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REVIEW ARTICLE

Glia in brain energy metabolism: A perspective

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Abstract

Early views of glia as relatively inert, housekeeping cells have evolved, and glia are now recognized as dynamic cells that not only respond to neuronal activity but also sense metabolic changes and regulate neuronal metabolism. This evolution has been aided in part by technical advances permitting progressively better spatial and temporal resolution. Recent advances in cell-type specific genetic manipulation and sub-cellular metabolic probes promise to further this evolution by enabling study of metabolic interactions between intertwined fine neuronal and glial processes *in vivo*. Views of glia in disease processes have also evolved. Long considered purely reactive, glia and particularly microglia are now seen to play active roles in both promoting and limiting brain injury. At the same time, established concepts of glial energetics are now being linked to areas such as learning and neural network function, topics previously considered far removed from glial biology.

KEYWORDS

axon, glucose, glutamate, glycogen, lactate, nitric oxide, superoxide

1 | INTRODUCTION

Energy metabolism in the central nervous system (CNS) differs from other tissues with respect to its relatively high resting rate and local, activity-dependent fluctuations. These features have been successfully exploited using fluorodeoxyglucose positron emission tomography (2DG PET), functional magnetic resonance imaging (fMRI), and other methods to detail the neuroanatomical substrates and connectivity that underlie brain function. It has only more recently been recognized how CNS glial cells—astrocytes, oligodendrocytes, and microglia—regulate, respond to, and contribute to these unique features. Untangling these bidirectional relationships between glia and neurons will be essential for a more complete understanding of brain energetics and function. The perspective presented here aims to highlight key milestones in this area to date, and identify areas of future interest.

2 | INITIAL RECOGNITION THAT GLIA DYNAMICALLY CONTRIBUTE TO BRAIN ENERGY EXPENDITURE

The recognition that brain energy metabolism differs in key respects from other tissues is based on two landmark observations. The first was that brain metabolic rate is exceedingly high, accounting for roughly 20% of total body basal energy expenditure in adult humans while comprising less than 2% of body weight (Kety, 1957).

Subsequent studies established that the primary source of this energy demand was plasma membrane ion pumps and the activation of post-synaptic receptors. The second landmark observation was that local brain activity produced local increases in brain glucose utilization (Sokoloff et al., 1977). The 2-deoxyglucose tracer method developed for these studies further revealed that basal rates of glucose metabolism varied between brain regions, and between white matter and gray matter structures.

Neither of these two fundamental observations directly indicated any particular role for glial cells in brain energy metabolism. Although glial cells actively maintain plasma membrane ion gradients, they do not generate action potentials, and were consequently long considered metabolically inert relative to neurons. That view was overturned by the finding that astrocytes respond to neurotransmitters with membrane depolarization (Kettenmann, Backus, & Schachner, 1984). The immediate implication of this finding was that astrocytes could participate in brain information processing, but a corollary aspect was that astrocytes must similarly expend energy in processing these neurotransmitter induced responses. Later work showed that neurotransmitter-induced responses in astrocytes activate a variety of secondary signal transduction pathways, including G-protein-mediated signaling, intracellular calcium elevations, intracellular sodium elevations, and others that require ATP consumption (Rose & Karus, 2013); and that microglia and oligodendrocytes likewise respond to extracellular signaling molecules with changes in membrane potential and second

messenger responses. Extracellular K^+ elevations caused by neuronal activity also drive astrocyte energy consumption by triggering active K^+ uptake, as the external cation site of astrocyte (but not neuronal) Na^+/K^+ ATPase is stimulated by small very increases in extracellular $[K^+]$ (Amedee, Robert, & Coles, 1997; Silver & Erecinska, 1997).

A second indication that glia play a key role in CNS energy metabolism came from studies of brain glycogen, which in adult mammalian brain is localized primarily to astrocytes (Brown & Ransom, 2007). Studies using cultured astrocytes showed that glycogen turnover was influenced by a variety of neurotransmitters and peptides (Magistretti, Manthorpe, Bloom, & Varon, 1983). Using a modification of the 2-deoxyglucose method to label glycogen in the intact brain, it was subsequently shown that sensory stimuli that induce local neuronal activity also induce local astrocyte glycogen turnover, (Swanson, Morton, Sagar, & Sharp, 1992). There is a net energy cost to cycling glucose into and out of glycogen polymers, and it remains uncertain what advantage is gained in utilizing glycogen over available glucose. An advantage may stem from the fact that glycogen can be mobilized extremely quickly, and without the initial ATP consumption required for glucose phosphorylation. Alternatively, astrocyte glycogen consumption may serve to spare interstitial glucose for direct neuronal uptake, particularly when neuronal activity outstrips local glucose supply, or to generate lactate as a substrate for oxidative neuronal metabolism (Dringen, Gebhardt, & Hamprecht, 1993). Intriguingly, observations from several recent studies suggest that learning and memory consolidation require astrocyte glycogen metabolism (Hertz & Chen, 2017).

3 | GLUTAMATE AS A NEXUS BETWEEN NEURONAL ACTIVITY AND GLIAL ENERGY METABOLISM

It is surprising that glutamate was not recognized as a neurotransmitter until the 1980s, decades after the identification of acetylcholine, norepinephrine, and serotonin. Resistance to this idea can be attributed to the fact that glutamate is ubiquitous and abundant in brain (>1 mM), and had established functions as an energy intermediate and protein building block. Pharmacological dissection of glutamate receptors eventually resolved this issue, and glutamate is now recognized as the dominant excitatory neurotransmitter in mammalian brain. The eventual acceptance of glutamate as an excitatory neurotransmitter led to the first mechanistic understanding of how brain signaling both influences and depends upon astrocyte energy metabolism. Unlike most other neurotransmitters, amino acid neurotransmitters like glutamate are removed from extracellular space by cellular uptake rather than by cleavage. The normal extracellular to intracellular gradient for glutamate is approximately 1:10,000, and the energetic cost for glutamate uptake is accordingly high; approximately 1.5 ATP per molecule transported. Perhaps for this reason, the majority of glutamate uptake is performed by astrocytes, relieving the metabolic burden on neurons (Danbolt, Furness, & Zhou, 2016). As glutamate uptake is also electrogenic, uptake by astrocytes may also serve to prevent neuronal membrane depolarization that would occur with neuronal glutamate uptake. Once in astrocytes, glutamate can be metabolized to glutamine, at the

cost of an additional ATP, for shuttling back to neurons. Alternatively, glutamate can itself be oxidatively metabolized by astrocytes to generate ATP (McKenna et al., 1996). More recently, other metabolites such as adenosine and lactate have been identified as having signaling functions, and the gradual acceptance of their signaling functions may be recapitulating the glutamate history (Barros, 2013). The dual roles for glutamate, lactate, and adenosine suggest a broad integration between neurons and glia in brain energy metabolism and information processing.

4 | TRAFFICKING OF ENERGY METABOLITES BETWEEN GLIA AND NEURONS

The recognition that astrocytes are primarily responsible for the clearance of glutamate released during synaptic activity was followed by the observation that glutamate can stimulate glucose uptake and lactate production by astrocytes, and led to the concept that neurons may be fueled “on demand” by astrocyte-derived lactate. By this model, astrocytes metabolize glucose to lactate (aerobic glycolysis) in a manner stimulated by glutamate uptake, with the lactate then released to be used by neurons for oxidative ATP production (Pellerin et al., 2007). There is substantial experimental support for the transfer of lactate from astrocytes (and possibly from oligodendrocytes) to neurons, but the quantitative and functional significance lactate versus glucose as neuronal energy substrates remains to be clarified (Dienel, 2012; Nehlig & Coles, 2007).

A special case of glial-neuronal metabolite shuttling is presented by myelinated axons. In these axons the vast majority of surface area is isolated from extracellular space by ensheathing oligodendrocytes, and consequently the oligodendrocytes can control the passage of energy substrates and other molecules to the neuronal axons. In the isolated optic nerve (which contains neuronal axons, myelinating oligodendrocytes, and astrocytes), the capacity of axons to maintain high frequency electrical conduction varies with the initial concentration of astrocyte glycogen. Blocking glycogen metabolism induces conduction failure, as does blocking lactate transport (Brown, Tekkok, & Ransom, 2003). Importantly, metabolite flux through oligodendrocytes can in turn be regulated by axonal activity: glutamate activation of NMDA receptors on oligodendrocytes increases their uptake of glucose, which may then be metabolized to lactate and released to axons for oxidative ATP production (Saab et al., 2016).

5 | ENERGY METABOLISM IN GLIAL SUBCELLULAR DOMAINS AND METABOLIC SENSING

Methodological advances have now refined our view of glia in brain energy metabolism to encompass not only intercellular communication and trafficking, but also subcellular compartmentation. Mitochondrial distribution in astrocytes is not random, and has been shown to be influenced by glutamate transport activity (Jackson, O'Donnell, Takano, Coulter, & Robinson, 2014). Moreover, astrocytes have extraordinarily complex shapes, each expressing hundreds of thin membranous



processes that wrap around synapses and other cellular elements. These processes act independently of one another, exhibiting local fluctuations in Ca^{2+} during local synaptic activity, and are thus termed microdomains (Grosche et al., 1999). How activity is fueled in these astrocyte microdomains remains uncertain, as only a minority of them contain mitochondria.

The concept that glia, particularly astrocytes, can function as metabolic sensors has gained support at multiple levels in recent years. Astrocytes express regional differences in their capacity to detect and respond to metabolic signals such as pO_2 , pCO_2 , and pH, and play an essential role in the activity induced local blood flow changes mediated by these signals (Attwell et al., 2010; Gordon, Mulligan, & MacVicar, 2007). Astrocyte responses to these and other metabolic signals likewise influence whole organism responses to their changes, such as respiratory rate (Gourine et al. 2010) and blood pressure.

6 | GLIAL ENERGY METABOLISM IN DISEASE AND INFLAMMATION

Brain energy metabolism is altered in many neurological disorders. In some, such as ischemia and severe hypoglycemia, energy failure is a direct cause of brain injury. Ischemia also causes injury through spreading depression, a process in which astrocytes are both mediators and regulators (Seidel, Escartin, Ayata, Bonvento, & Shuttleworth, 2016). Glycogen is the primary energy reserve in brain, and this reserve is small; equivalent to only a few minutes of brain glucose consumption under physiological conditions. Nevertheless, this astrocyte energy store has significant effects on the capacity of neurons to function and survive during hypoglycemia (Suh et al., 2007), in part because metabolic rate is suppressed during periods of insufficient glucose supply (Hochachka, 1999). Other disorders may be exacerbated by, if not directly caused by disordered energy metabolism. For example, subtle alterations in either mitochondrial function or mitochondrial quality control in Parkinson's disease may contribute to demise of the dopaminergic neurons that are preferentially affected in this disease. In Alzheimer's disease, decreases in brain glucose utilization precede symptom onset by decades, and is accompanied by a shift to more ketogenic metabolism (Ding, Yao, Rettberg, Chen, & Brinton, 2013). The contributions of astrocytes and oligodendrocytes to these changes remain to be established.

Microglia are now recognized to have diverse effects in neurological disorders. Though grouped with astrocytes and oligodendrocytes as "glia", microglia are more akin to circulating macrophages and the resident dendritic cells found in non-CNS tissues. Microglia shift to more glycolytic energy production and secrete lactate when stimulated by infection or tissue damage (Voloboueva, Emery, Sun, & Giffard, 2013). Activated microglia also release cytotoxic proteases and reactive oxygen species. While this response is likely adaptive to infection, it may have a net deleterious effect in non-infectious conditions such as stroke and neurodegenerative disorders. Glucose availability can be rate-limiting for the production of superoxide (Decoursey & Ligeti, 2005), and probably also nitric oxide, thus linking blood glucose levels to pro-inflammatory microglial function. Glucose levels also influence pro-inflammatory gene expression in microglia, including expression of

inducible nitric oxide synthase (Shen et al., 2017). Interestingly nitric oxide in turn affects energy metabolism by displacing oxygen from both hemoglobin and mitochondrial cytochrome C oxidase, and in astrocytes increases lactate release (San Martin, Arce-Molina, Galaz, Perez-Guerra, & Barros, 2017). The functional implications of these complex interactions between inflammation and brain energy metabolism are only beginning to be appreciated.

7 | FUTURE DIRECTIONS

Effects of neuronal activity on glial metabolism are well-established, and our understanding of the signaling mechanisms mediating these interactions continues to expand. We can expect that studies of these interactions will be particularly facilitated by advances in cell-type specific gene editing techniques. Genetically-encoded fluorescent metabolite nanosensors are now available with exquisite spatial sensitivity, and these may pave the way for untangling the most intractable aspects of subcellular glial and neuronal energy metabolism, particularly as they are targeted to mitochondria and peri-synaptic fine processes in vivo. Both of these approaches are also likely shed further light on the changes that occur in glia under disease conditions, and help to resolve which of these are reactive and which may be contributory factors. Perhaps most excitingly, established concepts of glial energetics are now being applied to fundamental questions in systems neuroscience involving mechanisms of learning and memory. We seem to be entering a "golden era" for integrating glial energetics with broader brain functions, and can look forward with anticipation to future advances in these areas.

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