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REVIEW ARTICLE

Ionic Channels as Potential Targets for the Treatment of Autism Spectrum Disorder: A Review

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Abstract: Autism spectrum disorder (ASD) is a neurological condition that directly affects brain functions and can culminate in delayed intellectual development, problems in verbal communication, difficulties in social interaction, and stereotyped behaviors. Its etiology reveals a genetic basis that can be strongly influenced by socio-environmental factors. Ion channels controlled by ligand voltage-activated calcium, sodium, and potassium channels may play important roles in modulating sensory and cognitive responses, and their dysfunctions may be closely associated with neurodevelopmental disorders such as ASD. This is due to ionic flow, which is of paramount importance to maintaining physiological conditions in the central nervous system and triggers action potentials, gene expression, and cell signaling. However, since ASD is a multifactorial disease, treatment is directed only to secondary symptoms. Therefore, this research aims to gather evidence concerning the principal pathophysiological mechanisms involving ion channels in order to recognize their importance as therapeutic targets for the treatment of central and secondary ASD symptoms.

Keywords: Channelopathies, ion channels controlled by ligands, ion channels controlled by voltage, neurodevelopmental disorders, autism, spectrum disorder, brain function.

1. INTRODUCTION

In 1980, Autistic spectrum disorder (ASD) was finally inserted into the Diagnostic and Statistics Manual for Mental Disorders III (DSM-III), yet ASD had been discovered about 70 years earlier [1]. ASD is characterized by varying degrees of impairment in language and social interactions and by the presentation of repetitive behaviors, as well as impairment in adapting to new activities in the routine of the affected individual [2]. In autistic individuals, evidence points to the development of abnormal cytoarchitecture in the first or second trimester of pregnancy, in which increased cell proliferation, abnormal cell migration, and reduced neuronal size and neurochemical alterations are observed [2]. Studies involving magnetic resonance imaging in children aged 18 months to 5 years diagnosed with ASD revealed a 5-10% increase in brain volume, with morphometric changes in the frontal and temporal lobes, and lower gray matter, and amygdala volumes when compared to the healthy control group [3]. It is known that brain volume increases during early childhood, followed by interrupted growth with possible decreases after 15 years of age [3]. One of the important areas in ASD development is the hippocampus, an area of the limbic system involved in the central functions of social behavior, learning and memory, processes that are compromised in the autistic individual [4-6].

Since the 1980s, in *post mortem* studies, hippocampus neuropathology has been studied, and cellular alterations in subiculum and CA1 have been evidenced. Therefore recent studies indicate that the hippocampus can be a potential biomarker, although not specific for the disorder [6].

All of these changes culminate in atypical brain connectivity, with disruption of neural communication, as well as imbalances in excitation and inhibition mechanisms [7]. Studies indicate that the development of ASD is influenced by environmental factors, such as advanced maternal and/or paternal age, smoking, mothers with hypertension, epilepsy or diabetes, as well as genetic factors, including mutations of the SHANK2 gene, involved in neuronal synapses, changes in the fragile X mental retardation 1 (FMR1) gene, or those associated with channelopathy pathogenesis that results in a phenotype associated with cognitive and neurobehavioral disorders [8-10]. Given this, our review aims to briefly evaluate the latest studies on ion channel mutation and its role in

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causing ASD and ASD associated comorbidities towards making ion channels important therapeutic targets in the treatment of ASD symptomology.

1.1. General Characteristics and Diagnosis of Autism Spectrum Disorders

ASD is a pathology that directly affects brain functions. It can be measured based on a series of specific clinical characteristics, which can vary in severity according to the individual. The condition can be expressed through changes in language, communication, stereotyped behaviors, and difficulties in social interaction. Recently, the American Pyschiatric Association (APA) diagnostic and statistical manual for mental disorders (DSM)-5, changed the diagnostic criteria, expanding the identification of symptoms, with an emphasis on observation of children's communication and social interactions. Thus, various diagnoses have been integrated, such as Asperger's syndrome, which was recategorized as ASD [11, 12]. According to data from the Center for Disease Control and Prevention (CDC), an estimated 1.5% of the population presents with some type of ASD. In the last two decades, an expenditure of approximately $ 130 billion for treatment has been mobilized [13-17].

Alterations in neurodevelopment are commonly identified during childhood. However, a marked number of cases continue without differential diagnosis until adulthood. This occurs due to symptoms in common with other psychiatric conditions, such as psychoses, mood disorders, cognitive disorders of another nature, or some development of special skills that limit recognition of ASD [12, 16, 18]. The diagnosis is multidisciplinary, based on clinical and behavioral indications, and takes into account the individual's history.

According to DSM-V requirements, a diagnosis must meet two of the criteria, deficits in social communication and restricted, repetitive patterns of behavior and/or interests, characterized by difficulties in diction and repetition, motor changes, ritualistic routinized behaviors with an aversion to changes, interests being restricted, whether individualized or atypical, and accompanied by hypo-hyper reactivity to sensory input. Irritability, hyperactivity, and aggression may be considered secondary symptoms, however, they are not decisive for diagnosis and do not imply functional loss [19-21].

1.2. Epidemiology

ASD has been studied for 70 years, with intense increases since the 1990s, a fact attributed to greater knowledge about the disorder and recognition through clinical diagnosis. From the first epidemiological study, the prevalence of autism has grown, reaching today about 0.6 to 1.5% of the world's population [20]. Autism spectrum disorder has increased dramatically with the contribution of genetic factors and environmental factors, one of the potent environmental factors is abnormal gestational age (preterm or postterm pregnancy), as well as exposure to pollutants, such as mercury, $PM_{2,5}$ and NO_2, exposure to maternal medication use and prenatal infection [22, 23]. Considering genetic factors, studies show that the prevalence among siblings is about 18 times higher, and among monozygotic twin brothers, the chance of both presenting ASD is from 70 to 90%, confirming the involvement of a hereditary factor in its development [24].

Recent CDC data in the United States indicate a prevalence of 1 in 54 children diagnosed with autism, with the prevalence being higher in boys than in girls, about 1 in 34 boys, and only 1 in 144 girls [25]. Theories have been postulated to understand differences in the diagnosis of autism, such as the influence of protective factors in females and fetal exposure to testosterone during male brain development. Yet taken together, an etiological origin that differs according to sexual imbalance remains inadequate and limited. It is essential to understand the disorder as multifactorial, in which (regardless of sex) genetic, epigenetic, and hormonal changes are involved in its development [26, 27].

Prevalence differences may also be attributed to the fact that women generally present with milder conditions than men, with other symptoms and a different presentation, making autism in women underdiagnosed [28]. These factors increase the chances of an individual presenting greater delay in cognitive development [29].

In Brazil, a public health system study revealed that mothers of children with ASD notice the symptoms and differences in the development of their children at around 24 months of age, yet the diagnosis generally comes only three years later, making the necessary treatment and follow-up difficult for these patients, despite the guarantee of the right to early diagnosis established by law 12.794 of 2012 [30].

1.3. Etiological Factors

Autism spectrum disorders present a multifactorial etiology, and the mechanisms are still poorly understood. It is known, however, that genetic and environmental factors can favor the phenotypic characteristics of autism. Genomic sequencing data indicate various ASD-associated genes which are also involved in other psychiatric disorders [31]. Recent studies report that heredity in ASD can be influenced (or not) by cumulative environmental, chemical, physical and biological factors that induce diffuse neuronal changes, and involve dysfunctions in various ion channels. Psychosocial stimuli such as prenatal stress can cause immune disorders, increasing the levels of circulating cytokines and chemokines and altering signaling in infantile neurodevelopment [32-36].

Understanding the influence of environmental factors on ASD can contribute to interventions and help minimize exposure to triggering agents that alter epigenetic mechanisms. For example, DNA methylation, when combined with genetic and environmental factors, may be responsible for neurological development disorders, according to the Trigger-Threshold-Target vulnerability model [37, 38]. The main environmental risk factors investigated in ASD include paternal age and chromosomal aberrations due to the accumulation of mutations in spermatogenesis (duplication of FOXK1 and KCNA4), fetal exposure to steroidal hormones (changes in sex steroid synthesis genes, ESR2, CYP11B1, CYP17A1, and CYP19A1), drugs, vitamin deficiencies, infectious conditions, smoking, alcoholism and obesity and their associated comorbidities [35, 39-43].

Although various environmental mechanisms are suggested as triggering autistic behavior; neuroinflammatory processes, oxidative stress, hypoxia, and increased hypothalamic-pituitary axis (HPA) reactivity associated with low-intensity inflammatory diseases are the main etiological

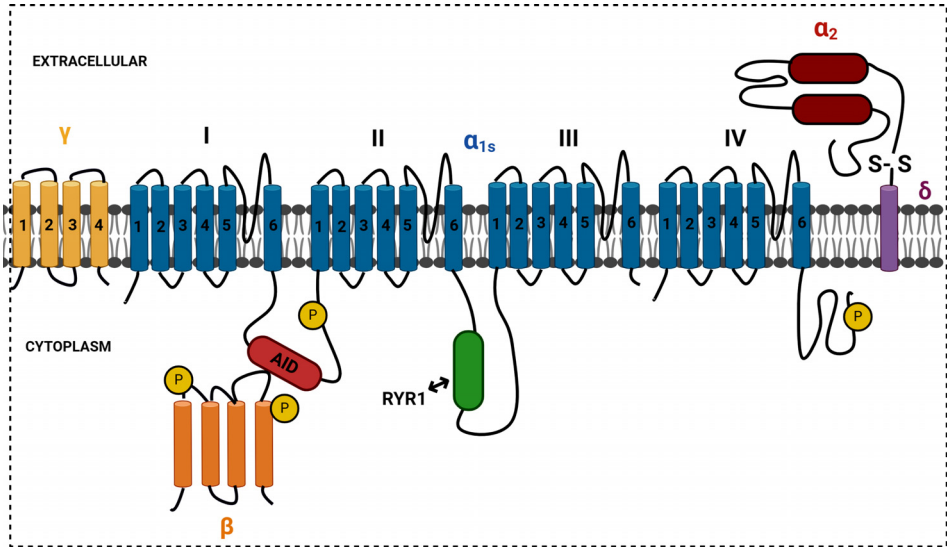

Fig. (1). Voltage-gated calcium channel-Tetrameric structure, formed by an α1 subunit with four repeated domains with six transmembrane segments (S1-S6), with the formation of the pore between the S5-S6 segments, a β intracellular subunit, an extracellular subunit α2δ -joined by disulfide bond, and a transmembrane γ subunit. (Created with BioRender.com) **Abbreviations:** AID: Alpha 1 interaction domain; RYR: Ryanodine Receptors. Source: adapted from Berridge (2014). *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

bases and are related to changes in fetal neurodevelopment. These factors deregulate serotonergic and dopaminergic signaling, induce neuronal apoptosis, alter synaptic plasticity, compromise various cognitive functions, and potentiate the possibility of short and long-term psychiatric disorders being generated in the offspring [44, 45]. Despite the relevance and influence of environmental and psychosocial factors which predispose to autism, it is necessary to expand studies that investigate gene-environment relationships, preventive measures, clinical variations, and disorder severity [34].

2. IONIC CHANNELS IN AUTISTIC SPECTRUM DISORDERS

Ion channels are transmembrane proteins assembled around a central pore, passively allowing the influx and/or efflux of ions by obeying the electrochemical gradient. The channels control numerous physiological processes, such as muscle contraction, neurotransmission, memory, and wakefulness, among others. Ion channel dysfunctions are associated with the pathophysiology of several diseases in the central nervous system (CNS) due to their wide expression in astrocytes and neurons, and responsible for alterations in different complexes and in different areas of the brain [46, 47]. Human genome studies on genetic variations, have identified several candidate genes (related to ASD), which are responsible for coding of proteins involved in neuronal development and regulation, such as ion channels. This review will examine the role of ion channels in ASD, and their respective validation as important therapeutic targets towards modulation of the many symptoms characteristic of the disorder [24].

The voltage-gated calcium channels (VGCC) are classified into 5 families: their subtypes, being the L (Cav1), N, P/Q, and R (Cav2) type channels (activated by high voltage), and the type T calcium channel (Cav3) activated by low voltage. The N, P/Q, and R type channels are mostly expressed in neurons [48]. Membrane depolarization and the consequent activation of these channels induce the influx of calcium into the cell, triggering several processes such as the release of neurotransmitters, intracellular signaling, and gene transcription [49]. VGCC are structurally composed of an α1 subunit, an α2δ dimer linked by a disulfide bond, a β intracellular subunit, and a γ transmembrane subunit (Fig. **1**) [22]

The α1 subunit presents 10 isoforms that are found in the subfamilies Cav1, Cav2 and Cav3. This subunit is responsible for the channel's calcium selectivity, as well as its pharmacological properties. The α1 subunit is formed by six transmembrane segments, the S5 -S6 segments form the central pore, and the S1 -S4 segments located on the periphery of the pore also act in the channel's selectivity [48, 49]. Changes in the structure of VGCCs are related to the development of diseases such as epilepsy, hemiplegic migraine, and autism [50]. Genetic modifications (mainly in the α1 subunit) are chiefly involved in both the development of ASD, and in the appearance of comorbidities, such as muscular, neurological, cardiac and vision syndromes., the most recurrent alterations are described in Table **1** [49, 51, 52].

The changes presented above induce alterations in voltage-gated calcium channel structure, which in turn cause calcium signaling modification within the cell, with actions on inositol-3-phosphate (IP3R), and Ryanodine (RyR) receptors (whose alterations can cause cardiac myopathies), as well calcium-ATPases of the plasma membrane (PMCA) [51]. One of the main changes in VGCC associated with individuals with autism is the modification of the α1C subunit in Cav1.2 receptors. Patients with this mutation develop Tim-othy Syndrome (TS), which is a multi-organ disease, mainly characterized by lethal cardiac arrhythmia in long QT syndrome. The mutation also causes neurodevelopment modulation since about 80% of patients with TS also have ASD [52]. Other ASD associated abnormalities are caused by the Cav 2.2 mutation, which delays speech due to

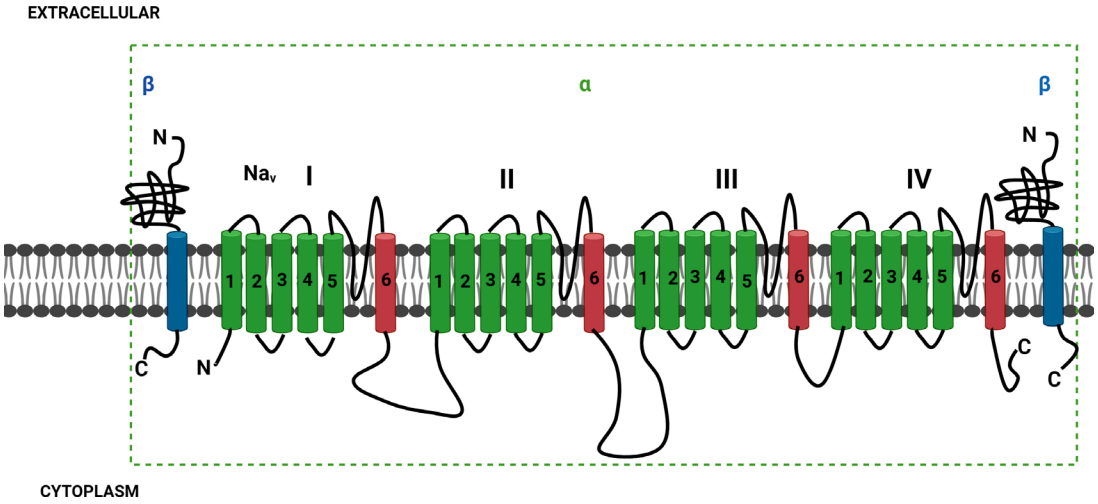

Fig. (2). Voltage-dependent sodium channel-structure formed by α subunit with four domains, presenting six transmembrane segments each associated with two β subunits. Source: adapted from Yamakawa (2016). (Created with BioRender.com) *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

impaired neuronal development; the Cav1.4 mutation that has been associated with the development of night blindness in patients with autism; and Cav3.2 mutations which are highly expressed in the brain and closely related to the development of the autistic phenotype [1].

Table 1. Variations of calcium channels subunits associated with ASD.

Gene	Channel		Subunit
CACNA1A	Cav 2.1	P/Q	Alpha 1A
CACNA1C	Cav 1.2	L	Alpha 1C
CACNA1D	Cav 1.3	L	Alpha 1D
CACNA1E	Cav 2.3	R	Alpha 1E
CACNA1F	Cav 1.4	L	Alpha 1F
CACNA1G	Cav 3.1	T	Alpha 1G
CACNA1H	Cav 3.2	T	Alpha 1H
CACNA2D4	Cav 1	L	Alpha 2-Delta 4
CACNB2	Cav 2.2	N	Beta 2

2.1. Voltage Activated Sodium Channels (Nav)

Voltage-gated sodium channels (Nav) are of great importance in the generation and propagation of electrical impulses in excitable cells, such as neurons. Activation of these channels and modulations are already known to be associated with diseases such as migraine and epilepsy, but recently they have also been found to be involved in disorders such as autism [53]. These channels are classified from Nav1.1 to Nav 1.9 with an atypical counterpart Nav 2.1. They are structurally composed of an α subunit determined by genes of the SCN1A to SCN11A family, which is responsible for the formation of the functional channel. The subunit contains four domains each with six segments, S4 is characterized by being sensitive to voltage, opening the channel when the membrane is depolarized, and segments S5-S6 form the selective sodium pore. Associated with the α subunit, the channel presents two β subunits that are formed by a single transmembrane segment encoded by the SCN1B through SCN4B genes (Fig. **2**) [53-55].

Four alpha subunits, SCN1A, SCN2A, SCN3A and SCN8A, are highly expressed in the central nervous system. However, mutations of SCN1A, SCN2A are largely related to the development of epilepsy and autism [54]. Research on the SCN2A gene in particular, responsible for encoding Nav 1.2, reveals an association with ASD and delays in intellectual development [56]. A hypothesis explaining the involvement of the Nav1.2 mutation in the appearance of ASD is that stimulation of immature excitatory cortical neurons (which express these modified channels) impairs neuronal activity, reducing excitability, and altering voltage channel kinetics [55, 57], (this hypothesis was reiterated by a Kacamarek study (2019) in which Scn2 +/-mice (in addition to abolishing long-term potentiation (LTP)) presented deficits in the social interaction test. Together these may be pathophysiological mechanisms associated with ASD, as observed in the missense mutation of Nav 1.2 [58].

2.2. High Conductivity Ca^{2+} Activated Potassium Channels (BK_{Ca})

BK_{Ca} channels are considered important membrane excitability modulators, presenting various functions in cell and tissue physiology, including neuronal excitability and regulation of vascular tone [59]. Morphologically, BK_{Ca} channels are tetrameric α subunit structures, forming a central pore permeable to K^+, with seven transmembrane segments (S0-S6), and a loop opening between S5 and S6 (Fig. **3A**).

Unlike other ion channels, the N-terminal domain of these channels is found in the extracellular region, and the intracellular carboxy-terminal domain presents potassium conductance regulators (RCK1 and RCK2) [60]. Voltage sensitive β subunits are associated with the α subunits and present a regulatory role, being responsible for the functional diversities of the channel (Fig. **3B**). Due to their importance in various signaling pathways, dysfunctions may be related to

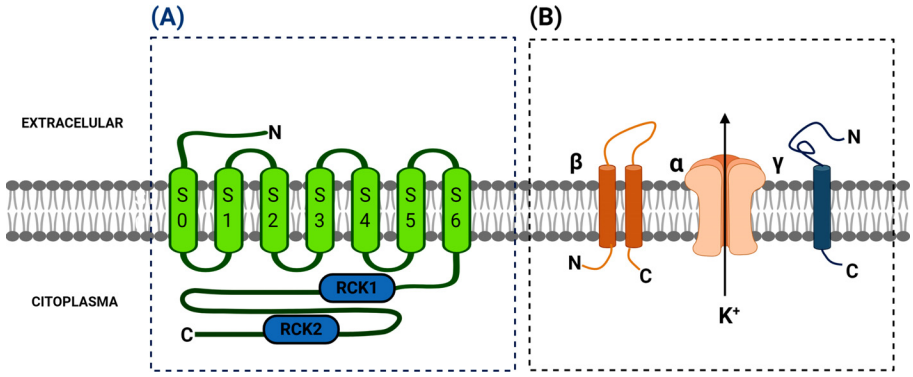

Fig. (3). (**A** e **B**) BK_{Ca} channel topographic characteristics: seven trans-membrane α helical segments (S0-S6); loop opening between S5-S6; extracellular N-terminal domain; and a C-terminal domain consisting of two cytoplasmic RCK1 and RCK2 domains (B) BK_{Ca} channel. Source: adapted from Hill *et al.* (2010). (Created with BioRender.com) *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

the pathophysiology of various diseases, including autistic spectrum associated mental retardation [61].

Molecular genetics analyses in patients with ASD, have demonstrated that the haploinsufficiency of the *KCNMA1* gene that encodes the alpha subunit of the BK_{Ca} channel can induce dysfunctions (by decreasing its activity). The agonist BMS-203452 increases the BK_{Ca} channel's opening, influencing neuronal excitability and circuits which encode defective cognitive responses, that contribute to the pathophysiology of autism and other mental deficiencies [61]. These channels are also influenced by the fragile X mental retardation protein (FMRP), decreasing BK_{ca}, current and changing its activation kinetics [62, 63].

The FMRP is of great importance for cognitive development, with a role in dendrite protein synthesis, the release of neurotransmitters, and action potential (AP) modulations. Changes in FMRP through transcriptional silencing of the Fmr1 gene lead to widening of the AP, increased presynaptic Ca^{2+} flow, and glutamate release [63]. The presynaptic processes are independent of transductional mechanisms, being specifically modulated by the BKCa channels through the interaction of the FMRP with the β-4 subunits. As a result, BK_{Ca} dysregulation (by FMPR) in mesocorticolimbic regions induces significant changes in synaptic information that manifests as behavioral changes [61, 63]. This hypothesis was confirmed by studies that treating mice with Fmr1 knock-outs, in a model of pathophysiology for fragile X syndrome (FXS), using BK_{Ca} channel opening modulators, to minimize the behavioral changes observed in FXS, while becoming an important therapeutic target for ASD symptoms as well [64-66].

2.3. Low Conductance Ca^{2+} Activated Potassium Channels (Sk_{Ca})

The SK_{ca} channel presents low conductance and is activated by cytosolic calcium, independently of voltage variations. Like most ion channels, it presents a tetrameric structure, with six transmembrane segments, forming a central pore that selectively al-lows the passage of K^+ (Fig. **4**) [67]. As to its cytosolic domains, the N-terminal region linked to the calmodulin-binding site regulates the opening of the channel after Ca^{2+} binding and causing membrane hyperpolarization [68, 69].

Despite a better understanding of genetic factors in the pathogenesis of autism, implications for cortical dysfunction resulting from mutagenic processes are still poorly understood. It is known that alterations involving deletion of the phosphatase gene and tensin homologue (PTEN) on chromosome ten, induces an overexpression of SK_{Ca} channels that alters excitability in cortical neurons (*via* potassium current), limiting neuronal firing and causing processing deficits characteristic of autistic or intellectually disabled. Mice with PTEN deletion exhibit stereotyped behaviors before sensory stimuli and difficulties in social interaction, common conditions in individuals with ASD. This is due to visually evoked firing rates in the primary cortex, extinguishing sensory processing [70].

2.4. Voltage Activated Potassium Channels (Kv4.2)

Voltage-dependent Kv4.2 channels are encoded by the KCND2 gene, and when assembled in the form of homotetrameric structures, they are activated by membrane potentials below the threshold (-90 mV). The conformations adopted by these channels can be open, closed, or preopened [71, 72]. The latter state is in turn regulated by the stress do-mains, though without hydrophobic pore opening [73, 74]. The channel is widely expressed in CA1 pyramidal neurons and is responsible for regulating the threshold for initiation and repolarization of the action potential, in addition to its propagation. Its functionality in regions such as the hippocampus is therefore of great importance in neuronal development stages, due to the maturation of synaptic signaling pathways, since deletion of these channels decreases or increases the threshold, thus respectively inducing long-term potentiation (LTP) or depression (LTD)[72-75].

In hippocampal synapses, the gradual postnatal reduction in the ratios of the GluN2B/GluN2A subunits influences AMPA expression and synaptic ripening processes [76]. *In vivo* studies in guinea pigs revealed that ablation of Kv4.2 compromises these processes, culminating in silent synapses in adulthood. It was thus evident that reentry of the channel on the cell surface and its activation influenced the composition of the NMDA subunit and synaptic inactivity, resulting in changes in plasticity and, consequently, regulation of the neuronal membrane excitability [72, 77]. Expression of these channels may indirectly influence the rise of ASD due to the

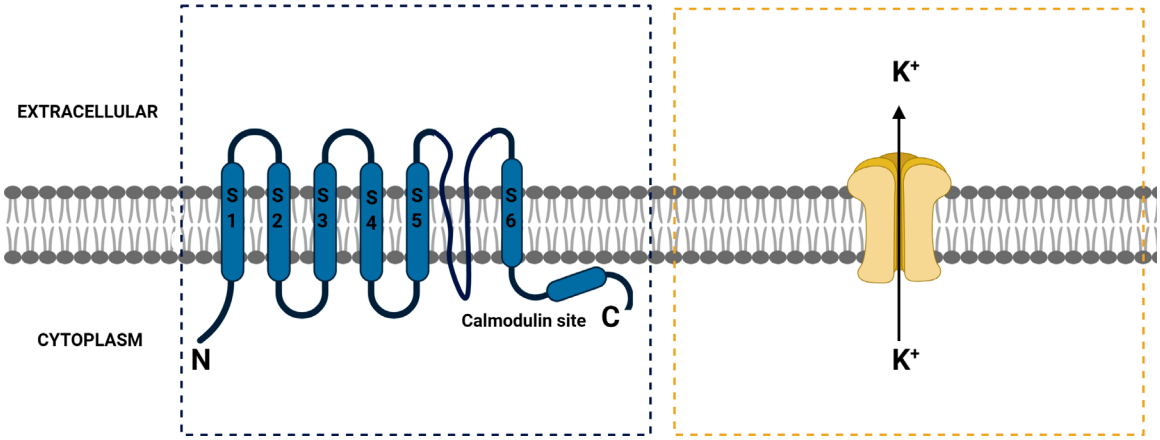

Fig. (4). SKca channel -Tetrameric structure, with six transmembrane segments (S1-S6), cytoplasmic N and C domains, with C domain calmodulin binding site. Source: adapted from Diniz *et al.* (2020). (Created with BioRender.com) *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

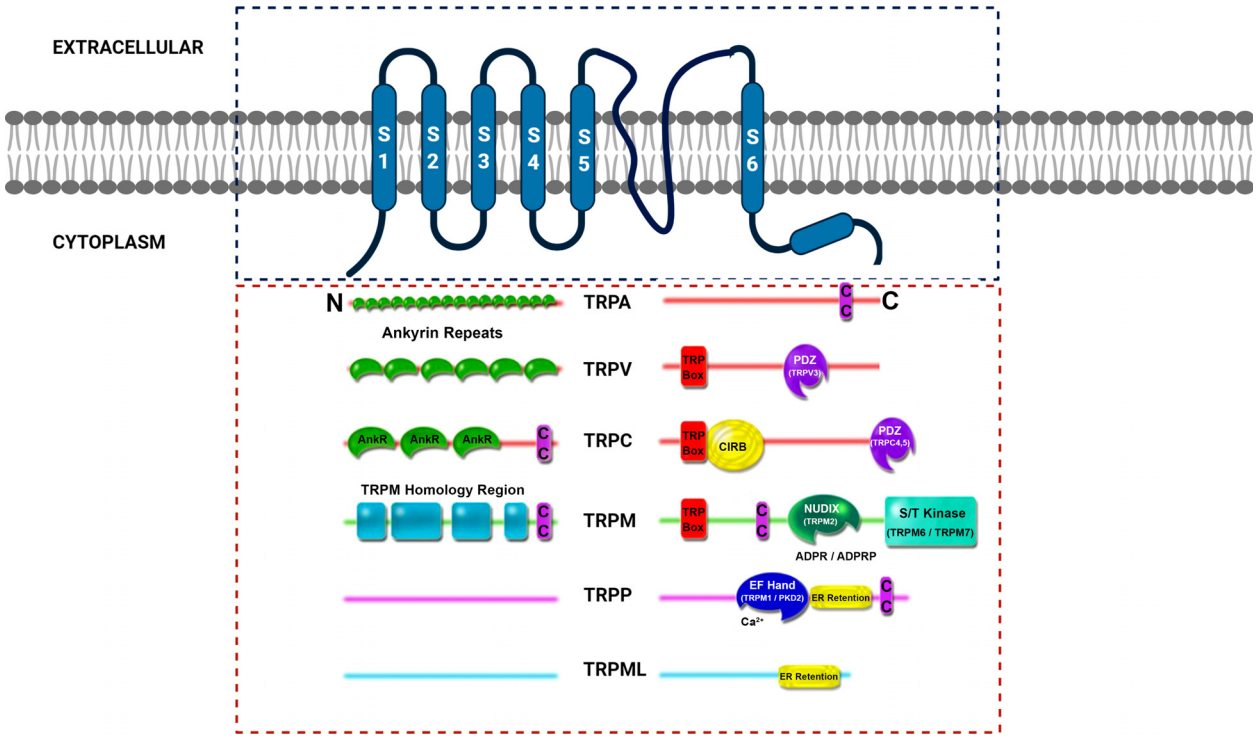

Fig. (5). TRPs channels -Topological structure: six transmembrane segments (S1-S6), hydrophobic pore be-tween S5 and S6, N and C domains. Differences in cytoplasmic domains for each subfamily. Legend: Ank (Ankyrin), CC (coiled-coil domain); S/T serine kinase/threonine intrinsic kinase; CIRB (calmodulin triphosphate and inositol InsP3R receptor binding site); PDZ (aminoacid motif binding domain), NUDIX (ADP ribose or ADPR-2'-phosphate homology domain); EF (Ca^{2+} canonical hand). Source: adapted from the Pharmacology Database Guide of the International Union of Basic and Clinical Pharmacology (IUPHAR), 2019. (Created with BioRender.com) *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

fact that mRNAKv4.2 binds to the FMRP protein, blocking its function, this as well as mutations of the *FMR1* gene that block FMRP expression, which results in FXS manifestation [75].

As described above, genetic alteration in this protein is one of the main causes of autism through the actuation of ribosomal processes. Recent experimental studies have revealed that the application of spider toxin; heteropodatoxin (HpTx2), specifically blocks Kv4.2 channels by restoring LTP in hippocampal regions in Fmr1 knockout mice, and reverting (in part) FMRP-dependent abnormalities and synaptic transmission [78, 79]. Thus, despite the limitations of the studies, it can be partially concluded that the expression and/or dysfunction of Kv4.2 channels can significantly contribute to the pathophysiology of FXS, a neurological event which increases the predisposition towards developing ASD [72].

2.5. Transient Potential Receptor Channels (TRPs)

TRPs constitute an extensive class of integral proteins, being present in various taxonomic groups with photoreceptor genes initially identified in the fly *Drosophila melanogaster* [80]. Channel classification is based on cytoplasmic domain differences and sequence analogies (Fig. **5**). Currently, there are about 28 types, subdivided into 6 families: TRPC (Canonical), TRPV (Vanilloid), TRPML (Mucolipin), and TRPP (Polycystic) [81-83]. The majority of these channels are permeable to cations, with low Ca^{2+} ion selectivity. The exceptions are TRPC6 and TRPV6, which present high permeability ($P_{Ca}{}^{2+}/P_{Na}{}^{+} > 100$), and TRPM4 and TRPM5 that are impermeable to Ca^{2+}, and in which the mechanisms of intracellular influx are regulated through store-operated channels (SOCs)[84, 85].

Morphologically, these channels occur in the homo or hetero-tetramer form, with six transmembrane segments (S1-S6) with intracellular amino and carboxy-terminal domains. A central hydrophobic pore is also observed between S5 and S6, responsible for the ionic passage of mono and divalent cations (Na^{+}, K^{+}, Ca^{2+} and Mg^{2+}) (Fig. **5**). The activity of these channels can be regulated by physiological, chemical, and sensory stimuli and by second messengers such as diacylglycerol (DAG), cyclic ADP ribose, and Ca^{2+} [67, 86, 87].

Studies have shown that interruption or haploinsufficiency of TRPC6 on neurons of non-syndromic autistic individuals lead to alterations on neuronal development, morphology and its function, inducing abnormal neuronal characteristics, such as, decreasing somatodendrite size, alteration of columnar denditric structure and reducing of excitatory glutamatergic sinapses [88]. These processes are known to be compromised in the manifestation of autism, since neuronal plasticity and the learning process are modulated by sensory stimuli and changes in the signaling pathways of memory occur in hippocampal regions, an area relevant to social behavior [89-91]. The neuronal phenotypes observed in ASD can be restored by treatment with insulin-like growth factor-1 (ICF) or TRPC6 specific hyperforin agonists [88].

The non-selective cationic channel TRPC3 also presents an indirect correlation with ASD. This is due to its wide expression in the Purkinje cells of the cerebellum, responsible for synaptic transmission dependent on glutamate 1 metabotropic receptor (mGluR1-Ca^{2+}). Genetic changes in TRPC3, such as its loss or mutations at the gain point of dominant Moonwalker function, can result in changes in calcium signaling; triggering ataxia, cerebellar degeneration, and deficiencies in dendritic growth and synapse formation during the early development of Purkinje cells [92, 93]. Currently, research has shown that the cerebellum is affected by autism, being an area responsible for supporting cognitive functions, language, motor control, and affective regulation [94]. Meta image analyses have demonstrated a reduction in cerebellar gray areas and in the density of Purkinje cells, factors that predict the severity of the disorder due to a greater degree of impairment in functional and cognitive processing functions [95, 96].

The physiological activity of TRPM2 and TRPM7 in the brain has recently been identified in neuronal structures, astrocytes, and glial cells as being primordial for cognitive function, as well as for hormonal modulation and embryonic neurogenesis [97]. Despite the mechanisms being still poorly understood, TRPM2 and TRPM7 channels likely contribute to the improvement of ASD social deficiencies. The channels can be activated by nicotinamide and adenine beta dinucleotides (β-NAD), and ADP-ribose, and by increased body temperature (34 to 47°C), regulating the release of oxytocin (OT) in hypothalamic oxytocinergic neurons, in a mechanism dependent on free intracellular calcium [97, 98]. Decreased OT release may increase the individual's predisposition to-wards social amnesia, a symptom also characteristic of ASD. Hyperthermia involving TRPM2 channels promotes a beneficial effect on the behavioral characteristics of patients with ASD, by facilitating the release of OT, or by normalizing the locus coeruleus-noradrenergic system [99].

The transient receptor potential vanilloid type 1 (TRPV1), has been extensively investigated and is associated with certain neurological disorders. The channels are controlled by thermal, mechanical, and chemical stimuli, and like the others previously mentioned, they are widely and especially found in dopaminergic neurons, playing an essential role in the reward system, and in the pathophysiology of diseases such as anxiety, depression, schizophrenia, autism spectrum disorders, and neurodegenerative diseases [100]. Evidence suggests that TRPV1 increase microglia activity, activating the NfκB pathway, and inducing the release of cytokines, altering synaptic transmission and plasticity [101]. More controversial studies associate these channels with group I mGluRs receptors, responsible for inducing low current postsynaptic (LCPS) excitation in the interneurons of the hippocampal CA3 stratum radiatum, mediating propagation through TRPV1 channels *via* PLC and Ca^{2+}. LCPS in interneurons can depolarize them, increasing GABA release. These channels can thus regulate the excitability of the hippocampal CA3 region, which is important for associative memory [102]. In relation to the other channels belonging to the TRP family, few studies in the literature correlate them with ASD; however, given what has been explored, selective inhibition or increased expression of a given TRP channel may contribute to modulation in various neuronal pathways, increasing the chances of minimizing cognitive, sensory, and behavioral deficits. Such discoveries enable a new path for pharmacotherapeutic diversification in treating ASD.

In autism, channel dysfunctions can alter neuronal development and synapse formation, compromising processing in brain circuits, most of the studies cited use animal models that mimic autism-like behavior. In clinical studies, they could only obtain imaging results that revealed changes in axonal connectivity as a key feature of autism. Finally, it is important to emphasize that despite advances in the understanding of channelopathies in the pathophysiology of autism, it is known that there is high genotypic variability, with no specific mutations associated with clinical autism. Therefore, a gene can lead to different clinical presentations, probably modulated by other genes or epigenetic chances, as we can see in SCN1A disorders [10, 26-28]. For this purpose, the genes involved in ion channels associated with ASD, their normal function and their association with neurodevelopmental disorders were grouped together in Table **2** [103-123].

Table 2. Genes related to ASD.

Gene	Description	Function	Related Disorders
Calcium Channels and Calcium Channel Subunits Implicated in ASD			
CACNA1A	Transmembrane pore-forming subunit of the P/Q-type or CaV2.1 voltage-gated calcium channel	Ca^{2+} dependent processes, including muscle contraction, hormone or neurotransmitter release, and gene expression.	Developemental and epileptic encephalopathy 42 (MIM:617106); Episodic ataxia, type 2 (MIM:108500); Migraine, familial hemiplegic, 1 (MIM: 141500); Spinocerebellar ataxia 6 (MIM: 183086); ASD [103].
CACNA1C	Alpha-1-subunit of a voltage-dependent L-type calcium channel	Regulate sentry of Ca^{2+} into excitable cells: muscle contraction, hormone/neurotransmitter release, gene expression, cell cycle	Síndrome de Brugada 3 (MIM: 611875); Síndrome do QT longo 8(MIM: 618447); Síndrome de Timothy (MIM:601005); ASD, epilepsy, psychiatric diseases [104].
CACNA1D	Alpha1D subunit of voltage-regulated calcium channel	High-voltage activated, long-lasting calcium activity	Primary aldosteronism, seizures, and neurologic abnormalities (MIM: 615474); Sinoatrial node dysfunction and deafness (MIM: 614896); ASD; Neurodevelopmental disorders [105].
CACNA1E	Alpha1 E subunit of voltage-regulated R-type calcium channel,	High voltage-activated, rapidly inactivating R-type calcium channel which initiates rapid synaptic transmission in the central nervous system	Developmental and epileptic encephalopathy 69 (MIM:618285); ASD, psychiatric diseases [106].
CACNA1F	Alpha 1F subunit of voltage-regulated L-type calcium channel	Regulate sentry of Ca^{2+} into excitable cells:muscle contraction, hormone/neurotransmitter release, gene expression, cell cycle	Aland Island eye disease (MIM: 300600); Cone-rod dystrophy, X-linked, 3 (MIM: 300476); Night blindness, congenital stationary (incomplete), 2A, X-linked (MIM:300071); ASD [107].
CACNA1G	Alpha 1 G subunit Of low voltage-regulated T-type calcium channel	Highly expressed in Purkinje neurons and deep cerebellar nuclei , their currents are both transient, owing to fast inactivation, and tiny, owing to small conductance	Spinocerebellar ataxia 42, early-onset, severe, with neurodevelopmental déficits (MIM: 618087); ASD; intelectual disability; juvenile myoclonic epilepsy [107, 108].
CACNA1H	Alpha 1 H subunit Voltage-regulated T-type calcium channel	Regulates neuronal and cardiac pace maker activity	Hyperaldosteronism, familial, type IV (MIM:617027); ASD;childhood absence, epilepsy, psychiatric diseases [48].
CACNA2D4	Alpha2/delta4subunit of voltage-regulated calcium channel	Accessory calcium channel subunit; regulate sentry of Ca^{2+} into excitable cells	ASD [109].
CACNB2	Accessory calcium channel beta-2 subunit	Modulates voltage dependence of activation and controls trafficking of the calcium channel family	ASD, psychiatric diseases [110].
Sodium Channels Implicated in ASD			
SCN1A	Sodium voltage-gated channel, alpha subunit 1	Expressed in brain and muscles; involved in generation/propagation of action potentials	Developmental and epileptic encephalopathy 6B, non-Dravet (MIM: 619317); Dravet syndrome (MIM: 607208); Epilepsy, generalized, with febrile seizures plus, type 2 (MIM: 604403); Febrile seizures, familial, 3 (MIM: 604403); Migraine, familial hemiplegic, 3 (MIM: 609634); ASD [111, 112].
SCN2A	Sodium voltage-gated channel, alpha subunit 2	Action potential initiation and propagation inexcitable cells	Developmental and epileptic encephalopathy 11 (MIM:613721); Episodic ataxia, type 9 (MIM:618924); Seizures, benign familial infantile, 3 (MIM:607745); ASD [113].
SCN3A	Sodium voltage-gated channel, alpha subunit 3	Action potential initiation and propagation inexcitable cells	Developmental and epileptic encephalopathy 62 (MIM: 617938); Epilepsy (MIM: 617935); ASD [114, 115].
SCN7A	Sodium voltage-gated channel, alpha subunit 7	Na^{+} specific channel, allowing the passive flow of ions down their electrochemical gradiente; controls oxytocin and vasopressin release	ASD [116].
SCN8A	Sodium voltage-gated channel, alpha subunit 8	Essential for the rapid membrane depolarization that occurs during the formation of the action potential in excitable	Myoclonus (MIM: 618364); Cognitive impairment with or without cerebellar ataxia (MIM: 614306); Developmental and epileptic encephalopathy 13 (MIM: 614558); Seizures, benign familial infantile, 5 (MIM:617080); ASD [117].

(Table 2) contd….

Potassium Channels and Potassium Channel Subunits Implicated in ASD			
KCNMA1	Potassium channel, calcium-activated, large conductance, subfamily m, alpha member 1	Both voltage-and calcium-sensing channel, controls smooth muscle to neand neuronal excitability	Cerebellar atrophy, developmental delay, and seizures (MIM: 617643); Liang-Wang syndrome (MIM: 618729); Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy (MIM: 609446); {Epilepsy, idiopathic generalized (MIM:618596); ASD [118].
KCNA4	Potassium channel, voltage-gated, shaker-related subfamily, member 4	Axonal targeting	Microcephaly, cataracts, impaired intellectual development, and dystonia with abnormal striatum (MIM: 618284); ASD [119].
KCND2	Potassium voltage-gated channel, shal-related subfamily, member 2	Mediates a rapidly inactivating out Ward K+ currentin neurons and the heart; repolarization phase of the action potential	ASD; epilepsy [120].
Transmembrane Receptor Genes Implicated in ASD			
TRPM2	Transient receptor potential cation channel subfamily M member 2	Ca^{2+} permeable cation channels localized predominantly to the plasma membrane	ASD, psychiatric diseases [97].
TRPM7	Long transient receptor potential channel 7	Phosphorylation of several substrates and in the regulation of oxidative stress; ion channel and a protein kinase function; displays autophosphorylation	Amyotrophic lateral sclerosis-parkinsonism/dementia complex (1055000); ASD [121]
TRPC6	Transient receptor potential cation channel, subfamily c, member 6	Nonselective cation channel activated by diacylglycerol	Glomerulosclerosis, focal segmental (MIM: 603965); ASD [88].
TRPC3	Transient receptor potential cation channel, subfamily c, member 3	Nonselective cation channel linked to intracellular signaling pathways, including metabotropic glutamate receptor-dependent synaptic transmission, highly expressed in Purkinje cells in the cerebellum	Spinocerebellar ataxia 41 (MIM:616410); ASD; neurodevelopmental disorders [122]
TRPV1	Transient receptor potential cation channel, subfamily v, member 1	Nonselective cation channels directly activated by harmful heat, extracellular protons, and vanilloid compounds	ASD [123].

Table 3. Drugs commonly prescribed for ASD.

Medication / (Therapeutic Class)	Indication	Mechanism	Side effects
Risperidone, (atypical antipsychotics) [125]	Irritability 0.5 -4 mg	5-HT_{2A} e D_2 Receptor inhibitor	↑ Appetite and weight, sedation, dizziness and constipation
Aripiprazole [125]	Irritability 0.5 -4 mg	Partial D_2 and 5-HT_{1A} Receptor agonist	Weight gain
Haloperidol (typical antipsychotic) [129]	Irritability 2 -15 mg	D_2 (Gi ↓AMPc) Receptor blocker	Sedation, fatigue, drowsiness, weight gain and tremors
Methylphenidate CNS stimulant [126]	Hyperactivity 0.2 -2mg	Dopamine reuptake inhibitor	↓ Appetite, insomnia, irritability and emotional lability
Guanfacine Sympatholytic [130]	Hyperactivity 1mg -2mg	α2 adrenergic agonist	Sedation, headache, nausea and stomach pain.
Atomoxetine Neurotonic [131]	Hyperactivity 0.5 -1.8mg/kg/day	Selective noradrenaline reuptake inhibitor	Nausea, vomiting, insomnia and reduced appetite
Fluoxetine Antidepressant [129]	Anxiety; Repetitive movements 20mg -80mg	Selective inhibitor of serotonin re-uptake	Moderate insomnia, headache and dry mouth.
Melatonin Hormone [132]	Insomnia 1 -3mg	MT1 and MT2 (Gi ↓AMPc) Receptor agonist	Drowsiness, headache, dizziness and nausea

2.7. Pharmacological and Psychotherapeutic Treatment

Treatment of ASD is performed according to the patient's clinical evaluation, and psychotherapeutic and pharmacological strategies applicable to central and secondary symptoms can be used. There is no cure for ASD with pharmacological treatment, drugs used are used to combat secondary symptoms related to disorders such as depression, insomnia, irritability, difficulties in concentration, and hyperactivity, among others. The therapeutic classes used are typical and atypical antipsychotics, antidepressants, mood stabilizers, and stimulants (Table **3**) [124-126]. Recent studies also indicate the therapeutic potential of the $GABA_A$ receptor in the treatment of FXS, since the manifestation of

abnormal behaviors is correlated with the loss of inhibitory tone in GABAergic activation in Fmr1 knockout mice. Diazepam, alfaxalone and gaboxadol, GABAergic agonists, have obtained significant results in reversing the clinical manifestations of FXS. Ganaloxone, a neurosteroid that is $GABA_A$ agonist, was used on a controlled trial and revealed positive trends in areas of anxiety, hyperactivity and attention [127]. Another double-blind placebo-controlled crossover, an human trial of arbaclofen, a $GABA_B$ agonist, for children and adults with FXS also showed significant improvement in social behaviors [127, 128]. Complementary alternative treatments can also be used [124-126], and studies demonstrate that pharmacological therapies associated with psychotherapeutic follow-up are more effective in combating the symptoms of ASD [129-132].

Another class of drugs widely used in the clinic since 2008 are serotonin reuptake inhibitors (SSRIs). However, new evidence suggests that there is limited benefit to their use considering that no difference was observed in patients treated with a placebo and those treated with fluoxetine, or with other SSRI intervention only, suggesting that SSRI have little or no significant effect on the treatment of children and adults patients with ASD [133-135].

To this end, new alternatives are being investigated to treat the principal symptoms of ASD. Antagonists of the glutamatergic metabotropic receptor 5 (mGluR5) have shown good results in preclinical tests [136]. The mGluR5 are anchored to Shank and Homer proteins, deletions of *Shank2*, *Shank3* as well as altered $mGluR_5$ -HOMER scaffolds, in these protein domains, induces perturbed function at striatal synapses, abnormal brain morphology, aberrant structural connectivity, which contributes to autism-like behavior [137, 138]. Although effective, conventional treatment with atypical neuroleptics and antidepressants applied to secondary ASD symptoms are limited by the high probability of triggering adverse effects, such as sedation, headache, obesity, dyslipidemia, diabetes mellitus, and thyroid disorders [139].

The brief pharmacological session reinforces the limited availability of the agents used, which act as the non-selective treatment on ASD treatment, implying a series of side effects. This reinforces the importance of new agents research which act on possible targets related to the modulation of neuronal circuits as ionic channels. As reported, dysfunctions in the aforementioned channels directly influence cognitive and social deficits, and their modulation can be an alternative to existing therapies.

CONCLUSION

In view of the evaluated results, ion channels appear to be adequate targets for central and palliative treatment of various neurological disorders, including ASD. As noted, the dysfunctions of the ion channels addressed in this review BK_{Ca}, SK_{Ca}, $Kv_{4.2}$, Ca_v, $Na_{.v1.2}$ and TRPs, have direct correlations with cognitive and behavioral disorders, and modulation may be a promising target for effective treatments and with better safety profiles. Although the ion channels addressed have emerged as important regulators of the symptoms associated with ASD, consistent data on potential pharmacological benefits remain limited and little explored, making it necessary to expand *in vivo* and clinical studies towards making their use feasible as part of the pharmacological strategy.

LIST OF ABBREVIATIONS

5 HT	=	5-hydroxytryptamine
ABA	=	Conduct Background Check
ADP	=	Adenosine diphosphate
AID	=	lpha 1 interaction domain
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Ank	=	Ankyrin
AP	=	Potential action
APA	=	American Psychiatric Association
ASD	=	Autistic spectrum disorder
BKCa	=	High conductivity Ca^{2+} activated potassium channels
CAMP		Cyclic adenosine monophosphate
CACNA1A	=	Calcium voltage-gated channel subunit alpha1 A gene
CACNA1C	=	Calcium voltage-gated channel subunit alpha1 C gene
CACNA1D	=	Calcium voltage-gated channel subunit alpha1 D gene
CACNA1E	=	Calcium voltage-gated channel subunit alpha1 E gene
CACNA1F	=	Calcium voltage-gated channel subunit alpha1 F gene
CACNA1G	=	Calcium voltage-gated channel subunit alpha1 G gene
CACNA1H	=	Calcium voltage-gated channel subunit alpha1 H gene
CACNA2D4	=	Calcium channel, voltage-dependent, alpha 2/delta subunit 4
CACNB2	=	Calcium Voltage-Gated Channel Auxiliary Subunit Beta 2

CC = Coiled-coil domain

CDC = Center for Disease Control and Prevention

CIRB = Calmodulin triphosphate and inositol

CNS = Central Nervous System

CREB = *cAMP-response element* binding protein

CYP11B1 = Cytochrome P450 Family 11 Subfamily B Member 1

CYP17A1 = Cytochrome P450 Family 17 Subfamily A Member 1

CYP19A1 = Cytochrome P450 Family 19 Subfamily A Member 1

D2R = Dopaminergic receptor

DAG = Diacylglycerol

DSM = Diagnostic and Statistics Manual for Mental Disorders

EF = Ca^{2+} canonical hand

ESR2 = Estrogen Receptor 2

FMR1 = Fragile X mental retardation 1

FMRP = Fragile X mental retardation *protein*

FOXK1 = Forkhead Box K1

FXS = Fragile X Syndrome

GABA = γ-*aminobutyric acid*

GluN2A = Glutamate receptor NMDA2A

GluN2B = Glutamate receptor NMDA2B

HPA = Hypothalamic pituitary axis

HpTx2 = Heteropodatoxin

IP3R = Inositol-3-phosphate receptor

IGF = Insulin like growth factor-1

IUPHAR = Guide of the International Union of Basic and Clinical Pharmacology

KCNA4 = Potassium Voltage-Gated Channel Subfamily A Member 4

KCND2 = Potassium Voltage-Gated Channel Subfamily D Member 2 gene

KCNMA1 = Potassium calcium-activated channel subfamily M alpha 1

Kv4.2 = Voltage activated potassium Channels

LCPS = Low current postsynaptic

LTD = Long-term potentiation depression

LTP = Long-term potentiation

mGluR1 = Metabotropic glutamate receptor 1

mGluR5 = Metabotropic glutamate receptor 5

MT1 = Melatonin receptor -1

MIM = Mendelian Inheritance in Man

Nav = Voltage-gated sodium channels

Nav 1.1 = Sodium channel, voltage-gated, type I, alpha subunit

Nav 1.2 = Sodium channel, voltage-gated, type II, alpha subunit

Nav 1.9 = Sodium channel, voltage-gated, type XI, alpha subunit

Nav 2.1 = Sodium channel, voltage-gated, type II, alpha subunit

NF-κB = Factor nuclear kappa B

NMDA = N-methyl D-Aspartate

NUDIX = ADPR-2'-phosphate homology domain

OT = Oxytocin

PDZ = Aminoacid motif binding domain

PLC = Phospholipase C

PMCA = Calcium-ATPases of the plasma membrane

PRT = Pivotal response training

PTEN = Phosphatase and tensin homologue

RCK1 = Serine/threonine-protein kinase *RCK1*

RCK2 = Serine/threonine-protein kinase *RCK2*

RyR = Ryanodine

SSRI = Selective serotonin reuptake inhibitors

SCN11A = Sodium Voltage-Gated Channel Alpha Subunit 11

SCN1A = Sodium voltage-gated channel alpha subunit 1

SCN1B = Sodium channel subunit beta-1 gene

Scn2 = Immortalized Rat Suprachiasmatic Nucleus Cells

SCN2A = Sodium voltage-gated channel alpha subunit 2

SCN3A = Sodium voltage-gated channel alpha subunit 3

SCN4B = Sodium Voltage-Gated Channel Beta Subunit 4

SCN8A = Sodium voltage-gated channel alpha subunit 8

SkCa = Low conductance Ca^{2+} activated potassium channels

SOCs = Store operated channels

TRP = Transient Potential Receptor Channels

TRPC = Transient Potential Receptor Canonical

TRPC3 = Short transient receptor potential channel 3

TRPC6 = Short transient receptor potential channel 6

TRPM2 = Transient receptor potential cation channel, subfamily M, member 2

TRPM4 = Transient receptor potential cation channel, subfamily M, member 4

TRPM5 = Transient receptor potential cation channel, subfamily M, member 5

TRPM7 = Transient receptor potential cation channel, subfamily M, member 7

TRPML = Transient Potential Receptor Mucolipin

TRPP = Transient Potential Receptor Polycystic

TRPV = Transient Potential Receptor Vanilloid

TRPV1 = Transient receptor potential cation channel subfamily V member 1

TRPV6 = Transient receptor potential cation channel subfamily V member 6

TS = Timothy Syndrome

VGCC = Voltage-gated calcium channels

β-NAD = Adenine beta dinucleotides

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