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Review

Molecular mechanisms involved in the adaptation to amino acid limitation in mammals

Cédric Chaveroux, Sarah Lambert-Langlais, Yoan Cherasse, Julien Averous, Laurent Parry, Valérie Carraro, Céline Jousse, Anne-Catherine Maurin, Alain Bruhat, Pierre Fafournoux*

Unité de Nutrition Humaine, UMR 1019, INRA de Theix, 63122 Saint Genès Champanelle, France

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ABSTRACT

In mammals, metabolic adaptations are required to cope with episodes of protein deprivation and malnutrition. Consequently, mammals have to adjust physiological functions involved in the adaptation to amino acid availability. Part of this regulation involves the modulation of the expression of numerous genes. In particular, it has been shown that amino acids by themselves can modify the expression of target genes. This review describes the regulation of amino acids homeostasis and the their role as signal molecules. The recent advances in the understanding of the molecular mechanisms involved in the control of mammalian gene expression in response to amino acid limitation will be described.

1. Introduction

Mammals have the ability to adapt their own metabolic demand to survive in a variable and sometimes hostile environment. External stimuli to which they must be able to respond include thermal variations, rhythmic changes imposed by alternation of day and night and the need to adapt to intermittent intake of food (including periods of malnutrition). Adaptation to these external factors requires metabolic responses resulting from various regulatory mechanisms.

The regulation of metabolism is achieved by coordinated actions between tissues and by mechanisms operating at cellular level. These mechanisms involve the conditional regulation of specific genes that involve complex interactions of hormonal, neuronal and nutritional factors. Although not as widely recognized, nutritional signals play an important role in controlling gene expression in mammals. It has been shown that major (carbohydrates, fatty acids, sterols) and minor (minerals, vitamins) dietary constituents participate in the regulation of gene expression [1–5]. In the last decade, significant progress has been achieved in the understanding of molecular mechanisms involved in the control of mammalian gene expression in response to amino acid availability [6–8]. On the basis of the characteristics of amino acid metabolism and homeostasis, the present article reviews the mechanisms involved in the adaptation to amino acid limitation in mammals.

2. Regulation of amino acid metabolism and homeostasis

Amino acids exhibit two important characteristics. Firstly, in healthy adult humans, 9 amino acids (valine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, histidine and tryptophan) cannot be synthesized *de novo* and are designated as indispensable (or essential) amino acids and have to be supplied by the food. In addition, under a particular set of conditions certain dispensable (non-essential) amino acids may become indispensable. These amino acids are called "conditionally indispensable". For example, enough arginine is synthesized by the liver (urea cycle) and by the kidney (from citrulline) to meet the needs of an adult but not those of a growing child. Secondly, there are no specific stores of amino acids. Consequently, if and when necessary, an organism has to hydrolyze muscle protein to produce free amino acids. This loss of protein will be at the expense of essential elements. Therefore complex and specific mechanisms are needed that take these amino acid characteristics into account in order to maintain the free amino acid pools.

2.1. Free amino acid pool

The size of the cellular pool of each amino acid is the result of a balance between input and removal (Fig. 1). The metabolic outlets for amino acids are protein synthesis and amino acid degradation whereas the inputs are de novo synthesis (for non-essential amino acids), protein breakdown and dietary supply. Changes in the rates of these systems lead to an adjustment in nitrogen balance. For example,

* Corresponding author. Tel.: +33 4 73 62 45 62; fax: +33 4 73 62 47 55.
E-mail address: pierre.fafournoux@clermont.inra.fr (P. Fafournoux).

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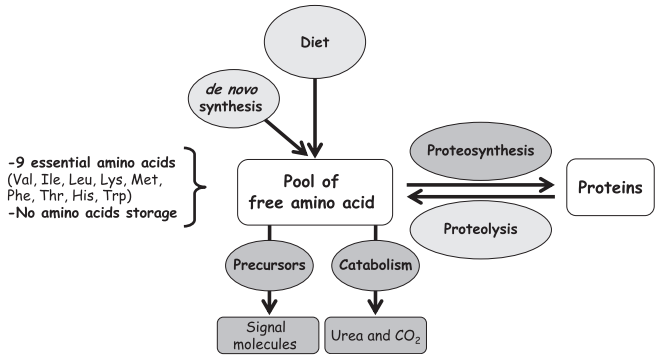

Fig. 1. Biochemical systems involved in the homeostasis of proteins and amino acids.

the plasma concentration of amino acids has been reported to rise following the administration of a protein-containing meal to animals or humans. The concentration of leucine and some other amino acids approximately doubles in peripheral blood following a protein-rich meal [9] and reaches much higher concentrations within the portal vein [10]. Most of the essential amino acids are degraded in the liver, except the branched chain amino acids and methionine that are poorly taken up by hepatocytes. Consequently, after a protein-rich meal, these amino acids pass through the liver into the general circulation and cause a much greater increment in systemic blood levels than other essential amino acids [11,12]. Several data demonstrate that the effect of a protein-rich meal on protein turn-over is due to postprandial increases in the concentrations of circulating amino acids [13,14].

On the other hand, an adjustment of the nitrogen balance is also necessary in case of protein malnutrition. Indeed, a dramatic drop in the plasma concentrations of certain essential amino acids has been shown to occur following insufficient amino acid or protein intake. A few examples of adaptation to a lack of dietary amino acid are described below in more detail.

2.2. Specific examples of adaptation to amino acid deficiency

2.2.1. Protein undernutrition

Protein undernutrition has its most devastating consequences during growth. Prolonged feeding on a low protein diet causes a fall in the plasma level of most essential amino acids [15,16]. It follows that individuals have to adjust several physiological functions in order to adapt to amino acid deficiency. One of the main consequences of feeding a low protein diet is the dramatic inhibition of growth in young individuals. Growth is controlled by a complex interaction of genetic, hormonal and nutritional factors. A large part of this control is due to growth hormone (GH) and insulin-like growth factors (IGFs). The biological activities of IGFs are modulated by the IGF-binding proteins (IGFBPs) that specifically bind IGF-I and IGF-II [17,18]. Straus et al. [19] demonstrated that a dramatic overexpression of IGFBP-1 was responsible for growth inhibition in response to prolonged feeding on a low protein diet. *In vivo*, the known regulators of IGFBP-1 expression are mainly GH, insulin and glucose. However, the high IGFBP-1 levels found in response to a protein-deficient diet cannot be explained by these factors. It has been demonstrated that a fall in blood amino acid concentration was directly responsible for IGFBP-1 induction [19–21]. Therefore, amino acid limitation, such as during dietary protein deficiency, contributes to the down-regulation of growth through the induction of IGFBP-1.

2.2.2. Imbalanced diet

Amino acid-imbalanced diets can be a frequent nutritional situation for wild omnivorous animals. For example, rodents are often confronted with poor food availability with a single plant protein source, which is most likely partially deficient for one essential amino acid. Indeed, most cereals are partially devoid of lysine while leguminous plants may be partially devoid of methionine. After eating an amino acid-imbalanced diet, animals first recognize the amino acid deficiency and then respond by reducing their food intake (Fig. 2). This innate aversive response biases the diet against imbalanced food sources. Recognition and anorexia resulting from an amino acid-imbalanced diet take place very rapidly [22–25]. The mechanisms that underlie the recognition of protein quality must act via the free amino acids resulting from intestinal digestion of proteins. The decrease in blood concentration of the limiting amino acid becomes apparent as early as a few minutes after feeding an imbalanced diet and depends on the extent of deficiency [25]. The anorectic response is correlated with a decreased concentration of the limiting amino acid in the plasma. Several lines of evidence have suggested that the fall in the limiting amino acid concentration is detected in the brain. It has been proposed that a specific brain area, the anterior piriform cortex (APC), can sense the variations in amino acid concentrations [24,22,26]. This recognition phase is associated with a localized decrease in the concentration of the limiting amino acid and changes in protein synthesis rate and gene expression [22].

2.2.3. Pathological situation

In addition to nutritional factors, various forms of stress (trauma, thermal burn, sepsis, fever etc) can affect nitrogen metabolism, amino acidemia and lead to a state of negative nitrogen balance and significant loss of body mass [27–32]. The hypercatabolic state observed during these stress situations is characterized by an increase in protein synthesis and degradation. However, protein synthesis remains insufficient to compensate for higher proteolysis. The amino acids freed by muscular proteolysis are mostly used by the liver to synthesize proteins involved in the inflammatory response. Consequently high variations of amino acid concentrations in plasma and urine can be observed. In such situations, changes in nitrogen metabolism can be ascribed to several hormonal, metabolic, and behavioral changes.

Taken together, these examples show that amino acidemia can be affected by various nutritional or pathological situations with one major consequence being a large variation of blood amino acid concentration. It follows that mammals have to adjust several of their physiological functions involved in the defense/adaptation to amino acid limitation by controlling physiological functions through regulation of the expression of numerous genes. Several steps forward have been made recently in our understanding of the mechanisms by which amino acid limitation controls the expression of specific genes. The present review focuses on the regulatory role of low amino acid availability. The effects of an excess of amino acids are not considered herein.

3. Target genes affected by amino acid limitation

Previous studies in the 1990's identified several genes regulated by amino acid availability [18,33]. More recently, array analyses of amino acid deprived cells identified two sets of amino acid-regulated genes: genes that are down or up-regulated [34–36]. Briefly, the functions of genes regulated by amino acid limitation illustrate the organism's need to adapt to a changing nutritional environment.

Genes that are specifically down-regulated by amino acid starvation encode proteins that are mainly involved in lipid and carbohydrate metabolic processes, regulation of transcription, signal transduction [35] etc. The molecular mechanisms involved in such down-regulation have not yet been identified.

Among the up-regulated genes in response to amino acid starvation, a large number encodes plasma membrane amino acid transporters. Other identified genes include genes encoding for