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Calcium Stores in Vertebrate Photoreceptors

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Abstract

This review lays out the emerging evidence for the fundamental role of Ca^{2+} stores and store-operated channels in the Ca^{2+} homeostasis of rods and cones. Calcium-induced calcium release (CICR) is a major contributor to steady-state and light-evoked photoreceptor Ca^{2+} homeostasis in the darkness whereas store-operated Ca^{2+} channels play a more significant role under sustained illumination conditions. The homeostatic response includes dynamic interactions between the plasma membrane, endoplasmic reticulum (ER), mitochondria and/or outer segment disk organelles which dynamically sequester, accumulate and release Ca^{2+} . Coordinated activation of SERCA transporters, ryanodine receptors (RyR), inositol triphosphate receptors (IP3Rs) and TRPC channels amplifies cytosolic voltage-operated signals but also provides a memory trace of previous exposures to light. Store-operated channels, activated by the STIM1 sensor, prevent pathological decrease in $[\text{Ca}^{2+}]_i$ mediated by excessive activation of PMCA transporters in saturating light. CICR and SOCE may also modulate the transmission of afferent and efferent signals in the outer retina. Thus, Ca^{2+} stores provide additional complexity, adaptability, tuneability and speed to photoreceptor signaling.

Keywords

Calcium store; Light; Photoreceptor; Retina; Ryanodine receptor

Introduction

Visual behavior in diurnal vertebrates is guided by two classes of retinal photoreceptor. Rods subserve highly sensitive black-and-white vision at starlight and moonlight whereas daytime vision is mediated by cones which provide color vision and spatial resolution. As is the case with all primary sensory neurons, both photoreceptor cell types are compartmentalized into input (outer segment, OS) and output domains that are distinct in terms of anatomy, physiology, molecular composition and ion homeostasis. The distinguishing characteristic of photoreceptor signaling is that release of the neurotransmitter glutamate occurs in the absence of external input (light) whereas absorption of photons in the OS elicits an intensity-dependent decrease in exocytosis. Signaling mechanisms that affect photoreceptor $[\text{Ca}^{2+}]_i$ levels inevitably modulate retinal output and perception of light by regulating light adaptation, gene expression, metabolic function and transmitter release in rods and cones. In particular, Ca^{2+} release from internal stores has been shown in recent years to modulate tonic signaling at photoreceptor synapses in a manner that is unparalleled in the CNS (reviewed in [32, 53, 96]). Ca^{2+} release from ER stores has a pro-found and non-redundant role in sustaining neurotransmitter release in darkness [52, 90] whereas light causes closure of voltage-operated Ca channels, resulting in depletion of Ca^{2+} stores in the

endoplasmic reticulum (ER). The resultant influx of Ca^{2+} through store-operated channels (SOCs) replenishes the stores but may also modulate synaptic transmission [94]. By dynamically regulating release and sequestration of Ca^{2+} and activation of SOCs, Ca^{2+} stores control the amplitude, response speed and sensitivity of photoreceptor signals [12, 90, 95]. Critical for photoreceptor cell health, ER and mitochondrial stores also maintain proper basal calcium levels within photoreceptor cytosol [4, 5, 92]. This essay reviews the current information regarding how Ca^{2+} stores participate in and maintain Ca^{2+} homeostasis, cellular adaptation and synaptic function.

Photoreceptor Ultrastructure Is Designed for Local Ca^{2+} Store Signaling

The ultrastructure of rod and cone photoreceptors follows the general design of primary sensory neurons. A vertebrate photoreceptor cell is constructed of two separate anatomical/functional compartments that process signal input and output, respectively (Fig. 39.1). An “outer segment” (OS) is uniquely designed to carry out transduction of the photon energy into an electrical signal, whereas the downstream “inner” regions host transcriptional, translational, metabolic and synaptic functions. Rod OSs differ from cone OSs in that they are tightly packed with hundreds of membrane sacs (“disks”), rather mysterious organelles spaced at ~ 0.3 nm that contain a high density of the visual pigment opsin ([8, 70]; Fig. 39.1a). The inner photoreceptor region consists of ellipsoid, subellipsoid and cell body domains connected to a synaptic terminal through a short but thick axon (Fig. 39.1). Unless otherwise indicated, the cell compartment downstream from the outer segment will be referred to as the “inner segment (IS)”.

The OS and IS compartments are separated by a thin nonmotile cilium which represents a bottleneck for diffusion of ions and molecules but also supports continuous translocation of proteins and lipids into the OS via specialized dynein/kinesin motors and Ca^{2+} buffers such as centrin, calmodulin, kinesin II, *unc117* and myosin VII (e.g., [61, 106]). The ellipsoid region represents the cell's powerhouse with up to 80% of its overall volume filled with mitochondria [34, 70, 76]. In some species (such as mouse), mitochondria are also found in synaptic terminals where they may occupy up to 25% of the volume [42]. The subellipsoid region near the perikaryon contains rough ER sacs and tubules which extend into the smooth ER that spans the entire IS (including the synaptic terminal) but does not enter the OS [66]. Transitional smooth ER, localized close to the Golgi apparatus in the subellipsoid space, regulates the incessant trafficking of proteins into the OS. Proximal to the inner segment is the perikaryon composed of the nucleus surrounded by ER-like membranes. The synaptic region also contains copious smooth ER tubules and sacs [66], which may play a role in the presynaptic synthesis of proteins (e.g., [29]) and transmitter release (see below).

Brief Overview of Ca Homeostasis in Photoreceptors

Calcium regulation lies at the heart of photoreceptor signaling. The spatiotemporal properties of Ca^{2+} signals in rods and cones are specific to each subcellular location and are markedly influenced by light/dark adaptation and metabolic status of the cell. In turn, changes in $[\text{Ca}^{2+}]_i$ spanning ~ 10 – 25 -fold dynamic range play a key role in the biological regulation of these processes that include phototransduction, energy metabolism, cytoskeletal dynamics and transmitter release (reviewed in [23, 32, 93, 96]). The peculiar feature of photoreceptor signaling is that “resting” $[\text{Ca}^{2+}]_i$ levels are high in darkness (estimated at ~ 300 – 700 nM) whereas the encoding of light is associated with a decrease in $[\text{Ca}^{2+}]_i$ (to ~ 5 – 50 nM; [81]). The functional separation between input and output regions is mirrored by molecular separation between different types of plasma membrane and intracellular store transporters and ion channels (Križaj and Copenhagen, 1998; 2002). These impart domain-specific amplitude and frequency modulation of light-evoked $[\text{Ca}^{2+}]_i$

levels with voltage-sensitivity, Ca^{2+} affinities, transport and modulation properties particular to each segment. The quasi-independent regulation of Ca influx and clearance allows for specific tuning a wide array of Ca^{2+} signaling systems that use sensors with differing affinities (Križaj and Copenhagen, 1998; [93]).

The Outer Segment

The sole function of the outer segment is to intercept photons and transduce photon energy into graded changes in the membrane potential. The OS possesses a single plasma membrane Ca^{2+} entry pathway (the cGMP-gated [CNG] channel) and one Ca^{2+} clearance pathway, the Na , K^+ - Ca^{2+} exchanger [NKCX] driven by combined Na^+ and K^+ gradients (NCKX1 in rods; NCKX2 in cones) [45, 69, 73]. In darkness, $[\text{Ca}^{2+}]_i$ is high due to sustained cation influx through CNG channels which are regulated by the dynamic equilibrium between cGMP synthesis and hydrolysis. Because both cation influx through CNG channels and cGMP synthesis are directly suppressed by Ca^{2+} , light-regulated $[\text{Ca}^{2+}]_i$ levels in the OS are essential for the ability of rods and cones to adapt to ambient light levels [23, 45, 102].

Using suction electrodes, Matthews and Fain [63] observed that the outer segment Ca^{2+} concentration in salamander rods was strictly proportional to the Ca^{2+} flux across the OS plasma membrane. There was no evidence of contributions from IP_3 -sensitive stores, leading them to conclude that intracellular compartments (i.e., disks) do not contribute to light-evoked changes in $[\text{Ca}^{2+}]_{\text{OS}}$. Despite the negative findings obtained through mostly electrophysiological means [41, 63], the exclusivity of the CNGC/NKCX mechanism has been challenged by biochemical and molecular data accumulated over the past 30 years. ROS disks were suggested to be close to impermeable in the darkness [109]. Early studies showed that disks are capable of accumulating significant amounts of Ca^{2+} [21, 44, 84] which was released in response to light. More recently, light was shown to *increase* cytosolic $[\text{Ca}^{2+}]_{\text{OS}}$ in rods and cones by releasing as much as 10–50 μM Ca^{2+} per liter tissue volume from some type of still uncharacterized buffer or store [10, 62, 63]. This phenomenon was sensitive to BAPTA and depletion of Ca^{2+} from intracellular storage sites. Although the intensity of light required to induce it was too strong to regulate physiological rod $[\text{Ca}^{2+}]_{\text{OS}}$, the mechanism could be more physiologically relevant for cones as it occurs at intensities that bleach only a few percent of the cone photopigment [10, 15]. Its independence of photochannel-mediated influx and cone phototransduction argues for the presence of a new signaling mechanism that could be associated with a new buffer site or store but is also likely to involve Ca^{2+} diffusion from mitochondrial stores within the adjacent ellipsoid.

Schnetkamp [84] estimated that the intradiskal $[\text{Ca}^{2+}]_i$ is ~3 orders of magnitude higher than in the cytosol (15–25 μM) with a capacity of 8–9 Ca^{2+} binding sites per rhodopsin molecule. This was confirmed by the Koutalos group which used fluorescent Ca^{2+} and pH dyes to measure $[\text{Ca}^{2+}]_i$ and pH within the intradiskal space. They found that concentrations of these two ions differ markedly from cytosolic and extracellular $[\text{Ca}^{2+}]$ and pH values with high intradiskal $[\text{Ca}^{2+}]$ at an acidic pH of 6.5 [13, 56]. Thus, with respect to Ca^{2+} and proton regulation, disks may not act as passive sacs but rather comprise an active cellular organelle. While the molecular identity of putative disk Ca^{2+} sequestration and release mechanisms has not been determined, circumstantial evidence has implicated ryanodine receptor, IP_3 receptor and/or SERCA mechanisms ([20, 86, 87, 101]; but see [15, 41, 63]). Biochemical studies have suggested that Ca^{2+} fluxes into the disks might be driven by a SERCA-like Ca^{2+} pump [18, 75, 87]. Conversely, cADPR, a known physiological activator of ryanodine receptor (RyR) channels, evoked Ca^{2+} release from suspensions of osmotically intact disks prepared from bovine ROS; ADPR cyclase activity was detected in disk, but not cytosolic

ROS fraction [20]. Finally, isolated disks contain a protein with high molecular weight similar to RyRs (~520 kDa; [119]) whereas RyR1 was localized to the disk rim using antibody staining and electron microscopy [87]. Taken together, these findings suggest that rod disks express the typical ER-like Ca^{2+} signaling arrangement possibly associated with SERCA3 and RyR1 [51, 87].

Another unresolved issue pertains to the role of phospholipase C (PLC) signaling in the OS. Phospholipase C plays a key role in Ca signaling through its hydrolysis of the membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate (IP_3 ; an agonist of IP_3 receptors) and diacylglycerol (DAG; an activator of protein kinase C and TRPC3/6/7 channels). The enzyme has been localized to OS membranes with molecular, biochemical, physiological and genetic approaches. $\text{PLC}\beta_4$ and/or $\text{PLC}\gamma_1$ activity was observed in rod disks and the plasma membrane ([27, 28]; Gehm et al., 1992), apparently under control of light ([31]; [118]; [28]), visual pigment [11] and Ca^{2+} [25]. Activation of $\text{PLC}\beta_4$ triggered Ca^{2+} release from bovine OS membranes [44, 84]. $\text{PLC}\beta_4$ was proposed to colocalize with $\text{G}_{\alpha q11}$ [74]. Consistent with such an arrangement, PLC function in light-activated ROS was suppressed by addition of $\text{GTP}\gamma\text{S}$ [114]. While a number of studies suggested that light activates PLC in parallel to transducin activation and cGMP hydrolysis ([26]; 1985; [108] 1987; [43]; [118]; [48]), the physiological function of such a mechanism in the OS is completely unknown. A potential clue may originate in measurements of light responses from $\text{PLC}\beta_4$ knockout mice which showed that the a-wave component of the ERG (thought to reflect the compound light response of retinal photoreceptors) is four times smaller in knockout eyes than in wild type eyes [40]. Taken together, biochemical studies seem to argue that rod OSs are capable of sequestering and releasing Ca^{2+} , however, this process may only be detected under appropriate experimental conditions that preclude dialysis of cytosol with patch pipettes (e.g., [41]).

The Cilium and the Ellipsoid

From the viewpoint of Ca^{2+} and pHi regulation, the outer and inner segment compartments are separated by a ciliary barrier that limits diffusion of H^+ , Ca^{2+} and cGMP [46]. A patch pipette filled with cGMP, when applied to the inner segment, is not very effective in increasing the concentration of cGMP and the photocurrent in the outer segment, in contrast to patched OSs when whole cell mode can sustain cGMP-induced currents of >1 nA for up to 30 min [112]. Likewise, linescan confocal imaging showed that large-scale Ca^{2+} release from internal stores in the rod IS does not affect Ca^{2+} signals in the OS [54]. It remains to be seen whether diffusion of Ca^{2+} across the cilium plays a greater role in intact tissue undergoing light–dark transitions.

The gatekeeper for Ca^{2+} diffusion across the cilium are the ellipsoid mitochondria. These organelles, which generate ATP required to drive the circulating dark current, possess a remarkable capacity for Ca^{2+} sequestration [92] which serves to protect the gain control mechanisms in the OS from interference by Ca^{2+} fluxes in the IS. On the other hand, it is not inconceivable that these mitochondria represent a releasable Ca^{2+} store that liberates Ca^{2+} in response to light (e.g., [15]).

ER Ca^{2+} Stores in the IS

Photoreceptor ER is a continuous, dynamic, constantly rearranging network of smooth cisternae that extend from the synaptic terminal to the subellipsoid space. This multifunctional organelle represents the site of synthesis and proper folding of newly synthesized proteins, phospholipids and glucosylphosphatidylinositols as well as a graveyard for unwanted molecules and toxins ([35, 64]; [121]). In addition, ER cisternae contain the highest intracellular Ca^{2+} content in photoreceptor cells [89, 98, 99], consistent

with their function as a cellular Ca^{2+} reservoir that represents the second line of defense, after the cytosolic buffer proteins, against pathologically high or low $[\text{Ca}^{2+}]_i$ [93].

ATP-dependent Ca^{2+} uptake into IS ER [99] is mediated by the SERCA (sarco-endoplasmic reticulum calcium ATPase) family mostly represented by the SERCA isoform 2 [2, 50, 51]. SERCA2 ($K_d \sim 0.7 \mu\text{M}$) shares Ca^{2+} clearance from the cytosol with high-affinity PMCA1 and PMCA2 pumps ($K_d \sim 0.2 \mu\text{M}$) [54, 94]. Under light-saturated conditions, Ca^{2+} sequestration into the ER lowers the steady-state $[\text{Ca}^{2+}]_{IS}$ by $\sim 25\text{--}40 \text{ nM}$; that is, SERCAs contribute $\sim 50\%$ to baseline $[\text{Ca}^{2+}]_i$ [54, 94]. SERCA contribution is considerably higher in depolarized cells where it can reach hundreds of nM (Fig. 39.2a). Episodes of darkness reload ER stores and consequently the ER reverts from a sink to source (e.g., [36]). The amount of releasable Ca^{2+} reflects the magnitude of the depolarizing stimulus and the amplitude of $[\text{Ca}^{2+}]_i$. ([52, 54]; Fig 39.2b). CICR contributes to steady-state $[\text{Ca}^{2+}]_i$, as suggested by $\sim 20\text{--}50\%$ reduction in the magnitude of depolarization-evoked $[\text{Ca}^{2+}]_i$ elevations in rod and cone perikarya following SERCA blockade [2, 54, 92].

Amphibian and mammalian photoreceptors express RyR1 and RyR2 isoforms (detailed descriptions of expression profiles, biophysical activation properties, mechanisms of activation and function of the 3 known RyRs are provided elsewhere; e.g., [58]). As in most brain regions, RyR2 are the dominant isoform in photoreceptors [51, 55] which may express a new retina-specific variant of RyR2 that includes a 21 bp deletion from exon 4 [87]. Physiological studies showed that CICR in the IS was a smoothly graded function of Ca^{2+} influx [52], a characteristic typical of RyR2 [88]. RT-PCR, in situ hybridization and antibody staining suggest mammalian photoreceptors might also express the skeletal RyR1 isoform ([86, 87]; [113]). RyR1s are typically Ca^{2+} -independent but can also participate in CICR, when in the “uncoupled mode” ([110]; [71]). The retina also expresses RyR3 mRNA and protein ([86]; [113]), a developmentally regulated isoform that can be co-expressed with RyR2 [64]. Surprisingly, developing avian photoreceptors were reported to express a thapsigargin-sensitive pool that does not contain RyRs or IP3Rs ([17]; but see [39]).

In contrast to voltage-operated entry that is characterized by rapid, local Ca^{2+} influx at the active zone [3, 65, 96], release from ER stores mediated by RyRs and possibly IP3Rs participates in slower, longer-range Ca^{2+} signaling. Under strong illumination when the resident L-type voltage-operated channels are closed and $[\text{Ca}^{2+}]_i$ is low, RyRs are likely to be constitutively active at a random frequency within the range of homeostatic fluctuation of the hyperpolarized membrane potential (~ -60 to -70 mV ; e.g.; [7]) whereas in the darkness, sustained Ca^{2+} release from ryanodine stores represents a significant additional source of cytosolic $[\text{Ca}^{2+}]_i$ [52, 54]. Release from ryanodine stores may contribute to the membrane potential either as positive or negative feedback, depending on the pattern of activation of Ca^{2+} -dependent K^+ and Cl^- conductances, and Ca^{2+} -induced inactivation of voltage-operated L-type channels [2, 52]. Given that CICR acts as an amplification device, its contribution is most pronounced in depolarized rods responding to flashes that evoke small changes in presynaptic voltage [90]. Parenthetically, the majority of studies that focused on photoreceptor CICR used pharmacological agents such as caffeine, ryanodine, Ruthenium Red, 2-APB and/or SERCA antagonists. These non-physiological modulators are often non-specific and/or have multiple targets. There is a pressing need to determine the function of physiological modulators such as NAAD⁺, cADP ribose and/or $\beta\text{-NAD}^+$.

CICR signals are far more prominent in rods than in cones. Stimulation with caffeine produced small $[\text{Ca}^{2+}]_i$ elevations in a tiny subset of amphibian cones whereas the majority of cells evinced no response whatsoever [54]. Consistent with this observation, the time course of depolarization-induced $[\text{Ca}^{2+}]_i$ elevations in rods, but not cones, was strongly dependent on store release [92]. The absolute capacity of cones to sequester Ca^{2+} in

intracellular compartments appears to be comparable to rods, however, because exposure to thapsigargin elicits comparable (~50%) decreases in the size of the residual intracellular Ca^{2+} pool [92]. This might suggest that the magnitude of caffeine-evoked Ca^{2+} transients in cones is reduced by stronger PMCA-mediated Ca^{2+} clearance (Križaj and Copenhagen, 1998), activation of K^+/Cl^- channels and/or by mitochondrial uptake through ER:mitochondrial microdomains. Consistent with this hypothesis, caffeine consistently induced significant Ca^{2+} responses in cones in the presence of PMCA or mitochondrial blockers [54].

While Ca^{2+} sequestration into ER stores plays a crucial role in IS Ca^{2+} homeostasis and tonic neurotransmitter release, depletion of ryanodine-sensitive Ca^{2+} stores empties only a fraction of total accumulated Ca^{2+} in rods [54]. This suggests that IP_3 stores, mitochondrial, lysosomal and Golgi apparatus also mediate Ca^{2+} sequestration and release in rods and cones (e.g., [92]). In contrast to the clear evidence of PLC- IP_3 signals in invertebrate photoreceptors [100], physiological investigations of IP_3R function in vertebrate photoreceptors have been lagging behind. The available evidence suggests that IS regions express PLC and IP_3 receptors [39, 55, 74] that may be associated with metabotropic mGluR signaling [47], synaptic output [40] and circadian rhythmicity mediated by presynaptic somatostatin 2A receptors and PLC [39].

Ca Stores and Neurotransmission at Photoreceptor Synapses

Ca^{2+} release from intracellular stores was suggested to regulate the level of tonic neuronal activity at some central synapses by contributing to spontaneous neurotransmitter release that sets the frequency of mEPSCs (reviewed in [9, 16]). The role of Ca^{2+} stores is particularly prominent in sensory “ribbon” synapses of photoreceptors and hair cells [2, 12, 59, 90]. EM and X-ray diffraction analyses have identified copious intracellular storage sites in synaptic terminals of rods and cones. These are represented mainly by smooth ER cisternae that contain both RyRs and IP_3Rs ([66, 99]; [120]; [2]).

The primary source of cytosolic Ca^{2+} at ribbon synapses are dihydropyridine-sensitive, L-type channels which are mainly localized at peri-ribbon sites near the active zone [65]. Within the synaptic terminal, release from Ca^{2+} stores and subsequent influx through store-operated channels act in parallel with voltage-operated Ca^{2+} entry. Wallace Thoreson's group at the University of Nebraska used paired recordings from photoreceptors and postsynaptic cells to show that high concentrations of ryanodine evince a reduction in the late component of the postsynaptic EPSC [12]. Calcium stores are located away from the active zone yet still within the diffusible distance of ~600 nm from the ribbon [2] at which they could stimulate release from the reserve pool(s) of synaptic vesicles [97]. Capacitance recordings from dissociated salamander photoreceptors showed that photolysis of caged presynaptic $[\text{Ca}^{2+}]_i$ can under certain conditions evoke slow exocytosis that presumably bypasses the early releasable pool [49], offering an alternative parallel route possibly consisting of ectopic release of synaptic vesicles from non-ribbon sites (e.g., [57, 105]).

Presynaptic $[\text{Ca}^{2+}]_i$ drives the exocytotic process and information transfer across the photoreceptor synapse at the astonishing rate of 100–400 vesicles/s [14, 79, 97]. The high rate of release is presumably required to support reliable transfer of presynaptic voltage changes in the order of 1 μV [22]. Indeed, the rod synapse was the first documented case where synaptic release was shown to be driven by submicro-molar to low micromolar levels of average cytosolic $[\text{Ca}^{2+}]_i$ [49, 79, 97] rather than hundreds of μM typically required at central synapses. In part, this is made possible by the high Ca^{2+} affinity of presynaptic SNAREs and buffering proteins (reviewed in [32]) and in part by the close proximity of L-type channels to the ribbon [65], which allows for the generation of local microdomains

where $[Ca^{2+}]_i$ is likely to be substantially higher. In addition to high affinity of Ca^{2+} binding, the synapse is characterized by its capacity for tonic release which is subserved by the resistance of presynaptic channels to inactivation (McRory et al., 2005) and by CICR which boosts synaptic release when rods are maintained at physiological resting membrane potentials of ~ -40 mV [12, 52, 90]. CICR is required for the maintenance of tonic release at physiological membrane potentials whereas the presynaptic potential required non-physiological depolarizations to ~ -20 mV in the absence of CICR [90]. Elimination of RyR-mediated Ca^{2+} release converted a tonic synaptic signals into phasic bursts of vesicle release [90]. Hence, over most of the dynamic range, Ca^{2+} release from internal stores is likely to contribute to maintaining linear synaptic transfer of information between photoreceptors and postsynaptic horizontal/bipolar cells [97, 103].

Store-Operated Channels

Although depolarization-evoked glutamate release from rods is completely suppressed by L-type channel antagonists that inhibit voltage-dependent Ca^{2+} entry, saturating white light blocked only a fraction of total released glutamate [82, 83]. This suggests that other, voltage-independent Ca^{2+} influx pathways that are activated in light-adapted and strongly hyperpolarized cells, regulate the dynamic range of rod signaling. One such mechanism might consist of transient receptor potential (TRP) channels localized to photoreceptor terminals. Data from amphibian and mammalian rods suggest that TRP-like channels contribute to baseline $[Ca^{2+}]_i$ [67, 94]. At least a subset of these channels appears to be regulated by depletion of intracellular Ca^{2+} stores through the STIM1 sensor mechanism [4, 5, 94, 95] (Fig. 39.3). While the physiological function of the SOCE is still unclear, depletion of ER cisternae in rod terminals caused an increase in presynaptic $[Ca^{2+}]_i$ that was capable of modulating release of FM1-43-labeled vesicles [94]. Consistent with this finding, inhibition of SOCE suppressed the slow component of the horizontal cell EPSC without having affecting voltage-operated signals [95] (Fig. 39.3e). The molecular identity of channel underlying SOCE has not been unequivocally established. Most retinal cells, including photoreceptors, appear to express multiple TRP subfamilies and isoforms [68, 80, 107]. TRPC1 isoform-specific siRNAs reduced SOCE in rods but had no effect on cone SOCE [94] whereas the TRPC3/6/7 channel antagonist diacylglycerol induces $[Ca^{2+}]_i$ elevations in mammalian rods and cones.

Summary

It has become increasingly clear that photoreceptor ER and mitochondria are capable of storing remarkable amounts of Ca^{2+} in a compartment-specific manner and that calcium stores and store-operated channels play a significant role in vertebrate photoreceptors Ca^{2+} homeostasis and synaptic signaling. Photoreceptor signaling in darkness is strongly associated with CICR whereas light-induced signaling is characterized by depleted ER stores and activation of SOCE. Rod and cone cells exhibit differences both in the magnitude/kinetics of the releasable Ca^{2+} pool, interactions with plasma membrane Ca^{2+} signaling mechanisms and in the physiological manifestations of CICR and SOCE. Thus, Ca^{2+} accumulation into and release from internal stores endow photoreceptor signaling with potential for far more complex, tunable and adaptable homeostatic regulation than believed so far.

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Fig. 39.1.

(**a**) Schematized generic rod photoreceptor. The outer segment (OS) is filled with stacked disk organelles (*arrows*) containing the visual pigment rhodopsin. The inner segment (IS) downstream from the OS is formed by three anatomically distinct domains: (i) ellipsoid, which contains most of cell's mitochondria; (ii) the cell body, which contains the cell nucleus, nuclear envelope formed by the ER cisternae and (iii) the synaptic terminal, packed with synaptic vesicles and cisternae of smooth ER. (**b**) Dissociated salamander rod and (**c**) Salamander cone photoreceptor. Abbreviations: *PMCA* plasma membrane Ca²⁺ ATP-ase, *CaBP4* calcium binding protein isoform 4, *IP3R* IP3 receptor, *RyR* ryanodine receptor, *SERCA* sarcoplasmic-endoplasmic reticulum Ca²⁺ ATPase, *VGCC* voltage-gated channel, *ER* endoplasmic reticulum, Ca²⁺ sequestration and release from the mitochondria occurs via Ca²⁺ uniporter channels and Na⁺/Ca²⁺ transporters, respectively. Scale bars = 5 mm

Fig. 39.2.

CICR in rod photoreceptor under hyperpolarized and depolarized conditions. The fura-2-loaded cell was stimulated with puffs of 10 mM caffeine to stimulate ryanodine receptors. Sustained superfusion with 20 mM KCl activated voltage-operated Ca^{2+} entry, resulting in a transient increase in $[\text{Ca}^{2+}]_i$ followed by a gradual decline to a stable plateau due to Ca^{2+} -dependent VOCC inactivation. Caffeine puffs evoked substantially larger $[\text{Ca}^{2+}]_i$ transients under depolarized conditions. Each transient response was followed by an undershoot caused by SERCA activation (arrows), and a transient overshoot resulting from the activation of store-operated Ca^{2+} entry (arrowhead). (b) The magnitude of caffeine-evoked Ca^{2+} release depends on the magnitude of the conditioning depolarization. Rod photoreceptor inner segment. Conditioning steps of high K^+ were followed by superfusion with 10 mM caffeine. Each star represents a single 128 ms KCl puff; bars denote superfusion. Increase in the duration of conditioning $[\text{Ca}^{2+}]_i$ steps caused a subsequent increase in the magnitude of caffeine-evoked $[\text{Ca}^{2+}]_i$ responses. These occurred after $[\text{Ca}^{2+}]_i$ returned to the baseline, implying a form of intracellular “memory”

Fig. 39.3.

Depletion of Ca^{2+} stores facilitates plasma membrane Ca^{2+} entry and modules synaptic transmission. (**a**) Depletion of Ca^{2+} stores evoked a $[\text{Ca}^{2+}]_i$ overshoot characteristic of SOCE. The same phenomenon was observed in depolarized cells (*inset*). (**b–e**) Paired whole cell recordings from rod-horizontal cell pairs. The SOCE antagonist MRS-1845 has no effect on the light response (**b**) or voltage-operated Ca^{2+} current (**c**). Injection of depolarizing current in the rod, however, evokes a reduction in the amplitude of the light-evoked horizontal cell response (**d**), reflected in the smaller amplitude of the late EPSC component (**e**)