EDITORIAL

Novel Therapeutic Drugs for Neuropsychiatric Disorders

Kenji Hashimoto*

Schizophrenia, major depression, and anxiety disorders are the major psychiatric diseases. Schizophrenia is a chronic, severe, and disabling brain disorder that affects about 1 percent in the world. Symptoms include hallucinations, delusions, disorganized thinking, movement disorders, flat affect, social withdrawal, and cognitive deficits. Although the causes of this disease have not yet been determined, current treatments with antipsychotic drugs can eliminate the part of the symptoms in patients with schizophrenia. Major depression is disabling and prevents a person from functioning normally. An episode of major depression may occur only once in a person's lifetime, but more often, it recurs throughout a person's life. A variety of treatments including antidepressant medications and short-term psychotherapies are proven effective for major depression. Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, and social phobia (social anxiety disorder). Anxiety disorders are treated with medications (e.g., antidepressants, anti-anxiety drugs, β-adrenergic blockers), specific types (e.g., cognitive-behavioral therapy) of psychotherapy, or both.

Alzheimer's disease is also a serious brain disorder named for German physician Alois Alzheimer, who first described it in 1906. This is a progressive and fatal brain disease, and is the most common form of dementia. Currently, there is no cure for this disease. Drug (e.g., donepezil, galantamine, memantine, rivastigmine, tacrine), and non-drug treatments may help with both cognitive and behavioral symptoms in patients with this disease.

Currently, a number of pharmaceutical industries have been developing the novel therapeutic drugs for these neuropsychiatric diseases although the precise causes of these diseases have not yet been determined. In the Special issue of the Journal, the following scientists review the recent topics on the novel therapeutic drugs for these diseases.

Multiple lines of evidence suggest that an abnormality of glutamatergic neurotransmission via *N*-methyl-D-aspartate (NMDA) receptors might be implicated in the pathophysiology of schizophrenia. Considering the NMDA receptor hypofunction hypothesis for schizophrenia, increasing NMDA receptor function by pharmacological manipulation could potentially be a new strategy for the management of schizophrenia [1-7]. Currently, the NMDA receptor glycine modulatory site is the most attractive therapeutic target for improving cognition and reducing negative symptoms in schizophrenia. Therefore, D-serine (an endogenous co-agonist at glycine modulatory site) and glycine transporter-1 (GlyT-1) inhibitors would be potential therapeutic drugs for schizophrenia [1-7].

Although D-amino acids including D-serine and D-alanine have been shown to be effective in the treatment of schizophrenia [8,9], these D-amino acids are metabolized by D-amino acid oxidase (DAAO), reducing their bioavailability in the brain. Recently, the novel DAAO inhibitors CBIO has been developed in order to minimize the dose of D-amino acids [10-12]. In the Special Issue, Sean Smith and his colleagues (Merck & Co., Inc., USA) review the recent topics on the novel DAAO inhibitors as novel therapeutic drugs for schizophrenia.

A number of pharmaceutical companies have been studying the novel therapeutic drugs that block GlyT-1 and thereby raise synaptic glycine levels in the brain [5-7]. The GlyT-1 inhibitor sarcosine (*N*-methyl glycine) was shown to be effective in the treatment of schizophrenia [13-15]. These clinical studies using sarcosine have stimulated the development of the selective GlyT-1 inhibitors because the uptake of sarcosine into the brain is not good. November 10, 2009, Roche reported the results from a 320 patient phase II proof-of-concept study with it's investigational GlyT-1 inhibitor RG1678. The study showed that the compound improved both the negative symptoms and the personal and social functioning of patients with schizophrenia reaching statistical significance on primary and secondary endpoints. The analysis of this double blind phase II study showed that RG1678 has a robust and clinically meaningful effect in patients with schizophrenia. RG1678 was given as an add-on treatment to patients who were stable on antipsychotic therapy and suffered mainly from negative or disorganized thought symptoms. The compound was well tolerated at all doses tested. In the Special Issue, Kenji Hashimoto (Chiba University, Japan) reviews the recent findings of novel GlyT-1 inhibitors as novel potential therapeutic drugs for schizophrenia. Metabotropic glutamate receptors (mGluRs) are also known to alter the neurotransmission of glutamate as well as other neurotransmissions involved in the pathophysiology of neuropsychiatric disorders such as schizophrenia, mood disorder, and anxiety disorder [16-18]. In the Special Issue, Akito Yasuhara and Shigeyuki Chaki (Taisho Pharmaceutical Ltd., Japan) review the recent topics of novel mGluR agonists/antagonists as novel potential therapeutic drugs for neuropsychiatric diseases.

Accumulating evidence suggests that α7 nicotinic receptors (α7 nAChRs), a subtype of nAChRs, play a role in the pathophysiology of neuropsychiatric diseases including schizophrenia and Alzheimer's disease [19,20]. It has been suggested that α7 nAChRs play an important role in the P50 auditory evoked-potential deficits in patients with schizophrenia, and that α7 nAChR agonists would be potential therapeutic drugs for cognitive impairments associated with P50 deficits in schizophrenia [19]. Furthermore, it is shown that α7 nAChRs might play a key role in the amyloid-β (Aβ)-mediated pathology of Alzheimer's

disease [20]. In the Special Issue, Jun Toyohara and Kenji Hashimoto (Chiba University, Japan) review the recent topics on α7 nAChRs in the pathophysiology of these diseases and on novel α7 nAChR agonists as potential therapeutic drugs of these diseases.

I would like to wish to thank the various contributors to this Special Issue for their participation. We hope that this Special Issue would be helpful for the development of novel therapeutic drugs for neuropsychiatric diseases such as schizophrenia, mood disorders, anxiety disorders, and Alzheimer's disease.

ACKNOWLEDGEMENTS

This study was supported in part by a grant from the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation of Japan (to K.H.).

REFERNCES

[1] Hashimoto, K.; Fukushima, T.; Shimizu, E.; Komatsu, N.; Watanabe, H.; Shinoda, N.; Nakazato, M.; Kumakiri, C.; Okada, S.; Hasegawa, H.; Imai, K.; Iyo, M. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the NMDA receptor hypofunction hypothesis of schizophrenia. *Arch. Gen. Psychiatry*, **2003**, *60*, 572-576.

[2] Hashimoto, K.; Okamura, N.; Shimizu, E.; Iyo, M. Glutamate hypothesis of schizophrenia and approach for possible therapeutic drugs. *Curr. Med. Chem. - CNS Agents*, **2004**, *4*, 147-154.

[3] Hashimoto, K.; Shimizu, E.; Iyo, M. Dysfunction of glia-neuron communication in pathophysiology of schizophrenia. *Curr. Psychiatry Rev.*, **2005**, *1*, 151-163.

[4] Hashimoto, K. The NMDA receptor hypofunction hypothesis for schizophrenia and glycine modulatory sites on the NMDA receptors as potential therapeutic drugs. *Clin. Psychopharmacol. Neurosci.*, **2006**, *4*, 3-10.

[5] Hashimoto, K. Glycine transporter inhibitors as therapeutic agents for schizophrenia. *Recent Pat. CNS Drug Discov.*, **2006**, *1*, 43-54.

[6] Hashimoto, K. Glycine transporter-1 inhibitors as novel therapeutic drugs for schizophrenia. *CNS Agents Med. Chem.*, **2007**, *7*, 177-182.

[7] Hashimoto, K. Glycine transporter inhibitors as therapeutic agents for schizophrenia. *Front. CNS Drug Discov.*, **2009**, (in press).

[8] Tsai, G.; Yang, P.; Chung, L.C.; Lange, N.; Coyle, J.T. D-serine added to antipsychotics for the treatment of schizophrenia. *Biol. Psychiatry*, **1998**, *44*, 1081-1089.

[9] Tsai, G.; Yang, P.; Chung, L.C.; Chong, M.Y. D-alanine added to antipsychotics for the treatment of schizophrenia. *Biol. Psychiatry*, **1998**, *59*, 230-234.

[10] Ferraris, D.; Duvall, B.; Ko, Y.S.; Thomas, A.G.; Rojas, C.; Majer, P.; Hashimoto, K.; Tsukamoto, T. Synthesis and biological evaluation of D-amino acid oxidase inhibitors. *J. Med. Chem.*, **2008**, *51*, 3357-3359.

[11] Hashimoto, K.; Fujita, Y.; Horio, M.; Kunitachi, S.; Iyo, M.; Ferraris, D.; Tsukamoto, T. Co-administration of a D-amino acid oxidase inhibitor potentiates the efficacy of D-serine in attenuating prepulse inhibition deficits after administration of dizocilpine. *Biol. Psychiatry*, **2009**, *65*, 1103-1106.

[12] Horio, M.; Fujita, Y.; Ishima, T.; Iyo, M.; Ferraris, D.; Tsukamoto, T.; Hashimoto, K. Effects of D-amino acid oxidase inhibitor on the extracellular D-alanine levels and the efficacy of D-alanine on dizocilpine-induced prepulse inhibition deficits in mice. *Open Clin. Chem. J.*, **2009**, *2*, 16-21.

[13] Tsai, G.; Lane, H.Y.; Yang, P.; Chong, M.Y.; Lange, N. Glycine transporter I inhibitor, *N*-methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. *Biol. Psychiatry*, **2004**, *55*, 452-456.

[14] Lane, H.Y.; Chang, Y.C.; Liu, Y.C.; Chiu, C.C.; Tsai, G.E. Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study. *Arch. Gen. Psychiatry*, **2005**, *62*, 1196-1204.

[15] Lane, H.Y.; Liu, Y.C.; Huang, C.L.; Chang, Y.C.; Liau, C.H.; Perng, C.H.; Tsai, G. Sarcosine (*N*-methylglycine) treatment for acute schizophrenia: a randomized, double-blind study. *Biol. Psychiatry*, **2008**, *63*, 9-12.

[16] Palucha, A.; Pilc, A. Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. *Pharmacol. Ther.*, **2007**, *115*, 116-147.

[17] Conn, P.J.; Lindsley, C.W.; Jones, C.K. Activation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. *Trends Pharmacol. Sci.*, **2009**, *30*, 25-31.

[18] Hashimoto, K. Emerging role of glutamate in the pathophysiology of major depressive disorder. *Brain Res. Rev.*, **2009**, *61*, 105-123.

[19] Hashimoto, K.; Koike, K.; Shimizu, E.; Iyo, M. α7 Nicotinic receptor agonists as potential therapeutic drugs for schizophrenia. *Curr. Med. Chem. CNS Agents*, **2005**, *5*, 171-184.

[20] Hashimoto, K.; Iyo, M. Amyloid cascade hypothesis of Alzheimer's disease and α7 nicotinic receptor agonists. *Nihon Shinkei Seishin Yakurigaku Zasshi*, **2002**, *22*, 49-53.

Kenji Hashimoto

(Guest Editor)

The Open Medicinal Chemistry Journal,

Division of Clinical Neuroscience,

Chiba University Center for Forensic Mental Health,

1-8-1 Inohana, Chiba 260-8670,

Japan

E-mail: hashimoto@faculty.chiba-u.jp