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BRAIN METABOLISM

Astrocytes bridge the gap

Neurons need glucose and oxygen to function, and the delivery of these essential substances from the blood is regulated by astrocytes. Two recent papers provide new mechanistic insights into this regulation: MacVicar and colleagues report that low local oxygen levels cause astrocytes to stimulate vasodilation, and Rouach and colleagues show that glucose delivery to neurons occurs through an astrocyte network, is dependent on the gap junction proteins CX30 (also known as GJB6) and CX43 (also known as GJA1), and sustains synaptic activity.

MacVicar and his team showed that in rat brain slices, stimulation of hippocampal neurons under high and low oxygen conditions caused constriction and dilation, respectively, of arterioles. Glutamatergic activity is known to increase astrocyte Ca^{2+} levels and thereby trigger the production of arachidonic acid, which in muscles is converted to 20-HETE, leading to vasoconstriction, and in astrocytes is converted to the prostaglandin PGE_2, causing vasodilation. The authors investigated why low-oxygen conditions seem to stimulate the latter process.

They showed that adding a metabotropic glutamate receptor (mGluR) agonist enhanced glycolysis in astrocytes, resulting in higher extracellular lactate levels; this effect was stronger in low-oxygen than in high-oxygen conditions. Addition of lactate under high-oxygen conditions increased extracellular PGE_2 levels and caused vasodilation, which could be blocked by indomethacin (an inhibitor of prostaglandin production), suggesting that it was mediated by PGE_2.

The authors also showed that blocking prostaglandin transporters increased extracellular PGE_2 levels and caused vasodilation. Addition of lactate did not further increase this effect, suggesting that lactate acts by inhibiting or reducing the efficacy of prostaglandin transporters.

Thus, in low-oxygen conditions astrocyte glycolysis is increased, resulting in elevated lactate levels. Lactate inhibits prostaglandin transporters, maintaining the high extracellular levels of PGE_2 (produced in response to mGluR activation) and causing arteriole dilation. When oxygen levels are high, PGE_2 is rapidly removed by prostaglandin transporters, preventing vasodilation.

Vasodilation increases the local availability of glucose, but how does the glucose reach the neurons? Rouach and colleagues demonstrated that in hippocampal slices a fluorescent glucose derivative spread through the astrocyte network within 20 minutes after injection into a single astrocyte. This trafficking was mediated by the astroglial gap junction proteins CX30 and CX43, as it did not occur in slices taken from mice lacking these proteins.

Reducing spontaneous neuronal activity in hippocampal slices using tetrodotoxin decreased trafficking of the glucose derivative, whereas increasing activity had the opposite effect. Moreover, stimulating neurons in one hippocampal layer could increase trafficking into this layer through the astrocyte network of a fluorescent glucose metabolite injected into a single astrocyte from a distant hippocampal layer.

To determine whether the glucose trafficking maintains neuronal activity, the authors deprived a hippocampal slice of glucose to induce a high metabolic demand; neuronal recordings showed that this depressed synaptic transmission. However, glucose administration to a single, remote astrocyte prevented this depression. This effect was inhibited by a lactate transport inhibitor, suggesting that the glucose metabolite lactate, rather than glucose itself, is taken up by neurons to sustain excitatory activity. Slices from mice lacking both CX30 and CX43 did not show the activity-sustaining effect of glucose administration, indicating that the trafficking of glucose and lactate is mediated by these gap-junction proteins.

Together, these studies describe how astrocytes provide metabolic support for active neurons: by regulating blood flow to increase the availability of glucose and subsequently by taking up and trafficking glucose through a network of connecting astrocytes. In this manner, glucose metabolites are delivered to neurons according to their metabolic demand.

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ORIGINAL RESEARCH PAPERS Gordon, G. R. J. *et al.* Brain metabolism dictates the polarity of astrocyte control over arterioles. *Nature* **456**, 745–749 (2008) | Rouach, N. *et al.* Astroglial metabolic networks sustain hippocampal synaptic transmission. *Science* **322**, 1551–1555 (2008)