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Calcium Channels: A Potential Therapeutic Target for Schizophrenia

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Abstract

Schizophrenia is a mental disorder in which perception and thought are severely impaired.It affects approximately 20 million people worldwide, with high suicidal rates and a high annual incidence of 1.5 per 1000 people. There are many hypotheses that define the pathogenesis of Schizophrenia (SCZ) among which excessive activation of dopamine (D2) receptors *via* the mesolimbic pathway, while low levels of dopamine in the nigrostriatal pathway are widely accepted. The hypothesis discusses the role of dopamine in causing alteration in the calcium homeostasis. Dopamine, N-methyl-D-aspartate (NMDA) receptor dysregulation and calcium homeostasis has been extensively studied to understand the mechanisms of neurodegeneration observed in Schizophrenia. Involvement of dopamine and NMDAR with the calcium and calcium ion channels on plasma membrane, endoplasmic reticulum, and mitochondria of the neuronal cells to form the vicious circle of calcium load. The disruption in the calcium homeostasis accompanies changes as observed in the whole brain pathology of SCZ. This includes synaptic dysfunction, impaired cognition, mitochondrial dysfunction, oxidative stress, inflammation, and cell apoptosis. This presents an immense need for the variety of potential therapeutic targets that could prevent or slow the progression of Schizophrenia. This review deals with the comprehensive source of information about mechanisms through which dopamine and NMDAR interacts with various calcium ion channels and the beneficial effect of calcium ion channel modulator in Schizophrenia.

Keywords: Schizophrenia, Calcium dyshomeostasis, Dopamine, NMDA, cognitive dysfunction

1. Introduction

Schizophrenia is a mental disorder in which perception and thought are severely impaired. People suffering from schizophrenia have delusional beliefs and, in many instances, these are accompanied by auditory or visual hallucinations and disturbances in social performance (Volkan et al., 2020), that affects over 20 million people globally, with

high suicidal rates and annual incidence of 1.5 per 1000 people (Mathew et al., 2020). Recent data suggests that1 % of the world population suffering from schizophrenia and having less improvement in life expectancy as the general population over the past decade (Laursen et al., 2014). There are Different neurotransmitterare involved in the pathogenesis of schizophrenia including dopamine, serotonin, glutamate, and γ-aminobutyric acid (GABA) Among these hypothesis 'dopamine hypothesis' is one of the longest standing hypotheses of schizophrenia and is based on multiple observations linking dopamine dysregulation. Dopaminergic projections are divided into the mesolimbic, mesocortical and nigrostriatal systems. Dopamine is produced in the substantia nigra and ventral tegmental regions of the brain. Impairments in the dopamine system result from dopamine dysfunctions in the substantia nigra, ventral tegmental region, striatum, prefrontal cortex, and hippocampus (Brisch, 2014). Negative/deficit symptom complex of schizophrenia associated with low dopamine activity in the prefrontal cortex and Positive symptoms occurs due to excessive dopamine activity in mesolimbic dopamine neurons. There are several drugs that may help in alleviating symptoms of Schizophrenia These include the dopamine D_2 receptor which is a drug target for all drugs against schizophrenia currently present on the market. First- and second-generation antipsychotics are dopamine D_2 receptor antagonists while third-generation drugs are partial agonists or biased ligands of this receptor (Luedtke et al., 2015). Histamine (H_3) receptor antagonists can be useful in treating cognitive deficits of schizophrenia (Ellenbroek et al., 2015). Therefore, there is a huge and pressing need in medicine for a development of advanced therapeutic approaches that may be able to deal with the underlying pathogenic pathways linked to schizophrenia. Ca^{2+} dysregulation in plasma membrane, endoplasmic reticulum, mitochondria, and cytosolic space have been reported in various schizophrenia models (Wang et al., 2017; Liang et al., 2015). Ca^{2+} channel blockers have demonstrated to show beneficial effects against memory impairment, cognition, inflammation, and oxidative stress in various experimental models of schizophrenia (Bobich et al., 2004; Singh,2016; Gupta et al., 2024). Therefore, The identification of abnormalities in the balance of calcium in bipolar illness and schizophrenia highlighted concerns regarding the effectiveness of the Ca2+ handling system, specifically with regard to alterations in the Ca^{2+} extrusion mechanism in neurons(Lisek et al., 2018).

2. Ca^{2+} Homeostasis

The regulation of Ca^{2+} dynamics is very complex in neurons Excitable cells fire an action potential in response to depolarization and contain functional voltage-gated ion channels. Neurons and muscle cells are excitable, but other cell types show oscillatory changes dependent on calcium entry (Dolphin, 2021). Voltage-gated calcium channels open to allow calcium ions to flow down their electrochemical gradient, driving processes like hormone secretion, neurotransmitter release, calcium-dependent gene transcription, and spontaneous pacemaker activity (Mangoni et al., 2003; Putzier et al., 2009; Zamponi et al; 2015).Voltage-gated calcium channel dysfunction is linked to various diseases, including autism spectrum disorder, schizophrenia, and bipolar disorder, and is currently of significant interest in psychiatric disorders.

Voltage gated ion channels are divided into L-type, P-type, N-type, R-type, and T-type Ca^{2+} channels depending upon the physiological and pharmacological properties of the current they carry, High-voltage activated calcium channels were referred to as N-type, P/Q-type, and R-type, while low-voltage activated channels were referred to as T-type. (Nowycky et al., 1985; Heyes et al 2015; Dolphin, 2006). Voltage-gated calcium channels can have up to four distinct subunits, including the pore-forming α1 subunit, auxiliary α 2δ and β in some cases (γ) subunits.

3. Voltage-gated Calcium Channel Distribution

CaV1.1 is a low-expression calcium channel found in skeletal muscle, while CaV1.2 is predominant in ventricular cardiac muscle and the brain. CaV1.3 is restricted, particularly in the heart and ear. CaV2 channels predominantly have a neuronal distribution, with CaV2.1 prevalent in the cerebellum. CaV2.3 triggers spontaneous glutamate release. At synapses, CaV2 channels form large signaling complexes in the presynaptic nerve terminal, which are responsible for the calcium entry that triggers neurotransmitter release and short-term presynaptic plasticity CaV3 channels, present in most neurons, play crucial roles in neuronal excitability and pacemaker activity, with CaV1.3, a low-voltage activated channel, also present in the thalamus (Perez-Reyes, 2003; Guzman et al., 2009; Putzier et al., 2009). CaV2 channels form large signaling complexes in the presynaptic nerve terminal at synapses, responsible for calcium entry, neurotransmitter release, and short-term presynaptic plasticity.

Calcium entry in the CNS and peripheral nervous system is primarily triggered by fast neurotransmission by P/Q-type calcium currents from CaV2.1 channels and N-type calcium currents from CaV2.2 channels (Dunlap et al., 1995; Olivera et al., 1994). Receptor gated Ca^{2+} channels require specific ligand binding, with L-Glutamate activating ionotropic and metabotropic receptors. iGluR, such as NMDAR and AMPAR, activate upon glutamate binding and membrane depolarization. Purinergic (P2X) receptors respond to extracellular ATP, causing membrane depolarization and Ca^{2+} influx, and modulating synaptic strength. (Pankratov et al., 2009). The endoplasmic reticulum and mitochondria store intracellular Ca^{2+} ions. Excess Ca^{2+} ions are removed by the SERCA pump, activated by RYR receptors and IP3R. This release is regulated by various proteins, including FK506-binding proteins, calmodulin, calcineurin, ankyrin, and sorcin. (Yamada et al., 1995; Pickel et al., 1997; Bourguignon et al., 1995; Brillantes et al., 1994). High Ca^{2+} levels in synapses indicate synaptic plasticity, with endoplasmic reticulum containing STIMs for re-filling depleted intracellular stores and communicating with SOCE channels. The plasma membrane has ARC channels that activate Ca2+ ion channels at low agonist concentrations. These channels, like SOCE channels, rely on STIM1 proteins. Ca^{2+} ions are extruded from the plasma membrane to the extracellular environment via Ca^{2+} ATPase and Na+/Ca2+ exchanger. Mitochondria regulate energy metabolism and cytoplasmic Ca2+ levels, with changes in cytosolic concentration allowing Ca^{2+} to enter the membrane (Nicholls, 2005). During signal decline, mitochondria release Ca^{2+}, increases ROS formation, inhibits ATP synthesis induces mitochondrial permeability transition pore (mPTP) opening, and releasing cytochrome c and AIF, affecting the local environment. (Brustovetsky et al., 2003). Disruption in cytosolic Ca^{2+} concentration and signaling affects essential neurological functions like neurotransmitter release, LTP, LTD, synaptic plasticity, neuronal plasticity, and cognition, affecting neurodegenerative disorders like Schizophrenia. Calcium channels, activated by membrane depolarization, conduct calcium into cells, initiates physiological responses like secretion, contraction, and gene transcription. Calcium binds to target proteins, creating a microdomain or nanodomain of calcium signaling (Stanley, 1997; Wang and Augustine, 2015) Calcium channel function is regulated by binding calcium, other ligands, and protein phosphorylation. Mutations in calcium channels are linked to various diseases, including hypertension, heart failure, skeletal muscle paralysis, diabetes, migraines, chronic pain, and brain disorder (Heyes et al., 2015; Ortner and Striessnig 2016). Ca^{2+} channels are considered a key target for the development of psychiatric disorders due to their fundamental role in the central nervous system. Recent research on calcium channel regulation in neuropsychiatric diseases like migraine, cerebellar ataxia, Parkinson's, autism, schizophrenia, bipolar disorder, and depression offers new implications for calcium channel mutation and dysfunction.

4. L-type Ca^{2+} channel

L-type calcium channels (Cav1) are one of three voltage-gated calcium channels targeted by clinically used calcium channel blockers (CCBs) and are the first class accessible

for biochemical characterization. Genomic evidence suggests common variants in VGCC subunit genes, particularly CACNA1C, which encodes the L-type calcium channel (LTCC) CaV1.2 subunit, are linked to psychiatric disorders like schizophrenia (Harrison 2022). The role of L-type voltage-gated calcium channels, specifically CaV 1.3, in neuronal activity regulation and lacking CaV 1.3 exhibit fear conditioning and depressive-like behaviors linked to hippocampus and amygdala function. Genetic variation in CaV 1.3 is linked to psychiatric disorders (Lauffer, 2022). L-type calcium channels (LTCC) play a crucial role in brain physiological processes, such as modulating dopamine signaling, transmitting auditory stimuli, and affecting learning and memory processes (Berger, 2014). LTCCs and VGCCs play a role in serious mental illnesses, with more knowledge about their function and structure. Clinical studies on LTCC blockers' efficacy in treating SCZ, and drug dependence show mixed results, emphasizing the need for further investigation into dysregulated Cav1.2 and Cav1.3 (Kabir et al., 2017).

Table 1: Therapeutic effect of voltage gated Ca^{2+} ion channel modulator in Schizophrenia

Treatment	Target (type of calcium channel)	Dose	Pharmacological effect	References
Nimodipine	L-type voltage-gated Ca2+channels	10mg/kg (i.p)	Nimodipine decreases cytoplasmic free Ca2+ and blocks L-type Ca2+ currents in NPY neurons.	Ishii et al., 2019
Lithium	L-type voltage-gated Ca2+channels	Mixed in Chow diet	lithium antagonizes dopaminergic neurotransmission and behaviors mediated by the Akt-Gsk3 signaling pathway	Luo et al., 2020
Memantine	L-type voltage-gated Ca2+channels	10mg/kg	The NMDA-receptor antagonist partially blocks NMDA receptors, preventing a toxic calcium influx and cell death.	Paraschakis, 2014; Czarnecka et al 2021
Isradipine	L-type voltage-gated Ca2+channels	5 mg/kg	Novel therapy option improving verbal memory and attention, both related to its activity in the hippocampus and the cerebellum	Vahdani et al., 2020
Urolithin	L-type voltage-gated Ca2+channels	2.5 mg/kg/day I.P.	Prevention of mitochondrial calcium influx and ROS production. antioxidative, anti-inflammatory, and	Chen et al., 2021

			antiapoptotic potential	
Nifedipine	L-type voltage-gated Ca2+channels	5 µM	Nifedipine inhibit the calcium signals and blocks the ROS production , enhance learning and memory in schizophrenic patients	Schwartzet al., 1997
pimozide	T-type voltage-gated calcium channels		Pimozide selectively blocks dopamine receptor D2 (DRD2), used to treat various mental/mood disorders, including chronic schizophrenia.	Dakir, 2018

5. Role of Ryanodine receptors in calcium homeostasis

Ryanodine receptors (RyRs) are a type of intracellular calcium release channels that mediate calcium-induced calcium release from the endoplasmic reticulum (Singh and Sharma, 2016). RyRs has three isoforms (RyR1, RyR2, and RyR3) that encoded by three distinct genes (Matsuo et al 2009). Theses isoform of RyRs are highly expressed in the cerebellum, hippocampus, cerebellar Purkinje cells, olfactory region, basal ganglia, cerebral cortex, and striatum (Abu-Omar et al., 2018). Increased intracellular Ca^{2+} in neurons via voltage-dependent calcium channels or N-methyl-d-aspartate receptors on the plasma membrane increases RyRs activity .Free cytosolic level (nanomolar concentrations) of Ca^{2+} may activate all RyRs in brain (Del Prete et al., 2014). RyRs may also interact with several governing proteins like: CaMKII and calcineurin, to monitor channel activity in the face of outside stimuli, which in turn controls intracellular calcium level (Zalk et al., 2007). Calcineurin-RyRs complexes was essential to stabilizes RyRs integrity, which could prevent calcium over-leakages in neurons (Matsuo et al., 2009). An imbalance in intracellular calcium levels brought on by impaired RyRs can compromise synaptic neuronal function, make cells more vulnerable, and subsequently trigger neuronal death (Abu Omar et al., 2018). Cognitive processes like neuronal synaptic plasticity, learning and memory were reported to depend on RyRs-mediated Ca^{2+} release for neuronal viability. RyRs mediated calcium signaling may interact with β-amyloid production in neurons, and causes synaptic dysfunctions and decline cognition, which leads to the progression of Alzheimer's disease (Del Prete et al., 2014). One important redox regulator, glutathione, is deficient in schizophrenia. Compromised glutathione might impair dopamine signaling in neurons through redox-sensitive RyRs. Reports suggests that stimulated RyRs in glutathione deficits may strengthens intracellular calcium-dependent pathways following activation of D2-type receptors and produces schizophrenia like phenotype (Steullet et al., 2008).

6. Role of Calcineurin in calcium homeostasis

Calcineurin (Cn) is a heterodimeric calcium/calmodulin-dependent serine/threonine protein phosphatase comprising of two subunits, a regulatory subunit of calcineurin B (CNB) and a catalytic subunit of calcineurin A (CNA) (Rusnak, 2000).CNA isoforms are expressed in the brain, with a particular abundance in the hippocampus, cortex, and striatum (Takaishi, 1991). There are three isoforms of the catalytic subunit, CNAα, β, and γ. CNAα and β are known to be abundant in the brain and to modulate neuronal processes (Sun et al 2010). CNAγ expression has been thought to be restricted to the testis (Muramatsu 1992). Recently,

de-novo mutations in PPP3CA, a gene encoding a CNA isoform, have been repeatedly reported as a cause of ID /developmental delay and epilepsy, which are often accompanied by autistic features (Li et al., 2019). It has also revealed that inRNA sequencing analysis expression of CNB1 (PPP3R1) is reduced in the cortex of patients with ASD (Voineagu et al., 2011). Mutant mice with forebrain neuron-specific deletion of Cnb1 (Cn mutants) exhibited multiple behavioral abnormalities related to schizophrenia and other neuropsychiatric disorders, including hyper-locomotor activity (mania-like behavior), reduced nest-building activity (a mimic of negative-like symptoms (Pedersen et al 2014), and working memory deficits (Miyakawa et al., 2003). Absence of CN activity in the amygdala, hippocampus, and entorhinal cortex could recapitulate some aspects of increased mesolimbic dopaminergic transmission. Moreover, because CN is activated by dopamine D2 receptor signaling (Greengard et al., 1999), CN is involved in NMDA and dopamine receptor signaling pathways, its absence could disrupt critical interactions between the glutamatergic and dopaminergic neurotransmitter systems (Miyakawa, 2003) and alterations in dopaminergic, glutamatergic signaling comprise a major contributing factor in schizophrenia pathogenesis (Carlsson, 1997).

7. Supraspinal Transient Receptor Potential Subfamily V Member 1 (TRPV1)

TRPV1 is a specialized channel expressed by peripheral sensory neurons involved in pain sensation and at various other neuronal and non-neuronal sites in the mammalian body (Bevan, 2014). TRPV1 receptors are found in various brain regions and interact with key neurotransmitter systems, including the endocannabinoid and opioid systems, which are associated with mental illnesses (Escelsior et al., 2019). When TRPV1 is activated, calcium and sodium ions flood the system, starting a series of events that include membrane depolarization, neuronal firing, and the release of chemicals that are implicated in the transmission of pain, including glutamate, bradykinin, and calcitonin gene-related peptide (CGRP) (Kort et al., 2012). The TRP superfamily comprises approximately 30 subtypes of tetrameric six transmembrane nonselective calcium-permeable ion channels divided into six subfamilies: ankyrin (TRPA), melastatin (TRPM), canonical, mucolipin, polycystin and vanilloid (TRPV). They are expressed on numerous cell types and gated by several different forms of sensory stimulation (González et al 2017). Several disorders have been studied as possible therapeutic targets for TRP channels, including the subtype 1 of the vanilloid subfamily (TRPV1) (Moran et al., 2011). Opening nonselective Ca^{2+}-permeable channels such TRPA1, TRPV1, and TRPM3 not only results in depolarization, which triggers action potential firing and sends a pain signal to the central nervous system (Vandewauw et al., 2018), but also an increase in local cytosolic Ca^{2+} that causes neurogenic inflammation and the release of neuropeptides. The TRPV1 subtype is the most relevant potential target to develop therapeutically beneficial modulators for the treatment of depression, anxiety, panic attacks, addiction disorders, obsessive compulsive disorder, schizophrenia, and epilepsy. Dopamine neurons in the midbrain's ventral tegmental region fire more often in response to TRPV1 activation; this response is concentration-dependent. When TRPV1 is triggered, dopamine neurons in the ventral tegmental area of the midbrain fire more frequently; this response is concentration-dependent (Marinelli et al., 2005). Positive symptoms of schizophrenia are known to be caused by activation of the dopaminergic system (Carlsson et al., 1963). The brain's reward system regulates dopaminergic transmission, which suggests that TRPV1 may be a key target for schizophrenia.

8. Role of Calpains in calcium homeostasis

Calpains are a type of non-lysosomal neutral proteases that are triggered by calcium and are found in the cytosol and mitochondria. They are involved in many different aspects of cellular activity (Smith, 2012). In general, there are two types of calpains: typical, or classical, and atypical, or non-classical. Typical calpains have a calcium binding domain that

is penta-EF-hand shaped. The penta-EF-hand, which is responsible for binding calcium, is absent from atypical (or non-classical) calpains, setting them apart from conventional calpains (Sorimachi, 2012; Macqueen, 2014). Necrotic cell death and neurodegeneration are associated with certain membrane receptor channels. An inflow of calcium ions occurs within postsynaptic neurons upon the gating of AMPA, NMDA, ASIC, and TRPM7 channels and NMDA, NCX channels are cleaved by activated calpains (Simpkins, 2003; Bano, 2005). Whereas NCX, which is involved in calcium extrusion, becomes inactive, NMDA stays active. In both necrosis and apoptosis, the primary death signaling event is a sudden rise in intracellular calcium concentration, which triggers the activation of calpains and Neurons may die by necrotic or apoptotic means, depending on the degree of calpain activation. Central neurons' NMDA channels may be downregulated by an increase in Ca2+ (Xin 2005). Schizophrenia and other neurodegenerative diseases can result from aberrant dopamine release caused by hypo-functioning NMDAR (Nakazawa, 2020).

Conclusion

An effective treatment strategy for schizophrenia may involve focusing on the Ca^{2+} channel and Ca^{2+} dysregulation pathways. Evidence for calcium homeostasis disruption in schizophrenia is abundant in the literature. Neuronal and synaptic loss, as observed in schizophrenia patients, may be avoided by focusing on Ca2+ signaling pathways and restoring Ca^{2+} homeostasis. In addition to additional Ca^{2+} signaling proteins, NMDAR, AMPAR, and other small molecule proteins that interact with these targets to produce neuroprotective effects are potential targets. The clinical studies' permissible levels of these drugs are a restriction, given the significance of calcium signaling in the body as a whole.

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