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IS HISTIDINE ESSENTIAL FOR THE ADULT MAN? A REVIEW

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SUMMARY

Recent experimental observations as well as theoretical considerations suggest that histidine may be an essential amino acid for the adult man. In this paper, an up-to-date review of the literature on the essentiality of histidine is presented. Some practical implications of the indispensability of this amino acid in the human diet are also discussed.

INTRODUCTION

Protein is one of the most important nutrients for man. It provides nitrogen as well as specific amino acids for synthesis of new tissue during growth, tissue repair and reproduction. It also furnishes biochemical precursors of important nitrogen-containing compounds essential for normal biological function and, thus,

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life. Those specific amino acids are called essential, meaning that they cannot be synthesized by the body and therefore must be provided in the diet for man to subsist. In fact, the quality of the protein depends on the presence and amount of these amino acids. Extensive research using experimental animals and human subjects has provided scientific information for the classification of those amino acids traditionally considered to be essential for the human species (isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine). The amino acid histidine has been later added to such list as an essential one, but only for the infant and not for the adult man. Nevertheless, recent experimental observations as well as theoretical considerations suggest that histidine may be an essential amino acid for the adult human species.

The purpose of this paper is to review the literature on the essentiality of histidine, hoping that it will stimulate further research in this area.

ON THE ESSENTIALITY OF HISTIDINE

The essentiality of histidine for the growing rat was first clearly demonstrated by Ackroyd and Hopkins in 1916 (1) and later established by Rose and Cox in 1924 (2). Since then, its indispensability has been determinated for other animal species from protozoa to insects, fish, birds and many mammals (3).

On the other hand, the non-essential nature of histidine for the human species had been established by the extensive work of Rose and co-workers in young college men (4,5-8). This classical Rose classification of histidine has been based on the accumulated data of 50 experimental subjects, from 1942 to 1955, who were able to maintain positive nitrogen balance when fed diets devoid of histidine (9). His conclusion is supported by similar reports on adult women (10) and children (11) by other investigators. In 1944, however, Albanese *et al.* (12) questioned the non-essentiality of histidine for the adult man. Their subjects, while on a histidine-deficient diet, remained in nitrogen equilibrium but lost weight. The deficient state was also characterized by the appearance of an "abnormal metabolite" in urine as indicated by an increased indican reaction (13). This latter finding, however, is of obscure significance and has not been reproduced by others (8,11). The loss of weight may have also been caused by an

insufficient caloric intake (9). Nevertheless, in 1963, Snyderman and co-workers clearly and conclusively demonstrated the essentiality of histidine for the infant (14). The experimental subjects were eight normal males whose ges ranged from two weeks to seven months These infants showed lower nitrogen retention, growth failure and even clinical signs characterized by skin lesions when histidine was omitted from their diet.

The idea then prevailed that histidine was a required amino acid for the growing animal but not for maintenance, thus, for example, histidine is essential for the baby pig but not for the adult pig and perhaps the rooster (3). On the other hand, it has been thought that histidine is essential for both the growing and the adult rat (15); nevertheless, evidence supporting this fact is very contradictory. There is no doubt about the true essentiality of this amino acid for the growing rat (1 2,3,15,16). It is even substantiated by the finding of no radioactive incorporation into histidine after the administration of ^{1}C-formate in no a and folate-deficient animals (17). On the other hand, the existing information for the adult is ambiguous. Burroughs, Burroughs and Mitchel (18) have demonstrated by means of nitrogen balance, using experimental periods of six to nine days, that histidine is a non-essential amino acid for the adult rat. In contrast when nitrogen balance is monitored by longer periods, histidine has been found to be essential for the maintenance of this adult animal (19, 20). The claim that histidine is non-essential for the adult rat is surprising since well-controlled studies of other adult mammals have shown, by using radioactive labeling, no incorporation into the histidine molecule of ^{14}C from amino acid precursors (21,22). In order to explain this discrepancy, Nasset and Gatewood (23) have proposed that the histidine requirement of the adult rat is probably very low and that histidine deficiency only slowly manifests itself in short nitrogen balance studies. It has also been postulated that when a histidine-deficient diet is fed, the breakdown of hemoglobin or that of carnosine, a dipeptide (β-alanyl-histidine found in muscle (24), can provide the required histidine to fulfill any metabolic need and thus mask the amino acid deficiency (15,23). Nasset and Gatewood in order to prove their point, performed a prolonged depletion of histidine in adult rats. The deficient animals showed negative nitrogen balance and decreased levels of hemoglobin (23).

Thu the work of Rose (9) in defining the essentiality of histidine can be criticized for being of short duration and his

conclusion based solely on nitrogen balance. It is interesting to note, however, that in two of the experimental subjects reported by Rose, although they were in positive nitrogen balance, both had a slight drop in the levels of hemoglobin when fed a histidine-deficient diet (6,7).

In the last eight years, data have accumulated that suggest the essentiality of histidine in the normal and diseased adult man (15, 25-32). Very low levels of plasma histidine have been found in men fed histidine-free diets (25). Kofranyi *et al.* (26), based on the observation of abnormally high levels of alanine transaminase and aspartate transaminase in experimental subjects fed diets devoid of histidine and arginine, concluded that continuous feeding in the absence of these amino acids was not possible, and therefore, at least one of them was essential (26). Bergstrom *et al.* (27) have also found a marked improvement of nitrogen balance when histidine, and no other non-essential amino acid, is added to amino acid mixtures given intravenously. Since their experimental subject was a uremic 48-year-old man, the authors suggested that histidine is an essential amino acid for the uremic individual. Another interesting observation has been that of Weller, Calloway and Margen (28) who failed in attaining positive nitrogen balance in six adult men using amino acid mixtures based on Rose's requirements. This situation was not corrected either by doubling the total nitrogen supply or increasing by one-third the amount of the eight essential amino acids given. They concluded that the Rose pattern is probably too low in one essential amino acid or an essential element is lacking in the diet, probably histidine. In 1972, after intravenous infusion of ^{15}N-urea, Furst (29) found no ^{15}N incorporation into any position of histidine in uremic adults, and thus concluded that this amino acid, as previously stated by Bergstrom *et al.* (27), is essential for the uremic adult man. More recently, a long-term and well-controlled study by Kopple and Swendseid (31) has shown that histidine is an essential amino acid for both the uremic and the normal adult human. Seven subjects were fed a diet containing very low amounts of histidine and after five to thirty days, their nitrogen balance became severely negative. There was also a marked drop in plasma and muscle histidine levels, anemia, lowered serum albumin and even clinical signs, among them, skin lesions similar to those previously found in infants by Snyderman *et al.* (14). It is interesting to note that Pinals *et al.* (30) had also found a significant increase in hematocrit in arthritic patients treated with histidine.

In spite of all this information, the essentiality of histidine for the human adult has not been yet widely accepted. Of course, the basic question concerning the synthesis of histidine in the human adult body has not been fully answered. There are some poor indications in the literature of its synthesis. Furst (29) based on ^{15}N incorporation claims that histidine can be synthesized by the healthy adult man. He does not specify, however, the site in the histidine molecule in which this incorporation takes place; therefore, his conclusion becomes debatable, especially on the grounds of the work of Schoenheimer, Rittengerg and Keston (33), showing that histidine undergoes a transamination process on the α-carbon; this, however, does not mean net synthesis. In 1952 there was also a very short report in abstract form and without experimental data by Levy and Coon (34). They found, after incubation of human liver slices with ^{14}C formate, the formation of a radioactive compound identified as histidine. Based on this report and on a personal communication by the same authors, Munro suggests that the liver may be the site of histidine synthesis in humans (3). Nevertheless, any follow-up studies after those preliminary findings are unknown. More recently, Sheng *et al.* (35) have demonstrated incorporation of ^{15}N into the imidazole ring of histidine in an adult man fed by parenteral alimentation. This finding suggests the synthesis of this amino acid by the human body, although in this experiment the role of intestinal microflora was not evaluated.

It appears then, at least from the biochemical point of view, that there is no conclusive evidence to support the fact that histidine is not an essential amino acid for the adult human. In contrast, numerous observations based on different criteria and methodology than those traditionally used to determine amino acid essentiality in man, strongly suggest that histidine may indeed be an essential amino acid for the human adult. In fact, before there is conclusive biochemical evidence, such as that of biosyntesis, histidine should be considered an essential amino acid for both infant and adult.

SOME PRACTICAL IMPLICATIONS

Examining the amino acid content of foods, especially the staple ones that provide most of the dietary protein in the developing countries, it can be concluded that histidine is not a

limiting amino acid. There are ample amounts of this amino acid in animal products; as an example, meats' contents roughly range between 160 and 210 mg histidine/gN. High amounts are also found in vegetable foods (see Table I).

TABLE I

HISTIDINE CONTENT OF SELECTED PLANT FOODS*

Product	mg/Histidine/g of nitrogen
Barley	132
Maize	170
Oats	131
Rice	156
Sorghum	134
Wheat	143
Cassava	129
Potato	94
Sweet potato	84
Yam	118
Beans	177
Chickpea	165
Groundnut	148
Soybean	158
Beet	97 (leaf)
	76 (root)

* Adapted from: *Amino Acid Content of Foods and Biological Data on Proteins.* Rome, Italy, 1970. (FAO Nutritional Studies No. 24).

Based on the recommended dietary allowances of the U. S. National Academy of Sciences for histidine for the infant of 33 mg/kg body weight/day, and for protein of 2 g/kg body weight/day (36) and also on data shown in Table I, it can be concluded that only potato, sweet potato and beets would be marginal in meeting the histidine requirement of the infant, if these food products are fed as the only protein source. All other proteins would amply satisfy the recommended dietary histidine level if the recommended amount of protein is met. There is no recommended dietary allowance of histidine for children and neither for

the adult. However, from experience on other essential amino acids, it is known that the amino acid requirements of the adult individual are far less that those of the infant. Therefore, from our previous quantitative analysis of dietary recommendations, it can be safely concluded that most, if not all protein will meet the histidine requirement of the adult man, provided that the level of protein fed meets the recommended dietary standards. In summary, a histidine deficiency can only be produced by diets providing suboptimal amounts of protein, that in any case may also be a protein deficiency.

RESUMEN

¿ES LA HISTIDINA UN AMINOACIDO ESENCIAL PARA EL HOMBRE ADULTO? UNA REVISION

Recientes observaciones experimentales y consideraciones teóricas sugieren que la histidina puede ser un aminoácido esencial para el hombre adulto. En este artículo se presenta una revisión bibliográfica actualizada acerca de la esencialidad de la histidina. Se discuten también algunas implicaciones prácticas sobre la indispensabilidad de este aminoácido en la dieta humana.

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