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Calcium Dysregulation and Homeostasis of Neural Calcium in the Molecular Mechanisms of Neurodegenerative Diseases Provide Multiple Targets for Neuroprotection

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Abstract

The intracellular free calcium concentration subserves complex signaling roles in brain. Calcium cations (Ca^{2+}) regulate neuronal plasticity underlying learning and memory and neuronal survival. Homo- and heterocellular control of Ca^{2+} homeostasis supports brain physiology maintaining neural integrity. Ca^{2+} fluxes across the plasma membrane and between intracellular organelles and compartments integrate diverse cellular functions. A vast array of checkpoints controls Ca^{2+}, like G protein-coupled receptors, ion channels, Ca^{2+} binding proteins, transcriptional networks, and ion exchangers, in both the plasma membrane and the membranes of mitochondria and endoplasmic reticulum. Interactions between Ca^{2+} and reactive oxygen species signaling coordinate signaling, which can be either beneficial or detrimental. In neurodegenerative disorders, cellular Ca^{2+}-regulating systems are compromised. Oxidative stress, perturbed energy metabolism, and alterations of disease-related proteins result in Ca^{2+}-dependent synaptic dysfunction, impaired plasticity, and neuronal demise. We review Ca^{2+} control processes relevant for physiological and pathophysiological conditions in brain tissue. Dysregulation of Ca^{2+} is decisive for brain cell death and degeneration after ischemic stroke, long-term neurodegeneration in Alzheimer's disease, Parkinson's disease, Huntington's disease, inflammatory processes, such as in multiple sclerosis, epileptic sclerosis, and leucodystrophies. Understanding the underlying molecular processes is of critical importance for the development of novel therapeutic strategies to prevent neurodegeneration and confer neuroprotection. *Antioxid. Redox Signal.* 14, 1275–1288.

Introduction: General Principles of Calcium Cations Signaling

CELLULAR SIGNALING requires harnessing protein functions by charge distribution in response to the changing environment (17). Besides phosphate anions, calcium cations (Ca^{2+}) are predestined to alter protein conformation, since Ca^{2+} can accommodate 4–12 oxygen atoms in its primary coordination sphere. Under physiological conditions, electrical pulses or receptor-mediated stimuli in the neuron generate different Ca^{2+} signals with distinct spatial dimensions, temporal extension, amplitude, subcellular localization, and, in some cases, oscillations. Spatial variability ranges from nanodomains in cellular organelles up to gradients covering the whole cell body.

The versatility of Ca^{2+} as an intracellular messenger is derived from varying cytosolic Ca^{2+} concentrations, most of which are generated by regulated openings of Ca^{2+}-permeable channels expressed in the plasma membrane and in different organelles.

High signal speed and effectiveness is achieved by a 20,000-fold gradient between the low intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) and high extracellular Ca^{2+} concentration during the resting state (100 nM *vs.* mM). This gradient is maintained by Ca^{2+}-buffering proteins as well as by membrane-intrinsic Ca^{2+} transport systems capable of removing Ca^{2+} from the cytosol into the extracellular milieu. The Ca^{2+} extrusion is possible even uphill this very large concentration gradient.

To trigger cellular processes, myriads of cellular proteins, acting both locally and globally, have been adapted to bind Ca^{2+}. Their affinities range from nanomolar to millimolar. In Ca^{2+} binding proteins, six to seven carboxyl and carbonyl groups are coordinated to surround Ca^{2+} in a pentagonal bipyramid (37). The helix-turn-helix motifs of the archetypical EF hand domain, the professional protein chelator of Ca^{2+}, have negatively charged oxygen atoms to encompass Ca^{2+} within a 12 amino acid loop between two orthogonal α-helices. The affinities of EF hand domains for Ca^{2+} vary, depending on a variety of factors, ranging from critical amino acids in the

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Ca^{2+} binding loop to side chain packing in the protein core. The subsequent readout of Ca^{2+} signals employs downstream signaling proteins, which transmit the Ca^{2+} message to cellular effectors.

Cellular Factors That Determine Ca^{2+} Signaling in the Brain

Role of mitochondria and endoplasmic reticulum

In intracellular Ca^{2+} signaling, mitochondria accumulate Ca^{2+} from the cytosol. Mitochondrial Ca^{2+} accumulation is a tightly controlled process. It regulates three Ca^{2+}-sensitive dehydrogenases of the citric acid cycle and thus controls the synthesis of ATP. Specifically, pyruvate dehydrogenase, isocitrate dehydrogenase, oxoglutarate dehydrogenase, the ATP synthase (complex V), and the adenine nucleotide translocase are activated by Ca^{2+}. Further, Ca^{2+} from mitochondria shapes the amplitude and spatio-temporal patterns of $[Ca^{2+}]_i$ signals, and is instrumental to determining cell death or survival. Mitochondria can store large amounts of Ca^{2+} in the matrix without dangerously increasing its osmotic concentration, since they accumulate inorganic phosphate alongside with Ca^{2+}, and thus precipitate in the matrix deposits of amorphous hydroxyapatite. When mitochondria accumulate excessive Ca^{2+}, however, they trigger a vicious cycle that will exacerbate the cellular Ca^{2+} overload. Further, mitochondria produce nitric oxide (NO), and in stress situations, mitochondria release apoptogenic factors into the cytosol. Moreover, mitochondrial dynamics (fission, fusion, and migration) is important for neurotransmission, synaptic maintenance, and neuronal survival.

Regulated Ca^{2+} release from the endoplasmic reticulum (ER) controls many neuronal functions, from plasmalemmal excitability to synaptic plasticity. Enzymatic cascades that are localized in the ER, dependent on the Ca^{2+} concentration in the ER lumen, integrate rapid Ca^{2+} signaling with long-lasting adaptive responses through modifications in protein synthesis and processing (14). Mitochondria form junctions with the ER that support signal transduction and biosynthetic pathways and affect distribution of the organelles. These junctions have a pivotal role in mediating Ca^{2+} signal propagation to the mitochondria. In the ER membrane, Ca^{2+} release channels and Ca^{2+} pumps provide for excitability (38).

In neurodegenerative diseases and aging, mitochondrial dysfunction is associated with compromised cellular energy production, the induction of apoptosis, and the generation of oxidative stress (33, 76).

Cross-talk between calcium and reactive oxygen species signaling

It is now well established that cross-talk between Ca^{2+} and redox signals plays a key role in physiological functions in the brain. However, conditions that promote oxidative/nitrosative stress result in excessive Ca^{2+} release that can provoke pathological responses and neuronal death (55, 101).

Reactive oxygen species (ROS) are generated by tightly regulated NADPH oxidases, which were found recently even in neurons (82, 93). Further, main sources of ROS are mitochondria, where free oxygen radicals are generated as by-products from the electron transport chain and from enzymes of the tricarbonic acid cycle (4, 25). Excessive stimulation of NADPH oxidases, disturbed electron transport chain, or tricarbonic acid cycle results in oxidative stress, a process that damages cell structures (5). This is particularly important in the nervous system, since this relatively small tissue accounts for over 20% of the oxygen consumption of the body and, as a result, produces large quantities of ROS. Additionally, the nervous system is particularly sensitive to oxidative stress because of enrichment of polyunsaturated fatty acids in many of the nerve cell membranes. Finally, oxygen radicals generated by xanthine oxidase are shown to play a significant role in neuronal cell death after ischemia (3).

Components of ROS homeostasis are regulated by Ca^{2+}-dependent pathways. Thus, a positive correlation between the Ca^{2+}-dependent mitochondrial metabolic rate and ROS generation was shown (107). Further, Ca^{2+} stimulates NO synthase, which has been shown to inhibit complex IV and in turn leads to ROS production at the complex III (41). Similarly, increased $[Ca^{2+}]_i$ during reoxygenation after anoxia correlates with ROS generation from NADPH oxidase in neurons (3). Free radical generation in response to β-amyloid (Aβ) was shown to be dependent on extracellular Ca^{2+} and to be prevented by inhibition of NADPH oxidase (2).

Conversely, ROS modify Ca^{2+} signaling proteins and reshape local and global Ca^{2+} amplitudes and kinetics. Many of the Ca^{2+} transporters and signaling proteins in the ER-mitochondrial web are sensitive to redox regulation and are directly exposed to the ROS produced in the mitochondria and ER (38). ROS have been shown to modulate directly ryanodine receptors (RyR). Moreover, ROS induce oxidation of NO to nitrosium ions (NO^+) and the subsequent reaction with free thiols in RyR to form S-nitrosothiol, which stimulates RyR-mediated Ca^{2+} release from the ER (48). Similarly, ROS has been shown to stimulate inositol(1,4,5)trisphosphate receptors ($InsP_3R$). Further, sarco(endo)plasmic reticulum Ca^{2+}-ATPases (SERCA) and plasma membrane Ca^{2+} ATPases (PMCAs) were shown to be inhibited by ROS in the heart, pancreas, and brain, and Na^+/Ca^{2+} exchangers (NCX) were shown to be stimulated or inhibited during oxidative stress (41).

Homo- and hetereocellular interactions in Ca^{2+} regulation of neural cells

The major cellular constituents of the central nervous system (CNS) are three cell types of neural descent, neurons, astrocytes, and oligodendrocytes, as well as one cell type of myeloid descent, namely, microglia. Whereas neurons comprise not more than 10% of the cells in the brain, astrocytes comprise approximately half of the volume of the adult mammalian brain. They represent the primary neuronal trophic element since they were shown to supplement neurons with nutrients, to modulate the extracellular milieu mainly by buffering the glutamate level and by eliminating ROS (52). Astrocytes, which are organized into distinct nonoverlapping domains, interact intimately with synapses and the cerebrovasculature (7). Astrocytes express a large variety of G protein-coupled receptors (GPCR) that affect a diverse set of signaling cascades, including many different GPCR coupled to G_q, which are activated by neurotransmitters released from presynaptic terminals to produce astrocytic increase of Ca^{2+} level. Prevailing evidence indicates that spontaneous astrocytic Ca^{2+} rise generally remains

localized and is unlikely to activate distant astrocytes *via* intercellular Ca^{2+} waves (15).

Neuroactive substances, primarily glutamate and ATP, are secreted from astrocytes. They act back onto synapses in a process known as gliotransmission (7). Very recently, it has been reported that neither increasing nor obliterating astrocytic Ca^{2+} fluxes affects spontaneous and evoked excitatory synaptic transmission or synaptic plasticity (6). These findings suggest that the mechanism of gliotransmission in the tripartite synapse might be Ca^{2+} independent and thus needs to be reconsidered.

Ca^{2+} Toolkit in Neural Signaling and in Control of Neurodegenerative Processes

Ca^{2+} fluxes across the plasma membrane and between intracellular compartments play critical roles in fundamental functions of neurons. Ca^{2+} signals are produced in response to stimuli, like membrane depolarization, mechanical stretch, noxious insults, extracellular agonists, intracellular messengers, and the depletion of intracellular Ca^{2+} stores. Neurite outgrowth, synaptogenesis, synaptic transmission, plasticity, and cell survival in degeneration processes are regulated by Ca^{2+} signals.

The diversity of events controlled by Ca^{2+} is a consequence of distinct types of signals that differ spatially, temporally, and in magnitude. A given change of the Ca^{2+} concentration modifies functions in the same type of neurons in a multitude of ways and, thus, produces distinct outcomes over short, medium, or long distances and times.

The following sections summarize important components of the Ca^{2+} signaling system in neural cells that are able to create a diverse array of signaling units that can deliver Ca^{2+} signals with very different spatial and temporal properties (17). Figure 1 schematically depicts the Ca^{2+} regulating proteins, which are involved in normal neurophysiological processes, firstly, in the plasma membrane and, secondly, in intracellular organelles, ER, mitochondria, and the nucleus. These proteins, in a coordinate manner, induce $[Ca^{2+}]_i$ changes, from where all Ca^{2+} signals emanate.

G protein-coupled receptors

Over 90% of nonsensory GPCR are expressed in the brain. In the CNS, GPCR function primarily, but not exclusively, as mediators of slow neuromodulators rather than of fast neurotransmitters, and their role is critical for normal brain function. After activation, GPCR can be desensitized by being phosphorylated by members of the family of GPCR kinases (44). Phosphorylated receptors are then bound by arrestins, which prevent further stimulation of G proteins and downstream signaling pathways. Under- or overactivity of many individual GPCR systems in the brain may contribute to pathological conditions, ranging from hypo-dopaminergic movement

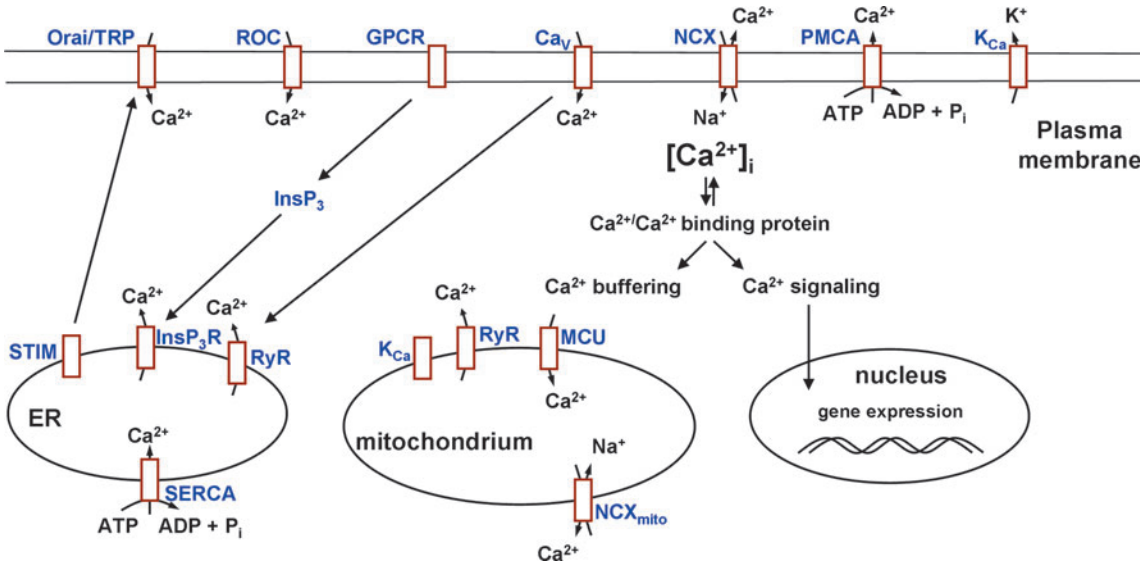

FIG. 1. Ca^{2+} homeostasis in brain under normal physiological conditions. Stimuli induce the entry of external Ca^{2+} *via* Ca_V, TRP channels, and ROC. Activation of GPCR and other signals enable release of internal Ca^{2+} from the ER by formation of second messengers that open channels of receptors for $InsP_3R$ and RyR. The latter pathway is also activated by Ca^{2+} through calcium influx. Ca^{2+} depletion of intracellular ER Ca^{2+} stores further signals to the activation of capacitative Ca^{2+} entry from the Ca^{2+} sensor STIM to Orai/TRP channels. Mitochondria sequester Ca^{2+} through the uniporter MCU, and Ca^{2+} is released back into the cytosol by the NCX_{mito}. In conditions of acute or lasting damage, Ca^{2+} is spilled out by the mPTP, which is shown in Figures 2 and 3; this pore might also have some physiological function, replenishing $[Ca^{2+}]_i$. K_{Ca} contribute to reducing overexcitation by hyperpolarizing the plasma membrane. Ca^{2+} is removed from the cell by extrusion of Ca^{2+} to the outside, mediated by the NCX and the PMCA. The SERCA pumps Ca^{2+} back into the ER. Intracellular Ca^{2+} spatiotemporally binds to buffers and effectors and, thus, activates a plethora of cellular processes. Ca^{2+}, calcium cations; $[Ca^{2+}]_i$, intracellular free Ca^{2+} concentration; Ca_V, voltage-gated Ca^{2+} channels; TRP, transient receptor potential; ROC, receptor-operated channels; GPCR, G protein-coupled receptors; ER, endoplasmic reticulum; $InsP_3R$, inositol(1,4,5)-trisphosphate receptor; RyR, ryanodine receptor; MCU, mitochondrial Ca^{2+} uniporter; NCX, Na^+/Ca^{2+} exchanger; NCX_{mito}, mitochondrial exchanger; mPTP, mitochondrial permeability transition pore; K_{Ca}, Ca^{2+}-activated K^+ channels; PMCA, plasma-membrane Ca^{2+}-ATPase; SERCA sarco(endo)plasmic reticulum Ca^{2+}-ATPase; STIM, stromal interacting molecule. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

disorders to mania and depression. Thus, these receptors are primary or downstream targets for a variety of useful therapeutic agents. Decreased levels of extracellular Ca^{2+} are sensed by G protein-coupled Ca^{2+} sensing receptors that initiate the phospholipase C pathway. Expression of these receptors in glial cells indicates potential roles in the maintenance of local ionic homeostasis (21). In gonadotropin-releasing hormone neurons the activation of these Ca^{2+} receptors promotes cell migration (35).

Ion channels

Ion channels provide for an aqueous bridge across the hydrophobic environment of the plasmalemma allowing for selective transition of ions across these membranes. The channel proteins are constantly flickering between an activated state (open), a deactivated state (closed), and an inactivated state (closed)—often in a voltage- and time dependent fashion. For any condition, there exists an equilibrium, which can be shifted by binding of particular ions or molecules.

Voltage-gated Ca^{2+} channels. The family of voltage-gated Ca^{2+} channels (Ca_V) transduces cell surface membrane potential changes into local rise of $[Ca^{2+}]_i$. These ion channels play a role in the generation and propagation of the nerve impulse and in cell homeostasis. Ca_V are formed as a complex of several subunits, such as α_1, $\alpha_2\delta$, β_{1-4}, and γ. The α_1 subunit forms the ion-conducting pore, whereas the associated subunits have several auxiliary functions, including control of channel expression and modulation of current kinetics. The voltage sensor in the pore-containing subunit comprises a series of positively charged amino acid residues, which are physically displaced by the change in the membrane electric field: the physical displacement in turn causes a conformational change in the ion channel protein, leading to channel opening.

Molecular biology studies have identified 10 different genes in mammals, each coding for a different α_1 subunit. According to sequence similarities, they are divided into three subfamilies, Ca_v1, Ca_v2, and Ca_v3. In the laboratory, it is possible to distinguish them by studying their physiological roles and/or inhibition by specific toxins. The Ca_v1 isoforms correspond to the dihydropyridine-sensitive L-type channels, which are responsible for excitation–contraction coupling of skeletal, smooth and cardiac muscle and for hormone secretion in endocrine cells. The Ca_v2 isoforms represent the neuronal currents (N-, R-, P/Q-), sensitive to spider and cone snail toxins. The N-type channel is blocked by ω-conotoxin, and the R-type channel (R stands for resistant to the other blockers and toxins) is involved in so far poorly defined processes in the brain. The closely related P/Q-type channel is blocked by ω-agatoxins. The Ca_v3 isoforms form the so-called T-type channels, which are insensitive to either the typical L-type blockers or the organic non-L-type inhibitors (32, 40). The modulation of voltage-gated ion channels by signaling pathways activated by GPCR constitutes widespread mechanisms for regulating neuronal excitability, neurotransmitter release, and neuronal plasticity.

Receptor-operated Ca^{2+} channels. Receptor-operated channels (ionotropic receptors) open in response to specific ligand molecules binding to the extracellular domain of the receptor. Ligand binding causes a conformational change in the structure of the channel protein that ultimately leads to the opening of the channel gate and subsequent ion flux across the plasma membrane. Examples of such channels include the monovalent cation-permeable nicotinic acetycholine receptor, ionotropic glutamate-gated receptors and ATP-gated P2X receptors, and the anion-permeable γ-aminobutyric acid-gated receptor.

Seven genes code for P2X receptor subunits, which are 40%–50% identical in amino acid sequence. All P2X receptors are permeable to small monovalent cations; some have significant Ca^{2+} permeability. Functional responses of P2X receptors are seen in neurons and glia cells. On sensory nerves, P2X receptors are involved in the initiation of afferent signals in several viscera (*e.g.*, bladder, intestine) and play a key role in sensing tissue damage, pain, and inflammatory stimuli. Paracrine roles for ATP signaling through P2X receptors are likely in the neurohypophysis (78).

N-methyl-D-aspartate receptors (NMDAR) are a subtype of ionotropic glutamate receptors with an important role in the physiology and pathophysiology in the mammalian CNS. Physiological levels of NMDAR activity play important roles in neurotransmission and synaptic plasticity and can promote neuronal survival and resistance to trauma.

Inappropriate levels of Ca^{2+} influx through the NMDAR, however, can contribute to neuronal loss under pathophysiological conditions. This is called excitotoxicity. Increased understanding of the molecular mechanisms underlying both the neuroprotective and neurodestructive effects of NMDAR activation will lead to the discovery of new therapeutic targets and strategies for excitotoxic disorders (47, 80).

Mitochondrial channels. An electrophoretic uniporter mediates the charge-uncompensated entry of Ca^{2+} into mitochondria in response to the high negative membrane potential generated by the asymmetric topography and operation of the respiratory chain components (54). This Ca^{2+} uptake is mediated by the mitochondrial Ca^{2+} uniporter located in the organelle's inner membrane. The uniporter passes Ca^{2+} down the electrochemical gradient maintained across this membrane without direct coupling to ATP hydrolysis or transport of other ions.

Additionally, Ca^{2+}-activated potassium channels (K_{Ca}; see the section Ca^{2+}-sensitive potassium channels) were found also in mitochondrial inner membranes. They might function to stabilize the mitochondrial membrane and thereby have a neuroprotective function (57).

Transient receptor potential ion channel. The family of transient receptor potential (TRP) channels now comprises >30 members subdivided into seven families. TRP channels are widely expressed in the CNS where they contribute to changes in $[Ca^{2+}]_i$ by providing Ca^{2+} entry pathways, by modulating the driving force for the Ca^{2+} entry, and very likely also by providing intracellular pathways for Ca^{2+} release from cellular organelles. TRP channels are activated by a wide range of stimuli, including intra- and extracellular messengers, chemical, mechanical, and osmotic stress, and some by the filling state of intracellular Ca^{2+} stores (77, 83).

Receptor-operated Ca^{2+} channels of the ER and acidic stores. RyR and $InsP_3R$ are localized in the ER and secondarily in the internal nuclear membrane (66) and predominantly operated by second messengers. Cyclic ADP ribose is

synthesized from NAD^+ by the bifunctional ectoenzymes of the CD38 family (49). $InsP_3$ originates from hydrolysis from membrane bound phosphatidylinositol (4,5)P_2, as induced by G_q-activated phospholipase Cβ (42). The depletion of Ca^{2+} from the ER is sensed by stromal interacting molecule (STIM) proteins. They oligomerize, translocate to junctions adjacent to the plasma membrane, organize Orai or TRP channel proteins into clusters, and open these channels to induce store-operated Ca^{2+} entry (27).

There are at least three different isoforms of RyR, but only RyR3 is expressed in the brain. Redox modification of RyR channels has physiological and pathological consequences for neuronal function (41, 48).

$InsP_3R$ constitute a family of three paralogs, from which $InsP_3R1$ is expressed in neurons. $InsP_3R$ mediate cell physiological processes ranging from gene transcription to forming learning traces for memory (42). Synaptic activity regulates the level of expression of $InsP_3R1$ in neurons (28). Metabotropic and ionotropic glutamate receptors collaborate to generate $InsP_3$ signals (50). Phosphorylation dynamics of $InsP_3R1$ modulate intracellular Ca^{2+} release (84). $InsP_3R$ were demonstrated to be activated furthermore by calmodulin-like neuronal Ca^{2+}-binding proteins (53).

Store-operated Ca^{2+} entry has been shown to be regulated by both Ca^{2+}-selective RyR or $InsP_3R$ and Ca^{2+}-independent phospholipase A_2 as described before (89, 91).

Ca^{2+} from intracellular acidic stores has been shown to be mobilized by nicotinic acid-adenine dinucleotide phosphate. Cellular levels change in response to a variety of agonists, confirming its role as a Ca^{2+}-mobilizing messenger also in the nervous system (18). Nicotinic acid-adenine dinucleotide phosphate interacts with $InsP_3$ and cyclic ADP-ribose in shaping cytosolic Ca^{2+} signals in the cytosol as well as in the nucleus (18).

Ca^{2+}-sensitive potassium channels. K_{Ca} share the basic architecture with voltage-gated potassium channels. On the basis of the size of ionic conductance, being big, intermediate, or small, K_{Ca} are divided into three categories, called BK channels ($K_{Ca}1.1$), IK channels ($K_{Ca}5.1$), and SK channels ($K_{Ca}2.1$, $K_{Ca}2.2$, $K_{Ca}2.3$, $K_{Ca}3.1$, $K_{Ca}4.1$, and $K_{Ca}4.2$) (104). They are present in a wide range of excitable and nonexcitable cells and are tightly associated with calmodulin. On activation by low concentrations of Ca^{2+}, K_{Ca} channel opening results in hyperpolarization of the membrane and changes in cellular excitability. Their activation limits the firing frequency of action potentials and is important for regulation of after-hyperpolarization in central neurons. K_{Ca} are involved in induction of synaptic plasticity and therefore play important roles in memory and learning (94).

Calcium binding proteins and transcriptional networks

Interaction of Ca^{2+} with specific sensors transduces the specificities of the $[Ca^{2+}]_i$ signal in terms of amplitude, duration, frequency, and spatial distributions into changes in the transcription rate of specific genes and cellular functions (86). Further, Ca^{2+}-mediated posttranslational modifications on appropriate molecules in the transcriptional machinery result in modified expression of specific single genes or in readjustments of the activity of entire transcriptional networks (70).

A number of Ca^{2+} binding proteins are expressed in the nervous system. Their affinity for Ca^{2+}, their localization in relation to the Ca^{2+} signal, and their interactions with other proteins determine their specific role. Functionally, they may be distinguished into two groups. Being chelators, they can act as Ca^{2+} buffers, which modify the spatiotemporal aspects of Ca^{2+} transients. As Ca^{2+} sensors, these proteins have a higher affinity and lower capacity towards Ca^{2+} and translate $[Ca^{2+}]_i$ changes into signaling cascades.

Three basic mechanisms that follow the recognition of changes in $[Ca^{2+}]_i$ by a Ca^{2+} sensor were differentiated (69). First, there is an activation of signaling cascades of phosphorylation and dephosphorylation that either modify the transactivating properties of transcription factors or affect the nucleosome structure. This changes the accessibility of the RNA polymerase II to specific genes. In some occasions, phosphorylation and dephosphorylation are coupled events that act on a particular protein or even on a particular phosphorylated amino acid residue. In those cases, the specificities of the Ca^{2+} signal to activate the two events of phosphorylation and dephosphorylation alternatively require a delicate fine-tuning. Two major phosphatases in this context are calcineurin, also termed protein phosphatase 2B (PP2B), and PP1 (70). Second, there is an induction of Ca^{2+}-dependent protein–protein interactions between the Ca^{2+} sensor and transcription factors. Because of this interaction, binding to DNA or recruitment of certain cofactors is modified. Third, Ca^{2+}-induced changes in the binding properties of the calcium sensor to specific sites in the DNA can be found.

The best studied example among the Ca^{2+} sensors is the ubiquitously occurring calmodulin with four EF-hand binding motifs (69). Neuronal Ca^{2+} sensor-1 (NCS-1) is a member of five NCS proteins and interacts with different other proteins in a Ca^{2+}-dependent or Ca^{2+}-independent manner (26). Recently, it has been shown that NCS-1 has a role in learning and memory (87). Calretinin, calbindin D-28, and parvalbumin belong to a family of Ca^{2+}-binding proteins, which in man comprises >200 members. They are particularly enriched in specific cerebellar neurons. Several studies suggest that these proteins have evolved as functionally distinct, physiologically relevant modulators of intracellular Ca^{2+} transients. They are involved in regulating the Ca^{2+} pools, which are critical for synaptic plasticity. Whether they play a major role as endogenous neuroprotectants is not clear.

The cAMP-dependent transcription factor CREB (cAMP response element binding) is thought in neurons to be involved in the formation of long-term memory and to mediate neuronal survival (29). Distinct protein kinase signaling pathways mediate converging effects of Ca^{2+} and cAMP on CREB activation. Binding of a neurotransmitter to its receptor may be coupled to activation of the cAMP-dependent protein kinase. Alternatively, elevation of $[Ca^{2+}]_i$ leads to activation of a Ca^{2+}/calmodulin-dependent kinase (CaMK) (90). CaMKs and the protein kinase C isoenzymes represent two major groups of Ca^{2+} sensitive enzymes. CaMKII represents between 1% and 2% of the protein in the brain. Besides transcription factor regulation, CaMKII plays a role in neurotransmitter secretion, glycogen metabolism, and synaptic plasticity (61).

Calcium pumps and exchangers

ATP-driven Ca^{2+} pumps and ion gradient-dependent Ca^{2+} exchangers are the major systems responsible for uphill transport of Ca^{2+} across membranes. Both types of transporters are simultaneously expressed in both astrocytes

and neurons. This implies that the two transporters with different kinetic properties have different functions in these cells.

Ca^{2+}/cation antiporter. Ca^{2+}/cation antiporters are a superfamily containing three members, which subserve a variety of roles, including neuronal signaling (92). The NCX, a 9-transmembrane domain protein able to couple the efflux/influx of Ca^{2+} to the influx/efflux of Na^+ ions, operates in a bidirectional way. It is the major regulator of Na^+ and Ca^{2+} homeostasis. In the brain, unlike in other tissues, this exchanger is present as three different gene products, NCX1, NCX2, and NCX3, with a distinct distribution pattern in different brain regions. Under physiological conditions, its primary role is to extrude Ca^{2+} through a forward mode of operation. NCX responds to a depolarization or to an increase in intracellular Ca^{2+} concentration coupled to receptor stimulation.

The Na^+/Ca^{2+}–K^+ exchanger (NCKX) transports K^+ and Ca^{2+} in exchange for Na^+, and comprises five members, four of which (NCKX2-5) are expressed in the brain. The NCKX proteins play a role in regulating Ca^{2+} flux in environments, which experience wide and frequent fluctuations in Na^+ concentration. Evidence emerges for multiple roles for these exchangers, also in processes such as synaptic plasticity.

The Ca^{2+}/cation exchanger branch has only one mammalian member, Na^+/Ca^{2+}–Li^+ exchanger (NCKX6 or NCLX), whose physiological function remains unclear, despite a broad pattern of expression (63).

Mitochondrial exchangers. While in nonexcitable cells the Ca^{2+} efflux from mitochondria is essentially mediated by the H^+/Ca^{2+} exchanger, in neurons and other excitable cells, the mitochondrial NCX (NCX_{mito}) is the main system extruding Ca^{2+} ions from the mitochondrial matrix. NCX_{mito} was shown to have an impact on mitochondrial physiology by controlling the activity of the Ca^{2+}-sensitive enzymes pyruvate-, α-ketoglutarate-, and isocitrate-dehydrogenase, and by consuming energy because of its indirect effect on the H^+ gradient (30). NCX_{mito} determines a shoulder in neuronal $[Ca^{2+}]_c$ responses to neurotransmitters and depolarizing stimuli. This shoulder may outlast the stimulus duration. The persistent NCX_{mito}-dependent Ca^{2+} release has a role in post-tetanic potentiation, a form of short-term synaptic plasticity. Published data suggest that the three isoforms of plasma membrane NCX contribute to NCX_{mito} in neurons and astrocytes (30).

Ca^{2+} shuttling between the ER and mitochondria was detected as the pacemaker of Ca^{2+} oscillations. Ca^{2+} release from the ER induces the initial Ca^{2+} oscillation and loads mitochondria with Ca^{2+}. The following Ca^{2+} peak is induced by means of NCX_{mito}. Increased $[(Ca^{2+}]_i$ provokes further peaks by regenerative Ca^{2+} release from ER, which generates partial reloading of the mitochondria. This sequence is repeated until mitochondrial Ca^{2+} is depleted (51).

Plasma membrane Ca^{2+} ATPases. PMCAs are quickly activated by a rise in $[Ca^{2+}]_i$ and affected by binding of Ca^{2+}-calmodulin. In the brain, four separate genes code for the major PMCA isoforms 1–4. In particular, PMCA2 is enriched primarily in neurons in some CNS regions. The identification of a growing number of further specific interacting proteins with regulatory, targeting, and signaling functions supports the paradigm that PMCAs are not only responsible for global Ca^{2+} homeostasis but are highly dynamic participants in spatially defined Ca^{2+} signaling (22).

Endoplasmic reticulum Ca^{2+}ATPase. The ER serves as a dynamic Ca^{2+} pool being thus involved in rapid signaling events in nerve cells associated with cell stimulation by either electrical (action potential) or chemical (neurotransmitters) signals. This function is supported by Ca^{2+} release channels ($InsP_3R$ and RyR) and SERCA Ca^{2+}-ATPases residing in the endoplasmic membrane (102). In addition, the ER provides a specific environment for the posttranslational protein processing and transport of various molecules toward their final destination. In parallel, the ER acts as a calcium tunnel, which facilitates Ca^{2+} movements within the cell by avoiding cytoplasmic routes. Finally, the ER appears as a source of numerous signals aimed at the nucleus and involved in long-lasting adaptive cellular responses. All these important functions are controlled by intra-ER free Ca^{2+}, which integrates various signaling events and establishes a link between fast signaling, associated with ER Ca^{2+} release/Ca^{2+} uptake, and long-lasting adaptive responses relying primarily on the regulation of protein synthesis (14, 22). Recently, SERCA has to been shown to be functionally coupled to the Ca^{2+} sensor in the ER, called STIM, and Orai, a member of the TRP family, to allow efficient refilling of the ER (65).

Disruption of ER Ca^{2+} homeostasis triggers several forms of cellular stress responses and is intimately involved in neurodegeneration and neuronal cell death (105).

Dysregulation of Ca^{2+} Signaling in Brain and Neural Degeneration

The central role of Ca^{2+} in signaling functions in brain underlines its potential relevance for neurodegenerative diseases, a heterogeneous group of disorders characterized by gradual and progressive, selective loss of anatomically or physiologically related neuronal systems. Despite the wide spectrum of appearances of these diseases, there are striking similarities in the molecular pathogenesis of these diseases as they all involve dysregulation of Ca^{2+} homeostasis and signaling. This is associated with alterations of Ca^{2+} buffering capacities, deregulation of Ca^{2+} channel activities, and alterations of other Ca^{2+}-regulating proteins due to excitotoxicity, perturbed energy metabolism, and oxidative stress. Abnormal cellular Ca^{2+} load can trigger cell death by activating proteases, by reinforcing signals leading to caspase activation or by triggering other catabolic processes mediated by lipases and nucleases.

Involvement of ER and mitochondria in Ca^{2+} homeostasis is an important common theme in neurodegenerative diseases, since these organelles are intimately involved in neuronal cell death (102). The link between Ca^{2+} dysregulation, mitochondria, and cellular derangement became particularly evident, when usage of animals as genetic disease models and analysis of the impact of environmental factors allowed to identify common traits in the pathogenic routes for these diseases (33, 60).

Neurological diseases should be also considered as gliopathologies, which determine the progression and final outcome of the neuropathological process (75). Glial function is closely regulated by cellular Ca^{2+} signaling that underlies the so-called glial calcium excitability. Glial Ca^{2+} signals

triggered by activation of multiple GPCR are primarily driven by Ca^{2+} release from the ER (52).

The identification of precise neurotoxic molecular events in neurodegenerative disorders is a challenging task. A recent collection of overviews covered the role of imbalanced Ca^{2+} homeostasis and pathological Ca^{2+} signaling in various neurological diseases (74). We will focus in the following section on the question of how perturbation of Ca^{2+} homeostasis contributes to the pathophysiology of specified neurodegenerative disorders (12, 36, 60, 67).

Aging

Oxidative and metabolic stress, and impaired cellular stress adaptation are mechanisms of aging that render neurons vulnerable to degeneration. Many Ca^{2+}-dependent processes, such as susceptibility to neurotoxicity, the after-hyperpolarization amplitude, induction of synaptic plasticity, long-term potentiation, long-term depression, and cell excitability are altered with age (43). Indeed, multiple lines of evidence have implicated Ca^{2+} dysregulation in brain aging and dementia. These changes have been associated with age-related deficits in learning and memory.

Aging-related increases in the Ca^{2+} spikes and currents result from changes in local Ca^{2+} levels. There is evidence for an increased L-type Ca^{2+} channel activity functionally linked to RyR. In turn, the increased Ca^{2+} transients result in dysregulation of multiple Ca^{2+}-dependent processes and, through different pathways, in accelerated functional decline during aging (43, 99).

Alzheimer's disease

Alzheimer's disease (AD) is the most common age-related dementia in which patients show neurodegeneration and loss of cognitive abilities. Cognitive impairment and emotional disturbances in AD result from the degeneration of synapses and neuronal death in the limbic system and some regions of the cerebral cortex. Biochemically, AD is characterized by the perturbed expression and subsequent accumulation of several proteins, such as reelin and presenilins (PS). Reelin is involved in regulation of neuronal migration, synaptic plasticity, and dendritic spine development. Presenilins are part of the γ-secretase protease complex and play a role in presynaptic neurotransmitter release, induction of long-term potentiation and in the modulation of $[Ca^{2+}]_i$. γ-Secretase in coordination with β-secretase induces overproduction of Aβ, which forms oligomers. Amyloid plaques and neurofibrillary tangles are found as protein aggregates in the brain cells in AD.

The Aβ hypothesis postulates that Aβ deposits are the fundamental cause of the disease. Figure 2 summarizes the Aβ-associated Ca^{2+} dysregulation combined with the Ca^{2+}-dependent cell death pathways that are prominent in AD cellular pathology. Under normal conditions, a sequential cleavage of the Aβ precursor protein (APP) by β-secretase and γ-secretase generates Aβ. AD-causing mutations in APP and PS compromise normal processing of these proteins in the plasma membrane.

Central to the neurodegenerative process is the inability of neurons to properly regulate intracellular Ca^{2+} levels (67, 99). Thus, toxic forms of Aβ may induce Ca^{2+} influx into neurons by formation of an oligomeric pore in the plasma membrane, thereby rendering neurons vulnerable to excitotoxicity and apoptosis (19). Aβ interacts with Fe^{2+} and Cu^{+} to generate hydrogen peroxide and hydroxyl radical ($HO^{\bullet}$), resulting in membrane lipid peroxidation, which generates aldehydes that impair the function of PMCA. As a result, the membrane becomes depolarized. NMDAR channels and Ca_V open, and a flux of toxic amounts of Ca^{2+} into the cytoplasm follows (16).

In addition, Aβ accumulates in mitochondria and thereby impairs the activity of complexes III and IV of the respiratory chain (9). Further, evidence for an involvement of NCX_{mito} in pathological mechanisms of AD was reported (30, 100). Aβ affects mitochondria, whereby it causes elevated cytoplasmic Ca^{2+} levels and oxidative stress, and it reduces ATP synthesis and further increases the Ca^{2+} overload and oxidative stress (60).

There is also evidence that PS modulate SERCA to alter Ca^{2+} uptake and release in the ER (19). This effect of PS results in excessive accumulation of Ca^{2+} in the ER and, as a consequence, enhances Ca^{2+} release through RyR, whose expression levels are increased in mutant PS1-expressing AD mouse models (96). In the cortex of AD patients, reelin levels were significantly increased compared with control brain. Interaction of reelin with the apolipoprotein E receptor 2 was shown to enhance Ca^{2+} influx through NMDAR channels by a mechanism involving a src family tyrosine kinsase. Amyloidogenic APP processing prevents the α-secretase from α-cleavage of APP, which would otherwise generate a secreted form of APP. The latter is normally produced in response to synaptic activity and is known to be involved in neuroprotective pathways. During AD, amyloidogenic processing also generates by proteolysis a free intracellular APP domain, designated amyloid intracellular C-terminal domain, which translocates to the nucleus and perturbs gene transcription that regulates Ca^{2+} homeostasis (19). Finally, Ca^{2+} homeostasis disruption mediated by TRP channels has been suggested in AD (106). High $[Ca^{2+}]_i$ induces stimulation of neuronal NO synthase, which leads to production of reactive oxygen and nitrogen species and to the feedforward activation of TRPM7 and TRPM2-like currents.

Ischemia and brain energy deprivation

A few minutes after uncompensated brain ischemia, cell death pathways overcome survival-promoting pathways, leading to neuronal death through three interacting mechanisms: excitotoxicity attributable to excess glutamate, oxidative stress, and/or stimulation of apoptotic-like pathways (12, 62). Figure 3 highlights the mechanisms connected to Ca^{2+} dysregulation in ischemia/stroke-induced cell death. These mechanisms were shown above in Figure 1 within the context of normal physiology.

Glutamate activates NMDAR at synaptic and extrasynaptic sites, causing prolonged neuronal depolarization and triggering deregulation of cellular ion homeostasis, mainly $[Ca^{2+}]_i$ and $[Na^{+}]_i$. The entry of Ca^{2+} through NMDAR is accepted as the major pathway leading to the excitotoxic, delayed cell death associated with the ischemic periods of stroke. As a consequence of the excitotoxic stimulus in neurons, calpains cleave NCX and PMCA (Fig. 3) and thus inhibit its capability to remove accumulated Ca^{2+} (13). On the other hand, during hypoxic conditions, a nuclear factor-κB-dependent increase of NCX1 activity was shown enabling Na^{+} extrusion and Ca^{2+} influx. This may help to refill the ER Ca^{2+} stores and to prevent

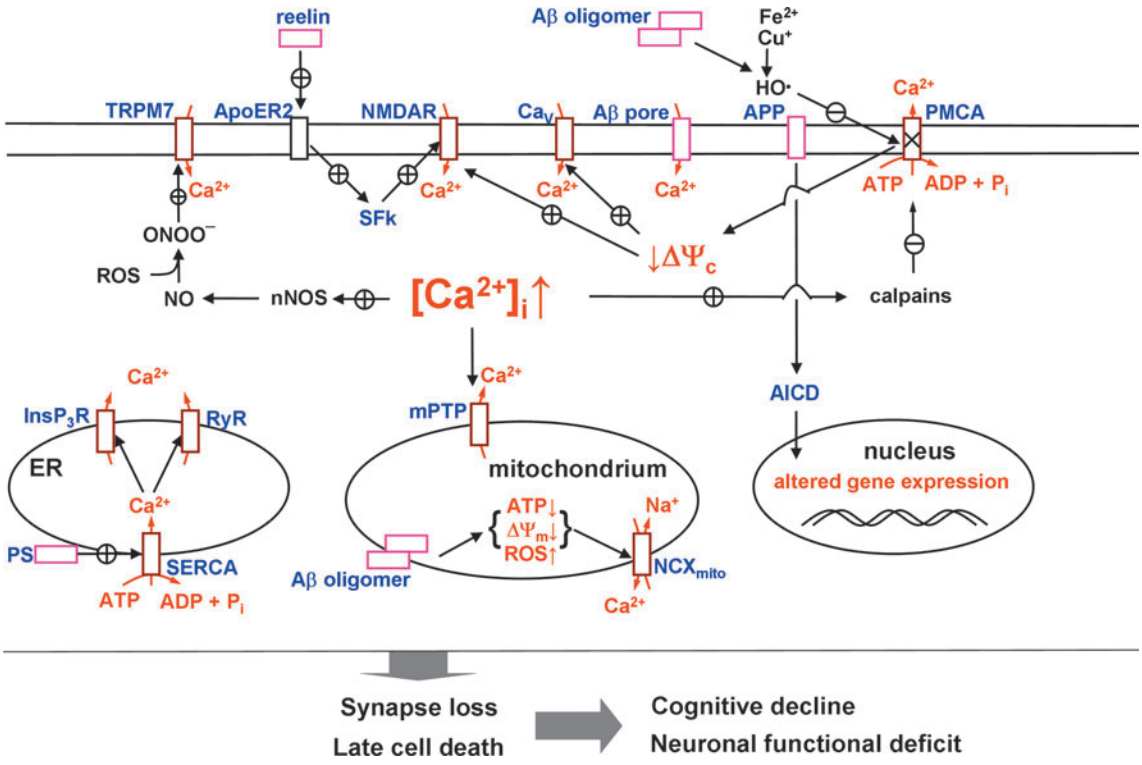

FIG. 2. Perturbed brain Ca^{2+} homeostasis in Alzheimer's disease due to mutations of several proteins and formation of protein aggregate deposits. Several pathways lead to $[Ca^{2+}]_i$ overload. Thus, Aβ oligomers form pores in the plasma membrane through which Ca^{2+} passes into the cytoplasm. Aβ can also interact with Fe^{2+} and Cu^{+} to generate $HOO^{\bullet}$ and $OH^{\bullet}$, resulting in membrane lipid peroxidation that impairs the function of PMCA. As a result, the plasma membrane becomes depolarized; NMDAR and Ca_V open and cause flux of Ca^{2+} into the cytoplasm. Interaction of reelin with the ApoER2 enhances Ca^{2+} influx through NMDAR by a mechanism involving a SFk. Increased $[Ca^{2+}]_i$ further increases $[Ca^{2+}]_i$ by calpain-mediated inhibition of PMCA and nNOS-induced activation of TRPM7. Aβ acts on mitochondria, to cause Ca^{2+} overload-increased ROS production, depolarization, and decreased ATP production. Mutations of PS result in excessive accumulation of Ca^{2+} in the ER *via* SERCA and, thus, enhance Ca^{2+} release through RyR and $InsP_3R$ channels. Further, the intracellular APP domain AICD, which is generated by proteolysis from amyloid precursor protein translocates to the nucleus and alters Ca^{2+}-dependent gene transcription. AICD, amyloid intracellular C-terminal domain; Aβ, β-amyloid; NMDAR, N-methyl-D-aspartate receptor; ApoER2, apolipoprotein E receptor; SFk, src family tyrosine kinase; NO, nitric oxide; nNOS, neuronal NO synthase; ROS, reactive oxygen species; PS, presenilins; APP, Aβ precursor protein; $\Delta\Psi_c$, cytosolic membrane potential; $\Delta\Psi_m$, mitochondrial membrane potential. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

ER stress during anoxic conditions, thus contributing to cell rescue (92).

The decrease in $[Ca^{2+}]$ in the extracellular space, resulting from NMDAR stimulation, disinhibits Ca^{2+}-sensing channel currents, leading to a further decrease in extracellular $[Ca^{2+}]$ and also membrane depolarization, which enhances removal of the Mg^{2+} block from NMDAR. Similarly, the decrease in extracellular $[Ca^{2+}]$ disinhibits some ion channels, thus resulting in a more pronounced depolarization and further relief of the block of NMDAR (64).

During ischemia, mitochondria release Ca^{2+} *via* NCX_{mito} inducing a depletion of ATP due to the decrease in mitochondrial membrane potential ($\Delta\Psi_m$) (73). In this condition, the operation of the NCX_{mito} is shifted to the Ca^{2+} accumulation mode. It has been shown that NCX_{mito} can go into its reverse mode of operation and then acts as an influx pathway for Ca^{2+} into the mitochondrial matrix (Fig. 3). Excessive rise of intramitochondrial Ca^{2+} is a trigger for mitochondrial permeability transition pore (mPTP) opening and apoptosis (30). The opening of the mPTP is a critical step in neurodegenerative processes (11, 45). This pore structure with its control elements provides a very promising target for neuroprotective strategies (45). Nevertheless, the biochemical composition of this pore is still a mystery despite many years of intense investigations.

Ischemia-induced local production of ROS increases high activity response of RyR2 by S-glutathionylation and thus amplifies the increase of $[Ca^{2+}]_i$ (8, 24).

Members of the melastatin subfamily of TRP proteins, particularly TRPM7 and TRPM2, may play key roles in neuronal death that is activated by oxidative stress downstream from excitotoxic signaling pathways (1, 64). Moreover, spreading depression-like hypoxic depolarization after vascular stroke is associated with an increase in $[Ca^{2+}]_i$. Intriguingly, TRPM4 and 5 could be candidates for triggering this dramatic event, although at present there is no direct experimental evidence in support of this conjecture (10).

Parkinson's disease

Parkinson's disease (PD), the most frequent movement disorder, is caused by the progressive loss of the dopamine neurons within the substantia nigra pars compacta (SNc) and

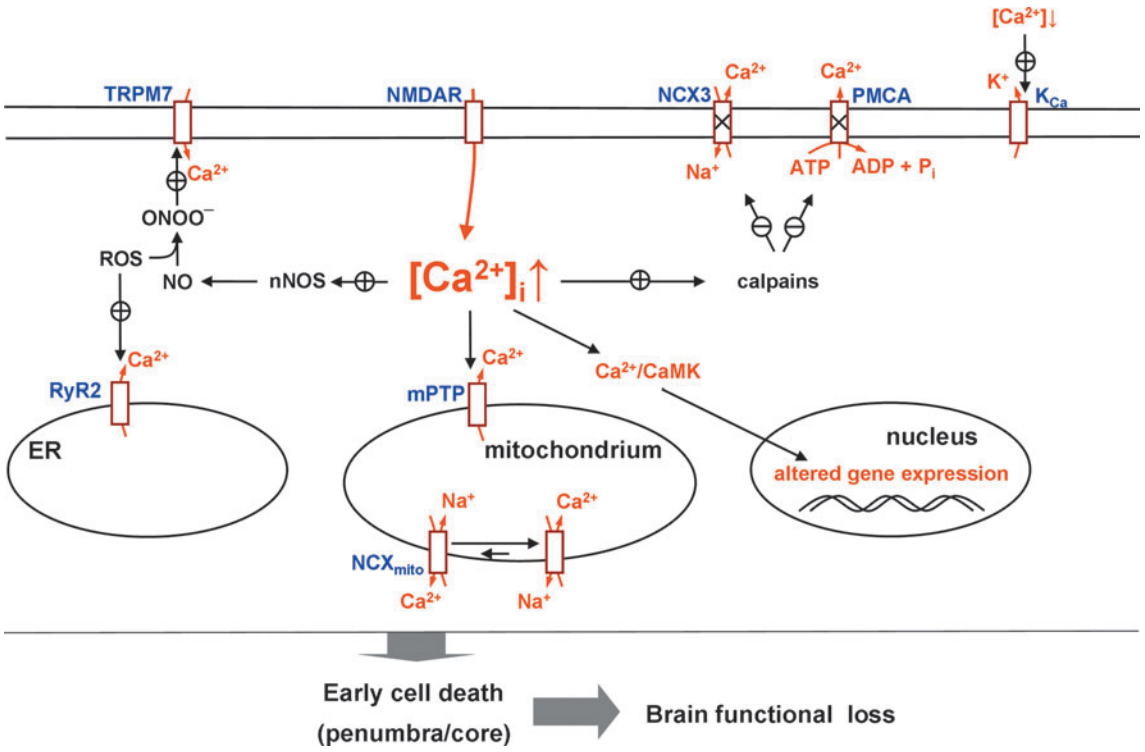

FIG. 3. Perturbation of neural Ca^{2+} homeostasis under ischemic conditions. Neuronal and glial cell death is primarily mediated by oxidative stress and excess glutamate. Ca^{2+} entry through NMDAR mainly triggers the excitotoxic Ca^{2+} overload. As a result, calpains are activated, which inactivate by cleavage both NCX3 and PMCA. This precludes the capability to remove accumulated Ca^{2+}. High $[Ca^{2+}]_i$ induces stimulation of nNOS, which leads to production of $ONOO^{\bullet-}$ and to the feedforward activation of TRPM7 currents. The decrease in $[Ca^{2+}]$ in the extracellular space disinhibits Ca^{2+}-sensing channels, such as $K_{Ca}3.1$, leading to a further membrane depolarization. As a result of high $[Ca^{2+}]_i$, excessive rise of intramitochondrial Ca^{2+} triggers the opening of the mPTP. Mitochondria also release Ca^{2+} *via* NCX_{mito}. This induces a depletion of ATP. Under ischemic conditions, the mode of operation of NCX_{mito} is reverted. Then, the NCX_{mito} acts as an influx pathway for Ca^{2+} into the mitochondrial matrix. ROS induce a high activity response of RyR2 and thus amplify the increase of $[Ca^{2+}]_i$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars).

the associated deficiency of the neurotransmitter dopamine in the striatum. Most cases of PD occur sporadically with unknown cause, but mutations in several genes, such as α-synuclein, Parkin, DJ-1, PINK1, and LRRK2, have been linked to genetic forms of PD.

In humans and animal models, mitochondrial dysfunction is a defect occurring early in the pathogenesis of both sporadic and familial PD. Both PINK1 and Parkin play crucial roles in the regulation of mitochondrial dynamics and function. Mutations in DJ-1 and Parkin render animals more susceptible to oxidative stress, and mitochondrial toxins were implicated in sporadic PD. Mitochondrial association of α-synuclein in cells was also linked to impairment of respiratory complex I activity, oxidative modification of mitochondrial proteins, and increased levels of Ca^{2+} and NO (81). In autoptic samples of *substantia nigra* from patients affected with the disease the activity of complex I was shown to be reduced (23, 30).

L-type Ca^{2+} channels are engaged during autonomous pacemaking rendering SNc dopaminergic neurons susceptible to mitochondrial toxins. This indicates that homeostatic Ca^{2+} stress could determine their selective vulnerability (34, 97). Further, reduction in the cell surface expression of the TRP channel isoform 1 may be involved in dopaminergic neurodegeneration, and TRP channel isoform 1 may provide neuroprotection against PD-inducing agents (20).

Multiple sclerosis and brain inflammatory processes

Multiple sclerosis is characterized by inflammation, demyelination, oligodendrocyte death, gliosis, axonal damage, and neurodegeneration. The clinical symptoms include paresthesia, optic neuritis, diplopia, fatigue, paralysis, and cognitive dysfunction. NCX, PMCA2, several ion channels, and SERCA play critical roles in this type of neuronal pathology. Increase of Na^+ concentration induces a reversal in the activity of NCX and the subsequent increase of $[Ca^{2+}]_i$. Reduction in PMCA2 expression causes injury due to activation of Ca^{2+}-dependent proteases, including calpains and PPs. One consequence is the dephosphorylation of cytoskeletal proteins, such as neurofilaments. This affects neuronal stability and increases the vulnerability of cytoskeletal proteins (58, 71).

Huntington's disease

Huntington's disease (HD) is characterized by motor, cognitive, and psychiatric symptoms, including depression, personality changes, weight loss, and movement irregularity (chorea) developing in the terminal stage into severe akinesia (33). The disease is inherited in an autosomal dominant fashion. The mutant huntingtin gene was identified to be reponsible for the disease. This protein is considered to play a role in axonal transport, regulation of transcription, exocytosis,

bioenergetic metabolism, prevention of apoptosis, and Ca^{2+} homeostasis (31).

Mitochondrial Ca^{2+} overload is a decisive commitment step for the disease. Thus, a facilitated opening of the mPTP in permeabilized mutant huntingtin-expressing cells was demonstrated (59). Mutant but not wild-type huntingtin directly impairs the mitochondrial function (98). Further, huntingtin forms a ternary complex with huntingtin-associated protein-1A and $InsP_3R1$. In this complex, mutant huntingtin facilitates Ca^{2+} release from the ER and renders neurons more sensitive to Ca^{2+}-mediated cellular dysfunction (98).

Epilepsy

Up to 50% of all cases of epilepsy are initiated by neurological insults. Status epilepticus, stroke, and traumatic brain injury are three major causes that can lead to the development of acquired epilepsy. The neurons that survive the increase in extracellular glutamate concentration and the perturbed Ca^{2+} homeostasis sustain long-term changes in Ca^{2+} signaling that are prominent features of the epileptic phenotype (39, 73).

Genes of Ca^{2+}-dependent ion channels and several other genes contribute to the genetic background of the pathogenesis of idiopathic epilepsy syndromes (72). Idiopathic generalized epilepsies are inherited with additive effects of genetic variation. Ca_V are involved in the release of neurotransmitters and in the sustained depolarization phase of paroxysomal depolarisation shifts; they are also the genetic substrate of generalized tonic-clonic convulsions. Various Ca^{2+}-regulated enzymes found in spines have been implicated in epileptogenesis, including the nonreceptor protein tyrosine kinases Src and Fyn, CaMKII, and calcineurin (68).

A broad variety of mutations in mitochondrial DNA or nuclear genes have been associated with epileptic phenotypes. Ca^{2+} entrance into mitochondria through the uniporter induces mitochondrial depolarization. Impairment of the mitochondrial respiratory chain causes an increased metabolic demand in epileptic neurons (30). Mitochondrial dysfunction has been identified as a cause of epileptic seizures. The cross-talk between astrocytes and neurons promotes increased dendritic Ca^{2+} levels and synchronous firing of neurons, a hallmark of epileptiform activity (56).

Refsum disease and accumulation of branched-chain phytanic acid

In a inherited peroxisomal disorder, Refsum disease, mutations in the PHYH gene cause a buildup of the saturated branched-chain fatty acid phytanic acid in the plasma and tissues. Clinical features of this and other leukosdystrophies result from the malformation of myelin sheaths and comprise neurologic damage, cerebellar degeneration, and peripheral neuropathy. Phytanic acid and its peroxisomal α-oxidation product pristanic acid were recently shown to induce mitochondrial depolarization, Ca^{2+} deregulation, ROS production, and cell death in brain cells (85).

Conclusions

Outlook: search for novel targets of protection against neurodegeneration related to Ca^{2+} dysregulation

The mechanisms of neural diseases reported in the Dysregulation of Ca^{2+} Signaling in Brain and Neural Degeneration section involve a broad spectrum of Ca^{2+} dysregulation. This proves that stabilization of neuronal Ca^{2+} homeostasis may retard cell degeneration in acute and chronic neurodegenerative conditions. Causal mutations of genes coding for Ca^{2+}-regulating proteins are genetic risk factors. These act together with environmental factors to determine whether a neurodegenerative disease process develops. If we were able to identify the mechanisms that determine whether the nervous system adapts positively and copes with the stress, or shows a disease phenotype during development, then the disease processes could be averted. For that purpose, drugs targeting the Ca^{2+} homeostasis might be helpful.

In line with this concept, it can be positively noted that drugs that suppress Ca^{2+} influx support neuronal survival in models of neurodegenerative disorders. Indeed, beneficial effects of the Ca_V1 (L-type Ca^{2+} channel) blocker nimodipine and the NMDAR channel blocker memantine have been shown in AD patients. On the other hand, clinical trials of NMDAR antagonists have failed to prevent ischemia-induced cell death since these antagonists may be protective only in the early phase of the insult, but not at later stages (67).

Recent exciting developments in therapeutics for neurodegenerative disorders have been the use of immunization. If antibodies were able to remove Aβ from the brain, immunization would be expected to prevent or reverse also the Aβ-induced neuronal Ca^{2+} dysregulation. For individuals at high risk for AD, prophylactic treatment may be prescribed, including anti-inflammatory drugs and immunization (19). Administration of the Ca_V blockers bepridil and nitrendipine significantly ameliorated experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis. Similar results were obtained by inhibition of receptor-operated and other Ca^{2+}-regulating channels (71). For HD, promising results have been published using a specific animal model of HD (79). In mice expressing the full-length mutant huntingtin, histone deacetylase inhibitors were shown to ameliorate the deficits in mitochondrion-dependent Ca^{2+} handling. Thus, the inhibitors induced neuroprotection by improving the neuronal ability to cope with excitotoxic stimuli. For PD, no proven neuroprotective therapy with regulation of the Ca^{2+} balance has been described up to now. The search for such treatments is vigorously pursued (97). For neuroprotection against damage after status epilepticus, early NMDAR antagonism has been proposed to block the fatal Ca^{2+} accumulation in neurons (103).

Open questions and further perspectives

To stimulate further the development of promising therapeutic agents, which target neuronal Ca^{2+} signaling, several open questions have to be elucidated. These questions concern (i) the impact of risk factors of disease on neuronal Ca^{2+} homeostasis, both at the molecular and the cellular level, (ii) the identification of the subset of neurons affected in a particular type of neuronal degeneration, (iii) further elucidation of interactions of different neural cell types in brain Ca^{2+} homeostasis, (iv) the role played by mitochondria in pathogenesis, and (v) the potential help of antioxidants and cellular energy-promoting agents in the context of Ca^{2+} homeostasis.

Development of neuroprotective strategies comprises the sophisticated analysis of the pathways to control Ca^{2+} homeostasis and the understanding of the sequences of

downstream events of Ca^{2+} signaling. Distinct Ca^{2+} signals may define whether protection is initiated or not. For example, the protease thrombin at low concentrations mediates hippocampal neuroprotection against ischemia *via* activation of protease-activated receptors, but thrombin causes neuronal degeneration at high concentrations (95). Further, the involvement of phospholipase A_2 activation in the up- or downregulation of $[Ca^{2+}]_i$ in astrocytes promises neuroprotection (88). The development of better-focused antiexcitotoxic strategies requires considerations of pro-survival NMDAR signaling. The selective targeting of pro-death pathways downstream of the NMDAR may represent an effective therapeutic strategy (47). Cell death in ischemia depends on the neuronal subtype, the severity, and duration of the episode, and the position of the neuron within the lesion (infarct core or penumbra). The use of NMDAR antagonists that are activated only in the pathological state is a promising strategy to consider this fact. This should minimize negative side effects (46).

Although in animal models of neurodegenerative disorders many Ca^{2+} targeting drugs have been demonstrated to protect neurons, only few have been successful in preclinical trials. To speed up the advancement of promising drugs to therapeutic intervention, rigorous scientific evidence for the suggested mechanism of action of the compound in question is needed; additionally, critical clinical evaluation of neuroprotectants in combination with other therapies is necessary. Further, growing attention has to be directed to the stimulation of neuroregeneration.

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Abbreviations Used

$A\beta$ = β-amyloid
AD = Alzheimer's disease
AICD = amyloid intracellular C-terminal domain
APP = $A\beta$ precursor protein
Ca^{2+} = calcium cations
$[Ca^{2+}]_i$ = intracellular free Ca^{2+} concentration
CaMK = Ca^{2+}/calmodulin-dependent kinase
Ca_V = voltage-gated Ca^{2+} channels
CNS = central nervous system
CREB = cAMP response element binding
ER = endoplasmic reticulum
GPCR = G protein-coupled receptor
HD = Huntington's disease
$InsP_3R$ = inositol(1,4,5)trisphosphate receptor
K_{Ca} = Ca^{2+}-activated potassium channels
MCU = mitochondrial Ca^{2+} uniporter
mPTP = mitochondrial permeability transition pore
NCKX = Na^+/Ca^{2+}–K^+ exchanger
NCS = neuronal Ca^{2+} sensor
NCX = Na^+/Ca^{2+} exchanger
NCX_{mito} = mitochondrial NCX
NMDAR = N-methyl-D-aspartate receptor
nNOS = neuronal NO synthase
NO = nitric oxide
PD = Parkinson's disease
PS = presenilins
PMCA = plasma membrane Ca^{2+} ATPases
PP = protein phosphatase
ROC = receptor-operated channels
ROS = reactive oxygen species
RyR = ryanodine receptor
SERCA = sarco(endo)plasmic reticulum Ca^{2+}-ATPases
SNc = substantia nigra pars compacta
STIM = stromal interacting molecule
TRP = transient receptor potential