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Review

Reactive astrocytes give neurons less support: implications for Alzheimer's disease

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Abstract

Astrocytes become activated in Alzheimer's disease (AD), contributing to and reinforcing an inflammatory cascade. It is proposed that by transforming from a basal to a reactive state, astrocytes neglect their neurosupportive functions, thus rendering neurons vulnerable to excitotoxicity and oxidative stress. This review considers 3 important astrocytic functions, that when disrupted, can affect neuronal metabolism. These are the uptake of glucose and release of lactate; the uptake of glutamate and release of glutamine; and the uptake of glutathione precursors and release of glutathione. Conditions under which these functions can be manipulated in vitro, as well as examples of possible loss of astrocytic function in AD, are discussed. It is proposed that the targeting of astrocytes with pharmacological agents that are specifically designed to return astrocytes to a quiescent phenotype could represent a fruitful new angle for the therapeutic treatment of AD and other neurodegenerative disorders.

Keywords: Neuron; Glutathione; Glutamate; Glucose; Neurodegeneration

1. Introduction

Astrocytes serve an array of important functions, including the regulation of extracellular ion concentrations, synaptic remodeling (addition and removal of synapses), and the maintenance of protective barriers, such as the glia limitans, glial scars, and blood-brain barrier. The ensheathment of blood vessels and synapses by astrocytic processes enables these cells to monitor the extracellular ionic environment and to mediate the transfer of metabolites between cerebral blood vessels and neurons. Three interrelated astrocyte-neuronal interactions, discussed herein, are glucose uptake and lactate release, glutamate recycling, and the synthesis of glutathione.

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2. Astrocytes take up glucose and release lactate

Glucose is transported from the blood to the abluminal surface of cerebral capillaries by vascular endothelial cells and is then taken up by a 45 kDa glucose transporter (GLUT1) located on the end feet of astrocytes or by GLUT2 transporters elsewhere on astrocytes (Benarroch, 2005, 2004). By contrast, neurons predominantly express the GLUT3 isoform (Leino et al., 1998; McEwen and Reagan, 2004). In cell culture, glucose taken up by astrocytes and neurons is phosphorylated by hexokinase, thus committing it to breakdown by glycolysis (Brown and Ransom, 2007). In the brain however, astrocytes may have a virtual monopoly over glucose due to the proximity of their end feet to capillary walls, and the fact that nearly all neuronal processes and cell bodies are ensheathed by astrocytes. Hence most of the metabolic substrates that reach neurons are likely to have first passed through astrocytes (Barros et al., 2005; Rouach et al., 2008). The direct transfer of glucose

from astrocytes to neurons was recently demonstrated in brain slices (Gandhi et al., 2009). The importance of such transfer is illustrated by GLUT1-deficiency which results in a 50% decrease in GLUT1 protein expression in vascular endothelial cells and astrocytes, and is associated with a global decrease in cortical glucose uptake and severe neurological deficits (Brockmann, 2009; Pascual et al., 2002).

Astrocytes metabolize glucose to lactate by glycolysis, or store glucose as glycogen; nearly all of the glycogen stores in the brain are located within astrocytes, because neurons lack the enzymes required to metabolize glycogen (Brown and Ransom, 2007). Astrocytes release lactate via the H^+-coupled monocarboxylate transporters (MCT) 1 and 4, and the extracellular lactate is taken up into neurons via MCT2. Neurons convert lactate to pyruvate which can serve as a substrate for oxidative metabolism (Benarroch, 2005). There has been considerable controversy concerning whether lactate released from astrocytes is a major substrate for neuronal energy metabolism during synaptic activity (Bouzier-Sore et al., 2003). Supporting evidence comes from in vitro demonstrations that astrocytes produce lactate in an activity-dependent, glutamate-mediated manner and that neurons can take up this lactate as a substrate for oxidative metabolism (Pellerin and Magistretti, 1994). Cytological support includes differences in enzyme subtypes and lactate transporter affinities between astrocytes and neurons. For example, astrocytes primarily express lactate dehydrogenase-5 (LDH-5), which catalyzes pyruvate to lactate, whereas neurons primarily express LDH-1, which catalyzes lactate to pyruvate (Bittar et al., 1996; Laughton et al., 2007).

Evidence against an astrocyte-neuron lactate shuttle is based on observations that astrocytes in culture can completely degrade glucose via the tricarboxylic acid (TCA) cycle (Hertz et al., 2007), that both astrocytes and neurons possess efficient transporters for the uptake of glucose (Vannucci et al., 1997), and that activated neurons are capable of releasing lactate (Dienel and Cruz, 2008). Indeed, Gandhi and colleagues (Gandhi et al., 2009) used a novel fluorometric approach to infer that much of the lactate released during brain activitation may originate from neurons, and be transported to capillaries by astrocytes, rather than serving as a metabolic substrate. Despite these objections, it is becoming increasingly accepted that synaptic activity is at least partly fueled by the transfer of metabolites from astrocytes to neurons, and that lactate is likely to be 1 of these metabolites (Aubert et al., 2005; Dienel and Cruz, 2008; Erlichman et al., 2008; Hyder et al., 2006). Another point of agreement is that the breakdown of glycogen to lactate provides astrocytes with a source of energy that can be obtained extremely rapidly and without a requirement for oxygen, so glycogen represents a valuable substrate during periods of high metabolic demand, when the availability of blood-borne glucose and oxygen are rate-limiting factors (Brown and Ransom, 2007).

It is widely agreed that neurons lack another critical step in energy metabolism. Pyruvate carboxylase combines a molecule of carbon dioxide with 1 of pyruvate to form oxaloacetate, which is needed to replenish carbon skeletons in the tricarboxylic acid (TCA) cycle (Serres et al., 2008). Pyruvate carboxylase is present in astrocytes and other glial cells but not in neurons (Murin et al., 2009). Alternative anaplerotic pathways are present in neurons (e.g., carboxylation of pyruvate to malate) but they do not proceed under normal conditions because the energetics of these reactions are not favorable (reviewed by Hertz et al., 2007; Murin et al., 2009). This unusual situation means that astrocytes must provide neurons with a constant supply of TCA intermediates (e.g., citrate, malate) or their derivatives (e.g., aspartate, glutamine) (Hertz et al., 1999) (Fig. 1). Without this critical support, the de novo synthesis of glutamate and γ-aminobutyric acid (GABA) would rapidly deplete neuronal reserves of TCA intermediates and compromise neuronal viability.

3. Astrocytes recycle glutamate for neuronal reuptake

Glutamate released into the synaptic cleft is mainly taken up by glutamate transporters on adjacent astrocytic processes, and a small amount is taken up by presynaptic neurons for immediate repackaging into vesicles. Astrocytes take up glutamate predominantly by Na^+-dependent glutamate transporters (GLAST and GLT1), but also by Na^+-independent glutamate transporters such as the Cl^--dependent glutamate-cystine (X^-_c) antiporter. By taking up glutamate, astrocytes are potentially able to regulate the levels of extracellular glutamate and thereby influence synaptic activity. Astrocytes, but not neurons, contain the enzyme glutamine synthetase (GS), which amidates glutamate to glutamine. Astrocytes release glutamine into the interstitial space for uptake by neurons, which deamidate it via phosphate-activated glutaminase to complete the glutamate-glutamine cycle (Anderson and Swanson, 2000; Hertz et al., 1999).

The functional importance of the glutamate-glutamine cycle is dramatically illustrated when the activity of astrocytic GS is inhibited by methionine sulfoximine. When this drug is administered into the central nervous system, behavioral deficits are observed that correspond to the function of the region injected. Injection of the eye with methionine sulfoximine for example, causes temporary blindness by rapidly depleting retinal neurons of glutamate and glutamine (Barnett et al., 2000; Pow and Robinson, 1994). In another example, this time in chicks, inactivation of GS in the hyperstriatum (homologue of the hippocampus) leaves vision unaffected but prevents the consolidation of new memories for visually learned discrimination tasks (Gibbs et al., 1996; Ng et al., 1997). In the experiments described above, both the blinding and the amnestic effects of methionine sulfoximine were fully reversed by the application of exogenous glutamine, indicating that the functional impair-