Eur Arch Psychiatry Clin Neurosci (2016) 266:83–85
DOI 10.1007/s00406-015-0602-4

LETTER TO THE EDITOR

Serine enantiomers as diagnostic biomarkers for schizophrenia and bipolar disorder

Kenji Hashimoto[1]

Received: 20 April 2015 / Accepted: 6 May 2015 / Published online: 12 May 2015

Schizophrenia and bipolar disorder (BD) are the two major psychiatric disorders significantly contributing to the global burden of diseases in children and adults. Both disorders have similarities: (a) lifetime prevalence of approximately 1 % in males and females, (b) early age of onset (between late adolescence and early adulthood), (c) familial aggregation because of genetic influences with very similar recurrence risks of the same disorder among relatives (~tenfold increase in children), and (d) comparable concordance rates for monozygotic and dizygotic twins with heritability estimates of 60–80 % [1]. As schizophrenia and BD have overlapping symptoms, numerous genetic studies have implicated a shared genetic susceptibility. However, these disorders possibly result from a combination of genetic and environmental factors. Their shared clinical features result in high rates of misdiagnosis because of a lack of differentiating biomarkers between these disorders. Therefore, the development of specific biomarkers for these disorders would be necessary for establishing the correct diagnosis and treatment of schizophrenia and BD.

The N-methyl-D-aspartate (NMDA) receptors play a key role in the pathogenesis of schizophrenia and BD [2–4]. D-serine, an obligatory endogenous co-agonist of NMDA receptors, is synthesized from L-serine by serine racemase (SRR), and it is degraded by D-amino acid oxidase (DAAO). D-serine is present in the brain at a high concentration of up to one-third that of L-serine, and D-serine is heterogeneously distributed in the brain with a pattern resembling that of NMDA receptors. Studies using the *Srr* knockout mice revealed that *Srr* is the major enzyme responsible for D-serine production in the mouse forebrain [3, 4].

We have previously reported that serum D-serine levels in patients with schizophrenia were significantly lower than those in controls and that serum L-serine levels in patients with schizophrenia were significantly higher than those in controls [5, 6], suggesting an aberrated serine metabolism in patients with schizophrenia. This finding was corroborated in a recent study [7]. Furthermore, we have also reported a decreased D-serine to total serine ratio in the cerebrospinal fluid (CSF) of first episode and drug-naive patients with schizophrenia [8]. Bendikov et al. [9] have reported a decrease in D-serine levels and D/L-serine ratio in the CSF of patients with schizophrenia. Furthermore, SRR in the frontal cortex and hippocampus and the hippocampal SRR/DAAO ratio decreased in patients with schizophrenia [9]. Decreased D-serine levels in patients with schizophrenia are supported by the therapeutic effects of D-serine in such patients [3, 4]. A recent genome-wide association study has confirmed the association of SRR with schizophrenia [10]. The DAAO activator gene (DAOA; G72/G30), located on chromosome 13q, is also associated with schizophrenia and BD [3, 4]. Interestingly, Habl et al. [11] reported increased expression of DAAO mRNA in the hippocampus of schizophrenia patients, suggesting that this increased expression could be responsible for a decrease in D-serine levels in the hippocampus. Altogether, a disturbed NMDA receptor neurotransmission, due to decreased D-serine levels, may play a causative role in the pathogenesis of schizophrenia.

We have recently reported that serum D-serine levels in mood-stabilized patients with BD were significantly higher than those in controls, while serum L-serine levels in

✉ Kenji Hashimoto
hashimoto@faculty.chiba-u.jp

[1] Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, 1-8-1 Inohana, Chiba 260-8670, Japan

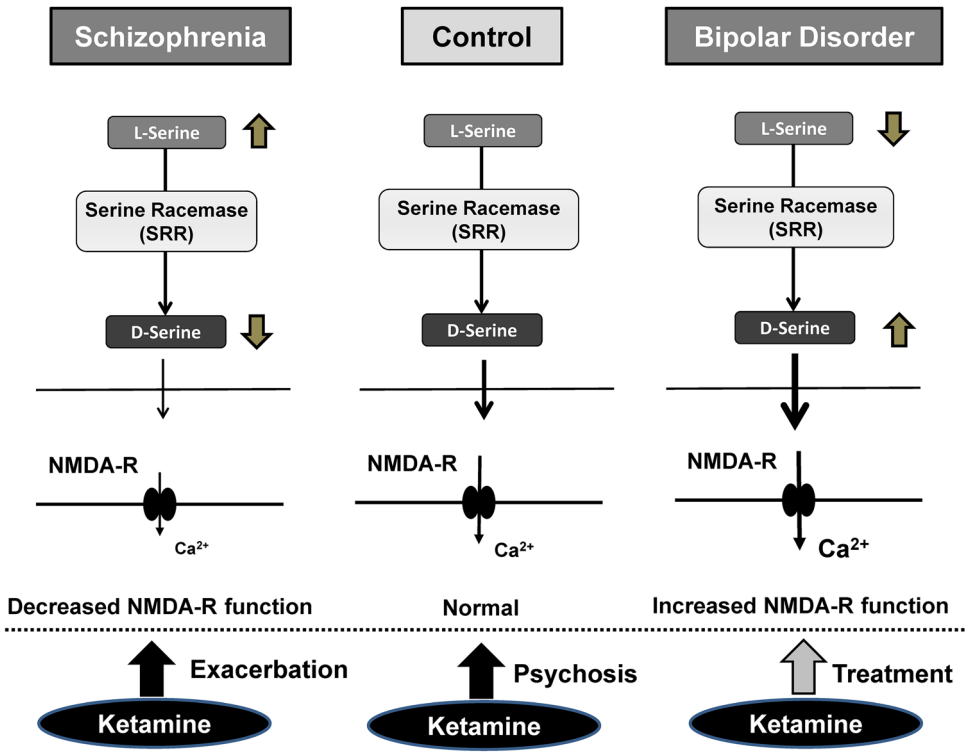

Fig. 1 D-serine-mediated *N*-methyl-D-aspartate receptor function in the pathogenesis of schizophrenia and bipolar disorder. The *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine is known to cause schizophrenia-like symptoms in healthy controls [12], and it exacerbates psychotic symptoms in patients with schizophrenia [13]. In contrast, ketamine causes a rapid and sustained antidepressant effect in depressed patients with bipolar disorder (BD) [14]. Our studies using measurement of amino acids have revealed that serum D-serine levels in patients with schizophrenia are lower than those in controls [5, 6], whereas serum D-serine levels in patients with BD are higher than those in controls [11]. In contrast, serum L-serine levels in patients with schizophrenia are higher than those in controls [5, 6], whereas serum L-serine levels in patients with BD are lower than those in controls [11]. Altogether, decreased neurotransmission via the NMDA receptor function, due to decreased D-serine levels, plays a role in the pathogenesis of schizophrenia. In contrast, increased neurotransmission via the NMDA receptor function, due to increased D-serine levels, may play a role in the pathogenesis of BD

patients with BD were significantly lower than those in controls [12], suggesting an aberrated serine metabolism in BD patients. It remains unclear whether changes in serum D- and L-serine levels are a trait or state marker for BD. Thus, serum D-serine levels in patients with schizophrenia are lower than those in controls, whereas serum D-serine levels in patients with BD are higher than those in controls. In contrast, serum L-serine levels in patients with schizophrenia are higher than those in controls, whereas serum L-serine levels in patients with BD are lower than those in controls. The former findings suggest a decreased function of NMDA receptors, owing to decreased D-serine levels, in schizophrenia. This is supported by data revealing that the NMDA receptor antagonist ketamine (0.5 mg/kg, 40-min intravenous infusion) could produce schizophrenia-like symptoms, including positive and negative symptoms, and cognitive impairment in healthy controls [13] (Fig. 1). Furthermore, ketamine exacerbated psychotic symptoms in patients with schizophrenia [14] (Fig. 1). The latter finding suggests an increased function of NMDA receptors, owing to increased D-serine levels, in BD [2, 12]. This may be supported by the rapid and sustained antidepressant effects of ketamine (0.5 mg/kg, 40-min intravenous infusion) in depressed patients with BD [15] (Fig. 1). Interestingly, Moaddel et al. [16] reported that blood level of D-serine at baseline may be a potential predictable biomarker for ketamine's antidepressant effect in patients with treatment-resistant depression. Given the key role of D-serine in NMDA receptor neurotransmission, its use as a biomarker for antidepressant response to the NMDA receptor antagonists will be highly useful in the clinical setting [17]. The current atypical antipsychotic drugs are approved as treatments for acute mania and as maintenance treatments for BD, indicating a similar pathophysiology (e.g., hyperdopaminergic state) in both disorders. Considering the contrasting effects of ketamine in schizophrenia or BD, it seems that contrasting abnormalities in the NMDA receptor function play a role in the pathogenesis of these disorders (Fig. 1).

In conclusion, considering the different roles of NMDA receptor neurotransmission in the pathogenesis of schizophrenia and BD, measurements of serine enantiomers (D- and L-serine) may represent diagnostic peripheral biomarkers for these disorders. Furthermore, this method may reduce misdiagnosis between these disorders, although further studies using larger sample sizes are required for confirming this theory.

Acknowledgments This study was supported by a grant from Comprehensive Research on Disability, Health and Welfare, Health and Labour Sciences Research Grants, Japan.

Conflict of interest Dr. Hashimoto is a holder of the patents "Method of examining and diagnosing schizophrenia" (US 2005/0164400 A1), which pertain to the measurement of D-serine as a biomarker. In addition, Dr. Hashimoto has served as a scientific consultant to Astellas, Dainippon-Sumitomo, and Taisho, and he has also received research support from Abbvie, Dainippon-Sumitomo, Mochida, Otsuka, and Taisho.

References

1. Maier W, Zobel A, Wagner M (2006) Schizophrenia and bipolar disorder: differences and overlaps. Curr Opin Psychiatry 19(2):165–170
2. Hashimoto K, Sawa A, Iyo M (2007) Increased levels of glutamate in brains from patients with mood disorders. Biol Psychiatry 62(11):1310–1316
3. Hashimoto K, Malchow B, Falkai P, Schmitt A (2013) Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. Eur Arch Psychiatry Clin Neurosci 263(5):367–377
4. Hashimoto K (2014) Targeting of NMDA receptors in new treatments for schizophrenia. Expert Opin Ther Targets 18(9):1049–1063
5. Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, Nakazato M, Kumakiri C, Okada S, Hasegawa H, Imai K, Iyo M (2003) Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the *N*-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch Gen Psychiatry 60(6):572–576
6. Yamada K, Ohnishi T, Hashimoto K, Ohba H, Iwayama-Shigeno Y, Toyoshima M, Okuno A, Takao H, Toyota T, Minabe Y, Nakamura K, Shimizu E, Itokawa M, Mori N, Iyo M, Yoshikawa T (2005) Identification of multiple serine racemase (SRR) mRNA isoforms and genetic analyses of SRR and DAO in schizophrenia and D-serine levels. Biol Psychiatry 57(12):1493–1503
7. Fukushima T, Iizuka H, Yokota A, Suzuki T, Ohno C, Kono Y, Nishikiori M, Seki A, Ichiba H, Watanabe Y, Hongo S, Utsunomiya M, Nakatani M, Sadamoto K, Yoshio T (2014) Quantitative analyses of schizophrenia-associated metabolites in serum: serum D-lactate levels are negatively correlated with gamma-glutamylcysteine in medicated schizophrenia patients. Plos One 9(7):e101652
8. Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindström LH, Iyo M (2005) Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naive schizophrenic patients. Prog Neuropsychopharmacol Biol Psychiatry 29(5):767–769
9. Bendikov I, Nadri C, Amar S, Panizzutti R, De Miranda J, Wolosker H, Agam G (2007) A CSF and postmortem brain study of D-serine metabolic parameters in schizophrenia. Schizophr Res 90(1–3):41–51
10. The Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510):421–427
11. Habl G, Zink M, Petroianu G, Bauer M, Schneider-Axmann T, von Wilmsdorff M, Falkai P, Henn FA, Schmitt A (2009) Increased D-amino acid oxidase expression in the bilateral hippocampal CA4 of schizophrenic patients: a post-mortem study. J Neural Transm 116(12):1657–1665
12. Pålsson E, Jakobsson J, Södersten K, Fujita Y, Sellgren C, Ekman CJ, Ågren H, Hashimoto K, Landén M (2015) Markers of glutamate signaling in cerebrospinal fluid and serum from patients with bipolar disorder and healthy controls. Eur Neuropsychopharmacol 25(1):133–140
13. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51(3):199–214
14. Lahti AC, Weiler MA, Tamara M, Parwani A, Tamminga CA (2001) Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacology 25(4):455–467
15. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, Kammerer WA, Quezado Z, Luckenbaugh DA, Salvadore G, Machado-Vieira R, Manji HK, Zarate CA Jr (2010) A randomized add-on trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 67(8):793–802
16. Moaddel R, Luckenbaugh DA, Xie Y, Villaseñor A, Brutsche NE, Machado-Vieira R, Ramamoorthy A, Lorenzo MP, Garcia A, Bernier M, Torjman MC, Barbas C, Zarate CA Jr, Wainer IW (2015) D-serine plasma concentration is a potential biomarker of (R, S)-ketamine antidepressant response in subjects with treatment-resistant depression. Psychopharmacology 232(2):399–409
17. Hashimoto K (2014) Blood D-serine levels as a predictive biomarker for the rapid antidepressant effects of the NMDA receptor antagonist ketamine. Psychopharmacology 231(20):4081–4082