Review

Calcium-activated chloride channels in the retina

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This review examines the function of calcium-activated chloride currents (ICl(Ca)) in the retina with an emphasis on their physiological role in photoreceptors. Although found in a variety of neurons and glial cells of the retina, ICl(Ca) has been most prominently studied in cones, where it activates in response to depolarization-evoked Ca2+ influx. The slow and complex gating kinetics of the chloride current have been considered to reflect the changing submembrane concentration of intracellular calcium. It is likely that the role of ICl(Ca) is to stabilize the membrane potential of cones during synaptic activity and presynaptic Ca channel modulation. Several candidates in the molecular identification of the channel have been put forward but the issue remains unresolved.

ICl(Ca) Is Activated by Depolarization-Evoked Ca2+ Influx

ICl(Ca) is elicited by depolarization-evoked Ca2+ influx. Figure 1 demonstrates a voltage-clamp recording of an isolated cone photoreceptor, responding to depolarizing voltage steps.1 The voltage steps to potentials of -20 and more positive open voltage-gated Ca channels, which leads to an influx of Ca2+ ions. Cl(Ca) channels responsible for ICl(Ca) are activated following this increased [Ca2+]i, which may be localized to the local submembrane area. Hence, during depolarizing voltage steps, the early current (measured a few ms into each voltage step) is predominantly a Ca2+ current (ICa) whereas both ICa and ICl(Ca) contribute to the late current (measured near the end of each voltage step). Following the return of the membrane potential to -60 mV, voltage-gated Ca channels deactivate rapidly (within 5 ms)2 but a large inward Ca2+-activated Cl− tail current develops in response to the elevated [Ca2+]i, from the preceding depolarizing voltage step, and the increased driving force for Cl− ions. A charge (Q)-V relation is shown in Figure 1B, exhibiting the typical shape of a calcium-activation conductance. Cadmium blocks ICa at zero mV (Fig. 1C) and ICl(Ca) following the return to -60 mV. The amplitude of Ca2+-activated Cl− tails is determined not only by [Ca2+]i at the submembrane level, but also by the number of Cl(Ca) channels activated by Ca2+, and the electrochemical gradient for Cl− ions. Since neuronal Ca2+-activated Cl− tail currents do not show evidence of inactivation, the complex time course of decay following repolarization is proposed to reflect the slow deactivation of Cl(Ca) channels as submembrane [Ca2+]i decreases due to Ca2+ handling and restoration to normal resting levels via a variety of cellular processes (reviewed in refs. 3 and 4).

A number of studies have proposed the exclusive regulation of Cl(Ca) channel activity by [Ca2+]i, in neurons.5-14 In cone photoreceptors, the steep dependence of Cl(Ca) channels on [Ca2+]i is linked to Ca2+ influx through voltage-gated Ca channels as the non-specific Ca channel blocker, Cd2+, inhibited Cl(Ca) channel activation.3,10,15 Such relationships between Ca2+ entry through voltage-gated Ca channels and ICl(Ca) activation have been observed in different systems including mammalian neurons and smooth muscles.16,17

Free [Ca2+]i, Sets the Amplitude and Kinetics of Ca2+-Activated Cl− Tail Current

The importance of [Ca2+]i for Cl(Ca) channel activation can be readily demonstrated by changing the Ca2+ buffering capacity in the patch-pipette solution. The kinetics of the Ca2+-activated Cl− tail current have previously been shown to be modulated in different cells by changing the buffering capacity of the intracellular environment.7,18 Large Ca2+-activated Cl− tail currents with slow deactivation kinetics can be obtained in cones in the presence of a low-capacity buffering system (0.1 mM BAPTA), whereas small Ca2+-activated Cl− tail currents (1 mM BAPTA) with fast kinetics are present when the free [Ca2+]i is reduced (Lalonde and Barnes, unpublished observations). Figure 2A, B, and C show a family of current traces, recorded with the standard depolarizing protocol, as described above, in the presence of intracellular BAPTA at concentrations of 0.001, 0.1, and 1 mM. For each experimental condition, differences in ICl(Ca) kinetics can be further investigated by fitting the largest Ca2+-activated Cl− tail currents with a saturated exponential function.

The saturated exponential approach used to fit the decay of ICl(Ca) (Box 1) suggests that the predominant factor governing deactivation of Cl(Ca) channels is simple one-dimensional diffusion of [Ca2+]i.3 The decaying Ca2+-activated Cl− tail currents was proposed to reflect a progressive decrease in [Ca2+]i, and not intrinsic inactivation of ICl(Ca).11,14 In that study, the authors observed the re-activation of declining Ca2+-activated Cl− tail currents in rat dorsal root ganglia (DRG) when generating a steep [Ca2+]i increase via the photorelease of caged Ca2+. Saturation of the exponential function, achieved by convolution with a modified Hill equation, is proposed to reflect...
occupancy of all available Ca\(^{2+}\) binding sites on Cl(Ca) channels or other regulatory partners. Single exponential behavior, as seen during the later part of the current trajectory, implies diffusion of Ca\(^{2+}\) away from the plane of the membrane, suggesting that Ca channels and Cl(Ca) channels are located in close proximity to each other at the membrane.

Since Ca\(^{2+}\) influx is required for vesicle fusion, Ca channels are presumably located in close proximity to the ribbon synapse, which orchestrates the flow of neurotransmitter-filled vesicles to the release site. Similarly, Cl(Ca) channels involved may be localized at the cone pedicle. In fact, ion channels mediating I_{Cl(Ca)} in rods are thought to be preferentially located at the terminal.\(^{19}\)

**Cone Photoreceptor Cl(Ca) Channels May Co-Localize with L-Type Ca Channels**

Tightly linked [Ca\(^{2+}\)]\(_{\text{r}}\)-Cl(Ca) channel coupling that is only suppressed under a high-capacity buffering system provides evidence that Cl(Ca) channels and voltage-gated Ca channels lie in close proximity to one another and form a submembrane microsystem. The co-localization of other Ca\(^{2+}\)-dependent channels and voltage-gated Ca channels has also been suggested for Ca\(^{2+}\)-activated K channels\(^{20}\) and Ca\(^{2+}\)-activated non-selective cation channels in Helix neurons.\(^{21}\) Given the prevalence of L-type Ca channels in cone photoreceptors,\(^{2}\) the specific co-localization of Cl(Ca) channels and L-type Ca channels is plausible. The activation of I_{Cl(Ca)} following Ca\(^{2+}\) influx specifically through L-type Ca channels has also been proposed in other systems, including cardiac myocytes\(^{22}\) and oesophageal smooth muscle cells,\(^{17}\) where L-type Ca channels are predominant. In cone photoreceptors, Cl(Ca) channels likely outnumber voltage-gated Ca channels. This postulation is based on single channel properties and maximum cell current amplitudes of both of these channels. Voltage-gated Ca channels have a large conductance and small whole-cell I_{Ca}. On the other hand, Cl(Ca) channels have a small conductance, as judged from the smoothness of the current trajectories, and large whole-cell I_{Cl(Ca)}\(^{\text{-norm}}\). Hence, a model in which a small number of Ca channels are closely surrounded by clusters of Cl(Ca) channels appears to be a reasonable proposal.

I_{Cl(Ca)} Is Outwardly Rectifying

As a basis for comparison with other reports of CLCA currents, the current-voltage (I-V) relation of Cl(Ca) channels in cones can be investigated using ionomycin, a Ca\(^{2+}\) ionophore that induces a sustained increase in [Ca\(^{2+}\)]\(_{\text{r}}\) (Lalonde and Barnes, unpublished observations). Superfusion of cones with ionomycin activates an outwardly rectifying current that reverses close to 0 mV (Fig. 3C). Figures 3A and B show representative examples of a family of current traces from a cone photoreceptor before and approximately 3 min after 5 \(\mu\)M ionomycin superfusion, respectively. Ionomycin evokes a sustained I_{Cl(Ca)} activation probably reflecting increased [Ca\(^{2+}\)]\(_{\text{r}}\). Figure 3C shows the constructed I-V relation from the recording before (Control; black circles) and after (IONO; white circle) ionomycin superfusion. The I-V relation in the presence of ionomycin approaches linearity and reverses close to E_{Cl}. This steady-state I-V relation is normalized at -40 mV (potential generating largest Ca\(^{2+}\)-activated Cl\(^{-}\) tail current) to correct for changes in current at the holding potential (IONO\(_{\text{norm}}\); grey circles). The normalized I-V relation in the presence of ionomycin also indicates outward rectification at positive potentials. Outward rectification, a typical observation for many conductances, is also seen in several CLCA channel currents, as discussed below.
Molecular Candidates for Cl(Ca) Channels

The molecular identity of Cl(Ca) channels in cones remains unresolved. This is largely attributable to the lack of specific pharmacological blockers and antibodies for Cl(Ca) channels, and is also related to the discrepancies in the Cl(Ca) channel phenotype between endogenous Cl(Ca) channel current and current recorded in photoreceptors. Cl(Ca) channels may therefore be co-localized with high voltage-gated Ca channels at the plasma membrane, to ensure efficient activation by localized domains of elevated Ca2+.23,24

The dependence of I_{Cl(Ca)} on submembrane [Ca^{2+}], has been readily demonstrated by replacing Ca^{2+} ions with Ba^{2+} in the extracellular solution.1,25 Ba^{2+} is commonly used as a charge carrier in voltage-gated Ca channels. In the presence of 3 mM Ba^{2+}, peak inward current measured near zero mV is significantly enhanced while peak Ca^{2+}-activated Cl- tail current is significantly inhibited. The increased current during depolarization reflects more current through voltage-gated Ca channels when Ba^{2+} is used as a charge carrier. A number of studies have reported that Ba^{2+} is ineffective in inducing Ca^{2+}-activated Cl- tail currents in neurons.6-9,16,18,26-30 While it is likely that Ba^{2+} ions do not activate Cl(Ca) channels, other explanations may account for the inhibited Ca^{2+}-activated Cl- tail current. For example, Ba^{2+} ions could be activating Cl(Ca) channels, but the diffusion of Ba^{2+} from the submembrane area may be faster than that of Ca^{2+}, which may account for the lack of tail currents.

I_{Cl(Ca)} Is Not Modulated by Calmodulin or by Calmodulin Inhibitors

Within the inner segment, Ca^{2+} may activate calmodulin (CaM) kinases that in turn could phosphorylate a number of targets within the synaptic terminal, including Cl(Ca) channels. CaM could be a direct intermediate between Cl(Ca) channel activation mediated by [Ca^{2+}], The effect of CaM on cone I_{Cl(Ca)} was investigated by including 1 µM CaM in the recording pipette solution. Ca^{2+}-activated Cl- tail currents remaining during depolarizing voltage steps and during repolarization following those steps was the same (Lalonde and Barnes, unpublished observations).

The effect of the CaM inhibitors, trifluoperazine and calmidazolium, on cone photoreceptor I_{Cl(Ca)} is also tested by adding these drugs to the superfusate. Although both of these CaM inhibitors have been shown to reduce I_{Cl(Ca)} in pulmonary artery endothelial cells,31 these drugs failed to modify I_{Cl(Ca)} in cone photoreceptors (Lalonde and Barnes, unpublished observations). These results suggest that CaM may not have a significant role in the activation of Cl(Ca) channels in cone photoreceptors. However, a number of Ca^{2+}-binding proteins are found in cone photoreceptors and the modulation of Cl(Ca) channels via Ca^{2+}-binding proteins other than CaM can not be ruled out.

Dependence of Cl(Ca) Channel Activation by Ca^{2+} Influx through L-Type Ca Channels

Dihydropyridine-sensitive L-type Ca channels have been identified and characterized in cone photoreceptors.2 BayK also significantly increases peak I_{Cl(Ca)}; A 50% increase can be observed in the Ca channel current in cones whereas I_{Cl(Ca)} measured from the Ca^{2+}-activated Cl- tail current is enhanced by the same amount, suggesting a near one-to-one correspondence between Ca^{2+} entry and Cl(Ca) channel activation (Lalonde and Barnes, unpublished observations). This potentiation of I_{Cl(Ca)} by BayK has also been previously observed in dorsal root ganglia (DRG) neurons.3 The activation of voltage-gated Ca^{2+} currents most likely increases Ca^{2+}-activated Cl- tail currents by increasing the Ca^{2+} available to activate Cl(Ca) channels. This suggest that Cl(Ca) channels are activated by local Ca^{2+} microdomains located at the plasma membrane as a result of Ca^{2+} entering via voltage-activated L-type Ca channels in cone photoreceptors.
mammalian cells expressing heterologous candidate Cl(Ca) channel proteins.32-37 Of the existing molecular candidates for Cl(Ca) channels, two different families of molecules have been proposed to form the Cl(Ca) channels found in many excitable cells. These are the gene families encoding the CLCA38,39 and bestrophins.40,41 Additional candidates that have also been proposed as putative Cl(Ca) proteins, include the CIC-3 protein, which has been suggested to give rise to the epithelial Cl(Ca) channels whose Ca2+ sensitivity is increased by Calmodulin Kinase II phosphorylation.42 Gene products for CLCA, bestrophins and CIC-3 are all present in mammalian retina 39,40,44 (reviewed in refs. 33 and 47). A similar quaternary structure was proposed for the homologs of bCLCA1 cloned from mouse (mCLCA1)48,49 and for the human homolog hCLCA1.46 The primary structure of bCLCA1 showed no similarity to any other cloned Cl-selective channel. Analysis of the primary amino acid sequence of bCLCA1 predicted at least four putative transmembrane domains with an extracellular N-terminus. Structural models suggest that it co-assembles as a homotetrameric protein complex (reviewed in refs. 33 and 47). A similar quaternary structure was proposed for the homologs of bCLCA1 cloned from mouse (mCLCA1)48,49 and for the human homolog hCLCA1.50 The likely topology of the CLCA channel protein is four or five transmembrane domains with an extracellular N-terminus, containing a number of conserved cysteine residues and an extracellular (if four transmembrane domains) or intracellular (if five transmembrane domains) C-terminus.38,50-53 It has been proposed that CLCA proteins are synthesized as precursor proteins of approximately 125 kD with 5 TM domains. This protein is subsequently cleaved into two fragments. A 90 kD amino-terminal fragment containing transmembrane spanning domains 1 to 3 and a carboxy terminal fragment with two transmembrane spanning domains51 (reviewed in refs. 32 and 33).

When expressed in Xenopus oocytes, bCLCA1 is characterized by an outwardly rectifying Cl− conductance, which is observed without raising [Ca2+].54 However, currents in transfected COS-7 cells were characterized by a linear I-V relation and were only observed upon raising [Ca2+].46 A second epithelial Cl(Ca) channel, hCLCA2, cloned from human lung, trachea, and mammary gland, when expressed in HEK293 cells, also requires high [Ca2+]i to be activated, is slightly outwardly rectifying and blocked by Cl channel blockers.51 Although, CLCA proteins are characterized by several consensus sites for PKC phosphorylation, the mechanism of activation of CLCA channels, either directly by Ca2+ or by phosphorylation, is still unclear. Moreover, acceptance of CLCA as being a Ca (Cl) channel has not been universal given that some members are secreted proteins and do not appear to be integral membrane proteins.42 Thus, the possibility that CLCA proteins activate endogenous Cl channels rather than being channels themselves has not been excluded.52,55 hCLCA2 and mCLCA5, the murine counterpart of hCLCA2, are expressed in high levels in the eye, notably in the corneal epithelium and retinal pigment epithelium.56 The CLCA epitope has also been detected in retinal Müller glia,53 however no conclusive evidence has been put forward for CLCA in photoreceptors. It has been suggested that CLCA may form a component of a heteroligomeric Ca2+-activated conductance that encompasses several distinct candidates, including bestrophin proteins.33
Bestrophins

Bestrophin proteins have been associated with Cl(Ca) channels and Cl− transport in the retinal pigment epithelium. Human bestrophin 2, which is a protein product of the vitelliform macular dystrophy (VMD2) gene, generates Ca2+-sensitive anion currents when expressed. Mutations in bestrophin 2 and bestrophin 3 are present in the autosomal dominant disorder Best disease, a vitelliform macular dystrophy in which accumulation of lipofuscin-like material in the retinal pigment epithelium (RPE) causes a progressive loss of central vision. The characteristic accumulation of fluid in Best disease is consistent with abnormal fluid transport by the RPE. Bestrophins from several species have now been demonstrated to form Ca2+-activated Cl conductances on heterologous expression with intermediate conductance channels with Cl conductances on heterologous expression.

Figure 4. Cl(Ca) channels responsible for ICl(Ca) are not vesicular ClC-3 channels that integrate with the plasma membrane upon Ca2+ influx. (A) Current traces ~5 min and (B) ~10 min following rupture in the presence of anti-CLC-3 in the pipette solution are similar. (C) V−I relations from the same cell also show no significant changes in current (~5 min: black circles; ~10 min: white circles). This experiment was carried out using methods identical to those described in ref. 1, except that here, anti-ClC-3 (Alomone Labs, Jerusalem, Israel) was dialyzed into the cell via the pipette solution. Intracellular dialysis of 5 μg/ml of this polyclonal antibody directed against one of the cytoplasmic domains of the C-terminus (residues 592–661) of the rat ClC-3 was used. This epitope is highly conserved in all known vertebrate ClC-3 proteins, and the anti-ClC-3 antibody recognizes a full-length ClC-3 voltage-gated Cl channel.

Additional Molecular Candidates for Cl(Ca) Channels

Additional candidates that have also been proposed as putative Cl(Ca) proteins are the long form of the human voltage-gated Cl channel gene, CLC-3 (reviewed in refs. 36, 37, 47 and 61), which gives rise to the epithelial Cl(Ca) channels whose Ca2+ sensitivity is increased by Calmodulin Kinase II phosphorylation. As ClC-3 is thought to primarily reside in intracellular organelles, such as synaptic vesicles, it has been proposed that ICl(Ca) could arise from Cl channels located in synaptic vesicles (i.e. ClC-3) that integrate with the plasma membrane during periods of depolarization. Synaptic vesicle docking is mediated by a complex between components of the synaptic vesicle membrane (synaptobrevin and synaptotagmin) and the presynaptic plasma membrane (syntaxin and SNAP-25). Synaptobrevin has been shown to be present in the outer plexiform layer of the rat retina. Since Ca2+ is required for the fusion of synaptic vesicles with the presynaptic plasma membrane, ClC-3 channels in vesicles may fuse with the plasma membrane in response to depolarization-mediated Ca2+ influx, giving rise to increased whole-cell Cl− conductance. A ClC-3 knockout mouse which showed selective postnatal degeneration of the hippocampus and photoreceptors, and impaired acidification of synaptic vesicles, supported the hypothesis that Cl(Ca) channels are vesicular ClC-3 channels that are integrated with the plasma membrane upon Ca2+ influx following depolarization. Lalonde et al. (unpublished data) examined the effect of a polyclonal antibody directed towards ClC-3 (anti-ClC-3) on ICl(Ca) in salamander cone photoreceptors. Inclusion of the CLC-3 antibody in the recording pipette solution did not inhibit cone photoreceptor Cl(Ca) currents (Fig. 4). This antibody was previously shown to inhibit CLC-3 trafficking to the plasma membrane and CLC-3-mediated Cl− current in mammalian ocular epithelial cells. Further examination of whether Cl(Ca) conductances could arise independently of ClC-3 via another Cl channel that may fuse with the cell membrane during Ca2+ dependent vesicle docking, was also tested in cone photoreceptors using tetanus toxin. Tetanus toxin, a neurotoxin produced by bacteria of the genus Clostridium, is a potent inhibitor of neurotransmitter release. This toxin functions as an endoprotease that selectively targets synapto-
The Physiological Role of Cl(Ca) Channels in Cone Photoreceptors

Although pharmacological and biophysical properties of I_{Cl(Ca)} have been characterized, the major role of Cl(Ca) channels in cones is unclear. Following light stimulation, cyclic-nucleotide gated channels (CNGCs) in the outer segment close and Ca\textsuperscript{2+} influx ceases, but extrusion at the inner segment continues, greatly decreasing [Ca\textsuperscript{2+}]. In saturating light, Ca\textsuperscript{2+} levels in cone inner segments may be as low as 10–50 nM. Therefore, I_{Cl(Ca)} must play a minor role under these conditions. In the dark, [Ca\textsuperscript{2+}] is high. Therefore, the Ca\textsuperscript{2+}-activated Cl\textsuperscript{-} conductance would be highest in darkness when voltage-gated Ca channels and light-sensitive cation channels are open, and lowest in bright light when both are closed.

The Role of I_{Cl(Ca)} During the Feedback Response Depends on E_{Cl}

Broad field or surround light stimuli strongly hyperpolarize horizontal cells and this causes, via the feedback synapse, an increase in both Ca channel and Cl(Ca) channel activity. The movement of Cl\textsuperscript{-} in and out of cells, and therefore, the polarity of the membrane...
Deactivating Cl(Ca) tail currents were fit with a saturating exponential function of the following form to emphasize possible features governing $I_{Cl(Ca)}$ activation:

$$I_{\text{deact}} = I_{\text{max}} \times (1 - 1/(1 + ([\text{Ca}^{2+}]/[E_{\text{Ca}}])^n)),$$

where $[\text{Ca}^{2+}] \propto I_{\text{exp}} = I_{\text{nat}} \times e^{(V/V_t)}$

A single exponential, $I_{\text{exp}}$, is first fit to the late stage of the deactivating current, a region typically well suited for exponential fitting. However, the amplitude of the exponential function exceeded by a large margin the amplitude of the tail current at times immediately following the voltage step back to -60 mV, and frequently deviated in this manner for tens of milliseconds. Convolution of the exponential function with a modified Hill equation (expressed as a function of current, not concentration) reduced or saturated the early large amplitude region of the tail current decay, yet had no effect on the late smaller amplitude stage. Since the magnitude of the exponential current, $I_{\text{exp}}$, is assumed to be proportional to the concentration of a gating factor (e.g., $[\text{Ca}^{2+}]$), this component replaced the concentration variable in the Hill equation. Adjusting the midpoint value for $I_{\text{exp}}$ saturation ($E_{\text{Ca}}$), the saturation amplitude ($I_{\text{max}}$), and cooperativity constant (Hill coefficient, $n$) optimized the fit.

After a duration of ~200 ms following the return to -60 mV, the decay followed an exponential time course. However, before this time, convolution with a sigmoidal dose-response function produced saturation of the exponential curve. At the lowest concentration of intracellular BAPTA tested (0.001 mM; example cell shown in Fig. 2A), the exponential portion of the peak Ca$^{2+}$-activated Cl tail current is fit with a mean $\tau$ value of about 190 ms, a relatively slow rate of deactivation. Figure 2B shows a family of current traces recorded with 0.1 mM BAPTA in the patch-pipette solution. The averaged $\tau$ calculated when this buffering system is used was about 109 ms. The saturated exponential fit of the largest Ca$^{2+}$-activated Cl tail current, which is recorded at 0 mV, is shown as a dotted line in Figure 2D. At the highest concentration of intracellular BAPTA tested (1 mM; Fig. 2C), the averaged $\tau$ calculated is about 57 ms. These results indicate that when free $[\text{Ca}^{2+}]$ is high, Ca$^{2+}$-activated Cl tail currents deactivate slowly. This agrees with the proposed model that the Ca$^{2+}$-activated Cl tail current decay reflects Ca$^{2+}$-ions diffusing away from the Cl(Ca) channels located at the plasma membrane. A relatively faster rate of Ca$^{2+}$-activated Cl tail current deactivation is observed when a high-capacity buffering system is used, in agreement with a fast decrease in free $[\text{Ca}^{2+}]$, near Cl(Ca) channels after the voltage-gated Ca channels had closed.

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