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Amino acids—their role as an energy source

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One of the subjects that has aroused great attention in hospital nutritional circles since the early 1970s is the relationship between energy and nitrogen metabolism. An enormous amount of confusion has arisen, largely through failure to differentiate between the metabolic changes of starvation and those of injury. Emphasis has largely been placed on N balance, either in terms of making negative balance smaller or achieving positive balance, and the importance of energy supply in its own right has been neglected until recently.

This paper will attempt to give a brief overview of amino acid metabolism as a general background and then describe developments that have occurred over the last decade in the application of knowledge in this area. The relationship between energy intake, N intake and N balance in various clinical circumstances will also be described.

An overview of amino acid metabolism

Like all other substances in the body, protein does not exist in a static state but is always in a flux, reflecting the balance between synthesis and breakdown. Estimates vary according to the exact methods used, but probably somewhere between 200 and 300 g protein are formed and destroyed during each day in an adult of average size. It is not the purpose of this paper to discuss the processes of protein synthesis or protein breakdown, but obviously breakdown involves the release of amino acids from cells and synthesis requires that amino acids are present in the correct places at the right times so that protein synthesis can occur. As well as being used in synthetic processes, amino acids can be oxidized after deamination to produce energy. Under normal circumstances about 15% of resting energy expenditure (REE) comes from the oxidation of amino acids. This occurs in various tissues, but of particular importance is the liver and branched-chain amino acid oxidation in muscle. Wherever amino groups are produced as a result of this process or direct absorption of ammonia, they must either be transported to the liver where they are metabolized to urea and excreted in the urine, or to the kidney to be disposed of after buffering. The mechanisms by which these objectives are achieved are illustrated in Fig. 1. Amino groups produced in muscle are combined with pyruvate to form alanine and with glutamate to form glutamine. These then circulate to the liver, where pyruvate (and from this, glucose) is regenerated and urea formed, and to the kidney where the glutamine can be deaminated. The gut is also an important metabolic organ, producing alanine and recycling glutamate. The fate of the non-nitrogenous parts of amino acids differs according to their

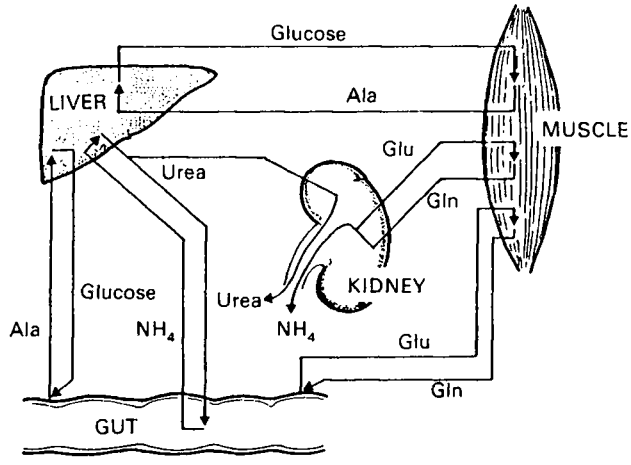

Fig. 1. Transport pathways for excretion of ammonia and amino residues.

individual structures, some entering metabolic pathways from which gluconeogenesis can occur (glucogenic amino acids) and others entering pathways associated with fat metabolism, from which ketones and not glucose are formed (ketogenic amino acids). Some are both glucogenic and ketogenic. There are a considerable number of points of entry to the metabolic pathways and they will not be described more fully here. The potential end-products of the metabolism of the amino acids are shown in Table 1. The energy released as a result of oxidation of amino acids varies slightly depending on individual tissue composition, but is of the order of 17 kJ (4·1 kcal) for each gram of protein lost.

Infusion of amino acids in starvation and injury

Injury (including surgical injury) and starvation both result in loss of weight and N (Cuthbertson, 1930; Kinney *et al.* 1970; Richards & Kinney, 1977; Woolfson, 1979). In starvation the metabolic rate falls slowly over several weeks. Certain tissues, particularly the central nervous system, require glucose for their energy supply and, once carbohydrate reserves are exhausted (i.e. about 48 h starvation), the necessary glucose must be formed by gluconeogenesis from amino acids. There is a gradual transition by these tissues to oxidize ketones and non-esterified fatty acids and eventually up to 95% of energy requirements are supplied by gradual

Table 1. *Metabolic fates of amino acids*

Glucogenic		Ketogenic	Glucogenic and ketogenic
Alanine	Hydroxyproline	Leucine	Isoleucine
Arginine	Methionine		Phenylalanine
Aspartate	Proline		Tyrosine
Cystine	Serine		Tryptophan
Glutamate	Threonine		
Glycine	Valine		
Histidine			

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consumption of body fat (Grande, 1968). This falling requirement for glucose helps to conserve body protein, which may be beneficial for survival. After injury, the metabolic rate rises, routine abdominal surgery causing an increase in REE of some 10% and major burns up to double the usual REE and, although most of the energy requirements are still met from fat stores in adipose tissue, muscle protein is not efficiently conserved and continuing production of glucose and loss of N occurs.

Blackburn and his colleagues (Blackburn *et al.* 1973*a*,*b*; Flatt & Blackburn, 1974) argued that, in the postoperative period (where there are usually only modest increases in metabolic expenditure), it would be beneficial in terms of protein conservation to keep plasma insulin concentrations low by replacing the standard 50 g glucose/l infusion with isotonic amino acid solutions. The lowered insulin concentrations would allow lipolysis to continue unimpeded and the extra availability of fat-derived energy substrates (non-esterified fatty acids and ketones) would prevent the loss of muscle protein. They demonstrated that N balance was improved by adding amino acids to 'hypocaloric' amounts of glucose and claimed that giving amino acids without any glucose resulted in further improvements. Unfortunately, they gave more amino acids during the periods without glucose, and so it is not possible to accept their conclusions about N-sparing from these studies. They also suggested that the improvement in N balance was due to lower insulin levels allowing fat to be mobilized. While it is true that insulin levels were marginally lower in the amino acid-only periods, and non-esterified fatty acid and ketone levels were higher, the insulin levels were considerably higher than those found in other studies in individuals given saline only, and the amino acid mixture contained a fairly high proportion of the ketogenic amino acids, leucine and isoleucine. In addition, it is clear that many of the patients described were undergoing therapeutic starvation for obesity and the metabolic effects of any of these treatments would in any case be quite different from those expected after routine surgery or injury not preceeded by starvation.

Many different aspects of these observations have been studied by subsequent workers. Although some general support for Blackburn's observations has been published (Hoover *et al.* 1975), the rationale remains unconvincing. The protein-sparing effect of amino acids in the absence of an adequate energy supply seems to be related mainly to the amino acids themselves (Freeman *et al.* 1975; Greenberg *et al.* 1976) and unrelated to changes in insulin (Freeman *et al.* 1977) or fat mobilization, as reflected in ketone concentrations (Craig *et al.* 1977; Rowlands & Clark, 1978; Foster *et al.* 1978). Depending on the exact circumstances, various proportions of infused amino acids are utilized when energy needs are not otherwise met, but in most of the studies referred to above, more than half are used as energy sources, the N being excreted as urea. For this purpose they have no specific advantage and, since no improvement in patient outcome has been documented and the cost is very much higher than the usual postoperative crystalloid solutions, their routine use, despite an undoubted improvement in N balance, cannot be justified.

The mechanism by which N balance is improved by infusing amino acids is not clear. Provision of branched-chain amino acids has been shown to increase protein turnover (Fulks *et al.* 1974) in vitro and it has been claimed that leucine is a major regulator of muscle protein turnover (Buse & Reid, 1975). As stated earlier, these amino acids are oxidized in muscle and Border *et al.* (1976) suggested that this occurred because of a local energy fuel deficit. This explanation is initially attractive, but measurements of intracellular concentrations of amino acids (Askanazi, Fürst *et al.* 1980; Fürst, 1982) have shown that they are increased and this suggests that there is impairment of substrate use rather than lack of availability.

The discussion in this paper so far relates to amino acids given either alone or as part of a regimen not meeting the body's energy requirements. In most of the studies referred to the total energy intakes were of the order of 1650–2600 kJ (400–600 kcal)/24 h—well below maintenance requirements even in prolonged starvation. In most clinical circumstances, the intention will be to aim towards providing adequate energy as well as N for metabolic needs. Although evidence of efficacy of artificial nutritional support in reducing morbidity or mortality in any group of patients is not entirely convincing (see Woolfson, 1979; Müller *et al.* 1982 for further information), in the absence of more definite evidence maintenance of body mass seems a reasonable minimum goal for which to aim.

Supplying energy alone in sufficient amounts will maintain fat stores and glycogen and is effective in minimizing N losses (O'Connell *et al.* 1974). The distribution of N within the body is affected by energy supply and, if no N is given, a syndrome akin to Kwashiorkor may ensue (Elwyn, 1973). This occurs because administration of energy prevents mobilization of muscle protein and may prevent the liver receiving an adequate supply of amino acid substrates for visceral protein synthesis. The composition and nature of energy substrate supply will not be discussed here, except to say that it is now generally accepted that for most patients a mixture of fat and carbohydrate is considered to be best. Reviews of this subject may be found elsewhere (Woolfson, 1979; Elwyn, 1980; Elia, 1982). Equally, consideration of amino acid profiles of mixtures given under different clinical circumstances is beyond the scope of this article and the reader is referred to the relevant sections of the Proceedings of the 4th ESPEN Congress (Kleinberger & Deutsch, 1982) for the most up-to-date discussion of this subject.

Some general comments regarding the relationships between energy intake, N intake and N balance can nonetheless be made:

1. At any given energy input, increasing the N intake will improve N balance.
2. At any given N input, increasing the energy supply will improve N balance.
3. Previous nutritional depletion results in an increased avidity of the body for N.
4. Hypermetabolism as part of the response to injury is associated with increased N losses and greater negative N balance at any given energy and N inputs.

These points are illustrated in Figs. 2 and 3. The best contemporary reviews of these inter-relationships are from Elwyn (1980) and Elia (1982). Energy requirements and N requirements should probably be considered separately. It has been recommended that between 625 kJ (150 kcal) (Dudrick *et al.* 1970) and 833 kJ (200 kcal) (Moore, 1959) of non-nitrogen energy should be given for each gram of administered N. The experimental basis for these suggestions was not altogether sound, but has stood the test of time, and is not unreasonable. The important

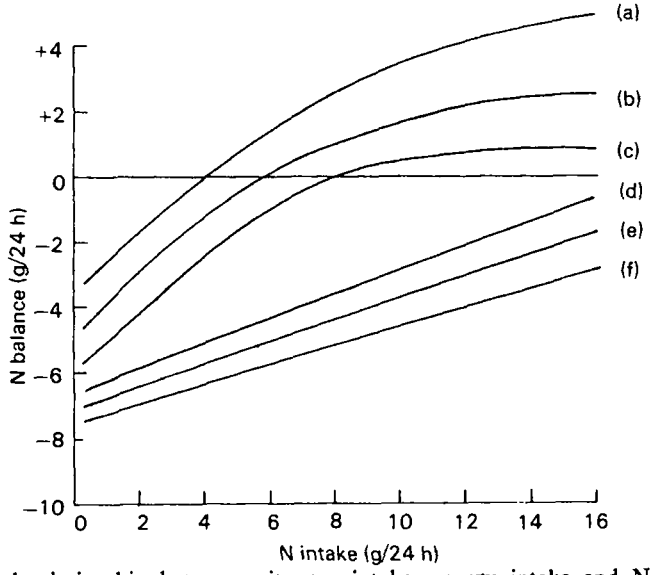

Fig. 2. General relationship between nitrogen intake, energy intake and N balance. Energy intake/resting energy expenditure: (a) 1·5, (b) 1·25, (c) 1·0, (d) 0·5, (e) 0·33, (f) 0·2.

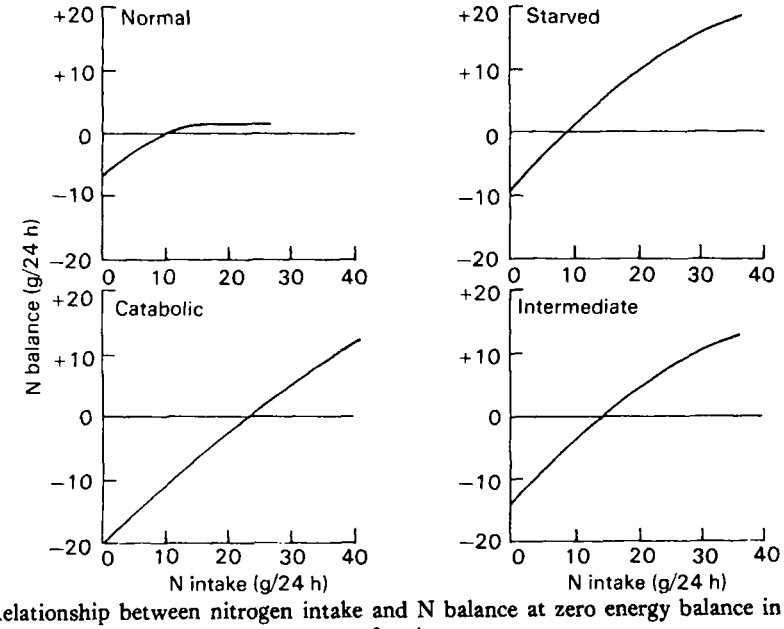

Fig. 3. Relationship between nitrogen intake and N balance at zero energy balance in different types of patients.

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Table 2. *Suggestions for maintenance nitrogen and energy intakes in different types of patients*

Patient type ...	Depleted	Intermediate	Catabolic
Energy (MJ/d)	6·7	10·0	14·6
(kcal/d)	1600	2400	3500
Nitrogen (g/d)	8	14	25
Ratio energy:N	200:1	170:1	140:1

thing to remember is that as catabolism increases, N requirements rise more than energy requirements, so that the ratio between energy and N falls. Approximate intakes for maintenance of body mass in different types of patients are shown in Table 2. The figures are intended as a guideline only.

If replacement of body tissue is the goal, then intakes can be increased. This may be appropriate in some circumstances, i.e. when an acute episode of illness is over and recovery is anticipated. However, care must be exercised in some acutely ill patients, particularly those with respiratory difficulties, since excess carbohydrate intakes can lead to an appreciable increase in energy expenditure and carbon dioxide production (Askanazi, Carpentier *et al.* 1980; Macfie *et al.* 1983) which may lead to respiratory failure. Even at appropriate doses, amino acids cause an increased sensitivity of the respiratory centre to CO_2 (Elwyn *et al.* 1983) which may be distressing to the patients and, if very high doses are used, the high urea production may cause water depletion due to a chronic osmotic diuresis.

In normal clinical practice, the reality is that the vast majority of patients needing artificial nutritional support will have energy expenditures of 6·67–10 MJ (1600–2400 kcal)/24 h, and a N intake of 12–16 g will normally provide sufficient N for maintenance of body mass and adequate visceral protein synthesis.

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