CEREBRAL METABOLISM and NEURAL FUNCTION

Editors

Janet V. Passonneau, Ph.D.

Chief, Laboratory of Neurochemistry
National Institute of Neurological and
Communicative Disorders and Stroke
National Institutes of Health

Richard A. Hawkins, Ph.D.

Professor of Physiology
Department of Anesthesia
The Pennsylvania State University College of Medicine
The Milton S. Hershey Medical Center

W. David Lust, Ph.D.

Research Pharmacologist
Laboratory of Neurochemistry
National Institute of Neurological and
Communicative Disorders and Stroke
National Institutes of Health

Frank A. Welsh, Ph.D.

Associate Professor of Biochemistry in Neurosurgery
and in Biochemistry and Biophysics
University of Pennsylvania
School of Medicine

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CHAPTER

26

Alternate Fuel Utilization by Brain*

George F. Cahill, Jr. and Thomas T. Aoki

In evolutionary-advanced animals, the brain poses a unique problem in energy support, and especially so in man, due to its voracious but yet finicky appetite.[6, 11-14, 23, 24, 62, 63, 65] In the adult, glucose is the sole substrate, except when levels of the ketoacids, acetoacetate, and β-hydroxybutyrate are sufficiently elevated to permit displacement of glucose utilization.[1, 18, 38, 39, 43 49, 52, 62, 73, 79] Mannose can also be utilized, but the needed concentration to create an adequate plasma-to-brain gradient can only be achieved by infusion.[76, 83]

In the neonate, lactate appears to be a significant albeit quantitatively minor fuel, as discussed by Vannucci et al. in Chapter 29. In certain pathological states characterized mainly or in part by lactic acidosis such as in children with type I glycogen storage disease or in adults with primary lactic acidosis, lactate may become a significant substrate, but this possibility has not been directly studied as yet. In addition, lactate would only be of use in those states with adequate perfusion and oxygenation, with high levels of lactic acid in blood and low levels of glucose, a pattern that occurs physiologically only with severe prolonged exercise and exhaustion. Thus, we are left with glucose and the ketoacids as the principal substrates for human brain. The chemistry and physiology of ketone utilization are discussed in Chapters 27 and 28 so this brief chapter will focus more on the integration of CNS fuel utilization into the remainder of the body, leaning heavily on some evolutional and anthropological speculations.

ARMOR

With the emergence of the vertebrates, the brain was encased with cartilage or bone, which effectively precluded more than minimal fluctuations in size. Thus, unlike liver and muscle, glycogen storage in brain, with its obligatory concomitant storage of 3–4 g of water per gram of glycogen,[28, 45, 57] cannot occur except for small amounts; yet, Karnovsky and colleagues discuss in Chapter 39 that even these very small amounts may have a physiologic role as in the sleep-awake cycle, a novel and unique observation.

BLOOD-BRAIN BARRIER

An even more challenging decision was made when brain was separated from circulating fluids by the blood-brain barrier.[69] In the eyes of a comparative neurochemistry watcher, it was the only maneuver whereby primitive external signals could be internalized into the more complex metazoan organism with not only differentiated and specialized cells but also with discrete organs. Thus, external factors such as GABA,[34, 53] glycine, or glutamate could be preserved as internal behavioral modulators. This concept is analogous to the gonadal hypothesis which considers that progesterone or some similar steroid was produced by marine flora and initially signaled the primitive gonadal systems of

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the fauna to undergo reproduction as evidence of a lush environment. Eventual internalization and even neural control of endogenous steroid production by the primitive pituitary became selectively advantageous and was eventually controlled by external stimuli, but then only after integration via the high centers.

The armoring and physiologic segregation of brain from body fuels made things metabolically more difficult, particularly in higher vertebrates, and especially in man. Only factors capable of crossing the luminal and contraluminal cell walls and the cytoplasm of endothelial cells could gain access,[69] thereby effectively excluding all macromolecules, including the free fatty acid-albumin complex (which could be metabolized if entered[81]) and various other lipoproteins. Thus, glucose alone remained in sufficient concentration in circulating fluids to meet the energy needs of the brain (except, in those instances where the ketoacids are in high concentration).

NEUROTRANSMITTERS

The third unique metabolic problem faced by brain is a function of both its high rate of metabolism and the almost "sterile saline" environment in which it resides. The very high oxidative rate in brain cells requires relatively high concentrations of tricarboxylic acid cycle intermediates such as α-ketoglutarate and oxalacetate. In most, if not all cells, these intermediates are in transamination equilibrium with glutamate and aspartate, and these in turn are in transamination equilibrium with all the other amino acids and their ketoanalogues which are capable of transamination. Thus, to be able to charge tRNAs for protein synthesis from other amino acids, glutamate and aspartate must be maintained in very high concentration in brain cytosol. Thus, the brain cell accumulates glutamate in 10mM concentrations, whereas in the extracellular fluid, the concentration of this amino acid is 3 orders of magnitude less. Other cells in the body have only a 1–2 order gradient and are thus more permeable to the dicarboxylic acids.

The unidirectional flux of many compounds across the blood-brain barrier has been studied in extenso, as discussed by Oldendorf in Chapter 15,[40–42, 58–60, 66, 78, 80] but net chemical flux has been more difficult to study, especially by arteriovenous differences because of the high rate of blood flow. These studies have been compounded by red cell-plasma interchanges.[20–22, 26, 48] A net uptake of amino acids has been demonstrated in man using plasma arterial-jugular vein differences,[23] but with whole blood we have been unable to demonstrate an uptake or release of any amino acid by brain in postabsorptive man. Chemical analyses, especially the recent studies of Wurtman, Fernstrom and their colleagues,[29–31, 36, 40, 44, 84, 85] and by Fisher's group[72, 77] and others, have shown that fluctuations in contents of certain neurotropic substances like acetylcholine and serotonin can be altered by nutritionally or metabolically related changes in their precursor concentrations in blood, namely, choline, tryptophan, and others such as the branched-chain amino acids. Thus, the brain's isolation from the remainder of the circulating factors in the organism is not as complete as implied above, yet glutamate, glycine, proline, and certain others are almost impermeant, as one would expect from their CSF/brain gradients.[2, 67]

CARCASS FUELS

To recapitulate, brain has a very high energy demand, it cannot store calories except as structural protein and lipid, and it has sequestered itself from the rest of the body by the blood-brain barrier, necessitating specific transport processes for those substances which do get across. Glucose is its sole fuel except when carbohydrate or carbohydrate precursors are lacking in the diet, as in starvation, or while eating high fat diets—in these states, ketoacid utilization becomes necessary for survival. To appreciate this observation,

especially as it applies to man, the physiology of body fuel storage and mobilization need to be briefly discussed.

Man in primitive society, as a forager and hunter, needed to be maximally mobile and yet able to preserve the muscle mass responsible for this mobility. In addition, he had to store what excess calories he could in the most efficient form with respect to the calorie/weight ratio. This second requirement was met only by triglyceride storage in adipose tissue in times of plenty and selective withdrawal of this lipid in times of need. Occasionally there were variable optimal ratios of muscle to adipose tissue, depending on man's mobility-to-sedentary existence as a survival factor. And this probably changed dramatically from time to time, as in the autumn prior to wintering in a cave or prior to boarding a vessel before a prolonged voyage. Thus, at times he might willingly overeat and expand his adipose tissue and at other times he might restrict the size of his lipid depot and cache the remaining food in stockpiles. Independence of seasonal cues was certainly an obvious survival advantage to this individual, thanks to his capacity to think better and to adapt to alterations in food or living habits by anticipating the need for calorie storage independent of fixed natural events. This relative independence from external control has obviously had its penalties and these include obesity, anorexia nervosa, and probably other hedonistic perversions such as smoking and drinking alcohol.

An average normal male of 176 cm, weighing 70 kg, might have 12 kg of triglyceride and 36 kg of muscle. These are listed with his other body fuels in Table 26.1. It is clear that free glucose and liver and muscle glycogen are calorically relatively trivial compared to adipose tissue triglyceride, even in normal man. On the other hand, skeletal muscle is a significant potential fuel component, but its conservation is obviously critical to survival. Conversely, lipid storage in adipose tissue provides both normal and obese man with the greatest number of otherwise unessential calories the body can store per unit weight of accumulated tissue. Furthermore, adipose tissue serves few purposes other than as a calorie depot. These purposes are comparatively trivial from a metabolic aspect and include thermal insulation (subcutaneous fat) and a mechanical (buttocks for sitting or buccal cheek pad for mastication) or cosmetic (the mammary tissue in most societies, or in certain extreme cases in man, examples like the unique steatopygian configuration of the Nama-Hottentot) function.

Table 26.1
Body Fuels in Adult Man (70 kg)

	Kg	Kilocalories
Adipose tissue triglyceride	12	110,000
Muscle protein	6	24,000
Carbohydrate		
glycogen-muscle	0.4	1,600
liver	0.07	280
blood glucose	0.02	80
Total		135,960

Special mention should be made of the human child whose brain at birth is two-thirds or more of the adult volume and in which cellularity is almost optimal.[15, 16] Myelinization comprises the bulk of postnatal growth, so brain oxygen consumption by the infant and child may comprise one-half of total basal fuel exchange. Thus, the infant needs to be fed frequently, and even with liver glycogen buffering the feeding-fasting cycle, hypoglycemia with only 12 or more hr of starvation is the norm. Ketoacidosis is also much more rapid with the average child, demonstrating significant ketonuria even after an overnight fast. In some children, the hypoglycemia appears more severe, and the ketoacids may be inadequate to prevent symptomatic cerebral fuel deficiency, the syndrome of ketotic hypoglycemia. This syndrome most probably is the end of the normal spectrum of physiologic variation in children being able to withstand starvation and may not be a discrete disease entity, but this is somewhat controversial.

STARVATION

During starvation, man goes through a series of overlapping metabolic phases.[11, 14, 73] In the interprandial period, hepatic glycogenolysis plus absorption of the residual fuel in the gut maintains the brain's glucose needs.[6] After an overnight fast, gluconeogenesis from amino acids released from muscle becomes more and more prominent, so that after 1–2 days of fasting gluconeogenesis is the sole support of blood glucose.[25, 61, 64, 68] A progressive decrease in glucose utilization by muscle occurs simultaneously. Other tissues such as red cells and renal medulla continue to glycolyze some glucose, but only to lactate, and these are returned to liver and kidney for resynthesis to glucose.[12] This energy shuttle, the Cori cycle, serves to deliver energy in the form of glucose to these glycolytic tissues, with the initial energy originating from fatty acid oxidation in liver and kidney. The remainder of the carcass uses free fatty acids derived from adipose tissue. By the 3rd day of starvation, hepatic ketogenesis has reached a maximum,[8, 31, 35, 71] but it takes over 1 week for circulating ketoacid levels to reach a plateau, and this is achieved by a gradual reduction in ketone utilization by muscle[64] as well as a more efficient renal reabsorption of filtered ketones.[74, 75]

Thus, initially, carcass becomes more and more efficient by first excluding glucose utilization over the initial 2–3 days of starvation[82] and by excluding ketone utilization by tissues other than brain over the succeeding week or 2. The net result is a progressive decrease in gluconeogenesis and, pari passu, a progressive decrease in the need to mobilize muscle protein, and this latter concept has been correlated with a more reduced state in muscle mitochondria.[4] Survival is thus months instead of weeks. Administration of glucose rapidly reverses the entire process, displacing gluconeogenesis and ketogenesis, as might be expected.[5, 74, 75]

Reichard and colleagues[70] have recently shown that acetone can be a small but significant pathway of acetoacetate metabolism and that, in man, acetone can be incorporated into glucose (Fig. 26.1). A previous utilization of acetone in cow udder was reported,[9] but this might be expected in the normally ketotic ruminant. Thus, there are four sources of glucose. The first is the continuous breakdown of some muscle protein and release of amino acids, and in man this cannot be effectively reduced further as it can in certain carnivores like the black bear[56] or in certain birds like the nesting emperor penguin,[50] in which net nitrogen loss approaches zero. The second is the glycerol from adipose tissue triglyceride, which in fasting man contributes 15–20 g of glucose daily. In the black bear, by the way, and probably also in the emperor penguin, its much larger carcass and relatively smaller brain permit glycerol to supply all the glucose needed. Hence the bear, even with its 3–4 months of total starvation, has only minimal ketone levels of about 1 mM, and brain can thereby continue to utilize mainly glucose, although this has not been directly measured. The third source in man is recycling lactate and pyruvate, in which even the brain contributes a little,[62] but this, of course, is of no value to net glucose syn-

FASTING HUMAN

Acetoacetate production 20-77 μmol/m^2/min

+ 37%

Acetone → 2-30% breath & urine

+ 59%

Glucose (11% of glucose production)

Figure 26.1 Contribution of acetoacetate to glucose synthesis. (Data from Reichard et al.[70])

thesis. The fourth is the 10 or so grams of glucose from acetoacetate via acetone, according to Reichard and colleagues.[71]

Could the entire human brain use ketoacids as its sole fuel? The regionalization of glucose and ketone uptake as shown by Hawkins and others (see Chap. 28) suggests that some cells may be obligate glucose users. The data in man are very circumstantial. Insulin administration to fasting man inhibits gluconeogenesis acutely but does not seem to alter ketoacid levels[3] (Fig. 26.2). Thus, glucose concentration may fall to 1 mM, and the subjects do remain completely asymptomatic.[19] In a similar fashion, elevated ketoacids prevent the autonomic response to acute hypoglycemia in experimental animals,[33, 54] and these data, although again very circumstantial, do suggest that the entire brain can function on ketoacids alone. Both the potential danger as well as the ethics involved probably prevent a direct assessment in man as to whether ketoacids can

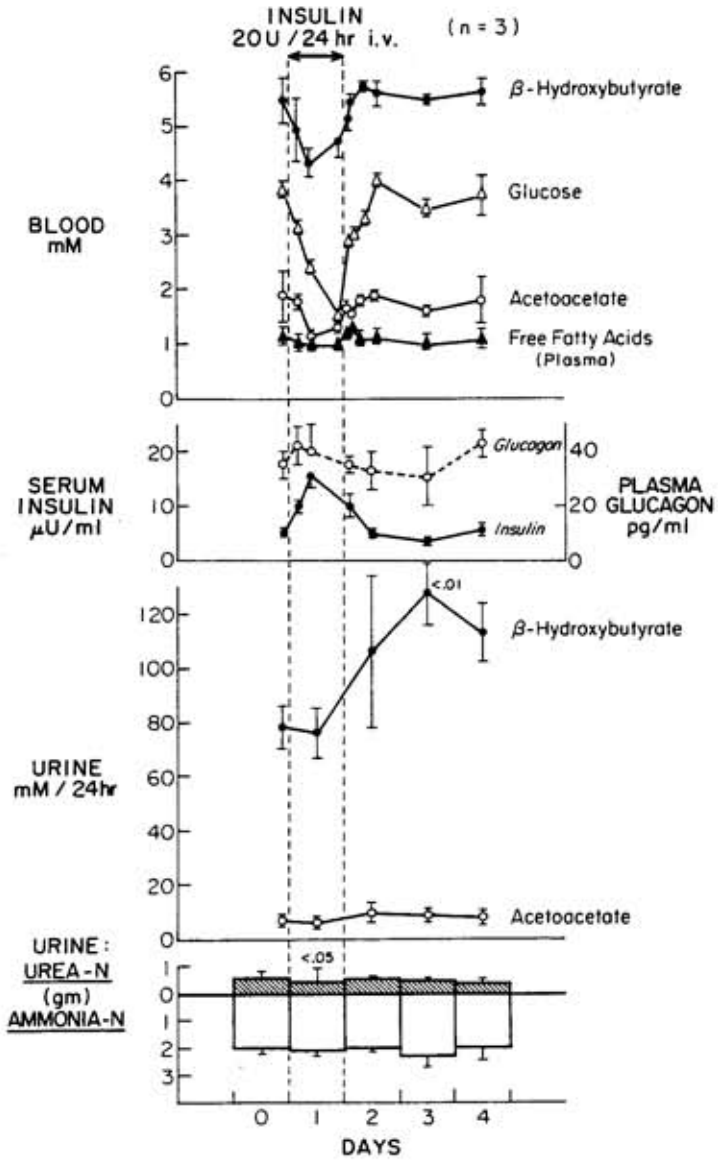

Figure 26.2 Insulin administration to three prolonged fasted obese subjects demonstrating asymptomatic hypoglycemia, thanks to maintenance of high levels of ketoacids.

provide sole substrate or almost sole substrate. In vitro studies have shown an obligate requirement of carbohydrate for maximal ketoacid oxidation,[46] but this may be due to leaching out of essential metabolites.

One phenomenon, not yet adequately studied—in fact, hardly even characterized—which makes any detailed study of human brain fuel utilization difficult, is the highly variable sensitivity of the human brain to hypoglycemia. The clinician is only too well aware of the fact that a true symptomatic hypoglycemia can occur in the diabetic when blood glucose is rapidly decreased from high levels such as 300 mg/dl to levels of 100 mg/dl. In the better controlled diabetic, symptomatic hypoglycemia may not occur until blood glucose levels fall to 50 mg/dl. In many normal young individuals after a glucose tolerance test, levels of 30–40 mg/dl may occur, without symptoms. The clinician, again, is aware of some patients with metastatic cell tumors with glucose levels of 20–30 mg/dl who are intellectually intact. Thus, the human brain appears to adapt to the ambient glucose concentration to a remarkable degree. In fact, like hemoglobin A_{1c}, which presumably integrates blood glucose concentrations to which the red cells have been exposed, the hypoglycemic threshold appears to integrate the glucose level to which the brain has been recently exposed. Whether a similar "adaptation," if indeed this is an adaptation, exists in other animals has yet to be demonstrated. One hypothesis is that the blood-brain transport mechanism is insulin sensitive. Against this is the fact that patients with hypoglycemia secondary to mesenchymal tumors such as fibrosarcomas and mesotheliomas appear to exhibit a similar adaptation but without increased insulin levels. This, however, is confused by the speculation that these tumors may produce insulin-like factors, so the insulin sensitive hypothesis is yet tenable. Other hypoglycemias such as those with type I (von-Gierke's) glycogen storage disease have increased levels of ketoacids as well as lactic acid, so the problem in them becomes confused. In a recent abstract, McCall[51] noted diminished glucose transport into brain of diabetic animals using the Oldendorf technique. A similar alteration in ketoacid transport has also been reported,[37] so the blood-brain barrier also appears to be a physiologically variable process.

In summary, human brain uses glucose but can use mannose as well when mannose is infused. Ketoacids can displace the major fraction of glucose utilization, but whether it can displace all glucose utilization in man has yet to be determined. Hypoglycemia with neurologic sequelae appears to be a relative and variable process and is not simply a function of circulating glucose levels. Further study is required for its clarification, particularly in man.

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