



# Physiology and pathology of calcium signaling in the brain

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Calcium ( $\text{Ca}^{2+}$ ) plays fundamental and diversified roles in neuronal plasticity. As second messenger of many signaling pathways,  $\text{Ca}^{2+}$  as been shown to regulate neuronal gene expression, energy production, membrane excitability, synaptogenesis, synaptic transmission, and other processes underlying learning and memory and cell survival. The flexibility of  $\text{Ca}^{2+}$  signaling is achieved by modifying cytosolic  $\text{Ca}^{2+}$  concentrations via regulated opening of plasma membrane and subcellular  $\text{Ca}^{2+}$  sensitive channels. The spatiotemporal patterns of intracellular  $\text{Ca}^{2+}$  signals, and the ultimate cellular biological outcome, are also dependent upon termination mechanism, such as  $\text{Ca}^{2+}$  buffering, extracellular extrusion, and intra-organelle sequestration. Because of the central role played by  $\text{Ca}^{2+}$  in neuronal physiology, it is not surprising that even modest impairments of  $\text{Ca}^{2+}$  homeostasis result in profound functional alterations. Despite their heterogeneous etiology neurodegenerative disorders, as well as the healthy aging process, are all characterized by disruption of  $\text{Ca}^{2+}$  homeostasis and signaling. In this review we provide an overview of the main types of neuronal  $\text{Ca}^{2+}$  channels and their role in neuronal plasticity. We will also discuss the participation of  $\text{Ca}^{2+}$  signaling in neuronal aging and degeneration.

**Keywords:** calcium channels, synaptic plasticity

## INTRODUCTION

Calcium ( $\text{Ca}^{2+}$ ) plays fundamental and diversified roles in neuronal physiology. For example, by regulating the release of neurotransmitters from the presynaptic terminals it influences both long-term potentiation (LTP; Grover and Teyler, 1990; Impey et al., 1996) and long-term depression (LTD; Bolshakov and Siegelbaum, 1994; Christie et al., 1996) forms of synaptic plasticity. As ubiquitous second messenger,  $\text{Ca}^{2+}$  has been shown to regulate gene expression (Berridge, 1998), membrane excitability (Sudhof, 2004), dendrite development (Lohmann and Wong, 2005; Redmond and Ghosh, 2005), synaptogenesis (Michaelsen and Lohmann, 2010), and many other processes contributing to the neuronal primary functions of information processing and memory storage (Berridge, 1998; Tanaka et al., 2008). The specificity of various biological outcomes is rendered possible by a complex protein network tightly regulating the amplitude, spatial, and temporal patterns of calcium movements through the neuronal cellular compartments. Under resting conditions neurons actively maintain a steep gradient between low intracellular free  $\text{Ca}^{2+}$  concentration [ $\text{Ca}^{2+}$ ]<sub>i</sub> (0.1–0.5  $\mu\text{M}$ ) and high extracellular  $\text{Ca}^{2+}$  levels ( $\sim 1$  mM). [ $\text{Ca}^{2+}$ ]<sub>i</sub> changes result from influx into the cell regulated through the opening of voltage-dependent  $\text{Ca}^{2+}$  channels (VDCCs), *N*-Methyl-D-Aspartate (NMDA) receptors, or transient receptor potential (TRP) channels located in the plasma membrane. Additionally [ $\text{Ca}^{2+}$ ]<sub>i</sub> levels can be increased via ryanodine receptors (RyRs) and inositol-1,4,5-triphosphate receptors (IP<sub>3</sub>Rs) mediated release from endoplasmic reticulum intracellular  $\text{Ca}^{2+}$  stores, or by sodium-dependent  $\text{Ca}^{2+}$  ( $\text{Na}^+/\text{Ca}^{2+}$  exchanger) efflux from mitochondria. The return to basal [ $\text{Ca}^{2+}$ ]<sub>i</sub> is achieved by  $\text{Ca}^{2+}$  extrusion (i.e., plasma membrane  $\text{Ca}^{2+}$ -ATPase, sodium calcium exchanger), binding to  $\text{Ca}^{2+}$  buffering proteins (e.g., calmodulin, calcineurin, calbindin,

calretinin), or organelle uptake (i.e., sarcoplasmic–endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase, mitochondrial uniporter; Carafoli, 1987; Miller, 1991; Zaidi et al., 2003; Pivovarova and Andrews, 2010).

The purpose of this review is to provide a brief overview of the main types of neuronal  $\text{Ca}^{2+}$  channels and their role in neuronal plasticity. We will also discuss the participation of altered  $\text{Ca}^{2+}$  homeostasis to the cognitive decline observed during aging and the neurodegenerative process.

## PLASMA MEMBRANE $\text{Ca}^{2+}$ CHANNELS

Neuronal  $\text{Ca}^{2+}$  influx is primarily regulated through two types of plasma membrane  $\text{Ca}^{2+}$  channels: VDCCs and receptor-operated (ligand-gated) channels (ROCs).

## VOLTAGE-DEPENDENT $\text{Ca}^{2+}$ CHANNELS

Voltage-dependent  $\text{Ca}^{2+}$  channels transduce electrical signals into local intracellular  $\text{Ca}^{2+}$  transients regulating intracellular processes such as neurotransmission, enzyme activation, gene expression, and neurite outgrowth or retraction (Tsien et al., 1988; Catterall, 2011). They are composed by an  $\alpha_{1-10}$  subunit forming the  $\text{Ca}^{2+}$  selective channel, and several accessory subunits,  $\alpha_{2\delta}$ ,  $\beta_{1-4}$ , and  $\gamma$  with anchorage, and regulatory functions. Based on their unique electrophysiological and pharmacological properties, and the type of  $\alpha_1$  subunit VDCCs are divided into five classes:  $\text{Ca}_v1.1$ – $\text{Ca}_v1.4$  (L-type  $\text{Ca}^{2+}$  current),  $\text{Ca}_v2.1$  (P/Q-type  $\text{Ca}^{2+}$  current),  $\text{Ca}_v2.2$  (N-type  $\text{Ca}^{2+}$  current),  $\text{Ca}_v2.3$  (R-type  $\text{Ca}^{2+}$  current), and  $\text{Ca}_v3.1$ – $\text{Ca}_v3.3$  (T-type  $\text{Ca}^{2+}$  currents; Tsien et al., 1988; Catterall et al., 2005; Catterall, 2011).

In the mammalian brain  $\text{Ca}_v1.2$  and  $\text{Ca}_v1.3$  are the predominant forms of L-type  $\text{Ca}^{2+}$  channels. They are localized in the cell bodies and proximal dendrites, both at presynaptic as well as postsynaptic locations, forming small clusters on dendritic shafts

and spines (Hell et al., 1993; Obermair et al., 2004) associated with regulatory proteins such as, protein kinase-A, A kinase anchoring proteins (AKAP15), calmodulin, and calcineurin (Davare et al., 2001). L-type channels have a high-voltage threshold for activation and are important for integrating synaptic inputs with the initiation of neurotransmitter release. Inward L-type  $\text{Ca}^{2+}$  currents can directly depolarize the membrane potential of neurons (Moyer and Disterhoft, 1994; Chan et al., 2007), or alternatively depress membrane excitability through coupling to  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels (Wisgirda and Dryer, 1994; Marrion and Tavalin, 1998). Because of their preferential cellular localization and interaction with  $\text{Ca}^{2+}$ -binding regulatory proteins (they have been shown to regulate nuclear gene transcription (Dolmetsch, 2003; Oliveria et al., 2007). In addition, L-type channels are required for NMDA receptor-independent LTP at synapses between CA3 pyramidal neurons and mossy fibers, and between dentate gyrus and the basolateral nucleus of the amygdala (Grover and Teyler, 1990; Cavus and Teyler, 1996; Raymond and Redman, 2002, 2006; Niikura et al., 2004), spatial memory (Moosmang et al., 2005) and heterosynaptic plasticity (Lee et al., 2009; Rose et al., 2009). L-type  $\text{Ca}^{2+}$  currents leading to global dysregulated calcium signals have been implicated in aging and neurodegenerative disease (Chang et al., 2009). Enhanced activity of L-type  $\text{Ca}^{2+}$  channels is observed with neuronal aging (Thibault and Landfield, 1996) and their expression is increased in hippocampi of patients with Alzheimer's disease (AD) compared to healthy subjects (Coon et al., 1999). Blockage of L-type currents has been shown to improve learning and memory in aged mice (Disterhoft and Oh, 2006), and in patients with dementia (Forette et al., 2002). In addition, inhibition of L-type channels reduces cell death in stroke (Korenkov et al., 2000) and Parkinson's disease (Chan et al., 2007). In young neurons, sustained depolarization or activation of NMDA receptors reduces L-type  $\text{Ca}^{2+}$  currents by internalization of  $\text{Ca}_v1.2$  channels through a dynamin-dependent endocytosis mechanism, protecting the neurons from excitotoxic cell death (Green et al., 2007). It is thus possible that some of the impairments observed in neurons in aging and degenerative disorders are due to an altered regulation of  $\text{Ca}_v1.2$  and  $\text{Ca}_v1.3$  levels at the membrane.

$\text{Ca}_v2.1$  (P/Q-type  $\text{Ca}^{2+}$  current) and  $\text{Ca}_v2.2$  (N-type  $\text{Ca}^{2+}$  current) channels are the predominant  $\text{Ca}^{2+}$ -dependent pathway triggering fast release of neurotransmitters like glutamate,  $\gamma$ -aminobutyric acid (GABA), and acetylcholine (Oliveria et al., 1994; Dunlap et al., 1995).  $\text{Ca}_v2$  are high-voltage threshold activated channels localized at presynaptic terminals, dendrites and cell bodies (Westenbroek et al., 1992).  $\text{Ca}_v2$  channels directly interact with the SNARE complex, formed by the vesicle-associated-v-SNARE protein synaptobrevin (VAMP/synaptobrevin) and two plasma-membrane-associated t-SNARE proteins, SNAP-25 and syntaxin-1 (Bajjalieh and Scheller, 1995; Sudhof, 2004). The interaction occurs at a specific site, synprint, in the large intracellular loop connecting domains II and III of the  $\alpha1$  subunit of  $\text{Ca}_v2$  channels (Sheng et al., 1994; Retting et al., 1996). This association is  $\text{Ca}^{2+}$  dependent and regulated by protein phosphorylation of the synprint domain by protein kinase C (PKC) and  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CaMKII; Sheng et al., 1996; Yokoyama et al., 2005). The same site is also responsible for the binding to synaptic vesicle  $\text{Ca}^{2+}$ -binding protein synaptotagmin (Charvin

et al., 1997; Wiser et al., 1997). During depolarization the presynaptic  $\text{Ca}_v2.1$  and  $\text{Ca}_v2.2$  channels open allowing the formation of high  $\text{Ca}^{2+}$  concentration microdomains in proximity of the pore (Stanley, 1997).  $\text{Ca}^{2+}$  then binds to synaptotagmin and the SNARE complex, resulting in the fusion of the vesicular membrane with the plasma membrane, and release of the neurotransmitter (Catterall and Few, 2008). Inhibition of presynaptic P/Q-types and N-type currents with reduction of neurotransmitter release is typically produced by a positive shift in the voltage dependence and a slowing of channel activation (Bean, 1989). The  $\text{G}\beta\gamma$  subunits released from receptor-coupled heteromeric G-proteins of the Gi/Go class are usually responsible for this inhibition by binding to the loop between domains I and II and the amino- and carboxy-terminal domains of  $\text{Ca}^{2+}$  channels (Herlitze et al., 1996; De Waard et al., 1997; Zamponi et al., 1997; Page et al., 1998; Li et al., 2004). Contrary to  $\text{Ca}_v2.1$  and  $\text{Ca}_v2.2$ ,  $\text{Ca}_v2.3$  (R-type  $\text{Ca}^{2+}$  current) channels control transmitter release with a lower efficacy (Wu et al., 1998). This is probably due to the fact that although they are localized at the cell body, dendrites and presynaptic terminal, their position is further away from the release sites (Yokoyama et al., 1995; Day et al., 1996; Wu et al., 1999). Nevertheless,  $\text{Ca}_v2.3$  still carries one-third of the total calcium current at presynaptic terminals during a presynaptic action potential (Wu et al., 1998). Dietrich et al. (2003) showed that  $\text{Ca}^{2+}$  influx through presynaptic  $\text{Ca}_v2.3$  contributes to LTP without playing a role in the fast synaptic transmission or facilitation at specific hippocampal synapse terminals. It has been suggested that  $\text{Ca}_v2.3$  currents may be involved in control of gene expression or dendritic excitability (Delmas et al., 2000). Pathophysiological changes of  $\text{Ca}_v2$  channels have been associated with chronic disorders. Mutations in the *CACNA1A* gene encoding the  $\text{Ca}_v2.1$  channels have been identified in patients affected by epileptic seizures, episodic ataxia type-2, spinocerebellar ataxia type-6, and familial hemiplegic migraine type 1 (Catterall et al., 2005; Cain and Snutch, 2011).

$\text{Ca}_v3.1$ – $3.3$  channels (T-type  $\text{Ca}^{2+}$  currents) are mainly distributed at cell bodies and dendrites of neurons in the olfactory bulb, amygdala, cerebellar cortex, hippocampus, thalamus, hypothalamus, and striatum (Talley et al., 1999). These channels play a critical role toward neuronal firing both in conducting  $\text{Ca}^{2+}$  during action potentials and in switching neurons between distinct rhythmic firing modes. T-types  $\text{Ca}^{2+}$  currents are activated at rather negative near resting membrane potentials (Huguenard, 1996). Specifically, they are activated during the initial depolarization phase although the highest conductance occur during the repolarization phase and return to resting membrane potential (McCobb and Beam, 1991). The  $\text{Ca}^{2+}$  entry through the  $\text{Ca}_v3.1$ – $3.3$  channels leads to depolarization of the membrane allowing the generation of low threshold spikes that trigger bursts of Na-dependent action potentials (Llinas, 1988). Depending on the specific channel subtype the time course of activation, inactivation, deactivation, and recovery from inactivation varies, resulting in unique biophysical properties and specific responses to action potential which can be extended during burst firing (Huguenard, 1996). Moreover the expression of individual or multiple  $\text{Ca}_v3$  subtypes and splice variants results in a variety of different burst patterns (Cain and Snutch, 2010). Bursts discharges controlled by T-type  $\text{Ca}^{2+}$  currents occur during physiological and pathological

forms of neuronal rhythmicity (Huguenard, 1996) such as slow sleep oscillations (<1 Hz; Crunelli et al., 2006), learning (Scotty et al., 2003) and hyper-synchronous oscillations during epilepsy (Zamponi et al., 2010). Mutations in the CACNA<sub>1</sub>H gene encoding the Cav3.2 channels have been linked to epilepsy and autism spectrum disorders (Heron et al., 2004; Splawski et al., 2006).

### RECEPTOR-OPERATED (LIGAND-GATED) CHANNELS

Receptor-operated (ligand-gated) channels open in response to the binding of specific ligands, such as neurotransmitters to the extracellular domain of the receptor. The interaction causes a conformational change in the structure of the protein that leads to the opening of the channel pore and subsequent ion flux across the plasma membrane. Most ROCs are permeable to Ca<sup>2+</sup> and represent an important mechanism for the generation of second messengers. Examples of ROCs include the glutamate receptors NMDA,  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate acid (AMPA; Isaac et al., 2007; Paoletti, 2011), and kainate (KARs; Chittajallu et al., 1999), nicotinic acetylcholine receptors (nACh; Shen and Yakel, 2009), serotonin (5-HT<sub>3</sub>) receptors (Yakel, 2000), and adenosine 5'-triphosphate (ATP) P2X receptors (Pankratov et al., 2008).

#### Glutamate receptors

Glutamate is the most abundant neurotransmitter in the central nervous system (CNS) playing an important role in neuronal physiology and pathology. At excitatory synapses glutamate release will primarily activate the ionotropic receptors, NMDA, AMPA, and KARs allowing rapid influx of ions into the postsynaptic terminal.

NMDA receptors are permeable to Na<sup>+</sup>, which contributes to postsynaptic depolarization, and Ca<sup>2+</sup>, which generate Ca<sup>2+</sup> transients and the ultimate intracellular physiological response. A unique feature of these receptors is that at resting potential the cation pore is blocked by extracellular Mg<sup>2+</sup>. Their activation thus relies upon glutamate binding to postsynaptic AMPA receptors and Na<sup>+</sup> and Ca<sup>2+</sup> influx to cause a partial membrane depolarization sufficient to lift the Mg<sup>2+</sup> blockage. Molecular cloning studies have identified several variants of the NMDA receptor subunits, NR1<sub>1-4a/b</sub> and NR2<sub>A-D</sub> (Hollmann and Heinemann, 1994). Each channel consists of two NR1 subunits, which are essential for the assembly of functional NMDA receptors, and two NR2 subunits that confer a unique set of characteristic upon the resultant NMDA receptor (Kutsuwada et al., 1992; Monyer et al., 1992). The cytoplasmic C-terminals of the NR1 and NR2 subunits link the receptor to a large multi-protein complex. This interaction facilitates the localization of the receptor in specific areas, such as the postsynaptic density (PSD), and the connection to a variety of downstream signaling molecules (Traynelis et al., 2010). In particular, NMDA-dependent Ca<sup>2+</sup> influxes are known to regulate CREB-dependent gene transcription (Hardingham et al., 1999, 2001a,b; Impey and Goodman, 2001; Wu et al., 2001) which has considerable physiological relevance for the establishment of long-term synaptic plasticity and learning and memory (Barco et al., 2002). The robust activation of CREB is achieved via activation of the Ras-ERK1/2 and the nuclear Ca<sup>2+</sup>-calmodulin (CaM) kinase pathways (Hardingham et al., 2001b). Because CaM kinase activity itself is Ca<sup>2+</sup>-dependent (Bading and Greenberg, 1991; Finkbeiner

and Greenberg, 1996) this pathway mediates CREB phosphorylation within the first few seconds of Ca<sup>2+</sup> influx. On the other hand, the more upstream position of the Ca<sup>2+</sup> dependent step (Ras) in the ERK1/2 pathway results in a slower yet prolonged activation after cessation of the synaptic input. The resulting CREB phosphorylation on Ser<sup>133</sup> allows the recruitment of the transcriptional co-activator, CREB-binding protein (CBP) to the target promoter (Chrivia et al., 1993). The trans-activating potential of CBP is further positively regulated by phosphorylation of Ser<sup>301</sup> by either calmodulin (Deisseroth et al., 1998) or CaM kinase IV (Chrivia et al., 1993; Chawla et al., 1998; Hardingham et al., 1999) after elevation of nuclear Ca<sup>2+</sup> (Impey et al., 2002). Growing evidence suggest that physiological levels of synaptic NMDA receptor activation may enhance resistance to trauma and promote survival of various neuronal types (Hardingham and Bading, 2010). Conversely, intense or chronic activation of extrasynaptic NMDA receptors has been implicated as the leading cause of neuronal death following acute traumas such as stroke, mechanical trauma, or seizure activity (Choi, 1990; Hardingham and Bading, 2010). Moreover, NMDA receptor activity is thought to contribute to the etiology of many chronic neurodegenerative disorders, such as Huntington's disease, HIV-associated dementia, and AD (Lancelot and Beal, 1998; Chohan and Iqbal, 2006; Fan and Raymond, 2007).

AMPA receptors are heterotetrameric structures composed of subunits encoded by four genes GluR1–4, and primarily conduct Na<sup>+</sup> and K<sup>+</sup> currents. The permeability to Ca<sup>2+</sup> is regulated by the presence of GluR2 subunits. Only the AMPA receptors lacking GluR2 are permeable to Ca<sup>2+</sup>, although with reduced affinity compared to NMDA receptors (Dingledine et al., 1999). The GluR2 lacking AMPA receptors are widely expressed in the CNS (including interneurons, stellate, and glial cells) where they contribute to synaptic transmission and changes in synaptic efficacy (Isaac et al., 2007), as well as induce multiple forms of synaptic plasticity, including LTP (Gu et al., 1996; Jia et al., 1996; Kullmann and Lamsa, 2007; Liu and Zukin, 2007). Similarly to the NMDA receptor, Ca<sup>2+</sup>-permeable AMPA receptors signal to the nucleus to activate CREB (Perkinton et al., 1999; Tian and Feig, 2006) and other transcription factors. In response to Ca<sup>2+</sup> transients both CaMKII and PKA phosphorylate specific AMPA subunits modifying the synaptic transmission strength (Lee and Kirkwood, 2011). Direct phosphorylation regulates the opening probability of the channels, as well as the insertion of the receptors into the postsynaptic membrane. During LTP phosphorylation increases the opening probability and the concentration of AMPA receptors at the synapse, whereas phosphorylation and receptor density decrease during LTD (Malenka, 2003).

KARs respond to kainate, glutamate, and, with very low affinity, to AMPA (Hollmann and Heinemann, 1994). KARs are tetrameric combinations of five subunits: GluK1, GluK2, GluK3, GluK4, and GluK5 (Hollmann and Heinemann, 1994; Collingridge et al., 2009). The GluK1–3 subunits are highly homologous and can form functional receptors as homotetramers, while GluK4–5 share only 45% homology with GluK1–3 and must combine with any of them in order to generate functional KARs (Herb et al., 1992). The receptor structure consist of extracellular N-terminal and ligand binding domains implicated respectively in subunit and ligand recognition, a transmembrane region, and intracellular

re-entrant loop (p loop), forming the  $\text{Ca}^{2+}$  pore and C-terminal regions (Hollmann et al., 1994; Wo and Oswald, 1994). Similarly to the GluR2 subunit of AMPA receptors GluK2 and GluK3 can undergo RNA editing resulting in changes from a conserved glutamine (Q) to an arginine (R) in the channel pore loop that completely abolish  $\text{Ca}^{2+}$  permeability (Egebjerg and Heinemann, 1993; Kohler et al., 1993). KARs functions are much less understood than those of AMPA and NMDA receptors. They are located both pre- and postsynaptically, and based on genetic and pharmacological studies they appear to act mostly as modulators rather than obligatory components of synaptic transmission and neuronal excitability (Chittajallu et al., 1999; Contractor et al., 2011). KARs can regulate both excitatory and inhibitory synaptic transmission (Rodríguez-Moreno et al., 1997; Contractor et al., 2000; Kamiya and Ozawa, 2000; Schmitz et al., 2000; Frerking et al., 2001; Jiang et al., 2001). In the hippocampus, at mossy fiber CA3 pyramidal neuron synapses, endogenous activation of presynaptic kainate receptors increases the probability of glutamate release (Schmitz et al., 2001; Huettner, 2003). A similar regulatory role on excitatory transmission has been observed for other types of synapses in the central and peripheral nervous system (Pinheiro and Mulle, 2006). In addition to facilitation, presynaptic activation of KARs has also been shown to lead to inhibition of glutamate release (Kamiya and Ozawa, 1998; Rozas et al., 2003; Lauri et al., 2005, 2006; Jin et al., 2006). KARs-mediated bidirectional modulation has also been observed for the inhibitory transmitter GABA. KARs stimulation enhances GABA release at synapses between interneurons (Mulle et al., 2000; Cossart et al., 2001), yet it inhibits GABA release at interneuron–pyramidal cell connections (Clarke et al., 1997; Rodríguez-Moreno et al., 1997; Rodríguez-Moreno and Lerma, 1998). These opposite effects seem to rely on the fact that KARs signaling can occur either via ion influx, or by coupling of the receptor to G-proteins and activation of PKC dependent mechanisms (Melyan et al., 2002; Rozas et al., 2003; Ruiz et al., 2005). Overall it is believed that ionotropic activity accounts for enhanced neurotransmitter release, while inhibition is triggered by the metabotropic signaling pathway. In addition to neurotransmitter release, KARs contribute to temporal summation of postsynaptic depolarization in response to bursts of action potentials (Castillo et al., 1997; Vignes and Collingridge, 1997; Frerking and Ohlinger-Frerking, 2002; Jin et al., 2006), modulation of short- and LTP, as well as LTD, thus to learning and memory (Bortolotto et al., 1999; Contractor et al., 2001; Lauri et al., 2003; Schmitz et al., 2003; Campbell et al., 2007), nociception (Ko et al., 2005), synaptogenesis, and neuronal development (Lerma, 2006; Lauri and Taira, 2011).

As per pathological scenarios, KARs are considered to contribute to the induction and propagation of seizures (Ben-Ari, 1985). Although unequivocal involvement of KARs in human epilepsies still has to be established, KAR mutant mice display altered susceptibility to kainic acid induced seizures (Mulle et al., 1998; Vissel et al., 2001), and selective agonism of GluK1 blocks pilocarpine-induced epileptiform activity in hippocampal slices and seizures *in vivo* (Smolders et al., 2002). Like other glutamate receptors, KARs have been implicated in a variety of neurodegenerative conditions where glutamate excitotoxicity is believed to contribute to neuronal cell death. For example, GluK1 antagonists

afford good neuroprotection in focal and global ischemic models (Bullock et al., 1994; Gill and Lodge, 1994; O'Neill et al., 1998, 2000). GluK2 genotype variations, and possibly excitotoxic mechanisms, have been linked to variations in the age of onset of Huntington's disease (Rubinsztein et al., 1997). Similar associations linking KARs with neuropsychiatric disorders have begun to emerge from various human genetic and post-mortem studies. KARs levels are reduced in bipolar and schizophrenic patients (Begni et al., 2002; Pickard et al., 2006; Wilson et al., 2006; Beneyto et al., 2007).

The human GluR6 KAR subunit, GRIK2, has been implicated in obsessive–compulsive disorder (Delorme et al., 2004), schizophrenia (Bah et al., 2004), and autism (Strutz-Seebohm et al., 2006). Human GluR7, GRIK3, and KA1 subunit, GRIK4, may be susceptible factors in major depressive disorders (Schiffer and Heinemann, 2007).

### Nicotinic acetylcholine receptors

The nACh receptors are included in the cys-loop ligand-gated ion channel superfamily, and are activated by the endogenous neurotransmitter acetylcholine (ACh), as well as nicotine, hence the name. The receptors are pentameric homo or hetero combinations of different subunits types,  $\alpha 2$ – $10$ ,  $\beta 2$ – $4$ , with non-selective cation permeability and unique affinity to  $\text{Ca}^{2+}$  (Fucile, 2004). The nACh receptors are widely expressed in the brain at pre- and postsynaptic, as well as extrasynaptic loci (Dani and Bertrand, 2007). Presynaptic and pre-terminal nACh receptors enhance neurotransmitter release; postsynaptic nACh receptors contribute to fast excitatory transmission, while extrasynaptic nACh receptors influence neuronal excitability and/or intracellular processes (Dani and Bertrand, 2007). The nACh receptors play important modulatory roles in neuronal development and synaptic plasticity, participating in cognitive functions such as learning, memory, and attention (Levin and Simon, 1998; Mansvelder and McGehee, 2000; Sweatt, 2001). Inhibition of nACh receptors results in memory deficits, while the use of agonist has proved beneficial in different types of memory, such as short-term and working memory, both in animals and humans (Wallace and Porter, 2011). Furthermore, diminution, disruption, or alteration in the function of nACh receptors contributes to dysfunctions associated with various neurodegenerative pathologies, including epilepsy, Parkinson's disease, Alzheimer's disease, schizophrenia, autism, and addiction (Dani and Bertrand, 2007). The mechanisms underlying the effects of nACh receptors in synaptic plasticity are still poorly understood. In most cases nACh currents are thought to contribute to postsynaptic depolarization, enabling the activation of the VDCCs and subsequent  $\text{Ca}^{2+}$  influx, which augments the primary  $\text{Ca}^{2+}$  signals generated by the direct  $\text{Ca}^{2+}$  influx through nACh receptors (Dajas-Bailador et al., 2002). On the other hand, the predominant neuronal form, the homomeric  $\alpha 7$  nACh receptor subtype has higher affinity for  $\text{Ca}^{2+}$  than  $\text{Na}^{+}$  (Shen and Yakel, 2009). Activation of  $\alpha 7$  nACh receptors can thus generate  $\text{Ca}^{2+}$  transients via its channel pore sufficient to trigger  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release from ryanodine-dependent stores and downstream  $\text{Ca}^{2+}$ -dependent intracellular processes independently of VDCCs activation (Sharma and Vijayaraghavan, 2001).

### Serotonin receptor (5-HT<sub>3</sub>)

5-HT<sub>3</sub> is the only serotonin receptor acting as a ligand-gated ion channel rather than a metabotropic receptor. Similarly to nACh it belongs to the family of cys-loop ligand-gated ion channel (Maricq et al., 1991). Within the CNS, 5-HT<sub>3</sub> receptors are highly expressed in brainstem areas, such as the area postrema and the nucleus of the solitary tract. Within the forebrain, 5-HT<sub>3</sub> receptors have been found in the entorhinal, frontal and cingulate cortices, hippocampus, and amygdala. Notably, despite clear pharmacological and physiological evidence that they affect dopamine neurotransmission, 5-HT<sub>3</sub> receptors are found at very low levels in areas such as striatum, substantia nigra, thalamus, or dorsal raphe nucleus (Kilpatrick et al., 1987; Tecott et al., 1993; Färber et al., 2004). 5-HT<sub>3</sub> receptor consist of five subunits with an extracellular N-terminal domain containing the ligand recognition site for serotonin, four transmembrane domains (T2–T4), and a short intracellular C-terminal (Maricq et al., 1991). T2 is responsible for the formation of the channel pore, which conducts primarily Na<sup>+</sup>- and K<sup>+</sup>- and Ca<sup>2+</sup> (Yang, 1990; Hargreaves et al., 1994), while the large intracellular loop between T3 and T4 is the site of protein kinase phosphorylation and alternative splicing (Maricq et al., 1991; Davies et al., 1999; Dubin et al., 1999). Of the five different isoforms cloned to date, A–E, only 5-HT<sub>3A</sub> can generate functional homomeric receptors, all others isoforms must heteropentamerize with 5-HT<sub>3A</sub> (Maricq et al., 1991; Davies et al., 1999; Dubin et al., 1999). The best characterized receptors are 5-HT<sub>3A</sub> and 5-HT<sub>3AB</sub>, with the homomeric form displaying lower single channel conductance, higher Ca<sup>2+</sup> permeability, and slower kinetics of activation, deactivation, and desensitization (Davies et al., 1999; Hayrapetyan et al., 2005). The 5-HT<sub>3</sub> receptors are expressed both pre- and postsynaptically. Presynaptic 5-HT<sub>3</sub> receptors display high permeability to Ca<sup>2+</sup> (Nichols and Mollard, 1996; Nayak et al., 1999), whereas postsynaptic receptors display a lower permeability to Ca<sup>2+</sup> compared to Na<sup>+</sup> and K<sup>+</sup> (Yakel et al., 1990; Yang, 1990). Presynaptic 5-HT<sub>3</sub> stimulation leads to opening of the ion channel, rapid membrane depolarization and release of various neurotransmitters, such as dopamine and GABA (Koyama et al., 2000; van Hooff and Vijverberg, 2000; Yakel, 2000). The activation of postsynaptic 5-HT<sub>3</sub> receptors contributes to fast excitatory synaptic transmission in various brain areas, such as the lateral amygdala (Sugita et al., 1992) and the visual cortex (Roerig et al., 1997). The best known physiological functions of 5-HT<sub>3</sub> receptors are the regulation of nausea and vomit (Fozard and Mobarok, 1978; Florczyk et al., 1982), and of mesocorticolimbic neurotransmission, which implicates these channels in the etiology of certain forms of drugs addiction (i.e., alcohol, cocaine; Engleman et al., 2008). In addition, modulation of 5-HT<sub>3</sub> receptors has also been suggested to have therapeutical relevance for schizophrenia, anxiety, cognition, and nociception (Thompson and Lummis, 2007).

### ATP P2X receptors

The ionotropic P2X receptors are channels that respond to extracellular ATP to induce membrane depolarization and Ca<sup>2+</sup> influx. P2X receptors are widely distributed pre- and postsynaptically on different cell types in the brain and spinal cord (Burnstock and Knight, 2004). Sensitivity to ATP, Ca<sup>2+</sup> permeability, desensitization, recovery from desensitization kinetics, and other biophysical

and pharmacological properties of the channels depend upon the subunit channel composition. Seven different subunits, P2x<sub>1–7</sub>, can contribute to the generation of heterotrimers, or, with the exception of P2X6, homotrimers (Browne et al., 2010). P2X receptors display considerably high Ca<sup>2+</sup> permeability, thus can mediate substantial Ca<sup>2+</sup> influx despite the fact that the amplitude of P2X-mediated currents is quite modest when compared for example to glutamate-evoked responses (Pankratov et al., 2008). Because of this, P2X are the main postsynaptic Ca<sup>2+</sup> entry channels at resting potential when NMDA receptors are blocked by Mg<sup>2+</sup> (Pankratov et al., 2003). P2X receptors can dynamically interact with other neurotransmitter receptors, including NMDA receptors, GABA<sub>A</sub> receptors, and nACh receptors (Surprenant and North, 2009). Activation of P2X receptors has multiple modulatory effects on synaptic plasticity, either inhibiting or facilitating the long-term changes of synaptic strength depending on the physiological context; however the precise mechanisms of P2X-dependent regulation of synaptic plasticity remain elusive (Pankratov et al., 2008).

### INTRACELLULAR CALCIUM STORES

It is well established that in addition to intracellular influx, global Ca<sup>2+</sup> signals comprise release from intracellular stores either as a result of Gq-coupled receptor activation, or secondary to the [Ca<sup>2+</sup>]<sub>i</sub> rise itself. The largest intracellular store able to accumulate Ca<sup>2+</sup> to concentrations of 10–100 mM is the endoplasmic reticulum (ER). ER Ca<sup>2+</sup> release is mediated by RyRs, and by IP<sub>3</sub>Rs. The function of the ER Ca<sup>2+</sup> channels is to amplify or trigger Ca<sup>2+</sup> rises initiated by the plasmalemma Ca<sup>2+</sup> influx. In addition to the ER, mitochondria have also been shown to act as intracellular Ca<sup>2+</sup> stores and play a prominent role in determining the shape, amplitude, and duration of the Ca<sup>2+</sup> transients.

### ENDOPLASMIC RETICULUM CALCIUM REGULATION

In neurons the ER is represented by a complex system of folded membranes extending from the nuclear envelope throughout perikaryon, axon (Henkart et al., 1978), presynaptic terminals (McGraw et al., 1980), dendrites, and dendritic spines (Sato et al., 1990). Since the first demonstrations of its Ca<sup>2+</sup> sequestering ability in squid giant axon (Henkart et al., 1978) and rat synaptosomes (McGraw et al., 1980), the ER has been the object of intensive studies in order to determine its role in neuronal Ca<sup>2+</sup> homeostasis (Andrews et al., 1988; Markram et al., 1995). It is now evident that ER Ca<sup>2+</sup> regulation plays important functions in neuronal physiology and plasticity regulating synaptic transmission both at the presynaptic and postsynaptic terminals (Berridge, 1998; Park et al., 2008). Notably, at the level of dendritic spines, the ER comes in contact with the postsynaptic density thanks to the protein Homer simultaneously binding IP<sub>3</sub>Rs on the ER, and group I metabotropic receptors at the plasma membrane (Tu et al., 1998). Similar juxtaposition are also observed in other areas of the neuron and are believed to regulate extracellular Ca<sup>2+</sup> entry through store operated channels or membrane excitability via activation of K<sup>+</sup> channels (Benedeczky et al., 1994; Berridge, 2002). ER Ca<sup>2+</sup> homeostasis relies upon Sarco/endoplasmic-reticulum Ca<sup>2+</sup> ATPase (SERCA) pumps and binding proteins regulating respectively Ca<sup>2+</sup> uptake from the cytosol and Ca<sup>2+</sup> sequestration (Prins

and Michalak, 2011; Vandecaetsbeek et al., 2011). Conversely,  $\text{Ca}^{2+}$  efflux from the ER is achieved through input activated  $\text{IP}_3\text{Rs}$  and  $\text{RyRs}$  release or  $\text{Ca}^{2+}$  leak. The importance of the ER  $\text{Ca}^{2+}$  homeostasis in brain physiology can be easily appreciated considering the number of neurodegenerative disorders have been linked to alterations with its various components (Mattson, 2007).

### Ryanodine receptors

To date, three mammalian isoforms of  $\text{RyRs}$  have been isolated displaying unique differential expression in the CNS.  $\text{RyR1}$  is found exclusively in Purkinje cells in the cerebellum (Furuichi et al., 1994),  $\text{RyR2}$  is highly expressed in Purkinje cells and the cerebral cortex (Sharp et al., 1993; Furuichi et al., 1994), while  $\text{RyR3}$  has a wider distribution and is also present in hippocampus, thalamus, and striatum (Hakamata et al., 1992).  $\text{RyRs}$  are homotetramers and the largest known ion channels with a mass greater than 2 MDa, a fact that has challenged the analysis and molecular understanding of their function. Nevertheless, in recent years it has been shown that due to their close physical interaction with  $\text{Ca}_v1.1$ – $1.2$  L-type  $\text{Ca}^{2+}$  channels,  $\text{RyRs}$  directly support  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release (CIRC) as consequence of  $\text{Ca}^{2+}$  influx through VDCCs or ROCs (Chavis et al., 1996). Cytosolic and luminal  $\text{Ca}^{2+}$  levels are the principal direct and indirect regulators of  $\text{RyRs}$  functions (Meissner, 2002).  $\text{RyRs}$  have multiple cytosolic allosteric  $\text{Ca}^{2+}$  binding sites, and in absence of other effectors are maximally activated at cytosolic  $\text{Ca}^{2+}$  concentrations of 1–10  $\mu\text{M}$ , while they are inhibited in the low millimolar range (Bezprozvanny et al., 1991). Luminal  $\text{Ca}^{2+}$  content has also been shown to modify the availability and open probability of  $\text{RyRs}$  (Shmigol et al., 1996), possibly by both direct interaction with luminal  $\text{Ca}^{2+}$  regulatory sites (Sitsapesan and Williams, 1995), and by binding to the cytoplasmic sites after permeating through the pore (Tripathy and Meissner, 1996; Laver, 2007).  $\text{RyRs}$ -dependent  $\text{Ca}^{2+}$  release is also potentiated by ATP and other adenine nucleotides (Meissner, 1984). Furthermore, as components of a regulatory macromolecular complex with PKA, FKBP12, FKBP12.6, calsequestrin, triadin, and junction, calmodulin and CaMKII are responsible for most of the indirect effects of  $\text{Ca}^{2+}$  on  $\text{RyRs}$ . Calmodulin binds all three forms of  $\text{RyRs}$ , both in its  $\text{Ca}^{2+}$ -free (ApoCaM) and  $\text{Ca}^{2+}$ -bound forms (CaCaM; Tripathy et al., 1995; Yamaguchi et al., 2005). ApoCaM is a partial agonist whereas CaCaM is an inhibitor (Rodney et al., 2000). In *Drosophila melanogaster*, CaMKII activation and  $\text{RyRs}$ -dependent  $\text{Ca}^{2+}$  release are fundamental for post-tetanic potentiation of neurotransmitter secretion (Shakiryanova et al., 2007). In addition to neurotransmitter release (Mothet et al., 1998),  $\text{RyRs}$  also regulate action potential hyperpolarization (Kawai and Watanabe, 1989) and axonal retrograde transport (Breuer et al., 1992). In hippocampus (Reyes and Stanton, 1996) and in Purkinje cells (Kohda et al., 1995), LTD has been shown to be  $\text{RyRs}$ -sensitive  $\text{Ca}^{2+}$  stores dependent. Despite the evidence suggesting a potential role in synaptic plasticity behavioral testing in  $\text{RyR}$  knock out mice have given discrepant results. Balschun et al. (1999) observed equivalent learning ability in  $\text{RyRs}$  knock out and wild-type animals. However, in the same knock out model others have reported facilitated CA1 LTP induction after short tetanic stimulation, absence of LTD and improved spatial ability (Futatsugi et al., 1999), as well as impairments of performance in

the contextual fear conditioning test, passive avoidance test, and Y-maze (Kouzu et al., 2000).

### Inositol-1,4,5-triphosphate receptors

Following activation of  $G_q$ -coupled or tyrosine kinase receptors by their ligands (i.e., hormones, growth factors, neurotransmitters) the activation of phospholipases leads to the cleavage of phosphatidylinositol 4,5-bisphosphate and generation of second messengers diacylglycerol and inositol-1,4,5-triphosphate ( $\text{IP}_3$ ) that can easily diffuse from the plasma membrane through the cell. Unique amongst the various cellular second messengers  $\text{IP}_3$  binds and activates an intracellular ligand-gated  $\text{Ca}^{2+}$  channel,  $\text{IP}_3\text{R}$ . In mammals the receptor is a homo- or hetero-tetramer formed by the product of three  $\text{IP}_3\text{R}$  genes ( $\text{IP}_3\text{R1}$ – $3$ ). Each gene is translated as several splicing variants, and its expression can be modulated by various stimuli providing an impressive level of channel diversity (Foskett et al., 2007). Like  $\text{RyRs}$  the cytosolic portion of the  $\text{IP}_3\text{Rs}$  provides scaffold to a host of regulatory proteins creating macromolecular complexes able to receive inputs from the majority of the signaling pathways, as well as to sense metabolic changes within the cell. The various receptor subtypes display different binding affinities for  $\text{IP}_3$  with  $\text{IP}_3\text{R2}$  being more sensitive than  $\text{IP}_3\text{R1}$ , and both considerably more sensitive than  $\text{IP}_3\text{R3}$  (Iwai et al., 2005). The binding of  $\text{IP}_3$  not only controls channel opening, but it is also necessary for its time dependent inactivation (Mikoshihba, 2007), and clustering of the receptors (Taylor et al., 2009).  $\text{IP}_3\text{R}$ -evoked  $\text{Ca}^{2+}$  signals can operate locally or globally thanks to the hierarchical recruitment of elementary  $\text{Ca}^{2+}$  release events, and ability to form clusters. The smallest event known as “ $\text{Ca}^{2+}$  blip” is likely the result of the random opening of single  $\text{IP}_3\text{R}$ , last about 130 ms and causes very small increases of cytosolic  $\text{Ca}^{2+}$  (<50 nM).  $\text{Ca}^{2+}$  puffs are larger (50–600 nM) and longer lasting events spreading few micrometers, and are caused by the near-simultaneous opening of several clustered  $\text{IP}_3\text{Rs}$  (Bootman and Berridge, 1996). If the inducing stimulus persists the frequency of  $\text{Ca}^{2+}$  puffs increases, and can originate regenerative  $\text{Ca}^{2+}$  waves as the  $\text{Ca}^{2+}$  diffusing from one site ignites the activity of another receptor (Berridge, 1997). In addition to  $\text{IP}_3$  the activation of the receptor requires  $\text{Ca}^{2+}$  as co-agonist (Finch et al., 1991). It is well established that cytosolic  $\text{Ca}^{2+}$  regulates  $\text{IP}_3\text{Rs}$  activity in a biphasic fashion, with isotype differences in the stimulatory and inhibitory ranges (Foskett et al., 2007; Mikoshihba, 2007). While it is overall agreed that modest increases in cytosolic  $\text{Ca}^{2+}$  enhance responses to  $\text{IP}_3$  and higher concentrations inhibit it, the modalities of  $\text{Ca}^{2+}$  regulation are still unclear. Both direct regulation via binding to stimulatory or inhibitory sites on the channel structure, and indirect regulation through one of the accessory regulatory proteins have been proposed (Taylor et al., 2004). Luminal levels of  $\text{Ca}^{2+}$  are also known to impact gating of  $\text{IP}_3\text{Rs}$  via mechanisms involving  $\text{Ca}^{2+}$  binding and interaction with chaperones such as calnexin and HRP44 (Higo et al., 2005). As seen with other  $\text{Ca}^{2+}$  channels,  $\text{IP}_3\text{R}$  activity is as well modified by phosphorylation (Foskett et al., 2007), ATP levels (Mak et al., 1999, 2001), redox status (Higo et al., 2005), and interaction with other proteins (Patterson et al., 2004; Foskett et al., 2007). One significant example is the interaction between  $\text{IP}_3\text{R1}$  and the voltage-dependent anion channels (VDACs) located in the mitochondria outer membrane (Szabadkai et al., 2006),

which facilitates mitochondrial  $\text{Ca}^{2+}$  uptake. Over the past decade, thanks to the generation of  $\text{IP}_3\text{R}$  knock out mice models it has been established that  $\text{IP}_3\text{Rs}$  play a crucial role in brain functions, enhancing neurotransmitter release following repetitive stimulation (Emptage et al., 2001), neurite formation and extension during development (Takei et al., 1998), hippocampal LTP (Fujii et al., 2000), cerebellar LTD (Inoue et al., 1998), learning, memory, and behavior (Matsumoto et al., 1996; Fujii et al., 2000; Nishiyama et al., 2000).

### **Presenilins as endoplasmic reticulum $\text{Ca}^{2+}$ leak channels**

The steady state  $\text{Ca}^{2+}$  within the lumen of the ER is maintained by balancing the influx created by SERCA pumps with “leak” mechanisms. In neurons, the addition of SERCA pumps inhibitors results in an immediate drop of the luminal  $\text{Ca}^{2+}$ , implying the existence of leak channels (Solovyova et al., 2002; Verkhratsky, 2005). In muscle cells it has been shown that RyRs under conditions causing their uncoupling from the luminal  $\text{Ca}^{2+}$  binding proteins can function as leak channels (Mark et al., 1998, 2000). The molecular identity of the ER leak channels under physiological conditions is still unresolved. However, recent evidence points to presenilins (PSs) as potential physiological ER  $\text{Ca}^{2+}$  leak channels (Tu et al., 2006; Nelson et al., 2007). Presenilin 1 and 2 are integral ER transmembrane proteins (Annaert et al., 1999) undergoing endoproteolytic cleavage that generates N-terminal and C-terminal fragments. The cleaved PSs fragments assemble in a complex with nicastrin, anterior pharynx defective 1, and presenilin enhancer 2, translocate to the plasma membrane where they function as the  $\gamma$ -secretase enzyme responsible of the amyloid precursor protein (APP) cleavage generating amyloid  $\beta$ , the primary component of amyloid plaques in AD (De Strooper et al., 1998; De Strooper and Annaert, 2010). Since the discovery that PSs mutations account for the majority of familiar forms of AD, PSs have been intensively studied (Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995). Together with the understanding of their role in the APP processing come the evidence that they participate to ER  $\text{Ca}^{2+}$  homeostasis. Evidence of deregulated ER  $\text{Ca}^{2+}$  signaling has been gathered from various experimental systems including human fibroblasts from AD patients and transgenic mouse models carrying PSs mutations (Ito et al., 1994; Guo et al., 1996, 1999; Leissring et al., 1999a,b; Stutzmann et al., 2004, 2006). The mechanisms proposed to explain PSs functions in  $\text{Ca}^{2+}$  homeostasis are based on physical interactions and indirect influence on others ER  $\text{Ca}^{2+}$  players, such as RyRs (Chan et al., 2000; Stutzmann et al., 2006),  $\text{IP}_3\text{Rs}$  (Cai et al., 2006; Cheung et al., 2008), SERCA pumps (Green et al., 2008), as well as on the influence on store operated  $\text{Ca}^{2+}$  influx (Leissring et al., 2000). However, recent experiments using planar lipid bilayers and neurons from double knock out PS1/PS2 and triple transgenic AD mice, showed that PSs themselves form low conductance  $\text{Ca}^{2+}$  channels responsible for about 80% of the passive  $\text{Ca}^{2+}$  leak from the ER (Tu et al., 2006; Nelson et al., 2007). This ER  $\text{Ca}^{2+}$  leak function appears to be independent from the  $\gamma$ -secretase activity, and is lost in most of the familiar AD PSs mutants studied to date resulting in ER  $\text{Ca}^{2+}$  overload (Tu et al., 2006; Nelson et al., 2007; Bezprozvanny and Mattson, 2008). Regardless of the type of mechanisms, a role for PSs in synaptic plasticity, learning, and memory via regulation of  $\text{Ca}^{2+}$  signaling has been well established.

PSs regulates homeostatic synaptic scaling (Pratt et al., 2011), neurotransmitter release from the presynaptic terminal (Zhang et al., 2009), LTP (Zhang et al., 2010), and the establishment of hippocampal memory (Saura et al., 2004).

### **MITOCHONDRIA AND CALCIUM**

Thanks to their ability to rapidly uptake large quantities of  $\text{Ca}^{2+}$ , mitochondria contribute to shaping the amplitude and duration of cytosolic  $\text{Ca}^{2+}$  signaling (Deluca and Engstrom, 1961; Vasington and Murphy, 1962). Structural dynamic junctions link the mitochondria to the ER, facilitating the signal transduction, and biosynthetic interplay existing between the two organelles (Csordás et al., 2006; Hayashi et al., 2009; Rizzuto et al., 2009; de Brito and Scorrano, 2010). Amongst the proteins identified as possible components of the ER-mitochondria coupling complexes are glucose-related protein 75 (Szabadkai et al., 2006), sigma-1 receptor (Hayashi and Su, 2007), mitofusin-2 (de Brito and Scorrano, 2009), phosphofurin acidic cluster sorting protein 2 (Simmen et al., 2005), BAP-31 (Wang et al., 2000), and dynamin like protein 1 (Pitts et al., 1999). These interactions regulate the trafficking of phospholipids, as well as the  $\text{Ca}^{2+}$  interchanges between the ER and the mitochondria.  $\text{Ca}^{2+}$  can cross both the outer and inner mitochondrial membranes to enter the matrix, using different pathways. The mitochondrial  $\text{Ca}^{2+}$  influx is a tightly controlled process, because under physiological concentrations  $\text{Ca}^{2+}$  modulates pyruvate, isocitrate, and  $\alpha$ -ketoglutarate dehydrogenases, thus the Krebs cycle (Denton et al., 1980; Hansford, 1980) and the production of ATP (Jouaville et al., 1999). The predominant mechanism of intake through the outer membrane is represented by high conductance and high-density VDACs channels (McEnery et al., 1993; Lee et al., 1998). The inner membrane  $\text{Ca}^{2+}$  import is primarily regulated through the mitochondrial  $\text{Ca}^{2+}$  uniporter (MCU) composed by a protein forming the channel itself (Baughman et al., 2011; De Stefani et al., 2011), and the accessory protein MICU1 regulating its function (Perocchi et al., 2010). The MCU allows the ion transport down its electrochemical gradient and it is functional only at high extra mitochondrial  $\text{Ca}^{2+}$  concentrations. Rapid  $\text{Ca}^{2+}$  intake independent from the electrochemical gradient is achieved through mitochondrial RyR (Beutner et al., 2001), and the rapid mode mitochondrial  $\text{Ca}^{2+}$  transport (Sparagna et al., 1995). Both systems operate at low physiological  $\text{Ca}^{2+}$  levels while they are inactivated at concentrations causing the activation of MCU.  $\text{Ca}^{2+}$  efflux is mostly dependent on the mitochondrial  $\text{Na}^+/\text{Ca}^{2+}$  exchanger that couples  $\text{Ca}^{2+}$  extrusion with the inward directed  $\text{Na}^+$  electrochemical gradient (Carafoli et al., 1974; Palty et al., 2010), and possibly by the transient openings of the permeability transition pore (PTP). The high conductance channel is a complex of yet non-identified molecular components, that once opened allows indiscriminate exchange of ions and solutes between the cytosol and the mitochondrial matrix. VDACs on the outer membrane, adenine nucleotide transferase on the inner one, and cyclophilin D in the matrix, have been proposed as possible channel components, but studies from knock out mice have raised doubts on their role as obligatory constituents of the PTP (Rizzuto et al., 2009). The opening of the PTP channel is induced by high matrix  $\text{Ca}^{2+}$ , free radicals, adenine nucleotide depletion, pH, and decreased mitochondrial membrane potential (Halestrap, 2009). The process is reversible, yet under non-physiological conditions

the PTP can become fixed in the open conformation leading to apoptotic cell death via release of apoptotic factors such as cytochrome *c*, apoptosis-inducing factor and Smac/Diablo, or necrotic cell death via massive ATP depletion (Abou-Sleiman et al., 2006; Leung and Halestrap, 2008). Finally the  $\text{Ca}^{2+}/\text{H}^{+}$  uniporter Letm1 can move  $\text{Ca}^{2+}$  in or out of the mitochondria in a  $\text{Ca}^{2+}$  and pH-gradient dependent manner (Jiang et al., 2009).

Neuronal synapse are highly enriched with mitochondria in order to fulfill the high energy requirements needed to fuel the active processes required for synaptic transmission, and to serve as  $\text{Ca}^{2+}$  sinks and modulators following  $\text{Ca}^{2+}$  entry (David and Barrett, 2000; Tsang et al., 2000). The local ATP production by mitochondria alone is important to maintain synaptic transmission. Impairment of mitochondria transport into the presynaptic terminal have been shown to cause abnormal neurotransmission during intense stimulation (Verstreken et al., 2005), impaired presynaptic short-term plasticity, and accelerated synaptic depression under high-frequency firing (Ma et al., 2009). Furthermore, genetically engineered mice with decrease mitochondrial respiratory function displayed altered retention and consolidation of spatial memory (Tanaka et al., 2008). As per the  $\text{Ca}^{2+}$  regulatory function, mice lacking mitochondrial VDACs show impaired fear conditioning and spatial learning, and deficits in long and short-term hippocampal synaptic plasticity (Weeber et al., 2002). Tetanus-induced synaptic potentiation, contrary to other forms of synaptic plasticity, does not require  $\text{Ca}^{2+}$  influx into the cell, but rather depend on  $\text{Na}^{+}$  influx into the nerve terminals to promote  $\text{Ca}^{2+}$  efflux from mitochondria through the  $\text{Na}^{+}/\text{Ca}^{2+}$  exchanger (Tang and Zucker, 1997; Yang et al., 2003). Additionally, while the majority of synapses requires the cooperation between ER and mitochondria to regulate  $\text{Ca}^{2+}$  signaling (Rizzuto et al., 2004), mitochondria appear to be the main  $\text{Ca}^{2+}$  regulating system, with minimal uptake into the ER during sustained prolonged stimulation in specialized structures, like the neuromuscular junction (David and Barrett, 2003) and the calyx of Held (Billups and Forsythe, 2002).

## CALCIUM AGING AND NEURODEGENERATION

The plasticity of the nervous system depends at any time point on the balance between degenerative and regenerative processes. Because  $\text{Ca}^{2+}$  is a fundamental signaling mechanism involved in almost all cellular physiological functions, subtle alterations of its homeostasis lead to profound functional changes. Several lines of evidence support the notion that  $\text{Ca}^{2+}$  dyshomeostasis is implicated in normal brain aging (Gibson and Peterson, 1987; Disterhoft et al., 1994; Khachaturian, 1994). The cognitive decline occurring with normal aging is not associated with significant neuronal loss (Gallagher et al., 1996), but is rather the result of changes in synaptic connectivity. Age-dependent alterations have been observed for multiple components the  $\text{Ca}^{2+}$  cellular machinery, and appear to strongly correlate with cognitive deficits (Power et al., 2002; Rosenzweig and Barnes, 2003). Aged hippocampal neurons display decreased synaptic plasticity with increased  $\text{Ca}^{2+}$  influx and density of L-type VDCCs (Campbell et al., 1996; Thibault and Landfield, 1996; Thibault et al., 2001). The increase could arise from altered gene or protein expression

(Herman et al., 1998), or phosphorylation changes of the L-type  $\text{Ca}^{2+}$  channels (Norris et al., 2002; Davare and Hell, 2003). GluR2 and NR1 protein expression is reduced in hippocampus (Liu et al., 2008; Yu et al., 2011) and postrhinal and entorhinal cortex of aged rats (Liu et al., 2008). Additionally, aged neurons show enhanced CIRC due to the increased ER  $\text{Ca}^{2+}$  release (Kumar and Foster, 2004; Gant et al., 2006), diminished  $\text{Ca}^{2+}$  extrusion through the plasma membrane ATPase (Michaelis et al., 1996; Gao et al., 1998), reduced cellular  $\text{Ca}^{2+}$  buffering capacity due to impairment of the SERCA pumps (Murchison and Griffith, 1999), and diminished mitochondrial  $\text{Ca}^{2+}$  sink capability (Xiong et al., 2002; Murchison et al., 2004), activation of calcineurin (Foster et al., 2001), and calpains (Nixon et al., 1994). The overall result is an increase of  $\text{Ca}^{2+}$  loads which negatively impact neuronal  $\text{Ca}^{2+}$ -dependent  $\text{K}^{+}$  channel slow after-hyperpolarization and excitability (Landfield and Pitler, 1984; Khachaturian, 1989; Matthews et al., 2009), increases the threshold frequency for induction of LTP (Shankar et al., 1998; Ris and Godaux, 2007), enhances the susceptibility to induction of LTD (Norris et al., 1996; Kumar and Foster, 2005; Lee et al., 2005), and ultimately learning and memory. The idea that  $\text{Ca}^{2+}$  dyshomeostasis is a key factor in determining brain aging is substantiated by various studies using pharmacological interventions aimed at counteracting the age-related  $\text{Ca}^{2+}$  signaling increase (Foster, 2006). Administration of BAPTA-AM, a membrane-permeant  $\text{Ca}^{2+}$  chelator, ameliorates impaired presynaptic cytosolic, and mitochondrial  $\text{Ca}^{2+}$  dynamics in hippocampal CA1 synapses of old rats (Tonkikh and Carlen, 2009), and enhances spatial learning (Tonkikh et al., 2006). Similarly, the L-type  $\text{Ca}^{2+}$  channel blocker nimodipine counteracts age-related learning impairments in rabbits (Deyo et al., 1989; Kowalska and Disterhoft, 1994), rodents (Leverre and Walker, 1992; Ingram et al., 1994), non-human primates (Sandin et al., 1990), and elderly patients with dementia (Ban et al., 1990; Tollefson, 1990). Aging is the greatest risk factor for neurodegenerative disorders, a heterogenous group of pathologies characterized by the gradual neuronal loss in motor, sensory, or cognitive systems. While *per se* not cause of neuronal loss, the age-dependent alterations of  $\text{Ca}^{2+}$  signaling can possibly enhance neuronal vulnerability to metabolic and functional stressors thus contribute to the initiation or progression of the neurodegenerative process (Toescu et al., 2004; Toescu and Vreugdenhil, 2010). Despite intrinsic different etiologies, dysregulated  $\text{Ca}^{2+}$ , and mitochondrial homeostasis have emerged as common underlying molecular mechanisms of neuronal loss in Alzheimer's, Parkinson's, Huntington's diseases, amyotrophic lateral sclerosis and other neurodegenerative disorders (Mattson, 2004, 2007; Bezprozvanny, 2009). The specificity of  $\text{Ca}^{2+}$  homeostatic and signaling machineries requirements that underlie the unique responses to the same stimuli of different neurons, accounts, at least partially, for the selective impairment of neuronal subtypes and brain areas observed during aging and neurodegeneration. While the sequence of pathological events and the kinetics of degeneration are still not completely understood, and likely differ amongst the various disorders, decreased mitochondrial functional capacity with diminished ATP production (Navarro, 2004) and increased reactive oxygen species generation (Floyd and Hensley, 2002), together with mitochondrial reduced  $\text{Ca}^{2+}$  buffering ability (Xiong et al., 2002), and enhanced  $\text{Ca}^{2+}$



responses are common key elements to ignite the necrotic or apoptotic cell death distinctive of most neurodegenerative disorders (Green and Kroemer, 2004; Lin and Beal, 2006).

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- Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Received: 17 January 2012; paper pending published: 12 February 2012; accepted: 26 March 2012; published online: 13 April 2012.
- Citation: Kawamoto EM, Vivar C and Camandola S (2012) Physiology and pathology of calcium signaling in the brain. *Front. Pharmacol.* 3:61. doi: 10.3389/fphar.2012.00061
- This article was submitted to *Frontiers in Neuropharmacology*, a specialty of *Frontiers in Pharmacology*.
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