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Research paper

Cerebrospinal fluid D-serine concentrations in major depressive disorder negatively correlate with depression severity

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ABSTRACT

Background: D-serine is an endogenous co-agonist of *N*-methyl-*D*-aspartate receptor (NMDAR) and plays an important role in glutamate neurotransmission. Several studies suggested the possible involvement of D-serine related in the pathophysiology of psychiatric disorders including major depression disorders (MDD). We tried to examine whether cerebrospinal fluid (CSF) or plasma D-serine concentrations are altered in MDD and whether D-serine concentrations correlated with disease severity.

Methods: 26 MDD patients and 27 healthy controls matched for age, sex and ethnicity were enrolled. We measured amino acids in these samples using by high-performance liquid chromatography with fluorometric detection.

Results: D-serine and L-serine, precursor of D-serine, levels in CSF or plasma were not significantly different in patients of MDD compared to controls. Furthermore, a significant correlation between D-serine levels in CSF and Hamilton Depression Rating Scale (HAMD)-17 score was observed ($r = -0.65$, $p = 0.006$). Furthermore, we found a positive correlation between CSF D-serine and HVA concentrations in MDD patients ($r = 0.54$, $p = 0.007$). CSF D-serine concentrations were correlated with those of plasma in MDD ($r = 0.61$, $p = 0.01$) but not in controls. In CSF, we also confirmed a significant correlation between D-serine and L-serine levels in MDD ($r = 0.72$, $p < 0.0001$) and controls ($r = 0.70$, $p < 0.0001$).

Conclusions: The study has some limitations; sample size was relatively small and most patients were medicated. We revealed that CSF D-serine concentrations were correlated with depression severity and HVA concentrations and further investigation were required to reveal the effect of medication and disease heterogeneity.

1. Introduction

Major depressive disorder (MDD) is a severe mental illness thought to be caused by genetic and epigenetic variants, emotional and social psychological factors, and early life stress (Belmaker and Agam, 2008; Krishnan and Nestler, 2008). In particular, the etiology of MDD has been linked to disrupted glutamatergic neurotransmission, resulting from altered *N*-methyl-*D*-aspartate receptor (NMDAR) function and insufficient glial reuptake of glutamate (Krishnan and Nestler, 2008; Sanacora et al., 2008). Indeed, an NMDAR antagonist, ketamine, shows rapid and sustained antidepressant effects in treatment-resistant MDD patients (Krystal et al., 2013; Hashimoto, 2014; Yang and Hashimoto, 2014; Yang et al., 2015). A clinical trial of high dose of D-cycloserine, a partial agonist of NMDAR, revealed significant improvement of depressive symptoms in treatment-resistant MDD (Heresco-Levy et al., 2013). However, the mechanisms of action of these drugs remain elusive.

D-serine, synthesized from L-serine by serine racemase, is an endogenous co-agonist of NMDAR that plays a critical role in the regulation of glutamatergic neurotransmission. D-serine concentrations in serum (Hashimoto et al., 2016) and total serine concentrations in plasma (Maes et al., 1995; Sumiyoshi et al., 2004) have been reported to be significantly higher in patients with MDD compared with healthy controls. Cerebrospinal fluid (CSF) D-serine levels were also increased in elderly MDD patients (Madeira et al., 2015). However, Mitani et al. (2006) reported that plasma D-serine and L-serine concentrations in patients with MDD were similar to those in controls. Interestingly, they reported that there was a significant negative correlation between

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Table 1
Demographics and clinical characteristics of this study patients.

	HC (n = 27)	MDD (n = 26)	Statistic
N			
CSF or Plasma	27	26	
Age (years)	41.6 ± 9.1	41.0 ± 7.4	N.S.[a]
Gender			
Female	13 (48.1%)	13 (50.0%)	
Male	14 (51.9%)	13 (50.0%)	
Drug free (DF)		4	
HAMD17 (≥ 8)		13.7 ± 6.0 (n = 18) DF: 2	

HAMD-17, 17-item Hamilton Depression Rating Scale.
[a] Unpaired *t*-test.

plasma L-serine levels and depression severity assessed with the 21-item Hamilton Depression Rating Scale in MDD patients and that D-serine levels showed a similar trend (Mitani et al., 2006). Furthermore, plasma D-serine levels in (*R, S*)-ketamine non-responders were significantly higher than in (*R, S*)-ketamine responders (Moaddel et al., 2015). These accumulating findings point to the potential importance of D-serine in MDD. However, the inconsistent findings require further investigation.

Abnormalities in dopamine function are also reported in MDD (Willner, 1983a, 1983b, 1983c; Kapur and Mann, 1992). Dopamine contributes to reward pathways and the regulation of psychomotor speed, concentration, attention, problem-solving, and motivation, which have been implicated in MDD (Dunlop and Nemeroff, 2007). Several studies have found low CSF homovanillic acid (HVA) levels in medication-free depressed patients compared with healthy controls (reviewed by Brown and Gershon (1993)). It would therefore be informative to examine the relationship between D-serine and HVA levels in CSF.

To gain insight into the relationship between D-serine concentrations and the pathophysiology of MDD, it is vital to reveal (1) the relationship between the D-serine concentrations of the CSF and plasma, (2) the correlation between D-serine levels and MDD severity, and (3) the association between D-serine and monoamine concentrations.

In this study, we examined whether the D-serine levels of CSF and plasma are altered in MDD patients. Furthermore, we examined the association of D-serine concentrations with depression severity and HVA

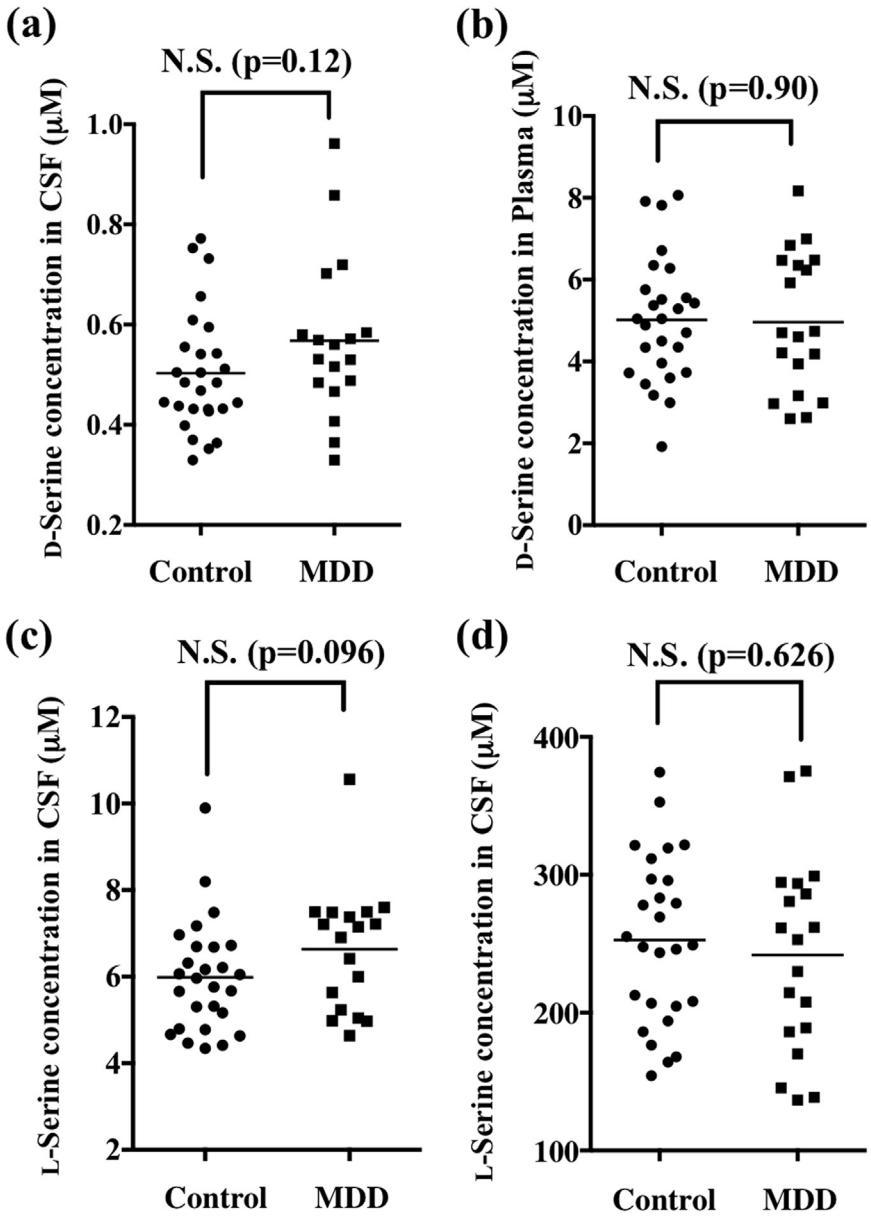

Fig. 1. Cerebrospinal fluid (CSF) and plasma D-serine or L-serine levels in patients with major depressive disorder (MDD) and healthy controls. Comparison of D-serine (a: CSF, b: plasma) and L-serine (c: CSF, d: plasma) concentrations between MDD patients and healthy controls.