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REVIEW

Calcium signaling in neurodevelopment and pathophysiology of autism spectrum disorders

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Abstract

Background Autism spectrum disorder (ASD) covers a group of neurodevelopmental disorders with complex genetic background. Several genetic mutations, epigenetic alterations, copy number variations and single nucleotide polymorphisms have been reported that cause ASD or modify its phenotype. Among signaling pathways that influence pathogenesis of ASD, calcium signaling has a prominent effect.

Methods We searched PubMed and Google Scholar databases with key words "Calcium signaling" and "Autism spectrum disorder".

Conclusion This type of signaling has essential roles in the cell physiology. Endoplasmic reticulum and mitochondria are the key organelles involved in this signaling. It is vastly accepted that organellar disorders intensely influence the central nervous system (CNS). Several lines of evidence indicate alterations in the function of calcium channels in polygenic disorders affecting CNS. In the current review, we describe the role of calcium signaling in normal function of CNS and pathophysiology of ASD.

Keywords Calcium signaling · Autism spectrum disorder · Neurodevelopment

Introduction

Autism spectrum disorder (ASD) constitutes a set of neurodevelopmental disorders described by essential deficits in social interactive skills, verbal and non-verbal communications, and repetitive interests and activities [1]. Statistics show a prevalence of 1 in 54 children for ASD [2]. Yet, figures vary by gender, race and ethnicity [3]. ASD is extremely heterogeneous in the terms of genetic background. Both inheritable and de novo genetic alterations have been found in association with ASD [4]. Although several genes have been shown to participate in the cognitive and behavioral deficits in ASD, these genes only explain 10–20% of genetic background of ASD [4]. In addition to known genetic mutations, copy number variations (CNVs), single nucleotide polymorphisms (SNPs), and epigenetic alterations have been reported to modulate the phenotypic spectrum in this disorder [4].

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A previous karyotype study of ASD cases has reported the presence of major or minor chromosomal aberrations in a significant number of patients, with the fra(X)(q27) marker being detected in 25% of male subjects [5]. In addition, authors have detected long Y chromosomes, fra(XXp22), fra(16Xq23) and fra(6Xq26) in several cases [5]. Further studies have reported ASD susceptibility loci on chromosomes 7q, 1p, 3q, 16p, and 15q (reviewed in [4]). Beginning in early 2000s, investigation have suggested participation of a number of genes, namely *RELN*, *Arx*, *MeCP2*, *NLGN3*, *NLGN4*, *TSC2*, and *UBE3A* in the pathogenesis of ASD through a candidate gene approach [6–11]. Soon after, high throughput sequencing technology permitted assessment of ASD risk loci in a genome-wide level revealing association between a number of genetic loci and ASD. Notably, synapse-related genes and ion transport genes have been among the mostly related group of genes with the pathoetiology of ASD [12–14]. Calcium signaling has importance in the regulation of synaptic function, including both synaptogenesis and synaptic transmission [15], thus it might be involved in the pathogenesis of ASD. Based on the importance of calcium signaling in the neurodevelopment, this signaling pathway represents an appropriate candidate for ASD.

Calcium signaling in the neurodevelopment and normal function of neurons

Calcium signaling has essential roles in the cell physiology. Two major cellular organelles, namely endoplasmic reticulum and mitochondria are implicated in this kind of signaling [16]. Although organelles exist in basically all cells, organellar disorders intensely influence the central nervous system (CNS).

Calcium channels have essential roles for the instigation and dissemination of action potential in neurons. When an action potential reaches the presynaptic terminus of an axon, voltage-gated calcium channels in this place are opened to allow entry of calcium ions. Moreover, this process is more intensified by the release of calcium from the intracellular supplies. Collectively, these actions prompt the merging of neurotransmitter-containing intracellular synaptic vesicles with the plasma membranes of the presynaptic cells to permit neurotransmitter release into the synaptic junction [17].

Voltage-sensitive calcium channels facilitate influx of calcium ions into the excitable cells. These channels also participate in diverse calcium-related functions, such as muscle contraction, release of neurotransmitters, regulation of genes expression, as well as cell mobility, division and death [18]. Moreover, Wnt/calcium signaling pathways have been reported to exert functional roles in the regulation of callosal axon growth and guidance, thus being involved in the development of the corpus callosum [19]. Precise regulation of intracellular calcium concentration has important effect in the physiological functions of neurons and governs neurons survival and physiological efficacy from early phases of neurogenesis through their functions as mature cells. In fact, in neurons, calcium not only acts as a charge carrier, but also serves as a ubiquitous second messenger [20, 21]. Thus, it has roles in the initiation of a wide range signals being recognized by spatial and temporal dimensions, amplitudes, frequencies of oscillations or localization to distinct neuronal sections [22, 23].

Moreover, inositol 1,4,5-trisphosphate 6 receptor (IP3R)-facilitated calcium release is implicated in synaptic plasticity in neurons, thus can affect memory function [24], excitability of neurons [25], release of neurotransmitters [26], growth and extension of axons [27] and continuing alterations in genes expression (26).

Calcium signaling in ASD

Bulks of evidence indicate alterations in the function of calcium channels in polygenic disorders affecting CNS [28]. Identification of mutations in ion channel genes in patients with ASD has led to the suggestion that ASD is a 'channelopathy' [29]. For instance, the dominantly inherited monogenic syndrome, Timothy syndrome, which is described by long QT arrhythmia and ASD features is associated with de novo mutations in *CACNA1C* gene, a gene that codes the main alpha subunit of a voltage-activated calcium channel [30]. Following membrane polarization, calcium channels facilitate inflow of calcium ions into the cell. These channels are made by a complex of α-1, α-2/Δ, β, and γ subunits. Notably, each of these proteins has several isoforms being encoded by diverse genes or being produced through alternative splicing of transcripts [31, 32]. The pore-forming α-1 subunit has the essential role in the activity of channels. Other subunits act as ancillary subunits regulating channel activity [33]. Auxiliary subunits regulate the channels and thus participate in the great functional diversity of calcium channels. In fact, association or dissociation of auxiliary subunits from pre-existing channel complexes permits dynamic regulation of channel characteristics [33].

Another study has detected reduction of inositol trisphosphate (IP3)-mediated calcium signaling as the common characteristics of three discrete monogenic syndromes with high comorbidity with ASD, i.e. fragile X syndrome and tuberous sclerosis syndrome types 1 and 2 (TSC1 and TSC2) [34]. Moreover, a high throughput assay in a group of patients with sporadic ASD without any identified mutations has indicated significant depression of IP3-mediated calcium discharge from the endoplasmic reticulum following induction of purinergic receptors both sporadic and rare syndromic types of ASD. These observations have led to suggestion of this signaling as a convergent feature ASD [35].

Mutations in other loci coding α subunits of the voltage-activated calcium channel, as well as genes coding their accessory subunits have also been detected in ASD patients [36]. Similarly, variants of other channel loci have been shown to participate in the genetic basis of ASD [37]. Moreover, insufficient levels of vitamin D_3 during mid-gestation and infancy have been shown to enhance risk of ASD [38]. Based on the importance of vitamin D signaling in the regulation of calcium homeostasis [39], it is possible contribution of vitamin D signaling in the pathogenesis of ASD is associated with its effects on calcium hemostasis and signaling.

Both gain and loss of function variants have been recognized in genes coding for voltage-activated calcium channel in association with ASD [40]. The former types of variants have been mostly detected in *CACNA1C*, *CACNA1D*, *CACNA1F* and *CACNB2* resulting in prevention of voltage-dependent inactivation of associated channels and disproportionate influx of calcium ions. Conversely, loss of function variants in *CACNA1A* and *CACNA1H* have been shown to

reduce conductance and shift voltage dependence of activation, leading to reduction of channel activity [40].

Moreover, mutations in Ryanodine receptors might also contribute to the pathogenesis of ASD. These receptors constitute a family of huge, homotetrameric calcium channels situated in the sarcoplasmic/endoplasmic reticulum membranes that discharge calcium from intracellular supplies. A maternally inherited duplication of the genomic region covering the RyR2 gene has been detected as the likely pathogenic alteration in some Lebanese ASD cases [41]. Another study has identified RyR2 missense de novo variants in sporadic form of childhood onset schizophrenia [42]. RyR3 is another member of this family which is located on the ASD-associated region 15q11–13. Although deletion of the RyR3 affects synaptic plasticity of hippocampal neurons and alters the adaptation of learned memory in response to external alterations or stimuli [43], genotyping of 14 tag SNPs within this gene has revealed no association between this locus and ASD among Japanese [44].

SNPs within *ATPase Plasma Membrane Ca2+Transporting 2* (*ATP2B2*) has been found to be associated with ASD in male subjects [45]. Moreover, this gene has been confirmed to be one of the most reproducible associations with ASD in resequencing assays [46].

SLC25A12 gene which encodes a brain-specific form of the mitochondrial calcium-regulated aspartate/glutamate carrier, has also been linked with ASD in a research enlisted 197 families [47].

Altered calcium signaling has also been detected in association with genetic alteration in *NRXN1* gene, a locus being associated with several neurologic disorders such as ASD [48], schizophrenia [49], intellectual defects [50, 51], epilepsy [52], and developmental delay [50]. *NRXN1α+/−* neurons has exhibited alterations in calcium dynamics, with high frequencies, durations, and amplitudes of calcium transients [53]. High throughput sequencing has shown changes in ion transport and activity of ion transporters in *NRXN1α+/−* neurons, with up-regulation of voltage-gated calcium channels being one of the most significant pathways in these cells [53].

Moreover, a whole exome resequencing study has reported de novo rare alleles in α subunit loci *CACNA1D* and *CACNA1E* as the most important de novo risk mutations for ASD [54]. An additional analysis of CNV hotspots in ASD has revealed CNV duplications of *SLC1A1* in two ASD cases [55]. Moreover, a common polymorphism *SLC6A4* has been reported to be associated with this disorder [56]. Duplications of the neuronal calcium-binding protein *CADPS2* has also been detected in ASD patients [55]. Table 1 shows calcium signaling-related genes that might be involved in the pathophysiology of ASD.

Figure 1 shows the altered genes in calcium signaling in ASD.

Discussion

Several lines of evidence indicate the involvement of organellar and intracellular calcium signaling in the pathoetiology of ASD [17]. This speculation is supported by molecular and biochemical assays as well as linkage, association and mutation studies in human subjects. *CACNA1E* and *CACNB2* have been among the firstly identified risk loci for ASD [4]. A systematic review conducted by Liao et al. has also verified the importance of other voltage-gated calcium channel-coding genes and their accessory subunits in the pathogenesis of ASD [40]. Moreover, assessment of variants within these genes has resulted in identification of inositol triphosphate/Ca2+ and MAPK as two important signaling pathways in the etiopathology of ASD [40].

In addition to experiments at genetic and genomic levels, assessment of transcriptome might help to identification of the role of calcium signaling in the pathoetiology of ASD, particularly those with polygenic inheritance. A recent in silico assessment of Genotype-Tissue Expression database and the human protein atlas dataset has led to identification of calcium signaling and the glutamatergic synapse pathways as two extremely interrelated pathways in the combined geneset [126]. Moreover, ASD pathways of abnormal synaptic functions, chromatin remodeling and ion channel activity have been found to be greatly linked by MAPK signaling and calcium channels [126], demonstrating the highly complicated nature of ASD and importance of calcium signaling in many aspects of pathophysiology of this disorder.

Taken together, calcium signaling is involved not only in the etiology of monogenic cases of ASD, but also in the polygenically inherited ones. Evidence in support of its involvement in the former type is obtained from mutation assays in affected individuals. For the latter type, expression assays have helped in identification of involved pathways and molecules. For instance, the observed reduction of IP3 -mediated Ca2+ release from the endoplasmic reticulum following activation of purinergic receptors in sporadic cases of ASD supports this speculation [35].

In other words, although numerous common alleles, i.e. SNPs in the genes encoding calcium signaling-related proteins might have relatively small impacts in the risk of ASD, their combination with rare alleles in these genes (including both CNVs and pathogenic mutations) may establish large increased risk. Moreover, calcium signaling has been shown to reverse epigenetic silencing of certain genes [127]. Thus, abnormal activity of this pathway might explain the impact of environmental elements in development of ASD.

Animal studies have also assisted in identification of relation between calcium signaling and ASD. For instance,

Table 1 Calcium signaling-related genes with probable roles in the pathophysiology of ASD

Gene family	Gene	locus	Protein	Function	Disease Association	Organism	References
Calcium voltage-gated channels	CACNA1C	12p13.33	Subunit alpha1 C	Mediates calcium ions influx into the cell upon polarization of membranes	Timothy Syndrome, ASD, Psychiatric diseases	Homo sapiens	[31, 32]
	CACNA1D	3p21.1	Subunit alpha1 D	Mediates the entry of calcium ions into excitable cells	Sinoatrial node dysfunction and deafness, ASD, Psychiatric diseases	Homo sapiens	[57, 58]
	CACNA1H	16p13.3	Subunit alpha1 H	Mediates calcium ions influx into the cell upon polarization of membranes	Familial autism, childhood absence	Homo sapiens	[59, 60]
	CACNA1F	Xp11.23	Subunit alpha1 F	Mediates the influx of calcium ions into the cell	ASD, X linked congenital stationary night blindness	Homo sapiens	[61, 62]
	CACNA1G	17q21.33	Subunit alpha1 G	Mediates calcium ions influx into the cell upon polarization of membranes, and is implicated in some calcium-dependent processes	ASD, intellectual disability, juvenile myoclonic epilepsy	Homo sapiens	[18]
	CACNA1I	22q13.1	Subunit alpha1 I	Might participate in calcium signaling in neurons	Possibly implicated in ASD	Homo sapiens	[63, 64]
	CACNA1E	1q25.3	Subunit alpha1 E	Mediates calcium ions influx into the cell upon polarization of membranes, and is implicated in some calcium-dependent processes	ASD, Psychiatric diseases	Homo sapiens	[65]
	CACNA1S	1q32.1	Subunit alpha1 S	Slowly inactivating L-type voltage-dependent calcium channel	ASD	Homo sapiens	[66, 67]
	CACNB2	10p12.33-p12.31	Auxiliary subunit beta 2	A subunit of a voltage-dependent calcium channel protein	ASD, Psychiatric diseases	Homo sapiens	[68, 69]
	CACNA2D3	3p21.1-p14.3	Auxiliary subunit alpha2delta 3	Mediates calcium ions influx into the cell upon polarization of membranes	ASD	Homo sapiens	[70, 71]
	CACNA2D2	3p21.31	Auxiliary subunit alpha2delta 2		Not defined	Homo sapiens	[72]
	CACNA2D4	12p13.33	Auxiliary subunit alpha2delta 4	A protein in the voltage-dependent calcium channel complex	ASD	Homo sapiens	[73, 74]
	CACNG2	22q12.3	Auxiliary subunit gamma 2	Regulates transferring and channel gating of the AMPA receptors	Not defined	Homo sapiens	[75, 76]

Table 1 (continued)

Gene family	Gene	locus	Protein	Function	Disease Association	Organism	References
Ryanodine receptors	RyR1	19q13.2	Type 1	Acts as a calcium release channel in the sarcoplasmic reticulum, links the sarcoplasmic reticulum and transverse tubule	Not defined	Homo sapiens	[77, 78]
	RyR2	1q43	Type 2	supplies calcium to Cardiac muscle	Childhood onset schizophrenia	Homo sapiens	[79, 80]
	RyR3	15q13.3-q14	Ryanodine receptor 3	Releases calcium from intracellular storage	Not defined (but ASD in mice)	Homo sapiens	[81, 82]
–	ATP2B2	3p25.3	ATPase plasma membrane Ca2+ transporting 2	Removes calcium ions from eukaryotic cells against very large concentration gradients and participates in homeostasis of intracellular calcium	ASD	Homo sapiens	[83, 84]
Solute carrier family	SLC1A1	9p24.2	Family 1 member 1	In transporting glutamate across plasma membranes	ASD	Homo sapiens	[85, 86]
	SLC25A12	2q31.1	Family 25 member 12	The exchange of aspartate for glutamate across the inner mitochondrial membrane	ASD	Homo sapiens	[87, 88]
	SLC6A4	17q11.2	Family 6 member 4	An integral membrane protein that carries serotonin from synaptic spaces into presynaptic neurons	ASD	Homo sapiens	[89, 90]
	SLC8A1	2p22.1	Family 8 member A1	Prevents overload of intracellular stores	Not defined	Homo sapiens	[91]
–	MFN2	1p36.22	Mitofusin 2	A mitochondrial membrane protein that is involved in mitochondrial fusion and participates in the preservation and function of the mitochondrial network	Charcot-Marie-Tooth axonal neuropathy	Homo sapiens	[68, 92, 93]
–	HSPA9	5q31.2	Heat shock protein family A (Hsp70) member 9	Contributes in cell proliferation, stress responses and preservation of the mitochondria	Sideroblastic anemia, anomaly syndrome, Parkinson	Homo sapiens	[94, 95]
–	MCU	10q22.1	Mitochondrial calcium uniporter	A calcium transporter in the mitochondrial inner membrane	Not defined	Homo sapiens	[96, 97]

Table 1 (continued)

Gene family	Gene	locus	Protein	Function	Disease Association	Organism	References
–	MICU1	10q22.1	Mitochondrial calcium uptake 1	Interacts with the mitochondrial calcium uniporter, and participates in prevention of mitochondrial calcium overload	Not defined	Homo sapiens	[98, 99]
–	MICU2	13q12.11	Mitochondrial calcium uptake 2	Involved in calcium import into the mitochondrion and negative regulation of mitochondrial calcium ion concentration	Not defined	Homo sapiens	[100, 101]
–	CADPS2	7q31.32	Calcium dependent secretion activator 2	Calcium binding proteins that regulates the exocytosis of synaptic and dense-core vesicles in neurons and neuroendocrine cells	ASD	Homo sapiens	[102, 103]
–	MHS2	17q11.2-q24	Malignant hyperthermia susceptibility 2	Mismatch DNA repair proteins	ASD	Homo sapiens	[104, 105]
Transient receptor potential cation channel subfamily	TRPM1	15q13.3	Subfamily M member 1	Calcium permeable cation channel that is expressed in melanocytes and might participate in melanin synthesis	ASD Congenital stationary night blindness	Homo sapiens	[106, 107]
	TRPC1	3q23	Subfamily C member 1	Form a non-selective channel permeable to calcium and other cations	Not defined	Homo sapiens	[108]
	TRPC3	4q27	Subfamily C member 3	Forms a non-selective channel permeable to calcium and other cations	Not defined	Homo sapiens	[109]
	TRPC5	Xq23	Subfamily C member 5	Calcium permeant cation channel	Not defined	Homo sapiens	[110, 111]
	TRPC4AP	20q11.22	Subfamily C member 4 associated protein	Involved in protein ubiquitination and ubiquitin-dependent protein catabolic process	Not defined	Homo sapiens	[112]
–	CAMK2N1	1p36.12	Calcium/calmodulin dependent protein kinase II inhibitor 1	Calcium-dependent protein kinase inhibitor activity and protein kinase binding activity	Not defined	Homo sapiens	[113, 114]

Table 1 (continued)

Gene family	Gene	locus	Protein	Function	Disease Association	Organism	References
Calcium/calmodulin-dependent protein kinases	CaMKII	102E2-102F2;	Type II	Involved in several processes, including long-term memory; peptidyl-threonine autophosphorylation; and regulation of filopodium assembly. Acts upstream of with a positive effect on positive regulation of dopaminergic synaptic transmission	Axon growth	Drosophila melanogaster	[115]
	CAMK2G	10q22.2	Type II gamma	A serine/threonine protein kinase and a Ca(2+)/calmodulin-dependent protein kinase	Not defined	Homo sapiens	[116]
–	RYK	3q22.2	Receptor like tyrosine kinase	Recruits a signaling-competent auxiliary protein	not defined	Homo sapiens	[117]
–	ALOX5	10q11.21	Arachidonate 5-lipoxygenase	Catalyzes the conversion of arachidonic acid to 5(S)-hydroperoxy-6-trans-8,11,14-cis-eicosatetraenoic acid, and further to the allylic epoxide 5(S)-trans-7,9-trans-11,14-cis-eicosatetrenoic acid	not defined	Homo sapiens	[118]
–	ORAI1	12q24.31	ORAI calcium release-activated calcium modulator 1	A membrane calcium channel subunit that is activated by the calcium sensor STIM1 in shortage of calcium store	Not defined	Homo sapiens	[119]
–	STIM1	11p15.4	Stromal interaction molecule 1	Mediates Ca2+ influx after shortage of intracellular Ca2+ stores by gating of store-operated Ca2+ influx channels	Not defined	Homo sapiens	[120]
–	PMCA	102B5-102B5	Plasma membrane calcium ATPase	Involved in cellular calcium ion homeostasis	Not defined	Drosophila melanogaster	[121]
–	CASR	3q13.33-q21.1	Calcium sensing receptor	Intracellular signaling pathways that modify parathyroid hormone	Not defined	Homo sapiens	[122, 123]

Table 1 (continued)

Gene family	Gene	locus	Protein	Function	Disease Association	Organism	References
–	VDAC1	5q31.1	Voltage dependent anion channel 1	enables the exchange of metabolites and ions across the outer mitochondrial membrane and might control mitochondrial function	Not defined	Homo sapiens	[124]
Glutamate ionotropic receptor NMDA types	GRIN1	9q34.3	Subunit 1	The plasticity of synapses, which is supposed to inspire memory and learning	Not defined	Homo sapiens	[125]
	GRIN2B	12p13.1	Subunit 2B		Not defined	Homo sapiens	[125]
	GRIN2A	16p13.2	Subunit 2A		Not defined	Homo sapiens	[125]
	GRIN3A	9q31.1	Subunit 3A		Not defined	Homo sapiens	[125]
–	SARAF	8p12	Store-operated calcium entry associated regulatory factor		Not defined	Homo sapiens	[125]
Gamma-aminobutyric acid type A receptors	GABRB3	15q12	Subunit beta3		Not defined	Homo sapiens	[125]
	GABRA1	5q34	Subunit alpha1		Not defined	Homo sapiens	[125]
	GABRG2	5q34	Subunit gamma2		Not defined	Homo sapiens	[125]
	GABRA3	Xq28	Subunit alpha3		Not defined	Homo sapiens	[125]
	GABBR2	9q22.33	Subunit 2		Not defined	Homo sapiens	[125]
	GABRA5	15q12	Subunit alpha5		Not defined	Homo sapiens	[125]
	GABRB2	5q34	Subunit beta2		Not defined	Homo sapiens	[125]
	GABRA2	4p12	Subunit alpha2		Not defined	Homo sapiens	[125]
–	GABBR1	6p22.1	Gamma-aminobutyric acid type B receptor subunit 1		Not defined	Homo sapiens	[125]

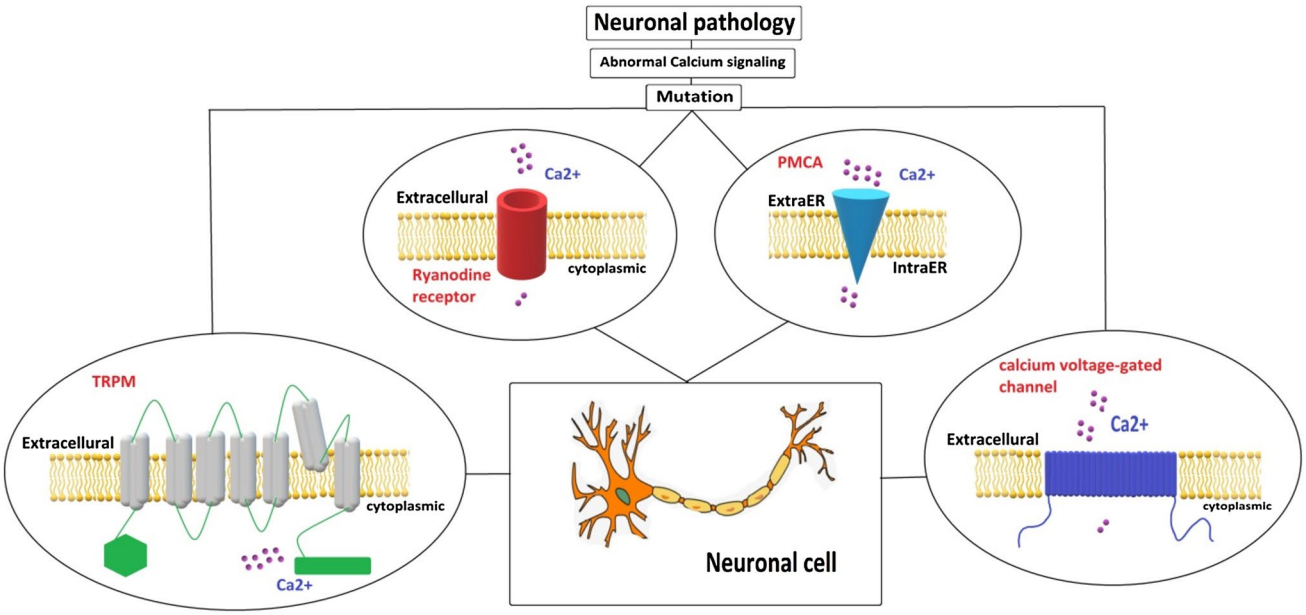

Fig. 1 A number of proteins including calcium voltage-gated channel, plasma membrane Ca2+ ATPase (PMCA), ryanodine receptor and transient receptor potential melastatin (TRPM) are involved in the regulation of calcium homeostasis in neurons. Alterations in the activity of these proteins disturb calcium homeostasis and participate in the pathoetiology of autism spectrum disorder

knockout of *IP3R2* gene which mediates calcium release from intracellular stores has resulted in induction of ASD-like behaviors in animals [128].

In brief, calcium signaling-related genes are implicated in the pathogenesis of ASD. Additional functional studies in this field would facilitate identification of novel therapeutic approaches for this neurodevelopmental disorder.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare they have no conflict of interest.

Ethical approval The study protocol was approved by ethical committee of Shahid Beheshti University of Medical Sciences. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent of publication Not applicable.

Informed consent Not applicable.

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