Regulation of potassium levels by Müller cells in the vertebrate retina[1]

ERIC A. NEWMAN
Eye Research Institute of Retina Foundation, 20 Staniford Street, Boston, MA, U.S.A. 02114

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The membrane properties of Müller cells, the principal glial cells of the vertebrate retina, have been characterized in a series of physiological experiments on freshly dissociated cells. In species lacking a retinal circulation (tiger salamander, rabbit, guinea pig), the end-foot of the Müller cell has a much higher K^+ conductance than do other cell regions. In species with retinal circulation (mouse, cat, owl monkey) the K^+ conductance of the end-foot is greater than the conductance of the proximal process of the cell. In these species, however, the K^+ conductance of the soma and distal process is equal to, or greater than, the end-foot conductance. Müller cells also possess four voltage-dependent ion channels, including an inward rectifying K^+ channel. These membrane specializations may aid in the regulation of extracellular K^+ levels by Müller cells in the retina. High end-foot conductance shunts excess K^+ out through the end-foot, where it diffuses into the vitreous humor. In vascularized retinae, excess K^+ may also be transferred to the ablumenal wall of capillaries, where it could be transported into the blood.

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On a caractérisé les propriétés membranaires des cellules de Müller, les principales cellules gliales de la rétine des vertébrés, dans une série d'expériences physiologiques sur des cellules fraîchement dissociées. Chez les espèces sans circulation rétinienne (salamandre tigrée, lapin, cobaye), l'extrémité de la cellule de Müller montre une conductance K^+ beaucoup plus élevée que les autres régions cellulaires. Chez les espèces avec circulation rétinienne (souris, chat, nyctipithèque), la conductance K^+ de l'extrémité est plus grande que la conductance de la partie proximale de la cellule. Chez ces espèces, toutefois, la conductance K^+ du soma et de la partie distale est égale ou plus grande que celle de l'extrémité. Les cellules de Müller possèdent aussi quatre canaux ioniques dépendants de la tension, incluant un canal de rectification entrante K^+. Ces spécificités membranaires peuvent contribuer à la régularisation des taux de K^+ extracellulaire par les cellules de Müller dans la rétine. Une grande conductance à l'extrémité dérive l'excès de K^+ vers l'extrémité, où il diffuse dans l'humeur aqueuse. Dans les réines vascularisées, l'excès de K^+ peut aussi être transféré vers la paroi abluminale des capillaires, où il est transporté dans le sang.

[Traduit par la revue]

Introduction

In the vertebrate retina, light-evoked neuronal activity generates a characteristic series of changes in the potassium concentration in extracellular space ($[K^+]_o$). In dark-adapted retinae, the hyperpolarization of rods generates a prolonged decrease in $[K^+]_o$ owing to a net K^+ influx into the inner segments (Oakley and Green 1976; Steinberg et al. 1980). In the inner and outer plexiform layers, K^+ efflux accompanying the activity of depolarizing bipolar, amacrine, and ganglion cells generates transient increases in $[K^+]_o$ (Kline et al. 1978; Dick and Miller 1985; Karwoski et al. 1985). These activity-dependent variations in $[K^+]_o$ are buffered so as to minimize their effects on retinal function; even small variations in $[K^+]_o$ produce significant changes in the resting potential of neurons, leading to changes in the efficacy of synaptic transmission and the threshold for the initiation of action potentials.

Several mechanisms help regulate, or buffer, local $[K^+]_o$ increases generated by neuronal activity in the central nervous system (CNS), including the retina (Varon and Somjen 1979). These mechanisms include (*i*) diffusion of K^+ through extracellular space, (*ii*) reuptake of K^+ by active neurons, (*iii*) active K^+ uptake by other neurons and glial cells, (*iv*) passive K^+ uptake accompanied by an influx of water and a counter ion (or efflux of a cation), and (*v*) K^+ spatial buffering by glial cells.

The relative importance of these five K^+ clearance mechanisms is not known. In the retina, evidence suggests that K^+ spatial buffering by Müller cells plays an important role in K^+ regulation (Newman et al. 1984; Newman 1985*a*). This review will focus on the membrane properties of Müller cells and the role that these cells play in K^+ regulation in the retina.

Müller cell membrane properties

Müller cells are the principal glial cells of the retina and are closely related in many respects to astrocytic glial cells of the brain (Polyak 1941; Newman 1986*c*). Müller cells are radial glial cells. They span the entire width of the neural retina, extending from the inner limiting membrane to the outer limiting membrane. Müller cell somata lie in the inner nuclear layer. Projecting from the soma are two radial processes, a proximal process, which extends towards the vitreous and is terminated by an end-foot lying along the inner limiting membrane, and a distal process, which ends at the level of the photoreceptor inner segments.

K^+ conductance distribution

Like other glial cells, Müller cells are almost exclusively permeable to K^+ (Newman 1985*a*; Conner et al. 1985). In salamander, Müller cells are approximately 490 times as permeable to K^+ as they are to Na^+ (Newman 1985*a*).

Over the past decade, evidence has accumulated suggesting that Müller cell K^+ conductance is not distributed uniformly over the cell surface, but rather is localized to the end-foot of the cell (Mori et al. 1976; Newman 1979; Fujimoto and Tomita 1981). I have tested this hypothesis in a number of experiments on enzymatically dissociated Müller cells from the salamander.

In one series of experiments, Müller cell input resistance was measured both before and after the cell end-foot was removed by

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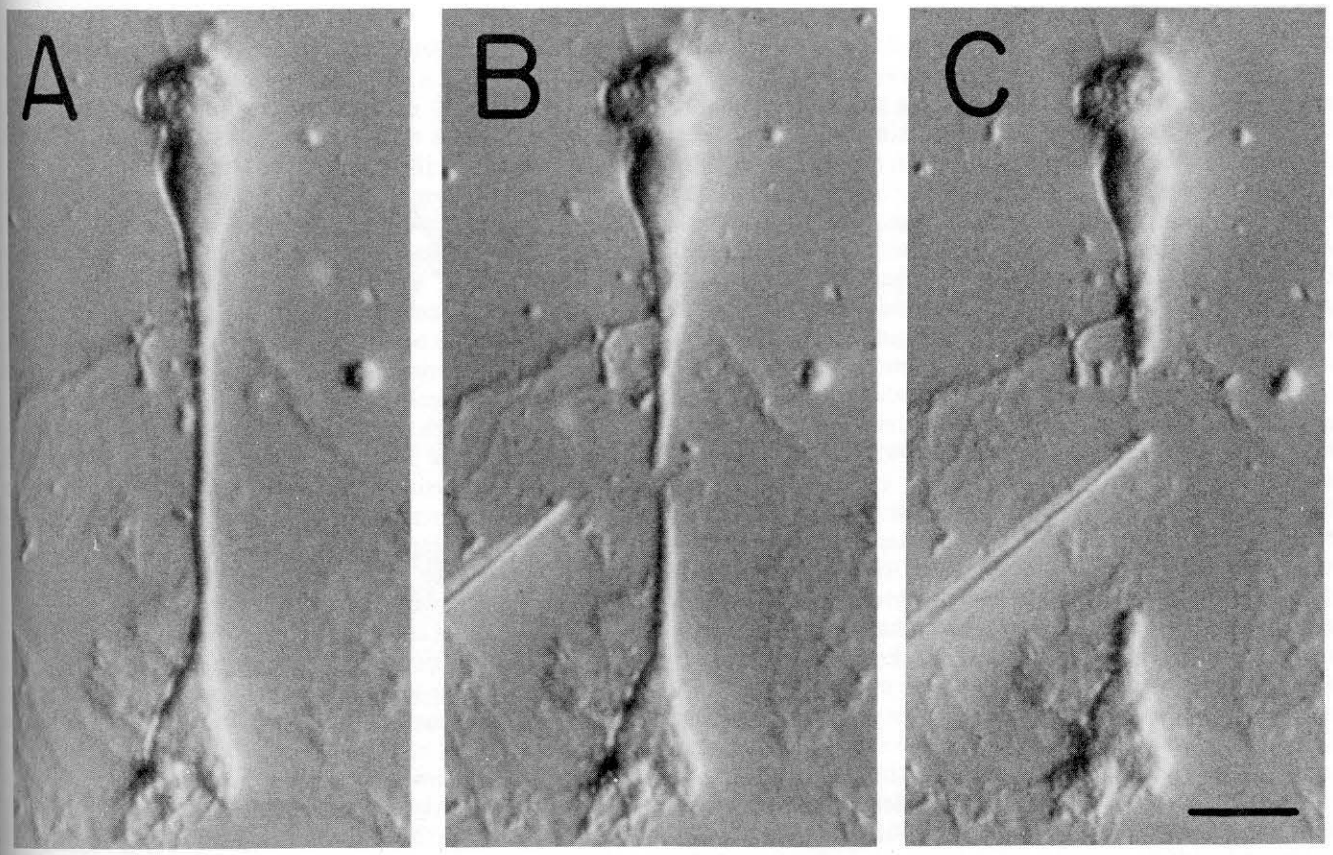

FIG. 1. Photomicrographs of a dissociated salamander Müller cell microdissected with a glass needle. (A) Intact cell. (B) Fifteen seconds after the proximal process of the cell was cut. (C) Several minutes later. Cell input resistance was measured with micropipettes attached to the somata of such microdissected cells both before and after the end-foot was removed. Scale bar, 20 μm. Reprinted with permission from J. Neurosci., Newman (1985*a*).

surgical microdissection (Newman 1984, 1985*a*). When the proximal process of a cell is cut by compressing it with a glass needle, the cut ends often reseal, producing two components, (*i*) an isolated end-foot and, (*ii*) a cell without its end-foot (Fig. 1). In these microdissection experiments, the input resistance of intact cells averaged 7.9 MΩ. The resistance of cells with their end-feet removed averaged 152 MΩ. These results indicate that approximately 95% of the total conductance of the cell lies in the portion removed by the microdissection procedure, in or near the end-foot.

This finding was confirmed in a second series of experiments on dissociated salamander Müller cells. The membrane potential of isolated cells was monitored as $[K^+]_o$ was raised over selected regions of the cell surface by pressure-ejecting a high K^+ solution (50–125 m*M*) from an extracellular pipette (Newman 1984, 1985*a*, 1986*b*). When K^+ was ejected onto the proximal surface of the end-foot (Fig. 2*a*) a large depolarization was recorded from the soma. If the K^+ ejection pipette was moved just 10 μm to the lateral face of the end-foot (Fig. 2*b*), a much smaller depolarization was produced. Even smaller depolarizations were evoked by K^+ ejections onto other regions of the cell (Figs. 2*c*, 2*d*, and 2*f*). However, a relatively large response was produced by K^+ ejection onto the distal process of the cell (Fig. 2*e*). The large K^+ response of the distal cell process was not observed in earlier studies (Newman 1984, 1985*a*) because that region of the cell was not tested. In a series of such K^+ ejection experiments, K^+ response magnitudes (normalized to the end-foot response) averaged the following: proximal end-foot, 100%; lateral end-foot, 18.4%; proximal process, 1.8%; soma, 1.6%; distal process, 13.0%; distal end of cell, 2.1% (data from Newman 1986*b*).

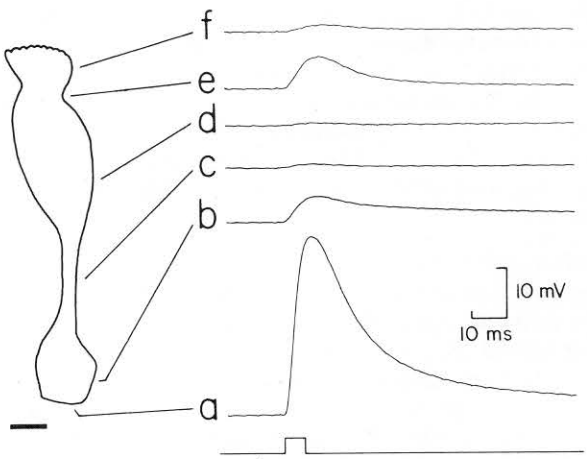

FIG. 2. Responses to focal K^+ ejections recorded from the cell body of a dissociated salamander Müller cell (shown schematically at left). Ejections were directed at *a*, proximal face of the end-foot; *b*, lateral face of the end-foot; *c*, proximal process; *d*, soma; *e*, distal process; *f*, distal end of the cell. The magnitudes of these K^+ responses demonstrate that the Müller cell end-foot has a much greater K^+ conductance than do other regions of the cell. Scale bar for drawing of cell, 10 μm. Reprinted with permission from Ann. N.Y. Acad. Sci., Newman (1986*b*).

The magnitude of a cell depolarization produced by a focal K^+ ejection is directly proportional to the K^+ conductance of the cell membrane experiencing the K^+ increase (Newman

1985*a*). Thus, the K^+ experiments described above confirm the finding that in salamanders, Müller cell end-feet have a significantly higher conductance than do other cell regions. Furthermore, the experiments demonstrate that end-foot conductance is largely restricted to the proximal end-foot (that region of the cell that is in direct contact with the vitreous humor *in situ*) and that the distal process of Müller cells (which lies in the outer plexiform layer *in situ*) has a markedly higher conductance than adjacent cell regions.

Voltage-dependent ion channels

Since the work of Kuffler and his colleagues (Kuffler 1967), glial cells have been considered to be electrically inexcitable. Recent experiments have shown, however, that several types of glial cells possess voltage-dependent ion channels (Chiu et al. 1984; MacVicar 1984; Bevan and Raff 1985). This is true of Müller cells as well.

When the resting K^+ conductance of salamander Müller cells is blocked with K^+ channel blockers, depolarizing current pulses can evoke a regenerative potential (Newman 1985*b*). Both *in situ* (retinal slices) and in dissociated cells, these action potentials are not affected by the Na^+ channel blocker tetrodotoxin but are blocked by Ca^{2+} channel blockers. This indicates that these spikes are generated by voltage-dependent Ca^{2+} channels.

This finding was confirmed in a series of voltage-clamp experiments on dissociated salamander Müller cells (Newman 1985*b*). A total of four voltage-dependent channels was identified. In addition to a Ca^{2+} channel, Müller cells possess a Ca^{2+}-dependent K^+ channel, a fast inactivating (type A) K^+ channel, and an inward rectifying K^+ channel.

Of these four types of channels, three open only after the cell is depolarized to -60 mV or less. The function of these three channels (the Ca^{2+} channel, the Ca^{2+}-activated K^+ channel, and the type A K^+ channel) in Müller cells is unclear, since Müller cells never depolarize to -60 mV under normal physiological conditions. However, the fourth voltage-dependent channel, the K^+ inward rectifier, is open at the normal resting potential of the cell (approximately -90 mV). As will be described below, the voltage- and K^+-dependent properties of this channel may play an important role in the regulation of $[K^+]_o$ in the retina.

Potassium spatial buffering

Based on their work on glial cell physiology, Orkand et al. (1966) suggested that glial cells may help to regulate $[K^+]_o$ by a process termed "K^+ spatial buffering." A localized increase in $[K^+]_o$ leads to K^+ influx into glial cells. To maintain net electrical neutrality, an equal amount of K^+ exits from other regions of the cell or from other electrically coupled cells. The net effect of this K^+ current is to transfer K^+ from regions where $[K^+]_o$ is raised to regions where $[K^+]_o$ is low.

In the retina, the radially oriented Müller cell is ideally suited to transfer excess K^+ away from the inner and outer plexiform layers, where light-evoked $[K^+]_o$ increases are largest (Karwoski et al. 1985). If K^+ conductance were distributed uniformly over the surface of Müller cells, excess K^+ would flow into Müller cells at the site of a $[K^+]_o$ increase and flow out through all other regions of the cell. This process would function to transfer excess K^+ away from the site of the initial increase, but only at a cost. Excess K^+ would be transferred to other retinal laminae.

Potassium siphoning

As demonstrated above, K^+ conductance is not distributed uniformly over the surface of Müller cells, but rather is localized to the end-foot. Thus, most of the K^+ current entering Müller cells at the site of a $[K^+]_o$ increase is shunted out through the end-foot. This K^+ diffuses directly into the vitreous humor, which functions as a large sink, or reservoir, where the K^+ is stored until retinal $[K^+]_o$ returns to normal.

This directed flow of spatial buffering current through Müller cell end-feet is a more effective K^+ homeostatic mechanism than is the traditionally envisioned spatial buffering process because excess K^+ is transferred to the vitreous rather than to other regions of neural tissue. This process is termed "K^+ siphoning" and has been demonstrated experimentally by monitoring K^+ efflux from dissociated salamander Müller cells with ion-selective microelectrodes (Newman et al. 1984).

To achieve a high end-foot conductance relative to the rest of the Müller cell, the absolute conductance over most of the cell surface is, of necessity, low. Computer simulations demonstrate that this low conductance is the limiting factor in the transfer of K^+ by K^+ siphoning (Newman et al. 1984; Brew and Attwell 1985). Two Müller cell membrane specializations counteract this limitation, however. As demonstrated above, the conductance of the Müller cell surface lying within the outer plexiform layer (one of the two layers where $[K^+]_o$ increases occur) is several-fold higher than the conductance in neighboring laminae. This higher conductance allows a larger influx of K^+ into the cell.

In addition, the inward rectifying properties of Müller cell K^+ conductance also enhance the process of K^+ siphoning. Over most of its surface, Müller cell conductance is primarily due to K^+ inward rectifying channels (Newman 1985*b*). In regions where $[K^+]_o$ is raised, K^+ influx into Müller cells will be facilitated because membrane conductance is higher than at rest. Thus, K^+ conductance is increased only where it is needed, in regions where $[K^+]_o$ is high. At the same time, efflux of K^+ from most other regions of the cell will be impeded owing to the rectifying properties of the channel. As a consequence, a greater fraction of the K^+ current will be directed out through the end-foot. (Whole cell voltage-clamp experiments (Newman 1985*b*) suggest that the K^+ channels of the end-foot, unlike those of the rest of the cell, are not inward rectifying. However, patch-clamp studies (Brew et al. 1986) have not to date revealed regional variations in the types of K^+ channels found over the Müller cell surface.)

Mammalian Müller cells

The membrane properties of Müller cells appear to make them ideal regulators of $[K^+]_o$ in the retina. However, Müller cell membrane properties have previously been characterized only in amphibians. It is important to determine whether Müller cells of mammals share the membrane specializations found in the cells of lower vertebrates. A recent study (Newman 1987) has addressed this issue by determining the distribution of K^+ conductance across the surface of Müller cells in a number of mammalian species.

Müller cell conductance was measured by monitoring cell depolarizations to focal K^+ ejections, the same experimental paradigm that was used to measure the K^+ conductance distribution in salamander cells (see Fig. 2). The results of these experiments are summarized in Fig. 3. Local values of K^+ response magnitude are expressed as the percentage of the end-foot response for each species. All end-foot responses are normalized to 100%.

For both rabbit and guinea pig Müller cells, the conductance of the end-foot membrane is significantly larger than the con-

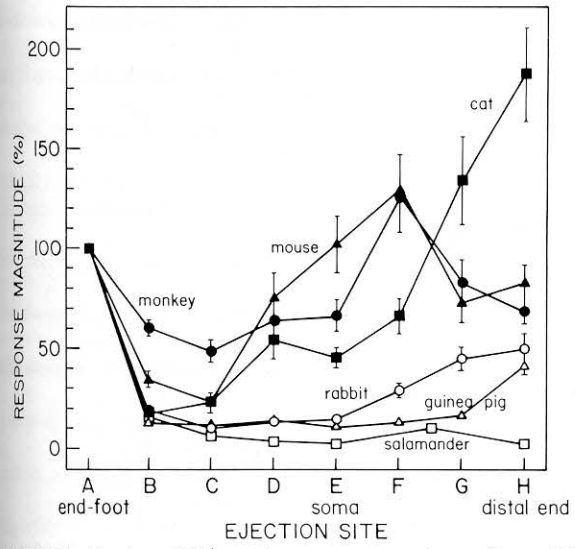

FIG. 3. Distribution of K^+ conductance across the surface of Müller cells of the tiger salamander (□), rabbit (○), guinea pig (△), mouse (▲), cat (■), and owl monkey (●). For each species, the average magnitude (± SEM) of the K^+ ejection response of each cell region is expressed as a percentage of the cell's end-foot response. The end-foot response of each species in normalized to 100%. In these experiments, response magnitude is roughly proportional to the K^+ conductance of each cell region. End-foot K^+ conductance is significantly larger than the conductance of all other cell regions in Müller cells of avascular retinae (salamander, rabbit, guinea pig), but not in cells of vascularized retinae (mouse, cat, monkey). Reprinted with permission from J. Neurosci., Newman (1987).

ductance of all other cell regions. In both species, the maximum conductance of the proximal cell process is only 14.0–19.2% of the end-foot conductance, while the maximum conductance of the distal process (excluding the distal end) is 16.4–44.9% of the end-foot value. Thus, in both of these species, the distribution of K^+ conductance qualitatively resembles that of salamander cells.

The distribution of K^+ conductance differs in three other mammalian species. In mouse, cat, and owl monkey, the maximum K^+ conductance of the proximal process is 46.8–75.5% of the conductance of the end-foot. In these species, as in salamander, rabbit, and guinea pig, the end-foot is a region of relatively high conductance. In the distal retina, however, the K^+ membrane conductance in mouse, cat, and monkey cells is larger than it is in salamander, rabbit, and guinea pig. The maximum conductance of the distal process of mouse, cat, and monkey cells (excluding the distal end) is 125.5–129.8% of the end-foot conductance. Although quantitative estimates are difficult to make, it appears that the conductance of the end-foot in mouse, cat, and monkey Müller cells is a much smaller fraction of total cell conductance than it is in salamander, rabbit, and guinea pig.

What accounts for the differences in the distribution of K^+ conductance amongst different mammalian species? A possible explanation lies in the pattern of retinal vascularization in the species (see Michaelson 1954; Chase 1982). As is the case for salamander, the retinae of the rabbit and the guinea pig are not vascularized. Their retinae are relatively thin and rely solely on the circulation of the choroid. The retinae of the mouse, cat, and monkey, on the other hand, are vascularized and are substantially thicker.

This difference in vascularization is suggestive. In those species without a retinal circulation, the most effective place to store excess K^+ is the vitreous humor. In these species, end-foot conductance must be significantly larger than the conductance of other cell regions to insure that most K^+ current is shunted out through the end-foot and into the vitreous.

In species with a retinal circulation, however, it might be more effective to transfer excess K^+ into the blood rather than into the vitreous. In this case, K^+ conductance must be large in those retinal laminae where retinal capillaries are found. In most mammals, deep retinal capillaries are located within the inner nuclear layer (Michaelson 1954). It is intriguing to note that the region of highest conductance on the distal process of mouse and monkey Müller cells occurs at approximately the same location as the deepest extent of this capillary network, at the border between the inner nuclear layer and the outer plexiform layer.

Several anatomical and physiological observations provide suggestive evidence for this hypothesis of the siphoning of excess K^+ into the blood. In the deeper capillary beds in the retina, capillaries are enveloped by Müller cell processes (Kuwabara 1969). These processes could be the site of K^+ siphoning efflux currents. Thus, at least on anatomical grounds, Müller cells are capable of transferring excess K^+ directly from regions of $[K^+]_o$ increase to the ablumenal wall of capillaries. Although K^+ flowing from Müller cells cannot diffuse directly into the capillary lumen (CNS capillaries are largely impermeable to K^+; Hansen et al. (1977)), the K^+ could be actively transported into the blood by the endothelial cell Na^+–K^+ pump (Goldstein 1979).

Cat Müller cells differed from the cells of all other species tested in that their highest conductance was located at the distal end of the cell (see Fig. 3). This K^+ conductance pattern suggests that in cat, excess retinal K^+ may be siphoned through the distal end of Müller cells into the subretinal space surrounding the photoreceptors. This K^+ may either be stored in the subretinal space or transferred across the pigment epithelium by spatial buffering currents (Immel and Steinberg 1986) into the choroidal circulation.

Potassium siphoning in the brain

If Müller cells (the principal glial cells of the retina) direct excess K^+ into capillaries, a similar regulatory process might occur in the brain. This appears to be the case. In the brain, capillaries are completely surrounded by the end-feet of astrocytes. A recent report (Newman 1986*a*) has shown that in freshly dissociated salamander astrocytes, end-feet have a 10-fold higher K^+ conductance than do other regions of the cell. This suggests that excess K^+ in the brain might be preferentially siphoned through astrocyte end-feet into the blood.

Summary

The membrane properties of Müller cells are far more complex than thought just a few years ago. Potassium membrane conductance in Müller cells is distributed nonuniformly over the cell surface. Conductance is concentrated in the end-foot and, in species with vascularized retinae, in the distal cell process. Müller cells also possess four voltage-dependent ion channels. These membrane specializations enable Müller cells to regulate $[K^+]_o$ in the retina by directing excess K^+ into the vitreous humor and, perhaps, into retinal capillaries.

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