

# Synaptic Plasticity and Structural Remodeling of Rod and Cone Cells

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## Introduction

It is well documented that neural activity affects synaptic plasticity, a phenomenon known as activity-dependent plasticity. Synaptic plasticity in response to injury, known as injury-induced plasticity, is also well recognized. The vertebrate photoreceptor cell displays plasticity, in the form of structural synaptic change, in both these situations. Structural synaptic change in the photoreceptor refers to 1) change in the size and shape of the rod or cone terminal, 2) increase or decrease in the number of presynaptic active zones, or 3) new growth of neurites and/or development of new presynaptic varicosities. As the first synapse in the visual pathway, structural changes in the synapse between photoreceptors and second order neurons may influence all subsequent visual processing. Thus, an understanding of the mechanisms that initiate and promote plasticity in the outer synaptic layer of the retina where rod and cone cells interact with horizontal and bipolar neurons is critical to understanding the plasticity of the visual system as a whole.

Activity-dependent change of the photoreceptor synapse will be briefly discussed first. Photoreceptor synaptic plasticity in response to disease, is a more recently recognized phenomenon and will be reviewed in more detail. Our own current work has focused on the mechanisms that might be involved in injury-induced plasticity and an overview of this work will be presented. Finally, some future directions and outstanding questions will be discussed.

## *Types of structural plasticity in photoreceptors*

### Activity-dependent plasticity

Neurotransmission by rod and cone cells occurs by calcium-dependent vesicle exocytosis. However, the photoreceptor synapse differs from most chemical

synapses because it is controlled by graded membrane potential changes, not action potentials. Its presynaptic active zone is distinguished by the presence of a flat sheet, known as the ribbon, surrounded by a halo of vesicles and attached to the plasma membrane by an arciform density. In addition, there are several molecular differences between photoreceptor synapses and conventional synapses. For instance, retinal ribbon synapses contain no synapsin (Mandell et al., 1990) and L-type calcium channels in rod cells and L-type and cGMP-gated channels in cone cells control exocytosis and neurotransmitter release (Rieke and Schwartz, 1994; Schmitz and Witkovsky, 1997; Taylor and Morgans, 1998; Nachman-Clewner et al., 1999; Morgans, 2001) whereas other calcium channel types are present in conventional synapses. Other molecular differences include the presence of syntaxin 3 in ribbon synapses, instead of syntaxin 1 for vesicle fusion (Morgans et al., 1996), and the protein RIBEYE, a unique component of the ribbon which may form the backbone of the ribbon structure (Schmitz et al., 2000).

In response to activity, both the size of the presynaptic terminal and the configuration of the ribbon change. In the dark, when the photoreceptor is depolarized, the size of the terminal increases whereas in the light, the terminal size decreases. This is presumably due to the balance of membrane exo- and endocytosis. Endocytosis dominates in the light but synaptic vesicle exocytosis proceeds continuously in the dark in the presence of endocytosis (Schaeffer and Raviola, 1978). Thus, in the light, plasma membrane is removed from the terminal whereas in the dark, more membrane is added than removed. For the ribbons, there are changes in shape, length, and location. Such changes occur in a diurnal pattern in many species (reviewed by Vollrath and Spiwoks-Becker, 1996). In rat rod cells, for instance, ribbons are flat and attached to the plasmalemma in the dark; in the light, spherical ribbons that are disconnected from the plasmalemma are more abundant (Adly et al., 1999). The change in ribbon shape to a spherical form and/or disassociation from the active zone is presumably due to inactivity and has also been observed in squirrel cone cells during hibernation (Remé and Young, 1977) and in cultured photoreceptors where the terminal is separated from its postsynaptic partners (Townes-Anderson, personal observations, Fig. 2.1). The molecular mechanism for the dissociation of the active zone in photoreceptors is unknown. However, mutant mice, lacking the protein bassoon in functional form, have aggregations of ribbons detached from the active zone (Dick et al., 2003) suggestive of what is seen with a reduction of activity (Abe and Yamamoto, 1984). It is possible therefore that bassoon plays some role in ribbon configuration and/or attachment to the membrane.

### Injury-induced plasticity

Although there are changes in the shape of the photoreceptor presynaptic ending and its synaptic ribbon in the adult retina, the terminal normally stays within the outer synaptic layer of the retina where it is in contact with post-

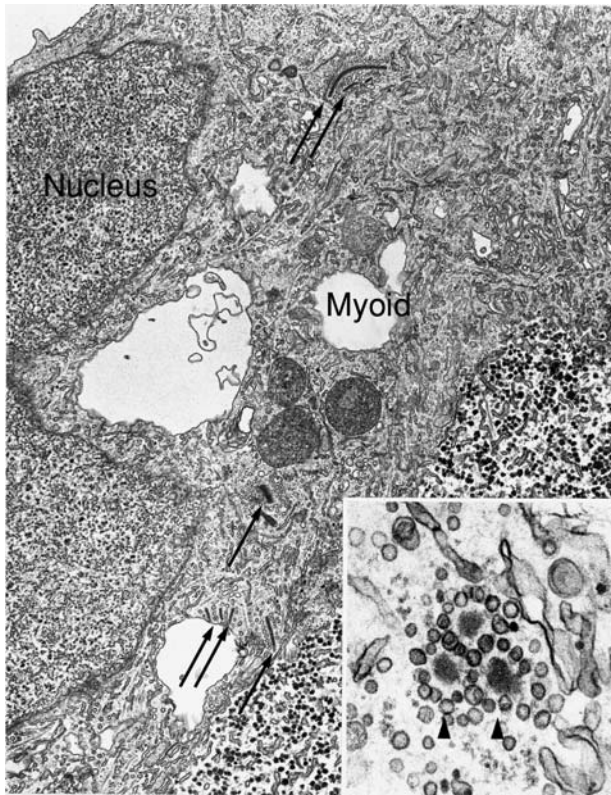


FIGURE 2.1. Movement and shape change are characteristics of ribbon plasticity. Electron micrographs from cultured cone cells isolated from the adult tiger salamander retina and maintained for 7 days in a defined medium. In vivo, cone terminals have multiple active zones and therefore ribbons. In cultured cone cells, ribbons are frequently observed in the myoid region (arrows), which normally contains only the cell organelles. The ribbons appear in linear form. Inset: Some ribbons, however, take on a spherical shape (arrowheads). Here three such ribbons share synaptic vesicles. It is highly likely that the spherical ribbons are detached from membrane. For linear ribbons, serial sectioning is necessary to determine whether or not they have remained associated with the plasma membrane.

synaptic bipolar and horizontal cell processes. In 1995, examination of several human retinas affected with retinitis pigmentosa (RP) revealed the presence of neurites coming from rod cells and extending into the inner retina (Li et al., 1995). These neurites could be observed because of the abnormally high levels of rod opsin in the plasma membrane of the cell. Some mutations of the opsin gene cause mislocalization of opsin because the C-terminus, which targets opsin to vesicles destined for the outer segment, is mutated.

In other cases, mislocalization of opsin occurs as the outer segment becomes disorganized and/or shortened. Opsin containing vesicles may then fuse with plasma membrane in the cell body by default. Finally, some conditions may lead to a fusion of the inner and outer segment membranes which allows a back flow of opsin from the outer to the inner segment and the rest of the cell (Spencer et al., 1988; Townes-Anderson, 1995). Regardless of the mechanism of mislocalization, the high density of the opsin protein in the plasmalemma of patients with RP demonstrated the extent of neurite growth and that the growth came from rod cell terminals. When stained for the presence of synaptic vesicles, the neurites were seen to have swellings along their length filled with synaptic vesicles. However, electron microscopy did not reveal differentiated synaptic contacts between these presynaptic varicosities and inner retinal neurons.

Retinitis pigmentosa is an inherited form of retinal degeneration that affects rod cells which degenerate and die leading to night blindness; cone cells die after rod cells have gone and the loss of cone cells results in total blindness. The mutations, which lead to blindness, occur in many different genes; most of them are for rod cell proteins (reviewed by Molday, 1998). The ectopic rod cell neurites were observed initially in retinas with autosomal dominant, X-linked, simplex and multiplex forms of the disease (Li et al., 1995; Milam et al., 1996). Since then, sprouting by rod cells has been observed in human retinas after laser photocoagulation, in age-related retinal degeneration, in retinal detachment, and in several animal models of retinal injury and disease (Table 2.1). In all cases, neurites were observed by immunolabeling for opsin; when synaptic immunolabels were applied, all presynaptic swellings were positive for synaptic vesicle proteins. Rodent models of retinal degeneration, however, do not show neuritic sprouting (Li et al., 1995). It has been suggested, for these models, that neurites are not formed due to the rapidity of the disease which does not provide time for neurite formation before cell death.

Rod axons have been reported to retract towards the cell body in response to injury as well. Initially observed as the early stages of rod cell degeneration several days after retinal detachment (Erickson et al., 1983), it is now apparent that axonal retraction occurs very soon after the detachment injury (Lewis et al., 1998) and that it does not necessarily lead to cell death: virtually all rod axons retract but not all rod cells die if reattachment is done in a timely fashion (Mervin et al., 1999). After reattachment of retina, rod cells have been shown, using anti-opsin immunolabeling, to extend neurites into the inner retina in a manner and with a morphology similar to what is seen in retinal disease (Table 2.1). Whether the same cell both retracts and extends neurites is likely and has been observed directly in cultured rod cells using video time-lapse microscopy (Nachmen-Clewner and Townes-Anderson, 1996).

Cone cells are affected by retinal detachment but appear not to dramatically retract their terminals. Instead the terminal shape changes by flattening so that the synaptic invagination is lost. This has been observed both in vivo and in vitro (Fisher et al., 2001; Khodair et al., 2003).

TABLE 2.1. Rod cell axonal plasticity in vivo.

| Species | Response                               | Insult or disease                         | Reference                                    |
|---------|--|---|--|
| human   | neurite sprouting/varicosity formation | retinitis pigmentosa (RP)                 | Li et al. 1995<br>Milam et al. 1996          |
| human   | neurite sprouting                      | laser irradiation in diabetic retina      | Xiao et al. 1998                             |
| human   | neurite sprouting/varicosity formation | reattachment after detachment             | Lewis et al. 2002a                           |
| human   | neurite sprouting                      | late-onset retinal degeneration           | Gupta et al. 2003                            |
| human   | neurite sprouting                      | age-related macular degeneration          | Gupta et al. 2003                            |
| human   | neurite sprouting/varicosity formation | detachment with proliferative retinopathy | Sethi et al. 2005                            |
| pig     | filopodial growth                      | transgenic for RP                         | Li et al. 1998                               |
| cat     | neurite sprouting                      | rod/cone dysplasia                        | Chong et al. 1999                            |
| cat     | neurite sprouting/varicosity formation | reattachment after detachment             | Lewis et al. 2002a                           |
| human   | retraction of spherule                 | detachment after reattachment             | Fisher and Lewis 2003                        |
| cat     | retraction of spherule                 | 3d after detachment                       | Erickson et al. 1983                         |
| cat     | retraction of spherule                 | 24hr after detachment                     | Lewis et al. 1998                            |
| mouse   | increased synaptic contacts            | rds mutation, homozygous                  | Jansen and Sanyal 1984<br>Jansen et al. 1997 |
| mouse   | increased synaptic contacts            | rds mutation, heterozygous                | Jansen and Sanyal 1992                       |
| mouse   | increased synaptic contacts            | rd/wild type chimeras                     | Jansen et al. 1997                           |
| mouse   | increased synaptic contacts            | constant light                            | Sanyal et al. 1992<br>Jansen and Sanyal 1987 |
| mouse   | increased synaptic contacts            | KO, cone cGMP channel & rod opsin         | Jansen et al. 1997<br>Claes et al. 2004      |

After retinal reattachment and in most diseases, cone cells do not form long neurites although smaller sprouts and filopodial extensions into the outer plexiform layer and sometimes into the inner retina have been described in retinitis pigmentosa (Table 2.2). These processes were observed with antibodies to cone transducin- $\alpha$  and synaptic proteins. It is possible that these markers are not as effective as rod opsin in highlighting cone synaptic change. In retinal detachment, for instance, the expression of many cone-specific proteins declines within a few days (Rex et al., 2002). Nonetheless, available evidence indicates that there is a significant difference in the response of rod and cone cell terminals to injury and disease.

TABLE 2.2. Cone cell axonal plasticity in vivo.

| Species | Response                               | Insult or disease             | Reference                           |
|---------|--|-------------------------------|-------------------------------------|
| human   | axon elongation                        | retinitis pigmentosa (RP)     | Li et al. 1995<br>Milam et al. 1996 |
| cat     | axon elongation                        | reattachment after detachment | Lewis et al. 2003                   |
| mouse   | neurite sprouting/varicosity formation | rd1 mutation                  | Fei 2002                            |
| human   | enlarged terminals                     | cone-rod dystrophy            | Gregory-Evans et al. 1998           |
| pig     | increased synaptic contacts            | transgenic for RP             | Peng et al. 2000                    |
| mouse   | increased synaptic contacts            | rd1 mutation                  | Peng et al. 2000                    |
| rat     | increased synaptic contacts            | RCS strain                    | Peng et al. 2003                    |
| rat     | increased synaptic contacts            | transgenic for RP             | Cuenca et al. 2004                  |

At present, there is one instance where long neurites have been reported to come from cone cells (Fei, 2002). This is the mouse model rd1, which is an autosomal recessive type of retinal degeneration with a mutation in the beta subunit of rod phosphodiesterase. The cone processes were visualized using transgenic mice with GFP linked to a cone promoter. The presence of GFP delineated long neurites with varicosities going both into the inner retina and horizontally in the outer plexiform layer. These neurites arose from multiple locations, cone terminals, axons and cell bodies. Canine models of this type of RP (Aquirre et al., 1978) have not yet been examined for cone, or rod, cell synaptic plasticity.

Finally, photoreceptors have been reported to make new synapses in response to retinal degeneration (Tables 2.1 and 2.2). Within the outer plexiform layer, rod cells will increase the number of synapses they make with existing postsynaptic bipolar dendrites in the rd and rds mouse models of RP, after light damage, and in a rod opsin knockout mouse. It is possible that as adjacent rod cells die, remaining cells try to compensate by increasing their synaptic input to second order neurons. Cone cells also have been reported to form new synapses. In transgenic pigs with a mutation in the opsin gene, in the rd1 mouse, and in the RCS and P23H transgenic rat (Table 2.2), all models of RP, cone cells make synapses with rod bipolar cells that would not be present in the normal, healthy mammalian retina.

In summary, several forms of structural plasticity are present in the photoreceptors of injured (detachment, reattachment and excess light) and diseased (retinitis pigmentosa and age-related macular degeneration) retina: retraction of axons, sprouting of axons, neurite formation, development of presynaptic varicosities, and synaptogenesis (Fig. 2.2). These structural changes require special morphological techniques to be discerned and would not be easily visible in routine histopathology. They can occur in the absence of an outer segment and in the presence of mislocalized opsin but it is not known if these are requirements. They can be a prelude to cell death but not necessarily. Finally, it is not known if these changes are permanent or

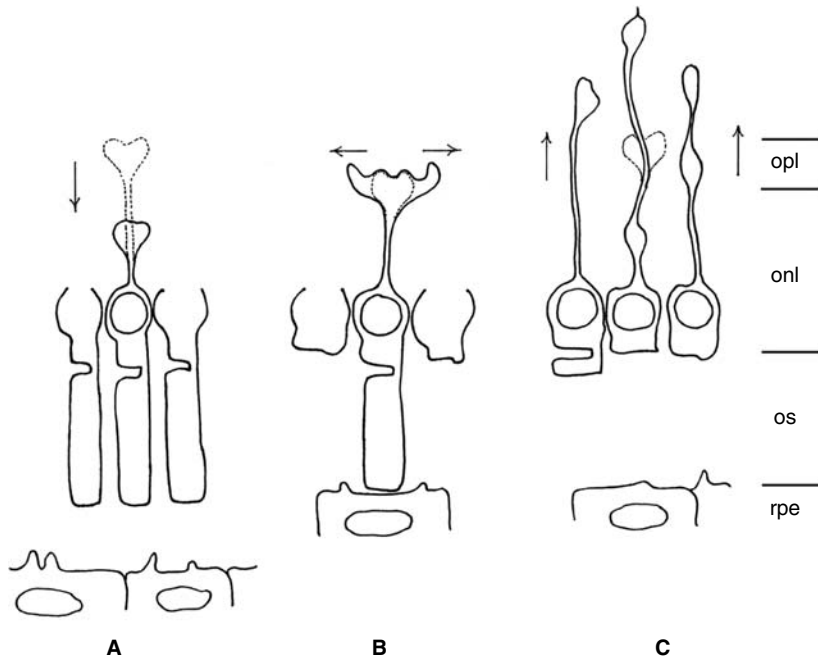


FIGURE 2.2. Summary of structural plasticity in adult photoreceptors. Rod cells show three general types of plasticity: A. retraction of the axon and terminal; B. enlargement of the terminal concomitant with new synaptic development; and C. neurite sprouting and varicosity development. Retraction occurs after retinal detachment, terminal enlargement occurs in retinal degeneration, and sprouting and varicosity formation have been seen in all types of degeneration and injury. Dotted lines indicate original synaptic outline before structural change. Arrows indicate overall direction of change. Cone cells (not shown) produce less plasticity. They do not exhibit retraction but do increase synaptic interaction in retinal disease. In one type of retinal degeneration (rd1) they produce varicosity-containing neurites similar to what is produced by rod cells. Opl, outer plexiform layer; onl, outer nuclear layer; os, outer segment layer; rpe, retinal pigmented epithelium.

transient or whether they can completely resolve or revert back to pre-injury morphology after therapeutic intervention (Lewis et al., 2002a, b, 2003).

### *Mechanisms producing structural plasticity in photoreceptors*

#### Calcium

Because the plasticity described for rod and cone terminals is different, a key assumption that can be made about the mechanisms of structural plasticity is that they differ between the two sensory receptor types. A known difference

between cone and rod terminals is the population of calcium channels that are present at the presynaptic active zone. In mammals, rod terminals have L-type channels with  $\alpha$ -1F subunits whereas cone terminals have L-type channels with  $\alpha$ -1D subunits (Taylor and Morgans, 1998; Morgans, 2001). Moreover, experiments in amphibians have shown that cone cells have cGMP-gated channels in their terminals which control exocytosis (Rieke and Schwartz, 1994; Savchenko et al., 1997).

Blockage of L-type and cGMP-gated channels affects plasticity. Retraction in rod axons can be prevented by blocking L-type channels (Nachman-Clewner et al., 1999) in cultured salamander rod cells. It is not known whether blocking L-type channels also affects the more subtle shape changes seen in cone cells. If blockage prevents retraction, it follows that influx of calcium must help initiate this activity. Retinal detachment, the injury associated with retraction, is accompanied by spreading depression, a depolarization that affects ion influxes and presumably would open L-type calcium channels. Thus, a possible scenario is that detachment causes an influx of calcium into the rod axon terminal and initiates cytoskeletal changes, which may include contraction of actinomyosin, that result in movement of the axon and terminal towards the cell body.

In cultures of salamander photoreceptors, about 24hrs after retraction of the axon, new filopodial growth is seen (Nachman-Clewner and Townes-Anderson, 1996). After 3 days in culture, thicker neuritic processes have formed and presynaptic varicosities start to develop. The outgrowth of rod processes is prevented by blocking L-type channels with nifedipine after 1 day in culture (Zhang and Townes-Anderson, 2002). Thus, the activity of L-type channels is also critical for development of neuritic structures in rod cells. In addition, blocking L-type channels prevents an increase in the production of the synaptic vesicle proteins SV2 and synaptophysin, which normally occurs by day 3 (Zhang and Townes-Anderson, 2002). This effect is specific for synaptic protein: blocking L-type channels has no effect on opsin synthesis. Other changes undoubtedly also occur with reduced calcium influx through L-type channels. Cone cell growth, however, is not noticeably affected. Instead, an antagonist to cGMP-gated channels, L-cis diltiazem, significantly reduces cone cell growth and the formation of varicosities (Zhang and Townes-Anderson, 2002). It appears, therefore, that both rod and cone cells require calcium influx for new neuritic development. The amount of required influx is probably either very small or highly localized since no effort was made to activate calcium channels in culture. Thus, the basal level of channel opening is adequate to sustain growth. Significantly, the channel *type* that primarily controls structural plasticity in rod and cone cells is different. With respect to disease and injury, one might speculate that because of the functional differences in these channels, one activated by voltage and the other by cGMP, the rod and cone photoreceptors will respond differently to the same insult depending on whether or not the function of L-type and/or cGMP-gated channel activity is affected.



## cGMP

Since cGMP-gated channels appeared to be involved in cone cell axonal plasticity, it was reasonable to test whether increases in cGMP would promote cone cell growth. Application of an analog to cGMP, 8-bromo-cGMP caused an increase in varicosity formation in cone but not rod cells (Zhang and Townes-Anderson, 2002). More recently, a systematic investigation of the nitric oxide (NO)-cGMP signaling pathway has been made using agonists and antagonists to the components of the pathway (Zhang et al., 2005). NO is produced by nitric oxide synthase which can be stimulated by calcium; NO stimulates soluble guanylyl cyclase (sGC) to produce cGMP; cGMP in turn can activate 1) phosphodiesterase (PDE) to hydrolyze cGMP to 5'-GMP, 2) protein kinase G (PKG), and 3) cGMP-gated cationic channels. Most of the components of the NO-cGMP pathway are known to exist in cone cells. NOS is present in photoreceptors as well as adjacent Müller cells and other retinal neurons (Liepe et al., 1994; Habrecht et al., 1998). Soluble GC is also present in cone cells (Habebrecht et al., 1998). Activating the pathway causes an increase in cone growth and inhibiting the pathway causes a decrease in growth (Zhang et al., 2005). The growth in cone cells presumably occurs because of calcium influx through cGMP-gated channels but also because of phosphorylation of protein by PKG. Inhibiting PKG using the cGMP analogue Rp-8-pCPT-cGMPs caused a decrease in the number of processes produced by cone cells. At present, we do not know what type of PKG is present in cone cells, nor what substrates it phosphorylates. It is possible that one of its targets is the cGMP-gated channel itself.

The effects of cGMP vary depending on the concentration of the reagent used. In cone cells, high concentrations of cGMP result in either no growth or inhibition of growth compared with lower levels of cGMP (Zhang et al., 2005). This suggests the presence of a feed-back loop which controls levels of cGMP in these photoreceptors. Such feedback could be provided by a cGMP-stimulated PDE. A similar feedback loop for cGMP exists in cerebellar neurons where it may play a role in controlling the form of synaptic plasticity known as long-term depression (Shimizu-Albergine et al., 2003).

Surprisingly and in contrast to cone cells, activation of the cGMP pathway in rod cells decreases growth, at all concentrations, whereas inhibiting the pathway increases rod cell growth. Thus, rod cells are also likely to contain the components of the NO-cGMP pathway although its effects on structural plasticity are different than those in cone cells. NOS is present in the inner segment of rod cells (Liepe et al., 1994). And we have recently been able to demonstrate the presence of sGC in cultured salamander rod cells (Zhang et al., 2005; Fig. 2.3). The enzyme is found not only in the cell body but in newly formed varicosities as well. Whether it is also present in the original axon terminal, before growth begins, is not known. It has been suggested that activation of the NO-cGMP pathway results in phosphorylation of L-type channels and their closure (Chik et al., 1995; Barnstable et al., 2004; Kourennyi et al., 2004).

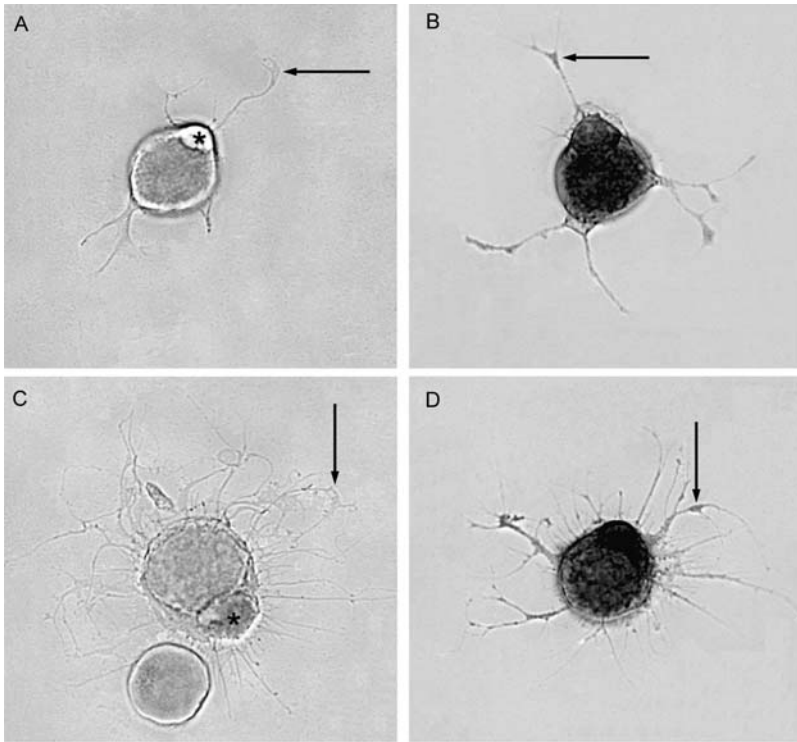


FIGURE 2.3. Both rod and cone cells contain soluble guanylyl cyclase (sGC) in the salamander. Bright field light micrographs from 3 day old cultures treated with an antibody against the alpha1 subunit of sGC (gift of Dr. Ari Sitaramayya) and ABC HRP immunocytochemistry. Photoreceptors have formed numerous new neuritic processes and created swellings along their length filled with synaptic vesicles, called presynaptic varicosities (arrows). \*, the ellipsoid, a collection of mitochondria which is a characteristic of amphibian photoreceptors.

Cone cells: A. control without primary antibody, B. staining with anti-alpha1 antibody. In control cells, there was very little staining; with the antibody, staining was present in the cell soma as well as newly developed presynaptic varicosities.

Rod cells: C. control staining, D. staining with anti-alpha1 antibody. There was little staining in the control cells but dark staining in the cell soma and presynaptic varicosities when anti-alpha 1 was applied.

Reduced calcium influx would lead to reduced growth and account at least in part for the negative effects of cGMP on rod cell plasticity.

Rod and cone cells also contain the membrane form of guanylyl cyclase (pGC) in their synaptic terminals. Thus, pGC exists both in outer segments of photoreceptors where it functions in the phototransduction cascade, and in the axon terminal (reviewed by Duda and Koch, 2002). Cyclic GMP could

therefore be increased both by NO activation of sGC and by pGC. Extracellular ligands that activate the pGC receptor are not known but calcium-binding proteins that control pGC activity are present in rod and cone terminals (Cuenca et al., 1998). How the membrane form of GC affects structural plasticity in photoreceptors remains to be determined.

The importance of the results regarding cGMP lies in their potential ability to explain the structural plasticity observed in rd1 mice. In this animal model of RP, the mutation in the beta subunit of rod PDE 6 results in very low PDE activity and high levels of cGMP in the photoreceptor layers (Lolley, 1994; Farber, 1995). Cone cells have long neuritic extensions (Fei, 2002) but rod cells have incomplete synaptic development (Blanks et al., 1974). This is precisely what increased levels of cGMP produced in cultured cells: increased cone cell growth and decreased rod cell growth. Since cone PDE is not affected in this form of retinal degeneration, cGMP must increase in cone cells by another route. It is possible that cGMP moves from rod to cone terminals via the gap junctions between these photoreceptors (Raviola and Gilula, 1973).

## cAMP

Cyclic AMP also appears to play a role in photoreceptor plasticity. An analogue of cAMP, Sp-cAMP increases growth of processes and development of presynaptic varicosities in rod cells but does not significantly affect cone cells in salamander retinal cell cultures (Townes-Anderson et al., 2003). This suggests that cGMP-dependent processes stimulate cone cell growth whereas rod cells use cAMP-dependent processes. A different analogue of cAMP, pCPT-cAMP, has been applied to an in vitro model of photoreceptor transplantation. Sheets of photoreceptors that would be used as transplants are prepared by vibratome from pig retina and maintained in culture (Khodair et al., 2003). In these sheets, axon retraction occurs as viewed by both synaptic vesicle and rod opsin antibodies (Khodair et al., 2003). Application of the cAMP analogue prevents this retraction; the effect is reversed if the analogue is removed (Khodair et al., 2005). In other cell types, neurite retraction is caused by cytoskeleton activity controlled by a small GTPase, RhoA (Jalink et al., 1994; Kozma et al., 1997; Lehmann et al., 1999). Cyclic AMP can inhibit RhoA and thereby inhibit retraction (Schoenwaelder and Burridge, 1999). The mechanism for retraction blockade in photoreceptors may therefore involve RhoA. RhoA has recently been immunolocalized in retina and is present in rod and cone terminals as well as the inner segments (Fontainhas et al., 2004). Cyclic GMP can also inhibit RhoA (Sauzeau et al., 2000) and high levels of cGMP in cone cells may allow cone cell growth in part because of the inhibition of RhoA.

Involvement of cAMP in rod cell plasticity in vitro is of interest because of the known increase in cAMP in some forms of retinal degeneration (Sanyal et al., 1984; Weiss et al., 1995; Nir et al., 2001; Traverso et al., 2002). If cAMP

increases in the rod terminal, this may lead to the neurite extension seen in RP. Similar increases in cone cells, if they occur, would not result in similar growth if results from cultures are correct. And indeed there is little growth of cone cell terminals in RP. The reason for increased cAMP in disease is not known, however, it has been suggested that mislocalized opsin, which occurs in retinal disease and injury, when activated by light, can interact with signaling pathways in the inner segment that lead to stimulation of adenylyl cyclase (Alfinito and Townes-Anderson, 2002).

### Extracellular Factors

Both different synaptic calcium channels and dependence on different cyclic nucleotide pathways could play a role in the differences observed in rod and cone cell structural plasticity. These might be considered intrinsic differences between the photoreceptor cell types. Environmental stimuli that activate or inhibit these pathways would then modify the expression of the plasticity. For instance, dopamine and adenosine released by the inner retina in response to light and dark affect the activity of photoreceptor adenylyl cyclase through their receptors. These neuromodulators may therefore affect the extent or time course of reactive neurite extension in rod cells. At present, however, the only transmitter that has been examined for possible effects on photoreceptor synaptic plasticity is GABA. In cultures where all retinal cell types are present, photoreceptors grow and contact GABAergic cells more often than other cell types (Sherry et al., 1996). In vivo, in retinas affected with RP, extensive sprouting by GABAergic amacrine cells has been observed and the rod neuritic sprouts appeared to grow towards and contact GABAergic amacrine cell somata preferentially (Fariss et al., 2000). The mechanism for this attraction is not known. Müller cells have also been suggested to be attractive to rod cell neuritic growth in RP retinas (Li et al., 1995). In one case of human autosomal dominant RP, synapse-like structures were observed between rod varicosities and Müller cells (Milam et al., 1996). The morphology of the new rod and cone growth strongly suggests that the inner retina is attractive: in all human and animal retinas where neuritic growth is observed, the processes extend into the inner retina with only one exception. In the exception, a retina with late-onset retinal degeneration, rod neurites filled the subretinal space (Gupta et al., 2003) and were not present in the inner retina. In salamander cultures, preliminary results indicate that the chemokine stromal-derived factor-1 $\alpha$  (SDF-1 $\alpha$ ) promotes rod photoreceptor cell neuritic growth (Zhang and Townes-Anderson, unpublished results). These results are consistent with the concept that neuritic growth of rod cells requires activation of the cAMP signaling pathway. The receptor for SDF-1 $\alpha$  is CXCR4 which is a G-protein-coupled receptor which can activate cAMP signaling (Chalasani et al., 2003). However, possible extrinsic factors that can influence plasticity of photoreceptors in either the inner or outer retina remain largely unexplored.

Although new rod and cone neuritic growth contains presynaptic varicosities, mature synapses are not observed between these varicosities and inner retinal neurons (Li et al., 1995). New synapses, however, are made between photoreceptors and bipolar cells in retinal disease: rod cells increase the number of synaptic contacts with bipolar cells with whom they are already in contact whereas cone cells have been shown to make synapses with new bipolar cells including neighboring rod bipolars denervated by rod cell death (Tables 2.1 & 2.2). So, synaptogenesis appears to be confined to the outer plexiform layer with cone cells innervating novel partners. This description of synaptogenesis in retinal disease is in sharp contrast to results from transplant studies where subretinal placement of photoreceptor cells does not yield synaptic interaction between the grafted photoreceptors and the host bipolar cells (reviewed by Lund et al., 2001). Most transplant paradigms use animals with rod-rich retinas. It is possible that cone cells will be more likely to make new synapses with host/novel bipolar cells. Recent work in culture suggests that both rod and cone cells will grow processes towards identified bipolar cells; moreover, cone cells seem to have a preference for bipolar over multipolar cells (Clarke et al., 2004). This is in contrast to the preference of rod cells for GABAergic multipolar cells (Sherry et al., 1996; Clarke et al., 2004).

### *Future Directions*

The effects of structural plasticity at the rod and cone terminal on visual processing are not known. However, it is difficult to imagine that sprouting and differentiation of new neurites as well as retraction will not change retinal processing. Indeed, electroretinograms of human and animal degenerate retinas indicate that there are postreceptoral abnormalities (Milam et al., 1996; Banin et al., 1999), although the precise cause of these changes is not yet clear.

To preserve normal vision it may be necessary to prevent plasticity in diseases and after retinal injury. Knowing the intrinsic and external stimuli for synaptic change will make it possible to develop strategies to preserve stability. There has already been some interest in calcium channel blockers as a preventive of rod cell degeneration. Although these blockers have had mixed results regarding the delay of degeneration (Frasson et al., 1999; Pearce-Kelling et al., 2001), it would be of interest to know if they prevent synaptic plasticity since both rod and cone plasticity depends on calcium influx. Drugs which affect the NO-cGMP pathway may also, unintentionally, affect photoreceptor synapses. Viagra, for instance, which blocks PDE 5 and possibly also PDE 6 activity, increases cGMP levels and has been shown to have some effects on postreceptoral elements in the outer retina (Jägle et al., 2004). Are these drugs inducing synaptic plasticity in retinal cells? Thus both to protect normal vision and to reduce the deleterious effects of disease continued exploration of the mechanisms of plasticity is needed.

Calcium, cGMP, and cAMP have been demonstrated recently to play interconnected roles in axonal growth and guidance of cortical and spinal cord neurons in developing mammalian and amphibian CNS and in invertebrate nerve cells (Song et al., 1998; van Wagenen and Rehder, 1999; Polleux et al., 2000; van Wagenen and Rehder, 2001; Xiang et al., 2002). Increasing cyclic nucleotides can increase growth toward certain guidance molecules or make what was a repulsive guidance factor into an attractive one. The ratio of cAMP to cGMP may influence growth in developing neurons (Nishiyama et al., 2003). In addition, numerous external factors guide axonal and dendritic growth during development. These factors include molecules known as guidance factors but also chemokines and neurotransmitters (Xiang et al., 2002; Lipton and Kater, 1989). Many of the findings observed in developing nervous tissue could be easily tested in adult retina and with adult retinal neurons. Interestingly, in ferret retinal development, rod and cone cells extend long neurites, that look similar to processes extended in adulthood after injury and disease, into the inner retina (Johnson et al., 1999). As development proceeds and the outer synaptic layer forms, the processes are retracted. The ferret may provide an additional and somewhat unique model of photoreceptor plasticity. Although regeneration does not faithfully follow the details of ontogeny, it nonetheless appears that if reactive plasticity was viewed as a facet of developmental neurobiology, it would result in new and productive lines of research.

## References

- H. Abe and T. Y. Yamamoto, Diurnal changes in synaptic ribbons of rod cells of the turtle, *J Ultrastruct Res* **86**(3), 246–51 (1984).
- M. A. Adly, I. Spiwoks-Becker and L. Vollrath, Ultrastructural changes of photoreceptor synaptic ribbons in relation to time of day and illumination, *Invest Ophthalmol Vis Sci* **40**(10), 2165–72 (1999).
- P. D. Alfinito and E. Townes-Anderson, Activation of mislocalized opsin kills rod cells: a novel mechanism for rod cell death in retinal disease, *Proc Natl Acad Sci U S A* **99**(8), 5655–60 (2002).
- G. Aquirre, D. Farber, R. Lolley, R. T. Fletcher and G. J. Chader, Rod-cone dysplasia in Irish setters: a defect in cyclic GMP metabolism in visual cells, *Science* **201**(4361), 1133–4 (1978).
- E. Banin, A. V. Cideciyan, T. S. Aleman, R. M. Petters, F. Wong, A. H. Milam and S.G. Jacobson, Retinal rod photoreceptor-specific gene mutation perturbs cone pathway development, *Neuron* **23**(3), 549–57 (1999).
- C. J. Barnstable, J. Y. Wei and M. H. Han, Modulation of synaptic function by cGMP and cGMP-gated cation channels, *Neurochem Int* **45**(6), 875–84 (2004).
- J. C. Blanks, A. M. Adinolfi and R. N. Lolley, Photoreceptor degeneration and synaptogenesis in retinal-degenerative (rd) mice, *J Comp Neurol* **156**(1), 95–106 (1974).
- S. H. Chalasani, K. A. Sabelko, M. J. Sunshine, D. R. Littman and J. A. Raper, A chemokine, SDF-1, reduces the effectiveness of multiple axonal repellents and is required for normal axon pathfinding, *J Neurosci* **23**(4), 1360–71 (2003).

- C. L. Chik, Q. Y. Liu, B. Li, E. Karpinski and A. K. Ho, cGMP inhibits L-type  $\text{Ca}^{2+}$  channel currents through protein phosphorylation in rat pinealocytes, *J Neurosci* **15**(4), 3104–9 (1995).
- N. H. Chong, R. A. Alexander, K. C. Barnett, A. C. Bird and P. J. Luthert, An immunohistochemical study of an autosomal dominant feline rod/cone dysplasia (Rdy cats), *Exp Eye Res* **68**(1), 51–7 (1999).
- E. Claes, M. Seeliger, S. Michalakakis, M. Biel, P. Humphries and S. Haverkamp, Morphological characterization of the retina of the CNGA3(-/-)Rho(-/-) mutant mouse lacking functional cones and rods, *Invest Ophthalmol Vis Sci* **45**(6), 2039–48 (2004).
- R. Clarke, K. Hognason, R. Chawla and E. Townes-Anderson Photoreceptor interactions with second- and third-order retinal neurons after optical tweezer micro-manipulation, ARVO: abstract#5368 (2004).
- N. Cuenca, S. Lopez, K. Howes and H. Kolb, The localization of guanylyl cyclase-activating proteins in the mammalian retina, *Invest Ophthalmol Vis Sci* **39**(7), 1243–50 (1998).
- N. Cuenca, I. Pinilla, Y. Sauve, B. Lu, S. Wang and R. D. Lund, Regressive and reactive changes in the connectivity patterns of rod and cone pathways of P23H transgenic rat retina, *Neuroscience* **127**(2), 301–17 (2004).
- O. Dick, S. tom Dieck, W. D. Altmann, J. Ammermüller, R. Weiler, C. C. Garner, E. D. Gundelfinger and J. H. Brandstätter, The presynaptic active zone protein bassoon is essential for photoreceptor ribbon synapse formation in the retina, *Neuron* **37**(5), 775–86 (2003).
- T. Duda and K. W. Koch, Calcium-modulated membrane guanylate cyclase in synaptic transmission?, *Mol Cell Biochem* **230**(1–2), 107–16 (2002).
- P. A. Erickson, S. K. Fisher, D. H. Anderson, W. H. Stern and G. A. Borgula, Retinal detachment in the cat: the outer nuclear and outer plexiform layers, *Invest Ophthalmol Vis Sci* **24**(7), 927–42 (1983).
- D. B. Farber, From mice to men: the cyclic GMP phosphodiesterase gene in vision and disease. The Proctor Lecture, *Invest Ophthalmol Vis Sci* **36**(2), 263–75 (1995).
- R. N. Fariss, Z. Y. Li and A. H. Milam, Abnormalities in rod photoreceptors, amacrine cells, and horizontal cells in human retinas with retinitis pigmentosa, *Am J Ophthalmol* **129**(2), 215–23 (2000).
- Y. Fei, Cone neurite sprouting: an early onset abnormality of the cone photoreceptors in the retinal degeneration mouse, *Mol Vis* **8**, 306–14 (2002).
- S. K. Fisher, J. Stone, T. S. Rex, K. A. Linberg and G. P. Lewis, Experimental retinal detachment: a paradigm for understanding the effects of induced photoreceptor degeneration, *Prog Brain Res* **131**, 679–98 (2001).
- S. K. Fisher and G. P. Lewis, Müller cell and neuronal remodeling in retinal detachment and reattachment and their potential consequences for visual recovery: a review and reconsideration of recent data, *Vision Res* **43**(8), 887–97 (2003).
- A. M. Fontainhas, N. Zhang, M. A. Khodair and E. Townes-Anderson Possible involvement of RhoA in synaptic plasticity of photoreceptors, ARVO: abstract#3646 (2004).
- M. Frasson, J. A. Sahel, M. Fabre, M. Simonutti, H. Dreyfus and S. Picaud, Retinitis pigmentosa: rod photoreceptor rescue by a calcium-channel blocker in the rd mouse, *Nat Med* **5**(10), 1183–7 (1999).
- K. Gregory-Evans, R. N. Fariss, D. E. Possin, C. Y. Gregory-Evans and A. H. Milam, Abnormal cone synapses in human cone-rod dystrophy, *Ophthalmology* **105**(12), 2306–12 (1998).

- N. Gupta, K. E. Brown and A. H. Milam, Activated microglia in human retinitis pigmentosa, late-onset retinal degeneration, and age-related macular degeneration, *Exp Eye Res* **76**(4), 463–71 (2003).
- M. F. Haberecht, H. H. Schmidt, S. L. Mills, S. C. Massey, M. Nakane and D. A. Redburn-Johnson, Localization of nitric oxide synthase, NADPH diaphorase and soluble guanylyl cyclase in adult rabbit retina, *Vis Neurosci* **15**(5), 881–90 (1998).
- H. Jägle, C. Jägle, L. Sérey, A. Yu, A. Rilk, B. Sadowski, D. Besch, E. Zrenner and L. T. Sharpe, Visual short-term effects of Viagra: double-blind study in healthy young subjects, *Am J Ophthalmol* **137**(5), 842–9 (2004).
- K. Jalink, E. J. van Corven, T. Hengeveld, N. Morii, S. Narumiya and W. H. Moolenaar, Inhibition of lysophosphatidate- and thrombin-induced neurite retraction and neuronal cell rounding by ADP ribosylation of the small GTP-binding protein Rho, *J Cell Biol* **126**(3), 801–10 (1994).
- H. G. Jansen and S. Sanyal, Development and degeneration of retina in rds mutant mice: electron microscopy, *J Comp Neurol* **224**(1), 71–84 (1984).
- H. G. Jansen and S. Sanyal, Synaptic changes in the terminals of rod photoreceptors of albino mice after partial visual cell loss induced by brief exposure to constant light, *Cell Tissue Res* **250**(1), 43–52 (1987).
- H. G. Jansen and S. Sanyal, Synaptic plasticity in the rod terminals after partial photoreceptor cell loss in the heterozygous rds mutant mouse, *J Comp Neurol* **316**(1), 117–25 (1992).
- H. G. Jansen, R. K. Hawkins and S. Sanyal, Synaptic growth in the rod terminals of mice after partial photoreceptor cell loss: a three-dimensional ultrastructural study, *Microsc Res Tech* **36**(2), 96–105 (1997).
- P. T. Johnson, R. R. Williams, K. Cusato and B. E. Reese, Rods and cones project to the inner plexiform layer during development, *J Comp Neurol* **414**(1), 1–12 (1999).
- M. A. Khodair, M. A. Zarbin and E. Townes-Anderson, Synaptic plasticity in mammalian photoreceptors prepared as sheets for retinal transplantation, *Invest Ophthalmol Vis Sci* **44**(11), 4976–88 (2003).
- M. A. Khodair, M. A. Zarbin and E. Townes-Anderson, Cyclic AMP prevents retraction of axon terminals in photoreceptors prepared for transplantation: an in vitro study, *Invest Ophthalmol Vis Sci* **46**(3), 967–73 (2005).
- D. E. Kourennyi, X. D. Liu, J. Hart, F. Mahmud, W. H. Baldrige and S. Barnes, Reciprocal modulation of calcium dynamics at rod and cone photoreceptor synapses by nitric oxide, *J Neurophysiol* **92**(1), 477–83 (2004).
- R. Kozma, S. Sarnar, S. Ahmed and L. Lim, Rho family GTPases and neuronal growth cone remodelling: relationship between increased complexity induced by Cdc42Hs, Rac1, and acetylcholine and collapse induced by RhoA and lysophosphatidic acid, *Mol Cell Biol* **17**(3), 1201–11 (1997).
- M. Lehmann, A. Fournier, I. Selles-Navarro, P. Dergham, A. Sebok, N. Leclerc, G. Tigyi and L. McKerracher, Inactivation of Rho signaling pathway promotes CNS axon regeneration, *J Neurosci* **19**(17), 7537–47 (1999).
- G. P. Lewis, K. A. Linberg and S. K. Fisher, Neurite outgrowth from bipolar and horizontal cells after experimental retinal detachment, *Invest Ophthalmol Vis Sci* **39**(2), 424–34 (1998).
- G. P. Lewis, D. G. Charteris, C. S. Sethi and S. K. Fisher, Animal models of retinal detachment and reattachment: identifying cellular events that may affect visual recovery, *Eye* **16**(4), 375–87 (2002a).



- G. P. Lewis, D. G. Charteris, C. S. Sethi, W. P. Leitner, K. A. Linberg and S. K. Fisher, The ability of rapid retinal reattachment to stop or reverse the cellular and molecular events initiated by detachment, *Invest Ophthalmol Vis Sci* **43**(7), 2412–20 (2002b).
- G. P. Lewis, C. S. Sethi, K. A. Linberg, D. G. Charteris and S. K. Fisher, Experimental retinal reattachment: a new perspective, *Mol Neurobiol* **28**(2), 159–75 (2003).
- Z. Y. Li, I. J. Kljavin and A. H. Milam, Rod photoreceptor neurite sprouting in retinitis pigmentosa, *J Neurosci* **15**(8), 5429–38 (1995).
- Z. Y. Li, F. Wong, J. H. Chang, D. E. Possin, Y. Hao, R. M. Petters and A. H. Milam, Rhodopsin transgenic pigs as a model for human retinitis pigmentosa, *Invest Ophthalmol Vis Sci* **39**(5), 808–19 (1998).
- B. A. Liepe, C. Stone, J. Koistinaho and D. R. Copenhagen, Nitric oxide synthase in Müller cells and neurons of salamander and fish retina, *J Neurosci* **14**(12), 7641–54 (1994).
- S. A. Lipton and S. B. Kater, Neurotransmitter regulation of neuronal outgrowth, plasticity and survival, *TINS* **12**(7), 265–70 (1989).
- R. N. Lolley, The rd gene defect triggers programmed rod cell death. The Proctor Lecture, *Invest Ophthalmol Vis Sci* **35**(13), 4182–91 (1994).
- R. D. Lund, A. S. Kwan, D. J. Keegan, Y. Sauve, P. J. Coffey and J. M. Lawrence, Cell transplantation as a treatment for retinal disease, *Prog Retin Eye Res* **20**(4), 415–49 (2001).
- J. W. Mandell, E. Townes-Anderson, A. J. Czernik, R. Cameron, P. Greengard and P. De Camilli, Synapsins in the vertebrate retina: absence from ribbon synapses and heterogeneous distribution among conventional synapses, *Neuron* **5**(1), 19–33 (1990).
- K. Mervin, K. Valter, J. Maslim, G. Lewis, S. Fisher and J. Stone, Limiting photoreceptor death and deconstruction during experimental retinal detachment: the value of oxygen supplementation, *Am J Ophthalmol* **128**(2), 155–64 (1999).
- A. H. Milam, Z. Y. Li, A. V. Cideciyan and S. G. Jacobson, Clinicopathologic effects of the Q64ter rhodopsin mutation in retinitis pigmentosa, *Invest Ophthalmol Vis Sci* **37**(5), 753–65 (1996).
- R. S. Molday, Photoreceptor membrane proteins, phototransduction, and retinal degenerative diseases. The Friedenwald Lecture, *Invest Ophthalmol Vis Sci* **39**(13), 2491–513 (1998).
- C. W. Morgans, J. H. Brandstätter, J. Kellerman, H. Betz and H. Wässle, A SNARE complex containing syntaxin 3 is present in ribbon synapses of the retina, *J Neurosci* **16**(21), 6713–21 (1996).
- C. W. Morgans, Localization of the alpha(1F) calcium channel subunit in the rat retina, *Invest Ophthalmol Vis Sci* **42**(10), 2414–8 (2001).
- M. Nachman-Clewner and E. Townes-Anderson, Injury-induced remodelling and regeneration of the ribbon presynaptic terminal in vitro, *J Neurocytol* **25**(10), 597–613 (1996).
- M. Nachman-Clewner, R. St Jules and E. Townes-Anderson, L-type calcium channels in the photoreceptor ribbon synapse: localization and role in plasticity, *J Comp Neurol* **415**(1), 1–16 (1999).
- I. Nir, R. Haque and P. M. Iuvone, Regulation of cAMP by light and dopamine receptors is dysfunctional in photoreceptors of dystrophic retinal degeneration slow(rds) mice, *Exp Eye Res* **73**(2), 265–72 (2001).
- M. Nishiyama, A. Hoshino, L. Tsai, J. R. Henley, Y. Goshima, M. Tessier-Lavigne, M. M. Poo and K. Hong, Cyclic AMP/GMP-dependent modulation of  $\text{Ca}^{2+}$  channels sets the polarity of nerve growth-cone turning, *Nature* **423**(6943), 990–5 (2003).

- S. E. Pearce-Kelling, T. S. Aleman, A. Nickle, A. M. Laties, G. D. Aguirre, S. G. Jacobson and G. M. Acland, Calcium channel blocker D-cis-diltiazem does not slow retinal degeneration in the PDE6B mutant *rd1* canine model of retinitis pigmentosa, *Mol Vis* **7**, 42–7 (2001).
- Y. W. Peng, Y. Hao, R. M. Petters and F. Wong, Ectopic synaptogenesis in the mammalian retina caused by rod photoreceptor-specific mutations, *Nat Neurosci* **3**(11), 1121–7 (2000).
- Y. W. Peng, T. Senda, Y. Hao, K. Matsuno and F. Wong, Ectopic synaptogenesis during retinal degeneration in the royal college of surgeons rat, *Neuroscience* **119**(3), 813–20 (2003).
- F. Polleux, T. Morrow and A. Ghosh, Semaphorin 3A is a chemoattractant for cortical apical dendrites, *Nature* **404**(6778), 567–73 (2000).
- E. Raviola and N. B. Gilula, Gap junctions between photoreceptor cells in the vertebrate retina, *Proc Natl Acad Sci U S A* **70**(6), 1677–81 (1973).
- C. E. Reme and R. W. Young, The effects of hibernation on cone visual cells in the ground squirrel, *Invest Ophthalmol Vis Sci* **16**(9), 815–40 (1977).
- T. S. Rex, R. N. Fariss, G. P. Lewis, K. A. Linberg, I. Sokal and S. K. Fisher, A survey of molecular expression by photoreceptors after experimental retinal detachment, *Invest Ophthalmol Vis Sci* **43**(4), 1234–47 (2002).
- F. Rieke and E. A. Schwartz, A cGMP-gated current can control exocytosis at cone synapses, *Neuron* **13**(4), 863–73 (1994).
- S. Sanyal, R. Fletcher, Y. P. Liu, G. Aguirre and G. Chader, Cyclic nucleotide content and phosphodiesterase activity in the *rds* mouse (O2O/A) retina, *Exp Eye Res* **38**, 247–56 (1984).
- S. Sanyal, R. K. Hawkins, H. G. Jansen and G. H. Zeilmaier, Compensatory synaptic growth in the rod terminals as a sequel to partial photoreceptor cell loss in the retina of chimaeric mice, *Development* **114**(3), 797–803 (1992).
- V. Sauzeau, H. Le Jeune, C. Cario-Toumaniantz, A. Smolenski, S. M. Lohmann, J. Bertoglio, P. Chardin, P. Pacaud and G. Loirand, Cyclic GMP-dependent protein kinase signaling pathway inhibits RhoA-induced  $\text{Ca}^{2+}$  sensitization of contraction in vascular smooth muscle, *J Biol Chem* **275**(28), 21722–9 (2000).
- A. Savchenko, S. Barnes and R. H. Kramer, Cyclic-nucleotide-gated channels mediate synaptic feedback by nitric oxide, *Nature* **390**(6661), 694–8 (1997).
- S. F. Schaeffer and E. Raviola, Membrane recycling in the cone cell endings of the turtle retina, *J Cell Biol* **79**(3), 802–25 (1978).
- Y. Schmitz and P. Witkovsky, Dependence of photoreceptor glutamate release on a dihydropyridine-sensitive calcium channel, *Neuroscience* **78**(4), 1209–16 (1997).
- F. Schmitz, A. Königstorfer and T. C. Südhof, RIBEYE, a component of synaptic ribbons: a protein's journey through evolution provides insight into synaptic ribbon function, *Neuron* **28**(3), 857–72 (2000).
- S. M. Schoenwaelder and K. Burridge, Bidirectional signaling between the cytoskeleton and integrins, *Curr Opin Cell Biol* **11**(2), 274–86 (1999).
- C. S. Sethi, G. P. Lewis, S. K. Fisher, W. P. Leitner, D. L. Mann, P. J. Luthert and D. G. Charteris, Glial remodeling and neural plasticity in human retinal detachment with proliferative vitreoretinopathy, *Invest Ophthalmol Vis Sci* **46**(1), 329–42 (2005).
- D. M. Sherry, R. S. St Jules and E. Townes-Anderson, Morphologic and neurochemical target selectivity of regenerating adult photoreceptors in vitro, *J Comp Neurol* **376**(3), 476–88 (1996).

- M. Shimizu-Albergine, S. D. Rybalkin, I. G. Rybalkina, R. Feil, W. Wolfsgruher, F. Hofmann and J. A. Beavo, Individual cerebellar Purkinje cells express different cGMP phosphodiesterases (PDEs): in vivo phosphorylation of cGMP-specific PDE (PDE5) as an indicator of cGMP-dependent protein kinase (PKG) activation, *J Neurosci* **23**(16), 6452–9 (2003).
- H. J. Song, G. L. Ming, Z. He, M. Lehmann, L. McKerracher, M. Tessier-Lavigne and M. M. Poo, Conversion of neuronal growth cone responses from repulsion to attraction by cyclic nucleotides, *Science* **281**(5382), 1515–8 (1998).
- M. Spencer, P. B. Detwiler and A. H. Bunt-Milam, Distribution of membrane proteins in mechanically dissociated retinal rods, *Invest Ophthalmol Vis Sci* **29**(7), 1012–20 (1988).
- W. R. Taylor and C. Morgans, Localization and properties of voltage-gated calcium channels in cone photoreceptors of *Tupaia belangeri*, *Vis Neurosci* **15**(3), 541–52 (1998).
- E. Townes-Anderson, Intersegmental fusion in vertebrate rod photoreceptors. Rod cell structure revisited, *Invest Ophthalmol Vis Sci* **36**(9), 1918–33 (1995).
- E. Townes-Anderson, R. Chawla and N. Zhang Differential roles of cAMP and cGMP in presynaptic plasticity of salamander cone and rod photoreceptors in vitro, ARVO: abstract#2847 (2003).
- V. Traverso, R. A. Bush, P. A. Sieving and D. Deretic, Retinal cAMP levels during the progression of retinal degeneration in rhodopsin P23H and S334ter transgenic rats, *Invest Ophthalmol Vis Sci* **43**(5), 1655–61 (2002).
- S. Van Wagenen and V. Rehder, Regulation of neuronal growth cone filopodia by nitric oxide, *J Neurobiol* **39**(2), 168–85 (1999).
- S. Van Wagenen and V. Rehder, Regulation of neuronal growth cone filopodia by nitric oxide depends on soluble guanylyl cyclase, *J Neurobiol* **46**(3), 206–19 (2001).
- L. Vollrath and I. Spiwoks-Becker, Plasticity of retinal ribbon synapses, *Microsc Res Tech* **35**(6), 472–87 (1996).
- E. R. Weiss, Y. Hao, C. D. Dickerson, S. Osawa, W. Shi, L. Zhang and F. Wong, Altered cAMP levels in retinas from transgenic mice expressing a rhodopsin mutant, *Biochem Biophys Res Commun* **216**(3), 755–61 (1995).
- Y. Xiang, Y. Li, Z. Zhang, K. Cui, S. Wang, X. B. Yuan, C. P. Wu, M. M. Poo and S. Duan, Nerve growth cone guidance mediated by G protein-coupled receptors, *Nat Neurosci* **5**(9), 843–8 (2002).
- M. Xiao, S. M. Sastry, Z. Y. Li, D. E. Possin, J. H. Chang, I. B. Klock and A. H. Milam, Effects of retinal laser photocoagulation on photoreceptor basic fibroblast growth factor and survival, *Invest Ophthalmol Vis Sci* **39**(3), 618–30 (1998).
- N. Zhang and E. Townes-Anderson, Regulation of structural plasticity by different channel types in rod and cone photoreceptors, *J Neurosci* **22**(16), 7065–79 (2002).
- N. Zhang, A. Beuve and E. Townes-Anderson, The nitric oxide-cGMP signaling pathway differentially regulates presynaptic structural plasticity in cone and rod cells, *J Neurosci* **25**(10), 2761–70 (2005).

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