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Calcium Signaling in Specialized Glial Cells

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Abstract

This article reviews calcium signaling in three specialized types of glial cells: Müller cells of the retina, Bergmann glial cells of the cerebellum, and radial glial cells of the developing cortex. Müller cells generate spontaneous and neuronal activity-evoked increases in Ca^{2+}. Neuron to Müller cell signaling is mediated by neuronal release of ATP and activation of glial P2Y receptors. Müller cells, in turn, modulate neuronal excitability and mediate vasomotor responses. Bergmann glial cells also generate spontaneous and activity-evoked Ca^{2+} increases. Neuron to Bergmann glia signaling is mediated by neuronal release of nitric oxide, noradrenaline, and glutamate. In Bergmann glia, Ca^{2+} increases control the structural and functional interactions between these cells and Purkinje cell synapses. In the ventricular zone of the developing cortex, radial glial cells generate spontaneous Ca^{2+} increases that propagate as Ca^{2+} waves through clusters of neighboring glial cells. These Ca^{2+} increases control cell proliferation and neurogenesis.

Keywords

glia; calcium; Müller cell; Bergmann glia; radial glia

INTRODUCTION

There is a dynamic, bidirectional signaling between glial cells and neurons in the CNS. Much of what we know of this interaction has been learned by monitoring changes in Ca^{2+} within glial cells. Glial Ca^{2+} signaling was first described in astrocytes. More recently, studies of Ca^{2+} signaling in specialized glial cells have added to our knowledge of neuron-glia interactions.

This review summarizes research on Ca^{2+} signaling in three types of specialized CNS glia: Müller cells of the retina, Bergmann glial cells of the cerebellum, and radial glia in the developing cortex. We will discuss Ca^{2+} signaling that is generated endogenously in these glial cells as well as Ca^{2+} signals evoked by neuronal activity. The physiological consequences of such glial Ca^{2+} increases will also be addressed.

MÜLLER CELLS

Müller cells are principal glial cells of the retina. They span the entire thickness of the retina from the photoreceptors to the inner retinal surface. They are the only type of macroglial cell present in most regions of the retina and function as specialized astrocytes. Müller cells signal to retinal neurons and blood vessels, modulating neuronal activity and regulating arteriole diameter. Ca^{2+} signaling in Müller cells is believed to play an essential role in these intercellular interactions.

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Spontaneous and Evoked Ca^{2+} Signaling in Müller Cells

Müller cells of the mammalian retina generate transient increases in Ca^{2+} in the absence of evoked neuronal activity (Newman, 2005). They occur at a frequency of 4.6 transients per cell per 1,000 s. The transients range from 2.5 to 6 s in duration and are similar to those observed in astrocytes in brain slices (Nett et al., 2002; Parri et al., 2001) and in vivo (Hirase et al., 2004).

The retina offers an important advantage over brain slice preparations in studies of Ca^{2+} signaling in that Ca^{2+} increases in Müller cells can be induced by a natural stimulus, light. Neuronal activity, evoked by light flashes, increases the frequency of Ca^{2+} transients in Müller cells by 28% (Fig. 1) (Newman, 2005). This increase in Ca^{2+} transient frequency is 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. Both endogenous and light-evoked Ca^{2+} increases reflect Ca^{2+} release from internal stores (Newman, 2005). The increases are blocked by cyclopiazonic acid, which depletes Ca^{2+} stores, and are abolished by heparin, which blocks IP_3 receptors (Newman and Zahs, 1997).

Signaling from neurons to Müller cells is mediated by release of ATP from neurons and activation of P2Y purinergic receptors (Newman, 2005), which evoke glial Ca^{2+} increases. Light-evoked Ca^{2+} increases are blocked by suramin, a purinergic antagonist, and by apyrase, which hydrolyzes ATP, but not by antagonists to metabotropic glutamate, GABA, or muscarinic receptors. Light-evoked Müller cell Ca^{2+} increases are also blocked by TTX, indicating that only those retinal neurons that generate action potentials, amacrine and ganglion cells, are signaling to glial cells. Ganglion to Müller cell signaling was confirmed by antidromic activation of ganglion cells, which evokes Ca^{2+} increases in Müller cells.

Studies on amphibian and mammalian Müller cells have identified receptors linked to Ca^{2+} increases. Responses to ATP analogs indicate that $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, and $P2Y_{11}$ receptors can mediate Ca^{2+} increases (Fries et al., 2005; Reifel Saltzberg et al., 2003). Activation of A_{2B} adenosine receptors greatly potentiates ATP-evoked responses (Newman, 2005), while activation of receptor tyrosine kinases causes a resensitization of P2Y receptors previously desensitized by agonist application (Weick et al., 2005). In addition to ATP analogs, Müller cell Ca^{2+} increases are evoked by dopamine, thrombin, and lysophosphatidic acid (Newman, 2003; Puro and Stuenkel, 1995). Calcium is released from internal stores by NAD^+ (Esguerra and Miller, 2002), by ryanodine, and caffeine (Keirstead and Miller, 1995) and following activation of metabotropic glutamate receptors (Keirstead and Miller, 1997). Interestingly, in the mammalian retina, glutamate is largely ineffective in evoking Ca^{2+} increases in Müller cells (Bringmann et al., 2002; Newman, 2005; Newman and Zahs, 1997). In contrast, glutamate evokes large Ca^{2+} increases in astrocytes, in brain slices, and in culture (Schipke and Kettenmann, 2004). The insensitivity of Müller cells to glutamate may be a specialization to conditions in the retina, where glutamate is released continuously from neurons. Mechanical stimulation of Müller cells also evokes Ca^{2+} increases mediated by release from internal stores (Newman, 2001; Newman and Zahs, 1997).

Stimulation of Müller cells and retinal astrocytes often evokes Ca^{2+} increases that propagate from the activated cell to adjacent glial cells as intercellular waves (Newman, 2001; Newman and Zahs, 1997). Agonist ejection or mechanical stimulation of Müller cells results in propagated intercellular Ca^{2+} increases that travel outwards from the point of stimulation through neighboring glia (Newman, 2001). Müller cell to Müller cell signaling occurs via release of ATP from one cell and activation of purinergic receptors on adjacent cells. These waves are blocked by the purinergic antagonist, suramin. It is not known whether intercellular

Ca^{2+} waves occur in vivo. However, experimentally evoked waves result in the modulation of neuronal activity and in vasomotor responses (see below).

Physiological Consequences of Ca^{2+} Increases in Müller Cells

Selective stimulation of Müller cells by agonist ejection evokes large Ca^{2+} increases in these cells and subsequent hyperpolarization of adjacent ganglion cells. The ganglion cell hyperpolarization is mediated by ATP release from the Müller cells (Newman, 2003). 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. It should be noted that although glial stimulation results in glial Ca^{2+} increases, it has not been demonstrated directly that ATP release from Müller cells is Ca^{2+} dependent (Newman, 2003).

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 (Stevens et al., 2003). Stimulation of astrocytes results in D-serine release (Schell et al., 1995), and a similar release of D-serine may occur in Müller cells.

Müller cell stimulation by photolysis of caged-IP_3 or caged-Ca^{2+} results in vasomotor responses in neighboring arterioles (Metea and Newman, 2006). Glial stimulation can evoke either vasodilation or vasoconstriction. Both responses are mediated by metabolites of arachidonic acid. Vasodilation is mediated by production of EETs, while vasoconstriction by production of 20-HETE. It is not known whether signaling from Müller cells to arterioles is Ca^{2+}-dependent, although stimulation of Müller cells in this study did evoke intracellular Ca^{2+} increases.

BERGMANN GLIAL CELLS

Bergmann glial cells are radial glia of the cerebellum and serve as specialized astrocytes. Their somata lie in the Purkinje cell layer and their processes extend through the molecular layer to the pial surface. Their processes are aligned with Purkinje cell dendrites and completely surround Purkinje cell synapses in the molecular layer. Calcium signaling in Bergmann glial cells plays a key role in regulating structural and functional interactions between these cells and Purkinje cell synapses.

Spontaneous Ca^{2+} Signaling in Bergmann Glial Cells

Spontaneous Ca^{2+} increases occur in restricted regions of Bergmann glial cell processes (Grosche et al., 1999). These restricted regions are termed microdomains and have been shown in EM studies to be thin membrane sheets that completely envelop Purkinje cell synapses. Each Bergmann glial cell microdomain contacts only a few synapses (Grosche et al., 2002). Microdomains are isolated from the remainder of the cell by a narrow neck and are electrotonically isolated (Grosche et al., 2002). Spontaneous Ca^{2+} signaling is not synchronized between microdomain regions.

Evoked Ca^{2+} Increases in Bergmann Glial Cells

Stimulation of parallel fibers evokes Ca^{2+} increases in Bergmann glial cells (Fig. 2) (Grosche et al., 1999). Single pulses (Matyash et al., 2001) and brief trains of pulses (Grosche et al., 1999) evoke Ca^{2+} increases in only a few Bergmann glial cell microdomains, while more intense stimulation results in widespread Ca^{2+} increases in cell processes and somata (Matyash et al., 2001).

Electrical stimulation within the granule cell layer also evokes Ca^{2+} increases in the somata and processes of Bergmann glial cells (Kulik et al., 1999). In contrast to Ca^{2+} responses evoked by parallel fiber activity, the Ca^{2+} responses evoked by granule cell layer stimulation are not confined to small microdomains in Bergmann glial cell processes.

Parallel fiber to Bergmann glial cell signaling is mediated by nitric oxide (NO) (Matyash et al., 2001), which is released from parallel fibers during stimulation (Kimura et al., 1998). Calcium signaling is blocked by the NO synthase inhibitor *N*-ω-nitro-L-arginine, but not by antagonists to α_1 adrenergic, AMPA or metabotropic glutamatergic or H_1 histaminergic receptors, which are expressed in Bergmann glial cells (Matyash et al., 2001). This activity-dependent Ca^{2+} increase is generated by Ca^{2+} influx rather than by release from internal stores. It is blocked by removal of external Ca^{2+} but not by depletion of internal Ca^{2+} stores with thapsigargin.

In contrast to parallel fiber-Bergmann glial cell signaling, Ca^{2+} increases evoked by stimulation within the granule cell layer is mediated by release of noradrenaline (Kulik et al., 1999). This Ca^{2+} response is blocked by the α_1 adrenergic receptor antagonist prazosin as well as by cyclopiazonic acid. Similar Ca^{2+} increases are evoked by bath-applied noradrenaline. The evoked response is not blocked by β receptor antagonists or by ionotropic or metabotropic glutamate receptor antagonists. The Bergmann glial cell responses evoked by granule cell layer stimulation are thought to be due to activation of noradrenaline-containing locus coeruleus fibers that project to the cerebellum.

Bergmann glial cells express AMPA receptors, which, unlike most neuronal AMPA receptors, are permeable to Ca^{2+}. The Ca^{2+}-permeability of these receptors arises because Bergmann glial cells lack the AMPA receptor subunit GluR2 (Burnashev et al., 1992; Iino et al., 2001). As a consequence, Ca^{2+} increases are evoked in Bergmann glia by AMPA receptor agonists. These responses are mediated by Ca^{2+} influx through the receptors and are blocked by the AMPA receptor antagonist CNQX and by the removal of external Ca^{2+} (Burnashev et al., 1992; Muller et al., 1992).

Stimulation of parallel fibers (Bellamy and Ogden, 2005; Clark and Barbour, 1997) as well as climbing fibers (Matsui and Jahr, 2004) activates Bergmann glial AMPA receptors. AMPA receptor activation by climbing fibers is mediated by ectopic vesicular release of glutamate from climbing fiber terminals (Matsui and Jahr, 2004). Bath application of glutamate can also evoke Ca^{2+} increases in Bergmann glial cells by release from internal stores (Kirischuk et al., 1999). This response is primarily responsible for generating slow glutamate-evoked Ca^{2+} responses.

Activation of both α_1 adrenergic receptors and H_1 histaminergic receptors can evoke Ca^{2+} release from internal stores in Bergmann glial cells (Kirischuk et al., 1996). The response is blocked by thapsigargin but not by removal of external Ca^{2+}. Activation of $endothelin_B$ receptors also evokes Ca^{2+} increases, which are mediated by release from internal stores (Tuschick et al., 1997).

In addition, ATP activation of metabotropic purinergic receptors can evoke Ca^{2+} increases in Bergmann glial cells. The response is blocked by the purinergic antagonist suramin, the IP_3 receptor blocker heparin, and by thapsigargin (Kirischuk et al., 1995). P2Y receptors can also be activated by nicotinic acid adenine dinucleotide phosphate, resulting in Bergmann glial cell Ca^{2+} increases (Singaravelu and Deitmer, 2006).

Physiological Consequences of Ca^{2+} Increases in Bergmann Glial Cells

As discussed above, Bergmann glial cells express Ca^{2+}-permeable AMPA receptors. Genetic manipulation, leading to a reduction in the Ca^{2+} permeability of these receptors, results in profound changes in glia-neuron interactions in the cerebellum. In an in vivo study, the AMPA receptors of Bergmann glial cells were converted from Ca^{2+}-permeable to Ca^{2+}-impermeable by adenoviral-mediated delivery of the GluR2 gene (Iino et al., 2001). The conversion of the glial AMPA receptors to a Ca^{2+}-impermeable type resulted in retraction of the glial cell processes ensheathing Purkinje cell synapses, which are normally completely surrounded by Bergmann glial processes. Glial process retraction resulted in decreased removal of synaptically released glutamate. It also led to multiple innervation of Purkinje cells by climbing fibers. Thus, Ca^{2+} permeable AMPA receptors in Bergmann glia play an essential role in determining the structural and functional relation between these cells and Purkinje cell glutamatergic synapses. In an additional study on cultured Bergmann glial cells, conversion of AMPA receptors to the Ca^{2+}-impermeable type resulted in retraction of glial processes, while overexpression of Ca^{2+} permeable receptors resulted in process extension (Ishiuchi et al., 2001).

Ca^{2+} permeable AMPA receptors may also regulate the expression of the glial glutamate transporter GLAST. In cultured Bergmann glial cells, prolonged glutamate exposure results in a decrease in GLAST transcription (Lopez-Bayghen et al., 2003). This response is blocked by the AMPA receptor antagonist DNQX and by removal of external Ca^{2+}. (The high affinity glycine transporter, GLY1, in Bergmann glial cells is also regulated by Ca^{2+}; Lopez et al., 2005.) Together, these experiments suggest that Ca^{2+}-permeable AMPA receptors play an essential role in enabling Bergmann glial cells to detect the presence of glutamatergic synapses and to extend processes to surround them.

RADIAL GLIA IN THE DEVELOPING CORTEX

Radial glial cells extend from the ventricular surface to the pial surface in the developing cortex. Their somata lie in the ventricular zone. Recent work has elucidated three important functions of these cells (Anthony et al., 2004; Gotz and Huttner, 2005; Noctor et al., 2001, 2004; Yokota and Anton, 2004). First, their elongated, vertically oriented processes serve as scaffolding for neurons as they migrate away from the ventricular zone. Second, through asymmetric division, radial glia give rise to neurons and neuronal progenitor cells. Third, as the brain matures, radial glia differentiate into astrocytes. Calcium signaling in radial glial cells plays an important role in these processes.

Spontaneous and Evoked Ca^{2+} Signaling in Radial Glial Cells

In cortical slices of the embryonic brain, spontaneous Ca^{2+} signaling occurs in individual radial glial cells, in pairs of cells where signaling is synchronized, and in large cell clusters through which Ca^{2+} waves propagate (Fig. 3) (Owens and Kriegstein, 1998;Weissman et al., 2004). The spontaneous Ca^{2+} waves traveling through cell clusters occur at a frequency of 1.1 event per min per mm of tissue and are largely restricted to cells in the ventricular zone (Weissman et al., 2004).

Calcium wave propagation between cells is mediated by release of ATP. Waves are blocked by P2Y receptor antagonists but not by TTX or by glutamate, GABA or glycine receptor antagonists (Owens and Kriegstein, 1998; Weissman et al., 2004). ATP appears to be released from radial glial cells through gap junctional hemichannels. Waves are abolished by gap junction blockers while the frequency of spontaneous waves varies as a function of external Ca^{2+} levels, which regulate hemichannels (Weissman et al., 2004). (These results are also consistent with ATP release through $P2X_7$ receptors, which are blocked by gap junctional

antagonists; Suadicani et al., 2006.) In addition, ATP application evokes Ca^{2+} increases in radial glial cells in the ventricular zone but not in neurons in more superficial cortical layers. Responses to ATP analogs indicate that ATP sensitivity is mediated by $P2Y_1$ receptors (Weissman et al., 2004). Ca^{2+} increases in radial glia are generated by Ca^{2+} release from internal stores rather than by influx from extracellular space. Calcium waves are blocked by thapsigargin and cyclopiazonic acid but not by removal of Ca^{2+} from extracellular space (Weissman et al., 2004). Calcium increases in radial glial cells are evoked by mechanical and electrical stimulation as well as by purinergic agonists (Weissman et al., 2004).

Physiological Consequences of Ca^{2+} Increases in Radial Glial Cells

The spontaneous Ca^{2+} waves observed in radial glial cells may be involved in cell proliferation and neurogenesis in the developing cortex (Weissman et al., 2004). The radial glial cells that initiate Ca^{2+} waves, identified by Lucifer yellow uptake through open hemichannels, are often in the upper third of the ventricular zone (Weissman et al., 2004). These cells are in the S phase of cell division and are undergoing active DNA synthesis, indicating a link between Ca^{2+} increases and cell division. In addition, there is a correlation between Ca^{2+} wave generation and neuronal proliferation (Weissman et al., 2004). From day E12 through E17 there is an increase, both in the frequency of Ca^{2+} wave generation and in the distance that the waves travel. During this time there is a corresponding increase in neurogenesis. The link between radial glial cell Ca^{2+} waves and neurogenesis is strengthened by the observation that blocking Ca^{2+} waves with a purinergic antagonist also reduces neurogenesis (Weissman et al., 2004).

Calcium signaling also plays an important role in the differentiation of neuronal precursor cells. In neurosphere-derived precursor striatal cells, Ca^{2+} signaling controls neurite outgrowth and acquisition of a neurotransmitter phenotype (Ciccolini et al., 2003). Experimental manipulations which increase Ca^{2+} signaling lead to increased neurite outgrowth and branching and to expression of a GABAergic phenotype. In addition, the frequency of Ca^{2+} transient generation in immature neurons modulates the rate of neuronal migration (Komuro and Rakic, 1996).

SUMMARY

Calcium signals in glial cells can be generated endogenously or by transmitters released from active neurons. Spontaneously generated Ca^{2+} transients occur in many types of glial cells, including Müller cells, Bergmann glial cells, and radial glial cells. In radial glial cells, spontaneous Ca^{2+} transients trigger Ca^{2+} waves that propagate through clusters of glia. These Ca^{2+} signals are likely to be involved in neurogenesis. The function of spontaneous signaling in Müller cells and Bergmann glial cells is unclear, but these Ca^{2+} transients may evoke release of gliotransmitters and lead to the modulation of neuronal activity.

Neuronal activity evokes Ca^{2+} signaling in Müller cells and Bergmann glial cells. Neuron to glia signaling is mediated by a number of neurotransmitters, including ATP for Müller cells and NO, noradrenaline, and glutamate for Bergmann glial cells. In Müller cells, Ca^{2+} increases are correlated with ATP release from the glial cells and inhibition of retinal neurons. The Ca^{2+} increases are also correlated with the production of arachidonic acid metabolites and dilation or constriction of retinal blood vessels. In Bergmann glial cells, Ca^{2+} increases play a key role in establishing glial contacts with Purkinje cell synapses and with regulating glutamate uptake into the glial cells.

Studies of specialized glial cells have revealed new aspects of glial Ca^{2+} signaling and function. These cells offer unique advantages in elucidating glial cell function based on their morphological and physiological interactions with neurons. Müller cells in the retina respond to the activation of neurons by natural light stimulation. More so than other glia, Bergmann

glial cell processes envelope neuronal synapses and can be experimentally manipulated. Radial glial cells are the progenitors of many CNS neurons, offering insights into the developmental consequences of Ca^{2+} signaling.

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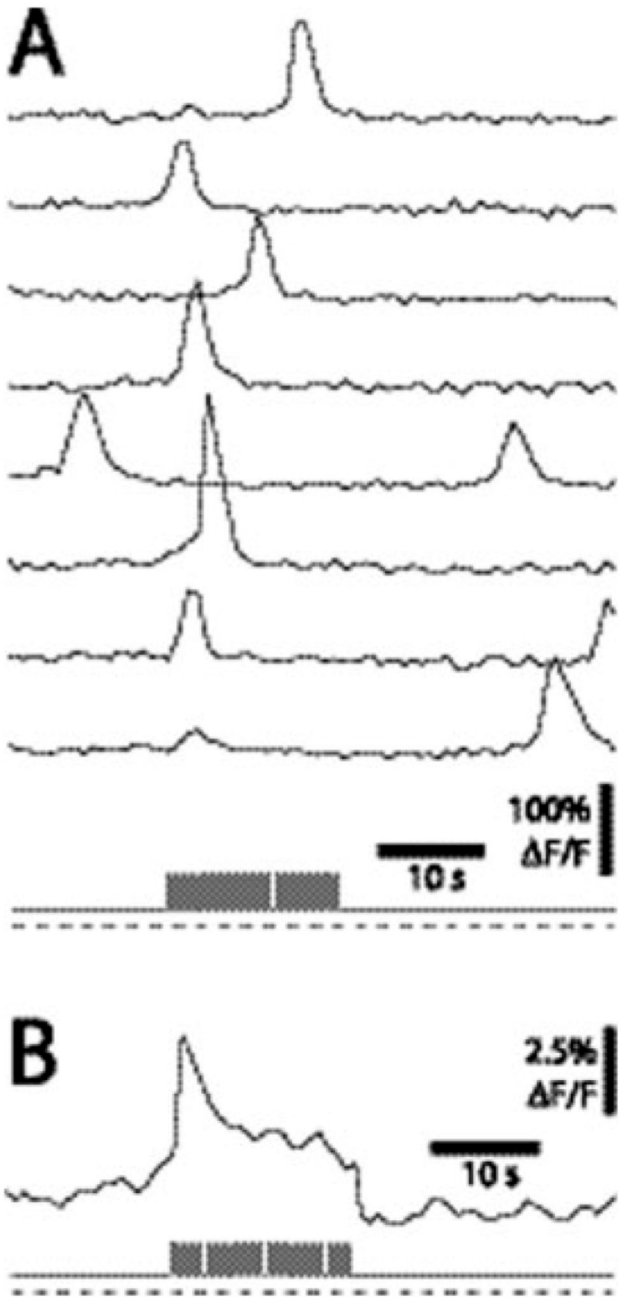

Fig. 1.

Light-evoked Ca^{2+} signaling in Müller cells. (**A**) Calcium fluorescence measured simultaneously in eight Müller cells. The retina was exposed sequentially to a dim light, a bright flickering light, and a dim light (the light stimulus is shown at the bottom in A and B). Calcium transients are more likely to be generated during the flickering light stimulus. (**B**) Mean Ca^{2+} fluorescence averaged over 84 trials. The flickering light evokes both a transient and a sustained increase in Ca^{2+}. From (Newman, 2005).

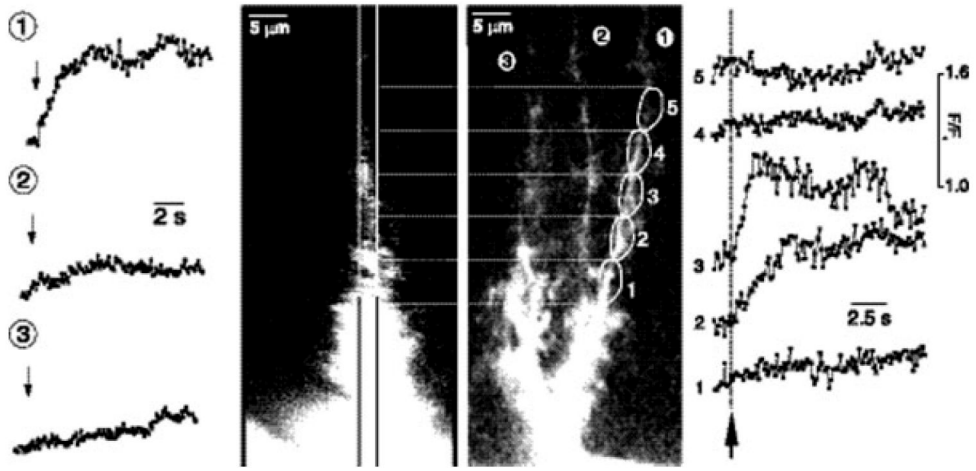

Fig. 2.

Activity-evoked Ca^{2+} signaling in Bergmann glial cells. Calcium fluorescence measured in three cell processes of a Bergmann glial cell following electrical stimulation of parallel fibers. Stimulation evokes a Ca^{2+} increase in process 1 but not in processes 2 and 3 (traces on the left). Within process 1, microdomains 2 and 3, but not 1, 4 or 5, display stimulus-evoked Ca^{2+} increases (traces on the right). The right hand image shows the Bergmann glial cell from which the measurements were made. From (Grosche et al., 1999).

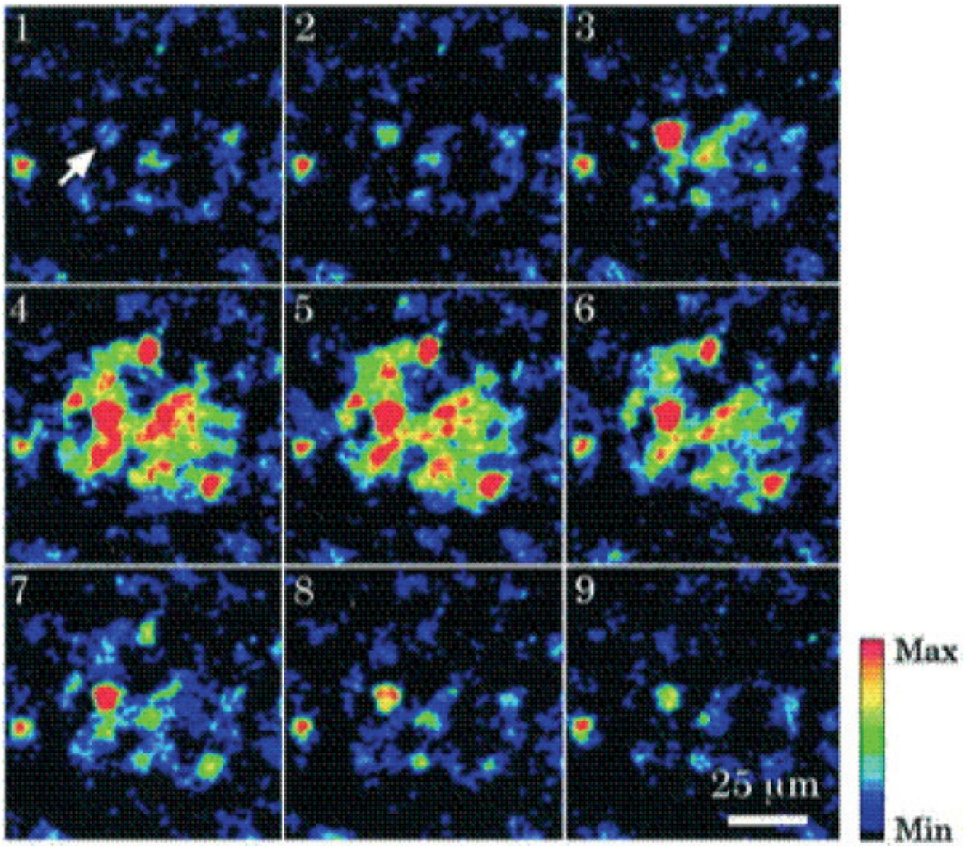

Fig. 3.

Calcium signaling in radial glial cells. The nine pseudocolor Ca^{2+} fluorescence images show a Ca^{2+} wave propagating through a cluster of radial glial cells in the ventricular zone in embryonic cortical tissue. The spontaneous wave was likely initiated in the cell indicated by the arrow and propagated to adjacent cells by release of ATP. The images were acquired at 4 s intervals. From (Owens and Kriegstein, 1998).