0031-6997/11/6303-700–727$25.00
PHARMACOLOGICAL REVIEWS
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Pharmacol Rev 63:700–727, 2011

Vol. 63, No. 3
3814/3690704
Printed in U.S.A.

ASSOCIATE EDITOR: DAVID R. SIBLEY

Endoplasmic Reticulum Ca^{2+} Handling in Excitable Cells in Health and Disease

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***Abstract*——The endoplasmic reticulum (ER) is a morphologically and functionally diverse organelle capable of integrating multiple extracellular and internal signals and generating adaptive cellular responses. It plays fundamental roles in protein synthesis and folding and in cellular responses to metabolic and proteotoxic stress. In addition, the ER stores and releases Ca^{2+} in sophisticated scenarios that regulate a range of processes in excitable cells throughout the body, including muscle contraction and relaxation, endocrine regulation of metabolism, learning and memory, and cell death. One or more Ca^{2+} ATPases and two types of ER membrane Ca^{2+} channels (inositol trisphosphate and ryanodine receptors) are the major proteins involved in ER Ca^{2+} uptake and release, respectively. There are also direct and indirect interactions**

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This article is available online at http://pharmrev.aspetjournals.org. doi:10.1124/pr.110.003814.

of ER Ca^{2+} stores with plasma membrane and mitochondrial Ca^{2+}-regulating systems. Pharmacological agents that selectively modify ER Ca^{2+} release or uptake have enabled studies that revealed many different physiological roles for ER Ca^{2+} signaling. Several inherited diseases are caused by mutations in ER Ca^{2+}-regulating proteins, and perturbed ER Ca^{2+} homeostasis is implicated in a range of acquired disorders. Preclinical investigations suggest a therapeutic potential for use of agents that target ER Ca^{2+} handling systems of excitable cells in disorders ranging from cardiac arrhythmias and skeletal muscle myopathies to Alzheimer disease.

I. Introduction

A. Primer on Endoplasmic Reticulum Structure and Function

The endoplasmic reticulum (ER[1]) is a membrane-bound organelle present in all eukaryotic cells, where it exhibits a range of structures, including tubules, vesicles, and complex net- or web-like formations (i.e., a reticulum). The ER membrane is believed to be initially generated as part of the nuclear envelop, which then expands and morphs into a complex reticulum that can extend for great distances within a cell (Petersen and Verkhratsky, 2007). Portions of the ER may then separate to form ER vesicles that can move to distant cellular compartments such as the long axons and dendrites of neurons (Aridor et al., 2004; Aridor and Fish, 2009). Two distinct types of ER are observed by electron microscopy: 1) rough ER is decorated by membrane-associated ribosomes and plays a major role in the synthesis of new proteins, and 2) smooth ER lacks ribosomes and is involved in lipid and steroid biosynthesis and Ca^{2+} signaling (Shibata et al., 2006). The amount of each type of ER and their structural organization vary considerably among different types of cells. For example, smooth ER is abundant in adrenocortical cells that produce glucocorticoids (cortisol in humans and corticosterone in rodents) (Black et al., 2005). In contrast, endocrine secretory cells that produce and release large amounts of protein and peptide hormones possess large amounts of rough ER (Bendayan, 1989).

The structural organization of the ER is highly complex, in that it forms a reticulated network of tubules and cisternal regions that is widely distributed throughout the cytoplasm (Griffing, 2010). Tubules can transform into cisternae and vice versa; cisternae can generate tubules by forming tubules at their edges, and nodes and branches may shift to re-organize the ER network. Several proteins have been shown to control the generation and modification of ER structure. The formation of ER tubules requires reticulon protein Rtn4a/NogoA and DP1, whereas the fusion of different tubules is controlled by p47 and p97 proteins (Uchiyama and Kondo, 2005; Voeltz et al., 2006). In general, the smaller vesicular and tubular forms of smooth ER are highly mobile and can move within the cytoplasm in a purposeful manner. The movement of the ER toward the cell periphery is controlled by microtubules. The generation, maintenance, and remodeling of the ER is controlled by microtubule-associated proteins (kinesins and dyneins) and by tip attachment complexes located at the plus (growing) end of the microtubule (Bola and Allan, 2009). Actin filaments may also control ER movement, as demonstrated using an in vitro preparation in which it was shown that myosin on the ER membrane interacts with actin filaments to translocate ER vesicles in an ATP-dependent manner. Although the functional significance of intra-ER morphological changes and movement in cells is not well understood, it seems likely that such changes provide molecules produced in the ER (proteins, steroids, Ca^{2+}) to sites where they are needed.

ER structure and motility within subcellular compartments may be regulated by Ca^{2+} signals. Ca^{2+} is a major regulator of cytoskeletal dynamics in cells; Ca^{2+} influx stimulates actin polymerization, and high levels of Ca^{2+} cause microtubule depolymerization (Mattson, 1992). Such changes in microtubules and actin filaments will alter ER structure and motility as described above.

The ER often interacts with the plasma membrane, thereby serving an important role in the Ca^{2+}-mediated transduction of extracellular signals to the cell interior, including the nucleus. Much of this occurs through junctional units formed between integral membrane proteins involved in Ca^{2+} homeostasis and adjacent channels in the ER. For example, stromal interaction molecule 1 (STIM1) is an ER transmembrane protein that interacts with proteins in the plasma membrane. STIM1 plays a pivotal role in store-operated Ca^{2+} entry

[1]Abbreviations: 2-APB, 2-aminoethoxydiphenyl borate; 5-HT, 5-hydroxytrypamine; Aβ, amyloid β-peptide; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BAPTA, 1,2-bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid; Bcl-2, B-cell lymphoma 2; CALHM1, calcium homeostasis modulator 1; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; CCD, central core disease; CICR, Ca^{2+}-induced Ca^{2+} release; CPA, cyclopiazonic acid; CPVT, catecholaminergic polymorphic ventricular tachycardia; ER, endoplasmic reticulum; FAD, familial Alzheimer disease; GRP, glucose-regulated protein; Herp, homocysteine-inducible ER stress protein; IP_3, inositol triphosphate; IP_3R, inositol trisphosphate receptor; LTD, long-term depression; LTP, long-term potentiation; MmD, multi-minicore disease; MRS1845, *N*-propylargylnitrendipine; NF-κB, nuclear factor-κB; NMDA, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; NPC, Niemann-Pick type C disease; PD, Parkinson disease; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; PN, peripheral neuropathy; PS, presenilin; PUMA, p53–up-regulated modulator of apoptosis; RyR, ryanodine receptor; SA, sinoatrial; SERCA, sarcoplasmic-endoplasmic reticulum Ca^{2+} ATPase; SKF96365, 1-(2-(3-(4-methoxyphenyl)-propoxy)-4-methoxyphenylethyl)-1*H*-imidazole; SOCE, store-operated calcium entry; SOD, superoxide dismutase; SR, sarcoplasmic reticulum; STIM, stromal interaction molecule; UPR, unfolded protein response; VAPB, vesicle-associated membrane protein-associated protein B; VGCC, voltage-gated Ca^{2+} channel.

through associating with the plasma membrane channel, Orai; this important aspect is discussed in section II.B. In the context of ER structure and motility, it has also been reported that STIM1 binds directly to the microtubule-plus-end-tracking protein EB1 and mediates ER tubule growth via the microtubule tip attachment complex mechanism (Grigoriev et al., 2008). This may be the mechanism by which local Ca^{2+} release from the ER, and/or influx through plasma membrane channels, increases (or decreases) the amount of ER associated with that particular region of the plasma membrane in which receptors that stimulate Ca^{2+} influx are activated. It is noteworthy that STIM1-rich regions of the ER may preferentially interact with domains of the plasma membrane that are rich in sphingolipids and cholesterol, the so-called lipid rafts (Pani et al., 2008). Studies of neurons have shown that metabolism of sphingomyelin in lipid rafts modifies cell excitability and Ca^{2+} influx through ligand-gated channels (Wheeler et al., 2009; Norman et al., 2010), suggesting a potential role for membrane lipids in controlling ER motility and Ca^{2+} release.

Other examples of the ER forming junctions with the plasma membrane include the sodium/Ca^{2+} exchanger NCX1, which forms Ca^{2+} signaling complexes with SERCA2 and inositol trisphosphate (IP_3) receptor 1 (IP_3R1) by linkages through the cytoskeletal network (Lencesova et al., 2004). Interaction of the ER network with other organelles also allows for the intracellular transfer of Ca^{2+}. Mitochondria-ER communication has been well studied, because these organelles are highly abundant and subserve functions essential for cellular metabolism and survival. Physical links tether the outer mitochondrial membrane to the adjacent ER (Boncompagni and Protasi, 2007; Franzini-Armstrong, 2007), and the ER regulates mitochondrial energy metabolism through these close contacts by generating high Ca^{2+} concentration microdomains that are a source for Ca^{2+} uptake into the mitochondria via mitochondrial uniporters (Duchen, 1999). This source of Ca^{2+} entry into the mitochondria has implications for cellular bioenergetics via IP_3R-mediated Ca^{2+} release (Cárdenas et al., 2010) as well as serving neuroprotective functions (Eckenrode et al., 2010; Renvoisé and Blackstone, 2010).

II. Endoplasmic Reticulum Ca^{2+} Homeostasis and Signaling

In most cell types, including those discussed here, the ER is the largest intracellular organelle and extends throughout most cellular compartments. In addition to its role in storing, modifying, and transporting newly synthesized proteins, the ER is a high-capacity reservoir for intracellular Ca^{2+}, with intraluminal concentrations ranging from the high micromolar to low millimolar range (Berridge, 2002; Solovyova and Verkhratsky, 2002), roughly 4 to 5 orders of magnitude higher than the surrounding cytosol. This steep concentration gradient is the predominant driving force by which Ca^{2+} exits the ER through one of several receptors/channels, such as the IP_3 receptor, ryanodine receptor (RyR), and leak channels. The ER can serve as a sink as well as a source for intracellular Ca^{2+} signaling, transporting cytosolic Ca^{2+} into the lumen through the sarcoplasmic-endoplasmic reticulum Ca^{2+} ATPase (SERCA) pumps.

A. Endoplasmic Reticulum Ca^{2+} Release Mechanisms

1. Inositol Trisphosphate Receptor. There are two ER Ca^{2+} channels that generate cell signaling-derived Ca^{2+} release from the ER lumen to the cytosol. The first to be discussed is the IP_3R, which is an intracellular ligand-gated Ca^{2+} channel, with six transmembrane domains in the carboxyl terminal, localized to the ER membrane (Bezprozvanny, 2005; Foskett et al., 2007; for review, see Yule et al., 2010). Its ligand, IP_3, is a second messenger generated from G_q-coupled or tyrosine kinase-linked receptors on the plasma membrane. These include, but are not limited to, the group I metabotropic glutamate receptors 1 and 5, 5-HT_{2A} receptors, muscarinic acetylcholine receptors m1 and m3, α1-adrenergic receptors, the $P2Y_1$ receptor, and several other types of P2Y and P2X receptors (James and Butt, 2002). Upon binding of the extracellular ligand to the receptor, phospholipase C is activated and hydrolyzes phosphatidylinositol bisphosphate into IP_3 and diacylglycerol; the former diffuses to the IP_3R on the ER, and the latter activates protein kinase C (PKC). There are three mammalian subtypes of the IP_3R (1, 2, and 3) with an overall sequence homology of 60 to 80%; however, the ligand binding domain, the Ca^{2+}-sensor domain, and the pore domains are highly conserved, and greater variability exists in the regulatory domains (Bezprozvanny, 2005; Foskett et al., 2007). This high sequence homology within binding and channel-forming domains is consistent with the experimental data demonstrating similar IP_3-binding, Ca^{2+}-gating, and ion conduction properties among the three IP_3R subtypes, with more salient differences in their modulation. For example, with Ba^{2+} (50 mM) as the charge carrier, the single-channel conductance for all subtypes is approximately 80 pS with a unitary current of ~1.9 pA. Affinity for IP_3 does seem to have subtle differences: IP_3R2 (0.10 μM) > IP_3R1 (0.27 μM) > IP_3R3 (0.40 μM) (Bezprozvanny, 2005; Tu et al., 2005). However, it should be noted that for most studies measuring unitary conductance properties (for IP_3R and RyR), artificial membranes with nonphysiological ion concentrations were often used; therefore, properties in native cell membranes may be different.

IP_3 is not the only regulator of IP_3R function; Ca^{2+} itself is an allosteric modulator of the IP_3R and plays a critical role in shaping the IP_3R-evoked Ca^{2+} response. In general, this regulation follows a biphasic bell-shaped curve for all subtypes, such that low Ca^{2+} concentrations (<300 nM) activate the channel and increase its

open probability, whereas high Ca^{2+} concentrations inhibit channel opening (Thrower et al., 2001; Foskett et al., 2007). This positive and negative feedback cycle is well suited for generating Ca^{2+} oscillations or waves. The shapes of the biphasic curves are generally similar among the three IP_3R subtypes, but minor differences may confer important functional differences. For example, the Ca^{2+} activation of the IP_3R1 channels exhibits positive cooperativity, allowing for sharp and rapid increases in channel opening within a narrow $[Ca^{2+}]$. This dynamic would strongly support Ca^{2+}-induced Ca^{2+} release (CICR), a process by which local elevations of intracellular Ca^{2+} are amplified by Ca^{2+} release from ER Ca^{2+} stores. The open probability of the IP_3R3 channels increases over a broader range of Ca^{2+} concentrations, with a higher affinity for Ca^{2+}, resulting in channel activity that is sensitive to low $[IP_3]$ (Mak and Foskett, 1997; Boehning et al., 2001; Tu et al., 2005; Foskett et al., 2007).

Ca^{2+} cannot independently open the IP_3R in the absence of IP_3; rather, it enhances the open probability of the IP_3R. This coordinates a scenario in which Ca^{2+} released from one channel can facilitate release from the other, triggering a regenerative release of Ca^{2+} within or between classes of Ca^{2+} channels (Berridge, 1997). Because Ca^{2+} signals can be encoded in both temporal and spatial domains, the oscillatory nature of IP_3-evoked Ca^{2+} release can carry important functional significance. For example, Ca^{2+} oscillations of specific frequencies can activate gene transcription or other signal transduction pathways (Li et al., 1998; Carrasco et al., 2004). The spatial spread and amplitude, or amount, of Ca^{2+} release can trigger a variety of downstream Ca^{2+}-sensitive cascades depending upon relative binding affinities. In general, cytosolic Ca^{2+} diffusion from the IP_3R is rather limited, largely because of the strong Ca^{2+} buffering capacity in the cytosol, and creates a steep concentration gradient originating from the ER release site. At the mouth of the channel, the Ca^{2+} concentration can exceed >100 μM, whereas a few micrometers away, the concentration may be 1 μM, leaving a functional range of approximately 5 μM under normal conditions (Allbritton et al., 1992). However, under conditions of exaggerated ER Ca^{2+} release, such as with certain Alzheimer disease-causing mutations or Huntington disease, these signaling patterns may be altered (Tang et al., 2005; Goussakov et al., 2010; Zhang et al., 2010).

The IP_3R can operate as a homo- or heterotetramer, but the functional significance of the heteromeric forms is not well understood. Even further diversity among channel subtypes emerge with multiple alternative splice variants for each (Arredouani, 2004). The IP_3R is ubiquitously expressed; the three subtypes have overlapping patterns of expression, and many cells express more than one form. Neurons are an exception, in that most express only the IP_3R1 subtype.

2. Ryanodine Receptor. The second ER Ca^{2+} channel to be discussed is the RyR, a high-conductance relatively nonspecific cation channel ($\sim$100–150 pS for Ca^{2+}) in the SR/ER membrane. It is ubiquitously expressed in a large number of cells and supports a wide variety of Ca^{2+} signaling events. It is similar in general structure to the IP_3R, particularly in the channel pore regions, yet at $\sim$560 kDa, with numerous accessory proteins, the RyR is one of the largest channel complexes thus far identified (Mackrill, 2010). The mammalian genome includes three genes, located on different chromosomes, that encode the ryanodine receptor proteins RyR1, RyR2, and RyR3; these three RyRs exhibit approximately 70% sequence homology. Each isoform can be subject to post-translational and post-transcriptional regulation and can express numerous splice variants (Fill and Copello, 2002 for review). Despite the potential variability, individual channels function as a homotetramer.

The RyR1 is the most studied isoform to date and is predominant in skeletal muscle, where it functions in excitation-contraction coupling and muscle contraction. It has also been described in the Purkinje neurons of the cerebellum (Furuichi et al., 1994; Hertle and Yeckel, 2007). The RyR2 is heavily expressed in cardiac muscle and is also the predominant form found in the brain. The RyR3 follows more of a low level and widespread expression pattern and is found in striated, smooth, and cardiac muscle, as well as in T lymphocytes and in the brain—particularly regions involved in learning and memory (cortex and hippocampus) (Arredouani, 2004; Hertle and Yeckel, 2007).

The principal activator for all three RyR isoforms is Ca^{2+} itself, generating the classic form of CICR. Other compounds can facilitate or modulate RyR-evoked Ca^{2+} release, but the binding of Ca^{2+} is a fundamental requirement for channel activation. The three isoforms display differing sensitivities to cytosolic Ca^{2+} (RyR1 $>$ RyR2 $>$ RyR3) but have similar permeation properties characterized by large single-channel conductance values ($>$100 pS) (Fill and Copello, 2002). Like the IP_3R1, the RyR1 subtype has a biphasic, bell-shaped response curve with maximal release at $\sim$5 μM and complete inhibition occurring in the low millimolar range. The RyR2 and RyR3 isoforms require substantially higher Ca^{2+} concentrations ($>$10 mM) for inhibition, which is out of the physiological range for most cells (Fill and Copello, 2002). In addition, luminal Ca^{2+} levels are thought to regulate the sensitivity of the RyR such that high luminal Ca^{2+} levels increase its responsiveness to certain cytosolic agonists (Sitsapesan and Williams, 1997; Györke and Györke, 1998). The RyR can also be positively regulated by ATP and negatively by Mg^{2+}. As with the IP_3Rs, numerous signaling cascades can also impinge on RyR function, including the kinases cAMP-dependent protein kinase (PKA), PKC, cGMP-dependent protein kinase, and Ca^{2+}/calmodulin-dependent

protein kinase II. Particularly relevant for the discussion on Alzheimer disease below (section VII), the RyR activity is also thought to be modulated by presenilin (PS), an ER-localized protease that cleaves a variety of type I membrane proteins (Rybalchenko et al., 2008; Zhang et al., 2010).

3. Leak Channels. The presence of the ER leak channel is inferred from the passive release of ER Ca^{2+} upon blocking the counterbalancing SERCA pumps with compounds such as thapsigargin or cyclopiazonic acid (CPA). Although the leak channel has yet to be identified, several studies have proposed potential leak channel mechanisms. Flourakis et al. (2006) suggest that a passive Ca^{2+} leak translocon-channel mediates the thapsigargin- and EGTA-induced Ca^{2+} release and have shown that translocon-triggered Ca^{2+} leak activates the store-operated Ca^{2+} current. Pannexin 1, a newly discovered family of gap junction molecules, may also form Ca^{2+}-permeable leak channels in the ER membrane; however, this hypothesis requires further corroboration (Vanden Abeele et al., 2006). Two other potential Ca^{2+} leak channels that may assist in maintaining ER Ca^{2+} homeostasis are the translocon (Camello et al., 2002) and presenilin (Tu et al., 2006). Mutations in presenilin are linked to early-onset familial AD (FAD), and data suggest that the mutations impair an ER Ca^{2+} leak function of presenilin (Tu et al., 2006; Nelson et al., 2007), resulting in increased ER Ca^{2+} levels and increased vulnerability to degeneration (Guo et al., 1996, 1997, 1999).

B. Endoplasmic Reticulum Ca^{2+} Uptake and Store Refilling

1. Sarcoplasmic-Endoplasmic Reticulum Ca^{2+} ATPase Pumps. Cytosolic Ca^{2+} entry into the ER is mediated through the SERCA pump, a Ca^{2+} ATPase that transfers Ca^{2+} from the cytosol to the SR/ER lumen via ATP hydrolysis. In vertebrates, three distinct genes encode for the SERCA1, -2, and -3 proteins, and alternative splicing leads to a total of seven known isoforms (SERCA1a and -1b, SERCA2a and -2b, and SERCA3a, -3b, and -3c) (Andersen and Vilsen, 1998). SERCA1a is expressed exclusively in adult fast skeletal muscle fibers, whereas SERCA1b is expressed only in fetal muscle fibers. SERCA2a is expressed both in cardiac muscle and in the slow skeletal muscle fibers, whereas SERCA2b is ubiquitously expressed in nonmuscle tissues, particularly in the brain (Carafoli and Brini, 2000). SERCA3a, -3b, and -3c are variably expressed in various nonmuscle tissues but overlap with SERCA2b (Pacifico et al., 2003).

There are no significant functional differences observed between SERCA1a and -1b. However, SERCA1 pumps Ca^{2+} twice as fast as SERCA2a, although their Ca^{2+} affinities seem similar (Lytton et al., 1992; Sumbilla et al., 1999). The Ca^{2+} affinity of SERCA2b (K_m, $\sim$0.17 μM) is 2-fold higher than that of SERCA2a. Functional studies of SERCA3 indicate it has a lower Ca^{2+} affinity (K_m, $\sim$2 μM), a high optimal pH (7.2–7.4 versus 6.8–7.0) and 10-fold higher sensitivity to inhibition. The affinity for ATP is similar for all SERCA isoforms (0.02–0.05 μM). The particular biochemical characteristics and the restricted tissue distribution of SERCA3 might suggest a role in specialized signaling functions. In terms of complementary roles within cells, ablation studies indicate that removal of one SERCA isoform often does not impair primary cellular function, suggesting distinct roles of different SERCA pumps for Ca^{2+} homeostasis (Dode et al., 1992; Arredouani, 2004).

2. Store-Operated Calcium Entry. Beyond SERCA pumps, there is much interest in the complex detection system by which the ER signals the Ca^{2+} store-refilling processes, and, until recently, this mechanism had eluded scientists for more than 20 years. In the past, ER Ca^{2+} depletion had been observed in many cell types to result in a Ca^{2+} current through the plasma membrane, which served to refill the ER stores (Cahalan, 2009), but the mystery lay in determining how an intracellular organelle signaled the plasma membrane to trigger Ca^{2+} entry and funnel it specifically to the ER. After extensive RNA interference screening, as well as cellular, molecular, and physiological analysis, two critical protein families were determined to be necessary and sufficient for the function of store-operated Ca^{2+} entry: STIM (stromal interacting molecule) and Orai. The discovery of STIM, and STIM1 function in particular, transformed the highly debated store-operated hypothesis into a validated mechanism. STIM1 is a type I membrane protein localized in the ER and, with an unpaired Ca^{2+}-binding EF hand, serves as a luminal Ca^{2+} sensor. Orai is a plasma membrane protein with four transmembrane domains and functions as the highly selective Ca^{2+} channel that is gated through interactions with STIM (Hewavitharana et al., 2007). An in-depth review of the molecular basis of store-operated Ca^{2+} entry (SOCE) was recently published (Smyth et al., 2010). A summary description of SOCE is as follows. When ER Ca^{2+} stores are filled sufficiently, Ca^{2+} binding to EF hands keeps STIM distributed in the ER membrane and distanced from the plasma membrane. However, upon depletion of ER stores and disassociation of Ca^{2+} from the EF hands, Stim1 will reassemble within the ER membrane and oligomerize at sites immediately adjacent to the plasma membrane. In this conformation, STIM1 binds with SOCE channels of the Orai family in the plasma membrane. The Stim1-Orai complex stimulates store-activated Ca^{2+} influx, thereby replenishing ER stores with Ca^{2+} funneled from the extracellular space directly into the ER (Lewis, 2007; Prakriya, 2009). It is noteworthy that the proximal step of STIM1 oligomerization is the key triggering event by which Ca^{2+} store depletion controls SOCE (Luik et al., 2008; Lee et al., 2010).

Additional mechanisms involved in SOCE have been suggested. These include post-translational modifications of STIM1 levels, cellular localization, and/or interaction with Orai proteins. Phosphorylation of STIM1 on Ser486 and Ser668 was found to inhibit the movement of STIM1 to plasma membrane foci and thereby to inhibit SOCE (Smyth et al., 2009). Studies of cultured hippocampal neurons suggest that STIM1 is ubiquitinated and that proteasome inhibition increases the amount of plasma membrane-associated STIM1 when ER stores are depleted (Keil et al., 2010). Moreover, overexpression of the E3 ubiquitin ligase PLOSH (plenty of SH3s) reduces STIM1 surface levels, suggesting that ubiquitination may play a role in SOCE (Keil et al., 2010), a process potentially involved in modification of SOCE under conditions of proteotoxic stress. Finally, although Orai proteins are the most established SOCE channels, STIM1 has also been reported to activate transient receptor potential C1 channels in ER-plasma membrane microdomains (Pani et al., 2009).

C. Regulation of Ca^{2+} within the Endoplasmic Reticulum

Much of the Ca^{2+} in the ER is in a free, unbuffered state; although the total store content may exceed 1 mM in some cells, estimates of free [Ca^{2+}] range from 100 to 800 μM (Bygrave and Benedetti, 1996; Alvarez and Montero, 2002; Solovyova and Verkhratsky, 2002). This allows for rapid diffusion of Ca^{2+} throughout the lumen (faster than through the cytosol) and, therefore, throughout most compartments of the cell (Park et al., 2008). Still, high-capacity Ca^{2+} buffers play an important role in maintaining ER homeostasis. Calreticulin is the most abundant buffering protein and contains 20 to 50 low-affinity (K_d, ~1 mM) Ca^{2+} binding sites. This particular buffer is unique in that it also serves as a chaperone protein and regulator/[Ca^{2+}] sensor for SERCA function by binding to and activating SERCA pump activity once Ca^{2+} levels fall below threshold levels (Verkhratsky, 2005). Calsequestrin, which is predominant in skeletal muscle cells, is another high-capacity and low-affinity Ca^{2+} buffer with binding properties similar to those of calreticulin. In addition, glucose-regulated protein (GRP) 94, GRP78 (also known as BiP), and the CREC family of proteins, which are multiple EF-hand proteins including reticulocalbin, 55-kDa ER Ca^{2+}-binding protein, reticulocalbin-3, 45-kDa Ca^{2+}-binding protein, and calumenin, can also be found as low-affinity Ca^{2+} buffering proteins in the ER (Verkhratsky, 2005).

The Ca^{2+} concentration within the ER lumen also regulates the opening of both IP_3 receptors and RyR (Burdakov et al., 2005). Early studies in permeabilized hepatocytes provided evidence that an increase of intraluminal Ca^{2+} levels increased the sensitivity of IP_3 receptors to IP_3 (Nunn and Taylor, 1992). Although subsequent studies confirmed a positive effect of intraluminal Ca^{2+} on IP_3 receptors (Parys et al., 1993), the molecular mechanism by which Ca^{2+} affects IP_3 receptor channel activity is unknown. In contrast to IP_3 receptors, the regulation of RyR by intraluminal Ca^{2+} is well established and understood, in part. The open probability of RyR, and their sensitivity to caffeine and cytosolic Ca^{2+}, are directly affected by intraluminal Ca^{2+} levels. It has been shown in studies of skeletal muscle and cardiac cells that the ER Ca^{2+} release is increased by as much as 20-fold by a 10-fold increase in the intraluminal ER Ca^{2+} concentration (Donoso et al., 1995).

Recordings of single RyR channels of native RyRs in SR vesicles in the presence of Mg-ATP using Cs^+ as the charge carrier showed that raising luminal Ca^{2+} concentration from 20 μM to 5 mM increased the open channel probability (Györke et al., 2004). By performing the recordings in the presence or absence of calsequestrin, triadin 1 and junctin provided evidence that these three proteins confer RyR luminal Ca^{2+} sensitivity. These data suggest that calsequestrin serves as a luminal Ca^{2+} sensor that inhibits the channel at low luminal Ca^{2+} levels, whereas triadin 1 and/or junctin may be required to mediate interactions of calsequestrin with RyR. In cultured pheochromocytoma cells and dorsal root ganglion neurons, an increase in ER Ca^{2+} resulted in increased sensitivity of Ca^{2+} release to caffeine (Shmigol et al., 1996; Koizumi et al., 1999).

Whereas changes in the cytosolic Ca^{2+} concentration within a physiological range do not have a major effect on SERCA activity, ER luminal Ca^{2+} plays a major role in regulating SERCA activity. In studies in which ER Ca^{2+} levels were directly compared with ER Ca^{2+} uptake velocity, a reduction of ER Ca^{2+} levels was found to result in an increased velocity of SERCA-mediated Ca^{2+} uptake (Mogami et al., 1998). The physiological importance of ER Ca^{2+} store depletion in activation of SERCA has been established in studies of cultured pancreatic acinar cells and neurons. Induced ER Ca^{2+} depletion resulted in a large 5- to 8-fold increase in the velocity of ER Ca^{2+} uptake (Mogami et al., 1998; Solovyova et al., 2002b). In the latter study, an additional experiment in which the cytosolic Ca^{2+} concentration was held constant demonstrated that the relationship between the ER Ca^{2+} concentration and the ER Ca^{2+} uptake velocity was independent of a change of cytosol Ca^{2+} levels.

D. Protein Translation and Quality Control

The ER is a protein synthesis factory and sensor of cellular stress (Naidoo, 2009). All integral membrane proteins and all secreted proteins are folded and post-translationally modified (primarily glycosylation) in the ER. Because many different proteins are being synthesized, folded, and glycosylated simultaneously, the concentration of proteins in the ER is much greater than elsewhere in the cell, possibly as high as 100 mg/ml (Stevens and Argon, 1999). To prevent the aggregation of newly generated proteins, the ER contains an array of

protein chaperones, foldases, and carbohydrate-processing enzymes. The folding of proteins begins during the translation process as the protein traverses the ER membrane through the translocon protein complex. Post-translational folding occurs within the ER lumen and involves the participation of protein chaperones and protein folding sensors that include GRP78 (also known as BiP), GRP94, calnexin, calreticulin, and protein sulfide isomerase. GRP78, a member of the 70-kDa heat-shock protein family, interacts with newly synthesized proteins as they pass through the translocon. GRP78 interacts with hydrophobic domains of proteins by an ATP-dependent process and thereby aids proper folding of the proteins. This critical chaperone function of GRP78 is therefore vulnerable to cellular energy depletion, which therefore results in the abnormal accumulation of unfolded proteins in the ER. GRP78 is a master regulator of the unfolded protein response (UPR), which is described later in this section.

Three major ER protein chaperones are Ca^{2+}-binding proteins. GRP94 is an abundant ER protein chaperone of the 90-kDa heat-shock protein family that binds up to 15 Ca^{2+} ions. GRP94 binds to proteins after they have been released from GRP78 but before they are completely assembled, in contrast to GRP78, which binds most if not all nascent proteins, GRP94 interacts with a limited number of proteins. Calreticulin and calnexin are Ca^{2+}-binding lectin proteins that play a major role in the quality control of glycated proteins in the ER; calreticulin is located in the ER lumen, and calnexin is a transmembrane protein. After N-linked oligosaccharides are added to proteins in the ER, enzymes trim the carbohydrate chains in a process that is tightly controlled by calreticulin and calnexin. In addition to its chaperone function, calreticulin plays important roles in the regulation of intracellular Ca^{2+} homoeostasis and ER Ca^{2+} pool size (Michalak et al., 2009). As described above, calreticulin negatively regulates SOCE. Calreticulin deficiency results in impaired agonist-induced Ca^{2+} release, reduced ER Ca^{2+} store capacity, and decreased concentration of free Ca^{2+} in the ER lumen. Calnexin may regulate ER Ca^{2+} homoeostasis by interacting with SERCA proteins. When calnexin was coexpressed with SERCA2b in frog oocytes, intracellular Ca^{2+} oscillations were inhibited (Roderick et al., 2000). C-terminal amino acids of calnexin are essential for its interaction with SERCA2b, and IP_3-mediated Ca^{2+} release results in dephosphorylation of Ser562, which then reduces the interaction of calnexin and SERCA2b.

E. Endoplasmic Reticulum Stress, Ca^{2+}, and Cell Death

The UPR is a programmed sequence of events that in the first instance protects cells against death under conditions of metabolic, ionic, and protopathic stress. When too many proteins are not being properly folded and post-translationally modified in the ER, GRP78 orchestrates multiple processes that result in the halting of translation of most proteins other than those necessary for maintenance of cell viability. The UPR can be triggered by glucose/energy deprivation, alterations in Ca^{2+} homeostasis, oxidative stress, and ischemia. Three key events of the UPR are as follows: a rapid increase in the expression of GRP78; activation of protein kinase RNA-like endoplasmic reticulum kinase, which inhibits protein translation by phosphorylating the eukaryotic initiation factor-2α; and proteasomal degradation of misfolded proteins via ER-associated degradation. In addition, the transcription factor NF-κB may be activated by ER stress, resulting in the up-regulation of proteins that promote cell survival, including Mn-SOD and Bcl-2 (Mattson and Meffert, 2006). Together, these events protect excitable cells by reducing ER and mitochondrial stress.

Cell death can be and often is triggered by ER Ca^{2+} release in both physiological and pathological settings (for review, see Pinton et al., 2008; Camandola and Mattson, 2011). Blockade of SERCAs with thapsigargin is sufficient to initiate the death of many types of excitable cells, including neurons (Guo et al., 1997), cardiac myocytes (Nickson et al., 2007), and pancreatic β cells (Luciani et al., 2009). In pancreatic β cells, thapsigargin induces apoptosis that involves phosphorylation of protein kinase RNA-like endoplasmic reticulum kinase and eukaryotic initiation factor-2α and activation of the classic mitochondria-mediated caspase 3-dependent apoptosis pathway (Luciani et al., 2009). Thapsigargin-induced apoptosis was mediated by Ca^{2+} release through IP_3 receptor and RyR channels. A key event in mitochondria-mediated apoptosis in excitable cells (and nonexcitable cells as well) is the opening of membrane permeability transition pores and the release of cytochrome *c* (for review, see Mattson and Kroemer, 2003). Proteins of the Bcl-2 family control the permeability of the mitochondrial membrane; some members of this protein family stabilize the mitochondrial membrane [e.g., Bcl-2 and B-cell lymphoma-extra large (Bcl-xL)], whereas others induce opening of the permeability transition pores [Bcl-2–associated X protein (Bax), Bcl-2-associated death promoter (Bad), and p53–up-regulated modulator of apoptosis (PUMA)]. For example, PUMA is a pro-apoptotic Bcl-2 family member that is rapidly up-regulated in cardiac myocytes in response to ER stress induced by either thapsigargin or tunicamycin (Nickson et al., 2007). Depletion of PUMA from cardiac myocytes using molecular genetic methods rendered the cells resistant to being killed by ER stress.

Increasing evidence suggests that Bcl-2 proteins also interact with the ER membrane, where they may modify Ca^{2+} release and control cross-talk between the ER and mitochondria (Lam et al., 1994; Rodriguez et al., 2011). It is noteworthy that a Ca^{2+}-mediated mitochondria–ER positive feedback pathway has been described that likely plays a role in hastening cell death once the apo-

ptotic process is triggered. In the latter mechanism, the cytochrome *c* released from mitochondria binds to IP_3 receptors and thereby promotes Ca^{2+} release, which, in turn, acts on mitochondria to enhance opening of permeability transition pores (Boehning et al., 2003).

III. Pharmacology of Endoplasmic Reticulum Ca^{2+}-Handling Systems

Agents that selectively activate or inhibit Ca^{2+} release from the ER range from the most widely used "drug" to exotic chemicals isolated from marine organisms. Caffeine (Fig. 1) is a chemical present in relatively high amounts in coffee and tea and is an additive to many soft drinks. It increases alertness and can improve performance in mental and physical tasks but can also have undesirable side effects, including dehydration, increased heart rate, and anxiety (Lara, 2010). Caffeine activates ryanodine receptors resulting in Ca^{2+} release from the ER, which is a mechanism by which caffeine affects the excitability of neurons, cardiac myocytes, and skeletal muscle cells (Butanda-Ochoa et al., 2006). In addition to activating RyR, caffeine is an effective inhibitor of IP_3 receptors (Toescu et al., 1992), an action that increases its ability to promote the selective release of Ca^{2+} from ryanodine-sensitive stores. Several endogenous bioactive molecules with structures similar to that of caffeine have been shown to increase the opening of RyR, including adenosine, inosine, xanthine, and uric acid (Butanda-Ochoa et al., 2006).

Agents other than caffeine that activate ryanodine receptors have been reported to exhibit therapeutic benefits in animal models of several different disorders. For example, in a rodent model of stroke in which there is unilateral damage to the sensorimotor cortex, treatment with inosine improved functional recovery by a mechanism that involved induction of genes encoding proteins involved in axon growth (Zai et al., 2009). The xanthine derivative propentofylline was reported to be effective in preserving cognitive function in patients with Alzheimer disease (Kittner et al., 1997), although whether its efficacy is the result of actions on ryanodine receptors, phosphodiesterases, or another mechanism is unknown. It is noteworthy that recent findings suggest that individuals with relatively higher plasma uric acid levels are at reduced risk of developing Alzheimer disease (Irizarry et al., 2009), and uric acid protected cultured neurons from being killed by amyloid β-peptide (Guo et al., 1999). Uric acid analogs with increased solubility were reported to protect the brain against ischemic injury (Haberman et al., 2007) and to accelerate cutaneous wound healing (Chigurupati et al., 2010). However, the relative contributions of the inherent antioxidant activity of uric acid, versus its potential actions on ryanodine receptors, to the beneficial effects of uric acid in these experimental models remains to be determined.

Although activation of RyR can improve the functionality of some cell types, including neurons, there are several diseases in which blocking RyR-mediated Ca^{2+} release is desirable. Malignant hyperthermia is a life-threatening inherited disorder most often caused by mutations in the gene encoding RyR1. Patients may exhibit no abnormalities until they are subjected to volatile anesthetics (halothane, isoflurane, and others) for surgery; the anesthetic triggers a rapid excessive opening of RyR1, resulting in muscle contraction and increased body temperature. Treatment of patients with the RyR

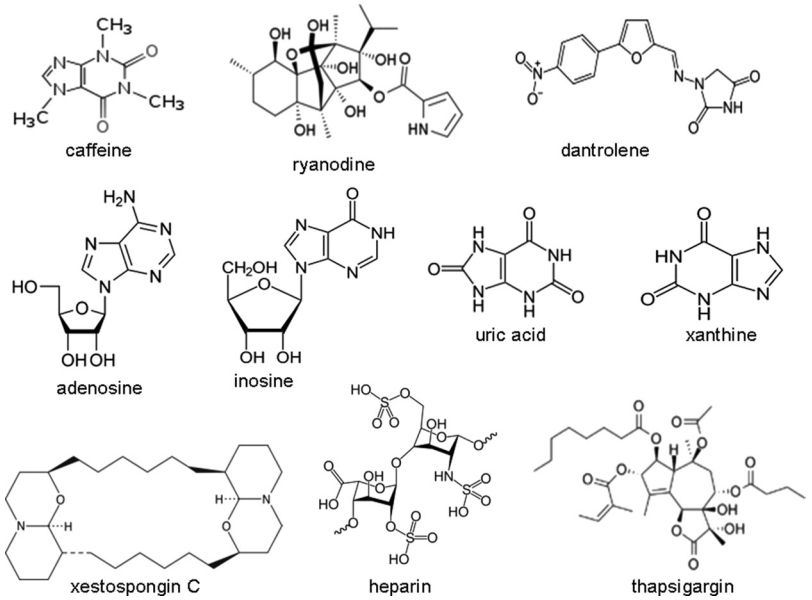

FIG. 1. Structures of agents that activate or inhibit ryanodine receptors, IP_3 receptors, or the ER Ca^{2+}-ATPase. Caffeine activates ryanodine receptors, ryanodine activates (low concentrations) or inhibits (high concentrations) ryanodine receptors, and dantrolene inhibits ryanodine receptors. Adenosine, inosine, uric acid, and xanthine have all been reported to modulate ryanodine-sensitive ER Ca^{2+} stores. Xestospongin C and low-molecular-weight heparin inhibit IP_3 receptor-mediated Ca^{2+} release. Thapsigargin selectively inhibits the ER Ca^{2+}-ATPase.

inhibitor dantrolene (Fig. 1) can greatly reduce mortality and morbidity (Rosenberg et al., 2007). Another type of disorder in which dantrolene is often used is spasticity, in which muscles contract uncontrollably (Young, 1987). Ischemia-reperfusion damage to the heart (myocardial infarction) and brain (stroke) is a common cause of morbidity and mortality. The ischemic damage involves cellular Ca^{2+} overload, and dantrolene treatment can reduce cellular damage and cell death and can improve functional outcome in animal models of myocardial infarction, stroke, and ischemia (Wei and Perry, 1996; Nakayama et al., 2002; Muehlschlegel and Sims, 2009; Boys et al., 2010). Preclinical studies also showed that dantrolene can protect neurons against damage caused by amyloid β-peptide in an experimental in vitro model relevant to Alzheimer disease (Guo et al., 1997). However, in vivo studies indicate that long-term dantrolene feeding resulted in increased amyloid load, loss of synaptic markers, and increased neuronal atrophy in an aged AD mouse model (Zhang et al., 2010).

As mentioned above, there are three types of IP_3Rs that function as Ca^{2+} release channels in the ER. IP_3Rs are phosphorylated by several major kinases, including PKA, cGMP-dependent protein kinase, and Ca^{2+}/calmodulin-dependent protein kinase (CaMK), that can modulate its sensitivity to Ca^{2+} and IP_3. IP_3R proteins have been shown to interact with several proteins involved in cellular signal transduction, including calmodulin, Homer, huntingtin-associated protein-1A, receptor of activated protein kinase C 1, protein phosphatase-2A, and ankyrin (Mikoshiba, 2007). It is noteworthy that IP_3R in the ER membrane may also interact with the plasma membrane Na^+/K^+-ATPase to regulate cellular excitability and Ca^{2+} oscillations (Miyakawa-Naito et al., 2003). Although numerous cell surface receptors are coupled to the GTP-binding protein G_{q11}, phospholipase C activation, and generation of IP_3 (Putney, 1987), surprisingly few low-molecular-weight agonists or antagonists of IP_3R have been identified. Because IP_3 is hydrophilic and so does not readily cross membranes, membrane-permeant analogs of IP_3 have been developed and used in cell culture systems to elucidate the effects of IP_3 generation (in the absence of diacylglycerol production) on cell behaviors. For example, treatment of cultured astrocytes with a membrane-permeant analog of IP_3 protected them from being damaged by oxidative stress, suggesting a role for ER Ca^{2+} release in the upregulation of cytoprotective pathways (Wu et al., 2007).

One naturally occurring chemical inhibitor of IP_3R is xestospongin C (Fig. 1), which was first isolated from Pacific basin sponges and has been shown to have vasodilatory properties (Nakagawa and Endo, 1984). More than a decade later, xestospongin C was shown to be a selective blocker of IP_3R (Gafni et al., 1997). By inhibiting IP_3-mediated ER Ca^{2+} release, xestospongin C has a range of biological activities on various cell types, including suppressing antigen-induced degranulation of mast cells (Oka et al., 2002), blocking IP_3R-mediated hypoxic preconditioning in hippocampal neurons (Bickler et al., 2009), and protecting neurons against the cell death-promoting action of a mutant form of presenilin-1 that causes early-onset inherited Alzheimer disease (Mattson et al., 2000). Xestospongin C also blocked the adverse effect of a presenilin-1 mutation in rendering neurons vulnerable to being damaged by the volatile anesthetic isoflurane (Liang et al., 2008). However, additional actions of xestospongin C on ER Ca^{2+} handling have been reported, including inhibition of SERCA pumps and depletion of Ca^{2+} stores without inhibiting IP_3-induced Ca^{2+} release in sensory neurons (Solovyova et al., 2002a).

Another antagonist at IP_3R that has been widely used to elucidate the involvement of Ca^{2+} release from IP_3-sensitive ER stores in experimental models is 2-aminoethoxydiphenyl borate (2-APB). For example, 2-APB was used to establish a role for IP_3-induced Ca^{2+} release in the generation of the entire physiological response of photoreceptors to light in the horseshoe crab (Fein, 2003); to show that IP_3R are essential for the propagation of Ca^{2+} oscillations in response to depolarization in sensory neurons (Zeng et al., 2008); and to demonstrate a pivotal role for IP_3R-mediated Ca^{2+} release in the vasoconstriction of small arteries (Snetkov et al., 2003). However, although 2-APB has been widely used to evaluate the involvement of IP_3 receptors in the generation of Ca^{2+} signals, it is not a very specific agent. Indeed, 2-APB has been shown to exert a greater inhibitory effect on SOCE than on Ca^{2+} release (Bootman et al., 2002). In addition to xestospongins and 2-APB, low-molecular-weight heparin has also been demonstrated to be a competitive antagonist of the IP_3 receptor (Wu et al., 1994), although its use in this capacity has been mostly limited to cell culture and in vitro studies.

Although the bulk of the data using IP_3R antagonists has come from studies of cultured cells, a few studies have demonstrated the ability of such agents to modify physiological and pathological processes in vivo. For example, treatment of chicks with xestospongin C impairs the formation of long-term memory (Baker et al., 2008), and treatment of worms (*Caenorhabditis elegans*) with xestospongin C phenocopies IP_3R mutant worms that exhibit defects in the migration of epithelial cells during development (Thomas-Virnig et al., 2004). Another study reported that intracerebroventricular administration of low-molecular-weight heparin reversed tolerance to morphine in mice (Smith et al., 1999), suggesting a role for IP_3R-mediated Ca^{2+} release in morphine tolerance. Additional studies also suggest that heparin may offer neuroprotection in Alzheimer disease, Huntington disease, and stroke (Mary et al., 2001; Bergamaschini et al., 2004; Tang et al., 2005). In a rat model of ischemia-reperfusion injury to the liver, administration of 2-APB protected liver cells from being damaged, and this was associated with reduced accumulation of Ca^{2+} in mito-

chondria of the liver cells (Nicoud et al., 2007). In another study, 2-APB treatment protected striatal neurons against neurodegeneration caused by mutant huntingtin protein in a mouse model of Huntington disease (Tang et al., 2005).

Thapsigargin (a guaianolide compound of plant origin) and CPA are highly selective inhibitors of the SERCA pump, without effects on the plasma membrane Ca^{2+} ATPase (Fig. 1). As a result, Ca^{2+} is released from the ER in amounts that depend upon the concentration of thapsigargin and CPA; high concentrations of these agents are often used to completely deplete the ER of Ca^{2+} (Darby et al., 1993). Thapsigargin is an irreversible inhibitor of SERCAs with a K_d of 20 nM. Although inhibition of SERCA is the most prominent mechanism by which thapsigargin affects cellular Ca^{2+} homeostasis, it can also inhibit voltage-gated Ca^{2+} channels (VGCCs) and Na^+ channels. Thapsigargin and CPA have been widely used to elucidate the roles of ER Ca^{2+} stores in a range of physiological processes. Indeed, more than 7000 publications in which thapsigargin was employed are listed on PubMed, and approximately 600 studies that used CPA. Treatment of cultured cells with thapsigargin or CPA in the absence of extracellular Ca^{2+} results in a transient elevation of the cytosolic Ca^{2+} concentration as the ER Ca^{2+} pool is depleted. In the presence of extracellular Ca^{2+}, treatment of cells with thapsigargin or CPA induces a larger and sustained elevation of cytosolic Ca^{2+} levels as the result of Ca^{2+} influx through plasma membrane channels (Fig. 2A). The influence of various genetic and environmental factors on the amount of Ca^{2+} stored in the ER can be determined by comparing the amounts of Ca^{2+} released from the ER in response to thapsigargin or CPA (in the absence of extracellular Ca^{2+}) in cells expressing different genes of interest or maintained under different environmental conditions. For example, thapsigargin was used to establish that mutant forms of presenilin-1 that cause Alzheimer disease result in an increased pool of ER Ca^{2+} (Guo et al., 1996) (Fig. 2B).

From the perspective of developing therapeutic agents that target ER Ca^{2+}-handling proteins, several major hurdles must be crossed. Small-molecular-weight agents that selectively inhibit or activate different ryanodine or IP_3 receptor subtypes should be developed. This might be accomplished by using high-throughput assays to screen libraries and/or by synthesizing analogs of existing ER Ca^{2+}-modulating agents (IP_3, ryanodine, caffeine, dantrolene, thapsigargin, xestospongins, etc.). A useful small molecule should be lipophilic so that it can pass through the plasma membrane and reach its molecular target in the ER; this property may also permit the agent to enter the central nervous system. Alternatively, known agonists or antagonists of IP_3R, ryanodine receptors, or SERCAs might be coupled to carrier molecules. One clever approach toward targeting ER Ca^{2+}-modulating drugs to specific cell types has been reported in which thapsigargin is coupled to a targeting peptide such that this "prodrug" is inactive and is then activated by the prostate cancer-specific protease prostate-specific antigen. The prostate-specific antigen-activated thapsigargin prodrug has been shown to be selectively toxic to prostate cancer cells in vivo (Denmeade and Isaacs, 2005).

IV. Endoplasmic Reticulum Ca^{2+} within Specific Cells and Systems

A. Cardiac Cells

The heart beats continuously throughout life, generating the rhythmic pumping force that propels the blood

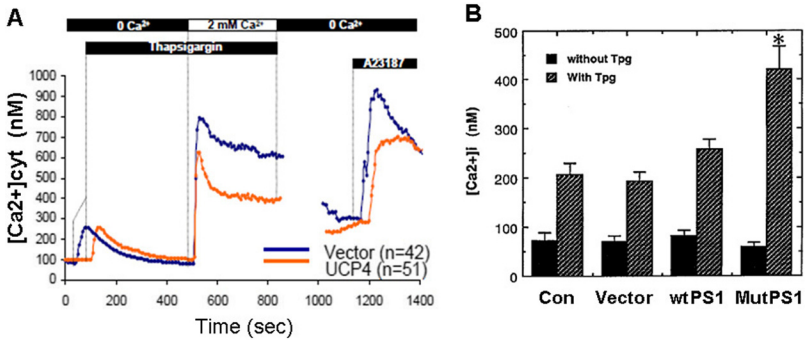

FIG. 2. Examples of pharmacological and genetic manipulations of ER Ca^{2+} dynamics. A, cultured neural cells were transfected with an empty control vector or with an expression vector containing the cDNA encoding the mitochondrial uncoupling protein 4 (UCP4). Intracellular Ca^{2+} concentrations were then monitored in the cells by ratiometric imaging of the Ca^{2+} indicator dye fura-2 at baseline and during exposures to the indicated experimental treatments. 0 Ca^{2+}, culture medium lacking Ca^{2+}; 2 mM Ca^{2+}, culture medium containing 2 mM Ca^{2+}; thapsigargin (1 μM); and A23187, the Ca^{2+} ionophore A23187 (calcimycin; 10 μM). Note that Ca^{2+}-induced Ca^{2+} influx (in response to addition of extracellular Ca^{2+} in the presence of thapsigargin is attenuated in cells overexpressing UCP4. See Chan et al. (2006) for additional information. B, neural cells expressing a presenilin-1 mutation that causes Alzheimer disease exhibit an elevated ER pool of Ca^{2+}. The indicated clones of PC12 cells were exposed to vehicle or 1 mM thapsigargin and the intracellular Ca^{2+} concentration was measured 30 min later. Con, untransfected control cells; vector, cells transfected with empty vector; wtPS1, cells overexpressing wild type presenilin-1; mutPS1, cells overexpressing the L286V presenilin-1 missense mutation. Note that thapsigargin-induced elevation of the intracellular Ca^{2+} level was greater in cells expressing mutant presenilin-1 compared with each of the other three cell clones. [Modified from Guo Q, Furukawa K, Sopher BL, Pham DG, Xie J, Robinson N, Martin GM, and Mattson MP (1996) Alzheimer's PS-1 mutation perturbs calcium homeostasis and sensitizes PC12 cells to death induced by amyloid beta-peptide. *Neuroreport* **8:**379–383. Copyright © 1996 Lippincott Williams & Wilkins. Used with permission.]

through the entire circulatory system to provide every cell in the body with nutrients and various signals that allow them to respond adaptively to environmental demands. The role of ER Ca^{2+} handling in the regulation of heart rate, myocardial contraction, blood pressure, and blood flow has been the subject of considerable investigation. In this section, we review some of the findings concerning characteristics of ER Ca^{2+} dynamics in several different cell types involved in the processes described in the preceding sentence with a focus on sinoatrial node (pacemaker) cells and ventricular myocytes. Evidence that perturbed ER Ca^{2+} regulation contributes to the pathogenesis of cardiovascular diseases will then be described.

Pacemaker cells in the sinoatrial (SA) node exhibit oscillations of cytosolic Ca^{2+} levels that seem to underlie the rhythmicity of the resting heart beat; these Ca^{2+} oscillations are controlled by both plasma membrane ion channels and Ca^{2+} release from the ER (Mangoni and Nargeot, 2008). The exact details of how pacemaker cells generate, maintain, and modulate the Ca^{2+} oscillations are not fully understood. However, multiple ER Ca^{2+}-handling proteins are central to this process. Early studies demonstrated the requirement of Ca^{2+} release through ryanodine receptors in the regulation of SA node automaticity (Hata et al., 1996). In addition, it is well established that the RyR agonist caffeine can increase heart rate and that this occurs, at least in part, by caffeine's agonistic action on the RyR (Dietrich et al., 1976). Other studies have suggested that the Ca^{2+}-pumping kinetics of the SERCA regulates the timing of ER Ca^{2+} release in SA node cells (Vinogradova et al., 2010). With regard to plasma membrane Ca^{2+}-handling systems, it has been suggested that the Na^+/Ca^{2+} exchanger is a critical component of the intrinsic SA node cellular clock (Bogdanov et al., 2001). Changing the tachometer setting of the SA node clock is controlled largely by activity of sympathetic nerves that innervate these cells; the norepinephrine released from sympathetic nerve terminals activates β-adrenergic receptors resulting in an increase in beats per minute of the heart.

The development of the cardiovascular system is critically dependent on ER Ca^{2+} release. Cardiomyocytes differentiated from embryonic stem cells lacking RyR2 exhibit impaired development of spontaneous rhythmic contractions, which is associated with an absence of ER Ca^{2+} sparks (Yang et al., 2002). Mice lacking both IP_3R1 and IP_3R2 (but not mice lacking either IP_3R alone) die during embryonic development at 11.5 days of gestation; the embryos exhibit severe defects of the ventricular myocardium and the atrioventricular canal of the heart (Uchida et al., 2010). The plasma and ER membranes that house proteins involved in excitation-contraction coupling are closely apposed to each other in cardiac myocytes in structures called *t*-tubules. In addition to voltage-dependent Ca^{2+} channels in the plasma membrane and RyR and IP3R in the ER, *t*-tubules are enriched in ion-motive ATPases and Na^+/Ca^{2+} exchange proteins, presumably to allow rapid restoration of cytosolic Ca^{2+} levels after excitation-induced Ca^{2+} influx and release (Orchard and Brette, 2008). In ventricular myocytes, Ca^{2+} is released from ER through ryanodine receptor channels (RyR2) in a process controlled by several RyR2-associated proteins, including FKBP12.6, triadin, junctin, and calsequestrin. Mice lacking triadin exhibit a large reduction in the amount of junctional ER, resulting in impaired excitation-contraction coupling, whereas calsequestrin deficiency does not have a major effect on excitation-contraction coupling but does promote arrhythmias (Knollmann, 2009). Ca^{2+} release through IP_3R2 channels is induced by activation of endothelin-1 receptors in atrial myocytes; in this way, endothelin-1 enhances action potential-induced Ca^{2+} transients and improves the efficiency of excitation-contraction coupling (Li et al., 2005). Cardiomyocyte-specific knockout of the *SERCA2* gene results in only moderate heart dysfunction despite a large reduction in the ER Ca^{2+} content in the myocytes (Andersson et al., 2009). It is noteworthy that the cardiac myocytes lacking SERCA2 adapted to the ER Ca^{2+} deficit by increasing Ca^{2+} influx through plasma membrane L-type channels and the Na^+/Ca^{2+} exchanger and by enhancing the responsiveness of myofilaments to Ca^{2+}.

The importance of perturbed ER Ca^{2+} regulation in cardiac function is highlighted by the fact that mutations in RyR2 cause inherited forms of several diseases characterized by cardiac arrhythmias and susceptibility to sudden death. One such inherited arrhythmogenic syndrome called catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by hypersensitivity of the heart rhythm to exercise or emotional stress (Liu and Priori, 2008; Betzenhauser and Marks, 2010; Thomas et al., 2010). CPVT is believed to affect approximately 1 in 10,000 individuals. More than 20 mutations in RyR2 have been linked to CPVT, and the mechanism(s) by which these mutations result in disease have been elucidated; in general, the mutations render the RyR2 channel hypersensitive to phosphorylation by PKA, thereby increasing Ca^{2+} release and elevating cytosolic Ca^{2+} levels (Betzenhauser and Marks, 2010). A similar pathogenic mechanism has been proposed for sudden infant death syndrome (Tester et al., 2007).

At least three different molecular events have been proposed to underlie perturbed RyR2 in CPVT. First, studies of CPVT-causing RyR2 mutations were shown to reduce the binding affinity of FKBP12.6 to RyR2, and this effect of the mutations was exacerbated after RyR2 phosphorylation by PKA (Wehrens et al., 2003). However, other studies have revealed that RyR2 mutations do not affect the interaction between FKBP12.6 and RyR2 and that PKA does not dissociate FKBP12.6 from RyR2 mutant channels (George et al., 2003; Jiang et al., 2005; Liu et al., 2006). A second proposed pathogenic

mechanism of RyR2 mutations is similar to that proposed for the effects of RyR1 mutations in skeletal muscle cells that result in malignant hyperthermia (see section V). In the closed state, individual RyR2 subunits associate with each other in a so-called zipper domain region, and RyR2 mutations that cause CPVT cause unzipping of these regions, resulting in RyR2 hyperactivation (Lehnart et al., 2005). A third mechanism by which RyR2 mutations may perturb ER Ca^{2+} regulation in CPVT is by increasing the sensitivity of RyR2 to lumenal Ca^{2+} (Jiang et al., 2005). An increased pool of ER Ca^{2+} similar to that caused by presenilin-1 mutations (see section VII) might also contribute to the perturbed Ca^{2+} regulation in cardiac cells caused by RyR2 mutations.

The Ca^{2+}-binding protein calsequestrin 2 is present in very high amounts in the ER of cardiac cells, where it is believed to function as a Ca^{2+} buffer (Beard et al., 2004). A few CPVT families have been identified in which the cause of the disease is a recessively inherited mutation in calsequestrin 2 (Lahat et al., 2001). The mutations in calsequestrin 2 may result in a loss of the Ca^{2+}-buffering function of the protein (Viatchenko-Karpinski et al., 2004), and/or the mutations may disrupt an interaction between calsequestrin 2 and the RyR2 channel (Terentyev et al., 2006).

Heart failure is a major cause of morbidity and mortality, affecting approximately 5 million Americans, the vast majority of whom are elderly (Rich, 2006). The pathogenesis of heart failure is complex, involving multiple structural and functional alterations, including increased production of oxygen free radicals, impaired excitation-contraction coupling, and deficient force- and relaxation-frequency responses (Janczewski and Lakatta, 2010). Considerable evidence suggests that, among the factors underlying impaired function of cardiomyocytes in heart failure, perturbed ER Ca^{2+} handling may play a particularly important role early in the disease process. Data suggest that heart failure involves hyperphosphorylation of RyR2 by PKA, resulting in excessive Ca^{2+} release and depletion of ER Ca^{2+} stores in cardiac myocytes, associated with an increased diastolic ER Ca^{2+} leak (Yano et al., 2000). Studies of animal models of heart failure have documented an increase in the frequency and duration of ER Ca^{2+} sparks, suggesting more and extended opening of RyR2 channels (Maier et al., 2003). The perturbed ER Ca^{2+} release may impair excitation-contraction coupling.

In addition to perturbed regulation of ER Ca^{2+} release, considerable evidence suggests that a deficiency in SERCA activity occurs in cardiac myocytes in heart failure. The expression of the gene encoding SERCA2, and the overall enzyme activity of SERCA2, are decreased in failing heart cells (Kawase and Hajjar, 2008). In addition, there is evidence that levels of phospholamban, which inhibits SERCA2 activity, is increased in heart failure. Reduced SERCA2 activity would be expected to result in a decreased ER Ca^{2+} pool and delayed restoration of the cytosolic Ca^{2+} concentration after stimulation. In this way, a SERCA2 deficiency would promote diastolic dysfunction and tachycardia. Studies of mice with a genetic deletion of one SERCA2 allele have demonstrated the importance of ER Ca^{2+} uptake in protecting cardiac myocytes against ischemic injury in a model of myocardial infarction (Talukder et al., 2008).

There has been considerable interest in the development of therapeutic interventions aimed at increasing the levels and/or activity of SERCA2 as a treatment for heart failure (Lipskaia et al., 2010). Viral vector-mediated expression of SERCA2a in failing human cardiomyocytes improved their contractility, which was associated with restoration of the Ca^{2+} transient as a result of increased ER Ca^{2+} uptake during diastole and greater Ca^{2+} efflux during systole (del Monte et al., 1999). Overexpression of SERCA2a in a model of cardiac arrhythmia suppressed arrhythmias and also reduced damage to cardiac myocytes (del Monte et al., 2004). Early phase clinical trials of adeno-associated virus-mediated delivery of SERCA2a in patients with heart failure are currently in progress. Small molecules that either enhance SERCA activity or inhibit phospholamban are being developed. For example, istaroxime [(*E*,*Z*)-3-((2-aminoethoxy)imino) androstane-6,17-dione hydrochloride] enhances ER Ca^{2+} uptake in failing cardiomyocytes and improves heart function in a pig model (Micheletti et al., 2007).

B. Skeletal Muscle

Motor neurons release the neurotransmitter acetylcholine, which activates nicotinic acetylcholine receptors in the plasma membrane of skeletal muscle cells, resulting in membrane depolarization and Ca^{2+} influx through voltage-gated L-type channels. The Ca^{2+} influx then activates ryanodine receptors (RyR1) in ER membranes closely apposed to the plasma membrane. Ca^{2+} released from the ER then binds troponin, resulting a conformational change that is transmitted from troponin to tropomyosin, thereby unmasking myosin-binding sites on actin filaments (Rome, 2006). Relaxation occurs when intracellular Ca^{2+} levels recover toward basal levels; recovery of Ca^{2+} levels is mediated in part by ATP-dependent Ca^{2+} uptake into the ER via SERCAs. Skeletal muscle cells predominantly express SERCA1a, although slow-twitch cells also express SERCA2a.

The critical importance of ER Ca^{2+} handling in skeletal muscle cells has been established by the identification of mutations in RyR1 as the cause of inherited disorders that manifest abnormalities in skeletal muscle cells. Malignant hyperthermia is an autosomal-dominant disease characterized by an unusual and dramatic metabolic response to volatile anesthetics, with symptoms that include a rapid rise in body temperature, skeletal muscle contracture, and damage and lysis of

muscle cells (Denborough, 1998). More than 80 different missense mutations in the gene encoding RyR1 have been linked to familial malignant hypothermia, accounting for approximately 50% of all cases of the disorder (Treves et al., 2005). The mutations are inherited in an autosomal dominant manner, consistent with a gain-of-function pathogenic action of the mutations. Each mutation consistently increases the sensitivity of RyR1 to opening in response to caffeine and volatile anesthetics such as halothane and also alters excitation-contraction coupling (Tong et al., 1997).

A second autosomal dominantly inherited muscle disorder caused by mutations in RyR1 is called central core disease (CCD); families with recessively inherited CCD caused by RyR1 mutations have also been reported (Jungbluth et al., 2002). CCD is a myopathy present early in life that typically does not progress; patients exhibit hypotonia, proximal muscle weakness, and a developmental delay in motor system maturation. The skeletal muscle cells of patients with CCD exhibit regions devoid of mitochondria called "cores." RyR1 mutations that cause CCD have been shown to increase RyR1 receptor channel activity (Ghassemi et al., 2009). A third muscle disorder caused by RyR1 mutations is multiminicore disease (MmD), which is inherited in a recessive manner and manifests at birth with hypotonia and distal joint laxity; later in life progressive scoliosis and respiratory insufficiency may develop (Guis et al., 2004). MmD muscle cells exhibit small cores that do not run the length of the muscle fiber. Although the mechanism by which MmD mutations affect the function of RyR1 remains to be established, it seems likely that perturbations in ER Ca^{2+} handling and excitation-contraction coupling are involved.

C. Exocrine and Endocrine Systems

Various hormones are released into the blood from exocrine and endocrine cells in a Ca^{2+}-dependent manner. Examples of such hormones include the following: insulin from pancreatic β cells; glucocorticoids and epinephrine from adrenal cortical and medullary cells, respectively; vasopressin and oxytocin from axon terminals in the posterior pituitary gland; adrenocorticotropin and gonadotropins from the anterior pituitary; and incretins from intestinal epithelial cells. Because this review focuses on the role of ER Ca^{2+} handling in the physiology and pathophysiology of excitable cells, we will present in this section only examples from exocrine and endocrine cells in which membrane depolarization can elicit an action potential.

Pancreatic β cells produce insulin and release it into the blood in response to an elevation of the circulating glucose concentration. Glucose induces electrical activity, first by causing a gradual membrane depolarization to a threshold potential at which action potentials are generated and VGCCs open (Best et al., 2010). Glucose causes membrane depolarization by reducing K^+ efflux through K-ATP channels and by opening volume-regulated anion channels. Studies of Ca^{2+} oscillations in mouse β cells during glucose stimulation exhibits a descending phase with two components: first, there was a rapid decrease of the cytosolic Ca^{2+} concentration that coincided with closing of VGCCs; second, there was a slower phase that was independent of Ca^{2+} influx (Gilon et al., 1999). When the SERCA was blocked with thapsigargin, the amplitude of the rising phase of cytosolic Ca^{2+} was elevated, and the slow recovery phase was impaired. It is noteworthy that thapsigargin caused depolarization of the plasma membrane, suggesting that Ca^{2+} filling of the ER modulates membrane potential thereby playing a pivotal role in the propagation and maintenance of Ca^{2+} oscillations. It has been suggested that a relatively simple biophysical re-equilibration of Ca^{2+} fluxes can explain such complex patterns of intracellular Ca^{2+} release (Burdakov and Verkhratsky, 2006). Pancreatic α-cells are also excitable and release glucagon in response to depolarization and epinephrine. It is noteworthy that in α-cells, the initial Ca^{2+} response is due to Ca^{2+} release from the ER, which, in turn, triggers Ca^{2+} -induced Ca^{2+} influx resulting in depolarization and Ca^{2+} influx through VGCCs (Liu et al., 2004). Whereas glucose depolarizes β cells, it hyperpolarizes α cells and stimulates Ca^{2+} retention in the ER.

Perturbed ER Ca^{2+} handling may play a role in the pathogenesis of type I diabetes, in which β cells become unresponsive to glucose and eventually die. Normally functioning β cells exhibit oscillations of intracellular Ca^{2+} levels that are controlled, in part, by ER Ca^{2+} uptake and release (Jahanshahi et al., 2009). Nonoscillatory islet cells exhibit elevated basal cytosolic Ca^{2+} levels and a reduced Ca^{2+} response to glucose. The reason for the defect in Ca^{2+} pulsatility seems to be a reduced pool of releasable ER Ca^{2+} and not an alteration in plasma membrane ion channels. The authors concluded that "Our data suggest the loss of oscillatory capacity may be an early indicator of diminished islet glucose sensitivity and ER dysfunction, suggesting targets to improve islet assessment" (Jahanshahi et al., 2009). In addition to diabetes, the damage of pancreatic cells that occurs in pancreatitis may result, in part, from toxic actions of biliary acids on acinar cells. Two-photon imaging studies from the ER and acidic compartments whithin acinar cells have demonstrated that the biliary acid taurolithocholic acid 3-sulfate causes Ca^{2+} release from both IP_3-sensitive and ryanodine-sensitive stores (Gerasimenko et al., 2006).

Anterior pituitary cells produce one or more peptide hormones in response to signals from the brain. For example, pituitary cells that produce adrenocorticotropin are stimulated by corticotropin-releasing hormone, which is produced in hypothalamic neurons in response to stress. The release of adrenocorticotropin is mediated by Ca^{2+} released from IP_3-sensitive ER stores and subsequent opening of store-operated Ca^{2+} channels in the plasma membrane (Yamashita et al., 2009). Adrenocorticotropin secretion

is blocked by thapsigargin pretreatment, by inhibitors of store-operated Ca^{2+} channels [1-(2-(3-(4-methoxyphenyl)-propoxy)-4-methoxyphenylethyl)-1*H*-imidazole (SKF96365) and *N*-propylargylnitrendipine (MRS1845)], and by L-type Ca^{2+} channel blockers (Won and Orth, 1995; Yamashita et al., 2009).

In addition to glucocorticoids, the adrenal gland produces epinephrine, a second major hormone involved in the response of the body and brain to stress. Epinephrine is produced by neurosecretory cells called chromaffin cells located in the medulla (middle) of the adrenal gland. A study that employed laser microscopy and amperometry showed that chromaffin cells contain both IP_3- and ryanodine-sensitive ER Ca^{2+} pools; agonist coupled to IP_3 production released approximately twice the amount of Ca^{2+} released in response to caffeine (Inoue et al., 2003). Muscarine-induced Ca^{2+} responses lasted for 10 to 20 s, whereas caffeine-induced Ca^{2+} responses lasted only 3 to 6 s.

D. Nervous System

Neurons represent a unique cell type with a complex morphology that includes a soma, arborized dendrites, dendritic spines, axons, and axon terminals (Fig. 3). The ER extends throughout these distinct compartments and supports functionally diverse roles within each, thereby earning the status of a "neuron-within-a-neuron" (Berridge, 1998, 2002). There is believed to be a single continuous ER store, providing the extensive continuum necessary for synchronization across the distinct spatial and functional compartments of the neuron (Terasaki et al., 1994; Park et al., 2008). For example, in the dendrites, ER Ca^{2+} release is involved in modulating postsynaptic responses and synaptic plasticity

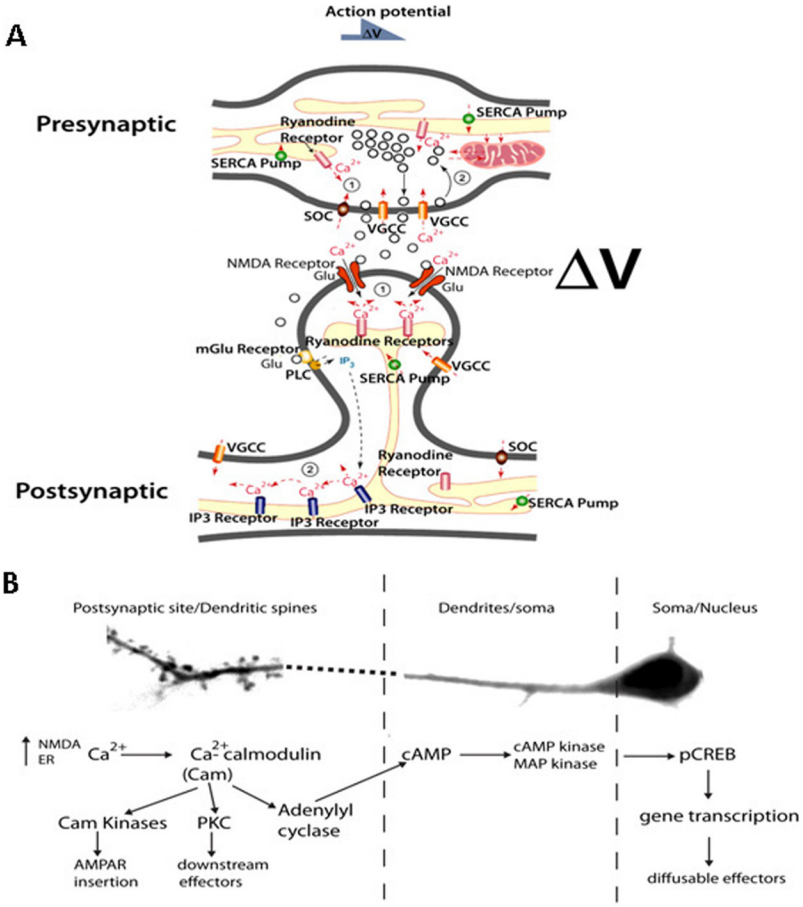

FIG. 3. The role of ER Ca^{2+} in synaptic plasticity. A, the ER can extend into both the pre- and postsynaptic compartments of a synapse. In presynaptic terminals, ER Ca^{2+} release can trigger spontaneous neurotransmitter release and can also integrate with voltage-gated Ca^{2+} entry elicited from action potential invasion to facilitate vesicle release and the repopulation of the ready-releasable pool of vesicles. NMDAR-mediated Ca^{2+} signals are amplified postsynaptically by RyR in dendritic spines and contribute to homosynaptic plasticity. At extrasynaptic sites, glutamate spillover triggers metabotropic glutamate (mGlu) receptor-mediated generation of IP_3 and activates a Ca^{2+} response outside of the synaptic contact point. Subsequent activation of IP_3Rs supports regenerative Ca^{2+} waves, which may be involved in heterosynaptic plasticity and gene expression. [Modified from Bardo S, Cavazzini MG, and Emptage N (2006) The role of endoplasmic reticulum Ca^{2+} store in the plasticity of central neurons. *Trends Pharmacol Sci* **27:**78–84.). B, the Ca^{2+} generated by both plasma membrane Ca^{2+}-permeable channels (e.g., NMDAR) and ER Ca^{2+} channels can subsequently trigger multiple Ca^{2+}-dependent cascades that encode long-term plasticity. In the case of LTP, Ca^{2+} in dendritic spines locally activates effectors, including calmodulin, which in turn activates several kinase pathways such as adenylyl cyclase, CamKII, and PKC. These then trigger longer term cascades, such as the cAMP/phosphorylated cAMP response element-binding protein (pCREB) pathway, which results in protein translation and long-term structural and functional alterations to the neuron that support learning and memory encoding. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

(Emptage et al., 1999; Fitzjohn and Collingridge, 2002; Holbro et al., 2009); in axon terminals, it is involved in vesicle fusion and neurotransmitter release (Emptage et al., 2001; Bouchard et al., 2003); in the soma, it is coupled to the activation of Ca^{2+}-sensitive signaling pathways such as kinase and phosphatase activities (Berridge, 1998); and in the perinuclear space, it can trigger gene transcription (Li et al., 1998). Local variations in ER morphology also correlate with dendritic spine density and maturation, linking ER morphology to changes in synaptic organization and function (Harris, 1999; Holbro et al., 2009).

One of the most complex aspects of neuronal communication is the feature of electrochemical synaptic transmission, which is a Ca^{2+}-dependent phenomenon that recruits ER stores under a variety of conditions. Although much of the Ca^{2+} entry into the neuron is predominantly mediated by plasma membrane ligand-gated channels (such as NMDA receptors) or VGCCs; IP_3R- and/or RyR-mediated Ca^{2+} release can be subsequently recruited via CICR (Finch et al., 1991; Friel and Tsien, 1992). The dynamic interplay between intra- and extracellular Ca^{2+} sources becomes particularly relevant when considering pre- and postsynaptic mechanisms underlying neurotransmission and synaptic plasticity (Berridge, 1998; Verkhratsky, 2002; Park et al., 2008).

RyR are found throughout the neuron, including presynaptic terminals, where CICR can trigger spontaneous neurotransmitter release via coupling of Ca^{2+}-binding sensors to neurotransmitter vesicles (Emptage et al., 2001; Bouchard et al., 2003). In addition, ER Ca^{2+} can facilitate subsequent vesicle release by mobilizing neurotransmitter vesicles from the reserve pool to the readily releasable pool. This occurs when presynaptic Ca^{2+} levels are elevated in response to VGCC activity (such as an incoming action potential), and then the readily releasable vesicle pool is released into the synaptic cleft, and vesicles are replenished with neurotransmitter from a reserve pool in a Ca^{2+}-dependent manner. RyR-mediated CICR can facilitate this process and thereby accelerate the rate of successful repetitive neurotransmission (Kuromi and Kidokoro, 2002; Zucker and Regehr, 2002). This Ca^{2+}-dependent phenomenon influences short-term presynaptic plasticity, such as paired-pulse facilitation, which reflects residual Ca^{2+} remaining in the presynaptic terminal and serves to increase the probability of neurotransmitter release (Zucker and Regehr, 2002; Bouchard et al., 2003). In this phenomenon, ER stores can be a source for the residual Ca^{2+} contributing to paired-pulse facilitation (Emptage et al., 1999). Another form of presynaptic plasticity, post-tetanic potentiation, reflects enhanced neurotransmitter release that briefly (seconds to minutes) leads to synaptic strengthening. RyR-mediated Ca^{2+} release contributes to the residual Ca^{2+} levels via CICR and facilitates post-tetanic potentiation (Zucker and Regehr, 2002; Bardo et al., 2006).

ER Ca^{2+} is involved in several postsynaptic long- and short-term physiological processes. Ca^{2+} partly regulates activity-dependent membrane excitability-sensitive K^+ channels, such as the SK channel, which contributes to the medium afterhyperpolarization. This current underlies spike-frequency adaptation, a phenomenon wherein accumulating Ca^{2+} entering though spiking activity reaches sufficient levels to activate hyperpolarizing K^+ currents and transiently suppress membrane excitability. Although these channels are largely triggered by VGCC, IP_3- and RyR-mediated Ca^{2+} release can also activate these channels and modify spiking patterns, thereby influencing local circuit activity (Stutzmann et al., 2003; Hagenston et al., 2008; Chakroborty et al., 2009). In hippocampal and cortical pyramidal neurons, the ER in the soma and dendritic shafts express both IP_3R and RyR, whereas ER networks in distal processes and dendritic spine heads express a greater proportion of RyR (Sharp et al., 1993; Fitzjohn and Collingridge, 2002; Hertle and Yeckel, 2007). This suggests that Ca^{2+} signaling involving these individual receptors may support different roles in synaptic activity. The somatic IP_3Rs may be involved in gene transcription and protein synthesis, whereas extrasynaptic IP_3R activation may be recruited with synaptic spillover events or require much higher threshold inputs (Nakamura et al., 1999; Mellström and Naranjo, 2001). In contrast, RyRs in dendritic spine heads may be better positioned to modulate incoming synaptic activity directly. For example, in dendritic spines of hippocampal CA1 neurons, the NMDAR-mediated Ca^{2+} signal is largely amplified by RyR-mediated CICR (Alford et al., 1993; Emptage et al., 1999).

The CICR-mediated enhancement of Ca^{2+} signals initiated by plasma membrane Ca^{2+} channels plays an important role in synaptic transmission and synaptic plasticity—the cellular mechanism by which learning and memory are thought to be encoded (Ross et al., 2005; Watanabe et al., 2006). Most commonly, synaptic plasticity is initiated within dendritic spines, which express several Ca^{2+} permeable channels, such as NMDAR, VGCCs, RyR, and IP_3R (Yuste et al., 2000; Yasuda et al., 2003). Although NMDAR-mediated Ca^{2+} entry is often necessary for LTP induction, this Ca^{2+} source alone is not sufficient to sustain long-term forms of plasticity (Raymond and Redman, 2006). ER Ca^{2+} stores are essential to this process by amplifying and extending the duration of the initial NMDAR-mediated signal and ensuring the proper spatial and temporal Ca^{2+} patterns necessary to activate the specific downstream cascades necessary to encode LTP or LTD. Therefore, manipulating the ER Ca^{2+} channels greatly affects the expression of plasticity. For example, the polarity and input specificity of long-term plasticity has been shown to be regulated by ER Ca^{2+} stores such that blocking IP_3R leads to

a conversion of LTD to LTP and elimination of heterosynaptic LTD, whereas blocking RyR eliminates homosynaptic LTD and LTP induction (Obenaus et al., 1989; Harvey and Collingridge, 1992; Nishiyama et al., 2000; Fitzjohn and Collingridge, 2002; Chakroborty et al., 2009).

Additional evidence for the fundamental role of RyR in synaptic plasticity emerges from studies using RyR knockout mice. For example, RyR3 knockout mice show enhanced LTP, which is independent of NMDAR-mediated mechanisms, but impaired LTD (Futatsugi et al., 1999); the RyR3 is expressed in dendritic processes of hippocampal neurons (Hertle and Yeckel, 2007), suggesting that RyR3 isoform may function to suppress LTP and facilitate LTD. This may in turn serve to maintain the balance of excitation and inhibition that determines the overall stability of the synapse. There also seems to be functional overlap between RyR- and IP_3R-mediated Ca^{2+} signaling and plasticity. Type 1 IP_3R knockout mice also demonstrate enhanced LTP, whereas LTD is not affected (Fujii et al., 2000), suggesting that IP_3R-sensitive ER Ca^{2+} stores in general have an inhibitory role in LTP induction. Furthermore, IP_3R-mediated Ca^{2+} stores outside dendritic spines may also suppress LTP in neighboring synapses, thus maintaining the input specificity that is characteristic of LTP. These and related studies demonstrate that ER Ca^{2+} is required for neuronal synaptic plasticity and, by association, supports memory and cognitive functions (Fig. 3).

V. Perturbed Endoplasmic Reticulum Ca^{2+} Handling and Disease

A. Ischemic Stroke

Ischemic stroke results when a clot forms in a cerebral blood vessel that, depending upon the vessel affected and for how long, results in varying amounts of morbidity or mortality. Stroke is a leading cause of death worldwide; risk factors include hypertension, obesity, diabetes, and smoking. More than any other cell type, neurons are exquisitely vulnerable to ischemia because of their high energy demand, their reliance on glucose as an energy source, and their excitability and sensitivity to the excitatory neurotransmitter glutamate (for review, see Mattson, 2003). Cellular Ca^{2+} overload is strongly implicated in the degeneration and death of neurons that occurs in ischemic stroke; studies of experimental models indicate that Ca^{2+} influx through NMDA receptors and VGCCs can be pivotal in such ischemic neuronal death (Verkhratsky and Toescu, 2003; MacDonald et al., 2006; Mattson, 2007). The pharmacology of glutamate and VGCC in relation to stroke and excitotoxic neuronal death has been reviewed in detail previously (Catterall et al., 2005; Traynelis et al., 2010). In this section, we focus instead on the role of perturbed ER Ca^{2+} handling in stroke, and the potential of agents that target ER Ca^{2+} regulation in stroke therapy.

Evidence for the involvement of ER Ca^{2+} handling systems in ischemic stroke comes from studies demonstrating changes in ER Ca^{2+} release or uptake in experimental models relevant to stroke. Release of Ca^{2+} from caffeine/ryanodine-sensitive stores occurs before the death of CA1 hippocampal neurons in a model of global cerebral ischemia—reperfusion injury (Xing et al., 2004). Dantrolene, which inhibits Ca^{2+} release from RyR, reduced brain damage in animal models of neonatal and adult hypoxia/ischemia (Wei and Perry, 1996; Gwak et al., 2008). Another study employed a model in which cultured hippocampal neurons were exposed to the glycolysis inhibitor iodoacetate, which causes a slowly progressing cell death that is exacerbated by caffeine, and 1 μM caffeine, which activates RyR (Hernández-Fonseca and Massieu, 2005). Dantrolene and a higher concentration of ryanodine (25 μM), which antagonizes RyR, attenuated neuronal death in iodoacetate-treated cultures.

ER Ca^{2+} overload impairs protein synthesis, and unfolded proteins accumulate in the ER lumen (Paschen, 2004). This accumulation of unfolded proteins in the ER can trigger two molecular stress responses: 1) UPR, which is required for inducing the new synthesis of chaperones to refold the unfolded proteins, and 2) ER-associated degradation, which targets damaged proteins for degradation in the proteasome. If sufficient synthesis of the ER chaperone GRP78 occurs, the unfolded proteins may be refolded, and the triggering of apoptotic cell death avoided (Yu et al., 1999).

In addition to impaired SERCA activity and enhanced release of Ca^{2+} through IP_3 and RyR, data suggest a role for presenilin-1 in ischemic neuronal injury. Thus, neurons in presenilin-1 mutant knockin mice exhibit increased vulnerability to focal ischemic stroke and an instability of ER Ca^{2+} homeostasis under hypoxic and energetic stress (Mattson et al., 2000). Capacitative Ca^{2+} entry may play an important role in ischemic neuronal death, because STIM1 is essential for capacitive Ca^{2+} entry and ischemia-induced Ca^{2+} overload in neurons (Berna-Erro et al., 2009). Neurons from STIM2-deficient mice showed significantly increased survival under hypoxic conditions compared with neurons from wild-type mice. It has been proposed that ischemia enhances *S*-glutathionylation of RyR, which allows RyR to sustain CICR, resulting in increased vulnerability of neurons to Ca^{2+} overload and cell death (Bull et al., 2008).

Although Ca^{2+} release from the ER may contribute to ischemic neuronal death, it may also play an important role in ischemic preconditioning hormesis (Bickler et al., 2009), a process in which exposure of neurons to a mild brief ischemia results in resistance to a more severe ischemic stroke (Calabrese et al., 2007). Transient anoxia has been shown to activate the transcription factor NF-κB, resulting in increased expression of Na^+/Ca^{2+} exchanger 1, which, in turn, enhances Ca^{2+} refilling

(Sirabella et al., 2009). Other studies have found that NF-κB can enhance whole-cell Ca^{2+} currents while down-regulating NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid currents in hippocampal neurons (Furukawa and Mattson, 1998). It is noteworthy that ER Ca^{2+} release can be a stimulus for NF-κB activation. Inhibition of Ca^{2+} release via IP_3R channels decreases basal NF-κB activity in cultured rat cortical neurons (Glazner et al., 2001). Moreover, activation of NF-κB in response to TNF and glutamate is abolished in neurons treated with an IP_3R inhibitor. Additional findings suggest that a factor, probably a protein, released from the ER when IP_3R are activated is responsible for activation of NF-κB (Glazner et al., 2001).

B. Lipid Storage Disorders: Gaucher, Sandhoff, and Niemann-Pick C Diseases

Deficiencies in enzymes involved in cellular lipid metabolism can result in diseases that involve neuronal dysfunction and degeneration. Gaucher disease is caused by deficiency of lysosomal glucocerebrosidase activity and accumulation of glucosylceramide, a glucocerebrosidase substrate. Mutations in glucocerebrosidase may destabilize its structure, resulting in misfolding and degradation of the enzyme (for review, see Vitner et al., 2010). The accumulation of glucosylceramide results in Ca^{2+} release through ER RyR, and blockade of RyR can restore normal folding of mutant glucocerebrosidase in fibroblasts from patients with Gaucher disease (Wang et al., 2011). Likewise, Ong et al. (2010) found that increasing ER Ca^{2+} levels by reducing ER Ca^{2+} efflux through RyR (with the use of antagonists or RNA interference) or by enhancing ER Ca^{2+} influx through SERCA2b overexpression increased glucocerebrosidase activity in fibroblasts from patients with Gaucher disease. There may be an increase in the size of the ER Ca^{2+} pool in Gaucher disease, because treatment of cultured hippocampal neurons with an inhibitor or glucosylceramidase results in increased density of ER and greater Ca^{2+} responses to glutamate and caffeine (Korkotian et al., 1999).

Sandhoff disease is caused by mutations in the β-chain of hexosaminidase, resulting in deficiency of hexosaminidases A and B, resulting in the intracellular accumulation of GM2 ganglioside (Kolter and Sandhoff, 2005). Patients with Sandhoff disease exhibit progressive neurological deficits that include developmental delay, gait disturbances, and speech impairment (Maegawa et al., 2006). Hexosaminidase B-deficient mice exhibit GM2 accumulation in their brain cells, and microsomes prepared from Hexb(−/−) mouse brain exhibit a reduced rate of Ca^{2+}-uptake via the SERCA that can be prevented by feeding the mice *N*-butyldeoxynojirimycin, an inhibitor of glycolipid synthesis that reduces GM2 storage (Pelled et al., 2003). Neurons cultured from embryonic Hexb(−/−) mice exhibit increased sensitivity to death induced by thapsigargin. The reduced SERCA activity and increased sensitivity to ER Ca^{2+} store depletion may contribute to the neuronal dysfunction and degeneration that occurs in Sandhoff disease. Overexpression of hexosaminidase B accomplished with the use of a bicistronic lentiviral vector can normalize the ER Ca^{2+} uptake defect and decrease GM2 in hippocampal neurons from embryonic Sandhoff mice (Arfi et al., 2006).

Niemann-Pick type C disease (NPC) is an inherited lipid storage disorder caused by deficiencies of lysosomal proteins (NPC1 and NPC2) involved in intracellular cholesterol-trafficking. Patients with NPC exhibit progressive neurological impairment and die at an early age; cerebellar Purkinje cells are particularly vulnerable (Tang et al., 2010). NPC1 mutations result in impaired Ca^{2+}-mediated fusion of endosomes with lysosomes, resulting in the accumulation of cholesterol and other lipids in late endosomes and lysosomes. Preclinical studies suggest that cyclodextrin, an agent known to reduce cholesterol accumulation in cells, can stimulate lysosomal exocytosis in a Ca^{2+}-mediated manner (Chen et al., 2010). It was reported that NPC1 mutant fibroblasts have a much reduced level of acidic compartment calcium stores compared with wild-type control cells (Lloyd-Evans et al., 2008). When luminal endocytic calcium was chelated in normal cells with high-affinity rhod-dextran, the cells exhibited an NPC-like disease phenotype. In another model, the same authors found that excessive sphingosine storage in the acidic compartment resulted in calcium depletion and increased cholesterol accumulation in the same compartment (Lloyd-Evans et al., 2008).

C. Peripheral Neuropathies and Amyotrophic Lateral Sclerosis

A common neurological complication of long-standing diabetes is peripheral neuropathy (PN), a condition that involves sensory neurons and typically results in severe pain (Tavakoli and Malik, 2008). Evidence for the involvement of perturbed Ca^{2+} regulation in peripheral nerve cells in PN has been reviewed (Fernyhough and Calcutt, 2010). ER Ca^{2+} signaling is altered in sensory neurons in animal models of PN. Diabetes results in a reduction in the ER Ca^{2+} content in sensory neurons, which, in turn, reduces the amount of Ca^{2+} released upon stimulation by ATP (via activation of purinergic receptors coupled to IP_3 production) or caffeine. The impaired Ca^{2+} release was more prominent in dorsal root ganglion neurons of the lumbar region compared with those in the cervical and thoracic regions (Huang et al., 2002). In the rat streptozotocin-induced diabetes model, fluorescence video imaging was used to measure free cytosolic Ca^{2+} levels in lumbar nociceptive neurons of control and diabetic rats. The basal Ca^{2+} concentration in the neurons rose progressively with the duration of diabetes, and Ca^{2+} mobilization from ER IP_3- and

ryanodine-sensitive Ca^{2+} stores was reduced in sensory neurons of the diabetic rats (Kruglikov et al., 2004). In a similar diabetes model, the soleus muscle exhibited decreased SERCA2a levels in type I (slow twitch) fibers compared with nondiabetic control rats (Rácz et al., 2009).

ALS is a fatal neurodegenerative disorders in which lower and upper motor neurons degenerate, resulting in progressive paralysis. Some cases of ALS are caused by mutations in Cu/Zn-SOD, and transgenic mice that express mutant human Cu/Zn-SOD provide a model that resembles the human disease (DiBernardo and Cudkowicz, 2006). Studies of Cu/Zn-SOD mutant mice and spinal cords of patients with ALS have provided evidence that motor neurons die as the result of increased oxidative stress, excessive activation of glutamate receptors, and cellular Ca^{2+} overload (Kruman et al., 1999; Guo et al., 2000). Release of Ca^{2+} from the ER is believed to contribute to motor neuron degeneration (Grosskreutz et al., 2010). The mechanism underlying the perturbed Ca^{2+} homeostasis in motor neurons may involve impaired ability of astrocytes to remove glutamate from the extracellular fluid (Rothstein, 2009). In addition, it has been proposed that some cases of ALS involve an autoimmune attack on motor neurons, mediated by antibodies against VGCC (Engelhardt et al., 1995). The reason that some motor neurons in the brainstem do not degenerate in ALS is not known, but those resistant neurons express much higher levels of Ca^{2+}-binding proteins such as calbinin (Grosskreutz et al., 2010) that are known to protect neurons against excitotoxicity (Mattson et al., 1991). A dominantly inherited mutation in the vesicle-associated membrane protein-associated protein B (VAPB) is responsible for some cases of ALS. Expression of mutant VAPB in motor neurons results in ER stress and dysregulation of ER and cellular Ca^{2+} homeostasis, and this abnormal Ca^{2+} handling plays a pivotal role in the death of motor neurons caused by the mutant VAPB (Langou et al., 2010). Collectively, the available data suggest a role for excessive elevation of intracellular Ca^{2+} levels in the degeneration of neurons in ALS, although the contribution of specific alterations in ER Ca^{2+} handling systems in this disease is unknown.

D. Parkinson Disease

Parkinson disease (PD), the most common movement disorder, is characterized by degeneration of monoaminergic neurons in the brainstem and basal ganglia, loss of dopaminergic neurons in the substantia nigra playing a major role in the motor symptoms. Although most cases of PD are sporadic, some families harbor mutations that result in inherited early-onset PD. The genetic abnormalities include mutations in genes inherited in either an autosomal dominant (α-synuclein and LRRK2) or recessive (Parkin, DJ-1, and PINK1) (Dawson et al., 2010). Several findings suggest that dopaminergic neurons die as the result of mitochondrial stress, with a possible role for perturbed Ca^{2+} homeostasis downstream of the mitochondrial alterations (Mattson et al., 2008). Studies of cultured cells and transgenic mice expressing mutant α-synuclein, LRRK2, Parkin and DJ-1 implicate the involvement of proteotoxic and oxidative stress in the ER and mitochondria in PD. As a result of the mutations and the aging process, Ca^{2+} handling in the ER and mitochondria may be disturbed (Chan et al., 2009). Cybrid cells containing mitochondria from patients with PD recover from IP_3-induced Ca^{2+} release more slowly than control subjects, a behavior similar to that seen in cells exposed to 1-methyl-4-phenylpyridinium ion (Sheehan et al., 1997). It would seem that mitochondrial alterations secondarily affect ER Ca^{2+} handling in this model. One protein that may protect the ER against aging and PD is called Herp (homocysteine-inducible ER stress protein), an integral membrane protein containing a ubiquitin-like domain. Knockdown of Herp increases, and overexpression of Herp decreases, the vulnerability of dopamine-producing cells to the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Herp prevents ER Ca^{2+} store depletion and mitochondrial Ca^{2+} accumulation by a mechanism requiring proteasomal degradation (Chigurupati et al., 2009).

E. Alzheimer Disease

The etiology of AD is currently unknown, but the classic diagnostic features are well categorized. Histological features include amyloid β-peptide (Aβ) plaques, neurofibrillary tangles composed of hyperphosphorylated τ, and cell death. Behavioral features include emotional and affective changes that may precede the devastating progressive and irreversible memory loss. It is noteworthy that neither of the histopathological markers correlates well with the cognitive changes; instead, decrements in dendritic spine density and synaptic integrity are better associated with memory loss (Goldman et al., 2001; Selkoe, 2002; Scheff et al., 2006). This makes functional sense, because synapses are the sites in which learning and memory are encoded; a loss of synaptic function would therefore impair these cognitive functions. What underlies these synaptic changes is thus a highly relevant, and currently unknown, critical question that must be answered to understand AD pathogenesis.

Dysregulated Ca^{2+} signaling has been given increasing attention as a significant contributing factor in AD, both in early and late stages of the disease (LaFerla, 2002; Stutzmann, 2007; Bezprozvanny and Mattson, 2008). Exquisitely controlled Ca^{2+} levels are fundamental to neuronal functioning and viability, and neurons enlist a host of Ca^{2+} buffers, binding proteins, pumps, and sequestering mechanisms to maintain proper homeostasis. Alterations in Ca^{2+} levels can therefore lead to a variety of neurodegenerative diseases. Specific to AD, it has been shown that sustained up-regulation of

Ca^{2+} levels can both initiate and accelerate the core diagnostic features—from amyloid plaque deposition to synapse loss (Stutzmann, 2007).

AD can be grouped into two categories; the most common is termed sporadic AD, with an unknown etiology and a late age of onset (>65 years). The relatively less common form (1–10% of cases) is termed familial or early-onset AD, and is caused by mutations in the presenilin 1 (*PS1*), presenilin 2 (*PS2*), or amyloid precursor protein (*APP*) genes, and is inherited in an autosomal dominant fashion. Regardless of the form, the disease progression follows the same course, albeit at an accelerated rate in familial cases. Mutations in PS1 are responsible for the majority of FAD. PS is located in the ER membrane and is part of the γ-secretase complex that cleaves APP into $A\beta_{40}$ or $A\beta_{42}$ peptide fragments, the latter being the most pathogenic form of $A\beta$ that preferentially contributes to plaque formation. PS mutations may cause early-onset AD, potentially through more than one mechanism. One mechanism is that the mutation results in the preferential cleavage of APP into the more amyloidogenic $A\beta_{42}$ form, and a second mechanism is that the mutation results in increased Ca^{2+} release from the ER (Mattson, 2004). It is noteworthy that the altered Ca^{2+} signaling is present early in development, long before the onset of measurable histopathology or cognitive deficits. Previous studies in human fibroblasts from asymptomatic FAD patients and in model cells demonstrated that expression of mutant PS1 or PS2 generated enhanced IP_3R-evoked Ca^{2+} responses (Ito et al., 1994). This was later validated in cultured neuronal-like cells expressing mutant PS1 (Guo et al., 1996, 1997; Cheung et al., 2010), in cultured primary neurons from PS1 mutant knockin mice (Guo et al., 1999a; Chan et al., 2000), and in brain slice preparations from young, adult, and aged mutant PS1-expressing mice (Stutzmann et al., 2006; Goussakov et al., 2010).

Perturbed ER Ca^{2+} handling has been shown to mediate several adverse effects of PS1 mutations on neurons. For example, hippocampal neurons from PS1 mutant knockin mice exhibit increased vulnerability to excitotoxicity that is associated with excessive elevations of intracellular Ca^{2+} levels; treatment of the neurons with dantrolene can protect them against the adverse effect of the PS1 mutation (Guo et al., 1999b). PS1 mutations also increase the vulnerability of neurons to mitochondrial impairment, again by a mechanism involving Ca^{2+} release from the ER (Keller et al., 1998). The combination of increased Aβ42 production and excessive ER Ca^{2+} release may explain the very early age of disease onset in those who inherit a PS1 mutation.

The mechanism by which mutant presenilin alters ER Ca^{2+} release is still under investigation, and current studies focus on the IP_3R, the RyR, and the ER leak channel, as well as interactions among these. The earliest studies identifying a link between mutant PS and ER Ca^{2+} release relied on IP_3R agonists and thereby implicated the IP_3R as the target Ca^{2+} channel (Ito et al., 1994; Leissring et al., 1999). More recent studies have provided a mechanism by which this can occur, such that mutant PS alters the properties of the IP_3 channel by increasing the open probability at low cytosolic $[IP_3]$ and shifting the channel gating toward a high open-probability burst mode (Cheung et al., 2008, 2010). This results in a greater IP_3-evoked Ca^{2+} response even at low concentrations of circulating IP_3. Consistent with this, experiments in mutant PS-expressing mice demonstrate that baseline levels of endogenous IP_3 are sufficient to trigger an IP_3R-Ca^{2+} response upon increased cytoplasmic Ca^{2+} levels via RyR activation (Goussakov et al., 2010).

In addition to IP_3R-mediated changes, RyR-mediated increases in Ca^{2+} release have also been implicated as an underlying factor. Initial studies in cultured neurons from mutant PS mutant mice demonstrated up-regulated RyR expression levels (Chan et al., 2000), and increased RyR-evoked calcium release in cultured cells (Smith et al., 2005; Zhang et al., 2010). Studies in brain slice preparations have also revealed increased RyR-evoked Ca^{2+} responses across specific neuronal compartments, including the soma and perinuclear regions, and particularly high release in dendrites and spine heads (Stutzmann et al., 2006; Goussakov et al., 2010). In asymptomatic young mice, this was associated with an increase in the RyR2 isoform (Chakroborty et al., 2009), whereas increased RyR3 expression has been observed at later disease stages concurrent with $A\beta_{1-42}$ expression (Supnet et al., 2006). Although mutant PS1-expressing mice seem to be cognitively and neurophysiologically normal at this younger, presymptomatic age (Oddo et al., 2003), upon manipulation of the RyR-sensitive stores, it is apparent that these neurons are using a markedly different Ca^{2+} signaling system to support neurotransmission and plasticity (Chakroborty et al., 2009). This suggests that a compensatory homeostatic mechanism is used in presymptomatic brains to maintain normal basal synaptic transmission as well as long- and short-term forms of plasticity. The long-term effects of maintaining this homeostasis are presently unclear but over a period of many years may influence the course of the disease process. Indeed, it was recently reported that as PS1 mutant knockin mice age, they develop a deficit in late LTP in synapses in cornu ammonis field 1 of the hippocampus (Auffret et al., 2010). Moreover, activation of muscarinic receptors, which normally enhances LTP at synapses in cornu ammonis field 1 of the hippocampus, impairs LTP in PS1 mutant knockin mice; the impaired LTP is associated with a reduction in NMDA current that is restored by intracellular Ca^{2+} chelation (Wang et al., 2009). Additional findings in the latter study revealed similar abnormalities in acetylcholine- and NMDA receptor-mediated components of synaptic plasticity in 3xTgAD mice with PS1, APP, and τ mutations, suggesting that the adverse effects of mutant

PS1 on synaptic plasticity can occur in the absence or presence of pathological amyloid and τ.

Another proposed mechanism by which mutant PS results in altered ER Ca^{2+} signaling involves the ER Ca^{2+} leak channel. The presence of an ER leak channel has primarily been inferred by blocking the SERCA pumps and observing the passive Ca^{2+} leak from the ER, but it has not yet been definitively identified at the molecular or channel level. One hypothesis posits that presenilin functions, in part, as the leak channel and contributes to the maintenance of optimal ER Ca^{2+} levels. AD-linked mutations in presenilin impair its leak properties and thereby result in increased ER Ca^{2+} store levels (Tu et al., 2006; Nelson et al., 2007). It is noteworthy that there is an apparent correlation between particular FAD-linked presenilin mutations and variants of AD clinical phenotypes (Nelson et al., 2010). Concomitant with the impairment in leak channel function, the increase in RyR expression is thought to be a compensatory and neuroprotective response to assume the leak channel role and normalize ER store levels (Zhang et al., 2010). Other neuroprotective roles of the RyR3 isoform have also been proposed at later disease stages, such that increased RyR3 expression is observed upon $A\beta_{42}$ exposure, whereas knockdown of RyR3 increases amyloid pathologic condition (Supnet et al., 2006, 2010). Likewise, long-term exposure to RyR blockers increases amyloid pathologic condition and cytotoxicity (Zhang et al., 2010). On the other hand, RyR blockers have been shown to protect neurons against the endangering effects of presenilin mutations in experimental models of excitotoxicity and Aβ toxicity (Guo et al., 1997, 1999b). The RyR-mediated Ca^{2+} signaling alterations do not occur in isolation, but probably reflect an enhanced CICR response, such that the Ca^{2+} threshold for activating a RyR response is greatly reduced in mutant PS neurons. Thus, Ca^{2+} released via IP_3R can drive a markedly enhanced RyR-Ca^{2+} response, as can Ca^{2+} entry through plasma membrane channels such as NMDA receptors in spines (Goussakov et al., 2010). This has more far-reaching implications for pathological synaptic conditions and for NMDA-targeted therapeutic strategies.

Evidence for Ca^{2+}-based signaling defects in sporadic AD exist as well; notably, most of the major hallmarks and known genetic risk factors for AD generate some form of Ca^{2+} dysregulation (Stutzmann, 2007; Bezprozvanny and Mattson, 2008). Aβ peptides, the oligomeric species in particular, have been shown to increase intracellular Ca^{2+} levels through a variety of mechanisms, the major underlying themes involving membrane-associated oxidative stress (lipid peroxidation), membrane disruption, and interactions with endogenous Ca^{2+} channels (Mark et al., 1997a,b; Bruce-Keller et al., 1998; Cutler et al., 2004; Demuro et al., 2010). Several studies have demonstrated that Aβ peptides interact with and alter the properties of membrane lipids, thereby increasing permeability to Ca^{2+} and other anions (Müller et al., 1995; Cribbs et al., 1997). With the high electrochemical gradient for Ca^{2+}, compromised plasma membranes will preferentially pass Ca^{2+} into the cytosol. Electrophysiological and structural studies have shown separately that Aβ peptides can incorporate into the plasma membrane and form cation-selective high-conductance pores that are capable of disrupting cellular homeostasis (Arispe et al., 1993; Pollard et al., 1993; Lashuel et al., 2002). The clinical relevance of the Aβ pores to AD pathology is supported by their selective presence in the brains of patients with AD and not in healthy subjects (Inoue, 2008). As a third proposed mechanism, Aβ peptides have been shown to interact with several Ca^{2+}-permeable channels and to increase Ca^{2+} flux. These include several voltage-gated Ca^{2+} channels, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and NMDA glutamate receptors, and serotonergic (5-HT_3) and cholinergic (nicotinic $\alpha7$ and $\alpha4\beta2$) receptors (Buckingham et al., 2009; Demuro et al., 2010; Verdurand et al., 2011).

Regarding intracellular Ca^{2+} signaling, Aβ specifically disrupts ER Ca^{2+} channels as well, contributing to broader Ca^{2+} signaling disruptions. $A\beta_{42}$ peptides have been shown to increase RyR3 expression in transgenic mouse models of AD (Supnet et al., 2006, 2010) as well as to increase the RyR open channel probability, resulting in increased Ca^{2+} flux (Shtifman et al., 2010). Likewise, Aβ peptides increase the IP_3-evoked Ca^{2+} response in neurons directly (Schapansky et al., 2007), as well as indirectly through the alteration of G_q-coupled mGlurR5 receptors (Casley et al., 2009; Renner et al., 2010). On the other hand, by impairing coupling of muscarinic acetylcholine receptors to Gq11 via a membrane lipid peroxidation-mediated mechanism, Aβ can suppress Ca^{2+} responses to acetylcholine (Kelly et al., 1996). In a cyclical fashion, it has also been shown that Ca^{2+} can initiate and accelerate the formation of pathogenic Aβ species (Isaacs et al., 2006), but relevant to this topic is that Ca^{2+} from RyR-sensitive stores in particular can enhance the production and release of Aβ peptides (Querfurth and Selkoe, 1994; Querfurth et al., 1997) (Fig. 4). More recently described is a novel Ca^{2+} channel (CALHM1) localized to the ER and plasma membranes. Although the channel's intended function is unclear, mutations in the *CALHM1* gene have been associated with AD and result in increased Aβ formation (Dreses-Werringloer et al., 2008; Boada et al., 2010; Cui et al., 2010; Cui et al., 2010). However, the role of CALHM1 in AD is still under debate, and several studies, albeit possibly underpowered (Boada et al., 2010), have either not supported or have modified the original findings (Bertram et al., 2008; Beecham et al., 2009; Minster et al., 2009; Lambert et al., 2010).

τ pathology, in the form of hyperphosphorylated τ aggregates that give rise to intracellular neurofibrillary tangles, is also a diagnostic component of AD. Upon accumulation within neurons, the tangles impair cellu-

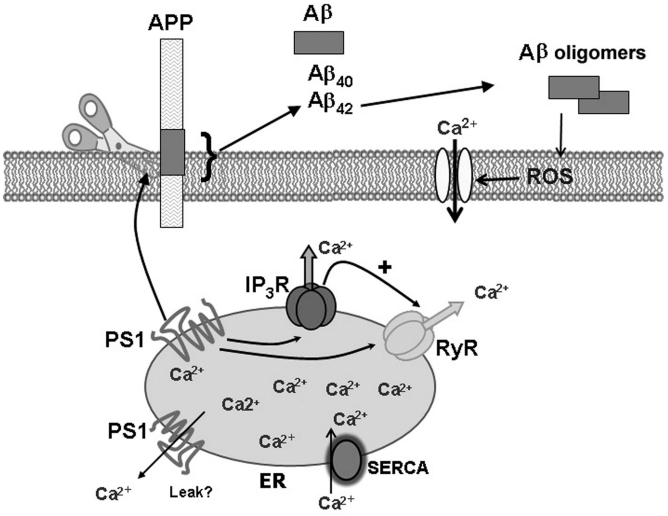

FIG. 4. The role of presenilin in ER Ca^{2+} signaling and dysregulation. The transmembrane-spanning presenilin protein largely functions as an aspartyl protease localized in the ER membrane. It cleaves several type 1 membrane proteins, including β-APP. As part of the γ-secretase complex, presenilin cleaves APP (scissors) to generate $A\beta_{40}$ and $A\beta_{42}$. $A\beta_{42}$ readily self-aggregates to form toxic oligomers that may damage neurons by inducing membrane-associated reactive oxygen species (ROS) that, in turn, impair the function of ion-motive ATPases, resulting in membrane depolarization and Ca^{2+} influx through glutamate and voltage-dependent channels. Ca^{2+} oligomers may also form Ca^{2+}-conducting pores in the membrane. Presenilin-1 (PS1) mutations that cause Alzheimer disease result in increased levels of $A\beta_{42}$, rather than the more commonly produced and relatively inert $A\beta_{40}$ fragment generated by wild-type PS1. PS1 mutations also result in increased Ca^{2+} release from ER stores through a mechanism that probably involves IP_3R and RyR. This increased Ca^{2+} flux also accelerates Aβ formation, which in turn contributes to Ca^{2+} dyshomeostasis. PS1 may also be involved in ER Ca^{2+} homeostasis by serving as a leak channel; and PS1 mutations may impair this Ca^{2+} leak channel function, thereby leading to increased resting Ca^{2+} store levels and increased Ca^{2+} release upon activation of IP_3R or RyR.

lar trafficking and synaptic function and ultimately contribute to cell death (Iqbal et al., 2005). Two decades ago, it was reported that excessive elevations of intracellular Ca^{2+} levels, such as occurs during chronic activation of glutamate receptors, can induce τ hyperphosphorylation and intracellular aggregation in hippocampal neurons similar to the alterations seen in neurofibrillary tangles in AD (Mattson, 1990). Several recent studies elegantly synthesize the pathogenic interrelationship of Aβ, τ phosphorylation, and Ca^{2+}, demonstrating how Ca^{2+} elevation, probably resulting from Aβ, causes mis-sorting and hyperphosphorylation of τ into dendrites, and it underlies the breakdown of dendritic spines and synaptic dysfunction (Hoover et al., 2010; Zempel et al., 2010). Many of the kinases that are involved in the pathogenic hyperphosphorylation process are regulated by Ca^{2+}, such as glycogen synthase kinase 3β and cyclin-dependent kinase 5 (Avila et al., 2004). Increases in cytosolic Ca^{2+} levels, originating from either intra- or extracellular sources, can therefore accelerate the activity of these kinases and facilitate tangle formation. Analogous to the Aβ/Ca^{2+} dynamic, phosphorylated or mutant τ can also increase Ca^{2+} levels within neurons (Gómez-Ramos et al., 2006), maintaining the feed-forward degenerative cycle between Ca^{2+} dysregulation and AD progression.

Although the cause(s) of sporadic late-onset AD are presently undefined, some genetic and environmental risk factors have been identified. *CALHM1* mutations were already mentioned, but expression of two apolipoprotein E ε4 alleles is one of the better studied examples and has been shown to increase the likelihood of developing sporadic AD by 15-fold (Farrer et al., 1997). Apolipoprotein E primarily functions in cholesterol and lipid transport, but the εE4 variant also impinges on Ca^{2+} signaling pathways and can alter intracellular Ca^{2+} levels through several pathways. These include up-regulation of NMDA-mediated Ca^{2+} influx, recruitment of intracellular stores and voltage-sensitive plasma membrane channels, and rises in resting Ca^{2+} levels (Tolar et al., 1999; Ohkubo et al., 2001; Qiu and Gruol, 2003). A sedentary lifestyle, excessive energy intake, and diabetes may increase the risk of AD (for review, see Kapogiannis and Mattson, 2011). Other studies have shown that exercise and dietary energy restriction can protect neurons against insults that disrupt cellular Ca^{2+} homeostasis, including overactivation of glutamate receptors, mitochondrial impairment, ischemia, and Aβ (Bruce-Keller et al., 1999; Halagappa et al., 2007; Arumugam et al., 2010). The impact of exercise and dietary energy intake on ER Ca^{2+}-regulating systems remains to be determined; however, it was reported that dietary energy restriction results in up-regulation of the ER protein chaperone GRP78 in brain cells (Duan and Mattson, 1999; Arumugam et al., 2010).

VI. Future Directions

A. Technological Advances

The full extent to which intracellular Ca^{2+} signaling supports cellular functioning is only beginning to be understood, the current knowledge state probably reflecting the tip of a large iceberg. The coming years will certainly provide a new level of understanding, in part because of the concurrent technological advances that can accelerate and target precise Ca^{2+}-signaling pathways within cells, as well as within specific organelles. Chemical Ca^{2+} indicators, such as the fura or Oregon Green series of BAPTA-based dyes, have been used for many years and have provided great flexibility in their design and specificity for binding affinity and ratiometric quantitation assays (Paredes et al., 2008). However, the relatively more recent development of genetically encoded Ca^{2+} indicators opens new doors in terms of experimental design and probe specificity. Because these indicators become incorporated at the genome level and are translated as fluorescent proteins that alter their emission intensity as a function of Ca^{2+} levels, they can be used in long-term experiments over days to months as well as introduced into intact animals for in vivo models or used to generate transgenic animals

for probing activity over a lifetime (Kotlikoff, 2007; Mank et al., 2008). Although beyond the scale of this review, the optimization of many genetically encoded Ca^{2+} indicators now provides the opportunity to probe Ca^{2+} signaling dynamics in both large and small scales (Rochefort and Konnerth, 2008). Imaging large populations of cells simultaneously allows for detailed insight into network activity (Wilms and Häusser, 2009) in vitro and in vivo, whereas fluorescence resonance energy transfer-based analysis can demonstrate Ca^{2+}-dependent responses at the single protein level (Rochefort and Konnerth, 2008). There is a large range of possible applications of these technologies, including single-cell imaging in vivo and the measurement of Ca^{2+} signaling within individual organelles and cellular compartments (Tian et al., 2009). Future developments in this arena will advance a better understanding of the dynamics of intracellular Ca^{2+} signaling.

Another interesting advance involves the modification of the channelrhodopsins, which function as light-activated ion channels in algae, to optically manipulate Ca^{2+} regulation within targeted cells and organelles (Boyden et al., 2005). Genetically redesigned channelrhodopsins can be expressed in a variety of cell types. For example, channelrhodopsin-2, a Ca^{2+}-permeable, light-activated ion channel, has been used for triggering Ca^{2+} influx and is particularly useful in excitable cells such as neurons. In this regard, it has been used to as a tool to activate and study synaptic transmission and plasticity. On even broader scales, the behavior of transgenic channelrhodopsin-2-expressing nematodes, fruit flies, zebrafish, and mice has been remote-controlled by optical stimulation. In the future, these types of experimental approaches may serve a variety of new applications and in basic science and translational research studies (Schoenenberger et al., 2011).

B. Therapeutic Opportunities

Because numerous cellular functions rely on intracellular Ca^{2+}, dysfunction in ER Ca^{2+} signaling is involved in a range of disease states. Malignant hyperthermia and central core disease are examples of RyR1-mediated neuromuscular diseases, RyR2 mutations play a role in stress-induced polymorphic ventricular tachycardia (a form of cardiac arrhythmia) and arrhythmogenic right ventricular dysplasia, and RyR3 dysfunction may be involved in mood and memory disorders (Mackrill, 2010). As described in section VII, alterations in the expression or function of RyR and IP_3R have been implicated in AD. Altered IP_3R activity has also been linked to cardiac hypertrophy, neurodegenerative diseases, cancer, and metabolic disorders (Stutzmann, 2005; Verkhratsky, 2005; Bezprozvanny and Mattson, 2008; Higazi et al., 2009; Cárdenas et al., 2010). As research progresses, this abbreviated list will probably lengthen considerably. As the awareness of the role of ER Ca^{2+} signaling dysregulation in disease grows, so will targeted therapeutic strategies directed at specific elements of intracellular Ca^{2+} signaling cascades. Some progress in these areas is already under way. For example, dantrolene is a RyR-blocker used in the treatment of malignant hypothermia, as well as neuroleptic malignant syndrome, and muscle spasticity. Other experimental applications for RyR-stabilizing compounds are being tested, such as the benzothiazepine K201 in treatments for heart failure and kidney disease (Mackrill, 2010). Significant hurdles still exist, but these may not be insurmountable. Because of the widespread distribution of the RyR and IP_3R, global targeting against an entire receptor class is likely to result in major side-effects; however, the anticipated development of reagents against specific receptor subtypes will better target and address disease states. With the confluence of technological advances under development to probe intracellular Ca^{2+}, and the growing knowledge of the functions and diseases in which ER Ca^{2+} is involved, the coming years will probably bring a surge of new information and therapeutic strategies targeting ER Ca^{2+} pathways.

Acknowledgments

This work was supported in part by the Intramural Research Program of the National Institutes of Health National Institute on Aging (to M.M.); and by the National Institutes of Health National Institute on Aging [Grant AG030205] (to G.E.S.). We thank K. C. Alexander for assistance in the preparation of figures and Corinne Schneider for editorial assistance.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Stutzmann and Mattson.

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