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Voltage- and calcium-gated ion channels of neurons in the vertebrate retina.

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Abstract

In this review, we summarize studies investigating the types and distribution of voltage- and calciumgated ion channels in the different classes of retinal neurons: rods, cones, horizontal cells, bipolar cells, amacrine cells, interplexiform cells, and ganglion cells. We discuss differences among cell subtypes within these major cell classes, as well as differences among species, and consider how different ion channels shape the responses of different neurons. For example, even though second-order bipolar and horizontal cells do not typically generate fast sodium-dependent action potentials, many of these cells nevertheless possess fast sodium currents that can enhance their kinetic response capabilities. Ca^{2+} channel activity can also shape response kinetics as well as regulating synaptic release. The L-type Ca^{2+} channel subtype, $Ca_V1.4$, expressed in photoreceptor cells exhibits specific properties matching the particular needs of these cells such as limited inactivation which allows sustained channel activity and maintained synaptic release in darkness. The particular properties of K^+ and Cl^- channels in different retinal neurons shape resting membrane potentials, response kinetics and spiking behavior. A remaining challenge is to characterize the specific distributions of ion channels in the more than 100 individual cell types that have been identified in the retina and to describe how these particular ion channels sculpt neuronal responses to assist in the processing of visual information by the retina.

Keywords

retina; ion channels; horizontal cell; amacrine cell; retinal bipolar cell; retinal ganglion cell; photoreceptor cell

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1. Introduction

Investigators have explored the complement of ion channels in retinal neurons using an array of electrophysiological, immunohistochemical and molecular approaches. Early electrophysiological studies focused largely on non-mammalian vertebrates but later investigations provided greater insight into the properties of mammalian retinas. In recent years, the number of identified cell types in retina has increased considerably. For example, initial studies distinguished ON and OFF types of bipolar cells but we now recognize more than a dozen subtypes of bipolar cells. There is an even larger number of amacrine and ganglion cell types. Accompanying this expansion of recognized cell types has been a tremendous expansion in our understanding of the molecular diversity of ion channels. In that context, we thought it useful to summarize the current state of knowledge regarding the types of ion channels present in different types of retinal neurons. We focus on voltage- and Ca^{2+}-dependent ion channels that transform photocurrents and synaptic currents into voltage responses. We do not focus on other ligand-gated ion channels such as the cyclic nucleotide-gated channels in photoreceptor outer segments or ion channels that couple directly to neurotransmitter receptors. Nor do we focus on aquaporins, gap junction hemichannels, TRP channels, or transporters. We use nomenclature recommended by the International Union of Pharmacology (IUPHAR) as summarized in “The Concise Guide to Pharmacology 2017/18” (Alexander et al., 2017a; Alexander et al., 2017b; Alexander et al., 2017c), supplemented by some of the more commonly used terms. Before turning to the different cell types, we begin with a summary of the subtypes and structural features of the ion channels that are the focus of this review.

1.1 K^+ channels

1.1.1 *Inwardly rectifying K^+ channels* are formed from a tetrameric complex of 4 individual subunit proteins that each possess 2 transmembrane domains linked by a short pore-forming reentrant loop (P-loop) (Hibino et al., 2010; Tao et al., 2009). These channels lack a genuine voltage sensor but nevertheless exhibit an inwardly rectifying voltage-dependence that arises from blockade of outward currents by divalent cations at the intracellular surface of the channel pore. Some inwardly rectifying K^+ channels (KIR1.1-7.1) are constitutively active, some are activated by $G\beta\gamma$ subunits of G-proteins (GIRK), and others are activated by a fall in intracellular ATP (K_{ATP}).

1.1.2 *Two-pore K^+ channels* are formed from dimers with each subunit containing 4 transmembrane alpha helices (M1-4) along with two P-loops linking M1 to M2 and M3 to M4 (Brohawn et al., 2012; Miller and Long, 2012). The presence of two P-loops in each subunit endows this group with its name. Like KIR channels, two-pore channels (K2P1.1-12.1) lack a genuine voltage sensor. Constitutive activity of two pore channels contributes to the leak K^+ current in many cells and is important for setting the resting membrane potential (Feliciangeli et al., 2015; Renigunta et al., 2015).

1.1.3 *Voltage-gated K^+ channels* (Armstrong, 2003; Kim and Nimigean, 2016; Kuang et al., 2015) are constructed from heteromeric or homomeric combinations of 4 individual subunits. Each subunit possesses 6 trans-membrane domains (S1-S6) with a P-loop located between S5 and S6. These channels are activated by depolarizing potentials. The voltage

sensor in these and other similar voltage-dependent channels is the S4 trans-membrane domain that contains a number of positively charged amino acid residues (typically arginine). Membrane depolarization causes these residues to move towards the extracellular side of the membrane and the resulting conformational change in the protein opens the channel pore. It was originally proposed that voltage-sensing involves an outward helical screw motion of the S4 segment (Cha et al., 1999; Glauner et al., 1999), but subsequent structural analysis suggested that the S4 domain undergoes a paddle-like outward movement in response to depolarization (Jiang et al., 2003). Functional subtypes of voltage-gated K^+ channels include delayed rectifier currents (I_{KDR}) in which outward currents inactivate slowly and A-type currents (I_{KA}) that inactivate rapidly. Rapid inactivation occurs through a "ball-and-chain" mechanism in which the amino terminus swings towards the channel pore to block conductance, involving either the K^+ channel subunit itself or a segment of an accessory β subunit (Hille, 2001; Kurata and Fedida, 2006). Slow inactivation of I_{KDR} involves conformational changes that restrict pore conductance. There are a few dozen subtypes of voltage-gated K^+ channels (K_v1.1 to 12.3). K_v1-4 channels can form both homomeric and heteromeric channels with members of the same subclass (e.g., K_v1.1 with K_v1.2). Homomeric and heteromeric combinations of different K_v7 subunits form a special type of delayed rectifier current known as M-type currents. M currents were named for the ability of muscarinic agonists to inhibit these channels. Other agents that activate $G_{q/11}$ signaling pathways can also inhibit these channels (Brown and Passmore, 2009; Greene and Hoshi, 2017). K_v5, 6, 8 and 9 subunits have a similar structure as other K^+ channels, but do not form functional homomeric channels. However, they can form functional channels in heteromeric combination with K_v2 subunits (Bocksteins, 2016).

K_v10-12 subunits encode ether-a-gogo (eag, K_v10), ether-a-gogo-related (erg, K_V11) and ether-a-gogo-like (elk, K_v12) channels (Bauer and Schwarz, 2018). Ether-a-go-go channels received their name because under ether anesthesia, Drosophila with mutations in this channel shake their legs like go-go dancers (Vandenberg et al., 2012). These channels have a much shorter domain linking S4 and S5 domains compared to Kv1-2 channels that suggests a different gating mechanism (Whicher and MacKinnon, 2016). K_v10-12 channels have a C-terminal domain that is homologous to the cyclic nucleotide binding domain of CNG and HCN channels but lacks certain key residues so that it does not bind cyclic nucleotides.

In addition to the many pore-forming K_v channel subunits, a number of accessory K^+ channel subunits have also been identified (Pongs and Schwarz, 2010). The many possible combinations of subunits and accessory proteins allows for an extremely large number of functionally and molecularly distinct K^+ channels tuned to meet the particular needs of different cells.

1.1.4 *Calcium-activated K^+ channels* (Adelman et al., 2012; Christophersen and Wulff, 2015; Kaczmarek et al., 2017; Kshatri et al., 2018; Latorre et al., 2017) are functionally classified as small, intermediate and large conductance channels. Like voltage-gated K^+ channels, Ca^{2+}-activated K^+ channels with small (K_{Ca}2.1-2.3; SK) and intermediate (K_{Ca}3.1; IK) single channel conductance are formed from four subunits, each containing 6 trans-membrane domains with one P-loop. Ca^{2+} activates these channels in a voltage-independent way by binding to calmodulin (CaM) associated with a CaM binding domain on

the C-terminus. Ca^{2+}-activated K^+ channels ($K_{Ca}1.1$) with a large single channel conductance (~250 pS in symmetrical K^+) are referred to as big K^+ (BK) or Maxi K^+ channels. In addition to the 6 transmembrane domains possessed by most other voltage-dependent channels, BK channels have an additional S0 trans-membrane domain, placing the N-terminus on the extracellular rather than the intracellular surface as is typical of channels with six transmembrane domains. In BK channels, binding of Ca^{2+} to domains on the intracellular surface can directly activate the channels (Yuan et al., 2011; Yuan et al., 2010). The accompanying allosteric changes to the protein also lower the threshold for voltage-dependent activation by shifting voltage-dependence to more negative potentials. There is only a single gene for BK channels, but as with other channels, there are multiple splice variants. Accessory beta and gamma subunits can further modify the activity of BK channels.

1.1.5 *Sodium-activated K^+ channels* ($K_{Na}1.1$-1.2) (Kaczmarek, 2013; Kaczmarek et al., 2017) are formed from 6 transmembrane domains and a P-loop, but the S4 segment appears less free to move and does not possess the sequence of positively charged amino acid characteristic of voltage-dependent K^+ channels (Hite et al., 2015). Elevation of intracellular Na^+ and Cl^- can both activate these channels. K_{Na} channels are expressed in many neurons but, to our knowledge, their presence in retinal neurons has not been investigated.

1.2 Voltage-gated Na^+ channels

Voltage-gated Na^+ (Na_V) channels are the key class of ion channels used to generate action potentials and are responsible for Na^+ entry during the rising phase of the action potential (Ahern et al., 2016; Catterall, 2017). Unlike K^+ channels that are formed from combinations of 2-4 individual subunits, the Na^+ channel pore is formed from a single large α1 subunit protein. The α1 subunit consists of 4 similar sequences (I-IV), each possessing six transmembrane alpha helices (S1-6) with a short P-loop between S5 and S6, similar to individual voltage-dependent K^+ channel subunits. As with most other voltage-dependent channels, the S4 domains function as the voltage sensor. Na^+ channels underlying regenerative spiking are characterized by rapid and pronounced inactivation. Na^+ channel inactivation involves a “hinged lid” mechanism in which the cytoplasmic loop between domains III and IV folds into the channel mouth to prevent conductance. There are currently 9 known isoforms of mammalian Na_V channel alpha subunits ($Na_V1.1$-1.9). $Na_V1.1$, $Na_V1.2$, and $Na_V1.6$ are highly expressed in neurons from the central nervous system including retinal ganglion cells. In addition to the α subunit, functional channels typically associate with β subunits that can modify voltage-sensitivity and gating of the channel.

1.3 Voltage-gated Ca^{2+} channels

Voltage-gated Ca^{2+} channels share a common structure with a large pore-forming α1 subunit that assembles with an intracellular β subunit and extracellular α2δ subunit (Catterall, 2011; Dolphin, 2016). Skeletal muscle channels ($Ca_V1.1$) also have accessory γ subunits but these do not appear to associate with Ca^{2+} channels in neurons. Similar to voltage-gated Na^+ channels, the pore-forming α subunit is a single large protein composed of four domains each with six transmembrane alpha helices, a voltage sensor on the transmembrane segment S4 and a P-loop between S5 and S6. Ca^{2+} channels are functionally classified into two major

classes: low- and high-voltage activated (LVA and HVA). LVA currents ($Ca_V3.1$-3.3) activate at more negative potentials than HVA currents. Because of their **t**iny single channel conductance and rapid inactivation resulting in **t**ransient currents, LVA currents are also referred to as T-type currents. HVA L-type currents ($Ca_V1.1$-1.4) were originally defined by their **l**arge single channel conductance and **l**ong-**l**asting activation due to slow inactivation. Pharmacologically, L-type Ca^{2+} currents (I_{Ca}) are selectively sensitive to dihydropyridine agonists (e.g., BayK8644) and antagonists (e.g., nifedipine). N-type currents ($Ca_V2.2$) are HVA channels that show intermediate properties between T and L-type channels. N-type currents were found to be **n**either too long-lasting **n**or too transient and N-type single channel conductance was **n**either too large **n**or too tiny. N-type currents are also predominantly expressed in **n**eurons. Selective block of another current by funnel web spider toxin revealed additional HVA Ca^{2+} channels in cerebellar **P**urkinje cells (P-type). Keeping to this largely alphabetical arrangement, the next subtype identified by use of selective blockers was then named Q. P and Q type channels ($Ca_V2.1$) both derive from a single gene, CACNA1A. Finally, the **r**esidual current that remains after blocking the other HVA types with a cocktail of toxins was named R ($Ca_V2.3$).

1.4 HCN and CNG channels

HCN and CNG channels are cation channels that share considerable homology with other voltage-gated channels. The channels consist of 4 subunits that each possess 6 transmembrane domains (S1-S6) with a pore-forming P-loop between S5 and S6. The S4 segment contains a number of positively charged amino acids, but despite this similarity to other voltage-dependent channels, CNG channels show little or no voltage-dependence (James and Zagotta, 2018) and HCN channels (HCN1-4) are activated by membrane hyperpolarization rather than depolarization (Craven and Zagotta, 2006; Wahl-Schott and Biel, 2009). CNG and HCN channels have an intracellular cyclic nucleotide binding domain. CNG channels are opened by cyclic nucleotide binding and the voltage-dependence of HCN channels is strongly modulated by cyclic nucleotides (James and Zagotta, 2018).

HCN subunits form cation channels that are weakly selective for K^+ over Na^+ (P_{Na}/P_K = 0.2-0.3) and show little Ca^{2+} permeability. Unlike other voltage-gated ion channels, depolarization of HCN channels causes the S4 segment to move inward rather than outward towards the extracellular surface (Lee and MacKinnon, 2017). HCN channels are therefore activated by hyperpolarization and are typically active only at quite negative membrane potentials. Binding of cAMP can shift HCN voltage-dependence to more positive potentials and thereby promote HCN activity at membrane potentials that are more often attained under physiological conditions. HCN channel activity promotes oscillatory behavior in many neurons where it is sometimes referred to as an anomalous rectifier current (I_a). It also contributes to pacemaker currents in the heart where it is termed the “funny” current (I_f). In this review, we refer to the current carried by HCN channels as “I_h” for hyperpolarization-activated current.

Our focus is on voltage- and Ca^{2+}-gated ion channels and so we touch only briefly on CNG channels. There are six mammalian subunits: CNGA1-3 form functional homotetrameric channels but CNGA4, CNGB1 and CNGB3 can only form functional channels in

combination with CNGA1-3 subunits. CNG channels are non-selective for monovalent cations and also conduct Ca^{2+}, allowing it to serve as a second messenger in regulating phototransduction and olfactory transduction. We refer the interested reader to other reviews (Biel, 2009; Craven and Zagotta, 2006; James and Zagotta, 2018; Kaupp and Seifert, 2002).

1.5 Ca^{2+}-activated Cl^- channels

Anoctamin 1 and 2 (Ano1 and 2, also known as TMEM16A and B) are Ca^{2+}-activated Cl^- channels (Falzone et al., 2018; Kunzelmann, 2015; Whitlock and Hartzell, 2017). Ano1 and 2 are members of a larger family of anoctamin proteins (1-10) that also includes lipid scramblases and some cation channels. Ano1 and 2 anion channels are synergistically activated by voltage and Ca^{2+}. The name “anoctamin” was given to TMEM proteins because it was originally thought that they possessed 8 transmembrane domains although it now appears that they have 10 transmembrane domains. Bestrophin proteins (Best1-4) can also form anion channels in expression system but there remains some question about whether these are truly Ca^{2+}-activated Cl^- channels (Hartzell et al., 2008). Best1 is strongly expressed in retinal pigment epithelium cells and mutations in this protein can cause Best vitelliform macular dystrophy (Johnson et al., 2017).

2. Rod and cone photoreceptor cells

There are two main classes of photoreceptor cells in the retina: rods and cones. Cones can be further classified into subtypes based on their spectral sensitivity. While the mechanisms of phototransduction are broadly similar in rods and cones, specific protein isoforms and structural differences promote greater sensitivity in rods and faster kinetics in cones. As we discuss below, rod and cone photoreceptors share many, but not all, of the same ion channels.

The outer segments of rods contain very few or no channels besides CNG channels involved in phototransduction (Baylor et al., 1984; Baylor and Nunn, 1986). Whole cell patch clamp recordings from dissociated rods and cones of amphibian retina revealed the presence of five types of ion channels in the inner segment and synaptic terminal (Attwell and Wilson, 1980; Bader et al., 1982; Barnes and Hille, 1989; MacLeish and Nurse, 2007): 1) inwardly rectifying cation currents activated by membrane hyperpolarization below −50 mV (I_h), 2) voltage-dependent K^+ currents activated by depolarization above −60 mV (I_{Kx}), 3) sustained voltage-dependent I_{Ca} activated by depolarization above −50 mV, 4) Ca^{2+}-activated K^+ currents, and 5) Ca^{2+}-activated Cl^- currents. Rods and cones from mammalian retina share many of the same currents although Ca^{2+}-activated K^+ currents have not been observed in mammals (Cia et al., 2005; Demontis et al., 1999; Demontis et al., 2002; Han et al., 2000).

2.1 Voltage-gated Na^+ channels

Recordings from many species, including non-human primates, have failed to reveal evidence for voltage-dependent Na^+ currents in rods or cones. However, in a series of studies on small pieces of human retina excised during surgery for severe retinal detachment, Kawai and colleagues observed prominent, tetrodotoxin-sensitive action potentials in human rods and cones (Kawai et al., 2005; Kawai et al., 2001). The presence of $Na_V1.2$ channels was

confirmed in these cells by single cell PCR (Kawai et al., 2005). Anode break activation of these channels by a hyperpolarizing voltage step generated spikes and so the authors suggested that these channels might speed depolarization at the end of a light flash. There is also some immunohistochemical evidence for Na^+ channels in rodent retina with labeling of cones by antibodies to $Na_V1.9$ and labeling of photoreceptor terminals by antibodies to $Na_V1.1$ (Mojumder et al., 2007; O'Brien et al., 2008). As discussed in a perspective by Copenhagen, the consistent observation that Na^+ channels are absent from all other preparations, including non-human primates (Gayet-Primo et al., 2018; Yagi and Macleish, 1994), suggests that these channels are either uniquely present in human retina or, more likely, up-regulated in photoreceptors cultured after severe retinal detachment (Copenhagen, 2001).

2.2 Ca^{2+} channels

At the output end of the cell, release of glutamate-filled vesicles from the synaptic terminals of rods and cones is controlled by the influx of Ca^{2+} through L-type Ca^{2+} channels (Schmitz and Witkovsky, 1997; Thoreson et al., 1997; Wilkinson and Barnes, 1996). L-type Ca^{2+} channels are the only type of Ca^{2+} channels found in rods and cones (Bader et al., 1982; Barnes and Hille, 1989; Corey et al., 1984; Lasater and Witkovsky, 1991; Taylor and Morgans, 1998; Wilkinson and Barnes, 1996; Yagi and Macleish, 1994). We highlight some key aspects of Ca^{2+} channels and their properties at photoreceptor synapses. For additional details, we refer the reader to recent reviews that focus in depth on the properties of Ca^{2+} channels at photoreceptor synapses (Pangrsic et al., 2018; Waldner et al., 2018).

Sites of Ca^{2+} influx and labeling by antibodies to L-type Ca^{2+} channels are both localized close to individual synaptic ribbons of rods and cones (Cadetti et al., 2006; Choi et al., 2008; Firth et al., 2001; Lee et al., 2015; Lv et al., 2012; Morgans, 2001; Morgans et al., 2001; Nachman-Clewner et al., 1999; Taylor and Morgans, 1998). Immuno-electron micrographs show that Ca^{2+} channels sit just beneath ribbons (tom Dieck et al., 2005). Beneath each ribbon, Ca^{2+} channels are clustered in tiny sub-domains (Lv et al., 2012). Ca^{2+} channels show limited membrane mobility, behaving as if tethered in place by a weak spring (Mercer et al., 2011a). The vast majority of channels appear to be located near ribbons since salamander rods lacking synaptic terminals exhibit reductions in I_{Ca} of 95% (Xu and Slaughter, 2005).

L-type Ca^{2+} channels in rods and cones are formed principally from the pore-forming $\alpha 1$ subunit, $Ca_V1.4$, in combination with accessory $\beta 2$ and $\alpha 2\delta 4$ subunits. $Ca_V1.4$ channels are expressed almost exclusively in retina although they also appear to be present in skeletal muscle (An et al., 2015) and T-lymphocytes (Kotturi and Jefferies, 2005). In the retina of many species (mouse, rat, chicken, human), labeling with antibodies to $Ca_V1.4$ is concentrated at synaptic ribbons of rods and cones (Firth et al., 2001; Lee et al., 2015; Liu et al., 2013b; Morgans, 2001; Morgans et al., 2001; Taylor and Morgans, 1998).

One of the initial findings suggesting a role for $Ca_V1.4$ at rod synapses was that mutations in this protein can lead to diminished synaptic output from rods and congenital stationary night blindness (Bech-Hansen et al., 1998; Strom et al., 1998; see review by Zeitz et al., 2015). Over 100 different nonsense, missense or frame-shift mutations in $Ca_V1.4$ have since been

identified. These mutations can lead to loss of function, altered function, or gain of function. The impact of a specific mutation on channel function influences the nature and extent of night blindness (Zeitz et al., 2015). Mice in which $Ca_V1.4$ is completely eliminated exhibit total loss of both rod and cone responses suggesting that this channel subtype is responsible for mediating release from both types of photoreceptors, at least in this species (Mansergh et al., 2005).

Like L-type channels in other tissues, photoreceptor Ca^{2+} channels are sensitive to dihydropyridines. However, photoreceptor Ca^{2+} channels *in vivo* and heterologously expressed $Ca_V1.4$ channels show a weaker sensitivity to dihydropyridine antagonists and the benzothiazepine, diltiazem, than cardiac $Ca_V1.2$ channels (Baumann et al., 2004; Hart et al., 2003; Koschak et al., 2003; Wilkinson and Barnes, 1996). Together with poor penetration across the blood-retinal barrier, this explains why dihydropyridines and other Ca^{2+} channel blockers used for cardiovascular treatment do not cause vision changes (Uchida et al., 1997).

2.2.1 Voltage-dependence.—The L-type Ca^{2+} channels in rods and cones begin to activate above −60 mV and reach a peak around −20 mV. Voltage dependence of I_{Ca} measured in rods and cones from a number of species yields a midpoint activation voltage near −38 mV, very close to the dark resting membrane potential of photoreceptors (Babai and Thoreson, 2009; Grassmeyer and Thoreson, 2017; Schneeweis and Schnapf, 1999; Taylor and Morgans, 1998; Wu, 1985).

More than 20 splice isoforms of $Ca_V1.4$ have been identified and splice variants can differ in their voltage-dependence (Lee et al., 2015; Tan et al., 2012). While most variants activate at voltages that are more positive than those that activate the native channel, truncation of exon 47 allows channels to activate at more hyperpolarized potentials (Haeseleer et al., 2016; Tan et al., 2012). The Ca^{2+}-binding protein, CaBP4, complexes with $Ca_V1.4$ and can shift activation to more negative potentials, although not in channels lacking exon 47 (Haeseleer et al., 2004; Haeseleer et al., 2016; Park et al., 2014; Shaltiel et al., 2012; Yang et al., 2014). For most channel isoforms, the presence of CaBP4 is thus essential for rods and cones to activate at potentials necessary to span the normal physiological voltage range in dark and light. Loss of CaBP4 can cause congenital stationary night blindness or cone-rod degeneration (Aldahmesh et al., 2010; Haeseleer et al., 2004; Khan et al., 2013; Littink et al., 2009; Maeda et al., 2005; Zeitz et al., 2006).

2.2.2 Inactivation.—L-type I_{Ca} in rods and cones show little or no voltage-dependent inactivation when activated by lengthy depolarizing voltage steps (Bader et al., 1982; Barnes and Hille, 1989; Corey et al., 1984; Rabl and Thoreson, 2002; Taylor and Morgans, 1998). This property allows them to remain active in darkness when photoreceptors are continuously depolarized. $Ca_V1.4$ channels originally characterized in heterologous expression systems showed very slow voltage-dependent inactivation along with little or no Ca^{2+}-dependent inactivation (Baumann et al., 2004; Koschak et al., 2003; McRory et al., 2004). Apo-CaM binds to the IQ domain and the conformational change that occurs when Ca^{2+} ions bind to CaM leads to Ca^{2+}-dependent inactivation. The absence of Ca^{2+}-dependent inactivation in most $Ca_V1.4$ channels is due to the presence of an autoinhibitory domain in the C terminus that competes with the binding of apo-CaM to an IQ domain on

the C-terminus. Because of these competitive interactions between apo-CaM and the autoinhibitory domain, higher endogenous levels of CaM promotes stronger Ca^{2+}-dependent inactivation by promoting more binding of apo-CaM to the IQ domain. Phosphorylation of the autoinhibitory domain of $Ca_V1.4$ by protein kinase (PKA) also promotes apo-CaM binding to the IQ domain, thus further promoting Ca^{2+}-dependent inactivation (Sang et al., 2016). Some splice isoforms of $Ca_V1.4$ have truncated C-termini that lack this autoinhibitory domain, thereby allowing Ca^{2+}-dependent inactivation (Haeseleer et al., 2016; Lee et al., 2015; Tan et al., 2012). Thus, differences in the level of endogenous CaM, PKA activity, and the expression of splice isoforms can all potentially influence the degree of Ca^{2+}-dependent inactivation.

2.2.3 Accessory subunits.—β2 subunits are the predominant accessory β subunits at rod and cone synapses. In electroretinogram (ERG) recordings, eliminating β2 subunits in a mouse knockout model almost completely eliminated rod- and cone-driven b-waves (that reflect On bipolar cell responses), with a-waves (that reflect photoreceptor responses) unchanged, showing a loss of synaptic transmission from photoreceptors (Ball et al., 2002). ERGs appear normal in mice lacking β1, 3 or 4 subunits. Antibodies to β2 label the OPL whereas antibodies to other β subunits do not (Ball et al., 2002; Lee et al., 2015). Direct interactions between β2 and $Ca_V1.4$ were confirmed with proximity ligation assays. A variant of β2 with an alternate exon 7, β2X13, appears to be the predominant subtype in human retina. This variant imparts greater voltage-dependent inactivation to the channel (Lee et al., 2015).

Mutations in α2δ4 also cause greatly attenuated b-waves and cone-rod dystrophy (Kerov et al., 2018; Wycisk et al., 2006a; Wycisk et al., 2006b). Deletion of α2δ4 in knockout mice eliminated rod-driven b-waves and reduced cone-driven b-waves, with little or no change in a-waves or rod and cone photocurrents (Kerov et al., 2018; Wang et al., 2017). Antibodies to α2δ4 label synaptic ribbons of rods and cones, forming a macromolecular complex with $Ca_V1.4$ and β2 (De Sevilla Muller et al., 2013; Lee et al., 2015; Mercer et al., 2011a). This suggests that α2δ4 is the predominant subunit at rod synapses although other isoforms may contribute in cones. α2δ4 subunits link to the extracellular membrane surface via glycosyl-phosphatidyl inositol interactions (Davies et al., 2010). In the photoreceptor synaptic cleft, α2δ4 interacts with ELFN1 and this interaction is important for proper formation of rod synapses (Kerov et al., 2018; Wang et al., 2017). Eliminating either α2δ4 or ELFN1 disrupts the formation of rod synapses (Cao et al., 2015; Kerov et al., 2018; Wang et al., 2017). Cone synapses do not possess ELFN1 and are less strongly affected by deletion of α2δ4 (Kerov et al., 2018; Wang et al., 2017). α2δ and β2 subunits assist in trafficking Ca^{2+} channel α1 subunits to the membrane (Dolphin, 2016) and so eliminating either subunit can reduce expression of functional $Ca_V1.4$ channels (Kerov et al., 2018; Wang et al., 2017). Diminished expression of $Ca_V1.4$ channels (Kerov et al., 2018; Liu et al., 2013b) may explain the diminished cone responses and impaired cone synapse formation seen after eliminating α2δ4 or β2 subunits (Katiyar et al., 2015; Kerov et al., 2018; Wang et al., 2017; Zabouri and Haverkamp, 2013) and may also contribute to impaired formation of rod synapses.

2.2.4 Single channel properties.—Single channel recordings of Ca^{2+} channels from salamander rod terminals and mean-variance analysis of I_{Ca} in salamander cones have both yielded single channel properties similar to other L-type channels including a single channel conductance in 82 mM Ba^{2+} of 22 pS and maximal open probability of 0.2-0.36 (Thoreson et al., 2000)(Bartoletti et al., 2011). By contrast, recordings of $Ca_V1.4$ channels expressed in tsA-201 cells yielded a single channel conductance of only 4 pS with 100 mM Ba^{2+} as the charge carrier and a peak open probability of <0.015 (Doering et al., 2005). Another expression study found a slightly larger single channel conductance of 10 pS but also a very low open probability (Burtscher et al., 2014). Is the unusually low open probability unique to $Ca_V1.4$ in mammalian preparations or does it only emerge in expression systems that lack protein partners such as CaBP4? Are the same properties present in different splice variants of $Ca_V1.4$? Using channels with a hundredfold lower open probability means that a hundredfold more channels would be needed to achieve the same current, which in turn implies a need for thousands of Ca^{2+} channels beneath each ribbon (Bartoletti et al., 2011). This appears inconsistent with freeze fracture electron micrographs showing ~400 particles thought to be Ca^{2+} channels beneath each macaque cone ribbon (each of which is 700-1000 nm long) (Raviola and Gilula, 1975).

2.2.5 Other Ca^{2+} channel subtypes.—*In situ* hybridization and immunohistochemical studies have suggested the presence of $Ca_V1.3$ in inner segments and synaptic terminals of rods and cones in a number of different species (Cristofanilli et al., 2007; Henderson et al., 2001; Kamphuis and Hendriksen, 1998; Kersten et al., 2010; Ko et al., 2007; Morgans, 1999; Morgans et al., 2005; Xiao et al., 2007; Zou et al., 2012). It has been suggested that $Ca_V1.3$ may interact with whirlin in a periciliary membrane complex to promote Usher disease (Kersten et al., 2010) but this interaction was not confirmed by a subsequent study (Zou et al., 2012). Zou et al. also showed that much of the labeling with various $Ca_V1.3$ Ca^{2+} channel antibodies was non-specific since it was not altered by elimination of $Ca_V1.3$ (Zou et al., 2012). However, elimination of $Ca_V1.3$ from mouse retina did cause some changes in ribbon structure (Busquet et al., 2010; Shi et al., 2017) and one study showed a reduction in ERG a- and b-waves (Shi et al., 2017). Another study on mice lacking $Ca_V1.3$ showed a small but statistically insignificant reduction in the b-wave and no significant changes in visual behavior assessed with a Morris water maze (Busquet et al., 2010). These data suggest that CaV1.3 channels may be present in photoreceptors but the role they play remains unclear. There is also immunohistochemical and *in situ* hybridization evidence for weak expression of $Ca_V1.2$ channels in photoreceptors (Kamphuis and Hendriksen, 1998; Ko et al., 2007; Nachman-Clewner et al., 1999; Xiao et al., 2007).

2.2.6 Ca^{2+} channel modulation.—Photoreceptor I_{Ca} can be modulated by many different signaling agents and pathways. Rods and cones can often be modulated differently by the same substance, suggesting differences in the regulation and channel composition at rod and cone synapses. For example, if we consider only salamander photoreceptors, activation of dopamine D4 receptors acts through pertussis toxin-sensitive G proteins to inhibit adenylate cyclase which in turn inhibits L-type I_{Ca} in large single cones, but these same pathways enhance I_{Ca} in rods and short wavelength-sensitive Scones (Stella and Thoreson, 2000). Likewise, inhibition of adenylate cyclase activity by CB1 cannabinoid

receptors also inhibits I_{Ca} in large single cones but enhances I_{Ca} in rods (Straiker and Sullivan, 2003). Nitric oxide acts through a different pathway not involving guanylate cyclase but also inhibits I_{Ca} in cones and enhances I_{Ca} in rods (Kourennyi et al., 2004; Kurenny et al., 1994). By contrast with these agents, somatostatin 2A receptors acts through pertussis toxin-sensitive G proteins similar to dopamine, but has the opposite effect, enhancing cone I_{Ca} and inhibiting rod I_{Ca} (Akopian et al., 2000). Stimulation of adenylate cyclase by activation of adenosine A2a receptors inhibits rod I_{Ca}. This is consistent with effects of PKA on rod I_{Ca} observed with dopamine or cannabinoids, but activation of A2A receptors also inhibits cone I_{Ca}, rather than stimulating cone I_{Ca} as occurs by direct stimulation of PKA (Stella et al., 2002; Stella et al., 2007). Finally, activation of Group III metabotropic glutamate receptors inhibits I_{Ca} in cones but not rods (Hosoi et al., 2005; Van Hook et al., 2017). Thus, even agents that act through some of the same signaling pathways (e.g., pertussis toxin-sensitive G proteins or adenylate cyclase) can have different effects on rod and cone I_{Ca}. In addition to divergent intracellular signaling pathways, one possible source for such differences could be the presence of splice variants of CaV1.4 that differ in the C-terminal autoinhibitory domain sensitive to phosphorylation by PKA (see section 2.2.2). Splice variants of $Ca_V1.4$ that lack this C-terminal autoinhibitory domain would be expected to be insensitive to PKA modulation (Sang et al., 2016). Non-GPCR signaling pathways can also regulate photoreceptor I_{Ca}. For example, insulin inhibits I_{Ca} in salamander rods by mechanisms that involve tyrosine kinase activity (Stella et al., 2001). Polyunsaturated fats and retinoids, including 11-cis-retinal, also inhibit I_{Ca} in salamander rods (Vellani et al., 2000). Levels of dopamine, adenosine, and glutamate vary with light and dark and so it is hypothesized that these modulatory effects on I_{Ca} help to adjust gain at photoreceptor synapses with changing illumination (Hosoi et al., 2005; Stella et al., 2007; Thoreson et al., 2002) but details of how these different signaling pathways interact with one another remain unknown.

Evidence from chicken cones suggests that modulation of I_{Ca} is under circadian regulation. For example, somatostatin and nitric oxide both inhibit cone I_{Ca} in subjective night but not subjective day (Jian et al., 2009; Ko et al., 2013). Expression of Ca^{2+} channels in chicken cones is also under circadian regulation by pathways involving Ras-ERK, PI3-Kinase-Akt, and microRNA 26a (Ko et al., 2007).

I_{Ca} can be regulated by a number of negative feedback mechanisms that operate locally at the synapse. Protons are a powerful regulator of synaptic release from photoreceptors, altering both voltage-dependence and amplitude of I_{Ca}. Extracellular protons inhibit the amplitude of I_{Ca} and shift voltage-dependence of activation in a positive direction with the net effect of reducing Ca^{2+} channel activity in the normal physiological voltage range for photoreceptors. Protons released during synaptic vesicle fusion in rods and cones can feed back to inhibit presynaptic I_{Ca} and synaptic release (DeVries, 2001). Synaptic cleft proton levels are also regulated by changes in horizontal cell membrane potential (Hirasawa and Kaneko, 2003; Wang et al., 2014). The ability of horizontal cells to alter cleft proton levels is central to the mechanism of surround antagonism in which depolarization of horizontal cells leads to cleft acidification which in turn inhibits rod and cone I_{Ca} (Thoreson and Mangel, 2012). In addition to containing protons, glutamatergic vesicles in rods and cones also contain Zn^{2+} ions that can inhibit I_{Ca} (Chappell et al., 2008; Wu et al., 1993).

The binding of Cl^- ions to the intracellular surface of L-type Ca^{2+} channels in photoreceptors promotes channel open probability and so reductions in intracellular Cl^- can inhibit I_{Ca} (Babai et al., 2010; Thoreson et al., 1997). In rods, E_{Cl} is positive to the resting membrane potential and so activation of Ca^{2+}-activated Cl^- channels in rod terminals promotes Cl^- efflux that can act as a feedback mechanism to inhibit I_{Ca}(Thoreson et al., 2003; Thoreson et al., 1997; Thoreson et al., 2002). In addition to effects of reducing cell input resistance during activation of $I_{Cl(Ca)}$, a reduction in intracellular [Cl^-] of only 10 mM can reduce I_{Ca} by 20% (Thoreson et al., 2003; Thoreson et al., 1997). In cones, E_{Cl} is close to the dark resting membrane potential (Thoreson and Bryson, 2004) so this sort of feedback inhibition will only occur when cones are hyperpolarized (e.g., by light). Local negative feedback mechanisms involving Cl^- ions, zinc, and protons may help to limit regenerative activation of I_{Ca} and the generation of Ca^{2+} spikes in rods and cones.

2.3 K^+ channels

2.3.1 Voltage-dependent K^+ channels—Beech and Barnes (Beech and Barnes, 1989) described the properties of a voltage-dependent K^+ current in cones that they named I_{Kx}. I_{Kx} activates quickly with depolarization and de-activates slowly upon hyperpolarization. This current is active between −70 and −30 mV with a midpoint activation value of −45 to −55 mV (Beech and Barnes, 1989; Gayet-Primo et al., 2018; Kurennyi and Barnes, 1997). A more transient K^+ current that activates at more positive potentials than I_{Kx} has also been identified in primate rods and cones, (Gayet-Primo et al., 2018; Yagi and Macleish, 1994) as well as lizard cones (Maricq and Korenbrot, 1990b).

I_{Kx} shares a number of similarities with M-type K^+ currents (K_v7) and there is evidence for M-type K_v7 channels in cone inner segments from immunohistochemistry and *in situ* hybridization (Zhang et al., 2011). However, I_{Kx} shows a different pharmacological profile from M-type currents, being more sensitive to Ba^{2+}, insensitive to acetylcholine and LHRH, and insensitive to a K_v7 blocker XE991 (Beech and Barnes, 1989; Gayet-Primo et al., 2018). *In situ* hybridization suggests the presence of ether-a-gogo-related (EAG; K_v11) channels in the inner segments of bovine rods (Frings et al., 1998). However, the pharmacological properties do not support a substantial contribution from this subtype in primate rods (Gayet-Primo et al., 2018).

Using a combination of immunohistochemistry, electrophysiology and pharmacology, Gayet-Primo et al. (Gayet-Primo et al., 2018) established the presence of $K_v8.2$ and K_v2 channels localized to the inner segments of primate rods and cones. Studies also indicate the presence of $K_v2.1$ and 8.2 in photoreceptor inner segments from human and mouse retina (Klumpp et al., 1995b; Pinto and Klumpp, 1998; Wu et al., 2006). $K_v8.2$ subunits do not form functional channels by themselves but can form functional heteromers with other subunits. The presence of $K_v8.2$ subunits in heteromeric channels shifts K_v2 current activation to more negative potentials, yielding electrophysiological properties similar to those of native I_{Kx} currents (Czirjak et al., 2007). Mutations to the $K_v8.2$ gene cause a cone dystrophy with supernormal rod ERGs (Ben Salah et al., 2008; Vincent et al., 2013; Wissinger et al., 2008; Wissinger et al., 2011; Zobor et al., 2012). Some of the disease-causing mutations result in complete elimination of Kv8.2 whereas others impair its

interaction with K_v2 subunits. When co-expressed with $K_v2.1$ in Xenopus oocytes, both types of mutations in $K_v8.2$ eliminate currents with properties similar to I_{Kx} (Czirjak et al., 2007). Cones express both $K_v2.1$ and $K_v2.2$, while rods predominantly express $K_v2.1$ (Gayet-Primo et al., 2018). $K_v2.2$ was also absent from mouse photoreceptors (Klumpp et al., 1995b). Using a combination of molecular, electrophysiological and pharmacological approaches, Gayet-Primo et al. concluded that the high voltage-activated K^+ currents in primate rods and cones arise from homomeric K_v2 channels ($K_v2.1$ in rods and a combination of $K_v2.1$ and $K_v2.2$ in cones) whereas lower threshold I_{Kx} are likely to arise from heteromeric $K_v2/K_v8.2$ channels (Gayet-Primo et al., 2018).

2.3.2 *Ca^{2+}-activated K^+ channels*—

In rods and cones of salamander retina, strong depolarizing steps that activate I_{Ca} (see section 2.2) also activate noisy outward currents carried by large conductance Ca^{2+}-activated K^+ currents (BK) currents (Bader et al., 1982; Barnes and Hille, 1989; MacLeish and Nurse, 2007; Moriondo et al., 2001; Pelucchi et al., 2008; Xu and Slaughter, 2005). Antibodies to BK ($K_{Ca}1.1$) and IK (KCa3.1) channels also label salamander rods, but not antibodies to SK channels (Pelucchi et al., 2008). The presence of IK and BK channels is also supported by pharmacology. Ca^{2+}-dependent K^+ currents in rods can be inhibited by a BK channel blocker, iberiotoxin; partially inhibited by the mycotoxin clotrimazole which inhibits IK channels (Pelucchi et al., 2008); but not inhibited by apamin which blocks SK channels (Pelucchi et al., 2008; Xu and Slaughter, 2005). IK channels are gated exclusively by Ca^{2+} (Sforna et al., 2018) whereas BK channels can be opened by both depolarizing voltage and Ca^{2+} (Latorre et al., 2017). These differences in gating may account for the finding that IK channels appear to contribute more strongly at positive voltages than BK channels (Pelucchi et al., 2008).

Blocking Ca^{2+}-activated K^+ channels enhances excitability and promotes regenerative spiking in photoreceptors (Fain et al., 1977; Moriondo et al., 2001), suggesting that one role for these channels may be to prevent regenerative activation of Ca^{2+} channels and thus maintain the membrane voltage in darkness near −40 mV. On the other hand, it has also been proposed that efflux of K^+ during activation of these channels can enhance I_{Ca} in rods which would promote excitability (Xu and Slaughter, 2005).

While there is clear evidence for these channels in salamander retina, there is no evidence for Ca^{2+}-activated K^+ currents in cones from lizard or primate retina (Cia et al., 2005; Maricq and Korenbrot, 1990b; Yagi and Macleish, 1994).

2.4 HCN channels

Both rods and cones exhibit prominent inwardly rectifying currents activated by hyperpolarization (I_h). I_h was first identified from its blockade by low millimolar concentrations of cesium (Fain et al., 1978). Although blocked by cesium, I_h is relatively insensitive to tetraethylammonium (TEA) (Bader and Bertrand, 1984; Bader et al., 1982; Demontis et al., 1999; Demontis et al., 2002; Hestrin, 1987; Maricq and Korenbrot, 1990a). I_h are similar to inwardly rectifying currents in a variety of other cells, including so-called “funny” currents in cardiac myocytes. Accordingly, I_h can be selectively inhibited by various bradycardic agents including ZD7288, ivabradine and zatebradine (Demontis et al., 2009;

Satoh and Yamada, 2000, 2002). I_h shows slow kinetics and a hyperpolarized voltage-dependence, activating below ca. −50 mV with an activation midpoint around −70 to −80 mV (Barrow and Wu, 2009; Demontis et al., 1999; Demontis et al., 2002; Malcolm et al., 2003; Maricq and Korenbrot, 1990a). I_h channels show a permeability ratio P_{Na}/P_K of 0.2-0.3 (Demontis et al., 1999; Demontis et al., 2002; Hestrin, 1987; Mao et al., 2003; Wollmuth and Hille, 1992), with a reversal potential under physiological conditions of −30-35 mV (Bader and Bertrand, 1984; Bader et al., 1982; Barnes and Hille, 1989; Demontis et al., 1999; Demontis et al., 2002; Maricq and Korenbrot, 1990a). The properties of I_h in cones are similar to those of rods (Barnes and Hille, 1989; Barrow and Wu, 2009; Maricq and Korenbrot, 1990a; Wollmuth and Hille, 1992; Yagi and Macleish, 1994). Properties of I_h are also similar in human rods and primate cones (Kawai et al., 2002; Yagi and Macleish, 1994). HCN1-type I_h channels are concentrated in the inner segment (Barrow and Wu, 2009; Della Santina et al., 2012; Demontis et al., 2002; MacLeish and Nurse, 2007). These channels have a small single channel conductance of <1 pS with an average of ~2,000 channels per rod or cone (Barrow and Wu, 2009). The low single channel conductance helps to reduce membrane noise.

In response to a bright light flash, rods show a transient hyperpolarization followed by a rapid depolarizing recovery of the membrane potential. This depolarizing rollback is due to the activation of I_h triggered during the initial light-evoked hyperpolarization of the rod. By eliminating this rollback, blocking I_h makes hyperpolarizing rod light responses more sustained and increases their peak amplitude. Cones do not normally show a prominent transient “nose” in response to light but blocking I_h increases the overall amplitude of their hyperpolarizing light responses (Barrow and Wu, 2009; Fain et al., 1978; Satoh and Yamada, 2000, 2002). In addition to changes in response waveform, the slow activation kinetics of I_h produces high-pass filtering of the hyperpolarizing photoreceptor light response (Attwell, 1986; Barrow and Wu, 2009; Demontis et al., 1999; Mao et al., 2003). Combined with low-pass filtering by the passive membrane properties and photocurrent, this yields a net band-pass filtering of photoreceptor light responses. By lowering cell input resistance to speed the membrane time constant, activation of I_h by membrane hyperpolarization improves the high frequency responses of cones (Howlett et al., 2017). This contributes to a form of light adaptation whereby high contrast changes that produce voltage excursions large enough to activate I_h can speed up cone responses. I_h also improves the ability of rods to adapt to light; rod photocurrents show a more significant reduction in sensitivity with increasing light levels than photovoltage (Pahlberg et al., 2017; Sothilingam et al., 2016). Eliminating I_h abolished these differences in the adaptation of photovoltage and photocurrent responses.

While loss of HCN1 does not directly cause retinal degeneration, it can worsen retinal degeneration caused by other mutations such as loss of CNG channel β subunits from rods or loss of CNG α subunits from cones (Schon et al., 2016). This worsening of degeneration does not appear to be due to an effect on resting membrane potential which did not differ in HCN1 KO rods but instead involves increased levels of calpain activity (Schon et al., 2016).

2.5 Ca^{2+}-activated Cl^- channels

Another prominent current in rods and cones is the Ca^{2+}-activated Cl^- current (Bader et al., 1982; Barnes and Hille, 1989). Immunohistochemical studies in salamander and mouse retina suggested the presence of Ano1 in both rod and cone terminals (Caputo et al., 2015; Jeon et al., 2013; Mercer et al., 2011b; Yang et al., 2008). Stohr et al. cloned Ano2 (aka TMEM16B) from mouse and human retina and showed that it formed Ca^{2+}-activated anion channels (Stohr et al., 2009). They went on to show that Ano2 was selectively expressed at photoreceptor ribbon synapses. In rat retina, Ano2 is selectively expressed in rods but not cones; Ano1 expression was not seen in either cell type (Dauner et al., 2013).

Ca^{2+}-activated Cl^- currents were almost wholly eliminated in salamander rods lacking synaptic terminals (MacLeish and Nurse, 2007). Antibodies to Ano1 and Ano2 label the entire synaptic terminal and are not tightly confined to ribbons like antibodies to Ca^{2+} channels (Dauner et al., 2013; Mercer et al., 2011b; Stohr et al., 2009). Effects of Ca^{2+} buffers on Ca^{2+}-activated Cl^- currents in salamander rods and cones also suggest that these channels are distributed throughout the terminal. However, the ability of Ca^{2+}-activated Cl^- currents to persist in the presence of the fast Ca^{2+} buffer BAPTA suggests that some of these channels are located within 100 nm of Ca^{2+} channels (Mercer et al., 2011b). Consistent with tight co-localization between Ca^{2+}-activated Cl^- channels and Ca^{2+} channels, Ano1 channels can coimmunoprecipitate with $Ca_V1.4$ Ca^{2+} channels when expressed in tsa201 cells (Caputo et al., 2015).

The evidence for Ano1 in photoreceptors rests largely on immunohistochemistry while there is both immunohistochemical and molecular evidence for Ano2. Transcriptome analyses of rods and cones also suggest significant levels of Ano2 but not Ano1 (Busskamp et al., 2014; Hartl et al., 2017; Mo et al., 2016). On the other hand, Ano1 channels are 10 times less sensitive to Ca^{2+} than Ano2 channels (Vocke et al., 2013) and so the ability of submicromolar Ca^{2+} to stimulate Ca^{2+}-activated Cl^- currents in salamander rods and cones is more consistent with Ano1 (Mercer et al., 2011b).

2.6 CNG channels

The only ion channels in the outer segments of intact rods and cones are CNG cation channels gated open by cGMP (Baylor et al., 1984). The channels in rods consist of CNGA1 and CNGB1 heteromers while cones have CNGA3 and CNGB3 heteromers. Cation influx through these channels support the dark current that is terminated by their closure during phototransduction. The reduced Ca^{2+} influx that accompanies channel closure plays a key role in adjusting the gain of phototransduction during light adaptation. Mutations in CNGA1 and CNGB1 cause autosomal recessive retinitis pigmentosa while mutations in CNGA3 and CNGB3 cause achromatopsia. A detailed consideration of phototransduction and outer segment CNG channels is beyond the scope of this review and is reviewed in detail elsewhere (Arshavsky and Burns, 2012; Biel, 2009; Burns and Baylor, 2001; Fu and Yau, 2007; Kaupp and Seifert, 2002; Michalakis et al., 2018).

CNG channels are also present in the synaptic terminals of cones. Ca^{2+} influx through these channels can trigger fusion of glutamate-filled vesicles (Rieke and Schwartz, 1994;

Savchenko et al., 1997). It has been suggested that the opening of CNG channels may extend the cone operating range, allowing release of glutamate at more negative potentials where the activity of Ca^{2+} channels begins to diminish. However, because of the increased driving force for cations, CNG currents typically increase with hyperpolarization, rather than diminishing like I_{Ca}. CNG channels in cone terminals can be regulated by constitutive levels of cGMP but can also be opened by increases in cGMP triggered by nitric oxide released from neighboring neurons and glia (Savchenko et al., 1997). Thus, these channels may help to regulate glutamate release in response to changes in nitric oxide levels.

2.7 Summary

The distribution of the principal ion channels in mammalian rods is summarized in Fig. 1 showing that homomeric $K_V2.1$ and heteromeric $K_V2.1/K_V8.2$ channels are distributed throughout the inner segment, along with HCN1 channels. $Ca_V1.4$ channels in a complex with β2a and α2δ4 subunits are clustered beneath the synaptic ribbon. Ano2 Ca^{2+}-activated Cl^- channels are distributed more diffusely throughout the synaptic terminal membrane. Ca^{2+}-activated Cl^- channels in cones appear to be a different subtype from Ano2. In primate cones, inner segments also possess $K_V2.2$.

Measurements of the membrane potential of rods and cones show it to be near −40 mV in darkness. These potentials are close to the activation midpoint value for I_{Kx} whereas I_h is minimally active at this potential (Attwell, 1986; Barnes, 1994). Thus, when light closes CNG channels in the outer segments, the dominant conductance will be I_{Kx}, and K^+ efflux through these channels will drive the membrane potential in a hyperpolarizing direction. Strong hyperpolarization will activate I_h, driving the membrane potential back in a depolarizing direction. Activation of I_h thus limits the amplitude of hyperpolarizing rod and cone light responses and makes rod responses more transient. There is immunohistochemical evidence for KCNK2 two pore channels in mouse cones suggesting that along with I_{Kx}, K^+ leak channels might also contribute to the negative driving force (Hughes et al., 2017).

The dark resting membrane potential of −40 mV in darkness is close to the activation midpoint value for I_{Ca}. Positioning the membrane potential close to the activation midpoint maximizes the changes in I_{Ca} caused by light-evoked voltage changes in membrane potential, which in turn maximizes the sensitivity of Ca^{2+}-dependent glutamate release. However, this also places the cone in an unstable region of negative slope conductance. The likelihood for regenerative activation of Ca^{2+} channels is limited by the activation of strong countervailing conductances, especially I_{KX}, and mechanisms that reduce Ca^{2+} channel activity during maintained darkness. The activation of Ca^{2+}-activated Cl^- channels leads to a conductance increase that tends to drive the membrane potential towards E_{Cl}. In cones, E_{Cl} is near the dark resting membrane potential; E_{Cl} is somewhat more depolarized in rods (Thoreson and Bryson, 2004; Thoreson et al., 2003). At potentials below E_{Cl}, the efflux of Cl^- through Ca^{2+}-activated Cl^- channels will also directly inhibit I_{Ca}. In those photoreceptors that possess them, activation of BK channels can also provide a hyperpolarizing driving force to limit excitability. With maintained depolarization as occurs in maintained darkness, I_{Ca} will slowly inactivate as a result of Ca^{2+} and/or voltage-

dependent inactivation. In addition, as found at calyceal synapses (Borst and Sakmann, 1999; Stanley, 2000), the constant influx of Ca^{2+} ions into tonically open Ca^{2+} channels at rod ribbons depletes extracellular Ca^{2+} ions from the synaptic cleft to further inhibit I_{Ca} (Rabl and Thoreson, 2002). The maintained activity of Ca^{2+} channels in darkness stimulates continuous release of glutamate-filled synaptic vesicles. The release of protons and Zn^{2+} ions from synaptic vesicles can further inhibit I_{Ca}. Acidification of the synaptic cleft accompanying negative feedback from depolarized horizontal cells will also inhibit rod and cone I_{Ca}.

While these various mechanisms work to limit the likelihood of regenerative Ca^{2+} action potentials, depolarizing stimulation can trigger regenerative activation of Ca^{2+} channels under certain conditions. Illumination of the receptive field surround acting through horizontal cell feedback can produce a leftward (negative) shift in I_{Ca} activation and increase in I_{Ca} peak amplitude. This causes a net increase in rod and cone I_{Ca} at physiological potentials that can in turn generate depolarizing Ca^{2+} spikes in rods and cones (Burkhardt et al., 1988; Burkhardt et al., 1991; Lasansky, 1986; Maricq and Korenbrot, 1988; Piccolino and Gerschenfeld, 1978, 1980; Thoreson and Burkhardt, 1991). The likelihood of such spikes can be dramatically increased by enhancing I_{Ca} with application of Sr^{2+} or Ba^{2+} (Piccolino and Gerschenfeld, 1980). When E_{Cl} is more positive than the resting membrane potential, the activation of Ca^{2+}-activated Cl^- currents helps to maintain the membrane in a depolarized state, promoting regenerative potentials that can last for seconds (Thoreson and Burkhardt, 1991). Thus, elevating intracellular Cl^- enhances the likelihood of these events (Barnes and Deschenes, 1992; Maricq and Korenbrot, 1988; Thoreson and Burkhardt, 1990). These long-lasting regenerative potentials are terminated when intracellular Ca^{2+} levels fall (Krizaj, 2012) and the activation of $I_{CI(Ca)}$ diminishes. These prolonged Ca^{2+} action potentials arise from bistability in the membrane voltage (Barnes and Deschenes, 1992; Kamiyama et al., 1996) that can be successfully simulated by computational models incorporating biophysical parameters of rod currents (Kamiyama et al., 1996). These long-lasting regenerative events are probably not normally experienced by healthy photoreceptors that have robust Ca^{2+} handling mechanisms. However, occurrence of such events in unhealthy photoreceptors might impair signaling in disease states.

3. Horizontal cells

Most vertebrate species have four types of horizontal cells while most mammals have only two types (Gallego, 1986; Peichl et al., 1998). Rodent retinas have only a single type of horizontal cell (Peichl and Gonzalez-Soriano, 1994). Five major types of ion currents are present in horizontal cells of most species: fast TTX-sensitive Na^+ current, Ca^{2+} current (I_{Ca}), transient outwardly rectifying K^+ current (I_{KA}), delayed rectifier outward K^+ current (I_{KDR}), and inwardly rectifying K^+ current (I_{KIR}) (Golard et al., 1992; Lasater, 1986; Lohrke and Hofmann, 1994; Malchow et al., 1990; Picaud et al., 1998; Shingai and Christensen, 1983, 1986; Tachibana, 1983a; Ueda et al., 1992). There is no evidence for significant voltage-dependent Cl^- currents in horizontal cells (Byzov and Trifonov Yu, 1981; Waloga and Pak, 1978). While the composition of ion channels is generally similar among horizontal cells, it can vary among species and among different types of horizontal cells. For example, rod-dominated H4 cells in white perch retina lack A-type K^+ currents that are present in H1-

H3 cells (Lasater, 1986) but in white bass retina, I_{KA} is present in H4 cells but not H1 cells (Sullivan and Lasater, 1990a). In rod-dominated skate retina, external horizontal cells lying closer to rods have a greater density of I_{KIR} and lower density of sustained outward currents than internal horizontal cells (Malchow et al., 1990). In cat retina, axonless A-type cells showed fast sodium currents whereas axon-bearing B-type cells did not (Ueda et al., 1992).

In every species, there appears to be at least one type of horizontal cell that has an axon that extends laterally through the OPL and then expands into a functionally distinct, large, axon-terminal compartment. The other horizontal cell subtype(s) are axonless. In fish retina, the axon terminal compartment does not appear to contact any photoreceptors but nevertheless shows light-evoked voltage responses similar in amplitude and spectral characteristics to responses recorded in the cell body (Stell, 1975; Weiler and Zettler, 1979). It has therefore been concluded that light responses generated in the soma pass almost without decrement to the axon terminal. Transmission along the axon does not appear to be boosted by activation of voltage-dependent Na^+ channels (Djamgoz and Stell, 1984; Weiler and Zettler, 1979). Recordings from enzymatically isolated axon terminals in fish retina show a similar complement of channels as somas, but a higher specific membrane resistance (Yagi and Kaneko, 1988). Similarly, the input resistance of axon terminals is much higher than somas of horizontal cells isolated from turtle retina (Golard et al., 1992). Thus, small currents that reach the high resistance axon terminal compartment can generate large voltage responses (Golard et al., 1992; Yagi and Kaneko, 1988).

In rodents and other mammals, the soma compartment contacts only cones whereas the axon terminal compartment contacts only rods. The only type of horizontal cell in rodent retina (B-type) is an axon-bearing horizontal cell. In mice that lack gap junctions between rods and cones, recordings from axon terminals that contact only rods nevertheless show the presence of cone inputs in their responses (Trumpler et al., 2008). By contrast, rod responses were not observed in somas of these same connexin 36 knockout mice. Trumpler et al. therefore concluded that cone signals can pass from soma to terminal but rod signals cannot go the other direction, from terminal to soma (Trumpler et al., 2008). On the other hand, Szikra et al. observed small depolarizing responses in cones evoked by light flashes that should only activate rods and concluded that rod signals can travel from terminal to soma (Szikra et al., 2014). However, the cone recordings were similar in size (< 2 mV) and waveform to intraretinal ERGs raising the possibility of contamination by extracellular field potentials. As discussed above, the ability of signals to flow between the two compartments depends on their relative input resistances. Lowering the somatic resistance by reducing glutamatergic input or uncoupling of gap junctions would be one mechanism for improving transmission of voltage signals from axon terminal to soma. Differences in the expression of ion currents between soma and axon terminals might also contribute. While the types of ion channels in the two compartments do not appear to differ in most species, this may not be the case for mouse horizontal cells (Feigenspan et al., 2009).

3.1 Voltage-gated Na^+ channels

Fast, TTX-sensitive Na^+ currents that activate above −50 mV have been observed in isolated horizontal cells from a variety of species (Golard et al., 1992; Lasater, 1986; Lohrke and

Hofmann, 1994; Malchow et al., 1990; Shingai and Christensen, 1983; Ueda et al., 1992). Antibodies to 1.1, 1.2 and 1.6 sodium channels show labeling throughout horizontal cells in rodent and rabbit retina (Mojumder et al., 2007). Na^+ currents in horizontal cells are not as large as those found in ganglion cells and action potentials are not normally observed in horizontal cells *in situ*. However, Na^+ channels can facilitate regenerative action potentials in horizontal cells that are isolated from the retina or uncoupled from their neighbors (Blanco et al., 1996; Shingai and Christensen, 1986; Tachibana, 1981). While it seems plausible that rapid activation of Na^+ channels might assist in speeding membrane depolarization at light offset, blocking these channels with TTX had no obvious effect on light responses (Akopian et al., 1997; Djamgoz and Stell, 1984; Perlman et al., 1993).

3.2 Ca^{2+} channels

Horizontal cells in all species studied exhibit a small, sustained inward I_{Ca} that begins to activate around −40 to −30 mV (Golard et al., 1992; Liu et al., 2013a; Lohrke and Hofmann, 1994; Malchow et al., 1990; Picaud et al., 1998; Schubert et al., 2006; Shingai and Christensen, 1983; Sullivan and Lasater, 1992; Tachibana, 1983a; Ueda et al., 1992). This sustained current is sensitive to dihydropyridine agonists and antagonists (Chapot et al., 2017; Golard et al., 1992; Liu et al., 2013a; Lohrke and Hofmann, 1994; Pfeiffer-Linn and Lasater, 1996b; Picaud et al., 1998; Ueda et al., 1992) indicating that it involves L-type channels. The single channel conductance is similar to other L-type channels (Pfeiffer-Linn and Lasater, 1996b). In mouse and fish retina, sustained I_{Ca} can also be weakly inhibited by ω-agatoxin IVA (Liu et al., 2013a; Pfeiffer-Linn and Lasater, 1996b; Schubert et al., 2006), suggesting the additional presence of $Ca_V2.1$ (P/Q-type) channels (Bourinet and Zamponi, 2017). In mouse horizontal cells, ω-conotoxin also inhibited I_{Ca} consistent with the presence of N-type channels (Liu et al., 2013a; Schubert et al., 2006). Immunohistochemical studies from mouse retina also show the presence of L, N and P/Q-type channels in the dendritic tips of horizontal cells. It has been proposed that Ca^{2+} channels in horizontal cell dendrites may mediate Ca^{2+}-dependent release of GABA (Liu et al., 2013a).

There is evidence for transient I_{Ca} in horizontal cells from fish, *Xenopus,* and rabbit (Akopian et al., 1997; Lohrke and Hofmann, 1994; Pfeiffer-Linn and Lasater, 1996b; Shingai and Christensen, 1983; Sullivan and Lasater, 1992) but not turtle, cat or mouse (Golard et al., 1992; Liu et al., 2013a; Schubert et al., 2006; Ueda et al., 1992). This transient I_{Ca} is insensitive to dihydropyridines, activates at more negative potentials than sustained inward currents, and can be inhibited by Ni^{2+} (Akopian et al., 1997; Pfeiffer-Linn and Lasater, 1996b; Sullivan and Lasater, 1992), consistent with T-type I_{Ca}. Although these currents are generally small in horizontal cells, voltage-dependent activation of Ca^{2+} channels as horizontal cells depolarize during light offset may help speed repolarization of the membrane (Akopian et al., 1997).

3.3 K^+ channels

3.3.1 Inwardly rectifying K^+ channels—One of the most prominent currents in horizontal cells is I_{KIR}. I_{KIR} is also referred to as the anomalous rectifier current. Unlike the inward rectifying cation current I_h in photoreceptors, the inward rectifier in horizontal cells is selective for K^+ ions (Golard et al., 1992; Shingai and Christensen, 1986; Yagi and

Kaneko, 1988). Unlike I_h, I_{KIR} is also not blocked by ZD7288 (Feigenspan et al., 2009). Like I_{KIR} in other preparations, horizontal cell currents are relatively insensitive to TEA or 4-AP but blocked by low concentrations of extracellular Cs^+ or Ba^{2+} (Shingai and Christensen, 1986; Tachibana, 1983a; Ueda et al., 1992). The single channel conductance of 20 pS in 125 mM external K^+ (Shingai and Quandt, 1986) is similar to that of I_{KIR} in other preparations (Newman, 1993; Park et al., 2008; Sakmann and Trube, 1984).

Small outward currents through inward rectifier K^+ channels at potentials above E_K contribute to maintenance of the resting membrane potential in many neurons (Hibino et al., 2010). I_{KIR} is active throughout the normal physiological voltage range of horizontal cells (−30 to −90 mV), contributing to the resting membrane potential of these cells in darkness and to the driving force for hyperpolarizing excursions during light (Dong and Werblin, 1995; Feigenspan et al., 2009). However, I_{KIR} is not the only current responsible for this hyperpolarizing driving force since even after blocking I_{KIR}, the light-evoked hyperpolarization of horizontal cells approaches E_K. Small leak K^+ currents in horizontal cells (Lasater, 1986; Tachibana, 1983a) may contribute the additional driving force. Transcriptome data from horizontal cells show significant levels of KCNK1 two pore channel mRNA (Hartl et al., 2017). Immunohistochemical studies also show evidence for KCNK1 and KCNK3 channels in horizontal cells early in development and KCNK2 channels in adult mouse retina (Hughes et al., 2017).

I_{KIR} may play other roles in horizontal cells besides setting the resting membrane potential. In adult rabbit retina, Kir2.1 channels are localized to a macromolecular complex with glutamate receptors and scaffold proteins at the dendritic tips of B-type horizontal cells in the OPL (Vila et al., 2017). The authors suggested that currents flowing through these channels could generate ephaptic changes in the extracellular voltage within the invaginating cone synapse that might contribute to negative feedback modulation of cone I_{Ca} by horizontal cells (Vila et al., 2017).

I_{KIR} in horizontal cells are larger than similar currents in many other neurons. Kir4.1 channels in glial Müller cells have been shown to be important for buffering extracellular K^+ changes by siphoning K^+ from regions of high extracellular K^+ (e.g., synaptic plexiform layers) to regions of lower K^+ (e.g., adjacent to the vitreous and vasculature) (Kofuji and Newman, 2004). In newborn mice, Kir4.1 channels are expressed in horizontal cells prior to their expression in Müller cells, leading Bosco et al. to propose that before Müller cells are fully developed, horizontal cells may play a similar role in buffering and siphoning of K^+ from the OPL (Bosco et al., 2005). In support of this, they noted close contacts between horizontal cells and outer retinal blood vessels. Kir4.1 expression disappears from horizontal cells in adult mice (Bosco et al., 2005), but these cells nevertheless continue to express prominent I_{KIR}. In rabbit retina, Kir 2.1 channels are expressed at the tips of horizontal cell dendrites within the synaptic invaginations of cone pedicles (Vila et al., 2017). We suggest that such channels would be well positioned to assist in buffering extracellular K^+ changes that can occur near the terminals of rods and cones in the OPL (Dick and Miller, 1985; Dick et al., 1985; Karwoski et al., 1985). Elevation of extracellular K^+ also substantially increases the conductance of I_{KIR} and shifts its reversal potential to more positive values (Dong and Werblin, 1995), promoting the influx of K^+ at more positive potentials. Thus, localized

changes in extracellular K^+ within invaginating rod and cone synapses might be buffered by the flux of K^+ in and out of horizontal cells via I_{KIR}.

3.3.2 Outwardly rectifying K^+ channels—Two types of outwardly rectifying K^+ currents are observed in most horizontal cells: rapidly inactivating A-type currents and sustained delayed rectifier currents. A-type K^+ currents activate around −40 mV whereas sustained K^+ currents activate at −30 to −10 mV (Shingai and Christensen, 1986; Sullivan and Lasater, 1990a, b; Tachibana, 1983a; Ueda et al., 1992). Sustained currents are therefore less likely to contribute to responses in the normal physiological voltage range (−30 to −90 mV). Similar to other preparations, sustained outward currents are more sensitive to extracellular TEA and intracellular Cs^+ whereas A-type currents are more readily blocked by 4-AP (Lasater, 1986; Lohrke and Hofmann, 1994; Malchow et al., 1990; Shingai and Christensen, 1986; Sullivan and Lasater, 1990a; Tachibana, 1983a; Ueda et al., 1992). The molecular identities of these channels have not been characterized.

3.3.3 Ca^{2+}-activated K^+ channels—While Ca^{2+}- activated K^+ channels have not been found in horizontal cells from fish, turtle, cat, and human retina (Golard et al., 1992; Picaud et al., 1998; Sullivan and Lasater, 1990a; Tachibana, 1983a; Ueda et al., 1992), a careful study of B-type horizontal cells established the presence of BK channels in mouse retina (Sun et al., 2017). Single channel recordings also showed evidence for large conductance Ca^{2+}-activated K^+ channels in B-type horizontal cells from rabbit retina (Lohrke and Hofmann, 1994). From the rapid inactivation kinetics of BK channels in mouse horizontal cells, Sun et al. suggested that the channel complex may incorporate β2 subunits (Sun et al., 2017).

3.4 Bistable membrane behavior in horizontal cells

Despite the presence of voltage-dependent Na^+ and Ca^{2+} currents, horizontal cells do not typically generate Na^+- or Ca^{2+}- dependent action potentials *in vivo*. This is because of the low input resistance of horizontal cells that arises from strong gap junction coupling between horizontal cells and from the tonic activation of ionotropic glutamate receptors by glutamate released from photoreceptors (Aoyama et al., 2005; Miyachi and Murakami, 1989; Winslow and Ma, 1990). However, Na^+ and Ca^{2+} - dependent action potentials are readily observed in solitary horizontal cells after enzymatic isolation (Blanco et al., 1996; Johnston and Lam, 1981; Shingai and Christensen, 1983; Tachibana, 1981, 1983b) and can be evoked in horizontal cells *in vivo* after inhibiting countervailing K^+ currents (Murakami and Takahashi, 1987). The membrane potential of isolated horizontal cells typically shows two stable values: one at a negative value approaching E_K and the other at a more positive value matching the plateau potential for action potentials. As in cardiac muscle cells, slow inactivation of I_{Ca} ultimately allows the continued activity of countervailing K^+ currents to drive an abrupt transition from the more positive potential back to the more negative stable membrane potential value, terminating the action potential. In mammalian horizontal cells, erg1 K^+ channels appear to contribute to this balancing act between Ca^{2+} and K^+ since blocking erg1 channels with haloperidol enhances depolarizing responses generated at light offset by horizontal cells *in vivo* and promotes Ca^{2+} spikes in isolated cells (Feigenspan et al., 2009). Similar to its role in ventricular myocytes (Hibino et al., 2010), diminished

activity of K_{IR} channels at more depolarized potentials also promotes Ca^{2+} action potentials in isolated horizontal cells. In intact fish retina, blocking A-type K^+ currents with 4AP enhanced depolarizing spikes at light offset in horizontal cells (Perlman et al., 1993). Computational models incorporating biophysical properties can reproduce horizontal cell responses, including the long-lasting action potentials seen in isolated horizontal cells (Aoyama et al., 2005; Usui et al., 1996; Winslow and Ma, 1990). While these long-lasting depolarizing action potentials do not appear to occur often in healthy tissue *in vivo*, the presence of two stable membrane potential values may help to speed both depolarizing responses at light offset and hyperpolarizing deflections at light onset.

3.5 Modulation of ion channels in horizontal cells

As in other neurons, ion currents in horizontal cells are subject to modulation by many factors. In fish retina, dopamine acting through D1 receptors of horizontal cells can stimulate both PKA and PKC to enhance L-type currents but depress T-type currents (Pfeiffer-Linn and Lasater, 1993; Pfeiffer-Linn and Lasater, 1996a, 1998). On the other hand, in mouse retina, activation of D1 receptors acting through Gβγ subunits *inhibits* L-type I_{Ca} (Liu et al., 2016). Activation of G proteins can also regulate A-type K^+ currents by shifting their voltage-dependence of inactivation towards more positive potentials (Akopian and Witkovsky, 1994).

Glutamate can modulate horizontal cell ion currents by acting through G proteins and by modulation of intracellular pH. Activation of Group I and III mGluRs enhances L-type I_{Ca} in catfish horizontal cells (Linn and Gafka, 1999). Group III mGluRs can also suppress inward rectifier currents, likely by acting through PKG (Dixon and Copenhagen, 1997; Kaneko and Tachibana, 1985a). Glutamate application to horizontal cells also lowers intracellular pH to inhibit L-type I_{Ca} (Dixon et al., 1993; Takahashi et al., 1993). Extracellular acidification can also inhibit L-type currents in horizontal cells (Jonz and Barnes, 2007). Extracellular acidification inhibits inward rectifier currents in horizontal cells (Jonz and Barnes, 2007) and intracellular alkalinization enhances those currents (Takahashi et al., 1993).

4. Bipolar cells

In mouse retina, at least 14 different types of bipolar cells have been identified based on functional, morphological and genetic criteria (Seung and Sümbül, 2014; Vlasits et al., 2018). All bipolar cells can be divided into two categories of roughly equal size based on the polarity of their light response, a fundamental classification criterion first described half a century ago (Dowling and Werblin, 1969; Kaneko, 1970; Werblin and Dowling, 1969). On cells depolarize to light and their axons terminate in the more proximal half of the inner plexiform layer (IPL) closer to the vitreous (sublamina B). Conversely, Off type bipolar cells hyperpolarize to light and their axons terminate in the distal sublamina A. The reason for this dichotomy is the type of glutamate receptor each class expresses: On bipolar cells express the L-AP4 sensitive metabotropic mGluR6 receptor that closes a cation conductance leading to membrane hyperpolarization (Masu et al., 1995; Nawy and Copenhagen, 1987; Shiells et al., 1981; Slaughter and Miller, 1981) while Off bipolar cells express ionotropic AMPA or kainate receptors whose activation generates cationic current (DeVries, 2000;

Saito and Kaneko, 1983; Slaughter and Miller, 1983). Voltage-gated channels play no role in this aspect of signaling. Bipolar cells are numbered from 1 to 9 according to the depth of their axon terminals, proceeding from the distal edge of sublamina A to the proximal border of sublamina B. An additional rod bipolar cell (RBC) projects to the most proximal position of any bipolar cell. Types 5 and 3 are further divided into subtypes, and an X-type has also recently been added. In retrospect, it might have been prudent to name bipolar cells using only odd or even numbers, leaving room for addition of newly discovered subtypes.

Why are 14 types necessary? Part of the explanation lies in the specificity of photoreceptor input. For example, the RBC receives input primarily from rods while other bipolar cells principally receive input from cones and are referred to as cone bipolar cells (CBCs). The RBC is functionally an On cell (Dacheux and Raviola, 1986; Dolan and Schiller, 1989; Karschin and Wassle, 1990). Another On type is specialized to receive input only from short wavelength-sensitive cones (Dacey and Lee, 1994; Li and DeVries, 2006; Mariani, 1984). In addition, bipolar cells may be optimally tuned to respond preferentially at specific temporal frequencies. There is wide consensus across species and studies that RGCs partly inherit their response characteristics from presynaptic bipolar cells. This is true for both On and Off subtypes. Thus each type of bipolar cell is thought to form a functional channel that carries kinetically distinct information to downstream RGCs. In support of this idea, ganglion cells that respond transiently to illumination and those with a sustained response collect input from distinct populations of bipolar cells within highly organized layers of the IPL. Both imaging and patch clamp studies have confirmed that synaptic Interactions between bipolar and transient RGCs are confined to the midline of the IPL, while the outer borders contain synapses formed between cells that have sustained responses to illumination (Baden et al., 2013; Borghuis et al., 2014; Borghuis et al., 2013; Ichinose et al., 2014). Perhaps more remarkably, synaptic input from bipolar cells carrying kinetically distinct information is segregated into separate dendritic compartments on the same postsynaptic starburst amacrine cell (Greene et al., 2016; Kim et al., 2014).

Evidence presented below suggests that selective expression of voltage-gated channels contributes to diversity of bipolar cell responses to light. An alternative possibility is that this diversity originates from differences in the response kinetics of the glutamate receptors expressed by bipolar cell subtypes at photoreceptor - bipolar cell synapses. Currently, support for this idea is not compelling. For example, it was postulated that sustained Off bipolar cells express slowly desensitizing kainate receptors while more transiently responding cells express rapidly desensitizing AMPAR receptors in squirrel retina (DeVries, 2000). However, this does not seem to be the case in mouse retina; as kainate receptors are thought to be expressed in transient bipolar cells (Borghuis et al., 2014; Ichinose and Hellmer, 2016; Puthussery et al., 2014). Differential expression of AMPAR auxiliary subunits such as TARPs, NETOs or cornichons would be expected to add complexity to both AMPA and kainate currents (Jackson and Nicoll, 2011; Tomita, 2010) and could potentially contribute to response diversity, but this next level analysis of Off bipolar cell glutamate receptors has not yet been undertaken.

As mentioned above, synaptic input to On bipolar cells is mediated by a single type of glutamate receptor, the metabotropic receptor mGluR6. During the presentation of light,

unbinding of glutamate from mGluR6 triggers opening of the downstream synaptic channel, Trpm1 (Koike et al., 2010; Morgans et al., 2009; Shen et al., 2009). There is a general consensus that the length of time that Trpm1 channels remain open in response to light or pharmacological block of mGluR6 can vary from cell to cell, thus generating relatively sustained or transient responses (Awatramani and Slaughter, 2000; Kaur and Nawy 2012; Zhao et al., 2017). However, analysis of the duration of synaptic currents suggests that they generate a single broad distribution, rather than discrete groups corresponding to transient vs. sustained On bipolar cells (Kaur and Nawy, 2012), and the role of the transduction cascade in generating a transient-sustained dichotomy amongst On bipolar cell types is still in doubt. As discussed below, intrinsic voltage gated channels appear to play a critical role in the generation of sustained and transien bipolar cell subtypes.

4.1 Voltage-gated Na^+ channels

4.1.1 Voltage-gated Na^+ channels and transient vs. sustained responses to light—

A classic view of bipolar cells is that regenerative voltage- gated channels are absent and that information passes from dendrites through the soma to the axon terminal in a passive way. A number of papers have challenged this assertion, showing functional evidence for Na^+ channel expression in bipolar cells of many species (Cui and Pan, 2008; Hellmer et al., 2016; Ichinose and Lukasiewicz, 2007; Ma et al. 2005; Margolis et al., 2014; Puthussery et al., 2013; Saszik and DeVries, 2012; Trenholm and Awatramani, 2015; Zenisek et al., 2001). Although a complete consensus has not been reached regarding their function, the specific types of bipolar cells that express them, their cellular location, or their regulation, several themes have emerged. One is the observation that they are expressed in CBCs, but not RBCs. These observations thus far hold across species varying from teleosts to primates. Anothe theme is that Na^+ channels are expressed in transient type bipolar cells, perhaps responsible for generating the transient responses observed in current clamp or imaging studies, but at the very least enhancing this response. Strict verification of this idea requires that several criteria be met. First, all types of bipolar cells must be identified, and this now appears to be the case, although such a claim has been made before. Second, the temporal properties of the light response of each type must be known. Third, evidence for Na^+ channel expression of each type must be known, and the effect of either genetic or pharmacologic Na^+ channel block on the temporal properties of the light response must be determined. The recent discovery of new types of bipolar cells, due in large part to efforts to define the mouse retinal connectome (Helmstaedter et al., 2013), has been invaluable in this regard.

Imaging of bipolar cell terminals In mouse using the Ca^{2+} dye OG1 revealed that cells near the IPL midline have more transient responses to light than cells at the IPL margins (Baden et al., 2013). These authors concluded that axon terminal clusters corresponding to cone bipolar cell (CBC) types 3a and 3b (Off cells) and CBC types 5 and 6 (On cells) exhibited the most transient responses to changes in illumination. This approach is valuable for sampling multiple bipolar cells to the same stimuli. However, without the use of genetic tools or markers to identify specific bipolar cell types, conclusive identification of individual bipolar cell types with bulk dye loading is difficult. Qualitatively similar results were obtained by expressing the glutamate “sniffer” iGluSnFR in cells postsynaptic to bipolar

cells to monitor glutamate release (Borghuis et al., 2013). To date, supporting data from patch clamp studies has produced mixed results. For example, CBC type 2 might be expected to provide sustained input to sustained α Off RGCs based on their co-stratification (Della Santina et al., 2016), but their responses appear transient (Della Santina et al., 2016; Ichinose and Hellmer, 2016), perhaps important for providing input to On-Off direction selective RGCs (Duan et al., 2014). On CBC types 5a and 5b have been classified as transient, consistent with predictions based on their layers of axon termination (Hellmer et al., 2016), although it is unclear which 2 of the 3 currently accepted subtypes (Greene et al., 2016) were recorded from. CBC types X and 7 have been classified as transient (Ichinose et al., 2014). Based on its positioning near type 5 CBCs, this is expected for type X. However, the light response of type 7 might be expected to be sustained based on position in the IPL, and from imaging of Ca^{2+} signals from cells whose axons terminate in the proximal layers of sublamina b (Baden et al., 2013). A caveat to the designation of transient vs. sustained bipolar cell light responses is that the shape of the light response depends critically on a number of factors including adaptation state, stimulus intensity, the presence or absence of inhibition, and current vs. voltage clamp. For example, the response of type 2 CBCs is often sustained when measured in current clamp, but the excitatory component, isolated by measuring in voltage clamp near the reversal potential for inhibitory conductances, is transient (Della Santina et al., 2016).

Examination of bipolar cell types that exhibit regenerative Na^+ currents in mouse retina is roughly consistent with the idea that Na^+ channels are preferentially expressed in transient bipolar cells. Currents were absent or rarely seen in type 2 and type 7 bipolar cells, both of which are predicted to produced sustained responses based on stratification layer (Hellmer et al., 2016). Conversely, type XBC and type 5-2 CBCs, which most likely is identical to the type 5f CBC of a previous study (Ichinose et al., 2014), expressed robust Na^+ currents, as did type 3A. The same study showed evidence for labeling of axons in these same bipolar cell populations by a Na^+ channel antibody (Hellmer et al., 2016). A TTX-sensitive current was also detected in one subtype of the rat homolog of CBC type 5 and type 3 (Cui and Pan, 2008). Both types of cells responded to depolarization with regenerative spike-like activity, but effects of light were not examined, nor was the contribution of Na^+ channels to transient signaling. Thus, although Na^+ currents have been clearly documented in mouse and rat retina, their role in shaping the output of bipolar cells needs further investigation: they appear to be expressed preferentially in bipolar cells that contact transiently responding RGCs, but it is unclear if selective block of Na^+ channels that are expressed in bipolar cells would significantly alter RGC response properties.

In ground squirrel retina, only one type of bipolar cell, the On type cb5, was found to have Na^+ currents (Saszik and DeVries, 2012). The authors went on to divide cb5 bipolar cells into two groups: one group, termed cb5b, had large Na^+ currents (>400 pA) and was immunoreactive for both calbindin and PKC, while another group, cb5a, had smaller Na^+ currents and was labeled only by calbindin antibodies. Using perforated patch recording to maintain the native resting potential of cb5b cells, the authors showed that light rarely initiated spiking, as Na^+ channels were largely inactivated at the dark membrane potential. Importantly, cb5b cells were capable of generating spikes during presentation of flickering stimuli, as rebound hyperpolarization during the dark phase of the stimulus was sufficient to

remove channel inactivation. Thus, Na^+ channels may amplify responses to rapidly changing visual input, but stay silent during low temporal frequency stimuli. As expected, cb5b bipolar cells co-stratified with transient On RGC dendrites.

In primate retina, large Na^+ currents (≈ 400 pA at −60 mV) were observed in an Off (DB3a) and On (DB4) bipolar cell, both of which are part of the rapidly responding magnocellular pathway of primates. In current clamp, depolarizing pulses from resting potential were able to evoke fast TTX-sensitive spikes (Puthussery et al., 2013). These authors went on to show localization of Na^+ channels to the initial segment of the axon using antisera to $Na_V1.1$. Finally, following TTX application, they showed a marked reduction in excitatory input to parasol RGCs that likely collect input from these bipolar cells. Although the reduction was relatively modest, this may be due to the nature of the light stimulus paradigm, which did not contain temporal frequencies that are likely to be optimal for spike generation in presynaptic bipolar cells, and so the contribution to ganglion cell signaling may have been underestimated.

Expression of Na^+ channels would seem to be a strategy for amplifying or speeding responses in bipolar cells that mediate photopic, but not scotopic vision. This is evident in mouse retina, where Na^+ currents are not observed in rod bipolar cells (Ma et al., 2005; Tian et al., 2010), and in teleost retina, where Mb1 cells that received mixed rod/cone input also lack Na^+ currents (Zenisek et al., 2001). In primate retina there is anatomical evidence that a mixture of rod and cone input is conveyed to parasol RGCs by giant bipolar (GB) On type cells and cb3b Off bipolar cells (Tsukamoto and Omi, 2014, 2016). It will be interesting to determine whether primate bipolar cells that receive rod input are capable of producing Na^+ spikes.

4.1.2 Na^+ channel modulation—There is substantial evidence that Na_V channel function in cone bipolar cells is subject to modulation, particularly by dopamine receptors. Not surprisingly, results vary depending upon variables such as species, adaptation state, bipolar cell type, and time of day. Dopamine released in the light-adapted state inhibits Na_V function in amphibian retina. Thus, TTX reduces light responses of On cone bipolar cells in the dark-adapted but not light-adapted retina (Ichinose and Lukasiewicz, 2007). The underlying mechanism is primarily a shift in the voltage-dependence of Na^+ channel inactivation, such that Na^+ channels are mostly inactivated at resting potentials in the light adapted state. These authors went on to show that the suppressive effects of light adaptation on Na^+ current were mimicked by application of dopamine receptor agonists in the dark adapted state, and that D1 antagonists prevented inhibition of Na^+ current in the light-adapted state. Presumably this form of dopamine-dependent plasticity allows for amplification of bipolar cell pathways by Na^+ channels during times when light is scarce, and reduces saturation when light is plentiful. Roles for dopamine receptors may differ in mammalian retina, as the b-wave, an indicator of On bipolar cell activity, is reduced in D1 receptor knockouts in the light, but not dark-adapted retina (Jackson et al., 2012). In addition, the b wave is reduced in the light-adapted state following intravitreal injection of TTX or in mice lacking functional $Na_V1.6$ channels (Mojumder et al., 2008; Smith and Cote, 2012; Smith et al., 2015a). This apparent conflict may be explained by the observation that the suppressive effect of dopamine on the b wave in the light adapted retina is not due to a

direct effect of dopamine on Na^+ channels of bipolar cells, but rather through an amacrine cell disinhibition circuit (Smith et al., 2015b). In this scenario, inhibition of amacrine cell Na^+ channels decreases tonic inhibitory drive onto a downstream amacrine cell. This downstream amacrine cell now more strongly inhibits rod bipolar cells via $GABA_C$ mediated feedback (Smith et al., 2015b). Modulation of Na^+ currents may be a critical factor in extending the dynamic range of bipolar cells as lighting conditions change, and our current knowledge is insufficient to draw firm conclusions regarding the role of dopamine or other potential modulators.

4.2 Ca^{2+} channels

High voltage-activated L-type Ca^{2+} channels mediate transmitter release from bipolar cell ribbon synapses (Heidelberger and Matthews, 1992; Tachibana and Okada, 1991; Tachibana et al., 1993), as they do for photoreceptors. The molecular composition of L-type channels in photoreceptors is more clearly established (see section 2.2), but the identity or even the number of isoforms expressed in bipolar cells remains unclear. In goldfish, $Ca_V1.3$ was identified using RT-PCR as the major constituent of Ca^{2+} channels (Logiudice et al., 2006), but the field of candidates appears to be more crowded in mammalian bipolar terminals, as there is also evidence for expression of $Ca_V1.4$ (Baumann et al., 2004; Berntson et al., 2003) and $Ca_V1.2$ (Satoh et al., 1998). T-type channels are also expressed in rat bipolar cells (de la Villa et al., 1998; Kaneko et al., 1989; Pan, 2000; Protti and Llano, 1998), but their role in transmission is controversial: experiments showing that T-type, but not L-type I_{Ca} are present when recording from the cell body of bipolar cells with severed axons suggest that T type channels are not present on the axon terminal (Hartveit, 1999), a conclusion supported by immunolabeling and local application of L- and T-type antagonists to axon terminals (Satoh et al., 1998). This has led to the idea that T-type channels play a role in signal propagation rather than the gating of transmitter release. Conversely, work from the Pan lab suggests that transmitter release persists following pharmacological blockade of L-type channels at voltages that activate primarily T-type channels (Pan et al., 2001). A potential explanation for this paradox is the differential expression of Ca^{2+} channel isoform by cone- and rod-driven bipolar cells, as T-type channels are preferentially expressed in CBCs, particularly type 3 (Cui et al., 2012; Hu et al., 2009). Understanding why T-type channels are selectively expressed on a single type of CBC would provide insight into channel-specific processing of visual information.

Regenerative currents originating from activation of Ca^{2+} channels have also been detected in bipolar cells of goldfish (Burrone and Lagnado, 1997; Cui and Pan, 2008; Palmer, 2006; Protti et al., 2000; Zenisek and Matthews, 1998) and zebrafish (Baden et al., 2011; Dreosti et al., 2011). In some cases, depolarizing current pulses resulted in maintained and stereotyped electrical resonance, due to the interaction of L-type and Ca^{2+}-sensing BK channels (Burrone and Lagnado, 1997). Non-invasive monitoring of Ca^{2+} using the GCaMP reporter demonstrated that the occurrence of spikes did not alter the frequency, but enhanced the amplitude of Ca^{2+} transients locked to the frequency of the light stimulus (Baden et al., 2011; Dreosti et al., 2011). Thus, L-type channels appear to perform two functions in fish bipolar cells, gating transmitter release and generating spikes that allow for periods of maintained Ca^{2+} influx. A single spike is thought to be sufficient to empty the readily

releasable pool of vesicles (Mennerick and Matthews, 1996; Palmer, 2006). Although such an event would prevent further signaling until the pool is replenished, such signals are produced relatively rarely (Baden et al., 2011). Thus, a single presynaptic terminal has the potential to signal both tonic and phasic information.

Although Ca^{2+} channels underlie regenerative currents in goldfish Mb1 cells, they appear to play a more limited role in generating spikes in bipolar cells of mammalian retina than Na^+ channels. Instead, their role seems to be more focused on gating transmitter release. In mouse rod bipolar cells, the opening of a single L-type channel per active zone is sufficient to support univesicular release from bipolar cell terminals (Jarsky et al., 2010) but the opening of multiple channels per active zone is required in goldfish Mb1 bipolar cells (Coggins and Zenisek, 2009). This difference may arise because spikes generated by the interplay of Na^+ and K^+ channels allow for higher spike frequency than L-type Ca^{2+} channels. Importantly, expression of Ca^{2+} and Na^+ channels allows for separate populations of channels dedicated to the tasks of synaptic transmission and spiking, allowing for selective placement of spike-generating channels in specific bipolar cell populations.

4.3 K^+ channels

4.3.1 Voltage-gated K^+ channels—An outwardly rectifying K^+ channel was first described by Kaneko and Tachibana in isolated On bipolar cells of the goldfish (Kaneko and Tachibana, 1985a) and subsequently found in perch (Kaneko and Tachibana, 1985b; Lasater, 1988), zebrafish (Connaughton and Maguire, 1998), mouse and rat (Kaneko et al., 1989; Karschin and Wassle, 1990; Klumpp et al., 1995a; Klumpp et al., 1995b). This current can be regulated by a variety of second messenger pathways, potentiated by dopamine via D1 receptors and inhibited by endocannabinoids via CB1 receptors (Fan and Yazulla, 2005). There may be differences in expression patterns of outward rectifiers in cone- and rod-driven bipolar cells in rat as currents recorded from CBCs were of larger magnitude and activated at more negative voltages than their counterparts in RBCs (Hu and Pan, 2002; Ma et al., 2005). The reason for these differences is unclear. They could potentially play a role in repolarization following Na^+ channel activation since, as discussed above (section 4.1.1), Na^+ channels are preferentially expressed in CBCs. Indeed, CBCs with robust Na^+ currents had matching outward rectifying currents (Ma et al., 2005), although correlation with specific CBC subtypes was not attempted. Immunohistochemical evidence suggests that shaker ($K_V1.2$) and shab ($K_V1.3$) channels are expressed in bipolar cells of goldfish retina (Yazulla and Studholme, 1998) and in mouse RBCs (Klumpp et al., 1995a; Klumpp et al., 1995b). The role of these channels is unknown. Mammalian RBCs have a dark potential of about −45 to −50 mV (Berntson and Taylor, 2000; Euler and Masland, 2000; Oesch and Diamond, 2011), and peak depolarizing light responses are generally less than 20 mV in amplitude (Berntson and Taylor, 2000; Euler and Masland, 2000; Trexler et al., 2005), a voltage excursion that is not sufficient to substantially activate the delayed rectifier expressed in RBCs (Kaneko et al., 1989; Karschin and Wassle, 1990). Furthermore, comparison of current and voltage-clamped light responses obtained from the same cell confirm that voltage-gated channels do not significantly shape the light response in RBCs (Berntson and Taylor, 2000). In salamander retina, activation of outwardly rectifying K^+ currents restrains the membrane potential from depolarizing above −30 mV (Thoreson and Burkhardt, 2003).

A-type currents have been described in bipolar cells from cold blooded vertebrates (Connaughton and Maguire, 1998; Lasater, 1988; Tessier-Lavigne et al., 1988) but not mouse (Klumpp et al., 1995a) or rat (Karschin and Wassle, 1990). The cell type-specific distribution of these and other K^+ currents among different types of bipolar cells in cold-blooded vertebrates has not been carefully investigated.

4.3.2 BK channels—As discussed in section 1.1.4, BK channels are large conductance K^+ channels activated by both voltage and micromolar concentrations of Ca^{2+}. Opening in response to local increases in Ca^{2+}, they repolarize membrane potential. They often co-localize with Ca^{2+} channels, together regulating Ca^{2+} levels on a nanoscale (Lee and Cui, 2010). Depending upon their relative distance and numbers, these two channels can act in concert to generate oscillating responses at specific frequencies (Roberts et al., 1990). In bipolar cells, such an intimate relationship between BK and L-type Ca^{2+} channels also exists and has been studied extensively (Burrone and Lagnado, 1997; Llobet et al., 2003; Palmer, 2006; Protti et al., 2000; Sakaba et al., 1997; Zenisek and Matthews, 1998). In particular, work from the Lagnado laboratory using whole cell and cell-attached patch clamp recording has demonstrated that co-localized BK and Ca^{2+} channels contribute to electronic resonance that serves to amplify bipolar cell responses (Burrone and Lagnado, 1997; Llobet et al., 2003).

It should be noted that all of the studies cited above were carried out in On type bipolar cells of the goldfish retina. The situation in mammalian retina may be quite different. To date BK channels have not been detected immunohistochemically on terminals of bipolar cells in mouse or rat retina, but rather on A17 amacrine cell processes in close apposition to rod bipolar cell terminals (Grimes et al., 2009; Tanimoto et al., 2012). Furthermore, an ERG study taking advantage of a BK channel knockout mouse failed to demonstrate any functional deficit other than a change in the duration of the b-wave at low light intensities that was attributed to increased inhibitory feedback from BK-expressing A17 amacrine cells (Tanimoto et al., 2012), although horizontal cells, which also express BK channels, might be expected to play a role as well (Sun et al., 2017). It remains to be determined whether BK channels have thus far escaped detection in higher mammals, or are confined to horizontal, amacrine and ganglion cells. If so, this serves as a reminder that findings in lower vertebrates may not necessarily translate to mammalian retina. It is tempting to speculate that regenerative activity in mammalian bipolar cells relies on Na^+-dependent action potentials, rather than Ca^{2+} channels, reducing the need for a Ca^{2+}-sensing K^+ channel.

4.4 HCN channels

In rat retina, type 3 Off cells stain for HCN4, while type 5 cells express HCN1, HCN2 and HCN4 (Fyk-Kolodziej and Pourcho, 2007; Müller et al., 2003). Interestingly, only the CB5b subtype of type 5 CBC was shown to express HCN channels, while the CB5a subtype did not (Fyk-Kolodziej and Pourcho, 2007). Anatomically, the two subtypes can be distinguished by the pattern of axon stratification, as CB5b exhibit diffuse axon terminals, whereas CB5a have a narrower stratification. Functionally, CB5a cells have low pass filtering characteristics, while CB5b have band pass characteristics (Ichinose et al., 2014), consistent with the predicted roles of HCN channels. Unlike Na_v expression, there is

functional and immunohistochemical evidence for expression of HCN channels in the rod pathway. HCN2 channels are found in rod bipolar cells (Cangiano et al., 2007; Müller et al., 2003), although differing reports on the location of the channels point to localization in either dendrites (Cangiano et al., 2007) or axon terminals(Müller et al., 2003). In mouse, they appear restricted to bipolar cell dendrites, colocalizing with mGluR6. In primate retina, an HCN current with kinetic properties similar to HCN1 has been described for DB3a, DB3b and DB4 cells (Puthussery et al., 2013), suggesting that HCN currents are highly conserved amongst bipolar cells that comprise transient signaling in the retina. In primate bipolar cells, HCN channels are localized to axon terminals.

4.5 Summary

Bipolar cells are high resistance, electrically compact cells, ensuring that small currents evoked by fluctuations in photoreceptor transmitter release can be reliably transmitted to the inner retina. The distribution of ion channels among different subtypes of bipolar cells is summarized in Table 1. In addition to channels that maintain resting potential and passive flow of information, strategically placed Na^+, Ca^{2+} and K^+ channels in specific subsets of bipolar cells generate regenerative responses that allow for the encoding of information with greater fidelity at high temporal frequencies. In mammalian retina evidence collected to date suggests that these channels are preferentially expressed in bipolar cells that terminate in the middle layers of the IPL, providing input to transiently responding RGCs. In addition to intrinsic, voltage-gated channels, retinal circuitry undoubtedly contributes to generating sustained or transiently responding bipolar cells. In particular, the precise timing of negative feedback from amacrine cells is of critical importance (Eggers and Lukasiewicz, 2011; Eggers et al., 2007; Moore-Dotson et al., 2015). A thorough understanding of the role of voltage-gated channels will require a complete wiring diagram of bipolar cell to ganglion cell connections, and bipolar cell specific knockouts of voltage-gated channels, allowing for the assessment of the impact of each channel on RGC kinetics and sensitivity.

5. Amacrine cells

Amacrine cells (ACs) are the most diverse population of neurons in the retina and are responsible for shaping the visual signal as it is passed from bipolar cells to RGCs. They do this by making feedback inhibitory synapses (GABAergic or glycinergic) onto bipolar cell axon terminals and by providing feed-forward inhibition onto RGCs (Diamond, 2017; Eggers and Lukasiewicz, 2011; Masland, 2012b). ACs also provide inhibition to other ACs, creating complex feedback and feed-forward inhibitory networks.

AC cell bodies occupy the inner nuclear layer (INL) and the RGC layer and are often referred to as “displaced” ACs when found in the RGC layer. Their dendrites and, in some cases, axons occupy strata of the IPL along with the bipolar cell axon terminals and ganglion cell dendrites. The selective layering of AC processes in the IPL gives clues to the identities of the bipolar cells and retinal ganglion cells with which they communicate. Bi- or multi-stratified ACs (with dendrites spanning multiple sublayers of the IPL) provide “crossover inhibition”, the relay of signals between On and Off channels of the retina (Diamond, 2017) and are conventionally thought to be glycinergic (Menger et al., 1998). Wide-field ACs, on

the other hand, are conventionally thought to be GABAergic (Pourcho and Goebel, 1983; Vaney, 1990). As discussed in the following sections, wide-field ACs are able to fire action potentials, which allow them to carry signals along the length of their dendrites and axons, while narrow-field ACs are thought to signal via passive mechanisms (Bloomfield, 1992). However, as we describe for AII ACs below, this “rule” is not hard and fast.

ACs also release other neurotransmitters and neuromodulators. Dopaminergic ACs (DACs), for instance, are the sole source of dopamine, a signal for light adaptation in many retinas (Witkovsky, 2004), although they also release GABA (Hirasawa et al., 2012; Hirasawa et al., 2009). Starburst ACs (SACs) are cholinergic and are identified in immunolabeling experiments by their expression of choline acetyltransferase (Taylor and Smith, 2012). Like DACs, they also release GABA, which is key for providing directional selectivity of direction-selective ganglion cells (DSGCs). An additional strange AC class was recently identified based on expression of a vesicular glutamate transporter, vGlut3. The vGlut3 AC has numerous identified post-synaptic targets, providing glutamatergic input to some and glycinergic input to others (Grimes et al., 2011; Lee et al., 2016).

Current estimates from mouse and rat studies indicate that there are >45 distinct AC classes (Diamond, 2017; Helmstaedter et al., 2013; MacNeil et al., 1999; MacNeil and Masland, 1998; Masland, 2012a; Masland, 2012b), yet only a handful have been studied in detail. Generally, several ion channel subunits as well as voltage-gated currents such as I_{Ca}, I_{Na}, I_h, I_{KA}, and I_{KDR} have been described in various ACs from several species (Barnes and Werblin, 1986; Bloomfield and Völgyi, 2007; Cameron et al., 2017; Eliasof et al., 1987; Horio et al., 2018; Huba et al., 1992; Koizumi et al., 2004; Lasater and Witkovsky, 1990; Maguire, 1999; Mitra and Slaughter, 2002; Solessio et al., 2002; Taylor, 1996; Yang et al., 1991). A particularly nice body of literature from groups studying amphibian retinas has shown the presence of multiple voltage-gated currents in ACs and explored their roles in shaping spiking and synaptic output. In salamander retina, 95% of ACs exhibit I_{Na} (Heflin and Cook, 2007). Some ACs are capable of repetitive spiking whereas others can generate only a single spike in response to depolarizing voltage steps and often fail to spike altogether during light-evoked depolarization. ACs that generate repetitive spiking have larger I_{Na} and those that generate a single spike have smaller I_{Na} (Heflin and Cook, 2007). The tendency to fire a single spike can also be promoted by the presence of a slowly activating I_K that fails to provide sufficient hyperpolarizing relief of Na^+ channel inactivation (Barnes and Werblin, 1986; Eliasof et al., 1987). Although a number of exceptions to this generalization were observed, wide-field ACs are more likely to generate bursts of spikes whereas small-field ACs are more likely to generate only a single spike (Heflin and Cook, 2007). Cells that are only capable of firing single spikes are not always transient ACs but can also exhibit sustained post-synaptic potentials. Similarly, not all ACs that exhibit repetitive spiking are “sustained” ACs (Heflin and Cook, 2007).

Release of GABA and glycine from salamander ACs involves both Na^+-dependent spiking and graded potentials (Bieda and Copenhagen, 1999; Cook and Werblin, 1994). Release evoked by widefield illumination is more sensitive to inhibition of Na^+ channels than release evoked by illumination restricted to the receptive field center (Bieda and Copenhagen, 1999). The generation of dendritic spikes in large field ACs can boost excitatory post-

synaptic potentials and thereby coordinate release from multiple sites (Cook and Werblin, 1994; Miller and Dacheux, 1976; Miller et al., 2006; Werblin, 1977). Both N- and L-type Ca^{2+} channels localized primarily to dendrites (Maguire, 1999) contribute to the Ca^{2+} influx that triggers glycine release from ACs (Bieda and Copenhagen, 2004). Although widefield ACs of teleost retina also possess both N and L-type Ca^{2+} channels, only L-type channels appear to mediate release from these cells (Vigh and Lasater, 2004). This was also true for GABAergic ACs from chick retina (Gleason et al., 1994).

In ACs that have been enzymatically isolated from salamander retina, the close association between L-type Ca^{2+} channels and Ca^{2+}-activated K^+ (BK) channels promote the appearance of spontaneous outward currents (Mitra and Slaughter, 2002). Similar to muscle cells and a number of other neurons, Ca^{2+} influx that accompanies opening of a Ca^{2+} channel can be boosted by Ca^{2+}-induced Ca^{2+} release from intracellular stores leading to activation of nearby BK channels that generate an outward current. Spontaneous outward currents involving similar mechanisms have also been observed in teleost ACs, although there is a role for both BK and SK channels in these cells (Solessio et al., 2002; Vigh et al., 2003). These currents contribute to oscillatory behavior and shape bandpass filtering characteristics of the AC membrane (Vigh et al., 2003). Amacrine cells in salamander retina also exhibit I_{KA} and I_{KDR} (Eliasof et al., 1987; Mitra and Slaughter, 2002).

Rodent retinas are the current preferred model system for studying retinal function. Because of the diverse structure and function of retinal ACs in rodent retinas, it is challenging to describe function of specific ion channels in ACs in general terms. Therefore, rather than organizing this section by ion channel type, we have organized it by AC type, describing the role of various ion channels in the function of several well-characterized AC classes: AII's, A17's, SACs, DACs, and wide-field CRH ACs. The principal ion channels in these different subtypes, as well as amacrine cells from salamander retina, are summarized in Table 2.

5.1. AII amacrine cells

AII ACs are a key hub for information flow in the inner retina and largely function to transmit signals arising from rods and RBCs to CBCs under scotopic conditions as part of the "primary rod pathway" (Bloomfield and Vülgyi, 2009; Demb and Singer, 2012). These retinal interneurons have been studied extensively in retinas of mammals such as rat, mouse, and rabbit. All's receive excitatory glutamatergic synaptic input from RBCs in their distal dendrites near the border of the IPL and GCL. Alls then relay that On depolarization to On cone bipolar cells via gap junction electrical synapses in their distal dendrites. Off signals are relayed to Off CBCs via inhibitory glycinergic synapses at All lobular dendrites. All's are also important in photopic (cone-driven) signaling conditions, where they contribute to crossover inhibition and provide a direct inhibitory drive to some classes of Off RGCs (Manookin et al., 2008).

Glycinergic synaptic transmission from All's is mediated by Ca^{2+} influx exclusively through $Ca_V1.3$ L-type channels (Balakrishnan et al., 2015; Bieda and Copenhagen, 2004; Habermann et al., 2003). L-type channels are key for synaptic transmission at excitatory ribbon synapses of photoreceptors, bipolar cells, and hair cells, where sustained calcium entry supports tonic neurotransmitter release (Joiner and Lee, 2015; Matthews and Fuchs,

2010). Despite their lack of a ribbon, AII synaptic output is also quite sustained, which appears to result in part from the use of L-type channels (Balakrishnan et al., 2015). I_{Ca} are present in early postnatal AII's, but dramatically increase in amplitude by P9 in mice, which is around the same time at which glycinergic inputs can be detected in Off cone BCs (Balakrishnan et al., 2015; Schubert et al., 2008). This time course is also associated with a refinement of Ca^{2+} channel localization; Ca^{2+} imaging studies indicate that Ca^{2+} influx is more diffuse in early postnatal AII's, but is refined by adulthood and localized exclusively to the lobular dendrites (Balakrishnan et al., 2015; Habermann et al., 2003).

Despite being narrow-field ACs, AII's are known to possess voltage-gated Na^+ channels and fire small and relatively slow action potentials that are blocked by TTX (Bloomfield and Xin, 2000; Boos et al., 1993; Cembrowski et al., 2012; Mørkve et al., 2002; Tamalu and Watanabe, 2007; Tian et al., 2010; Veruki and Hartveit, 2002). These are likely mediated largely by $Na_V1.1$ channels, which have been identified in AII's by *in situ* hybridization in rats (Kaneko and Watanabe, 2007). The sluggish action potential kinetics in somatic recordings suggest that the action potentials are generated in a distal compartment of the AII (Cembrowski et al., 2012; Tamalu and Watanabe, 2007). Consistent with this, labeling with anti-$Na_V1.1$ and anti-pan Na_V antibodies has been shown to localize to a short AII process that branches off of dendrites near the AII somata in mice (Cembrowski et al., 2012; Wu et al., 2011). This region also appears enriched for ankyrin-G and neurofascin, which localize Na^+ channels to the axon initial segment in many neurons (Cembrowski et al., 2012; Wu et al., 2011). Extracellular stimulation near these processes triggers a spike and excision or localized application of TTX will block AII spiking behavior and Na^+ currents (Cembrowski et al., 2012; Tamalu and Watanabe, 2007). AII's also possess K^+ currents that support spiking behavior including a delayed-rectifier and A-type current (Boos et al., 1993; Tian et al., 2010). Much of the K^+ current in AII's is sensitive to TEA, while a smaller portion is blocked by 4-AP (Boos et al., 1993; Tian et al., 2010).

The consequences of AII sodium currents and spiking are still largely unclear. AII spike frequency encodes the strength of excitatory input (Tamalu and Watanabe, 2007) and AII Na^+ currents also appear to play a major role in the oscillatory activity detected in RGCs and other inner retinal neurons (Margolis et al., 2008; Stasheff, 2008) following photoreceptor degeneration (Trenholm et al., 2012).

Work by Tian and colleagues (Tian et al., 2010) examined the influence of AII Na^+ channels on the inputs from rod bipolar cells and how that process affects propagation of scotopic signals from AII's to cone BCs and RGCs in mouse retinas. In paired recordings from AII's and RBCs, they found that TTX blockade of Na^+ channels had the dual effect of attenuating and slowing post-synaptic potentials. Thus, Na^+ channels accelerate and amplify synaptic responses in AIIs, which, along with the kinetics of RBC exocytosis (Singer and Diamond, 2003), might contribute to the phenomenon that AII light responses are faster than those of presynaptic RBCs (Nelson, 1982). Additionally, this effect depended on the AII membrane potential; the EPSP was not enhanced at either depolarized potentials (>−45mV), where most Na^+ channels would be unavailable due to inactivation, or at hyperpolarized potentials (<−80 mV), below the Na channel activation threshold (Tian et al., 2010). Recordings of light responses from RGCs showed that inhibition of Na^+ channels slowed inhibitory and

excitatory synaptic inputs to RGCs without affecting amplitude. Thus, while potentially serving to threshold synaptic inputs to AII's, Na^+ currents appear only to accelerate AII output to downstream RGCs (Tian et al., 2010). The implications of this for RGC output are still unclear. Because the AII resting membrane potential appears to vary with background lighting (Dunn, 2006; Tian et al., 2010), this might slightly shift the strength of AII-mediated synaptic acceleration as a result of changing Na^+ channel availability.

5.2 A17 amacrine cells

The A17 AC (which likely corresponds to S2 ACs in rabbit) receives input from, and sends its output to, the same RBC, regulating synaptic transmission from RBC to AII ACs (Menger and Wassle, 2000; Nelson and Kolb, 1985; Raviola and Dacheux, 1987; Vaney, 1986; Volgyi et al., 2002; Zhang et al., 2002). A17 ACs extend individual thin processes to the innermost layer of the IPL, contacting only RBCs and no other cell type. Each of these contacts has been likened to an electrically-isolated, individual microcircuit (Grimes et al., 2010). Elegant support for this idea comes from 2-photon imaging of Ca^{2+} transients in synaptic boutons during electrical stimulation. These experiments revealed that stimulation of individual boutons generated I_{Ca} that could be detected in somatic patch clamp recordings, but did not activate neighboring synaptic boutons. Such electrical isolation would imply the absence of action potential generation in A17 cells. Indeed, although Na^+ channels are expressed in A17 ACs, they do not appear capable of supporting robust regenerative currents (Bloomfield, 1996; Grimes et al., 2010; Menger and Wassle, 2000; Nelson and Kolb, 1985). Both A-type and outward rectifying K^+ currents have been reported in A17 ACs as well (Grimes et al., 2010). What might be the function of Na^+ and K^+ channels if not to augment signal propagation? Modeling of signal spread through A17 processes shows that the presence of these voltage-gated channels, expressed at low density, actually reduce spread of signals produced by opening of postsynaptic AMPA channels, compared to a purely passive membrane. Channel activation increases membrane conductance and reduces the length constant of the cell, effectively reducing signal conduction. This curious arrangement serves as a reminder that the presence of voltage-gated channels does not always result in the enhancement of signal conduction.

A17 ACs express L-type Ca^{2+} channels (Grimes et al., 2009; Menger and Wassle, 2000), but it was initially thought that Ca^{2+} influx through Ca^{2+}-permeable AMPA receptors (CP-AMPARs), rather Ca^{2+} channels, triggers release of GABA onto RBC terminals (Chavez et al., 2006). These authors also showed that Ca^{2+}-induced Ca^{2+} release from stores provided a second source of Ca^{2+} for triggering GABA release. NMDA receptors, which are highly Ca^{2+} permeable, situated close to GABA release sites, and activated by glutamate released from RBC terminals, may also contribute to GABA release in this feedback circuit (Zhou et al., 2016). However, an additional layer of complexity was revealed by experiments demonstrating a role for Ca^{2+} channels at some, but not all A17 release sites (Grimes et al., 2009; Grimes et al., 2015). Specifically, they found that terminals using CP-AMPARs to couple Ca^{2+} to GABA release were presynaptic to rapidly activating $GABA_A$ receptors, while a second terminal, contacting the same RBC, used Ca^{2+} channels to gate GABA release. This second terminal was presynaptic to slower activating $GABA_C$ receptors.

What mechanisms are used by A17 ACs to terminate transmitter release? Expression of BK channels at synaptic varicosities has been reported (Grimes et al., 2009). As discussed previously, BK channels are both voltage and Ca^{2+}-sensitive, and their opening repolarizes the membrane and contributes to rapid closure of L-type Ca^{2+} channels. Close apposition of BK and L-type channels appears to be an important mechanism for presynaptic regulation of synapses (Roberts et al., 1990; Skinner et al., 2003; Xu and Slaughter, 2005). Conversely, closure of AMPA receptors is not voltage-dependent, but is dictated by the lifetime of glutamate in the synaptic cleft (Diamond and Jahr, 1995). Thus, association of CP-AMPARs with BK channels affords no obvious advantage to regulation of GABA release from terminals that express CP-AMPARs. In support of this, both immunogold labeling of BK channels and electrophysiological evidence suggest that BK channels colocalize with L-type channels, but are too far from CP-AMPARs to be activated by Ca^{2+} influx through these receptors (Grimes et al., 2015). The authors go on to speculate that in the dark, release rates of RBCs are sufficient to depolarize A17 boutons and activate BK channels, thus limiting GABA release from L-type Ca^{2+} channel-expressing boutons and allowing for high throughput from RBCs to AII's. As ambient light increases, this concomitantly raises release rates of presynaptic RBCs, leading to further depolarization of A17 dendrites. This triggers a voltage-dependent switch within the BK channel to an inactive state, mediated by the auxiliary β2 subunit (Hicks and Marrion, 1998; Wallner et al., 1999; Xia et al., 2003). Inactivation of BK channels would allow for maintained L-type channel activation, allowing for strong feedback inhibition onto RBC terminals. In this way, BK channels expressed in A17 ACs are proposed to play a role in extending the operating range of the RBC-AII AC synapse by reducing RBC transmitter release at higher light intensities (Grimes et al., 2009; Grimes et al., 2015). A powerful tool to further explore this hypothesis would be cre-mediated deletion of the β2 subunit gene *kcnmb2*, provided that a cre line specific for A17 ACs becomes available.

5.3 Starburst amacrine cells (SACs)

SACs provide GABAergic inhibition to DSGCs. Glutamatergic excitation from bipolar cells to DSGCs lacks direction selectivity. Rather it is the direction-selective inhibitory output of SACs onto DSGCs that generates preferred and null directions. Mechanisms responsible for generation of direction selectivity of SACs have been studied extensively and there are a number of recent reviews summarizing this progress (Franke and Baden, 2017; Mauss et al., 2017; Wei, 2018). A key feature of information processing in the SAC is the preference of motion away from (centrifugal) rather than toward (centripetal) the soma (Euler et al., 2002; Hausselt et al., 2007; Lee and Zhou, 2006). As an object moves through the receptive field of a SAC, it stimulates bipolar cells that subsequently release glutamate along the entire length of the radially extending dendrites of the SAC in a sequential manner. Objects moving centrifugally generate a wave of depolarization that ultimately results in Ca^{2+} dependent release of GABA from distal processes, while the depolarizing wave generated from centripetal movement, presumably activating the same presynaptic bipolar cells as an object moving in the centrifugal direction, is much more modest. The reason for this differential effect of direction is still unclear, but a recent model suggesting that it is due to differences in the response kinetics of bipolar cell types providing input is particularly intriguing (Greene et al., 2016; Kim et al., 2014). However, this so-called "space time

wiring" hypothesis is controversial (Fransen and Borghuis, 2017; Morrie and Feller, 2018; Stincic et al., 2016) and probably cannot account for the directional effect entirely.

Although no single mechanism has been shown to be necessary or sufficient to generate direction selectivity of SAC processes, voltage-gated channels appear to enhance this selectivity (Hausselt et al., 2007; Jensen, 1995a; Oesch and Taylor, 2010; Tukker et al., 2004). Studies of the contribution of Na^+ channels to the physiological properties of SACs have provided conflicting results, with some reporting robust spiking (Bloomfield, 1992; Cohen, 2001; Jensen, 1995b) and others suggesting that they lack Na^+ currents completely (Kaneda et al., 2007; Ozaita et al., 2004; Taylor and Wassle, 1995; Zhou and Fain, 1996). The resolution may be provided by more recent studies showing that SACs express TTX-resistant $Na_V1.8$ channels (O'Brien et al., 2008; Oesch and Taylor, 2010), and thus studies using TTX to block inward or regenerative currents would have attributed them to another type of channel. Using a blocker of TTX-insensitive Na^+ channels, Oesch and Taylor (2010) demonstrated a significant reduction in centrifugal, compared to centripetal light stimulation. However, even in the absence of TTX-resistant Na^+ channels the difference in the response to centrifugal and centripetal stimulation was still quite robust, suggesting only a modest effect on direction selectivity. There is evidence for expression of N, P and Q (but not L) type I_{Ca} (Cohen, 2001; Kaneda et al., 2007; Lee et al., 2010). Interestingly, SACs release both acetylcholine and GABA, and it has been suggested that release of each transmitter is gated by a different subset of Ca^{2+} channels: agatoxin, a P/Q channel antagonist blocked release of predominantly GABA, while the N type channel blocker ω-conotoxin almost completely prevented release of acetylcholine, but not GABA (Lee et al., 2010).

Models of SAC direction selectivity require significant compartmentalization of processing (Miller and Bloomfield, 1983; Poznanski, 1996; Tukker et al., 2004; Velte and Miller, 1997). Specifically, the soma must have a low input resistance to prevent rapid spread of signals across to neighboring proximal dendrites. It has been proposed that delayed rectifier K_V3 channels fulfill this role (Ozaita et al., 2004). Immunolabeling of $K_V3.1$ and $K_V3.2$ channels showed a high to low gradient of expression from soma to distal dendrites, consistent with a role for somatic shunting of signals. Furthermore, outward rectification was nearly absent in SACs from $K_V3.1$- $K_V3.2$ double knockout mice, suggesting that these are the predominant isoforms expressed by this cell (Ozaita et al., 2004). It remains to be determined if direction selectivity is reduced in DSGCs in these knockout mice as a result of the loss of somatic shunting. Alternatively, or perhaps in addition, mGluR2 mediated regulation of Ca^{2+} channels may also participate in dynamically regulating somatic resistance (Koren et al., 2017). These authors showed that inhibition of mGluR2 increased spread of Ca^{2+} signals across the soma to dendrites on the opposite side of the SAC. Recordings from DSGCs revealed an increase in inhibition in response to movement in the preferred direction when mGluR2 receptors were blocked, thus reducing the selectivity for movement in the preferred direction. Inhibition of mGluR2 receptors also decreased the amplitude of N, P and Q Ca^{2+} channels, but not K_V3 channels (Koren et al., 2017). Thus, voltage-gated channels in SACs may play a greater role in preventing spread of signals across compartments than they do in generating the signals themselves.

5.4 Dopaminergic Amacrine Cells (DACs)

DAC somas reside on the very inner border of the INL (Dacey, 1990). These neurons possess a fairly sparse localized dendritic arbor with a diameter of ~500 microns and a much wider-reaching arbor of thin axons (Dacey, 1988; Dacey, 1990; Keeley and Reese, 2009; Witkovsky et al., 2005). Both the dendrites and axons stratify in the very outer sublamina of the IPL adjacent to the INL, although a few processes occasionally reach into other layers of the retina. DACs are excited by light (On cells) due to excitatory *en passant* or ectopic synaptic inputs from On bipolar cells and M1-type melanopsin-expressing ganglion cells, as revealed in studies of both mouse and rabbit retinas (Dumitrescu et al., 2009; Hoshi et al., 2009; Prigge et al., 2016; Zhang et al., 2008; Zhang et al., 2007). This triggers action potential firing and release of dopamine (Puopolo et al., 2001), which functions as a neuromodulatory signal for light adaptation in the retina (Witkovsky, 2004). Dopamine appears to act in a paracrine fashion (Puopolo et al., 2001; Witkovsky, 2004), diffusing to DA receptors expressed by all classes of neurons in all layers of the retina without requiring direct synaptic contacts. Additionally, DACs are also GABAergic and co-release GABA with dopamine (Hirasawa et al., 2012, 2009). DACs appear to play a major role in regulating the function of AII ACs, as DAC processes encircle and synapse onto the thick proximal dendrites of AII ACs (Contini and Raviola, 2003; Voigt and Wässle, 1987).

Several classes of voltage-gated current have been identified in recordings from DACs in multiple species. In keeping with their axons and relatively wide dendritic fields, DACs in mice fire action potentials (Gustincich et al., 1997) and can exhibit several distinct patterns of spiking, including silent, sustained, irregular, and bursting (Newkirk et al., 2013; Zhang et al., 2007). Bursting behavior appears to be a key trigger for dopamine release by DACs (Puopolo et al., 2001). In voltage-clamp recordings, both a transient, TTX-sensitive and persistent, TTX-insensitive Na^+ current have been characterized (Feigenspan et al., 1998; Steffen et al., 2003; Xiao et al., 2004). While TTX blocks regenerative spiking activity and transient Na^+ currents in DACs (Feigenspan et al., 1998), modeling indicates that the persistent I_{Na} is required for sustained spiking (Steffen et al., 2003).

DACs also have delayed rectifier and A-type K^+ currents (I_{KDR} and I_{KA}, respectively). A $K_V4.3$ channel (which generates an I_{KA}) has been found localized to the somatodendritic compartment of DACs, while $K_V3.1$ is not present in DACs (Tian et al., 2003). Other K^+ channel subunits including I_{KDR} channels $K_V1.1$, 1.3, and 2.1 are present in DACs, as is the I_{KA} channel $K_V4.3$ (Tian et al., 2003). Inhibiting I_{KDR} with a low concentration of TEA slightly broadened action potentials and blocked the action potential after-hyperpolarization (AHP) in mice (Feigenspan et al., 1998). A high concentration of TEA, on the other hand (40 mM), depolarized DACs and dramatically slowed the falling phase of the action potential (Feigenspan et al., 1998). 4-AP application, which is often used to inhibit I_{KA}, depolarized the DAC and increased spike rate (Feigenspan et al., 1998). This is consistent with modeling indicating that I_{KA} plays a major role in regulating DAC firing rate (Xiao et al., 2004).

HVA I_{Ca} are detectable in voltage-clamp recordings of DACs and several Ca_V isoforms including the L-type channel $Ca_V1.2$, P/Q channel $Ca_V2.1$, and R-type channel $Ca_V2.3$ have been localized to DAC somata and processed by immunofluorescence (Xu et al., 2002). The

N-type channel $Ca_V2.2$ is found only in DAC processes (Xu et al., 2002). It is likely that some combination of these channels is responsible for dopamine and/or GABA release by DACs, which is known to be Ca^{2+}-dependent (Hirasawa et al., 2012, 2009). Ca^{2+} influx through Ca^{2+} channels is also likely responsible for gating Ca^{2+}-activated K^+ channels (Feigenspan et al., 1998; Xiao et al., 2004). SK2 channels have been identified in DACs (Klöcker et al., 2001). However, application of the SK channel blocker apamin had minimal effect on DAC action potential waveforms or spiking frequency while the BK channel blocker charybdotoxin slightly accelerated spiking and blocked the action potential after-hyperpolarization (Feigenspan et al., 1998). Co^{2+} application, which blocks Ca^{2+} influx through voltage-gated Ca^{2+} channels, caused a small reduction in action potential amplitude without affecting frequency (Feigenspan et al., 1998).

Finally, DACs in current clamp display a modest depolarizing voltage “sag” in response to hyperpolarization and a small Cs^+-sensitive inwardly-rectifying hyperpolarization-activated current, consistent with the presence of the hyperpolarization activated cation current I_h. Cs^+ blockade of I_h, however, had minimal effect on DAC spiking behavior (Feigenspan et al., 1998), although modeling of DAC membrane currents indicated that I_h can function to subtly increase DAC firing rate (Xiao et al., 2004).

Thus, DACs respond to excitatory synaptic input by firing action potentials and releasing dopamine and GABA. The various classes of voltage-gated and Ca^{2+}-activated ion channels in DACs support this behavior, although only a handful have been shown to substantially alter DAC spike frequency when blocked. It remains to be determined what combinations of ion channel properties and synaptic inputs lead to the different spiking behaviors of DACs (Newkirk et al., 2013; Zhang et al., 2007) and whether or how these are dynamically regulated by patterns of synaptic input to favor dopamine and/or GABA release by DACs.

5.5 Wide-field CRH amacrine cells

The use of genetic lines has enabled identification of specific types of ACs not easily identified otherwise. An example is the CRH family of ACs, identified by screening of a corticotropin releasing hormone (CRH)-cre mouse line (Jacoby et al., 2015; Zhu et al., 2014). In the initial screen, two types of CRH ACs were described: a medium field cell with dendrites that extend approximately 200-300 μm in diameter and terminate deep in the IPL, and an axon-bearing bistratified wide field cell with dendrites that extend >1 mm (Zhu et al., 2014). The CRH-1 cell was later shown to provide feedforward inhibition to the “suppressed by contrast” RGC, a bistratified RGC that is inhibited by both positive and negative contrast (Jacoby et al., 2015). A subsequent study demonstrated a third type of axon-bearing wide field CRH AC (Park et al., 2018). This study went on to show that two of three classes of CRH cells, type 1 (medium field) and type 3 (axon-bearing wide field) provide inhibitory input to On alpha RGCs. Thus CRH-1 ACs provide input to both alpha ON and suppressed by contrast RGCs.

Comparison of CRH-1 and CRH-3 ACs illustrates a basic principle of Na^+ channel expression in ACs. CRH-1, a medium field cell, lacks Na^+ channels and communicates to postsynaptic RGCs using passive electronic spread (Jacoby et al., 2015; Park et al., 2018). Conversely, CRH-3 and CRH-2 are axonbearing wide field cells that contact postsynaptic

RGCs over a distance of 1 mm or more, express Na^+ channels and fire at high frequency in response to light (Park et al., 2018). They appear similar to a group of wide field axon-bearing ACs, including polyaxonal ACs, that are capable of generating Na^+ spikes (Cook and McReynolds, 1998; Flores-Herr et al., 2001; Freed et al., 1996; Greschner et al., 2014; Murphy-Baum and Taylor, 2015; Stafford and Dacey, 2009; Taylor, 1999; Volgyi et al., 2001). In primate A1 ACs, which are morphologically similar to the mouse CRH-2 (Zhu et al., 2014), action potentials recorded at the soma are initiated within the dendritic arbor (Freed et al., 1996; Stafford and Dacey, 2009). This is presumably in addition to axonal Na^+ channels required for propagation of signals to distant locations within the retina. Although the site of Na^+ channel expression on CRH-2/3 cells has not been determined, they appear necessary for propagation of signals to downstream α RGCs. Park et al (2018) drove IPSCs in ON α RGCs by expressing channelrhodopsin in CRH-1 and CRH-3 ACs. Blocking Na^+ channels with TTX reduced the inhibitory post-synaptic current by approximately 50%. Since both types of ACs drive ON α RGCs, but only CRH-3 ACs spike, this result implies that input from CRH-3 cells was severely reduced or perhaps eliminated following Na^+ channel blockade. Ca^{2+} and K^+ channels have not yet been characterized in CRH ACs.

Convergence of narrow and wide-field ACs onto a single RGC implies that postsynaptic inhibition is shaped by both global and local patterns of illumination. In addition, CRH-1 and CRH-3 ACs appear to differentially temporally filter input, as CRH-1 but not CRH-3 cells low pass filters flickering stimuli (Park et al., 2018). Differences in filtering between the two cell types are most apparent in current, rather than voltage clamp, highlighting the role of voltage-gated channels in temporal filtering. However, an analysis of other voltage-gated channels that may contribute to this temporal filtering has yet to be carried out.

6. Interplexiform cells

Interplexiform cells were first identified in teleost retina by Ehinger et al. (1969). Gallego (1971) found the same class of cells in cat retina and named them interplexiform cells because they have processes that terminate in both the inner and outer plexiform layers. Like amacrine cells, their cell bodies reside in the proximal INL and they have dendrites in the IPL, so some investigators have classified interplexiform cells as a subtype of amacrine cells (Witkovsky, 1980). However, unlike other amacrine cells, they extend processes into the OPL to terminate adjacent to bipolar, horizontal and cone photoreceptor cells (Dowling and Ehinger, 1975; Boycott et al., 1975; Kolb and West, 1977; Linberg and Fisher, 1986; Jiang and Shen, 2010). There are at least three neurochemically distinct subtypes in mouse retina: one that contains dopamine, one with GABA, and one with glycine (Dedek et al; Witkovsky et al 2008; Haverkamp and Wassle, 2000). At least three anatomically distinct types of interplexiform cells have also been identified in salamander retina (Maguire et al. 1990). There were no obvious differences in the types of ion channels in these three types (Maguire et al. 1990).

There are relatively few interplexiform cells in the retina and their ion currents have received little study. The few studies on these cells show currents similar to those of amacrine cells. In both salamander and mouse, interplexiform cells possess fast voltage-dependent I_{Na}, HVA L-type I_{Ca}, and I_{KDR} that can be blocked by extracellular TEA and intracellular Cs^+

(Feigenspan et al., 1998; Gustincich et al., 1997; Maguire et al., 1990). T-type I_{Ca} appear to be absent from interplexiform cells. Some interplexiform cells in mouse and salamander exhibit modest A-type K^+ currents that can be inhibited by 4-AP (Feigenspan et al., 1998; Maguire et al., 1990). In mouse retina, charybdotoxin-sensitive BK channels and weak I_h have also been found (Feigenspan et al., 1998). The ion channels that have been identified in interplexiform cells are summarized in the last column of Table 2.

7. Retinal Ganglion cells (RGCs)

RGCs are the output neurons of the retina and responsible for relaying information to visual areas of the brain. The combination of distance along which RGCs must carry visual information – several millimeters in mice to several centimeters in humans – and the speed necessary to support visually-guided behaviors requires that RGCs relay vision information as trains of regenerative action potentials. They accomplish this task by integrating excitatory synaptic inputs from bipolar cells and inhibitory inputs from ACs into a train of action potentials that propagate along RGC axons.

To date, anatomical and functional studies indicate that there are >30 classes of RGCs in mice (Baden et al., 2016; Bae et al., 2018) while a single-cell transcriptomics approach has clustered RGCs into 40 distinct subtypes (Rheaume et al., 2018). As with bipolar cells, the most fundamental classification scheme for RGCs segregates them by the sign of their response – whether they are excited by light onset (On cells) or light offset (Off cells) or respond to both light and dark (On-Off cells). Other classifying response properties include whether RGC responses are sustained or transient, whether RGCs are sensitive to directional motion, or whether they have chromatic preference. RGCs of the same class also share anatomical features including dendritic co-stratification in the IPL, similar soma sizes, similar dendritic branching patterns, and regular spacing across the retinal surface.

7.1 Voltage-gated Na^+ channels

Like most neurons that fire regenerative action potentials, RGCs do so using a combination of voltage-gated Na^+ and K^+ channels in a manner that follows Hodgkin and Huxley's experiments on the squid giant axon. RGCs in rodents have a resting potential of approx. −60 to −75 mV (O'Brien et al., 2002; Qu and Myhr, 2008; Wong et al., 2012), which appears to vary systematically by RGC type (Hu et al., 2013; O'Brien et al., 2002; Qu and Myhr, 2008; Wong et al., 2012). Upon depolarization, voltage-gated Na^+ channels open, allowing Na^+ ion entry that rapidly pulls the membrane potential toward the Na^+ equilibrium potential (approx. +50 mV) before inactivating. This is balanced by the slower gating of voltage-gated K^+ channels that act to pull V_m toward E_K (approx. −90 mV) to repolarize the membrane.

7.1.1. Functional compartmentalization of Na^+ channels in RGCs.—Several distinct compartments of RGCs each express different complements of ion channels and play unique roles in synaptic integration, spike generation, and spike propagation. Unmyelinated RGC axons fasciculate and course across the retina surface toward the optic nerve head, where they converge and form the optic nerve. An elegant study of amphibian RGCs demonstrated the existence of a short region of axonal thinning (~40-140 microns in length) located just after the axon initial segment (Carras et al., 1992). Detailed studies of

RGC axons in rat revealed that $Na_V1.1$ channels occupy a microdomain corresponding to the first ~10 microns of the axon immediately adjacent to the soma, while a region slightly more distal from the soma (10-40 microns) is occupied by $Na_V1.6$ channels (Boiko et al., 2003; Van Wart et al., 2005; Van Wart et al., 2007; Wollner and Catterall, 1986; Wollner et al., 1988). This might correspond to the thin region seen in amphibian RGCs (Carras et al., 1992; Fohlmeister and Miller, 1997b) and might therefore be the site of action potential generation in RGCs. Indeed, $Na_V1.6$ channels are localized to the axon initial segment of many neurons and appear to be ideally suited for action potential initiation. These channels typically have a more hyperpolarized activation curve and recover from inactivation at fairly hyperpolarized potentials (Qiao et al., 2014; Rush et al., 2005). Additionally, $Na_V1.6$ channel currents potentiate during repetitive depolarization (Zhou and Goldin, 2004), which can support higher-frequency firing. In healthy RGCs, the properties of $Na_V1.6$ and its localization to the axon initial segment would likely enhance excitability to promote efficient spike initiation. During early stages of glaucoma, an increase in $Na_V1.6$ expression appears to contribute to increased RGC excitability in mice (Risner et al., 2018). The opposite seems to be the case in a rodent model of multiple sclerosis in which $Na_V1.6$ expression and node localization is reduced and replaced by $Na_V1.2$ (Craner et al., 2003; Craner et al., 2004).

$Na_V1.2$ channels are present in unmyelinated RGC axons and likely underlie propagation of the action potential to the optic nerve head (Boiko et al., 2001; Boiko et al., 2003). Once the axon leaves the eye and becomes myelinated, Na^+ channels are localized principally at nodes of Ranvier. These are largely $Na_V1.6$ channels, although Boiko and colleagues have shown that some nodes have $Na_V1.2$ (Boiko et al., 2001). It is unclear whether those nodes contain a combination of $Na_V1.2/Na_V1.6$ or whether $Na_V1.2$ is present instead of $Na_{V1}.6$. In a $Na_V1.6$ null mouse, $Na_V1.2$ and $Na_V1.1$ localize to nodes in the optic nerve (Van Wart and Matthews, 2006b; Vega et al., 2008), suggesting that the presence of $Na_V1.6$ might play a role in excluding them from that location. A tetrodotoxin-resistant Na^+ channel ($Na_V1.8$) has also been shown to be present at nodes of very large RGC axons in the optic nerve and somata of very large RGCs in mouse retina (O'Brien et al., 2008). $Na_V1.8$ currents are relatively slow and sustained, showing little inactivation (Renganathan et al., 2000; Sangameswaran et al., 1996). This appears to aid in sustained high-frequency spiking, as blockade using a specific NaV1.8 inhibitor A803467 attenuates light-driven spiking of sustained On αRGCs (Smith et al., 2017).

RGC dendrites and cell bodies also participate in spike generation that appears to play important roles in visual processing. In a “textbook” model of neuronal structure and function, excitatory neurotransmitter release onto dendrites alters the gating of ion channels, leading to excitatory post-synaptic potentials (EPSPs) that passively propagate to the soma. If sufficient numbers of EPSPs of sufficiently large amplitude occur in a sufficiently narrow time window, they depolarize the membrane at the axon initial segment past the action potential threshold and initiate a spike. It is now clear, however, that dendrites of many neurons, including amacrine cells as discussed earlier, possess numerous active conductances that allow them to amplify EPSPs, participate in antidromic spiking, and generate their own regenerative action potentials (Holthoff et al., 2006; Johnston et al., 1996). The same is true for RGCs as well. For instance, Na^+ channel α and β subunits are expressed in the IPL of rats (Van Wart et al., 2005; Wollner et al., 1988). While these might

in part be the result of Na^+ channel expression in spiking ACs (Kaneko and Watanabe, 2007; Wu et al., 2011), faint $Na_V1.1$ expression has been observed in proximal dendrites and somata of rat RGCs (Van Wart et al., 2007) and slowly-inactivating, TTX-resistant $Na_V1.8$ channels are present in somata and dendrites of mouse RGCs (O'Brien et al., 2008).

A particularly elegant study by Velte and Masland used simultaneous paired whole-cell recordings of RGC somata and dendrites to show that dendrites are capable of generating action potentials (Velte and Masland, 1999). Using current steps to depolarize the soma evoked a train of spikes measured at both somatic and dendritic electrodes. Stimulation of dendrites likewise evoked a train of spikes recorded with the dendritic electrode. These could be measured as spikelets with the somatic electrode and, in some cases, dendritic spikes initiated full-amplitude somatic spikes. Additionally, while introducing the Na^+-channel blocker and lidocaine derivative QX-314 through the somatic patch pipette blocked somatic spikes, the spikes recorded with the dendritic electrode persisted. This indicates that RGC dendrites are able to generate action potentials.

Modeling studies based on empirically-recorded current properties indicate that voltage-gated Na^+ and K^+ channels present in dendrites are essential for regulating RGC spike rate (Fohlmeister et al., 1990; Fohlmeister and Miller, 1997a, b). Interestingly, these dendritic channels function to slow repetitive spiking by providing a shunt to discharge the membrane capacitance that would otherwise keep the membrane potential above spike threshold. This is similar to the shunting effect of Na^+ and K^+ channels in the dendrites of A17 ACs described in section 5.2.

For DSGCs, which preferentially respond to motion in one direction, active dendritic conductances amplify responses to motion in the preferred-direction by triggering dendritic action potentials that propagate and initiate somatic spiking (Oesch et al., 2005; Trenholm et al., 2011). Using simultaneous patch-clamp recordings of DSGC somata and dendrites, Sivyer and Williams showed that dendrites in the region of the dendritic field that is first activated by motion in the preferred direction fire spikes that precede spikes generated in the soma (Sivyer and Williams, 2013). This is consistent with work in amacrine cells and other RGC types showing that dendritic Na^+ channels amplify synaptic potentials and that blockade of voltage-gated Na^+ channels reduces the signal-to-noise ratio of RGC responses to stimuli of varying contrast (Dhingra, 2005). Dendritic spikes also allow for temporally-precise correlated spiking in a subpopulation of gap junction-coupled DSGCs, a process that likely favors strong temporal summation of their synaptic output to the dorsal lateral geniculate nucleus (Trenholm et al., 2013).

7.1.2 Na^+ channels during development—RGC spiking behavior, as with all CNS neurons, matures over the course of development, with RGCs becoming more excitable with maturity. Rat RGCs, for instance, appear to reach full maturity by ~25-27 days postnatal (P25-P27), firing trains of repetitive spikes in response to sustained current injection. Earlier postnatal stages (P7-P9) are characterized predominantly by single-spike behavior with increasing numbers of RGCs being able to fire a rapidly adapting series of spikes by P13. A similar progression, albeit with slightly different timing relative to birth, is seen for other species (Chalupa et al., 1993; Guenther et al., 1999; Qu et al., 2009; Robinson and Wang,

1998; Schmid and Guenther, 1996; Skaliora et al., 1995; Skaliora et al., 1993; Wang et al., 1997; Wollner et al., 1988).

This development of RGC excitability corresponds with the developmental progression of membrane currents and might be explained as well by shifts in both the density of channels in the membrane and the specific channel isoforms expressed by RGCs during development. Voltage-gated Na^+ current amplitudes and current density (current amplitude normalized to membrane capacitance) increase dramatically from embryonic RGCs and plateau around eye opening in both rodents and cats (Chalupa et al., 1993; Robinson and Wang, 1998; Rothe et al., 1999; Schmid and Guenther, 1996, 1998; Skaliora et al., 1993). This is accompanied by a hyperpolarizing shift in the I_{Na} activation curves progressing through development meaning that the population of Na^+ channels requires a weaker depolarization in order to open (Robinson and Wang, 1998; Rothe et al., 1999; Skaliora et al., 1993). Similarly, I_{Na} steady-state inactivation curves show a depolarizing (rightward) shift, meaning that relatively more channels are available in the range of RGC resting potentials (Robinson and Wang, 1998; Skaliora et al., 1993).

These functional shifts generally correspond with changes in the expression and localization of Na^+ channel isoforms (Miguel-Hidalgo et al., 1995). mRNA levels for both $Na_V1.2$ and $Na_V1.6$ increase during development along a similar time course (Van Wart and Matthews, 2006a). At both nodes and the axon initial segment, $Na_V1.2$ is expressed earlier in development and later replaced by $Na_V1.6$ (Boiko et al., 2001; Boiko et al., 2003; Van Wart and Matthews, 2006b; Vega et al., 2008). The increase in $Na_V1.6$ is likely important in the development of repetitive spiking behavior; RGC spiking in $Na_V1.6$ knockout is similar to wild-type at P12 (largely rapidly adapting spike behavior), but whereas WT RGCs develop repetitive spiking behavior by P14, $Na_V1.6$ knockout RGCs do not. Interestingly, myelination appears to have an instructive and/or regulatory effect on channel localization; in the *shiverer* mouse which is deficient in myelin, $Na_V1.6$ does not replace NaV1.2 at nodes. Additionally, in mice heterozygous for a $Na_V1.6$ knockout (Scn8a+/−), the gene dose-dependent reduction in $Na_V1.6$ protein leads to an increase in $Na_V1.2$ at nodes in the optic nerve (Vega et al., 2008). The alterations in optic nerve Nav1.6 and NaV1.2 expression and localization in a rodent multiple sclerosis model appear to represent a recapitulation of some of these developmental stages (Craner et al., 2003; Craner et al., 2004).

RGCs have D1-type dopamine receptors (Chen and Yang, 2007; Hayashida and Ishida, 2004; Hayashida et al., 2009; Ogata et al., 2012; Van Hook et al., 2012; Vaquero et al., 2001) and dopamine is known to alter RGC spiking behavior in multiple species including rodents and fish (Hayashida et al., 2009; Ogata et al., 2012; Van Hook et al., 2012; Vaquero et al., 2001). Regulation of Na^+ channel inactivation parameters appears to underlie some of this effect (Hayashida and Ishida, 2004; Hayashida et al., 2009), although HCN channels and K^+ channels have also been implicated (see below) (Chen and Yang, 2007; Prigge et al., 2016).

7.2 Ca^{2+} channels

As discussed below, several classes of voltage-gated Ca^{2+} channels can be distinguished by current kinetics, voltage-dependence, and pharmacology in RGCs.

7.2.1 Low-voltage activated (LVA) Ca^{2+} currents—LVA I_{Ca} activates at fairly hyperpolarized potentials (positive to −70 mV) and in whole-cell recordings in which I_{Ca} is isolated by blocking Na^+ and K^+ currents, the remaining macroscopic membrane current I-V relationship will show a discernable hump at more hyperpolarized voltages that corresponds to the LVA component. Voltage-clamp studies from isolated postnatal rat RGCs (P10) have identified these LVA (or T-type) currents in approximately 1/3 of recorded RCGs (Guenther et al., 1994; Karschin and Lipton, 1989; Sargoy et al., 2014; Schmid and Guenther, 1996). In intact retinas or retinal slices, LVA currents are present in 100% of early embryonic RGCs and the percentage of LVA current-possessing RGCs declines to 13% by eye opening (~P12) and to 0% by adulthood (Schmid and Guenther, 1996). Recordings of RGCs cultured from P13-17 or adult rats show that the proportion of RGCs with LVA current fell from ~33% at P13-17 to ~15% at adulthood. In intact retinas, LVA current amplitudes decreased from embryonic through postnatal stages (Rothe et al., 1999). Interestingly, isolated cat RGCs appeared to lack any discernable T-type current, having an I-V plot without the LVA hump and a pharmacological signature consistent with a predominant L-type current (Kaneda and Kaneko, 1991a). It is unclear how the presence in a subpopulation of RGCs in adult mice is reconciled with the apparent loss of LVA currents detected in adult rat RGCs.

In recordings from isolated salamander RGCs, Henderson and Miller found that LVA current was detectable in RGC somata. However, in cells that had dendritic processes remaining, the LVA current was larger and estimates of membrane surface area from whole-cell capacitance suggested that LVA current density was ~5-fold greater in dendritic compartment than in the soma. LVA currents appear to be constrained to Off RGCs in mouse (Margolis and Detwiler, 2007; Margolis et al., 2010) and additional evidence suggests that it is Off-transient RGCs, but not Off-sustained RGCs, that have LVA currents (Murphy and Rieke, 2011; Van Wyk et al., 2009).

The resting membrane potential for RGCs is typically between −65 and −80 mV (Coleman and Miller, 1989; Lee et al., 2003; O'Brien et al., 2002), a point at which the LVA current is largely inactivated in physiological conditions. However, at this point on the inactivation curve, even a small hyperpolarization, such as that mediated by GABA or glycine-gated chloride channels or K^+ channels gated by $GABA_B$ receptor activation, will be sufficient to relieve the LVA channel inactivation so that depolarization into LVA channels' activation range is able to trigger a low-threshold Ca^{2+} spike (LTS). Studies in amphibian retina suggest that this process is a major contributor to the rebound spiking of RGCs (along with contributions from HCN channels, below) (Mitra and Miller, 2007a, b), where Na^+ spikes ride atop the LTS following cessation of a hyperpolarizing stimulus. Indeed, in RGCs recorded in adult mouse flat-mount retinas (4-8 week postnatal), Ca^{2+} imaging combined with patch-clamp recordings showed that Ca^{2+} influx was associated with rebound spiking (depolarization and spiking at the termination of a hyperpolarization) only in Off RGCs, but not On RGCs (Margolis and Detwiler, 2007; Margolis et al., 2010). This was highly sensitive to Ni^{2+}, which is a strong blocker of LVA Ca^{2+} channels, but less effective at blocking HVA channels. Such rebound depolarization and spiking may serve as a thresholding mechanism to enhance post-synaptic responses and promote temporally precise

detection of changing light intensity (Mitra and Miller, 2007b) in a manner analogous to the phasic synaptic vesicle release at photoreceptor synapses (Jackman et al., 2009).

7.2.2 High voltage-activated (HVA) Ca^{2+} currents—HVA I_{Ca} have also been recorded from RGCs in multiple species and preparations and identified as L, P/Q, N, or R-type (Guenther et al., 1994; Henderson and Miller, 2003, 2007; Kaneda and Kaneko, 1991a; Karschin and Lipton, 1989; Lipton and Tauck, 1987; Schmid and Guenther, 1996). L-type currents have been identified in RGCs based on their sensitivity to dihydropyridines and large single channel conductance (Guenther et al., 1994; Kaneda and Kaneko, 1991a; Karschin and Lipton, 1989; Schmid and Guenther, 1996). Other HVA currents in RGCs are sensitive to ω-conotoxin-GVIA, which is a strong blocker of N-type $Ca_V2.2$ channels (Guenther et al., 1994; Karschin and Lipton, 1989; Schmid and Guenther, 1996). There is also a component of the HVA current in RGCs that is insensitive to dihydropyridines, ω-conotoxin, and ω-agatoxin-IVA (Guenther et al., 1994; Karschin and Lipton, 1989; Schmid and Guenther, 1996), possibly suggesting the presence of R-type currents ($Ca_V2.3$)

Immunofluorescence staining for L-type ($Ca_V1.2$ and $Ca_V1.3$), P/Q-type ($Ca_V2.1$) and N-type ($Ca_V2.2$) channel α subunits has demonstrated their localization to distinct compartments of RGCs (Ahlijanian et al., 1990; Sargoy et al., 2014; Xu et al., 2002). L-type channels are found in RGC somata (identified by RBPMS staining, which is a selective marker for RGCs) (Rodriguez et al., 2014) and strongly expressed in unmyelinated RGC axons within the retina, while P/Q and N-type channels appear largely constrained to RGC somata (Sargoy et al., 2014). HVA channels α subunits typically complex with α2δ and β subunits that affect membrane localization and gating. While photoreceptor L-type channels ($Ca_V1.4$) associate with α2δ4 and β2 accessory subunits, α2δ3 and α2δ1 subunits have been localized to RGC somata in rodents (Farrell et al., 2014).

7.2.3 Ca^{2+} channels during development.—The density of I_{Ca} in RGCs increases throughout development, consistent with an increase in channel insertion into the plasma membrane. As discussed above, LVA channels appear to be downregulated throughout development suggesting that the increase in I_{Ca} density from birth to adulthood is the result of an increase in HVA channels. However, the relative proportion of ω-conotoxin and nifedipine-sensitive current is relatively stable once they appear around embryonic day 20 or 21 in rats. The ω-conotoxin-sensitive current is ~50% of the total I_{Ca} at embryonic day 21, remains stable until eye opening, and declines to ~35% of the total I_{Ca} by adulthood. L-type currents make up ~10% of the whole-cell I_{Ca} around E21, ~20% throughout early postnatal period, and eventually settle at ~25% by adulthood. The residual I_{Ca} is toxin-resistant (Schmid and Guenther, 1996). T-type currents first appear around the same time as gap junction-mediated stage I retinal waves (Kerschensteiner, 2016; Schmid and Guenther, 1996). Retinal waves are important for refinement of RGC projections to targets in the brain (Firth et al., 2005; Kerschensteiner, 2016). Stage II waves (P1-10 in mouse) are mediated by cholinergic synaptic transmission while stage III are glutamatergic (P10-14). The similar timing of retinal waves with the appearance and gradual reduction in LVA currents raises the possibility that they might play a role in supporting wave-associated bursting behavior in RGCs, although this has not been tested.

7.2.4 Ca^{2+} channel function.—Action potential firing in myelinated axons triggers Ca^{2+} influx along the length of the axon (not just at the nodes of Ranvier). This does not appear to be the result of L-type channels, as Ca^{2+} influx along the axon is insensitive to nifedipine (Zhang et al., 2006). ω-conotoxin dramatically reduces action potential-triggered Ca^{2+} influx in neonatal rat optic nerves suggesting that N-type channels might instead play a major role (Sun and Chiu, 1999). In contrast, in unmyelinated RGC axons, L-type channels appear to contribute to depolarization-evoked calcium influx (Sargoy et al., 2014). The role for axonal Ca^{2+} influx is unclear, although it is may regulate axonal excitability by gating Ca^{2+}-activated K^+ or Cl^- channels (Lev-Ram and Grinvald, 1986), which play important roles in spike frequency adaptation in neurons (Ha and Cheong, 2017). Additionally, autophosphorylation of CaM kinase II, a downstream effector enzyme for intracellular Ca^{2+} signals, alters spike propagation in the optic nerve (Partida et al., 2018).

While Na^+ and K^+ channels are key for changing membrane voltage and LVA Ca^{2+} channels contribute to the low-threshold spike and rebound spiking, HVA Ca^{2+} channels principally function to allow influx of Ca^{2+} so that it can act as a second messenger to mediate non-electrogenic cellular behaviors such as contraction, secretion, enzyme activity, and gene expression. For example, Ca^{2+} influx through L-type Ca^{2+} channels is essential for triggering tonic glutamate release at photoreceptors, bipolar cells, and hair cell ribbon synapses, while P/Q-, N- and R-type channels allow Ca^{2+} influx for action-potential-triggered release at most other CNS synapses. RGCs generally do not make intraretinal synapses. However, one exception is M1-type intrinsically photosensitive RGCs (ipRGCs), which have axon collaterals that are likely mediators of ipRGC glutamatergic synaptic output to DACs (Prigge et al., 2016; Zhang et al., 2008). ipRGC synaptic drive depends slightly on N-type channels as indicated by a modest inhibition (~30%) by ω-conotoxin. ipRGC-DAC synapses were insensitive to other L-, T-, R-, or P/Q-type blockers (Prigge et al., 2016). It is unclear what additional Ca^{2+} channel contributes at this synapse.

There is little firmly known about the Ca^{2+} channels that mediate synaptic release from RGC terminals at visual nuclei in the brain. In a RGC primary culture system in which RGCs form synapses with neighboring cultured neurons, Taschenberger and Grantyn used paired recordings and Ca^{2+} channel blockers to show that glutamate release from RGCs depends largely on N-type channels (~70% block of the post-synaptic current by ω-conotoxin) (Taschenberger and Grantyn, 1995). ω-agatoxin had no effect on glutamate release and release was slightly enhanced by an L-type blocker (nifedipine).

Glutamatergic output synapses of M1-type ipRGCs in the suprachiasmatic nucleus appear to depend on a combination of N-, P/Q-, T-, and R-type Ca^{2+} channels, without a contribution from L-type channels (Moldavan et al., 2006). RGC synaptic outputs to other visual brain nuclei presumably operate by a similar complement of presynaptic Ca^{2+} channel, although this has not yet been tested.

Modulation of presynaptic Ca^{2+} influx is a powerful means of regulating synaptic strength and this appears to occur by multiple mechanisms at RGC output synapses in both the SCN and dLGN. In the SCN, $GABA_B$ receptor activation reduces the amplitude of excitatory post-synaptic currents by inhibiting presynaptic Ca^{2+} channels (Moldavan et al., 2006).

$GABA_B$ receptors likewise inhibit synaptic transmission at retinogeniculate synapses in the dLGN as does activation of 5HT1 receptors (Chen and Regehr, 2003). Metabotropic glutamate receptors also alter retinogeniculate synaptic transmission, possibly by impinging on presynaptic Ca^{2+} influx (Govindaiah et al., 2012; Lam and Sherman, 2013).

Although HVA channels (especially non-L-type HVA channels) are important for RGC synaptic output, it is not clear what role HVA channels expressed in RGC somata and axons play in the retina. In M1 ipRGCs, L-type channels are responsible for most of the Ca^{2+} influx during melanopsin-mediated depolarization, a process which might contribute to adaptation of the melanopsin transduction cascade (Do and Yau, 2013). L-type channels are also important in coupling excitation to transcription via CaM/CaM kinase (Catterall, 2011; Simms and Zamponi, 2014). Such a process has not been explored in RGCs. Additionally, L-type channels play a role in Ca^{2+}-dependent AMPA receptor trafficking associated with synaptic plasticity (Voglis and Tavernarakis, 2006). AMPA-type glutamate receptors in RGCs are subject to light-induced and intracellular Ca^{2+}-dependent plasticity, although that process appears to rely on NMDA-type receptors (Jones et al., 2012). As described above, Ca^{2+} influx might be important in regulating spike generation and firing properties via activation of Ca^{2+}-activated K^+ channels in RGCs (Wang et al., 1998).

7.3 K^+ channels

7.3.1 Voltage-gated K^+ channels—Voltage-clamp recordings from isolated adult rat RGCs revealed several distinguishable type of voltage-gated K^+ currents (Lipton and Tauck, 1987; Lukasiewicz and Werblin, 1988; Reiff and Guenther, 1999; Rothe et al., 1999). These include a TEA-sensitive, sustained delayed rectifier current (I_{KDR}), and a 4-AP-sensitive, transient A-type K^+ current (I_{KA}) (Lipton and Tauck, 1987; Reiff and Guenther, 1999). Several studies in rodent and amphibian RGCs have identified an additional TEA- and 4-AP-insensitive K^+ current with especially slow inactivation kinetics (Lukasiewicz and Werblin, 1988; Reiff and Guenther, 1999; Sucher and Lipton, 1992). Voltage-gated K^+ channels are necessary for proper membrane repolarization during the action potential. This is most clearly the case for delayed-rectifier currents in the classical Hodgkin-Huxley action potential model. A-type currents, however, because of their voltage-dependent inactivation, play important roles in regulating inter-spike timing and spike initiation (Hille, 2001).

There are >15 different isoforms of K^+ channels responsible for I_{KDR} and I_{KA} (Alexander et al., 2017c). Several different K^+ channels have been localized to RGCs using immunofluorescence techniques. $K_V1.2$, for instance, is present in the axon initial segment, in the same general region as $Na_V1.6$, and absent from the slightly more proximal $Na_V1.1$-enriched region (Van Wart et al., 2007). It is also expressed strongly in unmyelinated RGC axons near the optic nerve head, where it co-localizes with $Na_V1.2$ (Boiko et al., 2001). $K_V1.2$ is also present in regions of optic nerve adjacent to the nodes of Ranvier (Boiko et al., 2001; Rasband et al., 1999). $K_V1.1$, $K_V1.2$, and $K_V1.3$ are also found in RGC somata (Koeberle and Schlichter, 2010; Koeberle et al., 2010). $K_V4.2$ channels which carry I_{KA} have been identified in a subpopulation of RGCs in adult and developing mouse retina (Qu et al., 2009).

Whereas a developmental increase in Na^+ current density is fairly consistent across species and corresponds to documented developmental increases in RGC excitability, developmental shifts in K^+ currents are less well-defined (Sernagor et al., 2001). In mouse, for instance, both I_{KDR} and I_{KA} were largely unchanged from late embryonic through postnatal stages (Rothe et al., 1999). In rat, however, both K^+ current types appear to increase (Reiff and Guenther, 1999) while in cats, I_{KA} decrease and I_{KDR} increase in amplitude (Skaliora et al., 1995). In addition to the changes in current densities, these developmental changes also accompany shifts in current kinetics and voltage-dependence (Robinson and Wang, 1998; Rothe et al., 1999; Skaliora et al., 1995).

7.3.2 Other K^+ channels—Beyond delayed rectifier and A-type K^+ currents, several other K^+ channels have been identified in RGCs. A qRT-PCR and immunofluorescence analysis has shown the presence of numerous two-pore K^+ channels (K2P) in RGCs including TASK-1, TREK-1, TWIK-1, TWIK-2 and TWIK-3 (Hughes et al., 2017). As discussed in section 1.1.2, K2P channels are leak K^+ channels and therefore play important roles in setting RGC membrane potential. There appears to be some differences in expression of these channel genes in different RGC populations, as identified by gene clustering analysis (Rheaume et al., 2018). Varying levels of each K2P channel might help set unique resting potentials for distinct populations of RGCs (Hu et al., 2013; O'Brien et al., 2002; Schmidt and Kofuji, 2009).

Ca^{2+}-activated K^+ currents are important for coupling changes in intracellular Ca^{2+} to changes in neuronal spike patterns. Since Ca^{2+} entry and intracellular sequestration is relatively slow, the buildup of intracellular Ca^{2+} during a spike train can prolong the gating of Ca^{2+}-activated K^+ channels. This phenomenon regulates the both the fast after-hyperpolarization that occurs after a spike and a slow after-hyperpolarization that follows a train of spikes. Ca^{2+}- activated K^+ currents have been recorded from RGCs in trout, ferret, rat, and salamander and pharmacology studies indicate that both BK and SK channels contribute to these currents (Henne and Jeserich, 2004; Henne et al., 2000; Lipton and Tauck, 1987; Lukasiewicz and Werblin, 1988; Wang et al., 1998). SK2 channels have been localized to RGCs (Klöcker et al., 2001). Inhibition of either channel type increases RGC excitability (Wang et al., 1998) and SK channels appear to mediate an adenosine-evoked RGC hyperpolarization (Clark et al., 2009).

7.4 HCN channels

Like those of other preparations, including photoreceptors, HCN channels in RGCs are gated by hyperpolarization and are permeable to cations with a ~2- to 4-fold preference for K^+ over Na^+ (Wahl-Schott and Biel, 2009). This ion selectivity gives the resulting I_h an equilibrium potential of ~−20 mV so that gating of HCN channels in their activation range has a depolarizing influence. As a result, HCN channels in neurons are thought to play a role in setting the resting membrane potential, underlie rebound depolarization, and regulate the temporal summation of synaptic inputs by altering membrane resistance at hyperpolarized potentials. In intracellular recordings, many RGCs show a pronounced depolarizing voltage “sag” in response to hyperpolarizing current injection (Hu et al., 2013; O'Brien et al., 2002; Van Hook et al., 2012). A similar sag is seen in intra-axonal recordings from the rat optic

nerve (Eng et al., 1990). Voltage-clamp recordings in mammalian RGCs have identified and characterized I_h, showing that it is activated at quite hyperpolarized potentials (approx. −80 to −100 mV) (Lee and Ishida, 2007; Van Hook and Berson, 2010).

Contributions from I_h vary by RGC class. In recordings of cat RGCs, the depolarizing sag was more pronounced in some RGC classes than others and absent from alpha and possibly lambda RGCs (O'Brien et al., 2002). In melanopsin-expressing RGCs in mouse, all five classes of ipRGCs display a voltage sag, but it varies in amplitude (Hu et al., 2013). In voltage-clamp recordings, I_h has been identified in M1-type ipRGCs in rats identified by retrograde labeling from tracer injection into the suprachiasmatic nucleus (Van Hook and Berson, 2010). I_h has also been recorded from M2 and M4 (On sustained αRGC)-type ipRGCs from mouse (Jiang et al., 2018).

There are four known HCN channel isoforms (HCN1-4) that vary in their kinetics and voltage dependence (Ludwig et al., 1998; Moosmang et al., 2001; Santoro et al., 1998; Stieber et al., 2005). HCN1 and HCN4 have been identified by immunofluorescence in retrolabeled RGCs (to avoid accidentally counting ACs displaced in the RGC layer) (Stradleigh et al., 2011). Some RGCs are unlabeled by either HCN1 or HCN4 antibodies, while some express a mix of both channels in varying proportions. This labeling pattern is also consistent with physiology. The soma size and dendritic stratification (both measures used to differentiate RGC classes) of HCN1 and HCN4-immunopositive and immuno-negative RGCs varies, indicating that many different RGC populations express HCN channels.

In cases where a single neuron expresses multiple I_h channel subtypes, the whole-cell I_h takes on properties of both expressed isoforms. In co-immunoprecipitation assays with retinal plasma membrane preparations, HCN1 and HCN4 appear to interact physically with each other, suggesting that they can function as HCN1/HCN4 heteromers (Stradleigh et al., 2011). In M1-type ipRGCs, I_h activation voltage is especially hyperpolarized (threshold at ~ −75 mV) and the current is quite slow (activation time constant of ~900 ms at −120 mV) (Van Hook and Berson, 2010), consistent with the properties of HCN4. Other studies of I_h in RGCs have indicated that I_h is comprised of two kinetic components, with a fast activation time constant of ~100 ms and a slower component with a time constant of ~800-900 ms (Lee and Ishida, 2007; Stradleigh et al., 2011).

It is likely that a more extensive analysis of RGCs by subtype using traditional anatomical parameters (i.e., soma size, dendritic stratification, Sholl analysis, dendritic field diameter) will reveal subtype-specific patterns in HCN channel expression and I_h properties. Indeed, single-cell transcriptomics work shows that different HCN channel isoforms are enriched in different putative RGC populations (identified by clustering based on gene expression profiles) (Rheaume et al., 2018).

Immunostaining evidence shows that HCN channels are largely localized to RGC somata and axons, with some possible staining in proximal dendrites (Stradleigh et al., 2011). HCN channels might be expressed in more distal dendrites and simply escape detection due to low protein level, so this result does not necessarily indicate that they are absent from RGC

dendrites. HCN1 and HCN4 staining has also been detected in dendrites of RGC primary cell cultures (Abbas et al., 2013). Interestingly, HCN4 colocalizes and coimmunoprecipitates with Thy1, a glycophosphatidylinositol-anchored cell surface protein expressed in RGC somata (Partida et al., 2012). Thus, HCN channels appear to be most highly concentrated in RGC somata. Substantial staining of HCN channel isoforms in the IPL is likely to arise principally from labeling of bipolar cell axons and synaptic terminals (Ivanova and Müller, 2006; Müller et al., 2003).

These results suggest that in RGCs, HCN channels principally act to shape firing patterns and integration of synaptic inputs in the soma rather than shaping individual synaptic potentials in the dendrites. Contrary to this, however, a study using sequential uncaging of glutamate along the length of an RGC dendrite has shown that I_h contributes to directional summing of inputs by enhancing sequential responses to stimuli as they move away from the RGC soma (Abbas et al., 2013). Such a mechanism might be a cell-autonomous process allowing for the detection of looming motion by RGCs.

More in keeping with a role in regulating spiking behavior, I_h in amphibian RGCs has been shown to contribute to rebound depolarization and spiking after the cessation of a hyperpolarizing stimulus (Mitra and Miller, 2007a). Some evidence from rat ipRGCs hints at a similar role in mammalian RGCs (Van Hook and Berson, 2010). HCN channels also play a role in regulating RGC membrane potential and excitability and apparently contribute to the effects of dopamine on excitability (but see (Hayashida et al., 2009)). Blockade of HCN channels in M1 ipRGCs does little to affect resting membrane potential and does not alter spiking evoked by melanopsin phototransduction, making it unclear what role I_h plays in that class of RGCs (Van Hook and Berson, 2010). Recall that HCN channels can also modulated by cyclic nucleotides such as cAMP. Activation of D1-type dopamine receptors in RGCs leads to an increase in intracellular cAMP production, which can in turn modulate RGC excitability and resting membrane potential by altering the voltage-dependence of I_h activation (Chen and Yang, 2007) (but see (Hayashida et al., 2009)).

An especially novel role for HCN channels as an endpoint for melanopsin-based phototransduction has recently been demonstrated for M2 and M4-type ipRGCs (Jiang et al., 2018). While M1-type ipRGCs rely largely on a G_q/PLC cascade that gates TRPC6/7 channels (Perez-Leighton et al., 2011), Jiang and colleagues have shown that melanopsin-activated photocurrents that linger following TRPC6/7 knockout in M2 and M4 cells were almost entirely blocked by the HCN channel blocker ZD7288 and severely reduced in cells transfected to express a dominant-negative HCN channel (Jiang et al., 2018). This is difficult to reconcile, however, with another recent study showing that M4 transduction culminates in the closure of leak K^+ channels, as evidenced by voltage-dependence (reversal at E_K) and barium block (which will not substantially affect I_h) of melanopsin-mediated responses (Sonoda et al., 2018). A very small component of the M1 photocurrent also appears to result from HCN channel gating (Jiang et al., 2018).

7.5 Summary

In many respects, the ion channel complement in RGCs is typical of other spiking neurons. The distribution of ion channels in different compartments of RGCs is summarized in Table

3 and its associated diagram. RGCs possess voltage-gated Na^+ channels (predominantly $Na_V1.6$ in nodes of Ranvier, $Na_V1.2$ in unmyelinated axon, and $Na_V1.1$ and 1.8 in the soma and dendrites) as well as voltagegated K^+ channels that give rise to delayed rectifier and A-type K^+ currents. I_{Na} and I_{KDR} are responsible for the rising and falling phase of the action potential while I_{KA} is important in shaping spike timing. Dendritic action potentials play important computational roles including motion detection and amplification of post-synaptic potentials. N-, P/Q- and R-type voltage-gated Ca^{2+} channels are important for synaptic output, either at intraretinal synapses made by M1 ipRGC axon collaterals or at output synapses in visual nuclei of the brain, although this has not been firmly established at outputs other than those made by ipRGCs in the SCN. T-type I_{Ca} in dendrites and somata shape spiking behavior. The role of L-type and N-, P/Q- and R-type I_{Ca} in RGC somata are unclear, although they likely shape spiking behavior by gating Ca^{2+}-activated K^+ currents.

RGC receptive field centers are comprised of the pooled excitatory inputs arising from the population of presynaptic bipolar cells and fine substructure can be revealed using spatiotemporal white noise or naturalistic scene stimuli (Brown et al., 2000; Freed and Sterling, 1988; Freeman et al., 2015; Wienbar and Schwartz, 2018). Postsynaptic processes such as spike generation in dendrites and influences of voltage-gated conductances on local membrane properties are likely to influence spatial and temporal summation of synaptic inputs at these individual sub-regions of RGC receptive fields (Ujfalussy et al., 2018). This would be a fruitful avenue for future research.

A major open question concerns how and whether differential expression of ion channels is responsible for shaping the unique response properties of different RGC classes. There are at least 30 functionally-distinct classes of RGC identified in mouse retina, which is currently the principal animal model used for probing RGC function. Evidence from a variety of species indicates that the spiking properties of RGCs are heterogeneous (Hu et al., 2013; Kaneda and Kaneko, 1991b; O'Brien et al., 2002; Schmidt and Kofuji, 2009; Tabata and Kano, 2002). For instance, M1-type ipRGCs in mice are unable to maintain a high firing frequency and instead rapidly enter depolarization block (where Na^+ channel inactivation prevents further regenerative spiking). In contrast, other ipRGC types can sustain much higher firing frequencies (Hu et al., 2013; Schmidt and Kofuji, 2009). This implies that different RGC classes differ in their complement and/or densities of Na^+ and K^+ channels, which would be consistent with the documented diversity of expression patterns seen among RGCs for HCN, Ca^{2+}, and other channel types. There can be considerable variability even within distinct RGC subpopulations. For instance, M1-type ipRGCs display a strikingly heterogeneous range of biophysical parameters and melanopsin-driven light responses, hinting at variable ion channel expression and/or regulation in these RGCs (Emanuel and Do, 2015; Emanuel et al., 2017; Milner and Do, 2017). Studies of gene expression patterns along with exploration of the unique channel properties in distinct RGC classes and, in some cases, within RGC classes are needed to clarify how the diversity of channel expression and properties contribute to the unique signaling roles of different RGC populations.

8. Conclusions

Recent years have seen a dramatic expansion in the recognized number of individual cell types in the retina. In this review, we have outlined our current understanding of the numerous subtypes of voltage- and Ca^{2+}-gated ion channels present in many of these different retinal neurons. In addition to differences in ion channel distributions between species, it is clear that there are notable differences between major cell types and even differences among subtypes of the same cell. A major remaining challenge is to understand how this diversity of ion channel complement across different populations of retinal neurons contributes to visual processing performed as information is relayed through the retinal network and conveyed to the brain. What is the role of the particular ion channel subunit combinations and their localization in each of these cells in shaping their unique response properties? Can we identify specific ion channel finger-prints for each type of cell? How does ion channel expression change in response to changes in illumination, metabolism, or disease? Answers to these questions will come to light as the field develops a more complete wiring diagram and probes the function of the retinal network using a combination of computational, molecular, and physiological approaches. Electrophysiological recordings remain the dominant approach for studying the membrane currents and voltage responses of neurons. However, these techniques are increasingly supplemented by molecular techniques, imaging with activity-dependent dyes, pharmacological tools, genetic elimination of target proteins, and genetic introduction of mutant proteins, sensor proteins, DREADDs, or optogenetic tools. This diverse and powerful array of experimental tools provides an opportunity to unravel the mysteries of signal transmission in the retina. Along with a detailed understanding of the basis for single cell properties in different cell types, these experiments are sure to reveal new principles concerning the strategies used by the nervous system to shape activity in response to a dynamically changing visual environment.

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Abbrevations:

(I_{KA})	A-type K^+ currents
(AC)	Amacrine cell
(I_{Ca})	Ca^{2+} currents
(CaM)	Calmodulin
(CBC)	Cone bipolar cell
(CRH)	Corticotropin releasing hormone
(I_{KDR})	Delayed rectifier K^+ currents
(DSGC)	Direction-selective ganglion cells

(DAC)	Dopaminergic amacrine cell
(HVA)	High-voltage activated
(I_h)	Hyperpolarization-activated current
(IPL)	Inner plexiform layer
(ipRGC)	Intrinsically photosensitive retinal ganglion cell
(I_{KIR})	Inwardly rectifying K^+ current
(LVA)	Low-voltage activated
(OPL)	Outer plexiform layer
(PKA)	Protein kinase A
(RGC)	Retinal ganglion cell
(RBC)	Rod bipolar cell
(SAC)	Starburst amacrine cell
(TEA)	Tetraethylammonium
(Na_V)	Voltage-gated Na^+

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Highlights:

- There are many types of voltage- and calcium-gated ion channels.
- There are almost 100 subtypes of retinal neurons that differ in their ion channels.
- Ion channel type and distribution shape responses of retinal neurons.
- Ion channel dysfunction can contribute to retinal disease.

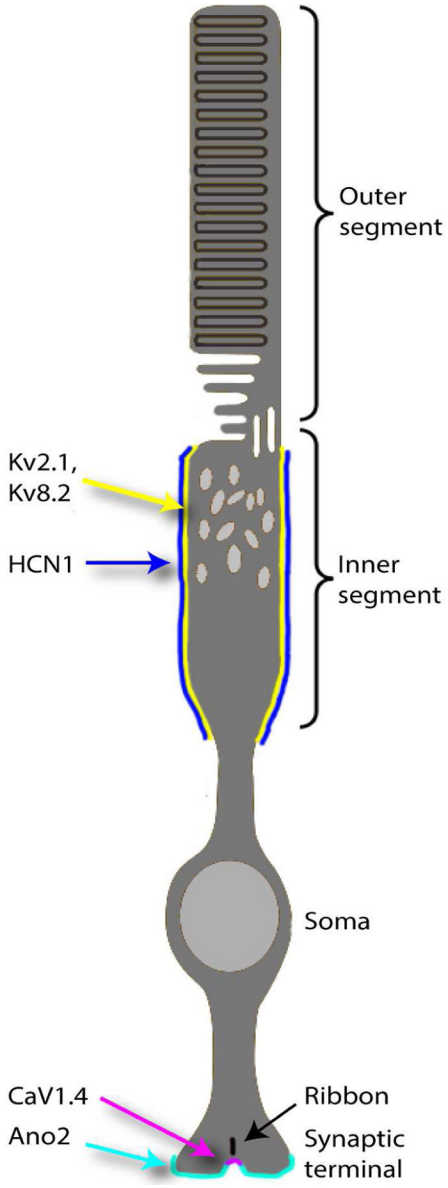
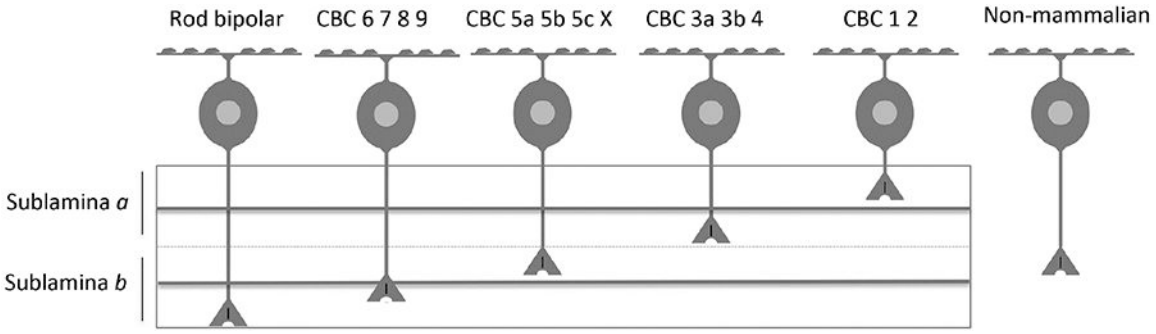


Figure 1.

Diagram of the ion channel distribution in a mammalian rod. HCN1, homomeric $K_V2.1$ and heteromeric $K_V2.1/K_V8.2$ channels are distributed throughout the inner segment. $Ca_V1.4$ channels in a complex with β2a and α2δ4 subunits are clustered beneath synaptic ribbons. Ano2 channels are distributed more diffusely in the synaptic terminal membrane. See text for details.

Table 1.

Ion channels in bipolar cells. Summary of voltage-gated ion channel expression in specific classes of bipolar cells in mammalian and non-mammalian retina. Evidence for expression is based on immunohistochemical and electrophysiological findings (see text for details). Na^+ channels are preferentially expressed in On and Off transient, cone-driven bipolar cells. The same appears true for HCN channels, although the differences in expression are not as dramatic. K_{vx} refers to unidentified K^+ channel isoforms, as no studies to date have molecularly characterized K^+ channels in cone bipolar cells.



Transient/ sustained	**sustained**	**sustained**	**transient**	**transient**	**sustained**	
Na^+ channels	–	–	Type X: ++ Type 5-1: − Type 5-2: +	Type 3a: ++	–	Mb1: − CBC: +
Ca^{2+} channels	L-Type T-Type	L-Type	L-Type	L-Type T-Type	L-Type	Mb1: L-Type,
K^+ channels	Kv1.2 Kv1.3	Kvx	Kvx	Kvx	Kvx	BK, Kv1.2, Kv1.3 A-type
HCN channels	HCN2	HCN2	HCN1,3,4 Type X: ++ Type 5-1: + Type 5-2: ++	HCN4	–	?

Table 2.

Summary of ion channels in interplexiform cells and different types of amacrine cells.

	Salamander ACs	**AII**	**A17**	**Starburst**	**Dopaminergic**	**Widefield CRH**	**Interplexiform cells (IPCs)**
Na^+ channels	I_{Na} (most ACs)	I_{Na}($Na_V1.1$)	Weak I_{Na}	TTX-insensitive $Na_V1.8$	TTX-sensitive and insensitive	I_{Na} (CRH2, 3) No I_{Na} (CRH1)	I_{Na}
Ca^{2+} channels	N- & L-type	L-type ($Ca_V1.3$)	L-type	N, P/Q	L- ($Ca_V1.2$), N- ($Ca_V2.2$), P/Q ($Ca_V2.1$), & R- ($Ca_V2.3$) type	?	L-type
K^+ channels	I_{KDR} I_{KA}	I_{KDR} I_{KA}	I_{KDR} I_{KA} BK	I_{KDR} (mostly $K_v3.1$-3.2)	I_{KDR} ($K_v1.1$, 1.3, 2.1) I_{KA} ($K_V4.3$) BK, SK	?	I_{KDR} I_{KA} (some IPCs) BK (mouse)
HCN channels					I_h	?	I_h (mouse)

Table 3.

Ion channels in retinal ganglion cells (RGCs). The distribution of multiple types and isoforms of voltage-gated ion channels in distinct RGC compartments is summarized in the table and illustrated in the diagram. See text for details.

	Synaptic terminal	Nodes of Ranvier	Unmyelinated axon	Axon initial segment	Soma	Dendrites
Na^+ channels		$Na_V1.6$, also 1.2, 1.8	$Na_V1.2$	$Na_V1.6$ (distal segment) NaV1.1(proximal segment)	$Na_V1.1$, 1.8	$Na_V1.1$, 1.8
Ca^{2+} channels	N, P/Q, R-type	N-type	L-type	L, N, P/Q-type		LVA (Off cells)
K^+ channels		$K_v1.2$		$K_V1.2$ (distal segment)	$K_V1.1$., 1.2, 1.3, 4.2, 4.3, SK2	Kv4.2, others?
HCN channels					HCN1, 4