Review

Biological Psychiatry

Defects in Bioenergetic Coupling in Schizophrenia

Courtney R. Sullivan, Sinead M. O'Donovan, Robert E. McCullumsmith, and Amy Ramsey

ABSTRACT

Synaptic neurotransmission relies on maintenance of the synapse and meeting the energy demands of neurons. Defects in excitatory and inhibitory synapses have been implicated in schizophrenia, likely contributing to positive and negative symptoms as well as impaired cognition. Recently, accumulating evidence has suggested that bioenergetic systems, important in both synaptic function and cognition, are abnormal in psychiatric illnesses such as schizophrenia. Animal models of synaptic dysfunction demonstrated endophenotypes of schizophrenia as well as bioenergetic abnormalities. We report findings on the bioenergetic interplay of astrocytes and neurons and discuss how dysregulation of these pathways may contribute to the pathogenesis of schizophrenia, highlighting metabolic systems as important therapeutic targets.

Keywords: Bioenergetic coupling, Glucose utilization, Lactate shuttle, Metabolism, Mitochondria, Schizophrenia

https://doi.org/10.1016/j.biopsych.2017.10.014

Schizophrenia is a devastating illness that affects more than 2 million people in the United States and displays a wide range of psychotic symptoms as well as cognitive deficits and profound negative symptoms that are often treatment resistant (1–6). This illness is highly heritable, suggesting a major role for genetic variants in its complex pathophysiology. Large genome-wide association studies have reported more than 100 genetic loci containing common alleles conveying minor schizophrenia associations (7), whereas rare de novo copy number variations, which often span multiple genes, confer higher effects on risk (8,9). There is accumulating evidence of bioenergetic dysfunction in chronic schizophrenia, including deficits in energy storage and usage in the brain. While it is possible that genetic variation in metabolic genes contributes to these energetic deficits, genetic risk for schizophrenia is conferred by a large number of alleles, with risk variants each typically conferring a small portion of overall risk (10). Interestingly, these studies demonstrate a convergence of de novo mutations and altered gene expression on sets of functionally related proteins, pointing to the regulation of plasticity at excitatory synapses as a pathogenic mechanism in schizophrenia (9). Taken together, the bioenergetic deficits and genetic risk for synaptic dysfunction in schizophrenia lead to the following question: How do defects in bioenergetic function develop and contribute to the pathophysiology of this illness?

In this review, we describe bioenergetic coupling in detail and discuss, in turn, how metabolic dysfunction may contribute to impaired synapse activity and maintenance. We discuss the role of glucose and lactate utilization in cognition as well as evidence for bioenergetic changes in schizophrenia. We consider possible drivers of abnormal bioenergetic coupling, including genetic risk factors for schizophrenia, metabolic consequences of abnormal glutamatergic brain development, and the effects of antipsychotic medications. We integrate these data into a working model to understand the bioenergetic interplay of astrocytes and neurons in psychiatric disorders (such as schizophrenia) characterized by synaptic dysfunction and consider possible treatment strategies.

BIOENERGETIC COUPLING AND ENERGY SUPPLY AT THE SYNAPSE

Bioenergetic coupling in the brain requires the coordination of multiple systems and cell types to deliver energetic substrates in a spatiotemporal manner. There are multiple mechanisms in the brain to meet neuronal energy demands, including glycolysis, oxidative phosphorylation, and lactate uptake. Additionally, glutamate released at the synapse signals increased energetic demand to astrocytes and enhances production of bioenergetic substrates via increased glucose uptake, glycolytic rate, and lactate generation (11–13). To shape plasticity, glutamate levels in the synapse are normally tightly controlled by astrocytes, which remove extracellular glutamate via excitatory amino acid transporters (EAATs) (14). These transporters rely on the electrochemical gradient maintained by the adenosine triphosphate (ATP)–dependent Na^+,K^+-ATPase. Thus, the clearance of synaptic glutamate is bioenergetically costly as well.

Whereas the role of glutamate clearance in bioenergetic homeostasis is generally well understood, the principal mechanism fulfilling the energy requirements of neurons has been debated. Two bioenergetic ideologies offer viable energy production pathways under normal and pathological conditions. An early hypothesis stated that the main mechanism of energy production for neurotransmission was systemically derived glucose taken up by neurons and metabolized by oxidative phosphorylation (15). Conversely, a more recent and

ISSN: 0006-3223

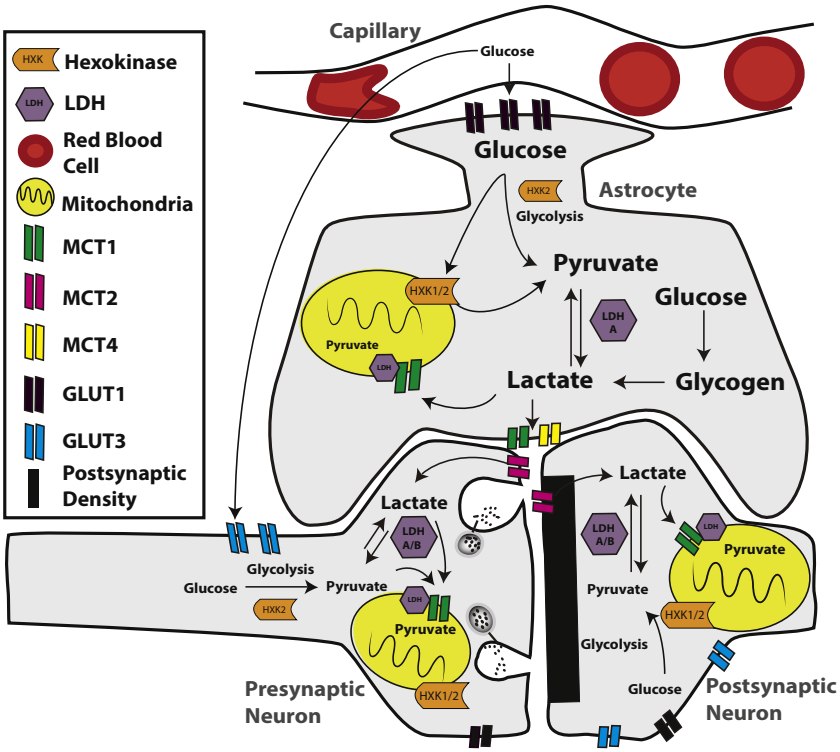

Figure 1. Bioenergetic coupling in normal brain. Glycolysis and oxidative metabolism via tricarboxylic acid (TCA) cycle are key pathways in maintaining synaptic function. Both neurons and astrocytes undergo glycolysis even during aerobic conditions. Glucose, which feeds the glycolytic pathway, can enter cells through glucose transporters (GLUTs). Meeting the energy demand of neurons is highly reliant on the metabolic coupling of neurons to glycolysis and lactate production in astrocytes. There are several key enzymes in glycolysis, including hexokinase and lactate dehydrogenase (LDH). This metabolic coupling also requires monocarboxylate transporters (MCTs), which rapidly transport lactate generated by astrocytes into the extracellular space and into neurons. Once in neurons, lactate is converted back to pyruvate by LDH. Pyruvate may then enter the TCA cycle and oxidative phosphorylation to generate 30–36 molecules of adenosine triphosphate. This net flow of energetic substrates from astrocytes to neurons to support neuronal activity is termed the astrocyte-neuron lactate shuttle.

well-supported hypothesis suggests that astrocytes produce lactate in aerobic conditions (Warburg effect), with lactate shuttling from astrocytes to meet the bioenergetic needs of neurons. Pellerin and Magistretti have termed the net flow of lactate from astrocytes to neurons the astrocyte-neuron lactate shuttle (16) (Figure 1), which may help fuel neuronal oxidative phosphorylation (17,18). This hypothesis posits that neuronal activation increases the concentration of glutamate in the synapse, activates glycolysis in glycogen-rich glial cells even in the presence of normal oxygen levels, and generates lactate that is transported out of astrocytes and into neurons via monocarboxylate transporters (MCTs) (15,19,20). For example, lactate generated by glycolysis in glial cells constitutively supports synaptic transmission even under conditions in which a sufficient supply of glucose and intracellular ATP is present (17). Lactate production in astrocytes and the lactate shuttle are now thought to be the main mechanisms supporting bioenergetic coupling (21–23). We discuss both hypotheses in detail in the Supplement.

GLUCOSE AND LACTATE UTILIZATION IN NORMAL COGNITION

The importance of glucose and lactate utilization in cognitive function is more resolved. The coupling mechanism between neuronal activity and astrocyte lactate production is essential for working memory performance and long-term memory formation in rodents, which is impaired following disruption of the MCTs and bioenergetic coupling (24,25). Breaking the lactate shuttle disrupts synaptic transmission, resulting in cognitive impairment (26,27). Patients with schizophrenia experience a wide range of psychotic symptoms as well as profound negative symptoms and cognitive deficits (1–6). As bioenergetic coupling and neurotransmission are tightly coupled to cognitive function, these pathways could be important pathophysiological substrates in schizophrenia.

EVIDENCE FOR ABNORMAL BIOENERGETIC FUNCTION IN SCHIZOPHRENIA FROM TRANSCRIPTOMIC AND PROTEOMIC STUDIES

Schizophrenia pathology features a number of abnormalities associated with glucose metabolism, the lactate shuttle, and bioenergetic coupling, suggesting energy storage and usage deficits in the brain in this illness (Table 1) (28–41). Studies employing microarrays found significant decreases in the expression of genes encoding proteins involving the malate shuttle, tricarboxylic acid (TCA) cycle, ornithine-polyamine, aspartate-alanine, and ubiquitin metabolism in the dorsolateral prefrontal cortex (DLPFC) in schizophrenia. These changes were not attributable to antipsychotic treatment, which may have a restorative effect (38). Alterations in these genes might have significant implications for oxidative phosphorylation, which is a key mechanism of ATP production for neurotransmission. Other studies implicate mitochondrial dysfunction in the pathophysiology of schizophrenia (40,41). Furthermore, a genetic study demonstrated evidence in schizophrenia for linkage between enzymes that control glycolysis, such as 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2, hexokinase 3, and pyruvate kinase 3, suggesting that genetic risk for this illness includes bioenergetic substrates (42).