New Pharmacological Approaches to the Treatment of Schizophrenia

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Abstract

Schizophrenia is a serious mental disorder with a challenging rational pharmacotherapy. Neurochemical transmission in the dopaminergic system, especially via D₂ receptors, and related changes in postsynaptic signal transduction are very important in both the formation of schizophrenia and current pharmacotherapeutic treatment with antipsychotic drugs. Blocking the serotonergic 5-HT₂A and 5-HT₂C receptors is growing importance with regard to the action mechanisms of new generation antipsychotic medications. Recent preclinical and clinical data show that dysfunction of central neurotrophins, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurophin-3 (NT-3) might contribute to impaired brain development and neuroplasticity, leading to schizophrenia. In addition, some recent studies suggest that there is an important relationship between alcohol and substance addiction, and schizophrenia. There is also some preclinical data indicating that the central nitrergic system and agmatine—a biologically active agent produced after decarboxylation of arginine—might be interesting and important targets for understanding the etiopathogenesis of schizophrenia and for development of new drugs. Selective dopamine D₃ receptor antagonists, specific agonists for metabotropic and NMDA receptors of the glutamatergic system, and nicotinic α-7 receptor agonists were reported in preclinical and a limited number of clinical studies as potential new targets for schizophrenia treatment. In this review, new advances in the pharmacotherapy of schizophrenia and possible new targets are discussed in the light of the current literature.

Key Words: Agmatine, antipsychotic drugs, dopaminergic system, nitric oxide, schizophrenia

INTRODUCTION

Schizophrenia is considered to be the most serious psychiatric disorder. It is an important neurodevelopmental disorder that affects about 1% of the general population. Neurodevelopmental disorder causes a complex spectrum of problems by affecting almost all brain functions, including perception, cognitive functions and emotions. Additionally, genetic, environmental, and social factors contribute to the neurodevelopmental problems associated with schizophrenia—all of which are important factors that affect the treatment of the disorder (Stefan et al., 2002; Uzbay, 2007).

If we consider that the incidence of schizophrenia is not affected by demographic factors, we can presume that there are over 60 million schizophrenia patients worldwide. Records for Turkey are about 350 thousand patients. Disability of finding a certain solution by recent pharmacotherapy, recent drug’s severe side effects, most commonly causes drug discontinuation or drug alterations and lower drug compliance ratios of schizophrenia patients are the reasons of new pharmacological seeking. Researchers continue to search for more effective and tolerable drugs with fewer side effects. Clarifying the etiopathogenesis of schizophrenia and the development of new drugs to treat schizophrenia treatment remain the most heavily invested areas of neuropsychopharmacology. Intensive research has resulted in the development of new molecules for the treatment of schizophrenia that will be used in the near future. Some have successfully passed the preclinical processes with encouraging results in limited number of clinical studies. In addition,
research into the etiopathogenesis of schizophrenia has revealed some important results.

The aim of this review was to discuss the development of new drugs for the treatment of schizophrenia that have been approved for use in near future and actual innovations to reveal schizophrenia etiopathogenesis by compilation of current literature.

Basic Approaches in the Current Treatment of Schizophrenia

Neurochemical transmission in the dopaminergic system, especially via D₂ receptors, and related changes in postsynaptic signal transduction are very important in both the development of schizophrenia and its current pharmacotherapeutic treatment with antipsychotic drugs. Along with D₃ and D₄ receptors, dopamine D₂ receptors and their synaptic localization remain important in schizophrenia pharmacotherapy. While efforts to reduce the extrapyramidal side effects of dopamine blockade, there seemed, other neurotransmitter systems can also take place in pharmacotherapy. In particular, serotonergic 5-HT₂ₐ and 5-HT₂c receptor blockade is the mechanism of action of new-generation antipsychotics mechanism of action (Table 1). The hypothesis that there is relationship between the serotonergic system and schizophrenia predates the dopaminergic hypothesis. The theory was introduced in the 1950s (Wolley and Shaw, 1954), following the discovery that the hallucinogen lysergic acid diethyl ester (LSD) acts via the serotonergic system. There is also a functional interaction between the serotonergic and dopaminergic systems. For instance, blockage of 5-HT₂ₐ receptors can reinforce dopaminergic activity. In contrast to classic antipsychotic drugs, many recently developed atypical antipsychotics bind to 5-HT₂ₐ receptors more than to dopamine D₂ receptors and bind with higher affinity than classical antipsychotics (Stefan et al., 2002; Schatzberg et al., 2003).

Neurodevelopmental dysfunction in the GABAergic and glutamatergic systems are also related to the development of schizophrenia (Konradi and Heckers, 2001; Stefan et al., 2002). Recently, neuroplasticity concept takes place in schizophrenia formation. Contemporary research into the etiopathogenesis of schizophrenia focuses on the expanding role of neurogenesis and neurotrophic factors, primarily in the dopaminergic system, but also in the serotonergic, GABAergic, and glutamatergic systems (Frost et al., 2004; Showal and Weizman, 2005).

Recent Improvements in the Neurobiology of Schizophrenia and their Importance in the Treatment of Schizophrenia

Schizophrenia and Neuroplasticity

Antipsychotic drugs have a latent period of time to act through brain. Scientists thought that the latent period of antipsychotics to become active is a reason of a hypothesis that necessity of time to form synaptic plasticity and neurogenesis therefore, they attract attention to effects of antipsychotics on neuroplasticity. The most frequently analyzed classical antidopaminergic drug is haloperidol and most studies on haloperidol focused on the striatum. Chronic haloperidol injection in rats increased striatal volume (Chakos et al., 1998). A number of studies reported that haloperidol increases striatal volume

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<th>Table. Comparison of receptor affinity between some atypical antipsychotics and haloperidol.*</th>
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*Modified from Uzbay, 2007. 0: No receptor affinity; +: low receptor affinity; ++: moderate receptor affinity; +++: high receptor affinity; ++++: very high receptor affinity.
**High receptor affinity to D₂ receptors (Xiberas et al., 2001).
in schizophrenia patients (Swayze et al., 1992; Bilder et al., 1994; Doraiswamy et al., 1995; Gur et al., 1998; Shiabuddin et al., 1998). In rats that were chronically administered haloperidol striatal axon endings increased in volume. When haloperidol treatment was withdrawn the effect was lost (Benes et al., 1985; Uranova et al., 1991; Kerns et al., 1992).

Haloperidol’s effect of increasing striatal volume is described as follows: Chronic haloperidol administration blocks dopaminergic D2 receptors, followed by adenylate cyclase activation and an increase in cAMP levels. Increased cAMP levels activate protein kinase A (PKA). While PKA modulates synaptic functions by phosphorylating ion channels and receptors on synapses, it also activates regulating factors of gene expression, such as cAMP response element-binding protein (CREB). CREB activation via PKA has an important role in neuroplasticity and formation of memory. Chronic haloperidol treatment decreases synaptic formation and stabilization can be remedied. This effect can be useful in treating the negative symptoms of schizophrenia (Konradi and Heckers, 2001).

Research on atypical antipsychotics has focused more on clozapine and olanzapine. The effects of these drugs on the striatum are weaker than those of haloperidol. The effect of clozapine and olanzapine on neuroplasticity, excluding the striatum, but mainly prefrontal cortex and other brain localizations investigated primarily on gene expression. Research indicates that these drugs induce cfos expression and that the effect on the striatum is weaker than that of conventional antipsychotics like haloperidol, but that they are more effective on areas other than striatum (Nguyen et al., 1992; Wan et al., 1995; Robertson and Fibiger, 1996; Deutsch and Duman, 1996; Leveque et al., 2000), which could be due to the fact that these atypical drugs have fewer extrapyramidal side effects.

Nerve growth factor (NGF) has an important role in cholinergic neuron development and postmortem studies of schizophrenia patients attract attention to lower cholinergic activity. Plasma NGF levels were reported to be significantly lower in schizophrenia patients than in normal controls before treatment and after treatment, primarily with haloperidol, but also with other antipsychotics (Berzani et al., 1999; Parikh et al., 2004a; Parikh et al., 2004b). In the light of these results it can be surmised that NGF deficiency might play a role in the symptoms of cognitive degeneration in schizophrenia and classical antipsychotic treatment did not achieve a meaningful effect on NGF deficiency.

Serum obtained from both the dorsolateral frontal cortex and hippocampus of schizophrenia patients contained low levels of brain-derived neurotrophic factor (BDNF) (Durany et al., 2001; Toyoka et al., 2002; Weickert et al., 2003). In rats exposed to stress, and in schizophrenia patients quetiapine, a new generation atypical antipsychotic, and clozapine had some positive effects on reduced BDNF levels, respectively (Grillo et al., 2007).

Postmortem studies of schizophrenic brain tissue showed that neurotrophin 3 (NT-3) concentrations in the frontal and parietal cortical regions were significantly reduced (Durany et al., 2001). It is commonly accepted that due to NT-3’s role in the development of dopaminergic neurons it can be considered as important a neurotensin as NGF and BDNF.

Clozapine treatment inhibited expression of a proapoptotic receptor (p75NTR) in a dose-dependent manner in the motor neurons of transgenic mice (Turner et al., 2003); however, its importance remains to be determined. While haloperidol administration down regulated the density of TrkB, an antiapoptotic receptor, in the rat hippocampus, clozapine treatment did not have a significant effect on TrkB receptor density (Parikh et al., 2004a).

Numerous studies report increased neurotrophin levels in the hippocampus, forebrain, and prefrontal cortex in schizophrenia patients and schizophrenic rats. Additionally, mainly with haloperidol but also with other antipsychotic treatment decreased to normal levels even though decreased more than normal levels (Shoval and Weizman, 2005). These elevations can be considered to be a reaction to problems in early neuronal development.

The direct effects of antipsychotic drugs on neuroplasticity can be more important than their effects on the dopaminergic and serotonergic neurochemistry systems. The effect of haloperidol and other antipsychotics on hippocampal neuroplasticity supports this idea; however, haloperidol increased neurogenesis in the gerbil hippocampus (Shoval and Weizman, 2005) and had no effect in the rat hippocampus (Malberg et al., 2000), suggesting that antipsychotic effects on neurogenesis could be species dependent. There is a need for research on brain areas more important to schizophrenia than the hippocampus, such as the thalamus and prefrontal cortex.

The Relationship between Schizophrenia, and Alcohol and Drug Addiction

A relationship has been proposed between alcohol and drug addiction, and schizophrenia (Batel, 2000;
Davidson, 2005); however, the neurobiological basis of this relationship is not clearly defined. There are reports on the relationship between a lack of dopamine D₂ receptors or their desensitization, and reward deficiency syndrome, and alcohol and drug addiction (Blum et al., 2000; Comings and Blum, 2000; Bowirrat and Oscar-Berman, 2005). Reward deficiency syndrome could be associated with other addictions, such as pathological gambling and hypersexuality; beyond this, it is associated with disorders characterized by exaggerated impulsive-compulsive behaviors, including attention deficit hyperactivity disorder, Tourette’s syndrome, schizophrenia, and antisocial behavior (Blum et al., 2000; Comings and Blum, 2000; Bowirrat and Oscar-Berman, 2005). Interestingly, recent results of preclinical (Unsalan et al., 2008) and clinical (Kranzler et al., 2008; Anton et al., 2008) trials show that new generation atypical antipsychotics are more effective in the treatment of alcohol addiction. Results of research into the neurobiological basis of the relationship between alcohol addiction and schizophrenia, made us think about beside known role of neurotransmitters in schizophrenia etiopathogenesis any other neurotransmitters can also have a role in it.

**Central Nitrergic System and Schizophrenia**

Nitric Oxide (NO) is a labile, free radical gas with a very short half-life (6-10 s) and an important biological role in the central nervous system as well as the peripheral system. NO is synthesized from precursor L-arginine via NO synthase (NOS) (Snyder and Bredt, 1992). It was suggested that NO might be a novel neurotransmitter in the central nervous system and, therefore, indicates the existence of an L-arginine-NO pathway (Moncada and Higgs, 1993). NO has beneficial scientific evidences in nociception (Moore et al., 1993), learning and memory (Yamada et al., 1995), anxiety (Yıldız et al., 2000), epileptic activity (Kaputlu and Uzbay, 1997), eating and drinking behaviors (Calapai et al., 1992), the release of some important neurotransmitters such as dopamine (Yamada et al., 1995), and development of physical dependence to alcohol, opioids, nicotine, and other substances (Uzbay and Oglesby, 2001).

![Figure 1. Agmatine synthesis and metabolism.](image)
A relationship between modification of the central nitrergic system and schizophrenia has been reported. Results from post mortem brain investigations (Karson et al., 1996; Yao et al., 2004), as well as biochemistry investigations on plasma samples of schizophrenic patients (Yanık et al., 2003; Taneli et al., 2004) indicate that there is an increase in NO in schizophrenic patients. These data also support the reported beneficial effect of NO in a schizophrenic mouse model in response to L-NAME administration, an NOS enzyme blocker (Klamer et al., 2001). In contrast, preclinical (Black et al., 1999) and clinical (Bernstein et al., 2005) data suggest there is need for further research. In order to clarify the role of the nitrergic system in the development of schizophrenia research is ongoing.

**Agmatine and Schizophrenia**

Agmatine is a cationic amine that is synthesized from arginine via the enzyme arginine decarboxylase (Figure 1). Agmatine is a biologically active substance that binds to imidazoline and \( \alpha_2 \)-adrenergic receptors with high affinity (Li et al., 1994; Piletz et al., 1995; Regunathan and Reis, 1996).

In rodents agmatine reduced many of the symptoms of morphine and alcohol withdrawal syndrome. Agmatine's affect on NOS inhibition or NMDA receptor blockage may be responsible for this action (Arıcıoglu-Kartal and Uzbay, 1997; Uzbay et al., 2000). The NOS inhibiting and NMDA receptor antagonistic properties of agmatine can be useful in treating excitatory neuropsychiatric disorders or can be used as an adjunct to recent prescribed drugs effects to treat neuropsychiatric disorders. Because the negative symptoms of schizophrenia can be related with glutamate hypofunction, NMDA receptor blockage effect of agmatine can contribute schizophrenia development. In animal models, the induction of schizophrenia-like symptoms with spermine and spermidine, which are final products of the arginine metabolism pathway (Ramchand et al., 1994), strongly supports the hypothesis that agmatine can be a new target in the treatment of schizophrenia. Results of our previous research also support this hypothesis (Uzbay et al., 2008a,b; Uzbay et al., 2009). In the present study, by using the prepulse inhibition of the startle reflex (PPI) method, agmatine produced a response similar to apomorphine's to form a model of schizophrenia (Swerdlow et al., 2000) and when given consequently strengthen apomorphine's effects. Research on this effect is ongoing.

**New Schizophrenia Drugs**

**Glutamate Receptor Agonists**

Glutamate is the most important excitatory neurotransmitter in the central nervous system. The role of glutamate in anxiety, epilepsy, and modulation of drug addiction withdrawal symptoms is well known. Glutamate released pre-synaptically acts on its own receptors, which are localized post-synaptically. Recently, numerous studies on glutamate-specific receptors, such as NMDA receptors and metabotropic glutamate receptors, were conducted to determine if they have a fundamental role in the physiopathology of schizophrenia and if they could be the target of pharmacotherapy (Lindsley et al., 2006; Harrison, 2008). The relationship between the negative symptoms of schizophrenia and glutamate hypofunction is under investigation; however, drugs that have evident dopaminergic influence have limited effects on schizophrenia's negative symptoms. In contrast, in both experimental animals and humans NMDA receptor antagonists, such as phencyclidine and ketamine, induced positive, negative, and cognitive schizophrenic symptoms (Tsai and Coyle, 2002; Lindley et al., 2006). Functional impairment of group I as mGluR1 and mGluR5 and group II as mGlu2/3 metabotropic glutamate receptors may cause schizophrenia (Pietraszek et al., 2006; Imre, 2007). While a potent mGlu2/3 receptor agonist (LY379268) reduced locomotor hyperactivity and motor dysfunction in a schizophrenia animal model via NMDA antagonists like phencyclidine and ketamine, it was ineffective in the PPI model of schizophrenia in which habituation can be conceptualized as a fundamental gating mechanism that filters sensory information and inhibits response to disruptive or extraneous information (Imre, 2007). These data suggest the effectiveness of LY379268 in schizophrenia will be limited.

Modulating the NMDA/glycine-binding domain with complete or partial glycine agonists like glycine, D-serine, and D-cycloserine was considered effective in a limited number of clinical schizophrenia cases. In order to enhance glycine activity, glycine transport inhibitors, such as NFPS (ALX-NPS 5407), Org 24461/24598, SSR 504734, and sarcosine (N-methylglycine), may prove to be novel schizophrenia medications in the near future (Javitt, 2002, Jawitt, 2008). There were some clinical trials performed with sarcosine, especially in Taiwan, but its safety could not be proven. While sarcosine in combination with clozapine elicited no effect, in combination with risperidone it elicited an effect greater than risperidone's alone on the positive and negative symptoms of...
schizophrenia (Lane et al., 2005; Jawitt, 2008). Notable results obtained in Asia using sarcosine in schizophrenia patients is viewed cautiously by American and European authorities. Although positive results were obtained with the sarcosine and risperidone combination in those Asian studies, the mechanism of action of this combination’s ineffectiveness is yet to be determined.

In order to evaluate the effectiveness of full or partial glycine agonists, such as glycine and D-serine, in schizophrenia treatment, results of a performed broadly participated, controlled CONSIST study elicits the effects of these drugs are not significantly different from placebo on the cognitive and negative symptoms of schizophrenia (Buchanan et al., 2007). In order to clarify the exact effects of glycine agonists in the treatment of schizophrenia, further research is necessary.

**Selective Dopamine D₃ Receptor Antagonists**

Reports of the importance of dopamine D₃ receptors in schizophrenia’s pathophysiology and treatment have been published. Selective D₃ receptor antagonists were synthesized and positive results obtained in experimental animals treated with these drugs. Recently, selective SB 277011 and S 33084, and non-selective asenapine D₃ receptor antagonists were reported to be effective in reducing the positive and negative symptoms of schizophrenia, and in improving cognitive functions in schizophrenic animal models (Joyce and Millan, 2005; Micheli and Heidbreder, 2006; Gyertyan and Saghy, 2007). Asenapine also had an effect on 5-HT₂₅α, 5-HT₂₈α, 5-HT₂₅ε, 5-HT₂₇τ, and adrenergic alpha₂ receptors other than D3 receptors (Shahid et al., 2008).

**Selective Nicotinic α-7 Receptor Agonists**

Another group of receptors shown to play a role in the pathophysiology of schizophrenia is the cholinergic α-7 nicotinic receptors. There is established a bound between especially reduced hippocampal alpha 7 nicotinic receptor number or activity and schizophrenia (Woodruff-Pak and Gould, 2002; Olincy and Stevens, 2008). The ability to stimulate hippocampal interneurons to increase the release of GABA by specific α-7 nicotinic receptor agonists is a new focus of schizophrenia treatment. Selective agonists like 3-((2,4 dimethoxy)benzyliden-anabaseine (DMXBA) were effective in animal models and a limited number of clinical cases, especially on cognitive dysfunction in schizophrenia (Martin et al., 2004; Martin and Freedman, 2007).

**CONCLUSION**

In conclusion, selective D₃ receptor antagonists, metabotropic glutamate, specific NMDA receptor agonists, and nicotinic α-7 receptor agonists are expected to be used in the treatment of schizophrenia as new generation antipsychotics. The central nitrergic system and, in particular, agmatine may be an interesting and important target for both understanding the etiopathogenesis of schizophrenia and for the discovery of novel medications.

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