The Ketogenic Diet

Interactions With Brain Amino Acid Handling

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1. BRAIN GLUCOSE METABOLISM: A SYNOPSIS

The energy requirements of the human brain are enormous. Cerebral oxygen consumption is 35 mL/min/kg or approx 50 mL/min in the adult brain. The rate of whole-body O₂ consumption is 250 mL/min, indicating that approx 20% of oxygen utilization is directed toward the needs of the brain, which occupies only 2% of body weight. Virtually no oxygen is stored in the brain, implying that to maintain the integrity of this vital organ, cerebral blood flow (approx 800 mL/min), which constitutes about 15% of cardiac output, must proceed in an uninterrupted manner. If flow is completely shut down, a state of unconsciousness would ensue within 10 s.

Virtually the sole metabolic substrate of the adult brain is glucose, which is consumed at a rate of 310 µmol/min per kilogram of brain tissue. The stoichiometry of glucose oxidation (C₆H₁₂O₆ + 6O₂ → 6CO₂ + 6H₂O) implies a rate of oxygen consumption that would be six times that of glucose utilization, or 1860 µmol/min/kg. In fact, brain oxygen consumption is only five times that of glucose utilization (1560 µmol/min/kg) because a fraction of glucose is not oxidized completely but is converted to lactate, a portion of which is released from brain to blood. In addition, a relatively minor fraction of brain glucose utilization is given over to the synthesis of macromolecules and other cellular constituents (1,2).

Both neurons and astrocytes process glucose via the glycolytic pathway. However, glycolysis may be relatively more active in glia, which release lactate to neurons, where this intermediate serves as an important metabolic substrate (3). The rate of glial lactate production is coupled to neuronal activity because neuronal depolarization favors release of glutamate and K⁺, both of which are taken up by astrocytes in an energy-dependent manner. To fuel these processes, astrocytic glycolysis increases in intensity.

The metabolism of glucose does not proceed in a straightforward manner through glycolysis and the tricarboxylic acid cycle to yield CO₂ and H₂O. This is because two essential intermediates of the tricarboxylic acid cycle, oxaloacetate and 2-ketoglutarate, are in very rapid equilibrium with the large aspartate and glutamate pools of the brain (Fig. 1) (4,5). Such equilibrium is sustained by highly efficient transamination reactions.
that effectively link brain metabolism of these amino acids with that of glucose (6). If there is an apparent “delay” in the production of CO₂ from glucose carbon, the primary reason is that this carbon flows virtually seamlessly not only through the tricarboxylic acid cycle, but through large pools of amino acids such as aspartate, glutamate, glutamine, and γ-aminobutyric acid (GABA).

As we shall discuss, in the ketotic brain, there may occur a significant change in the interrelationship of metabolism through the tricarboxylic acid cycle and through the brain glutamate pools. We have hypothesized that the net effect of these changes is to favor the flow of glutamate carbon into GABA and to glutamine, which the brain readily converts to GABA (7–9). This chapter explains the details of these putative adaptations. To better understand the relevant biochemistry and physiology, we must first consider the handling by brain of glutamate, the most important excitatory neurotransmitter.

2. BRAIN GLUTAMATE HANDLING: AN OVERVIEW

Glutamic acid is the major excitatory neurotransmitter of the mammalian nervous system. This amino acid must be quickly cleared from the extracellular fluid following its release from nerve endings. A persistently high glutamate concentration in the synaptic cleft would obscure the high signal-to-noise ratio that is essential to effective neurotransmission. By efficiently removing glutamate from the extracellular space, the system is repoised to detect the release of additional glutamate from presynaptic neurons. In addition, an untoward external glutamate level would favor the development of excitotoxicity because of excessive stimulation of vulnerable neurons. Considerable evidence now points to astrocytes as the major site of brain glutamate uptake (Fig. 2) (10–12). Glial cells are favored with a plenitude of excitatory amino acid transporters that abet the rapid and efficient removal of glutamate from the synapse. They also have

![Fig. 1. Schema of interaction of metabolism in brain of glucose and glutamate. The crucial site of intersection occurs via the aspartate aminotransferase reaction, which, in effect, couples the glutamate-aspartate interchange via transamination to the metabolism of glucose through the tricarboxylic acid (TCA) cycle. Glutamate is converted to aspartate by reacting with oxaloacetate. The other major routes of glutamate disposition consist of the synthesis of either glutamine or GABA.](image-url)