Retinal Glia

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Introduction

Glial cells outnumber neurons in the central nervous system (CNS) by ~10 to 1. Traditionally, glia were believed to provide only passive structural and metabolic support for neurons. Recent work has demonstrated, however, that glial cells in the retina as well as in the brain interact actively with neurons and have many essential functions.

There are three principal types of glial cells in the mammalian retina: Müller cells, astrocytes, and microglial cells. Müller cells are the most prominent retinal glial cell. They are a specialized form of radial glia which span nearly the entire depth of the retina. Astrocytes, the second type of retinal macroglial cell, are present only in species having a retinal circulation and, in these species, are restricted largely to the nerve fiber layer at the inner boundary of the retina. Microglia, the third type of retinal glial cell, are present in the nerve fiber layer and the inner and outer plexiform layers of the retina. Oligodendrocytes, the glial cells that form the insulating sheath of myelinated axons in the CNS, are completely absent from the retina, except in those species, including rabbit and guinea pig, possessing myelinated axons in the nerve fiber layer.

Retinal Glial Cell Development and Morphology

Müller Cells

Müller cells differentiate from progenitor cells at the outer margin of the retinal neuroepithelium during the second phase of cell differentiation, following the birth of ganglion cells, horizontal cells, and cones. The developing Müller cells migrate toward the vitreous humor and extend processes towards the inner and outer retinal margins. Their radial processes serve to guide migrating neurons during subsequent retinal development.

In the mature retina, Müller cell somata lie in the middle region of the inner nuclear layer (Figure 1). Single or multiple radial processes extend inwards toward the vitreous and end in enlarged structures termed endfeet. A second cell process extends outward to the outer limiting membrane, where apical microvilli project into the subretinal space. Secondary Müller cell processes project from the main trunk of the cell, surrounding neuronal somata and processes in all retinal layers. Müller cell endfeet terminate at the vitreal border of the retina as well as onto blood vessels, both at the vitreal surface and within the retina.

Müller cells contain numerous glycogen granules which represent the main retinal glucose store. They also contain numerous mitochondria and intermediate filaments, composed both of vimentin and glial fibrillary acidic protein (GFAP). GFAP distribution is normally sparse in Müller cells but is dramatically upregulated following retinal injury.

Astrocytes

Astrocytes migrate into the developing retina from the optic nerve and advance across the retinal surface as the retina matures. The distribution of astrocytes over the surface of the retina is determined by a 'contact-spacing' interaction between cells.

In the mature retina, astrocytes are restricted largely to the nerve fiber layer (Figure 2). They are closely associated with blood vessels and are only present in species having a retinal circulation. Their processes are confined largely to the plane parallel to the retinal surface, although processes sometimes follow blood vessels into deeper retinal layers. Astrocyte processes are terminated by endfeet which contact superficial retinal blood vessels. Astrocytes contain glycogen granules and dense bundles of intermediate filaments composed of GFAP.

Microglia

Microglia are the resident macrophages of the retina. They are derived from blood monocytes and enter the retina along with blood vessels during development. Microglia are normally present in the retina in their dormant state and are found principally in the nerve fiber layer and the inner and outer plexiform layers. They have small somata and short, irregular processes. The cells are normally flat in appearance and have slender hair-like extensions protruding from their processes.

Microglial cells proliferate following retinal injury and differentiate into macrophage-like cells that remove degenerating retinal neurons by phagocytosis. Microglia also phagocytose neurons that die during the course of normal retinal development.

Glial Induction and Guidance of Retinal Blood Vessels

Glial cells induce the formation of blood vessels and guide their growth into the retina. During development, astrocytes migrate into the retina from the

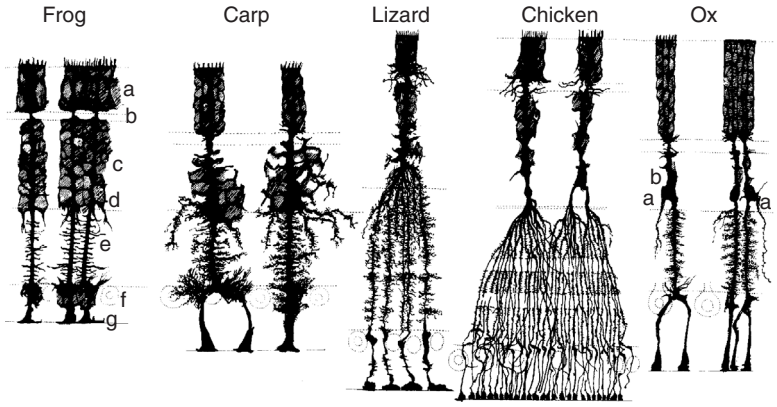

Figure 1 Drawings of Golgi-stained Müller cells from the retinas of several species. Retinal layers, indicated to the right of the frog Müller cells, are (a) outer nuclear layer; (b) outer plexiform layer; (c) inner nuclear layer; (e) inner plexiform layer; (f) ganglion cell layer; (g) nerve fiber layer. The basal endfeet of the Müller cells are seen as enlargements of the processes in the nerve fiber layer. From Ramon y Cajal S (1972) *The Structure of the Retina*. Springfield, IL: Thomas, C.C.

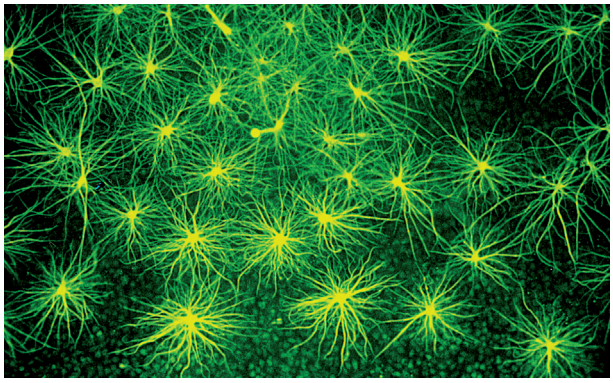

Figure 2 Fluorescence micrograph of astrocytes within the nerve fiber layer of the cat retina. The tissue was labeled with fluorescently tagged antibodies against glial fibrillary acidic protein (GFAP) which forms the intermediate filaments expressed in astrocytes. From Karschin A, Wassle H, and Schnitzer J (1986) Shape and distribution of astrocyte in the cat retina. *Investigative Ophthalmology and Visual Science* 27: 828–831.

optic nerve, first appearing at the optic disk and then advancing outwards across the retinal surface. Retinal blood vessels, which also originate from the optic nerve, grow along newly formed astrocyte processes, which function as templates for angiogenesis. Vessel growth is stimulated by the secretion of vascular endothelial growth factor (VEGF), which is released by glial cells in response to hypoxic conditions generated by neuronal activity. Astrocytes serve as guides for developing vessels as they grow across the inner surface of the retina while Müller cells serve as templates for vessel growth into the retina and across the inner nuclear layer.

Retinal Glial Cell Membrane Properties

Retinal glial cells possess many of the same voltage-gated ion channels and neurotransmitter receptors that are expressed in neurons. These glial channels and receptors play a key role in mediating glia–neuron interactions in the retina. Most research on retinal glial cell properties has been conducted on Müller cells and the following discussion will focus on the properties of these specialized glial cells.

Ion Channels

Müller cells have a high membrane permeability to K^+, which results in a negative resting membrane potential of –80 to –90 mV, near the K^+ equilibrium potential of the cell. Expression of Kir4.1, an inwardly rectifying K^+ channel, is largely responsible for this K^+ membrane permeability. In Kir4.1 knockout animals, which lack Kir4.1 channels, Müller cell input resistance increases from a wild-type level of 25 to 310 MΩ, demonstrating that Kir4.1 channels account for over 90% of the cell membrane conductance. Kir4.1 channels are not distributed uniformly over the cell surface but rather are localized to cell endfeet, which terminate at the vitreal surface of the retina and on retinal blood vessels. The dystrophin–dystroglycan complex plays a critical role in the clustering of K^+ channels to cell endfeet. As discussed below, clustering of K^+ channels contributes to Müller cell clearance of excess K^+ from the retina.

In addition to Kir4.1, Müller cells express a number of other voltage-gated ion channels, including Ca^{2+}-activated K^+ channels, fast inactivating K^+ channels, Ca^{2+} channels (which share some of the properties of L-type Ca^{2+} channels), and Na^+ channels. Müller cells also express aquaporin-4 (AQP4). These water-permeable channels are co-localized with Kir4.1 at Müller cell endfeet. Together, Kir4.1 and AQP4 make up a macromolecular complex that can be visualized in freeze-fracture electron

micrographs of endfoot membranes as orthogonal arrays of particles (OAPs).

Müller cells and astrocytes are extensively coupled to each other by gap junctions, composed of connexin43 and 45 in Müller cells and connexin30 and 43 in astrocytes. Gap junctional coupling imparts both electrical and chemical tracer coupling to these networks of glial cells. Coupling is stronger between astrocytes than between astrocytes and Müller cells. Coupling is very weak (or may not exist) between Müller cells, except in amphibians. Interestingly, coupling between astrocytes and Müller cells, as assessed by tracer spread, is asymmetric, with tracer passing from astrocytes to Müller cells more freely than from Müller cells to astrocytes. In rabbit, astrocytes are coupled to oligodendrocytes as well as to Müller cells.

Neurotransmitter Receptors

Retinal Müller cells and astrocytes express a number of neurotransmitter and neuromodulator receptors. The most prominent among these are P2Y purinergic receptors. Amphibian Müller cells express $P2Y_1$, $P2Y_2$, $P2Y_6$, and $P2Y_{11}$ purinergic receptors. Müller cells of different species also express a number of glutamate receptors, including AMPA (GluR4), NMDA, and metabotropic types. $GABA_A$, acetylcholine, dopamine, noradrenaline, adenosine (A_{2B}), thrombin, and lysophosphatidic acid receptors as well as several neuroactive peptides receptors are expressed. Activation of many of these receptors evokes glial Ca^{2+} increases (see below). Interestingly, in the mammalian retina, glutamate is largely ineffective in evoking Ca^{2+} increases in Müller cells or astrocytes. In contrast, glutamate evokes large Ca^{2+} increases in astrocytes in brain slices and in culture. The insensitivity of retinal glial cells to glutamate may be a specialization to conditions in the retina, where glutamate is released continuously from neurons.

Receptors to a number of growth factors, including basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and nerve growth factor (NGF) are expressed. The effects of these factors are varied, and include the stimulation of DNA synthesis, mitosis, and cell proliferation, expression of cytoskeletal filaments, and the modulation of ion channels. $Endothelin_B$ receptors are expressed in Müller cells and are upregulated following retinal injury.

Transporter systems

The high-affinity glutamate/aspartate transporter (GLAST, also named EAAT1) is present in Müller cells and serves to maintain a low concentration ($<1\ \mu M$) of glutamate in extracellular space. It utilizes the gradients of Na^+, K^+, and H^+ across the plasma membrane to transport glutamate into cells. A high-affinity GABA transporter of the GAT-3 type is also present in Müller cells.

Several acid/base transport systems are expressed in Müller cells. The transporters regulate intracellular pH (pH_i) and can influence extracellular pH. An electrogenic Na^+/HCO_3^- co-transporter is preferentially localized to the basal endfoot of Müller cells. A Na^+/H^+ exchanger and a Cl^-/HCO_3^- anion exchanger are also present in Müller cells. The anion exchanger is of the AE3 type and is localized to the cell endfoot. Intracellular as well as membrane-bound forms of the enzyme carbonic anhydrase (CA) are also expressed in Müller cells at high activity levels. The enzyme contributes to pH and CO_2 regulation in the retina (see below).

Calcium Signaling in Retinal Glial Cells

Calcium Waves

Activation of P2Y and other metabotropic receptors on Müller cells and astrocytes results in the release of Ca^{2+} from internal stores and to increases in intracellular Ca^{2+}. Calcium increases can also be evoked by mechanical or electrical stimulation of glial cells. Stimulation of a single glial cell often leads to the generation of propagated Ca^{2+} waves that travel through many astrocytes and Müller cells (Figure 3). Propagated Ca^{2+} waves travel at a velocity of approximately $23\ \mu m\ s^{-1}$ and can extend outwards for distances as great as $180\ \mu m$.

Glial cell-to-glial cell signaling during Ca^{2+} wave propagation is mediated by two mechanisms: by movement of the intracellular messenger IP_3, which diffuses through gap junctions coupling glial cells together; and by release of ATP, which functions as an extracellular messenger. Calcium wave propagation between astrocytes is mediated by both IP_3 diffusion and by ATP release while signaling between astrocytes and Müller cells and between Müller cells occurs solely by ATP release. The component of glial Ca^{2+} waves mediated by ATP release is blocked by purinergic antagonists.

Light-Evoked Ca^{2+} Signaling

In addition to agonist-evoked Ca^{2+} signals, Müller cells generate spontaneous, transient increases in Ca^{2+} in the absence of any applied stimulus. These endogenously generated Ca^{2+} increases occur at a frequency of 4.6 transients per cell per 1000 s in mammalian Müller cells. The transients range from 2.5 to 6 s in duration and are similar to those observed in astrocytes in the brain.

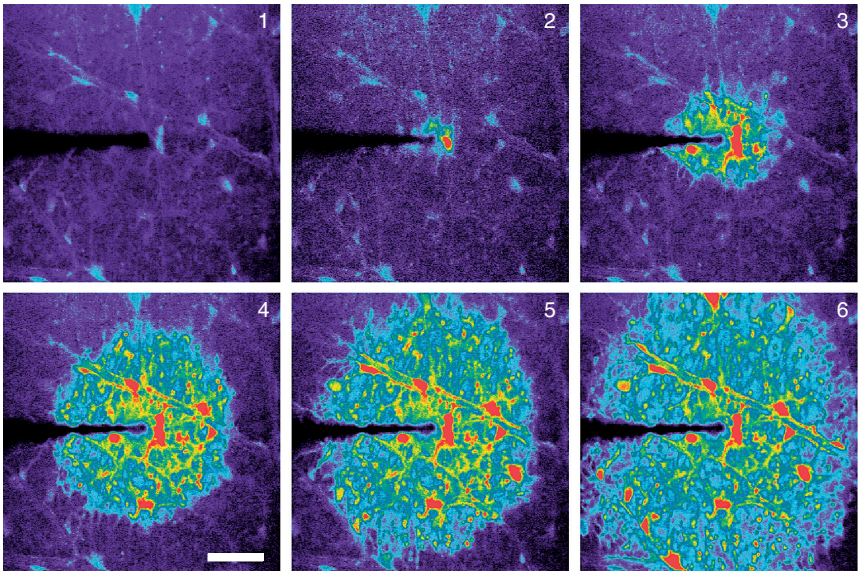

Figure 3 A Ca^{2+} wave propagated through retinal glial cells. Pseudocolor images of Ca^{2+} fluorescence within astrocytes (larger cells) and Müller cells (smaller spots) at the vitreal surface of the retina are shown. The Ca^{2+} wave is evoked by a mechanical stimulus applied to a single astrocyte. The wave is initiated at the stimulated cell (panel 2) and propagates outwards through neighboring astrocytes and Müller cells. Elapsed times following stimulation in panels 1–6 are 0, 0.2, 1.5, 3.5, 5.5, and 9.5 s, respectively. Scale bar = 50 μm. From Newman EA, unpublished.

Neuronal activity, evoked by light flashes, increases the frequency of Ca^{2+} transient generation in Müller cells by 28% (Figure 4). Signaling from activated neurons to Müller cells is mediated by release of ATP from the neurons and activation of glial P2Y purinergic receptors. Light-evoked Ca^{2+} increases are blocked by suramin, a purinergic antagonist, and by apyrase, which hydrolyzes ATP. Light-evoked Müller cell Ca^{2+} increases are also blocked by TTX, indicating that only retinal neurons that generate action potentials, amacrine and ganglion cells, are signaling to glial cells. Light-evoked increases in Müller cell Ca^{2+} transients are greatly potentiated by adenosine, which is a degradation product of ATP. Adenosine potentiation of neuron-glia signaling is of clinical interest as adenosine levels increase in certain pathological states.

Functions of Retinal Glial Cells

Regulation of the Extracellular Microenvironment

One of the principal functions of retinal glial cells is to regulate the composition of the fluid in which neurons are bathed. Neuronal activity results in changes in neurotransmitter, K^+, and H^+ levels in the extracellular space, all of which can, in turn, influence subsequent neuronal excitability. Müller cells play a major role in regulating these extracellular constituents.

Regulation of neurotransmitters Glutamate released from the synaptic terminals of photoreceptors and bipolar cells is removed from extracellular space primarily by uptake into Müller cells, mediated by GLAST, the high-affinity glutamate transporter. Glutamate, once taken up by the glial cells, is converted to glutamine and recycled back to the neuronal terminals where it serves as a substrate for the synthesis of additional neurotransmitter. Glutamate uptake by Müller cells influences the efficacy of synaptic transmission. When the Müller cell transporter GLAST is blocked, the magnitude of bipolar-to-ganglion cell synaptic transmission increases dramatically. Müller cells also express a high-affinity GABA transporter that removes this inhibitory transmitter from extracellular space following release from horizontal cell and amacrine cell synaptic terminals.

Regulation of pH Müller cells contribute to the regulation of extracellular pH (pH_o) in the retina. Neuronal activity results in the alkalinization of the extracellular space, which can dramatically alter the efficacy of synaptic transmission and neuronal excitability. The magnitude of this alkalinization may be reduced by the action of the Müller cell Na^+/HCO_3^- co-transporter. Müller cell depolarization, induced by neuronal activity, generates an acid efflux through the Na^+/HCO_3^- co-transporter, countering the alkalinization generated by the neurons. Müller cells may also regulate pH_o through the action of carbonic anhydrase, which is expressed by Müller cells in both cytoplasmic and membrane-bound forms. Carbonic anhydrase contributes to pH buffering by catalyzing the conversion of H^+ and HCO_3^- to CO_2

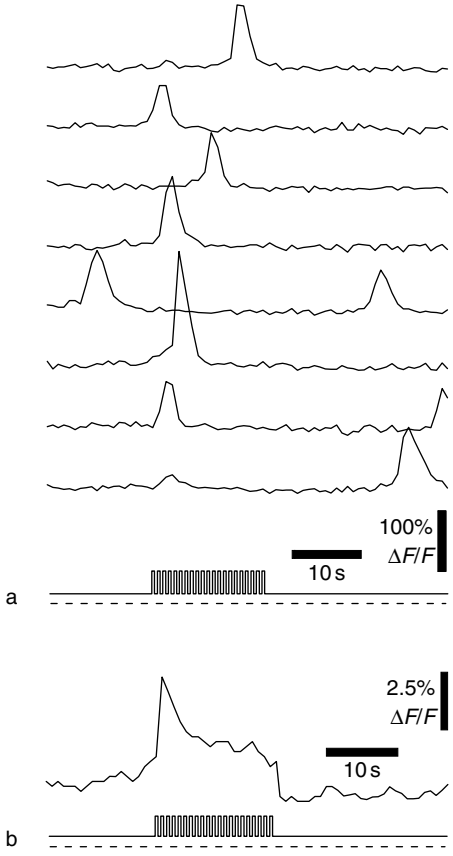

Figure 4 Light-evoked Ca^{2+} signaling in Müller cells. (a) Calcium fluorescence measured simultaneously in eight Müller cells. The retina was exposed sequentially to a uniform dim light, a bright flickering light, and a dim light (the light stimulus protocol is shown at the bottom in (a) and (b)). Calcium transients are more likely to be generated during the flickering light stimulus than during periods of constant illumination. (b) Mean Ca^{2+} fluorescence averaged over 84 trials. The flickering light evokes both a transient and a sustained increase in Ca^{2+} in Müller cells. From Newman EA (2005) Calcium increases in retinal glial cells evoked by light-induced neuronal activity. *Journal of Neuroscience* 25: 5502–5510.

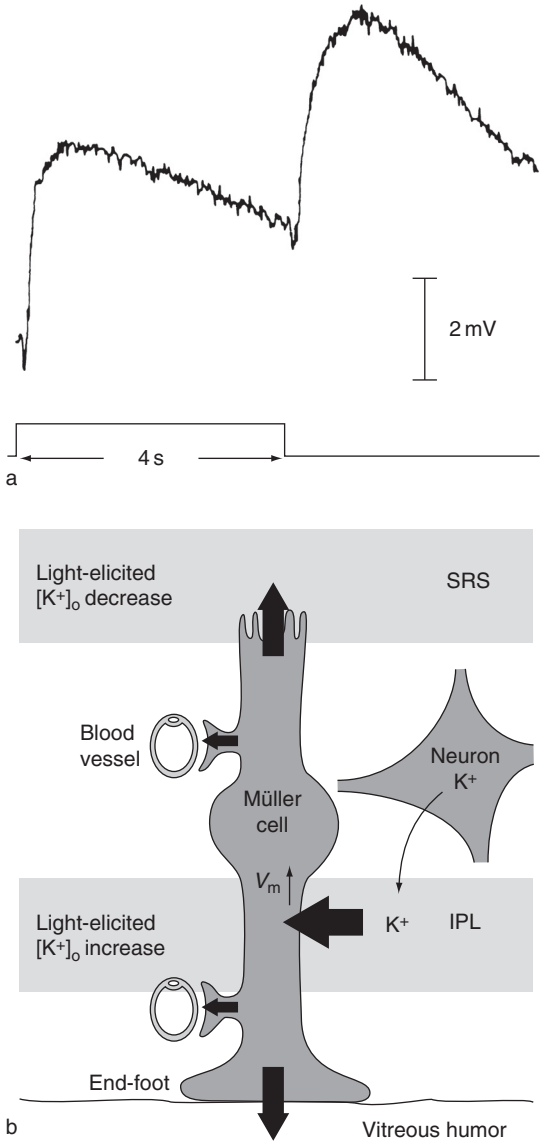

Figure 5 Müller cell regulation of K^+. (a) Light-evoked depolarizations recorded from a Müller cell of the mudpuppy. A 4 s light flash (bottom trace) evokes increases in extracellular K^+ concentration at light ON and OFF, resulting in K^+ influx into Müller cells and to cell depolarization. (b) Potassium siphoning in Müller cells. Active neurons release K^+ into the inner plexiform layer (IPL). The increase in extracellular K^+ concentration evokes a K^+ influx into Müller cells. The resulting cell depolarization generates an equal efflux of K^+ from other cell regions, into the vitreous humor, the subretinal space (SRS) and onto blood vessels. This K^+ current flowing through Müller cells reduces the initial K^+ increase in the IPL. (a) From Karwoski and Proenza (1977) Relationship between Müller cell responses, a local transretinal potential and potassium flux. *Journal of Neurophysiology* 40: 244–259. (b) From Newman (1966) *Neuroscientist* 2: 110–119.

and H_2O. Blocking the action of the enzyme leads to increases in the light-evoked pH_o alkalinization.

Regulation of potassium Müller cells play a key role in regulating extracellular K^+ ($[K^+]_o$) within the retina. Light-evoked neuronal activity results in increases in $[K^+]_o$ in the inner and outer plexiform layers and to a $[K^+]_o$ decrease in the distal retina. These $[K^+]_o$ variations will change the membrane potential of retinal neurons, altering their excitability. The $[K^+]_o$ variations are buffered by K^+ currents flowing through Müller cells, a process termed 'K^+ siphoning,' which is a specialized form of K^+ spatial buffering. Potassium released from active neurons results in an influx of K^+ into Müller cells. The K^+ influx depolarizes Müller cells (Figure 5(a)) and drives out an equal quantity of K^+ from other cell regions, primarily from cell endfeet, which have a high K^+ conductance. Potassium is released from basal endfeet into the vitreous humor, which acts as a large K^+ sink, and from apical processes into the subretinal space, where it counters the light-evoked $[K^+]_o$ decrease generated in this region (Figure 5(b)).

The influx and efflux of K^+ in Müller cells during the K^+ siphoning process occurs largely through Kir4.1 inwardly rectifying K^+ channels. The voltage- and K^+-dependent properties of these channels enhance the K^+ siphoning process; channel conductance increases with increased $[K^+]_o$, resulting in greater siphoning currents and a more rapid transfer of K^+ to the vitreous humor and the subretinal space. When Müller cell Kir4.1 channels are blocked by Ba^{2+}, the siphoning current is interrupted and $[K^+]_o$ regulation in the retina is compromised.

Generation of the electroretinogram A consequence of K^+ current flow through Müller cells is the generation of extracellular field potentials within the retina. These light-evoked potentials can be recorded with an electrode on the cornea as components of the electroretinogram (ERG). For many years, the b-wave, the most prominent component of the ERG, was believed to be generated by K^+ current flow through Müller cells. However, if K^+ siphoning is prevented by blocking Müller cell Kir channels with Ba^{2+}, or if the channels are eliminated by employing Kir4.1 knockout animals, the b-wave is not reduced. These experiments demonstrate conclusively that Müller cells do not generate the ERG b-wave. The b-wave is generated, instead, by bipolar cells, as originally suggested by Tomita.

Other components of the ERG are generated by light-evoked K^+ current flow through Müller cells, however. The slow PIII response, the retinal component of the ERG c-wave, is generated by Müller cell K^+ current flow established by a decrease in $[K^+]_o$ in the distal retina. Müller cells also generate the scotopic threshold response, a rod-driven response generated at the ON of light in mammals, and the M-wave, a negative response with prominent ON and OFF components. Both responses are generated by K^+ current flow through Müller cells established by $[K^+]_o$ increases in the inner plexiform layer.

Modulation of Neuronal Activity

In recent years, it has become clear that glial cells in the CNS modulate neuronal activity by releasing gliotransmitters. In the retina, stimulation of Müller cells results in changes in light-evoked spiking of ganglion cells. Spike activity can either be potentiated or depressed following glial cell stimulation and the initiation of Ca^{2+} waves in retinal glial cells. It is likely that Müller cells, in particular, modulate neuronal activity by several different mechanisms, two of which are described below.

Inhibition of ganglion cells Selective stimulation of Müller cells by agonist ejection evokes large Ca^{2+} increases in these cells and subsequent hyperpolarization of adjacent ganglion cells (Figure 6(a)). The hyperpolarization can be sufficiently strong to completely block the generation of action potentials (Figure 6(b)). The ganglion cell hyperpolarization is mediated by ATP release from the Müller cells. Released ATP is rapidly converted to adenosine by ecto-ATPases and ecto-nucleotidases. Adenosine, in turn, activates A_1 adenosine receptors on the ganglion cells, leading to the opening of K^+ channels and to cell hyperpolarization.

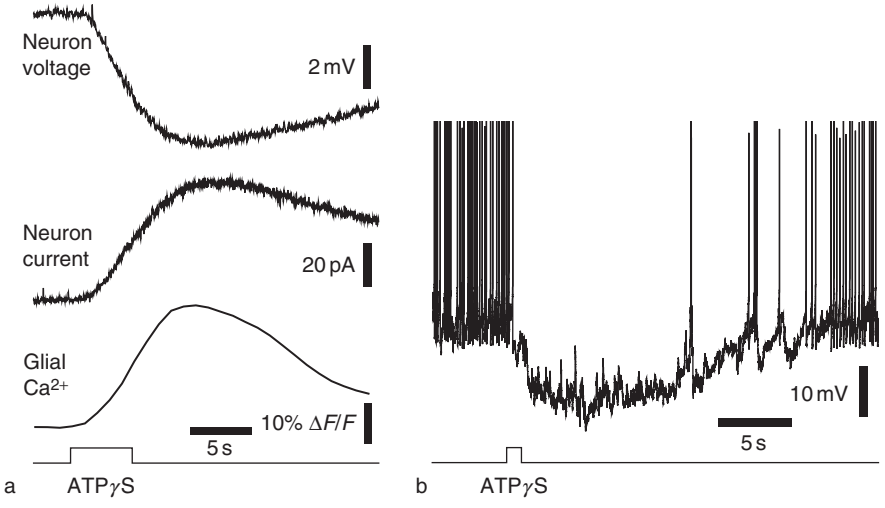

Figure 6 Glial cell inhibition of action potential generation in ganglion cells. (a) Ejection of ATPγS onto the retinal surface evokes a Ca^{2+} increase in glial cells (glial Ca^{2+}). This Ca^{2+} increase is associated with a hyperpolarization (neuron voltage) and an outward current (neuron current) in a neighboring ganglion cell. (b) ATPγS stimulation of glial cells hyperpolarizes a ganglion cell and blocks the generation of action potentials in the cell. From Newman EA (2003) Glial cell inhibition of neurons by release of ATP. *Journal of Neuroscience* 23: 1659–1666.

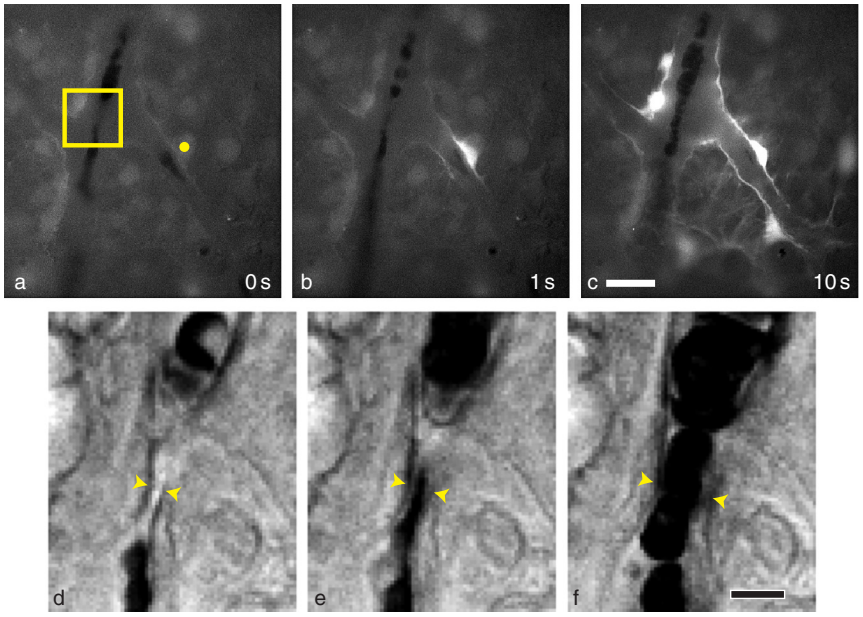

Figure 7 Glial cell-evoked dilation of a neighboring blood vessel. (a–c) Fluorescence images showing Ca^{2+} concentration within retinal glial cells. (d–f) Infrared differential interference contrast (IR-DIC) images showing the arteriole within the region indicated in (a). Photolysis of caged-Ca^{2+} in the glial cell indicated by the circle in (a) evokes a Ca^{2+} increase that propagates from the stimulated cell into neighboring glial cells surrounding the blood vessel (a–c). Glial cell stimulation results in the dilation of the adjacent arteriole (d–f). From Metea MR and Newman EA (2006) Glial cells both dilate and constrict blood vessels. A mechanism of neurovascular coupling. *Journal of Neuroscience* 26: 2862–2870.

D-serine regulation of NMDA receptors Müller cell stimulation may also lead to the release of D-serine and to potentiation of NMDA receptor neurotransmission in the retina. Müller cells contain D-serine, an endogenous NMDA receptor co-agonist, and serine racemase, the synthetic enzyme for D-serine. Stimulation of brain astrocytes results in D-serine release and a similar release of D-serine may occur in retinal Müller cells.

Regulation of Blood Flow

Light stimulation results in an increase in blood flow in retinal arteries, bringing increased oxygen and nutrients to activated neurons. Müller cells mediate neuron to blood vessel signaling, a process termed neurovascular coupling. When Müller cells are selectively stimulated, neighboring arterioles either dilate or constrict (Figure 7). Vasodilation is mediated by production of EETs while vasoconstriction is mediated by production of 20-HETE. Both vasoactive agents are metabolites of arachidonic acid. Light stimulation also evokes either vasodilation or constriction by generation of the same two arachidonic acid metabolites. When neuron to Müller cell signaling is blocked by a purinergic antagonist, light-evoked vasomotor responses are also blocked, indicating that Müller cells mediate neurovascular coupling.

Metabolic and Trophic Support of Neurons

Müller cells play an active role in supporting neuronal metabolism. Glucose is metabolized in Müller cells to lactate, which is then transferred to neurons where it serves as a primary energy source for oxidative metabolism. Müller cells also contain large reserves of glycogen, which serve as a source of glucose during times of high metabolic activity.

Retinal glial cells secrete a number of growth factors which have trophic effects on retinal neurons and blood vessels. Basic fibroblast growth factor (bFGF), which promotes photoreceptor survival, is synthesized by Müller cells and retinal astrocytes. Müller cells also secrete a number of other growth factors including brain-derived neurotrophic factor, NGF, neurotrophin-3, neurotrophin-4, and glial cell line-derived neurotrophic factor. Both Müller cells and astrocytes synthesize VEGF, which plays an essential role in the development of the retinal vasculature.

See also: Astrocyte: Calcium Signaling; Fovea: Primate; Retina: An Overview; Retinal Color Mechanisms; Retinal Development: An Overview; Retinal Development: Cell Type Specification; Retinal Pharmacology: Inner Retinal Layers.

Further Reading

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