinations and delusions), negative

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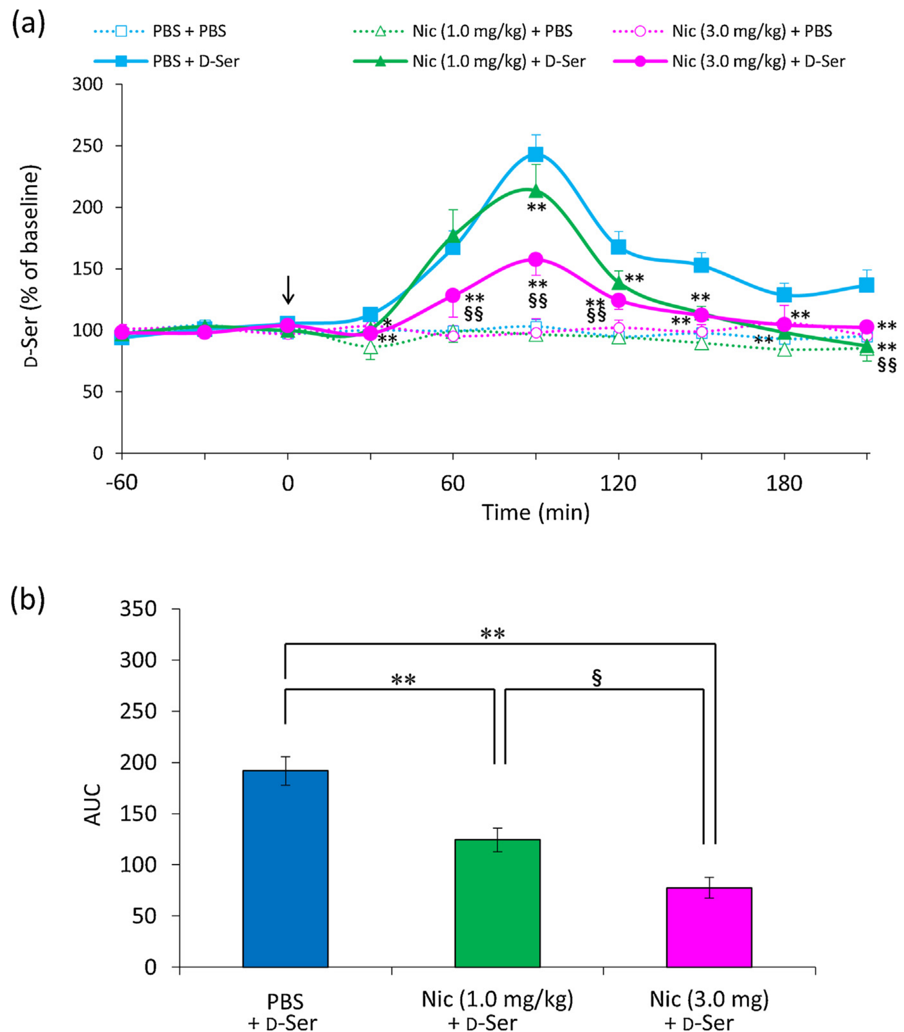

Fig. 4. (a) Comparison of the effects of Nic administration (0, 1.0, or 3.0 mg/kg, n = 5, 4, 4, respectively) followed by D-Ser on the concentrations of striatal D-Ser with control groups [Nic (0, 1.0, or 3.0 mg/kg, n = 6, 2, 2, respectively) without D-Ser]. The effects of Nic on the concentration of striatal D-Ser are expressed as a percentage of the baseline samples, which were considered 100%. The arrow indicates the time of Nic administration. $^*p < 0.05$, $^{**}p < 0.01$ for Nic (1.0 or 3.0 mg/kg) + D-Ser *vs*. PBS + D-Ser; $^{\S}p < 0.05$, $^{\S\S}p < 0.01$ for Nic 1.0 mg/kg + D-Ser *vs*. Nic 3.0 mg/kg + D-Ser. (b) The corresponding areas under the striatal d-Ser concentration-time curves (AUC) from 0 to 210 min. $^{**}p < 0.01$ for Nic (1.0 or 3.0 mg/kg) + D-Ser *vs*. PBS + D-Ser; $^{\S}p < 0.05$ for Nic 1.0 mg/kg + D-Ser *vs*. Nic 3.0 mg/kg + D-Ser.

symptoms (withdrawal, dullness, and lack of motivation), and cognitive deficits (decreased attention, working memory, and executive function) [15, 16]. Notably, D-Ser levels and the ratio of D-Ser to total Ser in patients with schizophrenia (*e.g.*, plasma or serum samples [17, 18, 19] and cerebrospinal fluid samples [20]) are significantly lower than those of healthy individuals. In addition, the expression of D-amino acid oxidase (DAO), an enzyme that degrades D-Ser *in vivo*, increases significantly in the postmortem brain of patients with schizophrenia [21, 22, 23]

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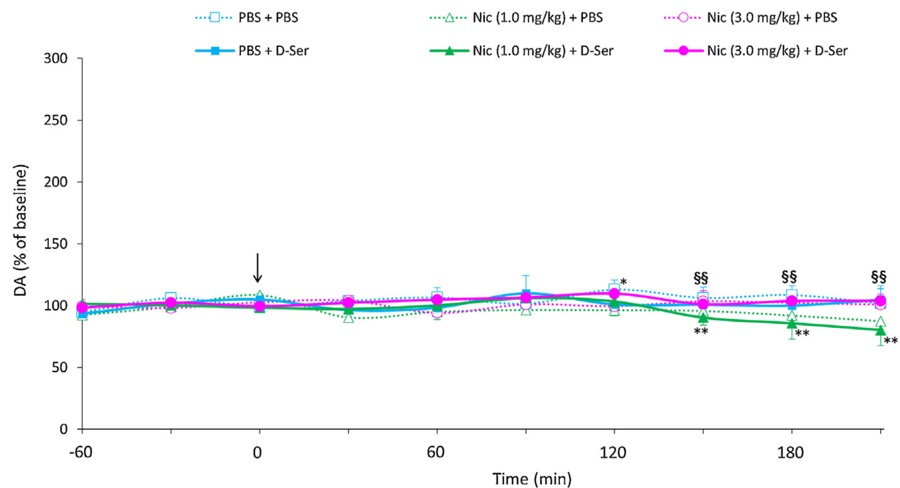

Fig. 5. Comparison of the effects of administration of Nic (0, 1.0, or 3.0 mg/kg, n = 5, 4, 4, respectively) with D-Ser on the concentration of striatal dopamine (DA) with control groups [Nic (0, 1.0, or 3.0 mg/kg, n = 6, 2, 2, respectively) without D-Ser]. The arrow indicates the time of Nic administration. $*p < 0.05$, $**p < 0.01$ for Nic (1.0 or 3.0 mg/kg) + D-Ser *vs*. PBS + D-Ser; $^{§§}p < 0.01$ for 1.0 mg/kg + D-Ser *vs*. 3.0 mg/kg of Nic + D-Ser.

suggesting that the enhancement of DAO expression may be involved in the onset of schizophrenia.

In transient ischemia, it has been reported that D-Ser concentration increases in the rabbit piriform cortex [24, 25] suggesting that D-Ser as an NMDAR co-agonist is involved in neural damage based on the overstimulation of NMDAR in cerebrovascular disorders. Endogenous D-Ser is produced from L-Ser by serine racemase, which is expressed in several tissues, including those of the CNS. In addition, D-Ser found in the CNS is not only biosynthesized from L-Ser; it may also be of dietary origin because D-Ser contained in some food items and beverages [5, 6, 7, 8, 9] can be distributed into the CNS through circulating blood. In the present study, the comparison of D-Ser concentrations in plasma and striatal MD samples following the administration of several doses of D-Ser evidenced that the profile of D-Ser levels differed between MD and plasma samples (Fig. 1); D-Ser levels in MD samples did not increase linearly at the 50.0 mg/kg dose contrary to that observed in plasma samples. One possible explanation for this difference was that the MD probe was not able to collect proportional D-Ser from the striatum when the D-Ser concentration was too high; therefore, the D-Ser concentration in striatal MD sample was underestimated. However, judging from the *in vitro* recovery test (Fig. 2), MD probes seem to be able to recover proportional concentrations to those that provided D-Ser to the striatum in the range from 100 to 1000 μM. Accordingly, it can be assumed that, in the striatum, D-Ser levels did not increase proportionally to the high D-Ser doses provided. Given that D-Ser transfer to CNS is mediated by a transporter—the alanine-serine-cysteine transporter 1 (Asc-1) expressed in the

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brain [26]—it is likely that the excess of D-Ser provided was not able to penetrate into the CNS through the blood-brain barrier owing to saturation of the binding site for D-Ser in Asc-1.

Clinically, D-Ser may be prescribed in combined therapies involving other CNS drugs. As D-Ser levels were significantly lower in patients with schizophrenia than in healthy individuals [17, 19, 20], D-Ser has been administered to increase D-Ser levels in these patients. In such cases, the co-administration of second-generation antipsychotic (SGA) drugs with D-Ser has improved both the positive and negative symptoms of patients [27, 28, 29, 30]. Thus, D-Ser can be used as a combined therapy with other CNS-active drugs.

Although Nic, a representative of the semi-synthetic ergot-alkaloids, was initially developed as a vasoactive drug for cerebrovascular disorders [31], it is currently being prescribed for the treatment of cognitive impairment associated with dementia. From the pharmacological perspective, Nic can elicit a high affinity for α_1-adrenergic and 5-HT_{1A} receptors and act as an antagonist at these sites. By blocking the α_1-adrenergic receptors, Nic is able to improve brain hemodynamics and metabolism, increasing energy production [32]. In fact, Nic has positive effects on several aspects of human cognitive performance, psychomotor performance, attention, reaction times, and other indicators of brain function [33]. Although Nic functions as a CNS-active drug, there is no information on the combined therapeutic effect of Nic and D-Ser.

As shown in Fig. 3, administration of Nic only did not affect endogenous D-Ser levels in plasma, although co-administration of Nic with D-Ser increased the plasma D-Ser levels in a dose-dependent manner similar to that previously reported for risperidone (Ris) [34]. In the risperidone study, it was revealed that that the administration of Ris (3.0 mg/kg) followed by the administration of D-Ser induced a significant increase in the concentration of plasma D-Ser after 120 min [34]. However, in the present study, the 3.0 mg/kg Nic + 20 mg/kg D-Ser-administered group showed a significant increase in D-Ser concentration at 15 and 30 min that then rapidly decreased (Fig. 3a). Together, these results suggest that exogenously administered D-Ser might be rapidly degraded by DAO or eliminated faster from plasma to urine when co-administered with Nic than when co-administrated with Ris. Systemic administration of Nic alone caused little change in the D-Ser levels in striatal MD samples as well as in plasma indicating that Nic itself hardly affects endogenous D-Ser in not only the plasma, but also the striatum. Regarding D-Ser distribution to the CNS, it is possible that Nic is able to prevent the distribution of exogenous D-Ser from circulating blood into the brain because extracellular D-Ser present in the striatum decreased in a Nic dose-dependent manner (Fig. 4). Accordingly, Nic may block the penetration of excess D-Ser to the CNS by inhibiting the transporter of D-Ser, *i.e.*, Asc-1. Thus far, Nic has been demonstrated

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to enhance glutamate uptake *via* glutamate transporters of synaptosomes as well as a subtype of glutamate transporter, EAAC1 [35]. However, there have been no studies on the pharmacological action of Nic on the function of Asc-1. Therefore, these results suggest that Nic not only affects D-Ser concentrations in rat plasma but also its ability to migrate into the brain. Thus, Nic may prevent excess exogenous D-Ser from food and drinks or circulating in the blood to penetrate into the brain. The direct or indirect effect of Nic on Asc-1, thus, is planned for future investigation.

In addition, increasing the extracellular DA levels is not a preferred method for treating schizophrenia because enhanced DA neurotransmission may exacerbate the positive symptoms of schizophrenia [15].

5. Conclusion

The AUC of D-Ser in rat striatum may not increase proportionally to D-Ser doses owing to saturation of D-Ser transporters such as Asc-1. The present study found that extracellular D-Ser levels may be affected by co-administering Nic and D-Ser, suggesting that Nic may prevent the distribution of excessive D-Ser in circulating blood into the brain, which is one of the pharmacological actions of Nic.

Declarations

Author contribution statement

M. Onozato: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

H. Nakazawa, K. Ishimaru, C. Nagashima, M. Fukumoto, H. Hakariya, T. Sakamoto: Performed the experiments.

H. Ichiba: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

T. Fukushima: Conceived and designed the experiments; Wrote the paper.

Competing interest statement

The authors declare no conflict of interest.

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Additional information

No additional information is available for this paper.

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