Editorial

See corresponding article on page 12.

Survival in starvation[1,2]

George F Cahill Jr

Humans sit high in phylogeny as the result of several evolutionary factors that affected metabolism and nutrition. Vertebrates have segregated their nervous system from the high and variable (millimolar) concentrations of water-soluble factors in the body's extracellular fluids to the lower (micromolar) concentrations bathing nerve cells, permitting rapid and sensitive changes to neurotransmitters such as glutamate. The downside of the blood-brain barrier, nutritionally speaking, is the inability of protein-bound fatty acids to provide energy to nerves. A second evolutionary factor is a vestige from invertebrates, namely, the use of an exoskeleton to protect and provide physical support to the brain. Thus, unlike liver and to a lesser extent muscle, the brain cannot expand or contract and thereby is unable to store energy as glycogen or triacylglycerol. It is critically dependent on a continuous supply of glucose and oxygen and continuous removal of carbon dioxide and heat. The third evolutionary factor, and unique to humans, is the tremendous hypertrophy of the neocortex, permitting, among other things, me to write this editorial and you to read it.

About one-quarter to one-fifth of resting metabolic energy in adults is expended by the brain; in children it is up to 50%. Interruption of perfusion for 1–2 min is incompatible with function and interruption for longer periods is incompatible with anatomic viability and even survival. The physiologic response in humans to the major trauma of volume loss is to preserve blood flow through the heart, lungs, and brain at the expense of other organs, such as the kidney and other viscera.

The aforementioned raises interesting nutritional strategies in starving humans, when stores of energy as adipose fat, as glycogen in liver and muscle, and as muscle protein are all used in optimal proportions to maintain survival, meaning that preserving muscle to meet subsequent environmental challenges is a high priority. Animals also share the metabolic deficiency of the total (or almost total) inability to convert fatty acids to glucose. This means that the primary source of substrates for gluconeogenesis is muscle-derived amino acid, with some help from glycerol from adipose tissue triacylglycerol and a little help from fatty acids via acetone production. These pathways are discussed in the special article by Owen et al (1) in this issue of the Journal.

To summarize briefly, liver glycogen provides 1 d or so of glucose for the brain as hepatic gluconeogenesis from muscle-derived amino acids is initiated in association with production of the ketone bodies acetoacetate and β-hydroxybutyrate. As blood concentrations of these ketone bodies increase, so do their concentrations in cerebrospinal fluid, and their metabolism by brain displaces glucose utilization (2) and accordingly spares muscle protein (3). Thus, the human brain derives energy from storage fat, permitting survival by starving, normal-weight individuals for up to 2–2.5 mo and by obese individuals for many months or even 1 y (1, 4). The 250 mL water produced daily by metabolism may even be adequate for covering water needs if the individual minimizes evaporative water loss in moderately warm and humid environments, thereby diminishing the need for water intake as minimal obligatory water excretion diminishes because of decreased urea.

Humans still cannot do as well as several other animals, such as black bears in winter sleep (5), nesting emperor penguins (6), or elephant seals nursing their pups (7), all of which survive prolonged starvation without any detectable urinary nitrogen excretion. None of these species develop significant ketosis (< 1 mmol/L in contrast with normal humans at 5–8 mmol/L) and one can calculate that the glycerol provided by their large adipose tissue mass is sufficient for providing all the glucose required by their smaller brain-to-carcass ratio. Thus, significant ketosis is not necessary. This may be why emperor penguins stand 1.5 m tall. Likewise, because of their greater brain-to-carcass ratio, children develop ketosis more severely and more rapidly than do adults.

Why do humans continue to draw on muscle nitrogen, which, as discussed (1), becomes incompatible with survival with the loss of one-third of body protein? Is the continuous excretion of nitrogen as ammonium and urea obligatory because certain brain cells require gluconeogenic-derived glucose? Or, is muscle unable to turn off proteolysis, perhaps because of its inability to diminish oxidation of the ketoanalogues of the essential (branched-chain) amino acids, leading to an inability to resynthesize muscle protein?

Owen et al (1) approached these questions by giving obese subjects phenylacetate after 2.5 wk of starvation, a compound that is quantitatively excreted in conjunction with glutamine, thereby potentially trapping nitrogen en route to urinary excretion as ammonium or urea. Their subjects increased their total nitrogen excretion by the amount excreted as phenylacetylglutamine, suggesting, but not proving, that the continuous loss of nitrogen in fasting humans is obligatory for some metabolic or energetic process. But if so, why do bears, or penguins or seals, and probably other marine mammals that may starve for many months or even a year survive on their adipose tissue alone without significant muscle loss?

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Another cogent hypothesis, based on energy requirements, was proposed by Owen et al (1) for the small but persistent nitrogen loss in humans during starvation. The tricarboxylic (Krebs) cycle can only oxidize acetate to carbon dioxide, dependent on the availability of oxaloacetate and other intermediates for the cycle to turn. A loss of these intermediates (cataplerosis) decreases energy production, which is corrected by resupplying the intermediates through anaplerosis. Anaplerosis in turn requires deamination of muscle-derived amino acids to replenish the Krebs cycle intermediates. Thus, some muscle catabolism continues in starvation.

Energy requirements may therefore be the driving force for the persistent nitrogen loss during starvation. Administration of as little as 7.5 g carbohydrate to an otherwise starving human halves urinary nitrogen loss (8), demonstrating the exquisite sensitivity of the human body in trying to maintain viability by preserving muscle mass. Surviving starvation was and continues to be a major challenge to evolutionary success. Further knowledge of this metabolic state is also needed to help solve the nutritional problems faced by humans in illnesses such as chronic renal failure, trauma, infection, and cancer, in which protein catabolism is a major terminal factor.

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