Some Implications of Amino Acid Supplementation

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Any discussion of this subject must start with the knowledge that for the past fifty years amino supplementation has been used successfully in animal experimentation to stimulate growth and to improve the biologic value of dietary proteins. The value of amino acid supplements was first demonstrated by Wilcock and Hopkins in 1906,[1] when they discovered that the amino acid, tryptophan, was an essential dietary component. It was established with certainty during the next ten years through the extensive studies of Osborne and Mendel[2] on protein nutrition. In the succeeding years, we have seen demonstration after demonstration of the benefits that may be obtained in experiments on animals from the judicious use of amino acid supplements.[3,4]

Why, then, is there any need to discuss the implications of amino acid supplementation? There are two main reasons: (1) the successful use of amino acid supplementation depends upon an accurate knowledge of the type of diet being consumed by the subject receiving the supplement, and (2) under some circumstances, amino acid supplements may not only be of no benefit but may actually cause adverse effects.[5–7]

A great deal of attention today is centered on the significance of the proportions of amino acids in diets or, as it is frequently referred to, the amino acid balance of the diet. The term "amino acid balance" refers only to the proportions of the essential or indispensable amino acids, because all proteins provide sufficient amounts of the nonessential or dispensable amino acids.

For normal performance, different quantities of the individual indispensable amino acids are required. Therefore, if the requirement for tryptophan, the amino acid required in least amount, is taken as one, amino acid requirements can be expressed as a proportion as shown in Figure 1 which is taken from a paper by Flodin.[3] The black bars represent the relative amino acid requirements of the rat. A similar figure, with slight modifications, can be prepared for the human infant, or for any other species. The shaded bars represent the relative quantities of the indispensable amino acids in the proteins of meat, milk and eggs. These proteins provide the indispensable amino acids in roughly the proportions in which they are required by the body. They are, therefore, said to be well balanced proteins, and they are used very efficiently.

Figure 2 shows a comparison of the amino acid proportions of wheat proteins and the proportional amino acid requirements of the rat.[3] Again, the black bars represent the proportional requirements; the shaded bars the relative quantities of the indispensable amino acids in wheat proteins. Such proteins are low in lysine. They are, therefore, said to be unbalanced or poorly balanced. They are not used efficiently by the body.

The efficiency of utilization of unbalanced proteins can be improved by amino acid supplementation. Also, the amino acid requirements of a subject can be met by increasing the total intake of such proteins.[8] This point is easily lost sight of in discussions of amino acid balance and amino acid proportions. We do not necessarily need to consume

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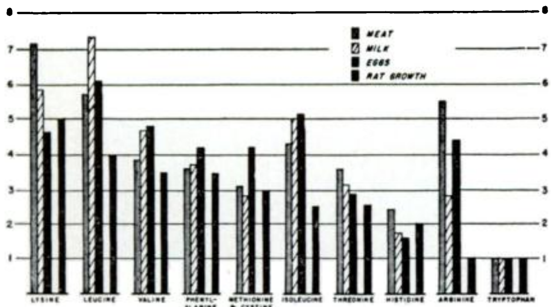

FIG. 1. Amino acid proportions in high quality proteins (calculated on the basis that tryptophan = 1.0). Amino acid proportions in meat, milk and egg protein compared with proportions utilized in rat growth. From FLODIN, N. W. *J. Agr. Food Chem.*, 1:222, 1953.[3]

food that is completely balanced. For example, if 25 gm. of egg proteins are needed to satisfy the amino acid requirements of a subject, and if protein A contains only half as much of one of the essential amino acids as the well-balanced whole-egg proteins, the amino acid requirements of the subject can be met by feeding twice as much, 50 gm., of protein A. It is, of course, possible for the amino acid balance of a protein to be so poor and the concentration of protein in a foodstuff to be so low that the subject cannot eat enough of it to satisfy his amino acid requirements. It is also possible, if the amino acid balance of a protein mixture is sufficiently poor, that some adverse effect, such as a depression in food intake or in the efficiency of protein utilization, may occur.[9]

Adverse effects of this type can readily be demonstrated in animal experiments in the laboratory as shown in Table I. The basal diet used in this experiment was a highly purified diet containing adequate quantities of vitamins and minerals, 6 per cent of alcohol-extracted casein, 0.3 per cent of DL-methionine, 5 per cent of corn oil and the balance carbohydrate, either sucrose or gelatinized cornstarch (dextrin).

The growth of rats fed this diet is limited primarily by a deficiency of threonine; therefore, supplementation with a small amount of threonine or gelatin stimulates growth. Gelatin, of course, lacks tryptophan which is also low in the basal diet; so, as the quantity of gelatin in the diet is increased, the amino acid pattern of the diet is thrown more and more out of balance. When 12 per cent of gelatin is added, we have a diet containing 18 per cent of poorly balanced protein. The growth rate of rats fed this diet is well below that of rats fed the diet containing only the 6 per cent of quite well balanced protein. We attribute the growth retardation to an amino acid imbalance. It is corrected by a supplement of the most limiting amino acid, in this case tryptophan. It can also be corrected by increasing the amount of well balanced protein in the diet.

Occasionally, amino acid imbalances occur when low protein diets are supplemented with relatively small quantities of amino acids other than the one which is most limiting in the diet.[5–9] An example is shown in Table II. Again a highly purified diet similar to the one mentioned previously was used, but this one was deficient in niacin and contained 9 per cent of casein as the entire protein source. Rats fed this diet grow about 10 gm. a week. Supplementation with methionine gives a very small improvement in growth. Supplementation with threonine alone gives no improvement at all. When methionine and threonine are added together growth is retarded. Apparently additional threonine increases the need for tryptophan because the condition is corrected by a small supplement of tryptophan.[5]

USE OF AMINO ACID SUPPLEMENTS

Such observations, and there are quite a few other examples, have led to the assump-

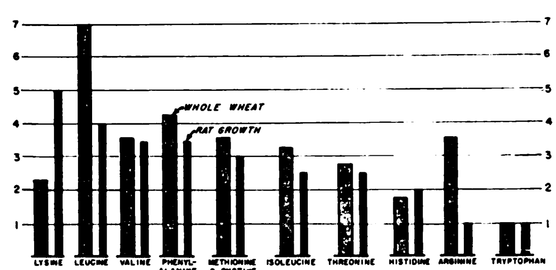

FIG. 2. Amino acid proportions in whole wheat protein (calculated on the basis that tryptophan = 1.0) compared with proportions utilized in rat growth. From FLODIN, N. W. *J. Agr. Food Chem.*, 1:222, 1953.[3]

tion that amino acid supplementation is a risky process. How well justified is this assumption? There are certainly grounds for exercising caution in the use of amino acid supplements, but I do not believe that there is cause for alarm.

A subject whose amino acid requirements are satisfied can tolerate a diet with quite a poor amino acid balance. Also, the quantities of amino acids required to produce toxic effects—and we can produce toxic effects with large quantities of many of the individual amino acids—are far beyond what could rationally be recommended as a supplement.[8]

What, then, are the cautions that should be observed in the use of amino acid supplements? And what are the possibilities of obtaining beneficial responses from amino acid supplementation?

If we begin with the well nourished subject who is receiving sufficient protein to meet his amino acid requirements, no benefit can be expected from supplementation of his diet with either amino acids or intact protein. The excess can serve only as a source of calories. Subjects receiving adequate quantities of all of the individual amino acids, also, can tolerate a considerable excess of many of the others, an excess of methionine, perhaps, being the least well tolerated. So, there is not much likelihood of causing adverse effects in well nourished subjects unless the intakes of individual amino acids are greatly excessive.

What, then, about the malnourished subject? Here the problem is more difficult. If his over-all protein intake is low, he will be consuming inadequate quantities of several amino acids. Therefore, supplements of several amino acids would be needed to improve his diet very much. The experiment summarized in Table II illustrates such a situation. The diet used in this experiment contained 9 per cent of casein. Methionine is the most limiting amino acid but the response to the addition of methionine was very small. Only after supplementation with three amino acids (methionine, tryptophan and threonine) was a substantial growth response obtained. In subsequent experiments, we have found that to improve growth still further, supplementation with a mixture of five other amino acids is required.[10] Thus the obvious procedure for subjects with low protein intakes, who probably need supplements of several amino acids, is to increase the intake of well balanced proteins. Also, it is under conditions of limited protein intake that amino acid imbalances and other adverse effects are most readily demonstrated, and these are most simply avoided by increasing the amount of well balanced protein in the diet.

If the diet is low in only one or two amino acids, supplementation with the missing amino acids will be beneficial, but it is important to know that the amino acids provided are the ones needed. It is also important that the diet be complete in other respects. For example, the type of imbalance shown in Table II can be corrected by the addition of niacin, and it appears that a niacin deficiency

TABLE I

Effect of Gelatin on the Growth of Rats Fed on Diets Containing 6 Per Cent Casein, 0.2 Per Cent DL-Methionine and Dextrin

Dietary Additions	Average Gain (gm./2 wk.)
None	27
0.2% DL-threonine	43
3% gelatin	36
6% gelatin	27
12% gelatin	13
12% gelatin plus 0.2% DL-tryptophan	47

TABLE II

Interrelationships Among Methionine, Threonine and Tryptophan in the Creation of an Amino Acid Imbalance in Rats Fed a Diet Containing 9 Per Cent Casein and Sucrose but Lacking Niacin

Diet Composition (%)				Weight gain (gm./wk.)
Casein	DL-methionine	DL-threonine	DL-tryptophan	
9	...	...	...	10
9	0.3	...	...	12
9	...	0.36	...	10
9	0.3	0.36	...	4
9	0.3	0.36	0.1	20

has been created indirectly by supplementation with threonine. If the diet is a mixed diet, it may be difficult to determine whether all required nutrients are present in the correct amounts. It is one thing to deal with laboratory diets that are highly purified and have been extensively analyzed, and quite another to deal with a mixed diet about which there is very little information.

I would conclude, therefore, that supplementation of the heterogeneous diets of man with one or a few amino acids, particularly in the form of a capsule comparable to vitamin capsules, has no place whatsoever as a general nutritional procedure. It is of no value to the subject receiving sufficient protein to meet his amino acid requirement. It is also unlikely to be of much value to the subject who has an inadequate over-all intake of protein and who probably needs more of most of the amino acids. Also, in such cases, the possibility exists of upsetting the amino acid balance so that some untoward or adverse effect may result.

CONCLUSION

Are we to conclude, then, in spite of the successful use of amino acid supplementation in animal experiments, that amino acid supplementation has no place in human nutrition? This may be unduly pessimistic. We know, for example, that certain foods which contain incomplete proteins can be improved by amino acid supplementation. The nutritive value of many cereal products can be improved by the addition of lysine. The nutritive value of products high in gelatin can be improved by the addition of tryptophan. The nutritive value of many legume proteins can be improved by supplementation with sulfur-containing amino acids. A case can therefore be made for improving the nutritive value of individual foodstuffs to provide *low cost* products with a better amino acid balance. Such products could be used as supplements for low protein diets. It is not possible to generalize about the role of such products in nutrition. It depends upon a great many factors, such as the cost of the products, the state of nutrition of the individual consuming them, and the percentage of the diet made up of such products. Unfortunately, we do not at this time have sufficient information to make a critical appraisal of most of these factors. Even with this information I doubt whether we could generalize. I expect that we would have a series of individual cases that would have to be considered separately. We do know, however, that for the person who is receiving an adequate intake of well balanced protein, there is no need for either amino acid or protein supplementation, and that for the person with a low protein intake the prime need is to increase the over-all intake of well balanced protein.

REFERENCES

1. WILCOCK, E. G. and HOPKINS, F. G. The importance of individual amino acids in metabolism; observations on the effect of adding tryptophane to a diet in which zein is the sole nitrogeneous constituent. *J. Physiol.*, 35: 88, 1906.
2. OSBORNE, T. B. and MENDEL, L. B. Amino acids in nutrition and growth. *J. Biol. Chem.*, 17: 325, 1914.
3. FLODIN, N. W. Amino acids and proteins; their place in human nutrition problems. *J. Agr. Food Chem.*, 1: 222, 1953.
4. HOWE, E. E. Amino acid supplementation. *Borden's Rev. Nutrition Res.*, 19: 19, 1958.
5. ELVEHJEM, C. A. and KREHL, W. A. Dietary interrelationships and imbalance in nutrition. *Borden's Rev. Nutrition Res.*, 16: 69, 1955.
6. HARPER, A. E. Balance and imbalance of amino acids. *Ann. New York Acad. Sc.*, 69: 1025, 1958.
7. SALMON, W. D. The significance of amino acid imbalance in nutrition. *Am. J. Clin. Nutrition*, 6: 487, 1958.
8. Evaluation of Protein Nutrition. Publication 711, 1959. National Academy of Sciences—National Research Council.
9. HARPER, A. E. and KUMTA, U. S. Amino acid balance and protein requirement. *Fed. Proc.*, 18: 1136, 1959.
10. HARPER, A. E. Sequence in which the amino acids of casein become limiting for the growth of the rat. *J. Nutrition*, 67: 109, 1959.