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REVIEW

Abnormal synaptic plasticity and impaired cognition in schizophrenia

Xiu-Lin Wu, Qiu-Jin Yan, Fan Zhu

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Abstract

Schizophrenia (SCZ) is a severe mental illness that affects several brain domains with relation to cognition and behaviour. SCZ symptoms are typically classified into three categories, namely, positive, negative, and cognitive. The etiology of SCZ is thought to be multifactorial and poorly understood. Accumulating evidence has indicated abnormal synaptic plasticity and cognitive impairments in SCZ. Synaptic plasticity is thought to be induced at appropriate synapses during memory formation and has a critical role in the cognitive symptoms of SCZ. Many factors, including synaptic structure changes, aberrant expression of plasticity-related genes, and abnormal synaptic transmission, may influence synaptic plasticity and play vital roles in SCZ. In this article, we briefly summarize the morphology of the synapse, the neurobiology of synaptic plasticity, and the role of synaptic plasticity, and review potential mechanisms underlying abnormal synaptic plasticity in SCZ. These abnormalities involve dendritic spines, postsynaptic density, and long-term potentiation-like plasticity. We also focus on cognitive dysfunction, which reflects impaired connectivity in SCZ. Additionally, the potential targets for the treatment of SCZ are discussed in this article. Therefore, understanding abnormal synaptic plasticity and impaired cognition in SCZ has an essential role in drug therapy.

Key Words: Schizophrenia; Synaptic plasticity; Synaptic structure; Synaptic transmission; Cognitive dysfunction; Abnormality

Core Tip: Schizophrenia (SCZ) is a severe mental illness that affects several domains of cognition and behaviour. SCZ symptoms are typically classified into three categories, namely, positive, negative, and cognitive. The etiology of SCZ is thought to be multifactorial and poorly understood. Accumulating evidence has indicated abnormal synaptic plasticity and cognitive impairments in SCZ. This article will briefly review abnormalities in synaptic plasticity, including synaptic structure, synaptic plasticity-related genes, neuroplasticity, synaptic transmission, and cognitive dysfunction in SCZ.

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INTRODUCTION

Schizophrenia (SCZ) is a chronic, dangerous psychiatric disorder that affects about 1% of people worldwide. Typically, SCZ, occurring in late adolescence or early adulthood, often results in lifetime disability if not effectively controlled. The symptoms of SCZ are generally grouped into three categories, addressed as follows: Positive symptoms (auditory hallucinations and persecutory delusions), negative symptoms (social withdrawal, self-neglect, loss of motivation and initiative, emotional blunting, and paucity of speech), and cognitive symptoms (problems with attention, certain types of memory, and executive functions)[1]. There are numerous hypotheses postulated to elaborate the pathophysiology of SCZ, including the neurodevelopmental hypothesis and synaptic hypothesis. The synaptic hypothesis involves abnormal synaptic transmission and impaired synaptic plasticity.

Synaptic plasticity consists of structural plasticity and functional plasticity. Various evidence discloses abnormal structural and functional plasticity in the pathogenesis of SCZ. Postmortem studies in the brain of SCZ patients point out that there is a significant decrease in the density of dendritic spines (DSs) and the size of postsynaptic density (PSD) in SCZ compared to healthy controls[2,3]. Similarly, functional imaging has revealed that the expression levels of synaptic structure related genes have changed in SCZ[4,5]. Change in morphology or distribution of synaptic structure is related to synaptic plasticity and contributes to SCZ. Additionally, a mouse model of SCZ induced by MK801 also proves that abnormal structural and functional plasticity can constitute to the etiology of SCZ. MK-801-induced mice display the disruption of long-term potentiation (LTP) and change of excitatory postsynaptic potential[6,7]. Furthermore, LTP-like plasticity deficits may result in impairments of learning and memory[8,9].

Abnormal synaptic plasticity might lead to cognitive impairments, including deficits in learning and memory, attention, and social cognition, in SCZ[9,10]. Cognitive impairments refer to aberrant functional connectivity or transmission. Cognitive deficit is an early warning sign of SCZ and contributes to poor functional outcomes[11]. Conventional antipsychotic drugs targeted by dopamine receptors have beneficial effects on positive symptoms but offer minimal benefit for negative symptoms or cognitive symptoms[12]. Therefore, in-depth research on abnormal synaptic plasticity and impaired cognition in SCZ could help understand the underlying mechanism of SCZ and find new drugs to treat it.

This review will focus on recent advances in the understanding of impaired synaptic plasticity and cognitive dysfunction, including changes in synaptic structure, synaptic plasticity-related genes, dysregulation of synaptic transmission, and disconnection, in SCZ, as well as the potential targets for SCZ.

MORPHOLOGY OF THE SYNAPSE

The synapse is a structure that allows a neuron (or nerve cell) to communicate electrical or chemical signals to another neuron or other target effector cell. There are three common types of synapses, respectively called axodendritic, axosomatic, and axoaxonic (Figure 1). In the mammalian brain, neuronal signals are transmitted by two fundamental types of synapses: The electrical synapse and the chemical synapse[13]. A classical chemical synapse is composed of three main parts: (1) The presynaptic components, enclosing neurotransmitter-filled synaptic vesicles (SVs) and proteins (SNARE complex, Munc13, and Munc18) which promote SV recruitment and neurotransmitters release[14]; (2) The postsynaptic components, containing specific receptors and proteins including scaffolding proteins, neurotransmitter receptors, enzymes, and cytoskeletal components, which receive and transmit signals and regulate the synaptic plasticity[15]; and (3) The synaptic cleft, physical space between the presynaptic and postsynaptic terminals which is 10-20 nm, also called synaptic gap (Figure 1D)[16].

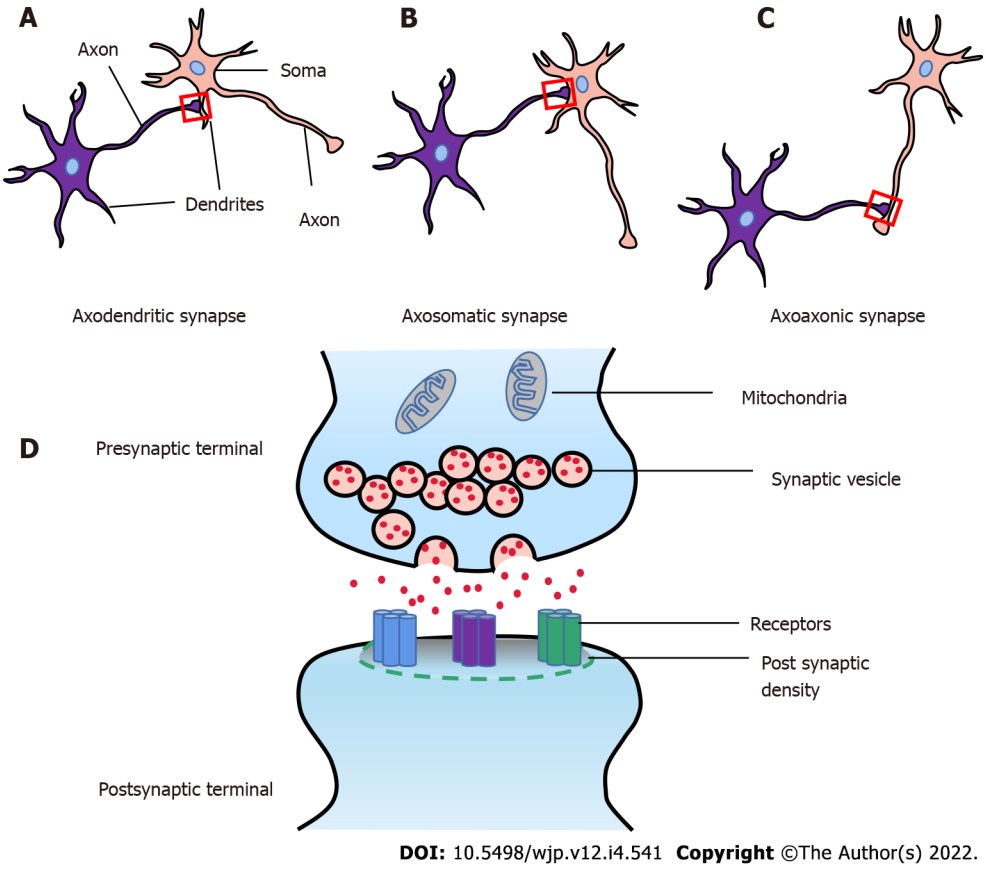

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Figure 1 Types of synapse and structure of a classical chemical synapse. A: Axodendritic synapse; B: Axosomatic synapse; C: Axoaxonic synapse; D: Structure of a classical chemical synapse. A typical chemical synapse usually consists of three parts: (1) Presynaptic membrane including clusters of neurotransmitter-filled synaptic vesicles, mitochondria, and so on; (2) Postsynaptic membrane including neurotransmitter-specific receptors; and (3) Synaptic cleft.

Furthermore, the surface where the presynaptic component and the postsynaptic component are connected is usually called the synaptic interface. It is determined by the width of the synaptic cleft, length of the synaptic active zone, the thickness of PSDs, and curvature of the synaptic interface[17-19]. Changes of synaptic interface closely relate to synaptic function.

In vivo imaging studies have shown that the decreased density of DSs may be a loss of synapse[20]. Spines have a critical role in synaptic transmission. The reduced spines directly correlate with the loss of synaptic function[21,22]. Many factors, including specific gene expression, signal transduction, and new synapse formation, can change synapse level. The total number of synapses is controlled by forming new synapses and pruning old or inappropriate synapses, and finally contributes to synaptic plasticity and memory consolidation[23].

NEUROBIOLOGY OF SYNAPTIC PLASTICITY

Synaptic plasticity (also called synaptic strengths) is the ability of neurons to modify synaptic strength in response to external stimuli. During this process, the structure and function of the synapse are highly dynamic.

Structurally, synaptic plasticity is characterized by the insertion or retention of neurotransmitter receptors, especially AMPAR, into the postsynaptic membrane. Many factors, including the size of DS, the pool of SVs, the areas of active zone, and the PSD, may influence synaptic plasticity[24-26]. Functionally, LTP and long-term depression (LTD) are two forms of synaptic plasticity. There are usually two LTP types, namely, NMDA receptor-dependent LTP and mossy fibre LTP (a cAMP-dependent presynaptic form of plasticity)[27]. The activation of NMDA receptors and increased calcium (Ca^{2+}) concentration are essential for the induction of NMDA receptor-dependent LTP[28,29]. Noteworthy, the spine Ca^{2+} signal is required to trigger LTP[30,31]. Thus, calcium/calmodulin-dependent protein kinase II (CaMKII) has an important role in NMDA receptor-dependent LTP. Besides, various kinases, including protein kinase C, the mitogen-activated protein kinase, and the tyrosine kinase Src, have been implicated in LTP induction[32-34]. Interestingly, some forms of LTP can only maintain 30-60 min, but some can last a very long time, from several hours to days, even for many weeks. The possibilities for the longer-term maintenance of LTP is involved in synaptic structural

remodeling, increased spines size, and enlargement of PSD[35,36].

In summary, synaptic structure, AMPAR trafficking, and DS dynamics are critical for the maintenance of synaptic plasticity.

ROLE OF SYNAPTIC PLASTICITY

Synaptic plasticity in learning and memory

The formation of memory involves four processes: Encoding, storing, consolidating, and retrieving information. Learning is viewed as the acquisition or encoding of the information to memory. The core hypothesis of synaptic plasticity and memory is as follows: Activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which plasticity is observed[37].

Changing the strength of synaptic connections is a prime process underlying learning and memory formation. Accumulative studies suggest that synaptic plasticity is necessary for learning and memory. The induction of synaptic plasticity requires NMDAR activation. NMDAR1 knockdown mice show deficit in spatial memory in the hippocampus[38]. Besides, synaptic plasticity may contribute to declarative and relational memory[39], sequence learning[40], motor learning[41,42], and perceptual learning at sensory cortex synapses[43]. The traditional view is that fast learning requires more robust synaptic changes[44]. However, some studies suggest that weak synaptic plasticity can support fast learning[45]. Synaptic plasticity has a requisite role in learning and memory across many regions of the brain.

Synaptic plasticity in brain maturation

Human brain maturation is a complex, dynamic, and lifelong process. Billions of cells proliferate, migrate, and maturate during early development, which leads to a brain with billions of neurons at birth, finally forming connections. As children become teenagers, the brain dynamically strengthens or weakens connections in response to environmental input[46]. Simultaneously, neural maturity is increased with age across various brain regions, including primary sensory, motor, associative learning, and cognition function[47]. The prefrontal cortex (PFC) is the last brain region to mature and can mediate executive function such as goal planning, working memory, and guided behavior[48].

Post-mortem studies suggest that the synaptic densities increase rapidly in the visual and auditory cortices, with a maximum of near 3 mo followed by pruning until the age of 12 years[49]. However, synaptic density in the PFC reaches the maximum during childhood, up to 150-200 percent of its adult level. Interestingly, synaptic elimination lasts to mid-adolescence in the PFC[50]. Furthermore, evidence shows that synaptic strength is reduced in the developing brain because it presents synaptic pruning [51]. The specialized and functionally-connected neural circuits accompany regional changes. Additionally, changes in brain volume occur in SCZ. Several reports suggest reducing cerebral cortical volume at premature birth compared to infants born at term[52]. Similarly, there are linearly decreased cortical gray matter and increased white matter across ages 4 years to 12 years[53,54]. In a word, the change of synaptic strength has an influential role in brain maturation and maintenance of a functional neuronal circuit.

IMPAIRED SYNAPTIC PLASTICITY IN SCZ

Abnormal structural plasticity in SCZ

Synaptic plasticity is mediated by structural changes (elongation, contraction, and shape changes) of DSs. DSs are tiny, actin-rich protrusions from the dendritic shaft of various types of neurons. Most of the excitatory synapses are on DSs. Postmortem studies suggest that the density of DSs is reduced in brain tissue of individuals with SCZ, including the neocortex (especially in layer deep 3) and hippocampus, while it may be increased in the dorsal striatum[3,55,56]. Moreover, reduced number of spines and decreased length of basilar dendrites have been observed in SCZ[3]. Deficits in DSs may contribute to the impairment of synaptic plasticity in SCZ.

DSs possess specialized subdomains, including PSD, scaffolding proteins, signal transduction molecules, ion channels, and cytoskeleton components. Under the electron microscope, PSD appears as a regular, dense band about 25 nm to 50 nm thick in the postsynaptic membrane. PSD has essentially different roles in the process of LTP formation[57]. Postmortem study demonstrates a drastic reduction of PSD in the nucleus accumbens in SCZ, especially in asymmetric synapse[2]. The alteration of the synaptic ultrastructure may result from overstimulation of the excitatory synapse. Thus, the alteration of PSD may contribute to SCZ.

Impaired LTP-like plasticity in SCZ

LTP and LTD are two primary forms for studying synaptic plasticity. Many factors, including transmitter release and NMDAR function, can affect LTP[58,59]. The dopaminergic or serotonergic systems can also modulate LTP. Impaired LTP and LTD-like plasticity have been reported in SCZ[60,61].

Evidence has shown altered LTP-like plasticity in SCZ compared to healthy subjects[61,62]. Furthermore, NMDAR antagonists (phencyclidine, MK801, and ketamine) can induce SCZ-like symptoms in healthy individuals[63,64]. Studies reveal NMDAR hypofunction in SCZ[65]. Those changes are involved in excitation and inhibition imbalance, controlled by excitatory neurotransmission glutamate and inhibitory neurotransmission gamma-aminobutyric acid (GABA). Electrophysiological recordings reveal that MK801 treatment can significantly suppress the frequency of miniature excitatory postsynaptic current/miniature inhibitory postsynaptic current ratio of layer (L) 2/3 PNs[66]. Neurogranin, a calmodulin-binding protein, modulates LTP in the hippocampus. The lower level of neurogranin results in hypo-phosphorylation of NMDAR subunit NR2A and finally contributes to NMDAR current decay[67]. Maybe, NMDAR hypofunction accounts for the lack of associative LTP-like plasticity in patients with SCZ.

Ca^{2+} entry is another crucial factor for the induction of LTP-like plasticity. The voltage-gated calcium channel is critical for mediating intracellular Ca^{2+} entry, especially the $Ca_v1.2$ or $Ca_v1.3$ channel. Clinical findings reveal the alteration of intracellular calcium homeostasis in SCZ[68]. Calcium concentration level increases in the cerebrospinal fluid (CSF) of patients with SCZ when acute psychotic symptoms are in remission[69]. It means a positive correlation between SCZ and calcium dysregulation. Therefore, dysregulation of calcium concentration is responsible for changing neuronal excitability and LTP-like plasticity.

Aberrant plasticity-related genes in SCZ

Gene expression studies, including microarray, have discovered the aberrant expression of synaptic plasticity-related genes in SCZ, such as GAP43 and PSD95. GAP43 is a phosphoprotein of the presynaptic membrane that regulates the growth state of axon terminals. Several postmortem studies show reduced GAP43 levels in the frontal cortex and the hippocampus of patients with SCZ[70,71]. What's more, PSD95 is the most abundant protein in the postsynaptic membrane. Postmortem studies show decreased PSD95 protein and mRNA expression levels in SCZ[72,73]. Interestingly, PSD95 can directly interact with ARC or IL1RAPL1 to regulate spine density and function[74,75]. Besides, TAOK2 kinase could directly phosphorylate Septin7 to regulate PSD95 stability and DS maturation[76]. The PSD proteins can directly reflect the number of synapses.

Additionally, some genes regulate the development and function of neuronal synapses. KIF3B, a member of the kinesin superfamily proteins, supports the NR2A/APC complex transport. Its dysfunction relates to SCZ[77]. The dynamic regulation of NR2A and NR2B is critical to the function of NMDAR, which has a substantial role in regulating synaptic plasticity. Besides, CaMKII, ARP2/3, Arc, and PI4KA affect NMDAR function and mediate Ca^{2+} entry[78]. A recent study reports that an envelope protein encoded by human endogenous retrovirus type W (also called syncytin-1) regulates Ca^{2+} entry *via* activating the TRPC3 channel[79], indicating that syncytin-1 may also regulate the development and function of neuronal synapses. Intriguingly, our results show that syncytin-1 can increase the expression of BDNF and IL-6 in SCZ[80,81]. BDNF, an essential member of the nerve growth factor family, regulates synapse formation and contributes to impaired plasticity in SCZ[82]. These data predict that syncytin-1 may participate in the regulation of synaptic plasticity.

In summary, abnormality of synapse morphology, LTP-like plasticity, and synaptic plasticity-related genes may contribute to the pathogenesis of SCZ.

DYSCONNECTION IN SCZ

The hypothesis of dysconnectivity gives two inconsistent explanations: (1) Robust connectivity: The synapse has not been cleared in time in the process of neural system development; and (2) Weak connectivity: Synaptic connectivity decreases and is responsible for the processing information in the brain involving multi brain regions[83,84]. Impaired connectivity is a failure of proper functional integration within the brain, and the connection between different neuron systems influences the functional integration[85]. Effective and functional connectivity plays a prominent role in brain function. Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetic resonance imaging (MRI), computer-assisted tomography, and magnetic resonance spectroscopy have been used to study brain structure or function.

With the development of brain imaging technology, impaired connectivity has been observed in SCZ. Evidence suggests that prefrontal-limbic cortices are hyperconnected with the mediodorsal thalamus and ventral parts of the striatum and pallidum by fMRI[86]. Impaired connectivity correlates with cognitive impairments. Additionally, PET reveals that SCZ involves dysfunction of a widely distributed cortico-thalamic circuitry[87].

Moreover, an MRI study shows reduced synaptic connectivity in SCZ[88]. These reductions are widespread in the left fronto-parietal network, lateral and medial visual network, motor network, default mode network, and auditory network. Reduced synaptic connectivity is also present in the first episode of psychosis but appears to progress throughout the disorder[89]. The reduction of synaptic connectivity may disturb brain development, including myelogenesis and synaptic pruning or disruption of maturation of inhibitory neural networks such as GABAergic interneurons[90-93]. Maybe, reduced synaptic connectivity involves impaired γ synchronization and increased excitation/inhibition ratio[94]. In conclusion, impaired connectivity found in the brain of patients with SCZ is related to the cognitive dysfunction in SCZ.

COGNITIVE DYSFUNCTION IN SCZ

Since the "dementia praecox" was proposed, cognitive dysfunction had received extensive attention and research in SCZ. It is until 1970s that Gallhofer proposed cognitive symptoms as the third symptoms of SCZ. Cognitive impairments are in the first episode of SCZ[95]. Those deficits include the speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning problem solving, and social cognitive[96]. Kudo *et al*[97] report that increased MMP-9 levels are associated with cognitive impairments in SCZ. High concentrations of S100B correlates with memory impairments, and the variants of S100B may lead to poor performance in patients with SCZ[98,99].

Cognitive deficits may impair global functioning or contribute to poor functional outcomes in SCZ [11]. A four-year follow-up study shows that first-episode SCZ with severe cognitive impairments has no social functioning improvement, even after therapy[100]. Besides, the function and structure of frontal-limbic brain regions have a meaningful role in functional outcome in SCZ[101]. Conventional antipsychotic drug treatment has minimal benefits on cognitive symptoms in SCZ, and even some may impair certain aspects of cognition, such as attention, short-term memory, and learning. However, second-generation (atypical) antipsychotics, such as clozapine, improve several cognitive function domains, especially attention and verbal fluency in SCZ[102-104]. In summary, cognitive deficits are core symptoms of SCZ and result in severe disability.

CASCADE OF NEUROTRANSMITTER AND CIRCUIT DYSFUNCTION IN SCZ

SCZ is currently considered as a polygenic and multifactorial disorder, involving abnormality of synaptic function and neurotransmission, including dopaminergic pathway, serotoninergic pathway, glutamatergic pathway, GABAergic pathway, cholinergic pathway, and other neurotransmitter pathways, such as norepinephrine (NE) and neurosteroids.

Dopaminergic pathway

Typically, the dopaminergic pathway consists of dopamine synthesis, release, and reuptake. It can activate the downstream signal cascades, which play a critical role in synaptic plasticity (Figure 2A). Dopamine is synthesized from tyrosine through two steps: (1) Tyrosine hydroxylase catalyzes the tyrosine to L-DOPA by hydroxylation; and (2) L-DOPA is converted to dopamine by DOPA decarboxylase[105,106]. Dopamine can be stored into SVs, transported to the presynaptic membrane by the vesicular monoamine transporter 2, and finally released to the synaptic cleft[107]. There are five subtypes of dopamine receptors (DRD1, DRD2, DRD3, DRD4, and DRD5) known to mediate dopaminergic physiological functions. Dopamine receptors, especially DRD2, can couple to Gαi/o protein and modulate the PI3K-Akt signal pathway[108,109]. The PI3K-Akt signal pathway has a critical role in cell survival, proliferation, differentiation, glucose metabolism, and gene transcription[110].

Dopaminergic dysfunction has a prominent role in the development of symptoms of SCZ. High dopamine levels in SCZ support this hypothesis[111]. Postmortem studies have suggested a hyperactive dopaminergic system in SCZ, compared to healthy controls[112]. Nowadays, most antipsychotic drugs target dopamine receptors to block dopamine transmission. Notably, DRD2 is considered as the primary target for antipsychotics to alleviate positive symptoms. Moreover, dopamine transporter and vesicular monoamine transporter are decreased in SCZ. However, increased expression of monoamine oxidase A appears to occur in the substantia nigra of patients with SCZ[113].

Serotonergic pathway

Brain 5-HT plays a crucial role in affect and mood control, memory, reward, and modulation of developmental, physiological, and behavioral processes[114-116]. Typically, 5-HT synthesis needs two enzymes: Tryptophan hydroxylase and DOPA decarboxylase. After synthesizing, 5-HT can be transported into SVs and release to the synaptic cleft. Some 5-HT directly binds to its receptors (HTR1A, HTR1B, HTR2A, HTR4, and HTR6), activates downstream signaling pathways to trigger ion channels, and regulates synaptic plasticity (Figure 2B).

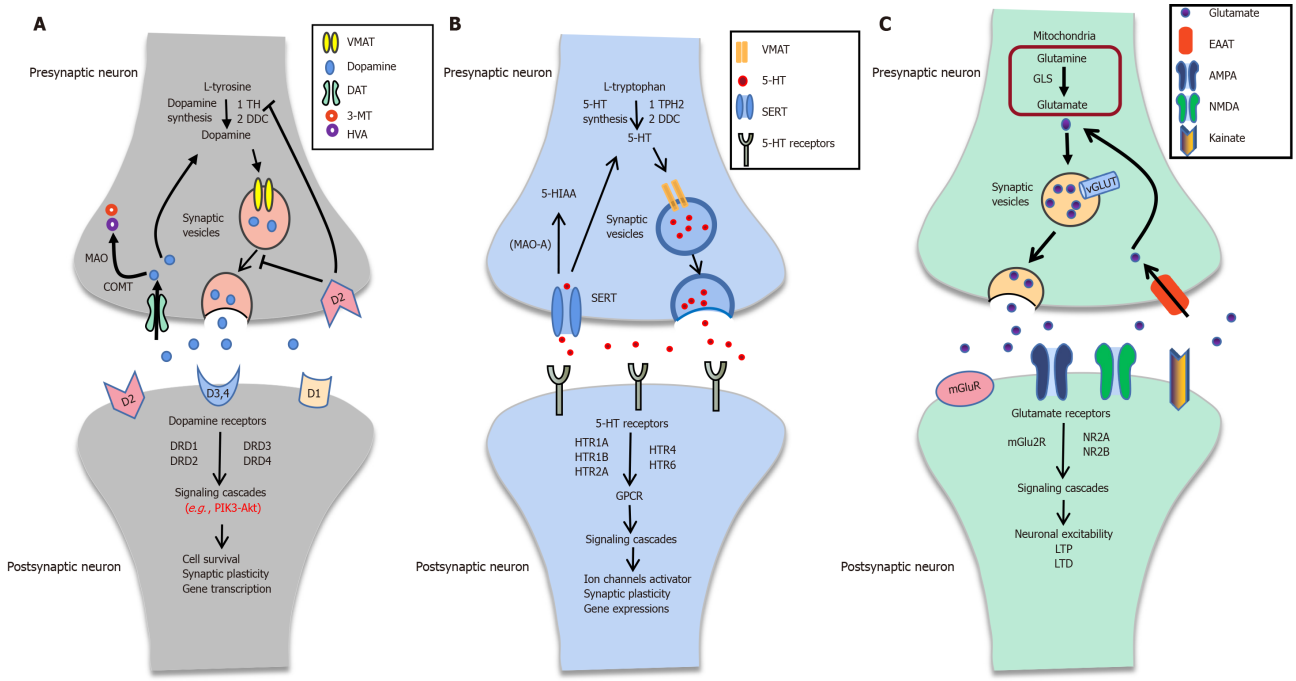

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Figure 2 Neurotransmission in dopaminergic, serotonergic, and glutamatergic neurons. Each pathway step is supplemented with associated genes according to KEGG. A: Dopaminergic pathway. Dopamine is synthesized from tyrosine through two steps: (1) Tyrosine hydroxylase catalyzes the tyrosine to L-DOPA by hydroxylation; and (2) L-DOPA converts to dopamine by DOPA decarboxylase (DDC). Dopamine can be stored into synaptic vesicles by the vesicular monoamine transporters and release to the synaptic cleft. Dopamine as a neurotransmitter, can directly bind to its receptor to activate downstream signaling cascades and influence cell survival, synaptic plasticity, and gene transcription. Besides, dopamine also can be transported back to the presynaptic membrane by the DAT and eliminated. DRD2, an auto-receptor, can inhibit the release of dopamine in the presynaptic membrane; B: Serotoninergic (5-HTergic) pathway. The synthesis of 5-HT needs two enzymes: Tryptophan hydroxylase and DDC. After synthesizing, 5-HT can be transported into synaptic vesicles and release to the synaptic cleft. Some of the 5-HT directly binds to its receptors (*e.g.*, HTR1A, HTR1B, HTR2A, HTR4, and HTR6), activates downstream signaling pathway to activate ion channels, and influences synaptic plasticity and gene expressions, and others are re-uptaken into the presynaptic membrane by the serotonin transporter; C: Glutamatergic pathway. Glutamate is converted from glutamine by phosphate-activated glutaminase in mitochondria and packaged into synaptic vesicles by vesicular glutamate transporters. Sequentially, the glutamate is released to the synaptic cleft and binds to the glutamate receptors, and then activates the downstream pathway or is repacked into presynaptic membrane by excitatory amino acid transporters. Signaling cascade activation might lead to the change of neural excitability and finally has effects on long-term potentiation or long-term depression. MAO: Monoamine oxidase; COMT: Catechol O-methyltransferase; 3-MT: 3-Methoxytyramine; HVA: Homovanillic acid; 5-HIAA: 5-Hydroxy indole acetic acid; EAATs: Excitatory amino acid transporters; 5-HT: Serotonin or 5-hydroxytryptamine; GPCR: G protein-coupled receptor; GLS: Glutaminase; NMDA: N-methyl-D-aspartate receptor; AMPA: α-Amino-3hydroxy-5methyl-4-isox-azolepropionic acid; mGluR: Metabotropic glutamate receptor; LTP: Long-term potentiation; LTD: Long-term depression.

Alteration of serotonin transmission has been implicated in the processes of SCZ. Tryptophan hydroxylase 2 (TPH2), a rate-limiting enzyme for serotonin synthesis, is selectively expressed in the raphe serotonergic neurons[117]. Postmortem studies and single nucleotide polymorphism (SNP) studies show a significant association of TPH2 with SCZ in Han Chinese[118,119]. Additionally, the expression level of SERT (5-HT transporter, also named 5-HTT) is reduced in the frontal cortex of subjects with SCZ[120]. Recently, a SNP meta-analysis shows a strong association between SERT polymorphism and SCZ[121]. Indeed, the 5-HT receptor has an outstanding role in 5-HT transmission. 5-HT1A agonist can directly bind to atypical antipsychotic drugs (AAPDs) to treat cognitive impairments associated with SCZ[122-124]. Maybe as a compensatory mechanism, the expression of serotonin 1A is increased or maybe due to the beneficial effects of AAPDs in SCZ, the 5-HT1A receptor is activated.

Glutamatergic pathway

Glutamate is the principal excitatory neurotransmitter in the central nervous system. Notedly, glutamate is converted from glutamine by phosphate-activated glutaminase in mitochondria and packaged into SVs by vesicular glutamate transporters (VGLUTs). Sequentially, the glutamate releases to the synaptic cleft. It then activates the downstream pathway or is re-uptaken into the presynaptic membrane by excitatory amino acid transporter after binding to the glutamate receptors (Figure 2C). Besides, the cystine/glutamate antiporter system x_c^-, which might exchange cystine for glutamate in a 1:1 ratio, has a vital role in releasing glutamate[125]. The "glutamate hypothesis" was first proposed by Kim *et al*[126]. They found that glutamate levels were decreased compared to healthy controls in CSF with SCZ[126]. The glutamatergic hypothesis of SCZ is based on the NMDAR hypofunction and the abnormality of glutamate transmission in SCZ.

Postmortem brain study shows a decreased expression level of VGLUT1 in the hippocampus of patients with SCZ[127]. However, VGLUT2 protein levels are increased in the inferior temporal gyrus (ITG) of SCZ[128]. The loss of VGLUT activity eliminates vesicular release and glutamatergic neurotransmission and regulates presynaptic quantal size or synaptic plasticity[129]. Postmortem studies have also revealed an increase in EAAT1 and EAAT2 transcripts in Brodmann's area (BA) 10 of subjects with SCZ, but not BA46[130]. Similar results have a relatively high agreement in the thalamus and cerebellar vermis[131,132]. These results indicate that EAAT is involved in glutamate reuptake in SCZ. Furthermore, evidence shows that mRNA expression levels of SLC3A2 and SLC7A11, two system x_c^- subunit genes, are decreased in peripheral white blood cells of SCZ patients compared to healthy controls. Abnormality of system x_c^- is involved in glutamatergic neurotransmission[125]. NMDAR-mediated glutamate transmission has been implicated in cognitive execution in the nucleus accumbens of SCZ[133]. Changes in the mRNA and protein levels of NMDAR subunits have been described in SCZ [134]. Suppressed NMDAR signaling through Src kinase may facilitate presynaptic glutamate release during synaptic activity[135]. In addition, the D-amino acid oxidase activator (DAOA, also called G72) protein, which has an important role in modulating NMDAR signaling, has a strong association with SCZ[136,137]. Those results indicate that alteration of glutamatergic transmission has a meaningful role in SCZ.

GABAergic pathway

Reduced GABAergic neurotransmission is in support of the 'GABA hypothesis' for SCZ[138]. RNA-Seq analysis reveals the disruption of GABA metabolite levels in SCZ[139]. Moreover, postmortem studies suggest that subjects with SCZ have lower mRNA and protein levels of synthetic enzyme GAD67 compared to healthy controls[140]. Lower expression of GAD67 may be a consequence of a deficiency of the immediate early gene Zif268, suggesting a potential mechanistic basis for altered cortical GABA synthesis and impaired cognition in SCZ[141]. GAD67 promoter methylation levels are associated with the SCZ-risk SNP rs3749034 and with the expression of GAD25 in the dorsolateral prefrontal cortex (DLPFC). Alternative splicing of GAD67 may contribute to GABA dysfunction in SCZ[142]. Similarly, the immunoreactivity of GAT1, a protein responsible for the reuptake of GABA, is decreased in SCZ [143]. Furthermore, GAD1 knockout rats exhibit SCZ-related phenotypes, such as cognitive impairments in spatial reference and working memory in the hippocampus[144]. A PET study using [^{11}C] Ro154513 has reported differential expression of GABA-A receptors in SCZ[145]. Therefore, the synthesis and reuptake of GABA are lower in SCZ. These abnormalities of GABAergic neurotransmission are related to cognitive impairments in SCZ.

Cholinergic pathway

Acetylcholine has a vital role in cognitive and behavioural/psychological function. Pharmacologic studies show that central cholinergic activity profoundly affects the storage and retrieval of information in memory. The choline acetyltransferase, a cholinergic function marker, is correlated with the severity of cognitive impairments in the parietal cortex of schizophrenic patients[146]. Furthermore, cholinesterase inhibitors (donepezil or rivastigmine) have positive effects on cognitive dysfunction in SCZ[147, 148]. These inhibitions increase the synaptic concentration of acetylcholine and finally enhance and prolong acetylcholine action on muscarinic and nicotinic receptors in the postsynaptic membrane.

SCZ patients show decreased α4β2 nicotinic acetylcholine receptors (nAChR)[149]. However, the α7 nAChR level is increased in the DLPFC of SCZ patients[150]. Besides, functional polymorphisms of the α7 nAChR have shown genetic linkage in SCZ[151]. Muscarinic receptors, also called the metabotropic muscarinic acetylcholine receptors, have five subtypes (M1-M5 receptors), encoded by the CHRM1-5 genes. Postmortem studies suggest lower CHRM1 levels in the cortex of patients with SCZ[152]. The loss of cortical CHRM1 may be regulated by miR-107 in SCZ[153]. What's more, CHRM1 is involved in memory processes, and blockade of hippocampal CHRM1 demonstrates a deficit in working memory [154]. Together, these results suggest that alterations in the cholinergic pathway may contribute to a breakdown in cholinergic homeostasis and have a key role in the pathophysiology of SCZ, particularly the cognitive impairments.

Other neurotransmitter pathways

Other neurotransmitter pathways, such as NE and neurosteroids, have also been implicated in the cognitive dysfunction of SCZ.

NE is a significant neuromodulator of brain function and neural gain. NE exerts its effects through noradrenergic receptors (α1, α2, and β). The alteration of noradrenergic neurotransmission has been studied for years. It is a consensus that patients with SCZ have higher NE levels than the control group [155,156]. Furthermore, α2-adrenergic receptor antagonist idazoxan has antipsychotic efficacy in the treatment of SCZ, especially the anxiety or depression symptoms[157]. It may be associated with the increased output of DA.

Additionally, the abnormality of neurosteroid transmission also has a crucial role in the pathobiology and symptomatology of SCZ[158]. Both the levels of progesterone and allopregnanolone (ALLO) are decremented in SCZ in a postmortem study[159,160]. Studies suggest that ALLO enhances NMDA

receptor neurotransmission by interaction with σ1 receptors in SCZ[161,162]. What's more, decreased levels of ALLO may modulate GABAergic transmission in the brain and finally lead to impairments of GABAergic function in SCZ[163].

POTENTIAL TARGETS FOR TREATMENT OF SCZ

Most antipsychotic drugs target serotonin-dopamine receptors or serotonin-glutamate receptors, suggesting disarranged neurotransmitter interaction. Newer AAPDs, such as clozapine, olanzapine, and risperidone, have been developed because of their significant effects on dopaminergic receptor subtypes and serotonergic receptors[164]. Interestingly, co-immunoprecipitation studies verify that HTR2A and DRD2 physically interact in HEK293 cells. Furthermore, shreds of evidence reveal that HTR2A and mGlu2 receptors can assemble into a functional heteromeric complex to modulate each other's function [165,166]. The expression of HTR2A is required for phosphorylation of mGlu2R at serine 843 and promotes mGlu2R-modulate G i/o signaling[167]. Therefore, there are potential antipsychotic drugs by targeting HTR2A, DRD2, and mGlu2R. DRD3 was found to be associated with SCZ in a case-control study[168]. Several pharmaceutical studies suggest that DRD1/5 agonists have potential therapeutic effects in SCZ by improving cognitive or negative symptoms[169,170]. What's more, HTR4/6 agonists can improve cognitive symptoms in SCZ. HTR4/6 may be a promising target for treatment of cognitive dysfunction in SCZ[171]. Additionally, sarcosine (a competitive inhibitor of the type 1 glycine transporter) and D-amino acid oxidase (DAAO or DAO) inhibitor can improve the clinical symptoms in SCZ patients. Therefore, glycine transporter and DAO may offer potential therapeutic targets for SCZ [172,173].

There are many other potential targets for the treatment of SCZ. Accumulated pieces of evidence have revealed various susceptibility genes in SCZ, including STAB2, GRIN1, GRIN2A, ARC, BDNF, NRGN, syncytin-1, and others[67,81,174]. Interestingly, many of those genes appear to be related to the control of synaptic plasticity and cognitive impairments in SCZ. BDNF plays a principal role in regulating synaptic organization, neurotransmitter synthesis, and the maintenance of synaptic plasticity[175]. Data from our lab provide evidence that syncytin-1 can regulate the expression of BDNF and DISC1. Furthermore, GNbAC1, a monoclonal antibody targeting syncytin-1, has been implicated in the treatment of multiple sclerosis and type 1 diabetes[176,177]. Thus, syncytin-1 is a promising therapeutic target for SCZ in the future.

CONCLUSION

Accumulated shreds of evidence indicate that changes in the morphology of synapses have a vital role in the incidence of SCZ. The potential role of synapse in SCZ appears much more complicated. In conclusion, the synapse can be involved in three aspects as follows: (1) The change of synaptic plasticity (*e.g.*, change in the dendrite spines, PSD, and alteration in LTP and LTD); (2) The abnormalities in neurotransmission (*e.g.*, dopaminergic transmission, serotoninergic transmission, and glutamatergic transmission); and (3) The impairment of cognition (*e.g.*, disconnection).

Impaired synaptic plasticity contributes to cognitive dysfunction in SCZ. These dysfunctions include abnormal brain connectivity and functional outcomes. With the development of brain imaging technology, research on cognitive impairments should do not focus on a single gene or brain regions but on neural circuits or brain networks to study the underlying mechanism in SCZ. SCZ is a complex disease, and there are still no available antipsychotic drugs to treat all symptoms of SCZ or accompany little side effects. Finding potential antipsychotic drug targets will help identify and develop novel therapeutic agents with fewer side effects.

FOOTNOTES

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