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Review

# Disturbed calcium signaling in spinocerebellar ataxias and Alzheimer's disease

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ABSTRACT

Neurodegenerative disorders, such as spinocerebellar ataxias (SCAs) and Alzheimer's disease (AD) represent a huge scientific and medical question, but the molecular mechanisms of these diseases are still not clear. There is increasing evidence that neuronal calcium signaling is abnormal in many neurodegenerative disorders. Abnormal neuronal calcium release from the endoplasmic reticulum may result in disturbances of cell homeostasis, synaptic dysfunction, and eventual cell death. Neuronal loss is observed in most cases of neurodegenerative diseases. Recent experimental evidence supporting the role of neuronal calcium signaling in the pathogenesis of SCAs and AD is discussed in this review.





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*Abbreviations:* AD, Alzheimer's disease; ADCA, autosomal dominant cerebellar ataxia; AMPA receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; APP, amyloid precursor protein; $Atx2^{mut}$, mutant ataxin-2; Aβ peptides, amyloid beta peptides; BACE1, beta site amyloid precursor protein cleaving enzyme 1; CaBPs, calcium-binding proteins; CaMKII, calcium/calmodulin-dependent protein kinase II; CAMTA1, calmodulin-binding transcription activator 1; CaN, calcineurin; $Ca^{2+}$, calcium; CB, calbindin D-28k; CF, climbing fiber; cGMP, cyclic guanosine monophosphate; Cyt c, cytochrome c; DUB, deubiquitinating enzyme; ER, endoplasmic reticulum; FAD, familial Alzheimer disease; HD, Huntington's disease; IICR, inositol 1,4,5-triphosphate-induced calcium release; $InsP_3$, inositol 1,4,5-triphosphate; $InsP_3R$, inositol 1,4,5-triphosphate receptor; KI, knock-in; LTD, long-term depression; LTP, long-term potentiation; MCU, mitochondrial calcium uniporter; mGluR, metabotropic glutamate receptor; Mito, mitochondria; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; nSOC, neuronal store-operated calcium; OPCA, olivopontocerebellar atrophy; Opt, *opisthotonos*; PC, Purkinje cell; PF, parallel fiber; polyQ, polyglutamine; PS, presenilin; PV, parvalbumin; Q, glutamine; QA, quisqualate; RyRs, ryanodine receptors; SCA, spinocerebellar ataxia; SOCE, store-operated calcium entry; SOC channels, store-operated calcium channels; STIM1, stromal interaction molecule 1; SUMF1, sulfatase modifying factor 1; VDCC, P/Q voltage-dependent calcium channel; 5PP, inositol 1,4,5-triphosphate-phosphatase enzyme.

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## 1. Spinocerebellar ataxias

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Spinocerebellar ataxias (SCAs) represent a group of progressive hereditary neurodegenerative diseases that differ from each other in clinical presentation and genetic basis. At present, about 30 different genes have been identified which can be the cause of these diseases [1]. In the case of some SCAs, molecular cloning methods revealed the expansion of CAG codons that leads to lengthening of polyglutamine (polyQ) tract in appropriate proteins, such as ataxins for SCA1, SCA2, SCA3 and SCA7 or α1A subunit of P/Q voltage-dependent calcium channel (VDCC) $Ca_v2.1$ for SCA6 [2]. These diseases relate to wide group of polyglutamine disorders. In addition to this, there are some types of SCAs caused by other DNA mutations with other trinucleotide repeat expansion, nucleotide repeats in non-coding regions of appropriate genes, or non-repeat mutations and deletions.

### 1.1. Spinocerebellar ataxia type 2 pathogenesis

In this section we will discuss SCA pathogenesis by the example of SCA2. This disorder is accompanied by a wide spectrum of severe clinical symptoms, such as ataxia of gait and stance, ataxia of limb movements, dysarthria, ophthalmoplegia, pyramidal and extrapyramidal disorders, muscular rigidity and other severe neurological symptoms [2–4]. Clinical investigations have shown that in SCA2 patients olivopontocerebellar atrophy (OPCA) is observed. OPCA is attended with the degeneration of Purkinje cells (PCs) – large neurons located in cerebellar cortex, also with the decay of inferior olive, pontine nuclei and pontocerebellar fibers – fibers that link pons with cerebellum. In clinical trials on humans different diagnostic tests were used: starting with general biochemical analysis, including additional screening-test for paraneoplastic antibodies to PCs and also neuro-ophthalmological examination, electroretinogram and electronystagmogram analysis and in some cases – autopsy [5].

MRI-morphometric examination of infratentorial region of the brain of SCA2 patients revealed significant atrophy of the cerebellar vermis, of the cerebellar hemispheres, of pons base, of middle cerebellar peduncle, of medulla oblongata, of cervical part of spinal cord and also hypertrophy of the fourth ventricle of the brain have been observed in all cases [6].

Some proteins with expanded polyQ tracts are neurotoxic, they disturb nuclear functions by means of misfolding or in other ways. Misfolding is linked with intranuclear inclusion formation. Immunolabeling of intranuclear inclusions revealed the presence of proteosomes, ubiquitin and chaperones and this fact indicates that these inclusions contain misfolded proteins which are exposed to ineffective proteolysis [7]. Ubiquitin-positive neuronal intranuclear inclusions are detected in brains of polyQ diseases patients in the case of Huntington's disease [8], dentatorubral–pallidoluysian atrophy [9], SCA1 [10], SCA3 [11] and SCA7 [12]. However, ubiquitin-positive nuclear inclusions have not been detected in the brain of SCA2 patients [7]. Therefore, misfolding and disturbances in protein metabolism are not essential and there is some other mechanism of neurodegeneration that plays a key role in SCA2 pathogenesis.

### 1.2. Calcium signaling in cerebellar PCs

The assertion that calcium signaling plays an important role in PCs functioning can be confirmed by the fact that these neurons express a lot of different calcium-dependent proteins and enzymes. Thus, cerebellar PCs contain extremely high amounts of dendritic calbindin D-28k (CB) and somatic parvalbumin (PV). These proteins belong to the large family of EF-hand calcium-binding proteins (CaBPs) [13]. It was demonstrated that the loss of PV and CB leads to the alterations in $Ca_v2.1$ channels (P/Q-type VDCCs), encoded by *CACNA1A* gene [14].

Recently it was reported that regulation of calcium influx to PCs through VDCCs is very important for the right connection from a climbing fiber (CF) to a PC during postnatal development. These data were obtained via simultaneous whole-cell recordings and two-photon calcium imaging from PCs in vivo in wild type and PC-selective P/Q-type VDCC knockout mice [15]. At the same time, in earlier studies with a use of flavoprotein autofluorescence optical imaging and extracellular field potential recordings methods it was shown that derangements in the CF-PC circuitry contribute to neuronal abnormality in SCA1 mice different transgenic lines [16]. PCs also highly express calmodulin-binding transcription activator 1 (CAMTA1) and deletion of *CAMTA1* gene in mice causes severe ataxia with PCs degeneration and cerebellar atrophy [17]. It is commonly thought that long-term depression (LTD) at parallel fiber (PF) on a PC is the main basis for motor learning. PCs express calcium/calmodulin-dependent protein kinase II (CaMKII) and it has been observed that CaMKII activation leads to prolonged increase of cGMP, supporting the signaling mechanism of LTD induction by CaMKII [18].

Summing up, we can conclude that PCs express various calcium sensors to maintain intraneuronal calcium homeostasis. There are two general ways that calcium can get into the cytoplasm of PC. Both include the presence of glutamate, an excitatory neurotransmitter. The first way is calcium influx through VGCCs from the interstitial fluid. These channels are activated by the membrane depolarization, caused by the activation of AMPA receptors. The second way is the activation of metabotropic glutamate receptors (mGluR) which leads to calcium release from the endoplasmic reticulum (ER) via activating inositol 1,4,5-triphosphate receptors ($InsP_3R$) and this calcium influx is called $InsP_3$-induced calcium release (IICR).

#### 1.2.1. $InsP_3$-induced calcium release

$InsP_3R$ is an intracellular calcium channel that mediates ion release mainly from the ER. More often $InsP_3R$ is activated by $InsP_3$ molecules and this leads to IICR. $InsP_3R$ is involved in the regulation of a large number of significant physiological processes including learning and memory, behavior, cell division and proliferation, differentiation, fertilization, development and cell death. There are three $InsP_3R$ subtypes, in neurons a predominant isoform is $InsP_3R$ type 1. There is evidence that dysfunction of $InsP_3R1$ may play a key role in the pathogenesis of certain neurodegenerative diseases. The hyperactivation of $InsP_3R1$ leads to enhanced calcium release from the ER. There is evidence to suggest that deranged neuronal calcium signaling might play an important role in pathogenesis of some neurodegenerative diseases such as Huntington's disease (HD), SCAs and AD. To support this idea, experimental studies on transgenic mice were carried out. This demonstrated a connection between abnormal calcium signaling and neuronal cell death in experiments with HD, SCA2 and SCA3 transgenic mouse models [19]. Additional data in the literature indicate that abnormal neuronal calcium signaling may also play an important role in pathogenesis of SCA1, SCA5, SCA6, SCA14 and SCA15/16. These data suggested that IICR might be one of the causes of pathophysiological processes in neurons, leading to the neurodegeneration.

#### 1.2.2. Mutations in *INSP$_3$R1* gene

$InsP_3R$ functions could be clearly identified by the observation of $InsP_3R$ mutant mice. It was demonstrated that most $InsP_3R1$ knockout mice die in the period of prenatal development and mutant mice that managed to survive have severe ataxia and tonic or tonic–clonic seizures and die by the weaning period. An electroencephalogram study with these animals revealed that they suffer



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