1. INTRODUCTION

In this chapter I discuss the molecular effects of changes in the diet on liver and brain metabolic fuel adaptation, with special reference to ketogenesis and the anticonvulsant ketogenic diet (KD). I examine metabolic adaptation in terms of the effects of diet-imposed blood hormone and fuel switches on metabolism of fatty acids, amino acids, and sugars, with special attention to the regulation of activity of multiple enzymes of intermediary metabolic pathways by metabolic sensor proteins. As an example of the effect of dietary change on genetic programming, I examine the regulation of a gene encoding the key enzyme of the ketogenic pathway. In the context of the antiepileptic action of the KD and the structural organization of brain cells, I discuss recent work indicating that the brain possesses both functional fuel sensors and the capacity for localized ketogenesis. Finally, I examine the implications for the anticonvulsant mechanism of the KD of changes in liver and brain ketogenesis and fuel adaptation.

2. METABOLIC FUEL ADAPTATION

The sugar glucose is an essential blood fuel for all the cells in the body (1). It is derived from the breakdown of carbohydrate provided by the typical low-fat/high-carbohydrate diet. Although glucose is the major cellular fuel, many cell types can also use alternative fuels such as fatty acids (derived from dietary fats and body fat stores), ketone bodies (derived from fatty acid breakdown by the liver), and amino acids (derived from dietary protein and muscle protein stores) (1). The brain can use such alternative fuels for part of its energy requirements; however, unlike liver, it has an absolute requirement for a continuous supply of blood glucose fuel. The liver is the major organ responsible for the maintenance of stable blood glucose concentrations under differing dietary conditions. At the cellular level, hepatocytes can detect and flexibly respond to changes in blood fuel concentrations resulting from alterations in the quality or quantity of the diet (1). Diet quantity ranges from “well fed” through varying degrees of calorie restriction to, ultimately, starvation; diet quality ranges, for example, from low fat to high fat. Thus, the liver of a child who switches from consuming a normal diet to the KD (2) must detect and respond to both quantitative (calorie unrestricted to calorie restricted), and qualitative (low fat, high carbohydrate and protein to high fat, low carbohydrate and protein) changes in blood fuel supply.

From: Epilepsy and the Ketogenic Diet
Edited by: C. E. Stafstrom and J. M. Rho © Humana Press Inc., Totowa, NJ
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Thus, when blood glucose concentrations begin to decrease, during starvation or the conditions imposed by the KD, liver hepatocytes respond by switching from using blood glucose as a fuel to using blood fatty acids. Furthermore, they use the energy derived from the catabolism ("burning") of fatty acid fuel to synthesize glucose from blood amino acid carbon skeletons. Such glucose is then exported back to the blood, thus compensating for the initial diet-imposed decreases in blood glucose concentrations. This process of generating blood glucose from the liver is known as gluconeogenesis and serves to maintain a steady supply of blood glucose fuel for the brain. The liver therefore acts as a "thermostat" for the maintenance of a steady concentration of blood glucose. A consequence of switching from using glucose to using fatty acids for fuel is that hepatocytes also return to the blood high concentrations of the ketone bodies acetoacetate and 3-hydroxybutyrate, partial breakdown products of such fatty acids. This is because under conditions of low blood glucose, hepatocytes cannot fully oxidize fatty acids to carbon dioxide (1). This process of converting fatty acids to ketone bodies by hepatocytes is termed ketogenesis, and a diet, i.e., the KD, a fuel, or a drug that stimulates ketogenesis is described as ketogenic.

Although liver hepatocytes are considered to be the major cell type that regulates fuel supply in blood, it is becoming clear that certain other cell types may have a similar role in regulating fuel supply in an organ (3). An emerging example of such a cell type, particularly relevant to the anticonvulsant action of the KD, is the brain astrocyte. Astrocytes are juxtaposed between the blood fuel supply and the neuronal cells, which are critical to conducting the electrical impulses involved in neurotransmission in brain. Moreover, astrocytes exhibit metabolic adaptations to dietary changes and, as such, may be regarded as a "dialysis machine" for neurons, acting as a fuel filter between neurons and the blood supply. Later in this chapter, I examine the growing body of evidence indicating that astrocytes perform ketogenesis under certain conditions, with implications for the supply of ketone body fuels on behalf of surrounding neurons.

3. ENZYMES OF FATTY ACID OXIDATION AND KETOGENESIS

Fatty acids, the precursors of ketone bodies, exist in a variety of chain lengths, from long-chain fatty acids, e.g., palmitate, through medium-chain fatty acids, e.g., octanoate, to short-chain fatty acids, e.g., butanoate. All such fatty acids can be catabolized in the mitochondria of hepatocytes by β-oxidation (1) (Fig. 1), whereby 2-carbon units are progressively removed from the fatty acid chain. The 2-carbon units generated are in the form of the ubiquitous cellular molecule, acetyl-coenzyme A (CoA) (Fig. 1). The ketone body acetoacetate is then formed by the condensation of acetyl-CoA, followed by the removal of the CoA moiety. Subsequently the ketone body 3-hydroxybutyrate is formed on reduction of acetoacetate, which in turn is dependent on reduced nicotinamide adenine dinucleotide (NADH). In addition, under conditions of high rates of ketogenesis, the ketone body acetone is formed spontaneously. A series of enzymes, upstream of acetyl-CoA, is responsible for catalyzing the breakdown of fatty acids of differing chain lengths. Subsequently, two enzymes downstream of acetyl-CoA are responsible for the formation of the first ketone body, acetoacetate. All such enzymes must be present for fatty acid oxidation and ketogenesis (FAOK) to be executed, as evidenced by the potentially lethal effects of inborn errors of FAOK (4). However, only certain enzymes appear to have a major regulatory role in the flux of fatty acids to ketone bodies (3). This is because such enzymes catalyze key branch-