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Metabolism as a tool for understanding human brain evolution: Lipid energy metabolism as an example

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ABSTRACT

Genes and the environment both influence the metabolic processes that determine fitness. To illustrate the importance of metabolism for human brain evolution and health, we use the example of lipid energy metabolism, i.e. the use of fat (lipid) to produce energy and the advantages that this metabolic pathway provides for the brain during environmental energy shortage. We briefly describe some features of metabolism in ancestral organisms, which provided a molecular toolkit for later development. In modern humans, lipid energy metabolism is a regulated multi-organ pathway that links triglycerides in fat tissue to the mitochondria of many tissues including the brain. Three important control points are each suppressed by insulin. (1) Lipid reserves in adipose tissue are released by lipolysis during fasting and stress, producing fatty acids (FAs) which circulate in the blood and are taken up by cells. (2) FA oxidation. Mitochondrial entry is controlled by carnitine palmitoyl transferase 1 (CPT1). Inside the mitochondria, FAs undergo beta oxidation and energy production in the Krebs cycle and respiratory chain. (3) In liver mitochondria, the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) pathway produces ketone bodies for the brain and other organs. Unlike most tissues, the brain does not capture and metabolize circulating FAs for energy production. However, the brain can use ketone bodies for energy. We discuss two examples of genetic metabolic traits that may be advantageous under most conditions but deleterious in others. (1) A CPT1A variant prevalent in Inuit people may allow increased FA oxidation under nonfasting conditions but also predispose to hypoglycemic episodes. (2) The thrifty genotype theory, which holds that energy expenditure is efficient so as to maximize energy stores, predicts that these adaptations may enhance survival in periods of famine but predispose to obesity in modern dietary environments.

Introduction

Biochemistry provides a link between two pillars of current studies of evolution, the genome and studies of the environmental conditions under which humans and their ancestors lived and evolved. We illustrate this using the model of lipid energy metabolism, the process by which energy is derived from fat stores.

Energy metabolism is important for human brain evolution: the adult human brain weighs only 2% of body mass but accounts for 20% of whole body resting energy expenditure; in human newborns, the corresponding figures are ~11% of body weight and >50% of energy consumption (Kennedy and Sokoloff, 1957; Sokoloff, 1989). Energy use is thought to be an important determinant of brain size (Laughlin and Sejnowski, 2003).

Mammals have developed complex strategies for storing and releasing energy. After fasting longer than a few hours, mammals derive energy principally from stores of fat. Lipid energy metabolism involves white adipose tissue, which stores and releases fatty acids, and fatty acid metabolizing tissues, which use fatty acids or their byproducts as fuel.

Abbreviations: AcAc, acetoacetate; CoA, coenzyme A; CPT, carnitine palmitoyl transferase; HMG, 3-hydroxy-3-methylglutaric acid; mHS, mitochondrial HMG-CoA synthase; SCOT, succinyl-CoA: 3-oxoacid transferase; TG, triglycerides.

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We begin this article with discussion of ancient metabolic pathways. Then we describe the general structure and control of lipid energy metabolism in humans today and how current metabolic pathways may have been pieced together from the prehistoric genomes. Finally, we note some examples of gene-environment combinations of current interest, which may be advantageous or cause disease depending upon environmental conditions, suggesting that the refinement of lipid energy metabolism is an ongoing process.

Ancient metabolism: the wellsprings of life

Oxygen, lipids and energy metabolism

Fascinating hypotheses have been advanced concerning (1) how organic compounds and chemical reactions resembling those used in metabolic pathways of modern humans may have arisen on earth before cellular life emerged (Bada and Lazcano, 2002; Melendez-Hevia et al., 2008; Fani and Fondi, 2009; Brown, 2012; Cleaves et al., 2012; Danger et al., 2012) and (2) how the first lipid-like molecules may have arisen (Segre et al., 2001). These subjects are beyond the scope of this review. The first cells did not use oxygen, i.e., they were anaerobic. Most anaerobic energy metabolism proceeds by partial degradation of molecules (fermentation), accompanied by the production of small amounts of energy and the release of the partially degraded, energy-rich molecules from the cell. One such metabolic pathway, that is found in nearly all organisms, is the partial degradation of glucose to pyruvate (glycolysis) in the cytoplasm, with two branches leading from pyruvate (Fig. 1). These core reactions permit energy production and provide many of the substrates for synthesis of amino acids and other essential compounds (Bada and Lazcano, 2002; Melendez-Hevia et al., 2008; Cleaves et al., 2012; Danger et al., 2012).

In aerobic organisms, oxygen is consumed to produce energy. Oxygen, produced by photosynthesis in plants, began to accumulate in the atmosphere about 500 million years ago (Gould, 1994). Oxidative metabolism offered a new, much more efficient way than simple glycolysis to obtain energy from food.

Fatty acids are degraded by oxidation. The oxidation of fatty acids can be viewed in three steps, beta oxidation, the Krebs cycle and the respiratory chain. Fatty acids are long molecules. Each cycle of beta oxidation shortens the fatty acid and produces a molecule of acetyl-coenzyme A (CoA), plus energy-rich reduced nucleotides. The shortened fatty acyl-CoA that is produced can undergo further beta oxidation. Eventually most fatty acids are completely converted to acetyl-CoA.

In the Krebs cycle, acetyl-CoA enters carbon dioxide is released (Fig. 2a). In contrast to glycolysis, the Krebs cycle is located in the mitochondrion. The Krebs cycle could have arisen by the acquisition of a single enzyme, by which the end compounds of the two branches of the pathways of metabolism from pyruvate were connected (e.g., Melendez-Hevia et al., 2008), thus creating a cycle (Fig. 1). In the Krebs cycle, nucleotides such as nicotinamide adenine dinucleotide (NAD) undergo reduction and their reduced forms (e.g., NADH) are rich in energy.

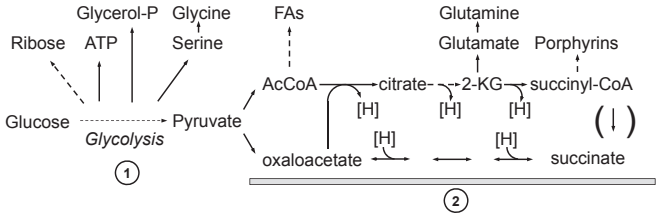

Figure 1. The core pathways of metabolism. The earliest cells are thought to have possessed a central core of anaerobic metabolism from which limited amounts of energy were derived and that furnished the precursors for synthesizing essential cell components such as ribonucleic acids, amino acids, FAs, porphyrins and reducing equivalents (here indicated as [H]). The Krebs cycle can be created by the addition of a single reaction (succinyl coenzyme A synthetase, shown between parentheses on the far right of the figure). Dashed lines indicate segments composed of more than one enzymatic reaction. Based on (Melendez-Hevia et al., 2008). Numbers in circles: 1 = glycolysis; 2 = Krebs cycle-related reactions.

The third step is terminal oxidation by the electron transport chain (also known as the respiratory chain). The electron transport chain is a marvel of complexity (DiMauro and Schon, 2003; Vafai and Mootha, 2012). Situated in the inner membrane of mitochondria, it receives high energy hydrogen atoms from NADH and from reduced flavin nucleotides. These high energy compounds are produced mainly by the Krebs cycle and by beta oxidation of fatty acids. In the course of oxidative metabolism, the hydrogen atom is split into its component proton and electron. The chemical energy derived from the sequential reactions along the electron transport chain is used to expel protons from the matrix space inside the mitochondrion. Three of the enzyme complexes of the electron transport chain, complexes I, III and IV, each expel protons from the matrix. This creates a proton (pH) gradient between the mitochondrial matrix and the extramitochondrial space, with a lower concentration of protons (higher pH) inside the mitochondrial matrix than outside. Complex V of the electron transport chain harnesses the proton gradient, and couples the reentry of protons into the mitochondrial matrix to the synthesis of adenosine triphosphate (ATP). ATP is the main fuel molecule of the cell. There is great interest in understanding how this elaborate system evolved from simpler elements (Albert et al., 2002; Muller and Gruber, 2003; Vafai and Mootha, 2012) but we will not pursue the question further in this review.

Mitochondria: the cellular furnace

Mitochondria are thought to be descendants of an aerobic monocellular organism that was engulfed by another cell but that survived. This relationship between two organisms, or endosymbiosis (Margulis and Chapman, 1998; Dyall et al., 2004), would have provided the host cell with the major advantage of deriving over ten-fold more energy from available fuels than from glycolysis alone. Arguably, endosymbiosis was one of the most important events in eukaryotic evolution.

Mitochondria retain many general features of prokaryotes, which differ from those of the rest of the cell (Gray, 2012; Vafai and Mootha, 2012). This includes the presence in mitochondria of multiple copies of a small circular chromosome that resembles a bacterial plasmid, of mitochondria-specific systems of DNA replication and RNA synthesis, of a genetic code that differs from that of nuclear DNA, and of distinct mitochondrial protein translation machinery. Also of note, mitochondria are bounded by two membranes, an outer membrane in which the lipid content is similar to that of other eukaryotic cell membranes, and an inner membrane with a distinct lipid composition and a specific set of mitochondrial transporters that ensure efficient movement of proteins and metabolites.

Thus, the earliest cells evolved a system for extracting a high fraction of the chemical energy of foods for the synthesis of the basic chemicals of life (Figs. 1 and 2a). This system provided the framework on which energy metabolism in multicellular organisms was constructed.

The mechanisms of metabolic evolution

Metabolic evolution has occurred by several mechanisms, leading to the metabolic state of today's higher organisms including humans. Lipid energy metabolism provides examples of at least