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The appropriation of glucose through primate neurodevelopment

Amy L. Bauernfeind [a, b, *], Courtney C. Babbitt [c]

[a] Department of Anthropology, The George Washington University, Washington, DC 20052, USA
[b] Department of Anatomy & Neurobiology, Washington University School of Medicine, St. Louis, MO 63110, USA
[c] Department of Biology, University of Massachusetts Amherst, Amherst, MA 01003, USA

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ABSTRACT

The human brain is considerably larger and more energetically costly than that of other primate species. As such, discovering how human ancestors were able to provide sufficient energy to their brains is a central theme in the study of hominin evolution. However, many discussions of metabolism frequently omit the different ways in which energy, primarily glucose, is used once made available to the brain. In this review, we discuss two glucose metabolic pathways, oxidative phosphorylation and aerobic glycolysis, and their respective contributions to the energetic and anabolic budgets of the brain. While oxidative phosphorylation is a more efficient producer of energy, aerobic glycolysis contributes essential molecules for the growth of the brain and maintaining the structure of its cells. Although both pathways occur in the brain throughout the lifetime, aerobic glycolysis is a critical pathway during development, and oxidative phosphorylation is highest during adulthood. We outline how elevated levels of aerobic glycolysis may support the protracted neurodevelopmental sequence of humans compared with other primates. Finally, we review the genetic evidence for differences in metabolic function in the brains of primates and explore genes that may provide insight into how glucose metabolism may differ across species.

Introduction

Although it makes up only 2% of total body mass, the adult modern human brain utilizes about 15–20% of the body's resting metabolic resources (Hofman, 1983). This is far greater than the brains of other primates that consume between 2 and 10% of their body's resting energy expenditure (Mink et al., 1981). The rate of glucose uptake needed to sustain the adult human brain imposes a substantial cost to the body that is thought to be met either by a greater input of energy through increased diet quality or cooking (Gaulin and Kurland, 1976; Leonard and Robertson, 1994; Aiello and Wheeler, 1995; Broadhurst et al., 2002; Fish and Lockwood, 2003; Wrangham, 2009) or by metabolic tradeoff with other organs, including musculature (Leonard et al., 2003) or the size of the digestive tract (Aiello and Wheeler, 1995 but see; Navarrete et al., 2011). It has also been suggested that modern humans coevolved an extended life history and period of childhood to support the growth and metabolic requirements of the brain (Foley and Lee, 1991; Bogin, 1997; Leigh, 2004; Barton and Capellini, 2011).

Although the human brain is very energetically expensive in adulthood, the rate of glucose uptake per gram of tissue reaches twice the adult level around the age of two or three years (Chugani et al., 1987). In contrast, the brain of the macaque monkey obtains its maximum rate of glucose uptake per gram of tissue at birth (Jacobs et al., 1995), which is about one-third greater than the rate of glucose uptake in the adult macaque brain. Therefore, the glucose requirements of the primate brain are dynamic throughout the lifetime, and the trajectory of how glucose uptake rates change over time appears to differ across species. Humans are unique among primates in that the extremely high metabolic costs of growing the large human brain must be sustained over a much longer period of neurodevelopment (Leigh, 2004; Barrickman et al., 2008). Additionally, the increased energy required for the human brain's maturation may not be met by glucose alone but may depend upon additional sources of energy, including ketones (Miller et al., 1982; Nehlig and Pereira de Vasconcelos, 1993). Although it is clear that meeting the metabolic costs imposed by the brain must have been a difficult challenge to meet during human evolution, the precise reasons for this high energetic cost deserve more attention.

All multicellular organisms use adenosine-5'-triphosphate (ATP) as their chief energy source, and it is most typically supplied

Abbreviations: Acetyl-CoA, acetyl coenzyme A; ATP, adenosine-5′-triphosphate; LDH, lactate dehydrogenase; PET, positron emission tomography; PPP, pentose phosphate pathway.

* Corresponding author.
E-mail address: amy81@gwu.edu (A.L. Bauernfeind).

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by the metabolic pathway of oxidative phosphorylation (Nelson and Cox, 2008). Oxidative phosphorylation includes the sequential processes of glycolysis, the citric acid cycle, and the electron transport chain, which, together, metabolize glucose into ATP. In this review, we use the definitions put forth by other authors (Pellerin and Magistretti, 1994; Vander Heiden et al., 2009; Vaishnavi et al., 2010) to distinguish between glycolysis and aerobic glycolysis. As described above, glycolysis digests glucose to pyruvate and is an integral step of oxidative phosphorylation. Aerobic glycolysis also refers to the breakdown of glucose to pyruvate but is not followed by the citric acid cycle and the electron transport chain. Despite its name and unlike oxidative phosphorylation, aerobic glycolysis does not consume oxygen and is therefore not an aerobic process. Although both aerobic glycolysis and oxidative phosphorylation produce ATP from glucose, oxidative phosphorylation is a much more efficient producer of energy. In most tissues of the body, aerobic glycolysis is a pathway typically associated with hypoxic conditions (insufficient oxygen availability) or dysfunction of the mitochondria that would prevent oxidative phosphorylation from occurring (Ullah et al., 2006; Soane et al., 2007; Perez de Heredia et al., 2010; Nielsen et al., 2013). However, aerobic glycolysis also occurs in the brain under normal conditions despite the presence of sufficient oxygen for oxidative phosphorylation (Raichle et al., 1970; Wyss et al., 2011). Moreover, some authors have noted the importance of aerobic glycolysis as a contributor of carbon to the anabolic processes that synthesize the constituent molecules of the brain, including lipids, proteins, and nucleotides (Raichle, 2010; Vaishnavi et al., 2010).

We review the contributions of the two major metabolic pathways, aerobic glycolysis and oxidative phosphorylation, toward meeting the developing brain's energy requirements and the necessary contribution of molecules to its biomass. Because protracted development is a hallmark of human brain growth and development (Leigh, 2004), we review how humans may differ from other primates in their reliance of these pathways over time. For more detail regarding the biochemical and neurological basis for these hypotheses, we refer the reader to a recent review by Bauernfeind et al. (2014). Finally, we consider what gene sequence evolution and differential gene expression tell us about how brain glucose metabolism may differ in humans compared with other primates. We discuss the importance of these issues for the development, function, and maintenance of the energetically expensive human brain.

A brief review of metabolic pathways and anabolic processes

When a molecule of glucose enters a cell, the typical outcome is for it to be immediately converted into pyruvate by glycolysis, a process that occurs in the cytoplasm of the cell and generates two molecules of ATP (Nelson and Cox, 2008). Pyruvate can be converted into lactate, for short-term energy storage, or acetyl coenzyme A (acetyl-CoA), which is used in the oxidative phosphorylation pathway. In oxidative phosphorylation, acetyl-CoA enters the mitochondria and is completely metabolized into carbon dioxide and water by the citric acid cycle. The electron transport chain follows and a total of around 36 molecules of ATP are produced per molecule of glucose (Fig. 1). Through aerobic glycolysis, one of the molecules derived from glucose may be used as a precursor to biosynthetic pathways, including the synthesis of fatty acids and other lipids required for myelination (Brown et al., 2001; Tekkök et al., 2005) or the synthesis of amino acids necessary for building the complex proteins that compose the cell's structural and functional elements including enzymes (Nelson and Cox, 2008). Indeed, the synthesis of enzymes by aerobic glycolysis may even be critical to the development and maintenance of the molecules that compose the citric acid cycle, suggesting interdependence between aerobic glycolysis and oxidative phosphorylation (Hovda et al., 1992, 2006). An intermediate molecule of glycolysis, glucose-6-phosphate, may be used by the pentose phosphate pathway (PPP) for the synthesis of nucleotides. Each of these anabolic processes

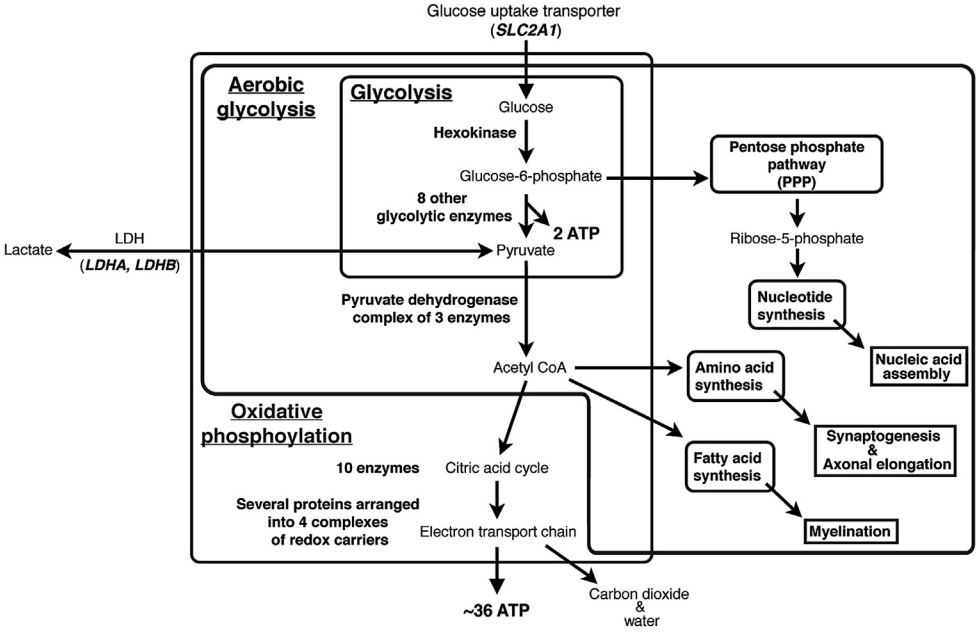

Figure 1. The potential outcomes of glucose entry into a neuron are diagramed. Larger boxes surround several stages of the metabolic pathways and encompass the steps that are referred to by glycolysis, oxidative phosphorylation, and aerobic glycolysis. Although aerobic glycolysis produces only two molecules of ATP, it provides molecules, glucose-6-phosphate and pyruvate, that can be used as substrates for nucleotide, amino acid, and fatty acid synthesis. Oxidative phosphorylation is an efficient producer of ATP, yielding approximately 36 molecules of ATP per molecule of glucose. The major steps within glycolysis and oxidative phosphorylation have the names of the enzymes or transporters next to them or a listing of how many molecules are involved in the process. Importantly, these molecules may be explored as potential targets of gene regulation that may change the kinetics of these glucose metabolism pathways. This figure is reproduced with permission from Bauernfeind et al. (2014).