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Macronutrient Metabolism in Starvation and Stress

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Abstract

In starvation and to a lesser extent in stress starvation, the loss of protein mass is spared as much as possible. This metabolic arrangement must have developed under the influence of evolutionary pressure in view of the importance of protein mass for function and longevity. Peripheral adipose tissue mass is only limiting when its mass is extremely small. Protein is the predominant precursor of glucose in (stress) starvation and glucose is an essential substrate for the synthesis and maintenance of cells and matrix and for the control of the redox state. To spare protein, glucose should be used efficiently only for those purposes that cannot be achieved by fat. It is suggested that this is achieved by limiting full glucose oxidation and increasing fatty acid and ketone body oxidation, which most likely can also largely cover energy needs of the central nervous system. In stress states, net negative nitrogen balance (catabolism) largely results from net losses of peripheral protein mass, predominantly muscles, whereas central organs (e.g. the liver), the immune system and wound healing are anabolic. A number of factors are responsible for a net negative nitrogen balance which may ultimately lead to death if stress persists. In stress, the amino acid mix derived from peripheral (predominantly muscle) tissues is modified in interplay with the liver and to a minor extent the kidney. This mix is different in non-stressed conditions, containing substantially increased amounts of the nonessential amino acids glutamine, alanine, glycine and (hydroxy)proline. Part of the amino acid skeletons released by muscles are substrates to produce glucose in the liver and kidney. Glucose and the amino acids produced especially serve as substrates for cell proliferation and matrix deposition. The catabolic processes in peripheral tissues cannot be countered completely by adequate nutritional support as long as stress persists. This metabolic arrangement dictates a nutritional mix containing liberal amounts of protein and carbohydrates and addition of lipids to cover energy requirements.

Introduction

In evolution, protein sparing is a first priority of the body, provided that enough energy is present in the form of adipose tissue or diet [1–3]. When this is not the case, the 'King Penguin syndrome' develops after which individuals quickly die [4–6].

To limit protein losses, amino acids should be reutilized as much as possible and used for survival purposes but not for purposes that can be achieved by other nutrients. Nevertheless, in starvation, some of the protein-derived amino acid nitrogen and nucleotide-derived base nitrogen is only partly reutilized and partly excreted in the urine as ammonia or urea. This is quantitatively even more important in stress starvation. In this process, peripheral protein (muscle, skin and bone) is lost to a limited degree in starvation and more extensively in stress starvation.

One of the crucial substances to be produced by the body is glucose, which is preferentially used for the synthesis of biomass (nucleotides and cell proliferation) in starvation, stress, inflammation and in situations with rapid growth. To promote these processes, glucose oxidation is inhibited to a major degree [7, 8]. This is achieved by insulin resistance, which in situations of stress and increased cell proliferation persists also in the presence of adequate ingestion of carbohydrates [8, 9].

In view of the priority given to protein sparing and the resulting limitation of the irreversible oxidation of glucose, the body necessarily relies on fat as fuel. Interestingly, predominantly fatty acids derived from peripheral adipose tissues are oxidized, whereas visceral and organ fat is spared or even accumulates.

The extent of fat oxidation is, therefore, predominantly the resultant of the degree of protein and glucose oxidation in all stress and growing states rather than a primary event. On this basis, protein metabolism (flux from peripheral to 'central' tissue muscle catabolism; composition of non-essential amino acid produced and how) will be first discussed, subsequently protein-related glucose metabolism and finally a short discussion will be devoted to fat metabolism.

Protein Metabolism

In starvation with or without stress (as a general term for trauma, and infectious and noninfectious inflammation), there is a net flux of amino acids from peripheral tissues (muscle, skin and bone) to 'central tissues', which utilize these amino acids predominantly for the synthesis of acute phase proteins, immunocytes, proliferating cells and matrix in healing wounds or growing tissues. In this process, nucleotides are important nitrogen-containing products. Peripheral tissue

release is generally achieved by the increase in protein degradation, whereas protein synthesis remains stable. Nitrogen accrual in the 'healing tissues' is achieved by increasing synthesis while degradation is less affected. In the stress states mentioned, this net flux of nitrogen from peripheral tissues to central tissues is an obligatory event and can only be lessened to a modest degree when patients are adequately nourished. However, it has been shown that growth hormone has anticatabolic properties, diminishing peripheral release of glutamine in trauma patients [10] and septic pigs [11] while also increasing infectious mortality in critically ill patients [12]. This signifies that the catabolic response is crucial for survival, and the damage caused by growth hormone treatment probably results from the inhibition of the central anabolic synthesis of acute phase proteins [13], immune cells and cells operative in wound healing, which may result from a decrease in the peripheral release of amino acids.

In stress, there is a loss of whole body nitrogen as evidenced by a negative nitrogen balance, which becomes more negative when the stress is more severe. Net nitrogen losses range from 6–7 g of nitrogen in starving adults [14] to approximately 15 g in critically ill patients with extremes up to 30 g in burns or severe infectious states. Simple reasoning might lead to the conclusion that these losses are related to the production of acute phase proteins, matrix proteins, immunocytes and other cells, but these also have a turnover, in which breakdown products may be suitable for reutilization. A process in which protein is definitively lost is the crucial production of glucose derived fatty acid/sterol/phospholipid largely for cell membrane synthesis. Another reason may be related to the influence of 'cycling'. Almost all metabolic pathways cycle, implying that in several reactions often in different organs an intermediate branches off from the cycle to produce a building stone for the synthesis of biomass and is later at least to some degree resynthesized. This arrangement may serve to rapidly adapt to changing circumstances or requirements. In nitrogen metabolism, cycling substrates are never regenerated completely because intermediates can branch off to be excreted or to be irreversibly oxidized. This leads to partial losses of intermediates which simultaneously have to be replenished somewhere else in the cycle. In nitrogen cycling, even in stable nonstressed states, the ability to excrete nitrogen into the urine requires a continuous and modest formation of urea in the liver (largely from alanine) and ammonia in the kidney (largely from glutamine). The amounts of urea produced in starving states are low [15] but much higher in stress states. This is comparable with the stationary running motor using little fuel, which can rapidly gear up when under influence of changing requirements substrate/fuel is added to the motor. When tissues grow (cancer or pregnancy) or pus is produced and lost from the body, net peripheral losses in the host (mother or cancer patient) may increase [16]. In conclusion, the causes of catabolism are manifold and are not defined in detail.

Changes in Amino Acid Metabolism as a Consequence of Stress

The net release of amino acids by peripheral tissues in response to stress yields a mixture that does not completely reflect the amino acid composition of muscle protein and that is different from the mixture released in nonstressed states. Specifically glutamine and alanine have been reported to be released in increased amounts. Almost all amino acids released during stress are to a significant extent taken up by the liver. The only amino acid produced in stress by the liver in a net fashion is glutamic acid. Glucogenic amino acids are partly metabolized in the liver producing glucose. Importantly, the kidney participates in the uptake and metabolism especially of glutamine, producing glucose and ammonia. Ammonia is partly excreted in the urine, partly in the venous effluent of the kidney and is in the absence of portal-systemic shunting the only ammonia present in the systemic circulation (fig. 1) [17].

After the release of glucose and glutamic acid by the liver, and of glucose by the kidney, they are partly taken up again in muscle and support the production of glutamine, alanine, glycine and proline far in excess of their composition in muscle protein. A substantial part of the amino nitrogen of glutamine is derived from branched chain amino acids. The central nervous system and possibly the lungs also produce glutamine. Net pulmonary uptake of glutamine has been found in patients having pulmonary inflammatory infiltrates and net release was found when the lungs where not suffering from inflammation [18].

As explained earlier, all these reaction processes branch off from the cycling of these substrates across organs, whereas the turnover of the intermediates in the cycle is far greater than their net utilization. The substantial net formation of the non-essential amino acids glutamine, alanine, glycine and proline takes most likely place in peripheral tissues, besides – to some degree – also in the proliferating cells themselves. They have an increased requirement of these amino acids and glucose for their proliferation and synthesis of matrix. In principle, these amino acids can be considered as conditionally essential amino acids, similar to glutamine, which may be lacking in depleted states or in states with longstanding and severe inflammatory activity. Although the estimation of requirements largely focuses on the synthesis of cells, it is noteworthy that collagen is a substantial part of our tissues and has an amino acid composition with high concentrations of (hydroxy-)proline, glycine and alanine. The turnover of collagen is slow, but a small pool with rapid turnover has been claimed to exist [19, 20].

Another example of cycling is the Cori cycle, in which glycolysis takes place in peripheral tissues and specifically in proliferating cells. Glucose uptake is far greater than lactate production whereas little glucose is fully oxidized. This

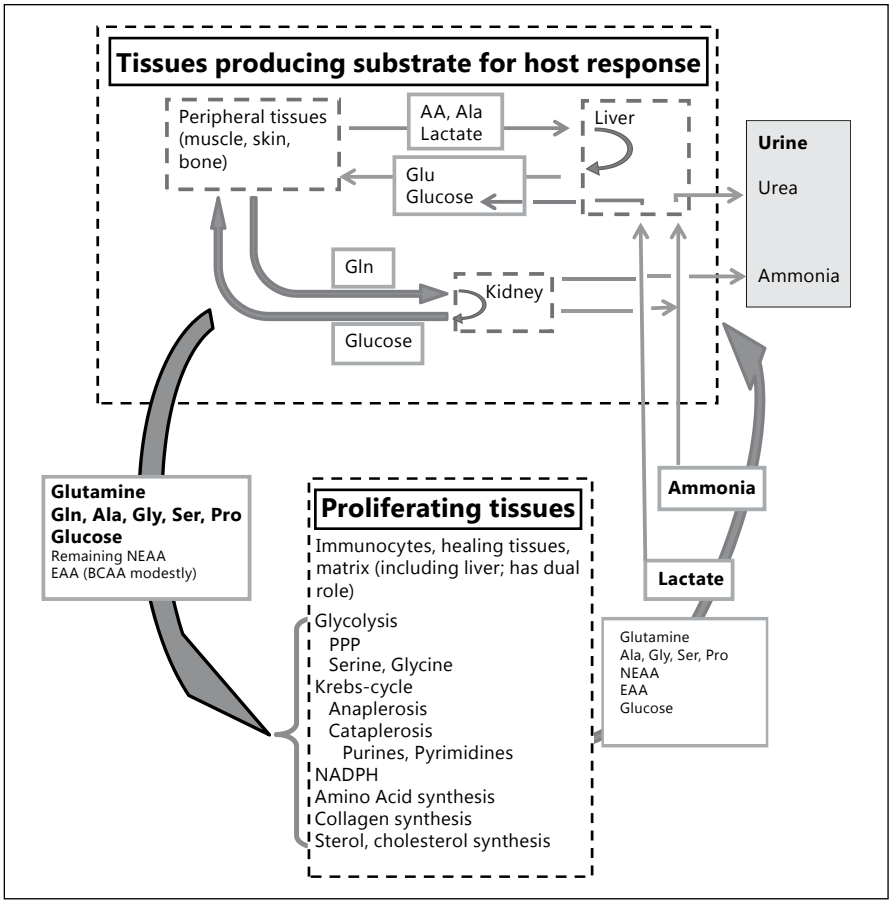

Fig. 1. Schematic representation of the concerted production of substrates for host response by peripheral tissues (muscle, skin, bone and brain?), liver and kidney and their uptake by proliferating tissues (immune cells, wound healing, matrix and liver). The liver plays a dual role, producing substrates as well as utilizing substrates to synthesize acute phase proteins and immune cells (Kupffer cells). The intermediary metabolism in the intestines and brain is not taken into account. AA = Amino acids; BCAA = branched chain AA; EAA = Essential AA; NEAA = non-EAA; PPP = pentose phosphate pathway.

supports the view that much of the glucose carbon skeleton is utilized for biosynthesis rather than complete oxidation. The lactate produced is released into the circulation and resynthesized into glucose in the liver and possibly also in the kidney. This happens in inflammatory (stress) states despite normal oxygenation. This increase in apparent senseless cycling plays, however, a similar role, as described earlier for the cycling of glutamine. At several points of the cycle, intermediates (e.g. glucose, glycerol and alanine) can replenish intermediates (anaplerosis) and at other points intermediates branch off and are used for cell

proliferation and maintenance of the redox state [for instance ribose and NADPH in the pentose phosphate pathway and glycereraldehyde-3 phosphate producing serine and subsequently glycine in high amounts also serving the synthesis of the bases of nucleotides (purines and pyrimidines)]. This is again the running motor which is geared up in stress because intermediates are required in increased amounts that can branch off from these cycles and act as substrate for the production of cell components.

Importantly, glucose and glutamine are the main anaplerotic substrates replenishing the intermediates of the Krebs cycle. They serve similar roles as described for the Cori cycle supplying reducing equivalents and supporting the synthesis of cell elements and matrix. Glutamine-derived glutamic acid is crucial in this process either directly or indirectly via aspartic acid serving as one of the substrates contributing to purine and pyrimidine synthesis. Several other glucogenic amino acids can act to a lesser degree in a similar way.

The Protein-Glucose Connection

Under the influence of evolutionary pressure, the generally accepted view that protein mass is the limiting factor in long-term survival during (stress) starvation provided normal fat mass is present [1, 2] has led to the preservation of protein mass as much as possible and to the accumulation of fat mass when food is abundant. Glucose is a crucial substrate serving many roles in building cells and matrix, and in maintaining a redox state by promoting the production of reducing equivalents (mainly NADPH). As glucose reserves are very limited in (stress) starvation, new glucose formation is required, which predominantly requires the use of glucogenic carbon skeletons of protein and to a much lesser extent of lipolysis-derived glycerol. To limit the requirements of glucose (and therefore protein breakdown), it should be utilized only for the survival purposes that can only be served by glucose, as mentioned earlier. Complete glucose oxidation is not or only to a very limited degree required, notwithstanding claims in the literature that immunocytes and the central nervous system need glucose for oxidation during critical illness. Referring to H.A. Krebs, Owen et al. [21] report that 100 g of muscle protein yield 57 g glucose. In starvation and stress starvation 7–14 g of net nitrogen loss per day would on the basis of this calculation lead to the net production of 25–50 g of glucose. These amounts would not cover the energy requirements of the brain, which are estimated to range between 100 and 150 g if all this glucose would be oxidized in the brain, which is unlikely and has been shown not to happen in the same report [21]. In fact, a very low respiratory quotient was found (0.62) across the brain, which

should have been much higher when all glucose taken up by the brain would have been oxidized. Consequently, this suggests that significant nonoxidative glucose disposal must have taken place, consistent with synthetic processes. In stress starvation, very limited glucose oxidation by the brain is supported, contrary to other claims, by the demonstration that ketone body formation is also present in septic states [22]. On the basis of indirect calorimetry and isotope technology, glucose oxidation at the whole body level has been estimated to contribute 10–15% of energy requirements. As this glucose is largely derived from amino acids, the contribution of amino acid oxidation is already included in these estimates; 85–90% of energy requirements must therefore be covered by fatty acid oxidation.

Protein-Glucose Sparing and Insulin Resistance

In all the stress states earlier mentioned, glucose is specifically channeled into biosynthetic pathways whereas complete glucose oxidation is inhibited. This is achieved by insulin resistance resulting from the activation of pyruvate dehydrogenase kinase which inhibits pyruvate dehydrogenase and catalyzes the dehydrogenation/decarboxylation of pyruvate to acetyl CoA, the fuel of the 'stove' of the Krebs cycle. The mechanisms described in this subchapter are supported by the finding that in all situations where food is limited, as well as in all situations where rapid cell proliferation is required, the organism is insulin resistant. Examples are starvation, trauma, infection, periods of growth (puberty, lactation, pregnancy, cancer and obesity), in the fat-loading period before hibernation, estivation and migration as well as during these periods. Longevity has also been shown to require insulin resistance in many other species, including worms, insects and nonhuman vertebrates [23]. The insulin-resistant state, which exists when fat loading occurs before long-term fasts before migration, hibernation and estivation, may have similar characteristics as insulin resistance in obesity. Building and maintaining a large fat mass as well as the pro-inflammatory influence of the ingestion of large amounts of pro-oxidative fat very likely contribute to the insulin-resistant state [9].

Fat Metabolism

The views expressed in the previous subchapters lead to the conclusion that in (stress) starvation fatty acid and ketone body oxidation is the predominant source of energy and is part of the integrated changes in protein/glucose/

fatty acid metabolism. High fatty acid levels present in these conditions are necessary to drive oxidation. The special role that has been attributed to high normal and abnormal fatty acid levels in insulin resistance may be questioned. The inhibition of pyruvate dehydrogenase and the subsequent inhibition of pyruvate-derived acetyl-CoA production is a crucial event in the chain of events in metabolism and decreases insulin sensitivity. Its regulation is not completely understood. The FOXO transcription factor family has been suggested to play a role in this respect [24]. However, the potential pro-oxidative effect of high fatty acid levels may secondarily contribute to insulin resistance.

Nutritional and Metabolic Consequences

The metabolic response to stress involves protein sparing and is achieved by insulin resistance. The crucial role of glucose in the response to stress and the necessity to utilize glucose efficiently leads to the recommendation to furnish liberal amounts of protein and carbohydrates in stress situations. In addition, the remaining requirement of energy should be covered by the addition of lipids, although slight underfeeding is less risky than overfeeding, provided the individual has normal adipose tissue stores. In view of the important role of insulin resistance, upregulation of insulin sensitivity may be harmful. Tight glucose control has not been discussed in this chapter but maintaining levels between 4 and 6 mmol and limiting glucose ingestion may interfere with an adequate metabolic response in critical illness. In volunteers receiving endotoxin and in septic patients, hyperinsulinemic euglycemic (4–6 mmol) clamp studies have shown that at moderate hyperinsulinemia, requiring low dosages of glucose, most glucose was oxidized and little nonoxidative disposal occurred [25, 26]. When more insulin was given or higher euglycemic levels (10 mmol) were aimed for, nonoxidative glucose disposal increased. Nonoxidative glucose disposal includes glycogen synthesis and biosynthetic pathways described in an earlier part of the chapter. We suggest that glucose levels between 4 and 6 mmol are not physiological in stressed states and interfere with adequate metabolic responses. This may be aggravated when low glucose-containing diets are administered.

Disclosure Statement

This author has no conflict of interest to disclose.

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