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Kynurenine pathway and cognitive impairments in schizophrenia: Pharmacogenetics of galantamine and memantine

Maju Mathew Koola *

Sheppard Pratt Health System, Baltimore, MD
Department of Psychiatry and Behavioral Sciences, George Washington University School of Medicine and Health Sciences, Washington, DC, USA

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ABSTRACT

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project designed to facilitate the development of new drugs for the treatment of cognitive impairments in people with schizophrenia, identified three drug mechanisms of particular interest: dopaminergic, cholinergic, and glutamatergic. Galantamine is an acetylcholinesterase inhibitor and a positive allosteric modulator of the α_7 nicotinic receptors. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist. There is evidence to suggest that the combination of galantamine and memantine may be effective in the treatment of cognitive impairments in schizophrenia. There is a growing body of evidence that excess kynurenic acid (KYNA) is associated with cognitive impairments in schizophrenia. The α-7 nicotinic and the NMDA receptors may counteract the effects of kynurenic acid (KYNA) resulting in cognitive enhancement. Galantamine and memantine through its α-7 nicotinic and NMDA receptors respectively may counteract the effects of KYNA thereby improving cognitive impairments. The Single Nucleotide Polymorphisms in the Cholinergic Receptor, Nicotinic, Alpha 7 gene (CHRNA7), Glutamate (NMDA) Receptor, Metabotropic 1 (GRM1) gene, Dystrobrevin Binding Protein 1 (DTNBP1) and kynurenine 3-monooxygenase (KMO) gene may predict treatment response to galantamine and memantine combination for cognitive impairments in schizophrenia in the kynurenine pathway.

1. Introduction

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project designed to facilitate the development of new drugs for the treatment of cognitive impairments in people with schizophrenia, identified three drug mechanisms of particular interest: dopaminergic, cholinergic, and glutamatergic (Buchanan et al., 2007). Galantamine and memantine are FDA approved medications to treat Alzheimer's dementia. Galantamine is not only an acetylcholinesterase inhibitor (AChEI), but also a positive allosteric modulator of the α4β2 and α7 nicotinic receptors. In participants with schizophrenia, galantamine has shown improvement in delayed memory and attention (Schubert et al., 2006), the Hopkins Verbal Learning Test (Lee et al., 2007), processing speed and verbal memory (Buchanan et al., 2008) and social cognition (Lindenmayer and Khan, 2011). Encenicline, an α7 nicotinic acetylcholine receptor agonist, was administered to participants with schizophrenia for cognitive impairments in a 12-week phase 2 randomized controlled trial (RCT). Out of 317 participants, 107 were on encenicline 0.27 mg, 105 were on encenicline 0.9 mg and 105 were on placebo. Encenicline 0.27 mg demonstrated significant beneficial effects across multiple measures of cognition. The findings from this first promising study in schizophrenia need to be validated in large phase 3 studies. Although the CogState overall cognition index was statistically superior to placebo, it had a modest effect size of 0.26 (Keefe et al., 2015). Hence, with the AChEI, positive allosteric modulator of the $\alpha_4\beta_2$ and α_7 nicotinic receptor properties of galantamine (other AChEIs such as donepezil and rivastigmine lack the latter two mechanisms of action) and glutamatergic modulation by memantine concurrently may significantly improve the effect size. Reduced activation of the glutamatergic signaling pathways through the NMDA receptor has been hypothesized to be associated with cognitive impairments in schizophrenia. Memantine is an N-methyl D-aspartate (NMDA) receptor antagonist. In a meta-analysis of the three RCTs ($N = 186$), memantine significantly ($p = 0.002$) improved some cognitive functioning in people with schizophrenia (Kishi and Iwata, 2013). Memantine 20 mg improved measures of sensorimotor gating and mismatch negativity that were associated with enhanced cognition in 84 participants with chronic psychotic disorders (Swerdlow et al., 2016). In vivo (magnetic resonance spectroscopy) evidence supported glutamatergic regulation of mismatch negativity and verbal working memory function in schizophrenia ($N = 45$); authors argued the potential role of memantine to target glutamatergic system (Rowland et al., 2016). Add-on memantine 20 mg for 12 weeks in 64 inpatients with schizophrenia was significantly effective in improving the

* Clinical Research Program, Sheppard Pratt Health System, 6501 N Charles St., Baltimore, MD, USA, 21204. Tel.: +1 410 938 5429; fax: +1 410 938 3111.
E-mail addresses: mkoola@sheppardpratt.org, majujuju@yahoo.com.

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global functioning as well as their quality of life (Omranifard et al., 2015). Finally, memantine 5–20 mg administered daily before electroconvulsive therapy (ECT) has been shown to improve cognitive performance after ECT (Abbasinazari et al., 2015; Alizadeh et al., 2015). Authors argued the possible role of glutamatergic system for ECT-associated cognitive impairments.

Targeting only one neurotransmitter system in the treatment of cognitive impairments in schizophrenia was not associated with a clinically meaningful efficacy signal. Galantamine–memantine combination (N = 53) was significantly better for cognition than donepezil–memantine (N = 61) in Alzheimer's dementia patients (Matsuzono et al., 2015). There is evidence to suggest that the combination of galantamine and memantine may be effective in the treatment of cognitive impairments in schizophrenia to broaden the selective benefits produced by either medication alone. In this paper, the rationale of how this combination may act synergistically to enhance cognition in schizophrenia was discussed (Koola et al., 2014). To date, the cholinergic and glutamatergic systems have not been concurrently targeted in people with schizophrenia to examine the effectiveness for cognitive impairments in schizophrenia. A mechanism- and computer-based quantitative systems pharmacology model that combines biophysically realistic preclinical neurophysiology and neuropharmacology with clinical information has been suggested. In this model, combining antipsychotics, galantamine and memantine showed a positive or neutral synergistic effect with certain antipsychotics such as haloperidol and olanzapine in the improvement of working memory, but a negative interaction with quetiapine and aripiprazole (Geerts et al., 2015).

Excess kynurenic acid (KYNA) is associated with cognitive impairments in schizophrenia (Wonodi and Schwarcz, 2010). The α-7 nicotinic and the NMDA receptors may counteract the effects of kynurenic acid (KYNA) resulting in cognitive enhancement as shown in Fig. 1 (Wonodi and Schwarcz, 2010). Galantamine and memantine through its α-7 nicotinic and NMDA receptors respectively may counteract the effects of KYNA thereby improving cognitive impairments (Koola et al., 2014).

The purpose of this paper is to discuss the rationale how the Single Nucleotide Polymorphisms (SNPs) rs904952; rs2337980 in the Cholinergic Receptor, Nicotinic, Alpha 7 gene (CHRNA7), rs6923492 in the Glutamate (NMDA) Receptor, Metabotropic 1 (GRM1) gene and rs2275163, rs1053230 at the kynurenine 3-monooxygenase (KMO) gene may predict treatment response to galantamine and memantine combination to cognitive impairments in schizophrenia in the kynurenine pathway.

2. Pathophysiology of kynurenine pathway in schizophrenia

Kynurenic acid (KYNA) is the only NMDA receptor antagonist in the human central nervous system (Krystal et al., 1994; Stone, 1993). The kynurenine pathway regulates the synthesis of KYNA by an enzymatic cascade. KYNA has been identified as a potent antagonist of the α-7 nicotinic and NMDA receptors (Hilmas et al., 2001; Parsons et al., 1997). This antagonism may be associated with cognitive impairment. There is more evidence supporting this hypothesis which is the genes involved in the glutamatergic system (Collier and Li, 2003). KYNA concentration is increased in the prefrontal cortex of people with schizophrenia; KYNA concentration correlated with dopamine, acetylcholine and glutamate levels which reflect the degree of cognitive impairment (Petrova and Dorofeykova, 2014). KYNA may be a valuable candidate for future therapeutic discovery for the treatment of neurodegenerative diseases (Majláth et al., 2016) such as schizophrenia.

Both NMDA and nicotinic receptors are implicated in the pathophysiology of schizophrenia and Alzheimer's dementia, two disorders with cognitive impairments and increased KYNA concentration (Baran et al., 1999; Erhardt et al., 2001; Nilsson et al., 2005; Schwarcz et al., 2001). Increased brain KYNA concentration was found in 11 postmortem Alzheimer's dementia subjects compared to 13 controls (Baran et al., 1999). In a postmortem study comparing 30 subjects with schizophrenia and 31 controls, kynurenine and kynurenate concentrations were significantly higher in schizophrenia brain (Schwarcz et al., 2001).

Significantly increased cerebrospinal fluid (CSF) KYNA was found in 28 people with schizophrenia compared to 17 healthy controls (Erhardt et al., 2001). CSF KYNA was significantly elevated in 90 participants with schizophrenia compared to 49 healthy controls (Nilsson et al., 2005). CSF KYNA was increased in 16 participants with schizophrenia compared to 29 healthy controls. In all participants kynurenine positively correlated with KYNA (Linderholm et al., 2012). This is important because kynurenine (KYN) crosses the blood brain barrier and KYNA does not because of the polar structure. Quinolinic acid (QUIN), a neuroactive metabolite of the kynurenine pathway, is normally presented in human brain and CSF; QUIN is an agonist of NMDA receptor. CSF quinolinic acid (QUIN) concentration from stable outpatients with schizophrenia (N = 22) and healthy controls (N = 26) was measured. No difference in CSF QUIN concentration between patients and controls was observed. CSF QUIN was positively correlated to CSF KYN and CSF KYNA in schizophrenia but not in controls. The CSF QUIN/KYNA ratio was significantly lower in schizophrenia than in controls. Authors argued for an over-activated and imbalanced kynurenine pathway, favoring the production of KYNA over QUIN in people with schizophrenia (Kegel et al., 2014). Finally, CSF KYN and KYNA concentrations were elevated in 23 participants with schizophrenia compared to 37 healthy volunteers (Schwieler et al., 2015).

3. Potential treatment mechanisms targeting kynurenine pathway

The kynurenine pathway is controlled by the immune system. Stimulation of the cholinergic system downregulates the inflammatory immune response which is known as cholinergic anti-inflammatory pathway (van Westerloo and van der Poll, 2005). Alpha-7 nicotinic receptor antagonism of KYNA may lead to the inhibition of the cholinergic anti-inflammatory pathway. In addition to the immunological mechanism, selective cyclooxygenase-2 (COX-2) inhibitors reduce KYNA concentration by a prostaglandin-mediated mechanism (Müller et al., 2005; Schwieler et al., 2005). COX inhibition has differential effects on kynurenine metabolism: while COX-1 inhibitors increase the levels of KYNA, COX-2 inhibitors decrease them. Therefore, psychotic symptoms and cognitive impairments observed during therapy with COX-1 inhibitors had COX-1 mediated increase of KYNA (Clunie et al., 2003; Schwieler et al., 2005; Tharumaratnam et al., 2000). COX-2 inhibition directly attenuates inflammation-induced inhibition of long-term potentiation, an animal model of cognition (Cumiskey et al., 2007; Müller et al., 2005). Animals with a genetic over expression of COX-2 had more prominent deficits in cognition, which were attenuated by a selective COX-2 inhibitor (Melnikova et al., 2006).

There are several studies suggestive of the anti-inflammatory properties of galantamine (Giunta et al., 2004; Ji et al., 2014; Wenk et al., 2002). There is evidence that galantamine alleviated inflammation in high-fat diet fed mice (Satapathy et al., 2011). In mice, inhibition of brain acetylcholinesterase suppressed systemic inflammation through a central muscarinic receptor-mediated and vagal- and α-7nAChR-dependent mechanism. Authors concluded that a clinically used centrally-acting acetylcholinesterase inhibitor can be utilized to suppress abnormal inflammation to therapeutic advantage (Pavlov et al., 2009). Similarly, there are several studies that have reported the anti-inflammatory role of memantine (Cho et al., 2013; Lindblad et al., 2012). Memantine attenuated morphine addictive