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

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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

A R T I C L E   I N F O

A B S T R A C T

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.

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

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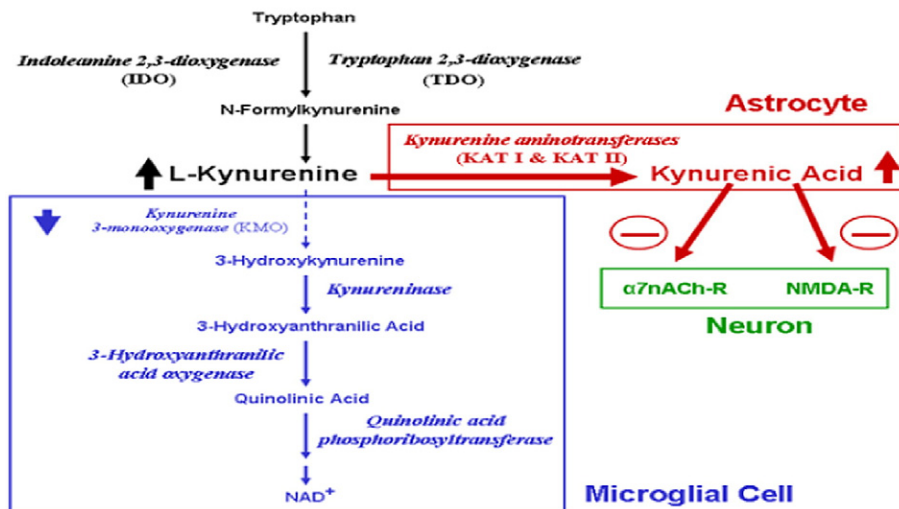
Fig. 1. Kynurenine pathway and cognitive impairments in schizophrenia and the association of α-7 nicotinic and the NMDA receptors. Kynurenine pathway metabolism is initiated by the oxidative ring opening of tryptophan by both indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase. In the brain, the metabolite L-kynurenine is enzymatically converted in microglial cells and astrocytes. In schizophrenia, there is a persistent reduction of microglial kynurenine 3-monooxygenase activity, along with increased L-kynurenine influx from the circulation. This results in increased kynurenic acid formation in astrocytes (Wonodi and Schwarcz et al., 2010). Galantamine and memantine through its α-7 nicotinic and NMDA receptors respectively may counteract the effects of KYNA thereby improving cognitive impairments.

behavior through its anti-inflammatory action and neurotrophic effects in rodents (Chen et al., 2012).

Early developmental increase in brain KYNA was associated with cognitive impairments in adult rodents which were reversed with galantamine (Alexander et al., 2013). Kynurenine aminotransferase II (KAT II) inhibitor (Fig. 1) restored nicotine-evoked glutamatergic activity in the cortex of rats and reduced brain KYNA concentration (Koshy Cherian et al., 2014). KAT II inhibitor reduced brain KYNA to 28% of baseline concentration, and prevented amphetamine- and ketamine-induced disruption of auditory gating and improved performance in a sustained attention task. It also prevented ketamine-induced disruption of performance in a working memory task and a spatial memory task in rodents and nonhuman primates, respectively (Kozak et al., 2014). Finally, the reduction of psychopathological symptoms and variations in 3-hydroxykynurenine levels (3-OHKYN; Fig. 1) as well as changes in KYNA/3-OHKYN and kynurenine/KYNA ratios are exciting for kynurenine pathway modifications. This may lead to novel target engagement for future antipsychotics discovery and development (Karakuła-Juchnowicz et al., 2014). Last, a 'two hit model' of schizophrenia to target both the glutamatergic system and the inflammatory system has been proposed (Muller and Schwarz, 2006).

4. Pharmacogenetics of kynurenine pathway

There are data suggestive that genetic factors have a significant role in the etiology of cognitive impairment in schizophrenia (Bilder et al., 2011; Glahn et al., 2007). Indoleamine 2,3-Dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO) and kynurenine 3-monooxygenase (KMO) genes are associated with cognitive impairments in schizophrenia (Aoyama et al., 2006; Miller et al., 2004). IDO, TDO and KMO genes may be of particular interest because of KYNA and the association with α-7 nicotinic and NMDA receptors. Specific SNPs associated with IDO and TDO genes are not known. CHRNA7 was the candidate gene of the α7nAChR in the NIMH Schizophrenia Genetics Initiative families (Freedman et al., 2001). The rationale of the SNPs that are proposed as predictors of treatment response

to the combination of galantamine and memantine is shown in Table 1. rs2275163 and rs1053230 are the KMO gene SNPs, rs904952 and rs2337980 in CHRNA7 gene, rs6923492 at the Glutamate (NMDA) Receptor, Metabotropic 1 (GRM1) and rs1018381, rs2619539, rs3213207, rs2619538 and rs760761 in the Dystrobrevin Binding Protein 1 (DTNBP1) gene. These SNPs are likely to predict response through α7nAChR and the NMDA receptors as shown in Fig. 1.

5. Conclusions and future directions

The combination of antipsychotic/s, galantamine and memantine may target dopaminergic, cholinergic and glutamatergic systems concurrently to improve cognitive improvements in schizophrenia (Buchanan et al., 2007; Geerts et al., 2015; Koola et al., 2014). Measuring KYNA and L-kynurenine concentrations could be the novel target engagement to measure the degree of cognitive impairment and to monitor prognosis with the treatment. There are ongoing studies to test this hypothesis (clinicaltrials.gov identifier NCT02234752). More stringent inclusion and exclusion criteria on antipsychotics (Geerts et al., 2015), anticholinergic treatment (Geerts et al., 2015; Wijegunaratne et al., 2014), careful analysis of smoking status (Geerts et al., 2015), paying more attention to pharmacokinetics and pharmacodynamics and using SNPs to predict response may enable the field to detect clinically meaningful effectiveness signal. KYNA and L-kynurenine concentrations decrease with anti-inflammatory treatment. Future studies are warranted to examine specific SNPs that may predict response in the kynurenine pathway with the anti-inflammatory treatment.

Contributors

Koola wrote the manuscript.

Table 1

Single nucleotide polymorphisms that may predict response to treatment through the α-7nAch and the NMDA receptors in the kynurenine pathway model.

Studies	Gene	SNPs	Cognition	Sample size	Effect size	P value	Function
Aoyama et al., 2006	Kynurenine 3-monooxygenase (KMO) gene	rs2275163–rs1053230–rs1053183 rs2275163–rs1053230–rs1053183	Haplotype distributions of KMO gene Independent sample confirmation analysis	SZ = 465 HC = 440 SZ = 480 HC = 448	Odds ratio = 4.1	0.00025 0.7	KYNA, a metabolite of the kynurenine pathway of tryptophan degradation, is an antagonist at N-methyl-D-aspartate and α7 nicotinic acetylcholine receptors and modulates glutamate, dopamine, and acetylcholine signaling NMDA receptor and α7nAChR
Holtze et al., 2012	KMO gene	rs1053230	CSF concentrations of KYNA	SZ = 17 HC = 50		0.002	NMDA and α7 nicotinic acetylcholine receptors
Wonodi et al., 2011 Wonodi et al., 2014	KMO gene	rs2275163 rs2275163	Predictive pursuit and visuospatial working memory endophenotypes Deficits in general neuropsychological performance	SZ = 248 HC = 228 SZ = 150 HC = 95	0.61 0.57	0.005 <0.001	NMDA and α7 nicotinic acetylcholine receptors
Freedman et al., 2001 Bakanidze et al., 2013	chromosome 15q13-14 locus of the Cholinergic Receptor, Nicotinic, Alpha 7 (CHRNA7 gene)	rs904952	Visual backward masking (VBM), a sensitive test for early visual information processing	50 families SZ = 224 HC = 224	0.48	<0.007 0.009	Alpha-7 nicotinic acetylcholine receptor
Rigbi et al., 2011	CHRNA7	rs2337980	Attention in Matching Familiar Figures Test and Continuous Performance Task	31 female smokers		0.01	Alpha-7 nicotinic acetylcholine receptor
Tregellas et al., 2011	CHRNA7	rs3087454	Posterior cingulate default network activity	SZ = 16		0.024	Alpha-7 nicotinic acetylcholine receptor
Liu et al., 2009	CHRNA7	rs3087454 rs1355920	Auditory oddball task	SZ = 20 HC = 43	r = 0.53	0.001	Alpha-7 nicotinic acetylcholine receptor
Greenwood et al., 2011	Glutamate Receptor, Metabotropic 1 (GRM1)	rs6923492	Verbal reasoning Spatial memory	SZ = 534 from 130 families		0.001	NMDA receptor
Burdick et al., 2006	Dystrobrevin Binding Protein 1 (DTNBP1)	rs1018381	Wide Range Achievement Test, Digit Span, Continuous Performance Test, California Verbal Learning Test, Controlled Oral Word Association Test and Trail Making Tests A&B	SZ = 213 HC = 126		0.0008	NMDA receptor
Donohoe et al., 2007	DTNBP1	rs2619539 rs3213207 rs2619538	Working memory	SZ = 52		0.009	NMDA receptor
Baek et al., 2012	DTNBP1	rs760761 rs1018381	Attention vigilance	SZ = 122 HC = 119		<0.001	NMDA receptor
Varela-Gomez et al., 2015	DTNBP1	rs2619539 rs3213207	Working memory (rs2619539; p = 0.01) Verbal memory (rs3213207; p = 0.02)	FEP = 238 HC = 47			NMDA receptor

SZ = schizophrenia, HC = healthy controls, FEP = first episode psychosis; r = correlation coefficient.

Conflict of Interest

Acknowledgements

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