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Review

Synaptic Vesicle Protein 2A:Basic Facts and Roles in Schizophrenia

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ABSTRACT

Schizophrenia (SCZ) is a serious mental disorder that affects several different people all around the world. There are lots of different causes of SCZ meanwhile the exact reason is still unknown. Synaptic vesicle protein 2A (SV2A) is a gene thought to be responsible for neurotransmission and some neurotransmitters which are related to SCZ. Although there is not a direct connection between them, recent studies show that there may be an interaction that is hopeful for the treatment of SCZ. In this review SCZ, its causes and treatments, SV2A and its roles, and the connection between SCZ and SV2A were discussed.

Keywords: Central nervous system, neurotransmitters, psychosis, schizophrenia, synaptic vesicle protein 2A

The term 'psychosis' is a condition involving a series of behavioral changes related to loss of contact with reality and loss of insight. It comes from the Greek word for abnormal mental state and has been used in a variety of ways in clinical medicine.[1] A common symptom of several psychiatric, neurodevelopmental, neurologic, and medical conditions is psychosis and it is a significant target for examination and treatment in neurologic and psychiatric practice. The Diagnostic and Statistical Manual of Mental Disorders Fifth Revision (DSM-5) categorization and criteria for primary psychotic disorders underline that these conditions occur on a spectrum, with schizoid, also known as, personality disorder and schizophrenia (SCZ) representing mild and severe ends of the spectrum, respectively.[2,3] Chromosome 22q11.2 microdeletion is the most prevalent genetic defect linked to psychotic disorders. The 22q11.2 deletion syndrome (also known as the velocardiofacial syndrome or the DiGeorge syndrome) is caused by this, and it affects about one out of every 4000 live births. This condition is linked to cardiac, facial, and limb abnormalities and about a quarter of those who are affected have symptoms of SCZ or SCZ-like traits that are difficult to identify from idiopathic SCZ.[1,4,5]

Schizophrenia is a psychiatric syndrome that is identified using DSM-5 by signs of disorganized speech and behaviors, as well as significant deficits in emotional expression and self-motivated activities, cognitive deficits, hallucinations, delusions, which together, significantly degrade functioning compared to a person's baseline.[6,7] At least 26 million people live with SCZ which is one of the top 10 causes of disability worldwide and it affects approximately 1% of the world population.[8-10] It is known that the causes of SCZ are %80 genetic but there are other causes. According to a recent study, a list of novel genes and mutations, calcium voltage-gated channel subunit alpha1 A (CACNA1A) and calcium voltage-gated channel subunit alpha1 B (CACNA1B), that are mostly expressed in the brain involves the communication of neurons with each other by chemical and electrical signals at synapses in people with SCZ.[11,12] Also, there are revealed abnormalities in patients with psychotic disorders. For instance, there are focal volume reductions in the temporal, frontal, parietal lobes in patients with SCZ, schizoaffective disorder, or bipolar disorder with psychosis. There is also reduced cortical thickness in other and these brain regions of the patients.[9] It is shown with positron emission tomography (PET) studies that there is an increase in dopamine levels in the ventral striatum

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and a decrease in the frontal cortex in patients with SCZ. There are increased glutamate levels in the prefrontal and medial temporal regions in SCZ patients, as well.[1,13,14] According to a study, patients with SCZ show anomalies in the expression and phosphorylation of mechanistic targets of rapamycin (mTOR). In the SCZ human brain, phosphorylation of proteins downstream of the mTOR complex signaling, such as ribosomal protein S6, is reduced, as well.[15,16]

The central nervous system consists of the brain and spinal cord. It has several responsibilities such as receiving, processing, and responding to sensory information. Meanwhile discharging these responsibilities, they communicate via neurotransmitters that bind to and influence receptors on synaptic neurons.[17,18] Synaptic vesicles that are located in synaptic boutons contain neurotransmitters and are critical for these processes. Synaptic vesicle protein 2 (SV2) is a small gene family and an integral membrane protein present on all synaptic vesicles (SV). It has three isoforms including synaptic vesicle protein 2A (SV2A), synaptic vesicle protein 2B (SV2B), and synaptic vesicle protein 2C (SV2C) and they generally possess a 12-transmembrane-spanning structure. SV2A presents ubiquitously in the central nervous system (CNS) and endocrine cells and it is the most widely distributed isoform.[16,19,20] It regulates the release of action potential-dependent neurotransmitters. It has been demonstrated that the absence of SV2A in animals caused severe seizures and growth failure which took them to death.[21,22] It can be implied that SV2A controls seizure induction. In addition, it has been shown that SV2A bind to an antiepileptic drug called levetiracetam (LEV) which is widely used in patients with epilepsy to treat myoclonus, partial seizures, or generalized tonic-clonic seizures.[21,23] It is claimed that there may be an interaction between SV2A and SCZ. According to a study, SV2A levels are considerably lower in the anterior cingulate cortex (ACC) and frontal cortex of SCZ brains.[24,25]

This review first introduces SCZ, its subtypes, risk factors, treatments, SV2A, roles of SV2A, and finally focuses on the interaction between SV2A and SCZ.

SCHIZOPHRENIA AND SUBTYPES

Schizophrenia is a prevalent psychiatric disorder. It has several subtypes and symptoms. The subtypes can be categorized as paranoid, hebephrenic, undifferentiated, residual, and catatonic with having lots of different symptoms.

Symptoms of SCZ usually appear in early adulthood. Men can experience initial symptoms in their late teens or 20s while women experience it in their 20s and early 30s. Troubled relationships, low school results, and a lack of motivation are some of the more subtle symptoms that could be present earlier. Diagnosing SCZ in teens may be difficult due to the effects of some first signs such as change of friends, a drop in grades, or sleep problems and some factors such as isolating oneself, withdrawing from others, or an increase in unusual thoughts and suspicions. This stage in young people is called the prodromal period.[26,27] Regardless of the types of mental disorders, it is important to get a thorough medical examination to get the most accurate diagnosis. Symptoms should be present for at least six months in order to be diagnosed with SCZ. Symptoms of SCZ vary from person to person so, not everyone with it will experience all of the symptoms. These symptoms can be categorized in four ways such as positive, negative, disorganized, and cognitive symptoms.[27,28]

A) Positive symptoms: The word 'positive' does not mean good or positive. It refers to added actions or thoughts that are not based on reality. These symptoms sometimes are called 'psychotic symptoms' and include hallucinations such as seeing or hearing things that are not around, exaggerated perceptions, beliefs, behaviors, paranoia, thought disorders which include unusual thinking or disorganized speech. Catatonia is an important symptom which is the ability to stay in a position without moving for a long time.[29,30]

B) Negative symptoms: The word 'negative' refers to an absence of things that normally existed. These symptoms can be reduced motivation, speaking, or expression of emotions via facial expression or voice tone, and diminished feelings of pleasure in everyday life.[29]

C) Disorganized symptoms: These are positive symptoms that the individual is unable to think clearly or react appropriately such as talking nonsense and irrelevantly, quickly changing thoughts, forgetting or losing things, repeating movements or gestures, and having problems with senses like sounds or feelings.[30]

D) Cognitive symptoms: These symptoms include problems in concentration, memory, and attention such as being unable to process information to make decisions, having problems using the information after learning it, and having trouble focusing or

paying attention.[29]

The paranoid SCZ is defined by a preoccupation with one or more delusions or recurrent auditory hallucinations, although cognitive function and effect are relatively intact. Disorganized speech and conduct, as well as flat or inappropriate affect, are all symptoms of disorganized (hebephrenic) SCZ. Immobility; excessive, purposeless motor activity; strong negativism (e.g., opposition to all commands, rigid posture, mutism); or abnormalities of voluntary movement are all characteristics of the catatonic SCZ.[31,32] Residual SCZ is defined by the persistence of negative symptoms and the existence of at least two attenuated positive symptoms. Unless one of the criteria for subtypes of SCZ is met, a patient is said to have undifferentiated SCZ.[33-35]

SCHIZOPHRENIA, CAUSES, AND TREATMENTS

Anyone can get SCZ. It affects people from all races and cultures. Researchers can not tell the exact cause of it but genetics, environment, brain structure and function, drugs, alcohol, or difficult childhood are some of the likely causes.[33,34]

Schizophrenia is also related to some other cancers, neurotransmitters, and disorders. For instance, it is claimed that SCZ is associated with breast cancer.[35,36] Some risk factors such as smoking, alcohol use, excess body weight, physical inactivity, and exposure to stress are generally present in SCZ like they present in breast cancer. A higher level of prolactin and increased risk of breast cancer might be induced by antipsychotics that are used in the treatment of SCZ. It is demonstrated that women with breast cancer are at risk of ensuing SCZ.[37] Schizophrenia has been linked to genetic abnormalities involving gamma-aminobutyric acid(GABA)ergic neuron alterations during early ontogeny, according to animal and neurobiology studies.[38] There have been consistent reports of a greater incidence of SCZ in people born in the late winter or early spring, in people born and/or raised in cities, and in people whose father was rather old, but there has also been evidence of a link with young parents. Other conditions that have been linked to increased risk include head injury, epilepsy, autoimmune illnesses, and severe infections.[28,30] Smoking can reduce levels of several antipsychotics used to treat SCZ by as much as 50% by increasing metabolism, requiring a greater dosage in smokers with SCZ to obtain therapeutic blood levels compared to non-smoking SCZ patients. There is also strong evidence that smoking in SCZ is a form of self-medication for some of the disorder's cognitive deficiencies.[39,40]

Dopamine stimulants like amphetamine can cause psychotic symptoms in healthy people, and persons with SCZ are especially susceptible to these side effects. Patients with it had higher subcortical synaptic dopamine concentration, atypically high dopamine release after amphetamine therapy, and enhanced basal dopamine synthesis capacity when compared to healthy controls, according to PET imaging studies. Enhanced subcortical dopamine synthesis and release capacity are significantly linked to patients' pleasant symptoms, and increased subcortical synaptic dopamine content predicts good treatment response.[3,41]

Schizophrenia is a lifelong disorder that causes cognitive impairment, debilitating positive and negative symptoms, and a shorter lifespan. Schizophrenia treatment aims to alleviate symptoms and reduce the likelihood of a relapse, or recurrence of symptoms. Treatment includes medications like antipsychotics that help to relieve some symptoms including hallucinations, delusions, or thinking problems, exercise therapy, coordinated specialty care that combines medicine and therapy with social services, employment, and educational interventions, psychosocial therapy, and electroconvulsive therapy that is a procedure of sending electric shocks to the brain. Using standard antipsychotics, scientists were able to successfully treat flies with behavioral issues linked to recently found SCZ-associated genes in people.[42-45]

SYNAPTIC VESICLE PROTEIN 2A

Only the secretory vesicles of the brain and endocrine cells have the membrane glycoprotein SV2. It appears to be a unique feature of vertebrates, implying that it originated as part of more complicated systems of signaling. Synaptic vesicle protein 2 genes, A, B, and C, are found in mammals.[46]

Synaptic vesicle protein 2A is a synaptic vesicle membrane protein that is expressed all over brain areas, apart from trigeminal and facial nerve nuclei, endocrine cells, and chiefly copious in subcortical areas like the thalamus and basal ganglia.[47,48] Its exact function is still unknown but it is known that it has lots of different roles in neurotransmission. It is demonstrated that SV2A has important homology with lots of yeast transport proteins that belong to the major facilitator superfamily (MFS).[49] The human

SV2A gene is found at locus 21.2 on chromosome 1's q arm, and it is around 14.565 bp in length. It encodes a 4353 bp messenger RNA (mRNA) with 13 exons, which is translated to an 82.6 kDa protein with 742 amino acids.[47,49] It is hypothesized that SV2A is involved in maintaining the readily releasable pool of SVs by facilitating the endocytosis of the SV protein synaptotagmin-1 (SYT1). Reduced SV2A expression is associated with lower levels of SYT1 in the synaptic vesicle, a finding corroborated in SV2A/B knock-out mice, where SYT1 and the ratio of SYT1 to synaptophysin are significantly reduced. Synaptic vesicle protein 2A has been discovered as the particular binding site for LEV, a second-generation antiepileptic medication for several diseases including epilepsy.[15,50] In the setting of idiopathic generalized epilepsy, LEV should be considered as an initial or early add-on therapy for partial epilepsy, as an initial or early add-on therapy for myoclonic seizures in patients with juvenile myoclonic epilepsy, and as an early add-on therapy for patients with generalized tonic-clonic seizures.[51] When SYT1 function is expressed in its disease-related context, a missense mutation in SV2A that causes human epilepsy is shown to be unable to restore deficiencies in SYT1 function. This suggests that the seizure activity observed as a result of the loss of SV2A function could be caused by a dysregulation of SYT1 function.[52,53] Synaptic vesicle protein 2A is expressed in many GABAergic and inhibitory neurons as being the only isoform of SV2 and it is also expressed in yeast cells to transport out-of-cell galactose into the cells.[53]

Synaptic vesicle protein 2B and SV2C have a more restricted expression pattern; SV2B is generally expressed in cortical regions and the hippocampus, where it overlaps with SV2A. The striatum, pallidum, midbrain, brainstem, substantia nigra, and olfactory bulb are the only subcortical regions where SV2B is absent, but SV2C is only found in the striatum, pallidum, midbrain, brainstem, substantia nigra, and olfactory bulb. In rat brain homogenates, the overall amount of SV2 proteins (including SV2B and C isoforms) is highly constant across vesicles, with 2-5 copies per vesicle.[15,47]

SYNAPTIC VESICLE PROTEIN 2A AND SCHIZOPHRENIA

There is not a direct connection between SCZ and SV2A, but there are several neurotransmitters or genes that connect them indirectly.

When the antiepileptic medicine LEV was discovered to bind to SV2A, it drew a lot of interest. The antiepileptic efficacy of LEV and its derivatives was also linked to their affinity for SV2A. Levetiracetam has been tested in an animal model of defective sensory gating and has been shown to enhance auditory gating in mice with SCZ-like-gating impairments.[17] According to a study, LEV is effective at improving memory performance. This is the first evidence that a therapy strategy targeting hippocampus overactivity may be advantageous for higher-level cognitive function in SCZ. Altogether, LEV's useful effects on normalization neural overactivity suggest that its ability to reduce neural overactivity may have potential utility in SCZ cognition.[17,54,55]

Animals lacking the SV2A protein had different evoked GABA and glutamate releases in the hippocampus, according to electrophysiological studies. Following the first week after birth, these animals develop spontaneous seizures. Furthermore, overexpression of SV2A in hippocampus neuronal cells has been linked to a decrease in evoked postsynaptic excitatory current amplitude and glutamate synaptic release probability. So, SV2A regulates inhibitory GABA release in the hippocampus, which could explain why Sv2aL174Q rats are more susceptible to pentylenetetrazol seizures and epileptogenesis.[38,56] It has been discovered that GABAergic interneurons, lower expression of the GABA-synthesizing enzyme glutamic acid decarboxylase-67, and parvalbumin in cortical neurons were abnormal in the brains of postmortem SCZ patients. Additionally, clinical studies in chronic SCZ and "first-episode SCZ" have revealed a decrease of GABA in the ACC as evaluated by proton magnetic resonance spectroscopy Schizophrenia has been linked to genetic abnormalities involving GABAergic neurons alterations during early ontogeny, according to animal and neurobiology studies. The findings backed with the theory of GABA-glutamate imbalances in SCZ, revealing that GABA levels in the ACC of SCZ patients tended to deplete more quickly.[38,56-58]

The term "SCZ-like psychosis of epilepsy" or SLPE is commonly used in the literature on the link between SCZ and epilepsy to describe signs and symptoms that are similar to those experienced or presented by individuals with SCZ. Epilepsy was linked to a higher risk of SCZ and SCZ-like psychosis in a study. Family histories of psychosis and epilepsy were found to be risk factors for both SCZ and SCZ-like psychosis, which is unsurprising. This population-based study

found a link between seizures and SCZ or SCZ-like psychosis, implying that the two conditions may have similar genetic or environmental origins.[59-61] Synaptic vesicle protein 2A gene's connectivity and network structure were found that they change between normal and epileptogenic dentate gyrus significantly which are highly connected in the epileptic brain. It is probable that in epilepsy, SV2A plays a bigger role in synaptic function than it does in normal circumstances.[62] The authors hypothesized that genes increased as a result of seizures govern neuronal excitability via effects on vesicular trafficking, with SV2A serving as a key player. Reduced SV2A expression, according to some research, may lead to neural network instability and, as a result, epilepsy progression.[63,64] The first evidence of an SV2A mutation causing epilepsy in people was recently published. In a patient with intractable epilepsy, researchers discovered a homozygous mutation in the SV2A gene. A homozygous arginine is revealed by exome sequencing which is in exon five of the SV2A gene to glutamine mutation in amino acid position 383 (R383Q). R383Q is a recessive mutation, as both parents were carriers. The patient's phenotype could not be explained by any other possible exome changes.[19,22,62]

In conclusion, it is known that schizophrenia is the most studied psychotic disorder and there is not a treatment for it still. Meanwhile, studies are ongoing, there is also a gene, SV2A, that role can not be solved completely. Still, current studies show SV2A has an important role in neurotransmission which makes it very significant for neurotransmitters and the central nervous system. As we know SCZ has lots of causes, the role of SV2A may be effective on SCZ. The interaction between SV2A and SCZ is not yet clear but research is ongoing. If scientists find a direct connection between them, then maybe SCZ will be treated. Hopefully, there are small studies that claim an interaction between them. Eventually, we will be working and waiting until we find a certain connection and treatment.

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