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Control of brain energy supply by astrocytes

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Astrocytes form an anatomical bridge between the vasculature and neuronal synapses. Recent work suggests that they play a key role in regulating brain energy supply by increasing blood flow to regions where neurons are active, and setting the baseline level of blood flow. Controversy persists over whether lactate derived from astrocyte glycolysis is used to power oxidative phosphorylation in neurons, but astrocytes sustain neuronal ATP production by recycling neurotransmitter glutamate that would otherwise need to be resynthesised from glucose, and by providing a short-term energy store in the form of glycogen that can be mobilised when neurons are active.

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Introduction

The human brain is critically dependent on a constant supply of energy (almost exclusively in the form of glucose) to meet its high metabolic demands. Despite comprising only 2% of the body's mass, the brain consumes approximately 20% of its resting energy, mainly to reverse ion fluxes that underlie synaptic potentials and action potentials [1–3], and if the energy supply of brain cells is compromised they quickly become injured or die. To ensure that the fluctuating activity-dependent energy requirements of neurons are met, the brain has evolved 'neurovascular coupling' mechanisms to regulate energy supply, which increase the blood flow to regions where neurons are active — a response termed 'functional hyperaemia' [4]. Once delivered to an active area, glucose must then be successfully transferred from the blood to brain cells, where it is used to generate ATP, converted to other forms of energy substrate (such as lactate or glutamate) or converted to the storable energy reserve glycogen [5,6].

Astrocytes, with 'endfoot' processes abutting blood vessels supplying glucose, and finer processes surrounding the synapses that are the brain's major energy consumers, are potentially important regulators of brain energy supply. Surprisingly, however, there has been intense debate about the role of astrocytes, both in regulating local blood flow to power active neurons, and in transforming glucose to other molecules that are the immediate substrate for ATP production. In this review we discuss the pivotal roles that astrocytes may play in the 'flow' of energy from the circulation to brain cells.

The role of astrocyte $[Ca^{2+}]_i$ transients in adjusting brain energy supply

Astrocytes, which are present in the brain at similar numbers to neurons [7•], are ideally positioned between the vasculature and neurons to fulfil several key roles in regulating the flow of energy to neurons, including mediation of neurovascular coupling. Astrocytes extend fine processes that ensheath neuronal synapses and more substantial 'endfeet' that wrap much of the surface of the brain vasculature. For example, astrocyte processes cover ~63% of capillaries, with most of the rest of the endothelial tube being covered by pericytes (the role of which we discuss below), and <1% of the endothelium facing clefts between these cells [8]. This topographical arrangement allows astrocytes to detect changes in neuronal activity (and hence metabolic demand) by sensing neurotransmitter release, and to relay this information to the vasculature to alter the energy supply. Classically, regulation of blood flow is achieved by vascular smooth muscle cells altering their tone to adjust the diameter of arterioles, and thus alter blood flow.

The first evidence that astrocytes can regulate arteriole diameter came from brain slices, where the Carmignoto group showed that raising astrocyte $[Ca^{2+}]_i$ with metabotropic glutamate receptor (mGluR) agonists dilated arterioles by generating a cyclooxygenase derivative of arachidonic acid [9], and the MacVicar group showed that raising astrocyte $[Ca^{2+}]_i$ by uncaging Ca^{2+} led to arteriole constriction (later found to become a dilation at physiological oxygen levels [10,11]). Similarly, Nedergaard's group reported that *in vivo* a similar mGluR-evoked arteriole dilation occurred in response to neuronal activity and was mediated by a cyclooxygenase derivative [12]. Subsequently, debate has raged over whether the astrocyte $[Ca^{2+}]_i$ transients evoked by neuronal activity are too small, too slow, or too infrequent to have a causative role in neurovascular coupling [13–15], and whether $[Ca^{2+}]_i$-raising mGluRs exist in adult astrocytes [16]. These arguments partly reflected the fact that conclusions were

based on measuring Ca^{2+} signals within astrocyte cell bodies rather than in the fine processes of astrocytes near synapses which are presumably the first responders to neuronal activity, and on using bulk loading of Ca^{2+}-sensing dyes which may go into both astrocytes and neurons thus making it hard to be certain which cell type is generating the observed Ca^{2+} signal [17,18•, reviewed in depth by 19].

In addition to releasing enzyme-derived chemical messengers, neuronal activity-driven astrocyte $[Ca^{2+}]_i$ transients may also signal to blood vessels by releasing K^+ ions onto vessels, through Ca^{2+}-activated K^+ (BK) channels in astrocyte endfeet [20]. In the physiological voltage range increasing $[K^+]_o$ hyperpolarises vascular smooth muscle, by increasing the conductance of, and thus increasing outward current through, inward rectifier K^+ channels. This hyperpolarisation reduces Ca^{2+} influx through voltage-gated channels, and leads to vessel dilation. A similar mechanism has been suggested to initiate a propagating hyperpolarisation along capillary endothelial cells, to send a signal instructing arterioles to dilate [21].

Astrocytes mediate neurovascular coupling at the capillary level

Despite a general focus on neurovascular coupling at the arteriole level, it was recently demonstrated that the majority of the hydraulic resistance which can be reduced to increase blood flow in the cortical vasculature is located in capillaries rather than arterioles [22]. This has shifted attention to the role of pericytes — spatially isolated contractile cells on capillaries — in controlling cerebral blood flow. Indeed, *in vivo* data suggest that a major fraction of the increase in blood flow evoked by neuronal activity reflects active relaxation of capillary pericytes [23,24•].

Dialysing astrocytes in brain slices with a high concentration of the rapid calcium buffer BAPTA was found to inhibit pericyte-mediated capillary dilation, while having no effect on arteriole dilation [25] (perhaps surprisingly, given previous reports [11,12] of astrocyte $[Ca^{2+}]$ regulating arteriole dilation), establishing a role for astrocyte $[Ca^{2+}]_i$ transients in regulating brain energy supply at the capillary level. Further pharmacological analysis demonstrated that the signalling evoked by neuronal activity to dilate the two types of vessel in the brain slices used for these experiments was different, with arterioles being dilated by nitric oxide release (presumably from interneurons), and capillaries being dilated by prostaglandin E_2 which was generated from arachidonic acid derived from the sequential action (in astrocytes) of phospholipase D2, diacylglycerol lipase and cyclooxygenase 1. (We note however that other studies [11,12] have reported that arachidonic acid metabolites such as PgE_2 can also dilate arterioles, suggesting that different neurovascular coupling mechanisms may occur in different circumstances.)

The astrocyte $[Ca^{2+}]_i$ transients evoked by neuronal activity to initiate capillary dilation were surprisingly shown to be produced, not by mGluRs as discussed above, but by postsynaptically released ATP activating $P2X_1$ receptors on astrocytes [25] (Figure 1). Similarly, in the retina, astrocyte (Müller cell) $[Ca^{2+}]_i$ transients were found to dilate intermediate layer capillaries but not arterioles [26•]. It has been suggested that a low level of neuronal activity can evoke arteriole dilation in the absence of astrocyte endfoot $[Ca^{2+}]_i$ transients, which are only detectable when a higher level of neuronal activity occurs [27] and it will be interesting to determine whether this dilation is mediated by NO, as found in [25]. If so this might imply that low levels of neuronal activity increase blood flow solely by dilating arterioles, while higher activity also dilates capillaries via astrocytes and pericytes.

The control of capillary diameter by astrocytes and pericytes may be relevant to developing strategies for preventing deleterious decreases of blood flow that occur in pathology. Both after ischaemia [23] and in epilepsy models [28] localised constrictions of capillaries produced by pericytes reduce local blood flow, which will contribute to neurodegeneration. An important issue for the future will be whether the normal control of pericyte tone by astrocytes can be harnessed therapeutically to maintain a normal energy supply to the tissue in such situations.

Tonic regulation of cerebral blood flow by astrocytes

Changes of blood flow evoked by neuronal activity, in part generated through astrocytes as discussed above, initiate the signals detected by the widely used BOLD fMRI (blood oxygen level dependent functional magnetic resonance imaging) technique. However, a tonic regulation of cerebral blood flow by astrocytes may be of equal importance for brain function. Introducing the calcium chelator BAPTA into astrocytes in brain slices was found to produce a constriction of arterioles that was prevented by blocking cyclooxygenase 1, but was unaffected by blocking neuronal activity with TTX [29]. Thus, either the mean resting level of astrocyte $[Ca^{2+}]_i$ or $[Ca^{2+}]_i$ transients generated independently of action potentials may tonically activate the prostaglandin-mediated pathway described above [25], although it is surprising that in this case it is affecting arterioles rather than capillary pericytes. Recently, astrocyte $[Ca^{2+}]_i$ transients generated independently of action potential evoked transmitter release were characterised as resulting from bursts of Ca^{2+} efflux through the mitochondrial permeability transition pore [30••]. Although these transients occur in TTX, their rate was raised when neuronal activity was increased by blocking synaptic inhibition with picrotoxin. This may occur because the mitochondrial permeability transition pore opens more when demand for oxidative