DOI: 10.5455/bcp.20130320010604

Antipsychotics: Neurobiological Bases for a Therapeutic Approach

Salih Gumru[1], Feyza Aricioglu[1]

ÖZET:

Antipsikotikler: Terapötik yaklaşım için nörobiyolojik temeller

Şizofreninin patofizyolojisi üzerine yapılan çalışmalar zaman içinde ilgi çekici bir serüvene dönüşmüştür. İddialar, pozitif semptomlara neden olan mezolimbik sistem kaynaklı dopaminerjik aktivite artışını işaret eden basit bir patolojik yaklaşımla başlayarak; birçok reseptör, çeşitli hücre içi sinyal yolakları ve gen - çevre etkileşimlerini de içeren farklı öğelerin katkısının keşfedilmesiyle çeşitlenmiştir. Bahsi geçen yeni yaklaşımlar, özellikle şizofrenide görülen negatif semptomlar ile kognitif fonksiyon bozukluklarının tedavisinde önemlidir. Birçok farklı mekanizmanın hastalığın nedeni olabileceği iddiaları, hipotetik olarak ortaya atılan olası tedavi yöntemlerinin sayısında da aynı oranda artışı beraberinde getirmiştir. En çok ilgi çeken patofizyolojik yaklaşımlar arasında glutamaterjik sistemin katılımı, nöroinflamasyon, nöroplastisite, nörotrofik faktörlerin katılımı, genetik faktörler ve bazı hücre içi sinyal yolakları bulunmaktadır. Bu derlemede, bahsi geçen faktörlerin şizofrenideki rolleri ve tedavideki potansiyelleri ayrıntılı olarak incelenmiştir.

Anahtar sözcükler: Şizofreni, glutamaterjik sistem, nöroinflamasyon, nöroplastisite, genetik

Klinik Psikofarmakoloji Bülteni 2013;23(1):91-8

ABSTRACT:

Antipsychotics: neurobiological bases for a therapeutic approach

Studies on the pathophysiology of schizophrenia have become an adventure. It started with a simple pathological approach, focusing only on positive symptoms caused by dopaminergic hyperactivity in mesolimbic system and then branched out with contributions of many different components, including many receptors, various intracellular signaling pathways and gene-environment interactions. These new approaches have been useful in treating the negative symptoms and cognitive impairment observed in schizophrenia. Since there is a bulk of information on the mechanisms causing the disease, a proportional increase in the number of possible new treatment options has been proposed. The most challenging approaches in the disease mechanism address the glutamatergic system, neuroinflammation, neuroplasticity and neurotrophic factors, genetic factors and some intracellular signaling pathways. In this review, all of the above listed factors are discussed in detail.

Key words: Schizophrenia, glutamatergic system, neuroinflammation, neuroplasticity, genetics

Bulletin of Clinical Psychopharmacology 2013;23(1):91-8

[1]Marmara University, School of Pharmacy Department of Pharmacology and Psychopharmacology Research Unit, Istanbul - Turkey

Yazışma Adresi / Address reprint requests to: Feyza Aricioglu, Marmara University, School of Pharmacy Department of Pharmacology and Psychopharmacology Research Unit, Haydarpasa, 34668, Istanbul - Turkey

Telefon / Phone: +90-216-418-9573

Faks / Fax: +90-216-345-2952

Elektronik posta adresi / E-mail address: feyza.aricioglu@gmail.com

Gönderme tarihi / Date of submission: 20 Mart 2013 / March 20, 2013

Kabul tarihi / Date of acceptance: 20 Mart 2013 / March 20, 2013

Bağıntı beyanı:
S.G., F.A.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
S.G., F.A.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Schizophrenia is among the most mysterious and costly mental disorders causing suffering and societal expenditure (1). The lifetime prevalence of the disease is 0.30-0.66% (2). It also results in death 12-15 years earlier than expected resulting from suicide, decreased access to medical care and common risk factors, such as poor diet, sedentary life style, obesity and smoking (3).

First generation antipsychotics, that cause extrapyramidal side effects (EPS) which nearly nullify the therapeutic outcomes, are quite useful in controlling positive symptoms, but they lack a consistent response to long-term efficacy for negative symptoms and cognitive impairments. The new generation of antipsychotics, led by clozapine, has provided a broader range of therapeutic outcomes by being effective on both positive and negative symptoms and by causing fewer extra-pyramidal side effects. These new agents appeared to cause a risk for metabolic syndrome, including diabetes, weight gain, and hyperlipidemia. This situation may be more complicated than EPS or tardive dyskinesia in long-term therapy. As a result, there is still a strong need for safer and more efficacious

antipsychotic drugs (4).

First generation antipsychotics are antagonists of D2 subtype dopaminergic receptors of the striatum. Second generation antipsychotics, additionally, act on 5-HT2 type serotonergic receptors of the frontal cortex. Some of them are partial agonists of dopaminergic receptors. It has also been found that newer antipsychotics may have other actions. One of these is enhancing glutamatergic N-methyl-D-aspartate (NMDA) functioning and blocking effects of phencyclidine, a noncompetitive NMDA receptor antagonist, which induces a syndrome in healthy individuals that resembles schizophrenia. Additionally, they also act on adrenergic α-2 receptors and muscarinic M1 and M4 receptors.

As newer antipsychotics are needed, other underlying pathologies in schizophrenia should be evaluated in detail.

Glutamatergic System Contribution in Schizophrenia

Impairment in NMDA receptor and metabotropic glutamate receptor (mGluR) subtype function is a component of the pathophysiology of schizophrenia (5). If this hypofunction is targeted, efficacious treatment for schizophrenia may be achieved (Fig. 1). The glycine binding site has been chosen as a treatment target in the last decade and clinical trials have been very successful. Full and partial agonists of the glycine site have been studied in different trials. Full agonists of the glycine site, glycine and D-serine and a glycine transporter-1 inhibitor, sarcosine, combined with antipsychotic drugs, have been shown to be effective in the treatment of negative symptoms and cognitive symptoms, without directly affecting the positive symptoms of schizophrenia. Positive symptoms may be treated with the regular antipsychotics (6,7). Since glycine transporter-1 is localized both on neurons and glia cells, glia have a second function in schizophrenia in addition to the inflammatory process. The effect of glycine potentiators should occur through blockage of apoptosis and similar neuropathological processes. A partial agonist of the glycine site, D-cycloserine, added to antipsychotic drugs, can be effective for the negative symptoms at the therapeutic doses. In combination with clozapine, these drugs were not found to be effective, pointing to a new drug - drug interaction. These results are encouraging for highlighting the importance of numerous other binding sites of NMDA receptors, because NMDA modulation looks like a unique solution for the treatment of negative symptoms and cognitive impairment in schizophrenia (6,8).

Another encouraging approach is modulation of glutamatergic receptor activity. The modulatory role of mGluRs is thought to be disrupted in schizophrenia (9). It has been found that mGlu5 positive allosteric modulators (mGlu5 PAMs) restore the motor and cognitive effects of NMDA receptor antagonists in rats (10,11). Recently, mGluR5 PAMs have been found to reduce a conditioned avoidance response in rats, which is a screening model for antipsychotic efficacy and they also prevent locomotor hyperactivity induced by PCP and amphetamine. They do not only affect glutamatergic pathways, but also modulate the mesolimbic dopaminergic pathway and the striatopallidal GABAergic pathway, which are the common targets for antipsychotics (11).

Inflammation in Schizophrenia: Microglial Hypothesis

Although microglia contribute to neurotransmission, they have the ability to respond quickly to every pathological condition in the brain by producing various pro-inflammatory cytokines and free radicals. Many antipsychotics have some effects on the release of cytokines and free radicals from glia cells (12).

Secreted cytokines may be directly involved in long term potentiation or act on metabotropic or ionotropic glutamate receptors. Additionally, neural nitric-oxide synthase (nNOS) is also activated and nitric oxide (NO) synthesis results in glial-induced neuronal death. This action of NO is partly related to inhibition of mitochondrial respiration (13).

Interaction of NMDA receptor-mediated Ca^{+2} influx and nNOS activation requires a coupling of

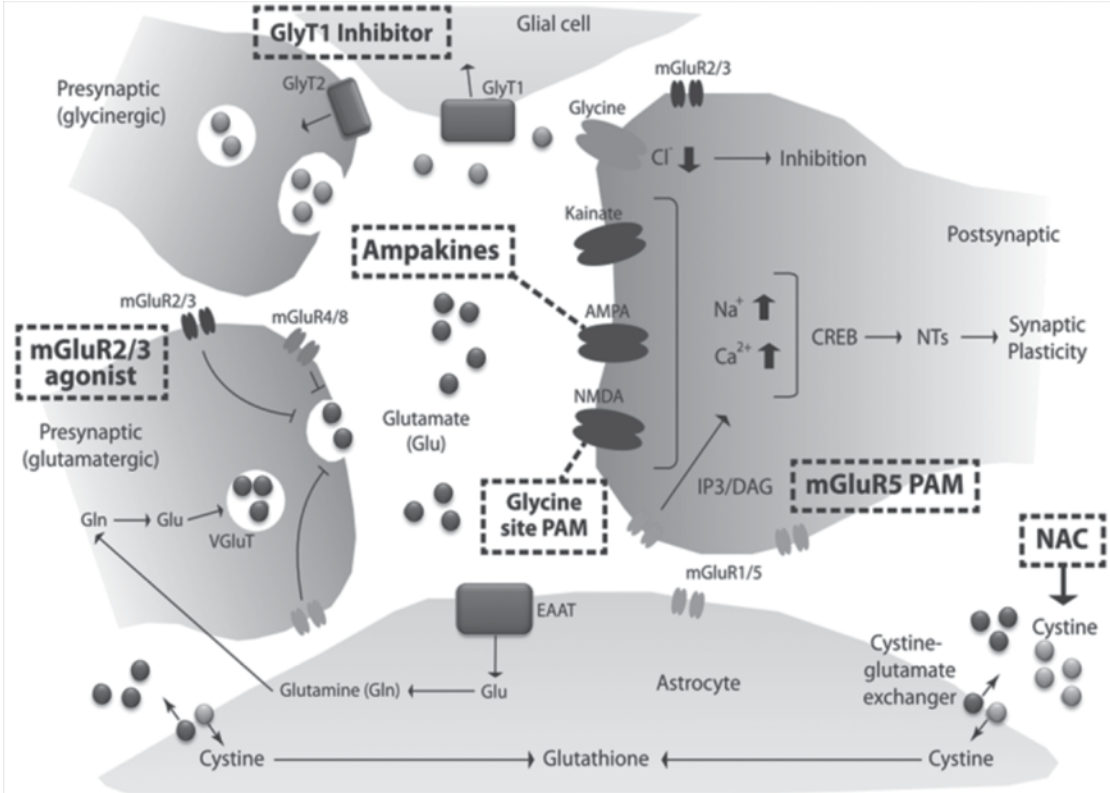

Figure 1: Components of the glutamatergic system, which seem to play a role in the pathophysiology of schizophrenia with some possible treatment options. In the central nervous system, presynaptic neurons release glutamate (Glu), acting with postsynaptic receptors, especially N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and kainate receptors. Glu is taken up by excitatory amino acid transporters (EAAT) of astrocytes and converted to glutamine (Gln) and given back to the presynaptic neurons. By the action of vesicular glutamate transporters (VGluT), Glu, reconverted from Gln, is packed into vesicles. Glycine (Gly) is the co-agonist of NMDA receptors and its occurrence is a must for the receptor functioning. There is a special site for Gly on NMDA receptors, and its positive allosteric modulators (PAMs) regulate the NMDA-mediated transmission. Gly is taken into the astrocytes by glycine transporter 1 (GlyT1) and into the presynaptic glycinergic neurons by glycine transporter 2 (GlyT2). Inhibitors of GlyT1 increase NMDA-mediated transmission via increasing the amount of Gly in the synaptic cleft. Ampakines are allosteric modulators of AMPA receptors and are effective on synaptic plasticity. Metabotropic glutamate receptors (mGluRs) also act on the same pathways as ionotropic glutamatergic receptors. Group I mGluRs (mGluR1/5) induce inositol 1,4,5-triposphate (IP3) and diacylglycerol (DAG). This results in activation of cAMP-response element-binding protein (CREB), and neurotrophins (NTs). This activation induces neuroplasticity. mGluR5 PAMs may enhance this excitatory pathway to provide plasticity. Group II mGluRs (mGluR2/3) are important in presynaptic regulation and their agonists inhibit Glu release. Extrasynaptic Glu concentrations are provided by cystine-glutamate transporter. The actions of this antiporter produce glutathione, the primary antioxidant and N-acetyl-cysteine (NAC) is its precursor.(Adapted from Miyamoto S et al. Mol Psychiatry 2012; 17(12):1206-27).

postsynaptic density protein 95 (PSD-95), an adapter postsynaptic density protein. This process occurs through a PDZ-domain protein interaction. The domain gene deserves attention, because its polymorphism may change Ca^{+2}-homeostasis during the pathology (14).

Neurotrophins and Schizophrenia

Neurotrophins are a large group of polypeptides, including brain-derived neurotrophic factor (BDNF), which have a survival promoting effect on neuronal cells with the ability to modulate dopaminergic, GABAergic and serotonergic receptors. The regulatory role of BDNF in synaptic transmission and plasticity in synapses is well known. Neurotrophins selectively bind to Tropomyosine-related kinase (Trk) receptors. Additionally, all neurotrophins have the ability to interact with the p75NTR receptor, which is a member of the tumor necrosis factor receptor superfamily. It is well known that Trk receptor activation leads to survival, while p75NTR signaling activates apoptotic pathways. Post-mortem studies

have shown that BDNF levels are decreased in hippocampus and increased in cerebral cortex in schizophrenia. It has been found that BDNF and TrkB mRNA levels are decreased in the prefrontal cortex of schizophrenic patients (15,16). The relationship between neurotrophic factors may be explained by progressive tissue loss and the contribution of the glutamatergic system to progression. Trk receptors mainly activate three signaling pathways; activation of extracellular signal-regulated kinases (ERK) and protein kinase C (PKC) signaling pathways provides differentiation, neuroplasticity and survival, while activation of protein kinase B (AKT) helps in survival only. AKT also inhibits the pro-apoptotic ability of activated p75NTR (17).

First and second generation antipsychotics differ in their effects on neurotrophic factor levels. It has been found that first generation antipsychotics decrease the level of BDNF in the brain, but the second generation antipsychotics have the opposite action. Haloperidol's toxic effects are related to the effect explained above, and second generation antipsychotics may even reverse the toxic effects of haloperidol. There are some claims, that this effect involves inverse agonism of 5-HT receptors (18).

Genetic Contributions to Schizoprenia

More than 240 genes have been found to be related to schizophrenia. Among these, excitatory synapse related genetic contributions have been observed as the most remarkable (Fig. 2). The most powerful linkages are detected in NRG1, ERBB4 and DISC1, which play a role in the coding of schizophrenia-related proteins. These three proteins also activate the PI3K/Akt pathway and their polymorphisms result in neuronal death (19). Neuregulins (NRGs) are trophic factors and activate postsynaptic ErbB receptor tyrosine kinases. These two factors are required for radial neuronal migration, axonal guidance, myelination of axons, oligodendrocyte formation as well as synapse and spine formation, which in unison mean neural development, neuronal survival and neuroplasticity (20). ErbB4, expressed mainly in interneurons and also in pyramidal cells and in spines, is the predominant receptor for NRG1 and a quite rare polymorphism of ERBB4 is detected in schizophrenic individuals. NRG1 and ErbB4 take part in spinal functioning and long term NRG1 treatment results in an increase of pyramidal neuronal spine density. Overexpression of ErbB4 causes not only an increase in spine density, but also enhances excitatory synaptic transmission. Since ErbB4 is localized not only in PSD95, but also in GABAergic interneurons, NRG1-ErbB4 signaling is thought to regulate both excitatory and inhibitory transmissions, which are disrupted in schizophrenic patients (21,22).

Spine morphology regulator molecules have been linked with schizophrenia and the DISC1 gene, which is disrupted in schizophrenia, is among these. DISC1 is expressed in dendritic spines and provides the connection with postsynaptic density. Due to its localization, it plays a role in changing the tempo of spine synaptic development and the rate of excitability (23). Cortical neurons with long-term DISC1 knockdown show shrinkage in spine area. In schizophrenics, it has been found that DISC1 mRNA levels are not affected, but expression of DISC1-interacting proteins is. DISC1 interacts most conspicuously with kalirin-7 (Kal-7), a GDP/GTP exchange factor for Rac1, which modulates dendritic spines in response to NMDA receptor activity. DISC1 forms a complex with Kal-7 and PSD-95 at the same time to initiate Rac1 activity. This interaction means that DISC1 modulates NMDA receptor-dependent Rac1 activity via Kal-7 to modulate spine function (24). Loss of kalirin accords with the loss of spines in the prefrontal cortex. In schizophrenic patients, reduced mRNA expression of the gene KALRN in dorsolateral prefrontal cortex has been detected (20).

Dysbindin-1, found in cortex, postsynaptic densities of spines and in glutamatergic nerve terminals, is an adaptor protein, which binds dystrophin-associated protein complex and intracellular signaling cascades. In glutamatergic nerve terminals, it binds to synapsin and co-primes vesicles for exocytosis. Over-expression of dysbindin-1 leads to increased glutamate release. A

couple of single nucleotide polymorphisms of dysbindin-1 are specifically related to schizophrenia. Dysbindin-1 mRNA is markedly decreased in the dorsolateral prefrontal cortex and hippocampus of schizophrenia patients (25). The decrease of dysbindin in hippocampus may be linked to loss of glutamatergic synapses (26).

The NMDA hypofunction hypothesis suggests that genes involved in the glutamatergic system are candidates for schizophrenia. NRG1, in accordance with the ErbB receptor family, regulates expression of NMDA receptor subunits. ErbB receptors are co-localized with NMDA receptors and they regulate the kinetic properties of the system by phosphorylating the NR2 subunit of the NMDA receptor. G72 or DAAO is the gene for the enzyme D-amino acid oxidase. DAAO is found both in neurons and glia and oxidizes D-serine to reduce its synaptic availability. RGS proteins negatively regulate G protein signaling and RGS4 inhibits mGlu5 receptor signaling. mGlu5 is located near the NMDA receptors and potentiates NMDA-mediated currents. This interaction between two receptor types requires a G protein activity. Dysbindin also regulates NOS, which influences NMDA activity by interacting with PSD. Additionally, the PPP3CC gene, encoding a calcineurin subunit, has an effect on NMDA-mediated plasticity (27). Metabotropic receptors also have their own genes, such as GRM3, which regulate the related receptor's activity (28,29).

Genetic findings regarding Ca^{+2} homeostasis have also been evaluated in schizophrenic patients. The Ca^{+2} process is mainly linked with the NMDA/glutamatergic system and there have been many genes encoding various proteins located in some areas. These include Dysbindin 1, NRG1 and ERBB4 (which were discussed earlier), NOS1 (neuronal nitric oxide synthase), NRGN (Neurogranin), DAO (D-amino acid oxidase), DAOA (D-amino acid oxidase activator) (30).

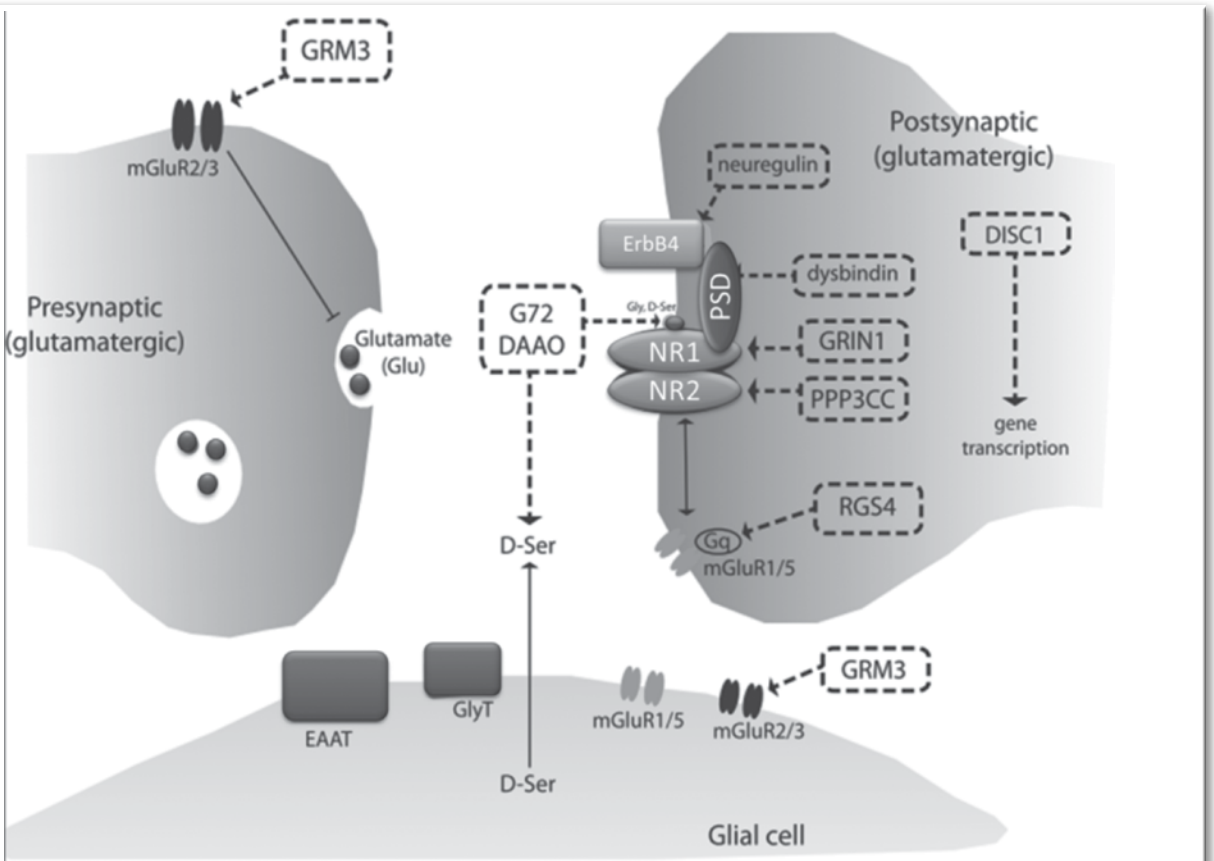

Figure 2: Schematization of the genetic components of an excitatory synapse in schizophrenia. Recently described genes influencing the synapse in the pathology of schizophrenia are showed in dotted boxes. (Adapted from Moghaddam B. Neuron 2003; 40:881-84)

GSK3 and Schizophrenia

Glycogen synthase kinase 3 (GSK3) is a protein with an ability to phosphorylate and inactivate the metabolic enzyme glycogen synthase. In recent years, GSK3 has been shown to have many substrates and a great influence in the neural systems regulating many neuronal functions, such as gene expression, neurogenesis, synaptic plasticity, neuronal structure, and neuronal death and survival. Several kinases, such as AKT, PKC and PKA phosphorylate GSK3 to inhibit its activity. GSK3 itself has also the ability to inhibit its own activity, which may be called "auto-phosphorylation". GSK3 is associated with different protein complexes, such as Wnt and β-catenin. All of these associations are involved in regulation of GSK3 activity (31). It has also been shown that mood stabilizers, such as lithium and some psychoactive drugs are direct inhibitors of GSK3 in a Mg^{+2} competitive manner (32).

GSK3 may be called a neuronal function regulator, which has a quantitative activity. It acts as an enzymatic sensor for the fate of the neuronal cell. Low levels of GSK3 in cells are a result of growth factor/Wnt signaling, which promotes proliferation and inhibits apoptosis. It also promotes survival in the case of intoxication, such as hypoxia (33). However, high levels of GSK3 and a dysregulation in the GSK3 regime results in destabilization of mood, characterized by decreased axonal growth and neurotransmitter release, induced by environmental and genetic factors (34). Low levels of GSK3 promote long-term potentiation and high levels result in long-term depression.

Possible Future Targets in Treatment

A group of next-generation antipsychotics under development targets mGlu2/3 receptors. It is thought that these agents would be effective on both positive and negative symptoms of the disease and would not induce weight gain or prolactin elevation, such as occurs with first and second generation antipsychotics (35). There is also an option to target NMDA receptors and binding sites. Phencyclidine, which has a specific binding site on the receptor, is known to produce schizophrenia-like symptoms and glycine and similar compounds, which act on the glycine site of NMDA, reverse negative symptoms and cognitive problems, when combined with antipsychotics.

Spine and synapse changes in schizophrenia should be interpreted properly, so that interest may be directed to mutations and genes affecting short and long-range connectivity. As a result of this, both the growth and the maintenance of spines, dendrites and axons may be achieved. Neuroplasticity enhancing treatment options may be useful in treatment.

Neurotrophic factors might be valuable in the treatment of schizophrenia due to their capacity to regulate central neurotransmission and to promote neuroplasticity. Recent studies show that pathological backgrounds contain the loss of amount and activity of neurotrophic factors. These agents may have a remarkable effect on the disease progression because of their neuroprotective effects (36).

When personalized medicine is possible and available worldwide, gene-environment interactions and genetic solutions will also bring a new approach to the treatment of schizophrenia. All the genes mentioned in the text will be different targets in related populations.

Dysregulated GSK3 levels are a risk factor for mood disorders. If chosen as a target, regulation of GSK3 levels may provide improvements in treatment of many disorders.

In recent years, the complexity of schizophrenia has been demonstrated. Since treatment options with high safety and efficacy are not available, there must still be efforts made to discover a superior therapy to provide a silver lining for patients.

References:

1. van Os J, Kapur S. Schizophrenia. Lancet 2009; 374:635-45.
2. Saha S, Chant D, McGrath J. A systemic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 2007; 64(10):1123-31.
3. McGrath J, Saha S, Chant D, Welhan J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemol Rev 2008; 30:67-76.
4. Glick ID, Peselow ED. New Antipsychotic Agents. Primary Psychiatry 2008; 15(12):57-64.
5. Field JR, Walker AG, Conn PJ. Targeting glutamate synapses in schizophrenia. Trends Mol Med 2011; 17(12):689-98.
6. Lane HY, Huang CL, Wu PL, Liu YC, Chang YC, Lin PY, et al. Glycine transporter-1 inhibitor, N-methylglycine (sarcosine), added to clozapine for the treatment of schizophrenia. Biol Psychiatry 2006; 60(6):645-9.
7. Javitt DC. Twenty-five years of glutamate in schizophrenia: are we there yet? Schizophr Bull 2012; 38(5):911-3.
8. Shim SS, Hammonds MD, Kee BS. Potentiation of the NMDA receptor in the treatment of schizophrenia: focused on the glycine site. Eur Arch Psychiatry Clin Neurosci 2008; 94(1-3):1-11.
9. Noetzel MJ, Jones CK, Conn PJ. Emerging approaches for treatment of schizophrenia: modulation of glutamatergic signaling. Discov Med 2012; 14(78):335-43.
10. Gastambide F, Gilmour G, Robbins TW, Tricklebank MD. The mGlu5 positive allosteric modulator LSN2463359 differentially modulates motor, instrumental and cognitive effects of NMDA receptor antagonists in the rat. Neuropharmacology 2013; 64:240-7.
11. Hovelsø N, Sotty F, Montezinho LP, Pinheiro PS, Herrik KF, Mørk A. Therapeutic potential of metabotropic glutamate receptor modulators. Curr Neuropharmacol 2012; 10(1):12-48.
12. Monji A, Kato T, Kanba S. Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. Psychitary Clin Neurosci 2009; 63(3):257-65.
13. Brown GC, Bal-Price A. Inflammatory neurodegeneration mediated by nitric oxide, glutamate, and mitochondria. Mol Neurobiol 2003; 27(3):325-55.
14. Kornau HC, Seeburg PH, Kennedy MB. Interaction of ion channels and receptors with PDZ domain proteins. Curr Opin Neurobiol 1997; 7(3):368-73.
15. Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. Reduced brain-derived neurotrophic factor in prefrontal cortex of patinets with schizophrenia. Mol Psychiatry 2003; 8(6):592-610.
16. Weickert CS, Ligons DL, Romanczyk T, Ungaro G, Hyde TM, Herman MM, et al. Reductions in neurotrophin receptor mRNAs in the prefrontal cortex of patients with schizophrenia. Mol Psychiatry 2005; 10(7):637-50.
17. Buckley PF, Mahadik S, Pillai A, Terry Jr A. Neurotrophins and schizophrenia. Schizophrenia Research 2007; 94:1-11.
18. Nandra KS, Aquis M. The differences between typical and atypical antipsychotics: the effects on neurogenesis. Psychiatr Danub 2012; 24(Suppl):S95-S9.
19. Zheng W, Wang H, Zeng Z, Lin J, Little PJ, Srivastava LK, et al. The possible role of the Akt signaling pathway in schizophrenia. Brain Research 2012; 1470:145-58.
20. Penzes P, Cahill ME, Jones KA, VanLeeuwen JE, Woolfrey KM. Dendritic spine pathology in neuropsychiatric disorders. Nat Neuroscience 2011; 14(3):285-93.
21. Rico B, Marion O. Neuregulin signaling, cortical circuitry development and schizphrenia. Curr Opin Genet Dev 2011; 21(3):262-70.
22. Mei L, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. Nat Rev Neurosci 2008; 9(6):437-52.
23. Porteous DJ, Millar JK, Brandon NJ, Sawa A. DISC1 at 10: connecting psychiatric genetics and neuroscience. Trends Mol Med 2011; 17(12):699-706.
24. Hayashi-Takaqi A, Takaki M, Graziane N, Seshadri S, Murdoch H, Dunlop AJ, et al. Disrupted-in-Schizophrenia (DISC1) regulates spines of the glutamate synapse via Rac1. Nat Neurosci 2010; 13(3):327-32.
25. Bennett MR. Schizophrenia: susceptibility genes, dendritic-spine pathology and grey matter loss. Progress in Neurology 2011; 95(3):275-300.
26. Talbot K, Cho DS, Ong WY, Benson MA, Han LY, Kazi HA, et al. Dysbindin-1 is a synaptic and microtubular protein that binds brain snapin. Hum Mol Genet 2006; 15(20):3041-54.
27. Moghaddam B. Bringing Order to the Glutamate Chaos in Schizophrenia. Neuron 2003; 40(5):881-84.
28. Wang H, Zhuo M. Group I metabotropic glutamate receptor-mediated gene transcription and implications for synaptic plasticity and diseases. Front Pharmacol 2012; 3:189.
29. Kordi-Tamandani DM, Dahmardeh N, Torkamanzehi A. Evaluation of hypermethylation and expression pattern of GMR2, GMR5, GMR8, and GRIA3 in patients with schizophrenia. Gene 2013; 515(1):163-6.
30. Giegling I, Genius J, Benninghoff J, Ruiescu D. Genetic findings in schizophrenia patients related to alterations in the intracellular Ca homeostasis. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34(8):1375-80.
31. Li X, Jope RS. Is glycogen synthase kinase-3 a central modulator in mood regulation? Neuropsychopharmacology 2010; 35(11):2143-54.
32. Jope RS, Bijur GN. Mood stabilizers, glycogen synthase-3β and cell survival. Mol Psychiatry 2002; 7(Suppl):S35-S45.
33. Cole AR. GSK3 as a Sensor Determining Cell Fate in the Brain. Front Mol Neurosci 2012; 5(4):1-10.

34. Beurel E, Mines MA, Song L, Jope RS. Glycogen synthase kinase-3 levels and phosphorylation undergo large fluctuations in Mouse brain during development. Bipolar Disord 2012; 14(8):822-30.

35. Kim S, Zavitsanou K, Gurguis G, Webster MJ. Neuropathology markers and pathways associated with molecular targets for antipsychotic drugs in postmortem brain tissues: Exploration of drug targets through the Stanley Neuropathology Integrative Database. European Neuropsychopharmacology 2012; 22(10):683-94.

36. Pandya CD; Kutiyanawalla A, Pillai A. BDNF-TrkB signaling and neuroprotection in schizophrenia. Asian J Psychiatr 2013; 6(1):22-8.