The Müller cell: a functional element of the retina

Eric Newman and Andreas Reichenbach

Müller cells are the principal glial cells of the retina, assuming many of the functions carried out by astrocytes, oligodendrocytes and ependymal cells in other CNS regions. Müller cells express numerous voltage-gated channels and neurotransmitter receptors, which recognize a variety of neuronal signals and trigger cell depolarization and intracellular Ca^{2+} waves. In turn, Müller cells modulate neuronal activity by regulating the extracellular concentration of neuroactive substances, including: (1) K^+, which is transported via Müller-cell spatial-buffering currents; (2) glutamate and GABA, which are taken up by Müller-cell high-affinity carriers; and (3) H^+, which is controlled by the action of Müller-cell Na^+–HCO_3^- co-transport and carbonic anhydrase. The two-way communication between Müller cells and retinal neurons indicates that Müller cells play an active role in retinal function.

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OF THE TWO principal types of macroglial cells in the brain, oligodendrocytes are completely absent in the retinae of most species and astrocytes are present only in mammalian species, and then only in the nerve fiber layer. In their stead, the Müller cell serves as the principal glial cell of the retina. It performs many of the functions subserved by astrocytes, oligodendrocytes and ependymal cells in other regions of the CNS.

Just as the retina has proved a valuable and accessible tissue for elucidating the cellular and network properties of neurons, the Müller cell has served as an important model system for investigations of glial cells. During the past quarter century, the physiological and morphological properties of Müller cells have been studied extensively. (See Refs 1–3 for recent reviews.) The amphibian retina, with its large, easily dissociated Müller cells, has been a particularly useful preparation in studies of cell function.

Müller-cell morphology

Müller cells are radial glial cells which span the entire depth of the neural retina[4–6] (Fig. 1). They are present in the retinae of all vertebrate species. Radiating from the soma (in the inner nuclear layer) is an inwardly directed process that terminates in an expanded endfoot at the inner border of the retina, adjacent to the vitreous humor. Also projecting from the soma is an outwardly directed process that ends in the photoreceptor layer. Microvilli project from this apical process into the subretinal space surrounding the photoreceptors. In mammalian species with vascularized retinae, *en passant* endfeet contact and surround blood vessels within the retina while the endfeet of some cells next to the vitreous humor terminate on surface blood vessels. Secondary processes branching from the main trunk of Müller cells form extensive sheaths that surround neuronal cell bodies, dendrites, and, in the optic-fiber layer, the axons of ganglion cells.

Müller-cell physiology

Müller cells, like other glial cells, express a wide variety of voltage-gated ion channels[8–12]. Their membrane conductance is dominated by inward-rectifier K^+ channels[9,13], which give these cells an extremely low membrane resistance, ranging from 10 to 21 MΩ in different species[14]. The inward-rectifier K^+ channels are distributed in a highly non-uniform manner over the cell surface. In amphibian species, 80–90% of all channels are localized to the endfoot at the retinal surface, while in mammalian species with vascularized retinae, channels are localized to the surface endfoot, soma, and, in the cat, apical microvilli[14]. Müller cells of various species also possess delayed-rectifier, fast-inactivating and Ca^{2+}-activated K^+ channels, Na^+ channels, and Ca^{2+} channels[8,11,12]. These channels probably do not modulate cell membrane potential significantly, however, as their cellular conductances are much smaller than that of the K^+ inward-rectifier channel. Amphibian Müller cells are coupled together by gap junctions[4], while mammalian cells are coupled to astrocytes lying at the surface of the retina[15].

Müller cells also express many types of neurotransmitter receptors, including a $GABA_A$ receptor[16,17] and several types of glutamate receptors[18–20]. They possess high-affinity uptake carriers for glutamate[21–23] and GABA (Refs 21,24).

Müller cells of the salamander express a number of acid–base transport systems, including an electrogenic Na^+–HCO_3^- co-transporter, an anion exchanger and a Na^+–H^+ exchanger[25,26]. They also have high levels of carbonic anhydrase, an enzyme that plays an important role in pH regulation by catalysing the hydration of CO_2 to H^+ and HCO_3^- (Refs 27,28).

How do these physiological properties contribute to glio–neuronal communication within the retina? Does neuronal activity result in changes in Müller-cell function? Can Müller cells modulate neuronal activity? These questions will be explored in this review.

Eric Newman is at the Dept of Physiology, University of Minnesota, Minneapolis, MN 55455, USA, and Andreas Reichenbach is at the Paul Flechsig Institute for Brain Research, Dept of Neurophysiology, Leipzig University, D-04109 Leipzig, Federal Republic of Germany.

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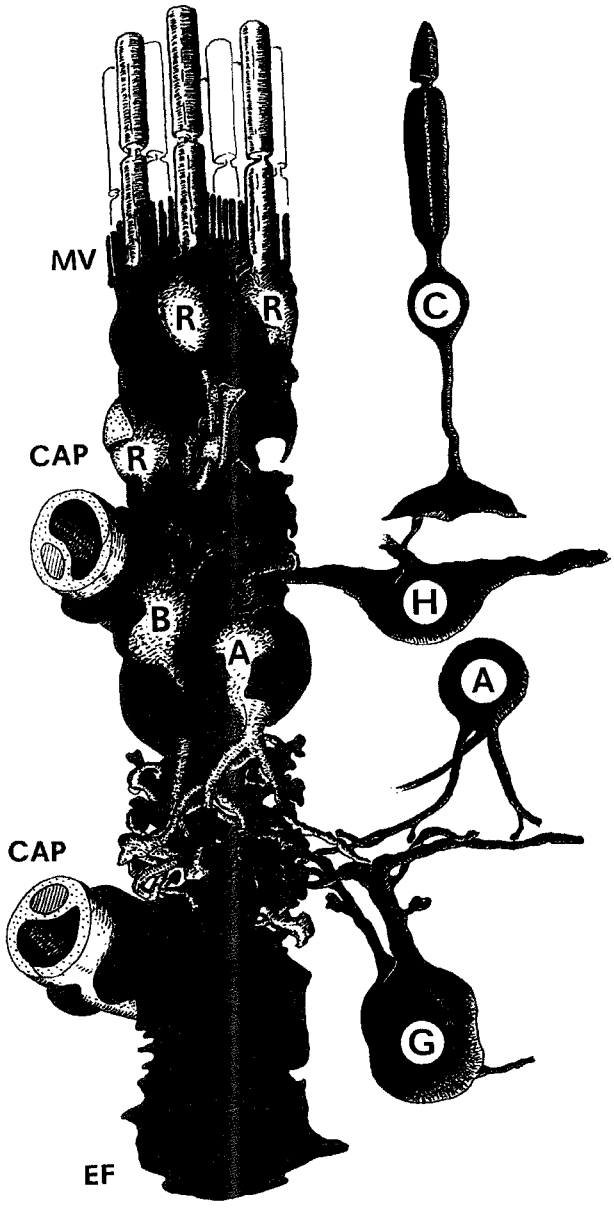

Fig. 1. ***Drawing of Müller cell in the mammalian retina.*** *Neuronal somata and processes are ensheathed by the processes of a Müller cell (shaded blue). Abbreviations: A, amacrine cell; B, bipolar cell; C, cone photoreceptor cell; CAP, capillary; EF, Müller-cell endfoot; G, ganglion cell; H, horizontal cell; M, Müller cell; MV, Müller-cell microvilli; R, rod photoreceptor cell.* Modified from Ref. 7.

Recognition of neuronal signals by Müller cells

Potassium

Many substances released from active neurons, including K^+, neurotransmitters and metabolites (such as CO_2), can potentially modulate Müller-cell behavior. Important signaling functions have been ascribed to increases in the extracellular K^+ concentration ($[K^+]_o$)[29]. Increases in $[K^+]_o$ result in rapid cell depolarization in Müller cells[30] and in slower activation of the (Na^+,K^+)-ATPase[31]. Localized increases in $[K^+]_o$ generate K^+ spatial-buffering currents within Müller cells, leading to the redistribution of excess extracellular K^+ and to the generation of field potentials within extracellular space[32]. Enhanced $[K^+]_o$ has also been shown to stimulate glycogenolysis in mammalian Müller cells[7], and can trigger increases in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$)[19,33].

Neurotransmitters

Neurotransmitters released from neurons constitute a second signaling mechanism by which neuronal activity can modulate Müller cells. Müller cells express a variety of receptors, including those for amino acids, catecholamines, neuroactive peptides, hormones and growth factors[16–20,34–36]. Generally, these receptors display high binding affinities and pharmacological properties similar to those described in neurons. In most cases where electrophysiological studies have been performed, ligand binding elicits cell depolarization, caused by direct opening of ion channels, as in the case of the $GABA_A$ receptor in the skate and baboon[16,17], or by second-messenger systems. For example, increases in glutamate, dopamine[18,36] and thrombin[10] are all believed to depolarize Müller cells by a second messenger-linked reduction in K^+ conductance in the cell.

Carbon dioxide

Active retinal neurons (particularly photoreceptors in the dark) release CO_2, leading to substantial increases in extracellular P_{CO_2}. Such increases can result in rapid intracellular acidification in Müller cells. This acidification is generated largely by the action of the enzyme carbonic anhydrase[28], and might modulate several pH-dependent functions of the Müller cell, including carrier-mediated glutamate uptake[37], acid–base transport, and gap-junctional coupling.

Signaling within Müller cells

Calcium

Neurotransmitters and ions released by neurons can activate second-messenger systems within Müller cells. One prominent example is the elevation of $[Ca^{2+}]_i$ within Müller cells, which can be triggered by K^+-induced depolarization as well as by activation of ligand-gated receptors[19,33]. In dissociated salamander Müller cells, raising $[K^+]_o$ results in an influx of Ca^{2+} (Ref. 33), presumably through voltage-gated Ca^{2+} channels, while in cultured rabbit cells, glutamate elicits a Ca^{2+} influx through non-NMDA receptors[19]. In the absence of external Ca^{2+}, stimulation of salamander Müller cells leads to the release of Ca^{2+} from internal stores and to increases in $[Ca^{2+}]_i$ which begin in the apical end of the cell and travel in a wave-like manner towards the cell endfoot[33] (Fig. 2). These intracellular Ca^{2+} waves can be stimulated by elevated K^+, glutamate and ATP, as well as by caffeine and ryanodine. It is interesting to speculate that these Ca^{2+} waves provide a second pathway, independent of the neuronal network, for signals to be relayed from the outer to the inner retina.

In addition to the release of Ca^{2+} from internal stores, several other second-messenger systems can be activated by signals derived from neurons. These include the inositol phosphate and adenylate cyclase–cAMP systems[34,35].

Control of neuronal microenvironment by Müller cells

Glial cells can modulate neuronal activity by controlling the concentration of neuroactive substances in the extracellular fluid bathing CNS cells. The concentrations of neurotransmitters and K^+, for example, are regulated by glial-cell homeostatic mechanisms. Studies on Müller cells have provided some of the

clearest examples of glial-cell control of the neuronal microenvironment.

Potassium

One of the most thoroughly characterized functions of Müller cells is their regulation of $[K^+]_o$ in the retina[3,29]. Stimulation of the retina with light results in neuronal activation and increases in $[K^+]_o$ in the two retinal synaptic layers (the inner and outer plexiform layers)[30]. These light-elicited increases in $[K^+]_o$ must be cleared rapidly in order to limit fluctuations in neuronal excitability. Müller cells remove excess K^+ from extracellular space by several mechanisms. As in other glial cells, K^+ is taken up and temporarily stored in Müller cells, with influx occurring by both passive (K^+ and Cl^- uptake) and active [(Na^+,K^+)-ATPase] processes[31]. Potassium is also removed from extracellular space by a spatial-buffering mechanism[32]: increases in $[K^+]_o$ within the two plexiform layers depolarize Müller cells and lead to K^+ efflux from other Müller-cell regions (Fig. 3). The resulting K^+ spatial-buffering current effectively redistributes extracellular K^+ from regions where $[K^+]_o$ is initially high to regions where it is low.

Spatial-buffering currents pass through inward-rectifying K^+ channels, the predominant channel in Müller cells[9,13]. Unlike other voltage-gated channels, these channels are open at the resting membrane potential. The voltage- and K^+-dependent properties of these channels serve to augment the spatial-buffering currents; in regions where $[K^+]_o$ is raised, channel conductance is increased[9]. Neurotransmitters and other factors can modulate the conductance of Müller-cell K^+ channels[10,18,36], suggesting that $[K^+]_o$ regulation by Müller cells is under neuronal control. Even a modest decrease in K^+ inward-rectifier conductance would reduce K^+ spatial-buffering currents and diminish $[K^+]_o$ regulation by Müller cells.

In amphibian species, a large fraction of all inward-rectifying K^+ channels in Müller cells is localized to the endfoot at the retinal surface[14,38]. Thus, K^+ spatial-buffering current preferentially exits from Müller cells at the endfoot. The result of this specialized form of spatial buffering, termed 'K^+ siphoning'[32], is that most excess K^+ released by active neurons is transferred to the vitreous humor, which acts as a large K^+ sink[39,40]. The pattern of the spatial-buffering current is more complex in mammalian species, with excess K^+ directed to both the vitreous humor and the fluid space surrounding the photoreceptors[41] (the subretinal space; Fig. 3).

Modeling studies of amphibian and mammalian retinae indicate that K^+ siphoning is 1.6–3.7 times more effective in clearing excess K^+ from the retina than is K^+ diffusion through extracellular space[31,32,42]. Experimental studies demonstrate directly that K^+ siphoning is a key mechanism for regulating retinal $[K^+]_o$. The light-elicited increases in $[K^+]_o$ more than double in the frog[40], and more than triple in the cat[41] when K^+-siphoning currents are blocked by Ba^{2+} (Fig. 4).

Neurotransmitters

Glial cells play an important role in removing neurotransmitters from extracellular space following their release from synaptic terminals. This uptake is essential for terminating synaptic transmission as well as for preventing the spread of transmitters away from the synaptic cleft. Müller cells possess high-affinity uptake carriers for many transmitters and are believed to regulate extracellular transmitter levels in the retina. Müller cells processes ramify extensively in the two synaptic layers of the retina, suggesting the importance of these cells for removing neurotransmitters from extracellular space.

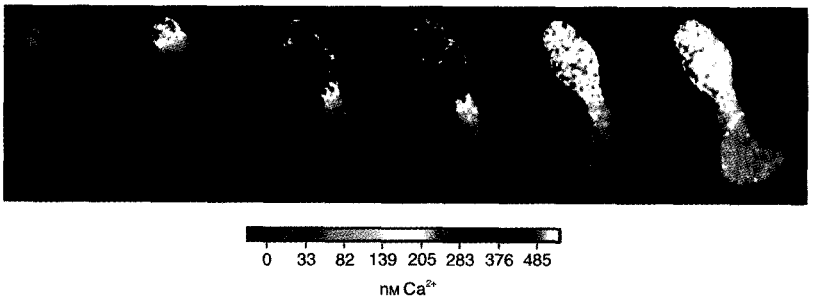

Fig. 2. ***Calcium wave in a dissociated salamander Müller cell.*** *The Ca^{2+} wave, elicited by addition of 100 nM ryanodine in the absence of extracellular Ca^{2+}, begins at the apical end of the cell and travels towards the cell endfoot. The intracellular Ca^{2+} concentration is imaged using the Ca^{2+}-indicator dye fura-2. Images were obtained at 7 s intervals.* From Ref. 33.

Glutamate

The high-affinity glutamate carrier of Müller cells has been studied extensively[21–23]. Expression of one such carrier, the L-glutamate–L-aspartate transporter (GLAST), has been demonstrated in rat Müller cells[43].

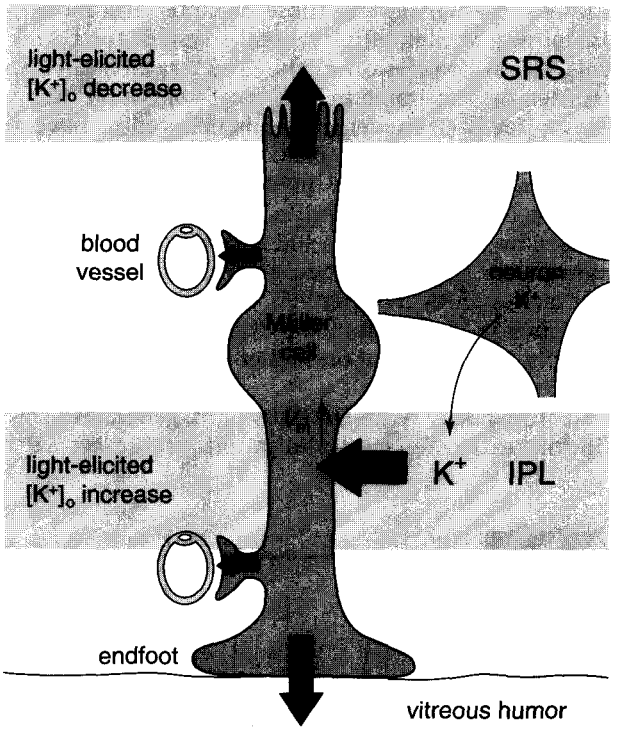

Fig. 3. ***Potassium spatial-buffering in Müller cells.*** *Potassium, released from active neurons into the inner plexiform layer, is removed from extracellular space by a K^+-siphoning current flow through the Müller cell. The excess K^+ entering the cell generates a depolarization and drives out an equal amount of K^+ from other cell regions. In vascularized mammalian retinae, K^+ efflux occurs from several cell regions having a high density of K^+ channels: (1) the endfoot at the inner surface of the retina; (2) the apical end of the cell; and (3) the endfeet terminating on blood vessels. Heavy arrows indicate K^+ fluxes into and out of the Müller cell. Abbreviations: IPL, inner plexiform layer; SRS, subretinal space; V_m, cell membrane potential. A second $[K^+]_o$ increase, in the outer plexiform layer, has been omitted for clarity. The apical end of the cell is shown at the top.* From Ref. 3.

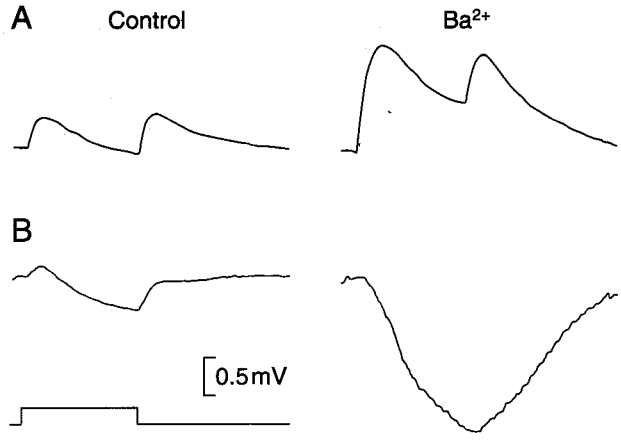

Fig. 4. *Müller cells regulate $[K^+]_o$ in the retina.* **(A)** *Light-elicited increases in the extracellular K^+ concentration ($[K^+]_o$) are recorded within the inner plexiform layer of the cat retina. When Müller-cell K^+ channels are blocked by the addition of 3 mM Ba^{2+}, thus reducing spatial-buffering currents, the light-elicited increase in $[K^+]_o$ more than triples.* **(B)** *The light-elicited decrease in $[K^+]_o$ in the subretinal space more than quadruples when Ba^{2+} is added, indicating that spatial-buffering currents normally transfer excess K^+ from the retina to the subretinal space as well as to the vitreous humor. The timecourse of the light stimulus, 4 s in duration, is indicated in the bottom trace.* Modified from Ref. 41.

The Müller-cell glutamate carrier has a complex stoichiometry and questions concerning its details remain. In one scheme, the inward transport of one glutamate molecule and two Na^+ is coupled to the outward transport of one K^+ and one OH^- (Ref. 44). Because the transporter is electrogenic, glutamate uptake is voltage-dependent; cell depolarization slows down or even reverses uptake of the excitatory amino acid[45] (Fig. 5). In addition, because OH^- is transported along with glutamate, uptake is pH dependent and is accompanied by an extracellular alkalinization[44].

GABA

Müller cells, including those of rabbit and mouse, also possess a high-affinity uptake system for GABA (Refs 21,46). Expression of the GABA carrier, GAT-3, has been demonstrated in Müller cells of the rat[47]. The transporter is electrogenic, and is believed to have a stoichiometry of two Na^+ plus one Cl^- plus one GABA molecule, all transported inwardly[24,48]. GABA is the primary inhibitory transmitter of the retina, and is released by horizontal cells and amacrine cells. In some mammalian species, including the rabbit, horizontal cells lack a GABA transporter[49], and the responsibility for removing GABA from the extracellular space presumably falls largely upon Müller cells.

pH and CO_2

Neuronal activity, triggered by light, generates a significant extracellular alkalinization in the retina[50]. This pH shift is thought to be regulated by Müller cells[3,26]. Salamander Müller cells possess a Na^+–HCO_3^- co-transport system which has a stoichiometry of approximately three HCO_3^- transported along with one Na^+ (Ref. 25). Because the transporter is electrogenic, cell depolarization results in an efflux of acid equivalents[26]. Thus, during periods of neuronal activity, when Müller cells are depolarized by increased $[K^+]_o$, the activity of the Na^+–HCO_3^- co-transport system will acidify extracellular space (Fig. 6). This acidification helps to muffle extracellular pH variations by partially neutralizing the neuronally generated extracellular alkalinization.

Müller cells might also regulate extracellular pH in the retina by facilitating the removal of CO_2 produced by neuronal activity. Excess retinal CO_2 will be rapidly converted to HCO_3^- and H^+ by the enzyme carbonic anhydrase, which is found both within Müller cells and on the cell surface[27,28]. The HCO_3^- might then be transported to the vitreous humor by Na^+–HCO_3^- co-transporters, which, in the salamander, are localized preferentially at the cell endfoot[25,26]. This homeostatic mechanism, termed 'CO_2 siphoning'[28] for its resemblance to K^+ siphoning, has yet to be demonstrated experimentally. Such a scheme is consistent, however, with the observation that in the frog inhibitors of carbonic anhydrase result in an enhancement of light-elicited pH variations within the retina[50].

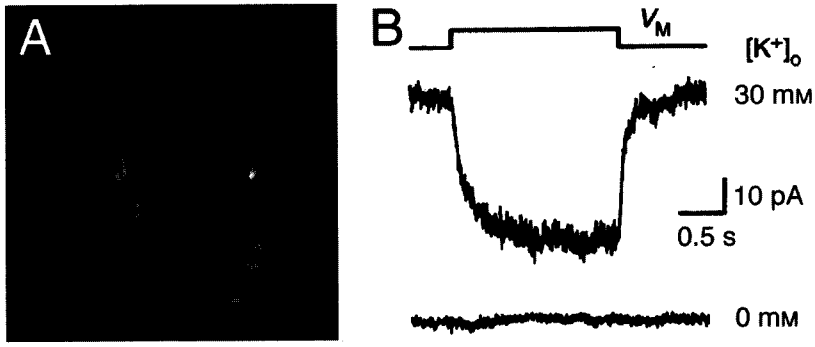

Fig. 5. *Depolarization-elicited release of glutamate generated by reversal of the Müller-cell glutamate uptake carrier.* **(A)** *Release of glutamate from a Müller cell (right) is monitored by recording glutamate-elicited currents from an adjacent Purkinje cell (left).* **(B)** *Depolarizing a Müller cell from –60 to +20 mV (top trace) elicits an inward current in the Purkinje cell (middle trace). The Purkinje-cell current is generated by activation of its glutamate-containing receptors. When extracellular K^+ is omitted (bottom trace) reversed glutamate transport by Müller cells is blocked and no glutamate current is recorded in the Purkinje cell.* Photograph in A, courtesy of Brian Billups and David Attwell; B, modified from Ref. 37.

Müller-cell modulation of neuronal activity

Müller cells, by controlling the concentration of neuroactive substances in extracellular space, can significantly modulate neuronal activity. A reduction in the uptake of glutamate or GABA will lead to enhancement of synaptic transmission. The accumulation of K^+ in extracellular space, resulting from a reduction in K^+ removal by Müller cells, will also lead to changes in neuronal excitability. Variations in pH can modulate neuronal activity as well. Even the small depolarization-induced extracellular acidification generated by Müller cells can have a dramatic inhibitory effect on synaptic transmission. For example, an acidification of 0.05 pH units in the salamander retina produces a 24% reduction in synaptic transmission between photoreceptors and second-order neurons[51].

Neurotransmitter release

Müller cells, in addition to influencing neuronal activity by regulating the levels of substances in the neuronal microenvironment, might control neuronal activity more directly. When depolarized sufficiently, glutamate uptake by salamander Müller cells is reversed and glutamate is actually released into extracellular space[45] (Fig. 5). This release might contribute to excitotoxic damage to neurons under pathological

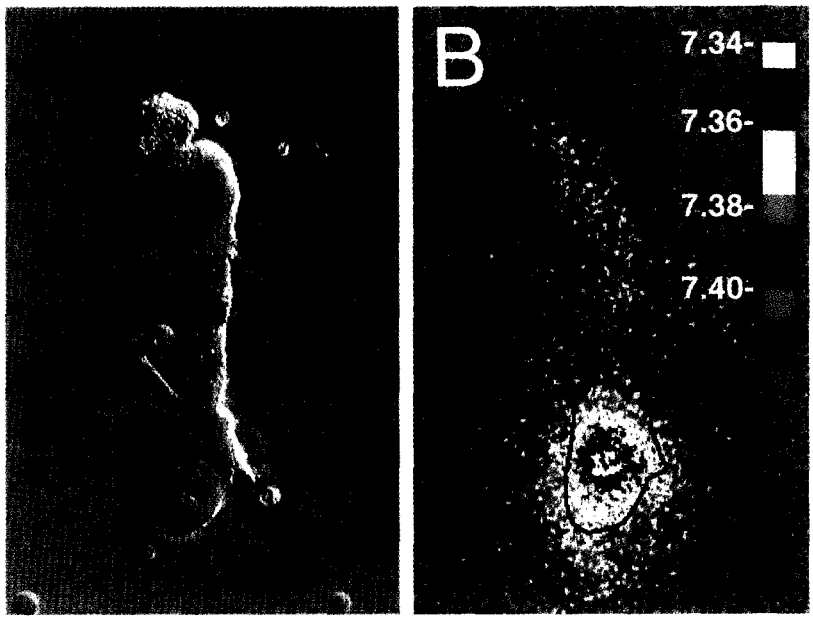

Fig. 6. ***Depolarization-induced acid efflux generated by the Müller-cell Na^+–HCO_3^- co-transport system.*** **(A)** *Micrograph of a dissociated salamander Müller cell. Scale bar, 20 μm.* **(B)** *Image of extracellular pH for the cell shown in A, measured by imaging the pH-indicator dye BCECF (2′,7′-biscarboxyethyl-5(6)carboxyfluorescein) fixed to a coverslip. The cell Na^+–HCO_3^- co-transporter is activated by depolarization ($[K^+]_o$ raised from 2.5 to 50 mM). The resulting acid efflux is largest at the cell endfoot, indicating that co-transporters are preferentially localized to this cell region. The pseudocolor image is calibrated in pH units (bar at right).* From Ref. 25.

conditions. Depolarization can also lead to the release of GABA from rat Müller cells[52]. It should be noted, however, that the release of glutamate and GABA from Müller cells has been demonstrated only in cells that have been pre-loaded with the transmitters. It remains to be shown that transmitter release occurs under *in vivo* conditions.

Nitric oxide (NO) synthase is expressed in Müller cells of salamander and fish[53], although release of NO from Müller cells has yet to be demonstrated. It is interesting to speculate that the Ca^{2+} waves observed in Müller cells might trigger the release of neurotransmitters, as is apparently the case for the release of glutamate from cultured astrocytes[54]. Such 'gliotransmitters' could potentially modulate neuronal activity.

Metabolic support

Retinal neurons are nourished by Müller cells. Glycogen stores in the retina are restricted to Müller cells[55]. Glycogenolysis in Müller cells is stimulated by neuronal activity[7], and the direct transfer of lactate from Müller cells to neurons has been observed in the guinea pig[56]. Müller cells might also regulate blood flow in retinal vessels in response to changes in neuronal activity. Retinal blood vessels are almost completely surrounded by Müller-cell endfeet which can release K^+, acid equivalents, and perhaps NO (all vasodilators) when Müller cells depolarize[26,53,57].

Moreover, glial uptake of glutamate and GABA are important initial steps in the process of transmitter recycling. Glutamine synthetase, an enzyme that transamidates glutamate to glutamine, is localized exclusively to Müller cells in the retina[27]. The glutamine synthesized by Müller cells is recycled back to retinal neurons, where it serves as a precursor for the synthesis of additional neurotransmitter. Inhibition of the glial enzyme in the rabbit causes a complete loss of neuronal function[58], demonstrating the crucial role that Müller cells play in neurotransmission in the retina.

Concluding remarks

To date, research on Müller cells has been concerned largely with their cellular properties and their contributions to the regulation of the retinal microenvironment. These distinctive glial cells recognize a variety of neuronal signals and actively control levels of K^+, H^+ and neurotransmitters in extracellular space. In the coming years, research will provide additional insights into the role of Müller cells in modulating neuronal activity and retinal function.

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Microglia: a sensor for pathological events in the CNS

Georg W. Kreutzberg

The most characteristic feature of microglial cells is their rapid activation in response to even minor pathological changes in the CNS. Microglia activation is a key factor in the defence of the neural parenchyma against infectious diseases, inflammation, trauma, ischaemia, brain tumours and neurodegeneration. Microglia activation occurs as a graded response *in vivo*. The transformation of microglia into potentially cytotoxic cells is under strict control and occurs mainly in response to neuronal or terminal degeneration, or both. Activated microglia are mainly scavenger cells but also perform various other functions in tissue repair and neural regeneration. They form a network of immune alert resident macrophages with a capacity for immune surveillance and control. Activated microglia can destroy invading micro-organisms, remove potentially deleterious debris, promote tissue repair by secreting growth factors and thus facilitate the return to tissue homeostasis. An understanding of intercellular signalling pathways for microglia proliferation and activation could form a rational basis for targeted intervention on glial reactions to injuries in the CNS.

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THERE IS HARDLY ANY PATHOLOGY in the brain without an involvement of glial cells. The reactivity of microglia provides a striking example of this principle[1]. Resting microglia show a downregulated immunophenotype adapted to the specialized microenvironment of the CNS. However, their ability to respond quickly to a variety of signalling molecules suggests that their apparent quiescence represents a state of vigilance to changes in their extracellular milieu.

The important role of microglia in various pathological conditions was first recognized by del Rio-Hortega, who also coined their name[2]. Their nature and identity have long been debated but it is now generally accepted that they are ontogenetically related to cells of the mononuclear phagocyte lineage, unlike all other cell types in the CNS (Refs 3,4). There is, however, a minority view based on *in vitro* experiments that postulates that microglia belong to the true glia of neuroectodermal lineage[5].

One of the characteristics of microglia is their activation at a very early stage in response to injury[1,6–10]. Microglia activation often precedes reactions of any other cell type in the brain. They respond not only to changes in the brain's structural integrity but also to very subtle alterations in their microenvironment, such as imbalances in ion homeostasis that precede pathological changes that are detectable histologically[11]. It is possible that the unique collection of membrane channels of microglia, including an inward-rectifying K^+ channel, is instrumental in this responsiveness[12,13]. Furthermore, microglia have receptors for CNS signalling molecules such as ATP (Refs 14,15), calcitonin gene-related peptide (CGRP)[16], ACh and noradrenaline[17], and can react both with changes in their extracellular ionic milieu[14,15,17] and by activation of transcriptional mechanisms[16]. Their ability to respond selectively to molecules involved in neurotransmission allows them in their 'resting' state to monitor the physiological integrity of their microenvironment continuously and to react rapidly in the event of pathological disturbances. Our ignorance of the physiological function of microglial cells in the normal brain must be understood also in the light of our inability to measure their functional changes *in vivo*.

The rapid transformation of microglia from a resting to an activated state has been clearly recognized for almost a century (Fig. 1)[19,20]. While the morphology of activated microglia was found to be extremely

Georg W. Kreutzberg is at the Dept of Neuromorphology, Max-Planck-Institute of Psychiatry, D-82152 Martinsried near Munich, Germany.

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