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Role of energy metabolism in regulation of protein requirements

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Energy intake and protein metabolism. An increase in energy intake with constant dietary protein can reduce nitrogen excretion and increase nitrogen balance[16]. This is more marked with protein intakes below or near the requirement level and it has also been demonstrated when energy in excess of expenditure is fed[1,2,6,8]. But there is a limit to the effect of dietary energy: when the diet does not provide adequate amounts of protein, additional intakes of energy beyond a given amount will not further improve nitrogen balance.

It is to be expected that, when energy intake cannot satisfy energy demands, more protein is oxidized, thus increasing urinary nitrogen excretion and decreasing nitrogen balance, but this is not always the case. In a study of the energy requirements of preschool children with a constant intake of vegetable proteins equivalent to 1.2 g milk protein/kg per d, two consecutive reductions of 10 per cent in dietary energy at 40 d intervals did not affect nitrogen retention measured 17–20 and 37–40 d after each dietary change[25]. Energy expenditure diminished with the first reduction in energy intake and weight gain decreased after the second reduction. growth in height was not affected and there were no consistent changes in urinary creatinine excretion related to the levels of energy intake. It may be that the compensatory decrease in energy expenditure, the protein ingestion at a safe level of intake, the good nutritional status of the children and their hygienic living conditions prevented a nitrogen loss with the reduction in energy intake. It is possible that if the low energy intake had continued longer, if the children had become ill with the frequency that is customary in developing countries or if their dietary protein had been marginal (ie, closer to the average requirement for their age), they might have gone into negative nitrogen balance.

Studies in India also failed to show an association between energy intake and nitrogen balance. In one study[10], children 4 years old ate diets that provided 1, 1.3, 1.6 and 2 g protein and 80 or 100 kcal (334 or 418 kJ)/kg per d. With three of those levels of protein intake, nitrogen balance fell with the lower energy intake in only two of three children. In another study with adults[9], an increase in dietary energy from 44–56 kcal (184–234 kJ)/kg per d improved nitrogen retention when the men ate 1.0 but not 1.2 g protein/kg per d.

These findings indicate that nitrogen balance is more sensitive to changes in dietary energy when protein intake is relatively low. They also suggest that when protein intake is adequate the body is better protected in terms of nitrogen metabolism against a moderate decrease in energy intake.

The protein-sparing effect of dietary energy has been demonstrated by means other than nitrogen balance. For example, amino acids labelled with stable isotopes showed that, in men with a protein intake of 0.6 g/kg per d, an energy intake 25 per cent in excess of maintenance requirements reduced the rate of leucine oxidation from (mean ± s.d.) 18.0 ± 8.3 to 12.4 ± 8.7 μmol kg per h, and increased net protein retention[15].

The experimental evidence of the effects of energy intake on protein metabolism has raised the question whether protein requirements have been underestimated for populations prone to have marginal or deficient energy intakes. On the other hand, have such populations adapted to use more efficiently their low energy intakes and preserve body protein? Although a decrease in energy expenditure in response to low energy intake may diminish the risk of body protein loss, it is not known how long such a response can be effectively sustained. Furthermore, this should be regarded as a transient compensation of low intakes and not as a desirable adaptation in view of the physical, emotional and social costs of diminished energy expenditure, which usually is achieved through a reduction in physical activity.

Another important related question is whether protein requirements are higher for individuals with low bodily store of energy and whose dietary intakes are sometimes marginal and sometimes adequate, as occurs in groups of migrant workers or persons subject to seasonal changes in food availability.

The most logical answer to these questions would be to raise the dietary protein recommendations. However, this is more expensive and often more difficult than increasing the availability of dietary energy sources. The question, then, that also needs to be answered is whether increasing the recommendations for energy intake in populations with constraints to eat more protein will reduce their protein requirements.

Dietary energy substrates. The effects of dietary energy on protein metabolism vary with the source of energy. Both carbohydrates and lipids enhance nitrogen and amino acid metabolism, but carbohydrates have specific actions that make them more effective than fats in promoting the utilization of dietary protein, at least transiently. The administration of carbohydrates at a given protein intake or while fasting, reduces the urinary excretion of nitrogen more than fat does and results in better nitrogen retention[17]. With isocaloric, isonitrogenous diets having carbohydrate: fat ratios of 1:1 and 2:1, the higher nitrogen-sparing effect of carbohydrate relative to fat was more pronounced at lower levels of energy and protein intakes[20] and it made no difference whether sucrose or dextrins and maltose were the principal dietary carbohydrates[19].

The effects of carbohydrates on protein metabolism have also been shown in relation to specific amino acids. The oral or i.v. administration of glucose produces a transient decrease in plasma amino acid concentration, specially the branched-chain amino acids and other large neutral amino acids, such as methionine, phenylalanine, tyrosine and tryptophan[13]. This is accompanied by an increase in synthesis or a reduction in catabolism of muscle protein. Conversely, dietary carbohydrate restriction, as in high-protein, low-carbohydrate diets, leads to increased accumulation of plasma branched-chain amino acids after protein feeding or after intravenous infusion of leucine[7]. This is probably due to reduced utilization of those amino acids, which are the major substrates for restoration of muscle tissue after protein feeding.

The effects of giving 25 per cent excess of dietary energy either as sucrose plus a glucose polymer, butter fat, or combination of both, on the metabolism of whole body leucine and lysine have been explored.[15]. The former is metabolized mainly in peripheral tissues and the latter in liver. Net leucine retention in the fed state increased more with the carbohydrate or mixed supplementations than with fat alone. Whole body flux of both amino acids did not change, but leucine flux was greater than lysine with the various energy sources and two levels of energy intake. This suggests that identical dietary conditions may elicit different responses from different essential amino acids.

Glucose administration also influences the metabolism of the non-essential amino acid alanine, increasing its *de novo* synthesis, its release to the circulating plasma and its whole body flux[4,21].

In addition to its influence on the metabolism of circulating amino acids, dietary

carbohydrate also interacts with amino acids from the same meal. Giving protein and carbohydrates as separate meals can lead to nitrogen loss from the body, which is reversed by giving these two nutrients in the same meal[3].

The mechanisms by which carbohydrate exerts these effects on protein metabolism are not fully understood. They are partly mediated by the insulin released in response to carbohydrate absorption or infusion[17]. The simultaneous infusion of insulin and glucose produces a decrease in plasma urea concentration and urinary nitrogen excretion several times greater than the decrease observed when glucose is infused alone[5]. Another possible mechanism of the effects of glucose may be through its suppression of glucagon release. Glucagon infusion increases the synthesis of urea at the expense of the free amino acid pool and probably also by hydrolysis of visceral protein, and it increases urinary nitrogen excretion[29]. A small increase in plasma glucagon concentration was observed when carbohydrates were restricted in the diet[7].

The evidence that carbohydrates spare protein more efficiently than fat raises important practical questions, such as: Is there a more efficient use of dietary proteins among populations whose dietary energy is derived 70–80 per cent from carbohydrates? If so, will their protein requirements be affected by the dietary changes induced by migrations, cultural changes and access to processed foods?

But there may also be adaptive changes in protein metabolism with the long-term ingestion of diets rich in fat. Although the stimulation of muscle protein synthesis and reduction of catabolism observed with carbohydrate are not the same when fat is fed as a single meal, the studies with patients on long-term parenteral feeding[11] indicate that the administration of fat as a major energy source on a regular basis over long periods of time may be as effective as carbohydrate in promoting nitrogen retention and net protein synthesis.

Physical activity and energy expenditure. Physical activity and its resultant energy expenditure influence protein metabolism. That influence appears to be transient during periods of physical training, but some effects may be long-lasting. However, their importance in terms of adaptation to chronically low dietary intakes by persons who are continuously active has not been clearly defined.

Weanling rats with dietary intakes retricted by 25 or 50 per cent grew better when they were forced to exercise daily in a revolving drum, than pair-fed animals forced to remain inactive in small metabolic cages that restricted their movements[26]. In spite of their higher energy expenditure with identical dietary intakes, the active rats gained more weight, retained more body protein as determined by carcass analysis and grew more in length than the inactive animals. These results were replicated in an experiment with a cross-over design, where on day 14 one half of the active animals were forced to remain inactive for two more weeks, and *vice versa*[27]. Further evidence of the beneficial effect of energy expenditure on protein metabolism and overall growth was provided by studies in preschool-aged children recovering from PEM[24]. When a programme of moderate systematic exercise was added to the dietary therapy, children with an increase of approximately 25 per cent in total daily energy expenditure compared with that of pair-fed control patients, grew more in height and although weight gains were similar in both groups, the more active children gained more lean body mass based on their urinary creatinine excretion, basal oxygen consumption and anthropometric measurements.

Investigators from Berkeley[1,23] studied the effects on nitrogen retention in young men of changes in energy balance, induced by modifying either energy intake or expenditure. In three separate experiments, energy balance was made positive by increasing intake relative to expenditure, or negative by either decreasing intake or increasing physical work. Protein intake was maintained constant at 0.57 or 0.8 g/kg per d. In every instance, mean nitrogen balance fell with the decrease in energy balance, but it fell less when the reduction in energy balance was due to increased work than to a lower energy intake. When energy balance was achieved through equivalent changes in energy intake and expenditure, nitrogen balance was more positive —or less negative— as physical activity and energy expenditure increased. On the average, the men were in negative nitrogen balance with 0.57 g dietary protein/kg per d, and in positive nitrogen balance when they were more active and ate 0.8 g protein/kg per d. These results indicate that physical activity has an anabolic effect on protein metabolism, even under conditions of

marginal protein intakes, but the effect is more pronounced when energy balance is maintained and dietary protein is not a limiting factor.

This protein-sparing effect of exercise was also reported in middle-aged men on a weight reducing diet, who lost less lean body mass when the restricted energy intake was accompanied by an increase in physcial activity[28]. In contrast with the beneficial effects of exercise, inactivity reduces the rate of protein synthesis and produces a marked negative nitrogen balance, eg in men who had been immobilized for several days in a plaster cast[22]. Post-mortem tissue analysis of active and inactive rats confirmed that muscle mass is lost with physical inactivity[26], and hypokinetic rats had increased muscle protein catabolism, as suggested by marked increments in urinary excretion of urea and 3-methylhistidine[18], contrary to the effects of exercise which depresses the degradation of 3-methylhistidine-containing proteins and reduces the urinary excretion of that amino acid[14].

Physical activity also influences the metabolism of specific amino acids. This has been reviewed by several authors[12,14,31,32]. In general, exercise increases the oxidation of branched-chain amino acids and the release of alanine from muscle. The significance of these changes in amino acid metabolism is not yet clear for persons who have a chronic marginal dietary protein intake or who regularly engage in heavy physical work and it is not known whether exercise induces a greater need for branched-chain amino acids among such persons.

In summary, most of the evidence indicates that increased energy expenditure has a beneficial effect on protein metabolism, particularly when the diet supplies enough energy to satisfy the demands of physical activity. These observations may be of major importance for persons in developing countries who have relatively low protein and energy intakes and whose occupations demand constant or seasonal heavy energy expenditures. It is conceivable that when energy balance is sustained, the protein requirement to maintain existing lean body mass may be less for a chronically active individual than for one who is inactive. Conversely, marked inactivity, as in immobilized patients, produces a loss of muscle mass. Whether greater protein intakes will help to counteract this negative effect, remains to be proven.

Conclusions. This review of the effects of energy intake and metabolism on amino acid protein metabolism raises important questions related to protein requirements, such as: Since protein recommendations are based on research done with adequate or surfeit dietary energy, have protein requirements been underestimated for populations prone to have marginal or deficient energy intakes? On the other hand, since exercise has an anabolic effect, are protein requirements lower for persons who are almost always physically active? Should dietary protein recommendations be higher for individuals with low body stores of energy and whose energy intakes fluctuate between adequate and deficient, or who engage in seasonal activities with different levels of energy expenditure? Will an increase in physical activity help to protect children from the deleterious effects of mild or moderate protein malnutrition? Since carbohydrates enhance protein metabolism more than fats, will protein requirements increase in persons who change the proportion of those energy sources in their diets? If that were the case, is this a transient effect that will disappear with metabolic adaptations to the higher fat intakes? The answer to these questions and others that may arise will shed further light on the interactions of energy and proteins, and allow us to make better dietary recommendations.

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