AN ALTERNATIVE APPROACH TO UNDERSTAND SCHIZOPHRENIA: POLYAMINE HYPOTHESIS THROUGH NMDA RECEPTORS

ŞİZOFRENİYİ ANLAMAKTA ALTERNATİF BİR YAKLAŞIM: NMDA RESEPTÖRLERİ ARACILIĞI İLE POLİAMİN HİPOTEZİ

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Abstract

The glutamate hypothesis of schizophrenia based on the observations that administration of drugs that block N-methyl-D-aspartate (NMDA) glutamate receptors could induce schizophrenia-like symptoms. There are several evidences linking abnormal glutamatergic transmission to cognitive, negative, and positive symptoms of schizophrenia and the glutamatergic system is now a major focus for the development of new compounds in schizophrenia. The polyamines are omnipresent aliphatic molecules comprising putrescine, spermidine, spermine and agmatine. The polyamines and their biosynthetic enzymes are found throughout the body, including the central nervous system (CNS), where they display specific regional distributions in the CNS. The polyamines have an important role in the modulation of cell growth and on cell membrane functions. It was hypothesized that schizophrenia may be related to a general abnormality in neuronal membranes. Agmatine, a polyamine, selectively blocks the NMDA subclass of glutamate receptors in rat hippocampal neurons. There are also several evidences indicate that a relationship between polyamines and etiopathogenesis of schizophrenia. In this review, a new approach for understanding schizophrenia via NMDA receptors and their interaction with agmatine which is a biological active polyamine transmitter in brain is proposed.

Keywords: Agmatine, glutamate, NMDA receptors, polyamines, schizophrenia

Özet

Şizofrenide glutamat hipotezi N-metil-D-aspartat (NMDA) reseptör antagonistlerinin insanlarda ve deney hayvanlarda şizofreni semptomları oluşturmasına dayanır. Anormal glutamaterjik iletinin şizofreninin bilişsel, pozitif ve negative semptomları ile ilişkisine işaret eden birçok kanıt vardır ve glutamaterjik sistem şizofreni tedavisinde yeni ilaçların geliştirilmesi için güncel ve önemli bir odaktır. Poliaminler doğada ve canlı organizmalarda yaygın olarak bulunan putresin, spermidin, spermin ve agmatin gibi birden fazla amin içeren alifatik moleküllerdir. Poliaminler ve bunların biyosentetik enzimleri vücutta merkezi sinir sistemi de (MSS) dâhil olmak üzere yaygın olarak bulunur. Poliaminler hücre büyümesinin modülasyonu ve hücre membran işlevlerinde önemli bir role sahiptir. Şizofreninin sinir hücresi membranlarındaki genel bir anomalite ile ilişkili olduğu hipotezi ileri sürülmüştür. Bir poliamin olan agmatin sıçan hipokampal nöronlarında glutamaterjik NMDA reseptörlerini seçici bir şekilde bloke eder. Poliaminlerle şizofreni hastalığının etyopatogenezi arasında ilişkiye işaret eden çeşitli kanıtlar da mevcuttur. Bu gözden geçirme yazısında biyolojik aktif bir nörotransmitter olan agmatin ile NMDA reseptörleri arasındaki etkileşme üzerinden şizofreninin anlaşılmasına yönelik yeni bir yaklaşım ileri sürülmektedir.

Anahtar Kelimeler: Agmatin, glutamat, NMDA reseptörleri, poliaminler, şizofreni

1. Introduction

Schizophrenia is a serious mental disorder with a challenging rational pharmacotherapy and is considered a neurodevelopmental disease. It is a disease affecting up to 1% of the population (Uzbay, 2009).

Plain hypothesis on schizophrenia is associated with excessive stimulation of dopamine D2 receptors in the associative striatum, with a lack of stimulation of dopamine D1 receptors in prefrontal cortex. Thus, drug therapies are based on the efficacy of chlorpromazine, discovered over 50 years ago. These drugs block dopamine D2-like receptors and are effective at primarily treating positive symptoms in a subset of patients. Unfortunately, current therapies are far from adequate, and novel treatments require (Laruelle, 2014; Perez and Lodge, 2014). In addition, the essential processes associated with schizophrenia still remain uncertain. Thus, new ways of searching to understand and treatment of schizophrenia is already ongoing.

Here, in this review, a new approach for understanding

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schizophrenia via NMDA receptors and their interaction with agmatine which is a biological active polyamine transmitter in brain is proposed.

2. Glutamate hypothesis in schizophrenia

Glutamate (Glutamic acid) (Figure 1) was initially discovered to be a neurotransmitter in insect studies in the early 1960s. L-glutamate is the major excitatory neurotransmitter in the mammalian CNS, being present in over 50% of nervous tissue. Glutamate has a key role for several biological (learning and memory, cognition) and pathological (epilepsy, neurodegenerative events) processes in mammals (Johnson, 1972).
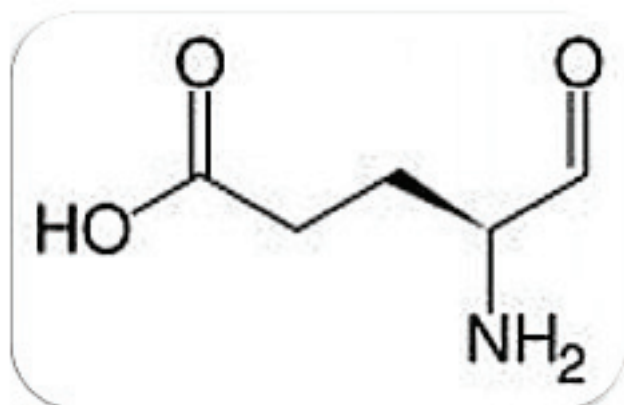
Figure 1. Glutamic acid (glutamate)

Glutamate acts via two classes of receptors. They are ligand gated ion channels or ionotropic receptors (i.e. NMDA, AMPA and kainite) and G-protein coupled (methabotropic) receptors (i.e. mGluR1-R8). NMDA receptors are ionotropic receptors mediating glutamatergic neurotransmission and play a role in several basic functions in the central nervous system (CNS), from regulating neurodevelopment and synaptic plasticity, learning and memory formation, cognitive processes, rhythm generation necessary for locomotor activity and breathing, and excitotoxicity. Due to their complex involvement in the above processes, NMDA receptors have been established to play a role in the etiopathology of several neuropsychiatric disorders such as ischaemia and traumatic brain injury, neurodegenerative disorders, pain syndromes, addiction, affective disorders and such neurodevelopmental disorders as autism or schizophrenia. NMDA receptors contain multiple types of subunits with distinct functional and pharmacological properties making the picture more complex. These receptors also offer multiple binding sites to be targeted with pharmacological agents (Gonda 2012; Rubio et al., 2012). A Schematic representation of a typical NMDA receptor has been shown in Figure 2.

The glutamate hypothesis of schizophrenia, proposed over two decades ago. This hypothesis based on the observations that administration of drugs that block N-methyl-D-aspartate (NMDA) glutamate receptors, such as ketamine and phencyclidine, could induce schizophrenia-like symptoms. NMDA antagonists also
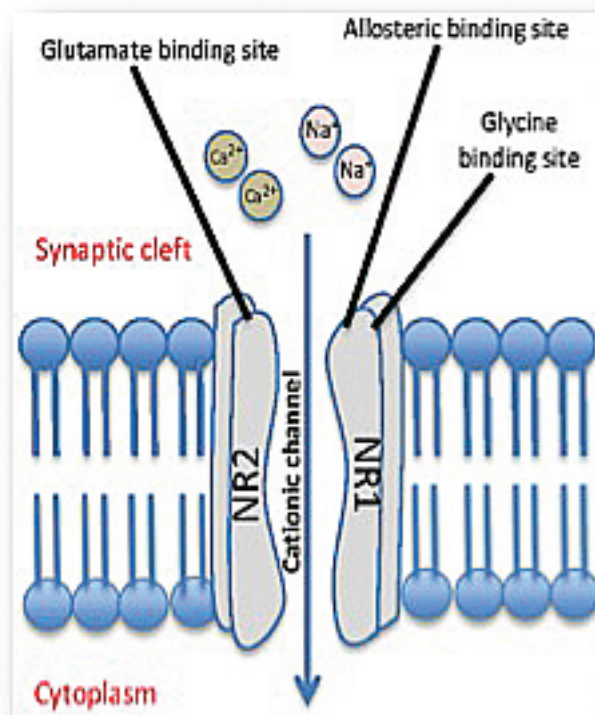
Figure 2. Schematic representation of a typical NMDA receptor. The NMDA contains four subunits, two glycine binding NR1 subunits and two glutamate binding NR2 subunits, and allows for cationic influx from the synaptic cleft into the cell (from Lakhan et al., 2013)

worsen positive, negative, and cognitive symptoms in patients with schizophrenia (Krystal et al., 1994; Lahti et al., 1995; Malhotra et al., 1997; Merritt et al., 2013). Thus, there are several evidences linking abnormal glutamatergic transmission to cognitive, negative, and positive symptoms of schizophrenia and the glutamatergic system is now a major focus for the development of new compounds in schizophrenia. Some new drugs due to glutamatergic mechanisms such as potent mGlu2/3 receptor agonism were also under the research in clinical phase studies (Patil et al., 2007). Some conflict results have been obtained from these researches. For example, while pornaglutemad methionil (LY2140023) which is an mGlu2/3 agonist failed to meet the primary efficacy end point, ADX71149 which is the mGlu2 positive allosteric modulator met the primary objectives of safety, tolerability and established an adequate effect on negative symptoms of schizophrenia (Hopkins, 2013).

3. Polyamines and agmatine

The polyamines are omnipresent aliphatic molecules comprising putrescine, spermidine and spermine, which contain 2, 3 and 4 amino groups, respectively. In addition, the guanidino-amine agmatine, whose presence in mammalian brains was discovered much more recently than that of the other polyamines, may also be considered among this group. The polyamines and their biosynthetic enzymes are found throughout the body, including the CNS, where they display specific regional distributions in

the CNS. The polyamines have an important role in cell proliferation and demonstrate both pro- and antiapoptotic effects. They are involved in many signaling pathways through their effects on G proteins, protein kinases, nucleotide cyclases and receptors, as well as by their regulation of the expression of proteins involved in these processes. Polyamines such as spermine and agmatine have been shown to be released from synaptic vesicles on depolarization, indicating that the polyamines may function as neuromodulators. They also influence the properties of several neurotransmitter pathways known to be involved in mental disorders, including the catecholamine, GABA, nitric oxide and glutamate. Alterations in the expression and activity of polyamine enzymes, as well as changes in the levels of the individual polyamines, were showed in various psychiatric conditions, including schizophrenia, mood disorders, anxiety and suicidal behavior. Additionally, these components have been found to be altered by various psychiatric treatments (Fiori and Turecki, 2008).

Agmatine was discovered in 1910 by Albrecht Kossel, the German scientist who first identified the substance in herring sperm (Kossel, 1910). Agmatine which is an endogenous biogenic polyamine, is synthesized from amino acid L-arginine with a reaction catalysed by enzyme arginine decarboxylase and it is metabolized by enzyme agmatinase to putrescine, spermine and spermidine, other polyamines (Reis and Regunathan, 2000). It is synthesized, stored, and released in brain and is distributed with highest concentrations in hypothalamus, forebrain, and cerebral cortex (Reis and Regunathan, 1999).

Agmatinergic neurons were present in the cerebral cortex (cingulate, primary somato-sensory and auditory cortices, and the subiculum), the lower brainstem (the nucleus tractus solitarii and pontine parabrachial complex, and periventricular areas including the dorsolateral nucleus, locus coeruleus and dorsal raphe), the midbrain (ventral tegmental area and periaquaductal gray) and the forebrain (preoptic area, amygdala, septum, bed nucleus of the stria terminalis, midline thalamus, and the hypothalamus) (Otake et al., 1998). Thus, it has been proposed that agmatine meets several criterions as a new neuromodulator or neurotransmitter in brain (Reis and Regunathan, 1998; Uzbay, 2012a). A possible agmatinergic synapse is also illustrated in Figure 3. However, major professional societies such as IUPHAR have not adopted this concept yet.

4. Polyamines, agmatine and schizophrenia

It has been showed that agmatine exhibited several pharmacological actions (i.e. anticonvulsant, antinociceptive, anxiolytic and antidepressant) and neuroprotective effects in experimental animals by interacting with imidazoline, alpha-2 adrenergic and NMDA receptors at a dose range from 1 to 100 mg/kg (Uzbay, 2012a; Uzbay, 2012b).

Agmatine selectively blocked the NMDA subclass of glutamate receptor, but not AMPA or kainite channels in rat hippocampal neurons (Yang and Reis, 1999). In addition, agmatine is an inhibitor of all isoforms of
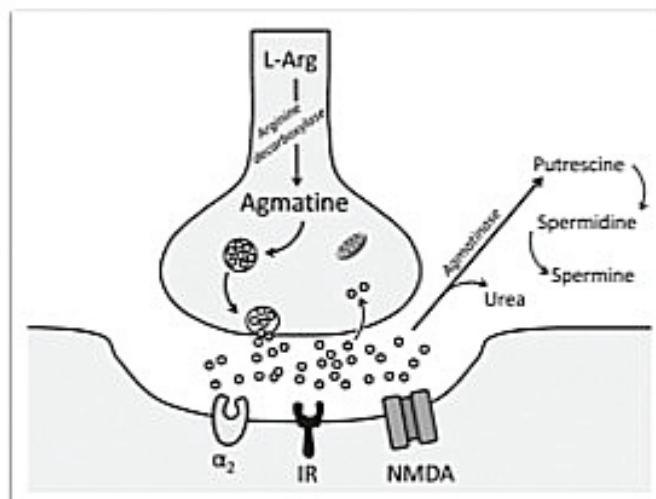
Figure 3. Schematic representation of agmatinergic synapse (IR= Imidazoline receptors) (from Uzbay, 2012a).

enzyme nitric oxide synthase (NOS) dose-dependently and competitively with the substrate L-arginine (Galea et al., 1996). Furthermore, it may inhibit glutamate releasing from presynaptic nerve terminals and prevent the activation of postsynaptic NMDA receptors by inhibiting postsynaptic NO generation and suppressing adenylate cyclase-cGMP cascade in presynaptic area (Uzbay and Oglesby, 2001) (Figure 4).
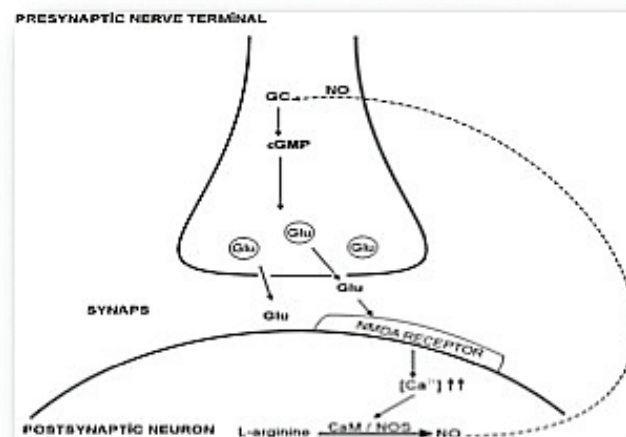
Figure 4. L-arginine is converted to NO in the postsynaptic neuron. The NO that is produced diffuses back to the presynaptic neuron, where it enhances the release of glutamate via guanylate cyclase (GC) and cGMP. Glutamate that is released from the presynaptic terminal activates NMDA receptors, and Ca^{2+} enters and, via calmodulin (CaM), activates the NOS again (from Uzbay and Oglesby, 2001).

Agmatine attenuates severity of morphine (Aricioglu-Kartal and Uzbay, 1997) and ethanol (Uzbay et al., 1997) withdrawal syndromes in rats. It has been suggested that the inhibitory effects of agmatine on NO-NMDA pathway may be responsible for the beneficial effects on ethanol and morphine dependence (Aricioglu-Kartal and Uzbay, 1997; Uzbay et al., 1997; Uzbay and Oglesby, 2001).

If considering the inhibitory effects of agmatine on NMDA receptors either directly or via NOS inhibition, it could be expected that agmatine may cause psychosis or worsen positive and negative symptoms of schizophrenia like other NMDA receptor antagonists such as phencyclidine and ketamine. Indeed, several evidences indicate that there may be a link between schizophrenia and polyamines.

The polyamines have an important role in the modulation of cell growth and on cell membrane functions. It was hypothesized that schizophrenia may be related to a general abnormality in neuronal membranes. Thus, polyamines may associate with etiopathogenesis of schizophrenia (Ramchand et al., 1994). It has been reported that poliamines like spermidine and spermine, might be involved in pathogenesis of schizophrenia. Some previous reports indicated significantly high levels of agmatine metabolites (i.e, spermine, spermidine) in blood, cerebrospinal fluids or brain tissue in patients with schizophrenia (Richardson-Andrews, 1983; Andrews, 1985; Ramchand et al., 1994) and these polyamines are the end products of agmatine metabolism. Furthermore, high levels of plasma asymmetric methyl-arginines, (i.e. asymmetric dimethylarginine), which is the precursor of cell-signaling molecules such as NO and agmatine, accompanied schizophrenia (Das et al., 1996; Kopieczna-Grzebieniak and Goss, 2005).

Previously, Uzbay et al. (2010) showed agmatine caused disruption of prepulse inhibition (PPI) of acoustic startle reflex and it potentiated significantly apomorphine-induced disruption of PPI. In this study, agmatine exhibited this action by a relatively high dose (160 mg/kg). Because PPI test is accepted as a screening test for experimental schizophrenia studies, this observation implies a strong relationship between agmatine and schizophrenia. Thus, Uzbay et al. hypothesized that because spermine and spermidine, agmatine metabolites, were found very high in patients with schizophrenia, and agmatine disrupts PPI in rats, unbalanced and/or excessive agmatine release may be related to schizophrenia. Results of the recent clinical study by Uzbay et al. (2013) supported to the hypothesis. In this study, significantly increased plasma levels of agmatine in patients with schizophrenia were found compared to healthy individuals (Figure 5).
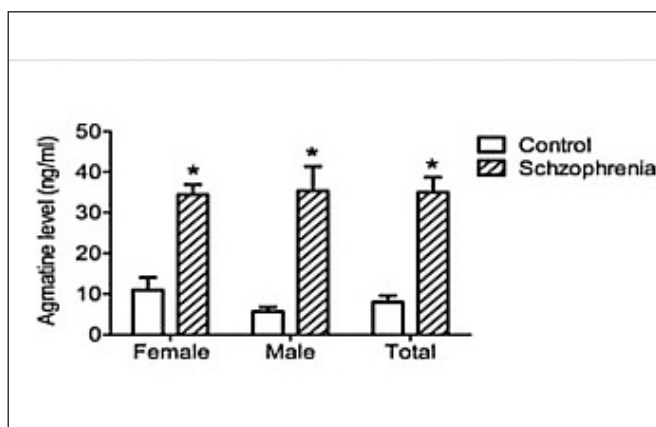
Figure 5. Mean plasma agmatine levels in the female, male and whole groups of healthy controls and of patients with schizophrenia (*p < 0.05, Mann-Whitney U test) (from Uzbay et al., 2013).

The receiver-operator characteristic (ROC) curve ROC analysis of the data indicated that the possibility of measuring higher agmatine levels in patients with schizophrenia than in normal individuals was as high as 96% (Figure 6). The ROC curve analysis is a fundamental tool for diagnostic test evaluation in medicine (Zou et al., 2007). In an ROC curve, the analysis sensitivity and specificity for different cut-off points of a parameter are calculated. The sensitivity of the agmatine level measurements between patients and controls was also found to be statistically significant. All of these evaluations imply that the measurement of agmatine in the plasma may have importance as a diagnostic and/or follow-up test in schizophrenia.
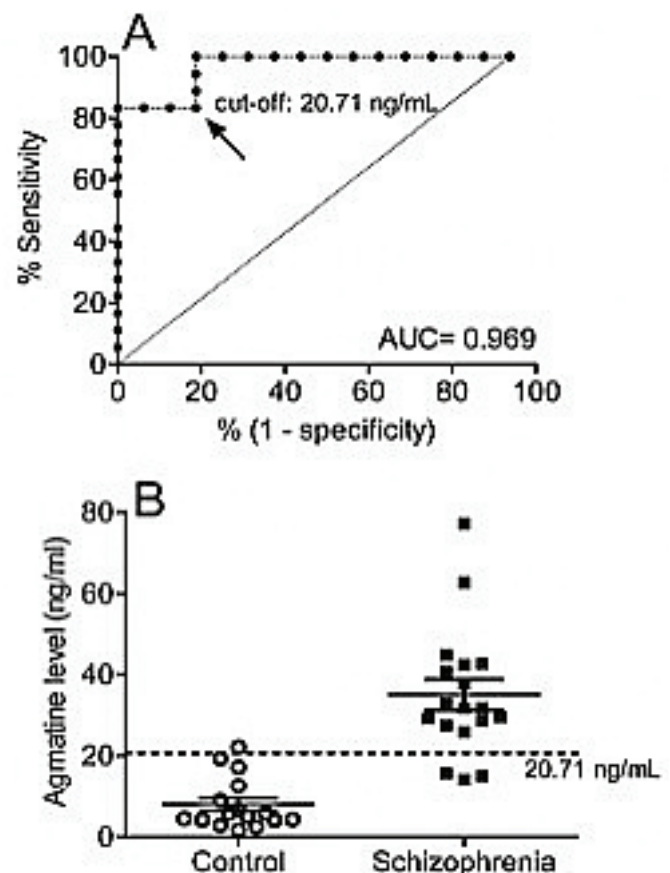
Figure 6. The receiver-operator characteristic (ROC) curve for plasma agmatine levels in schizophrenia (A) and the individual distribution of plasma agmatine levels in healthy controls and in patients with schizophrenia (B) (from Uzbay et al., 2013).

5. Conclusion

In conclusion, these evidences clearly support to hypothesis that polyamines and agmatine are related to etiopathogenezis of schizophrenia. NMDA-NO antagonistic action of agmatine may be responsible for its relation with schizophrenia. Agmatine and/or polyamines may also be as an indicator for diagnosis and treatment of schizophrenia.

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