CELLULAR ADAPTATION TO AMINO ACID AVAILABILITY: MECHANISMS INVOLVED IN THE REGULATION OF GENE EXPRESSION

ADAPTATION CELLULAIRE À LA DISPONIBILITÉ DES ACIDES AMINÉS : MÉCANISMES IMPLIQUÉS DANS LA RÉGULATION DE L'EXPRESSION DES GÈNES

By Anne-Catherine MAURIN, Alain BRUHAT, Céline JOUSSE, Yoan CHERASSE and Pierre FAFOURNOUX[1]

SUMMARY

In mammals, the impact of nutrients on gene expression has become an important area of research. Nevertheless, the current understanding of amino acid-dependent control of gene expression is limited. Amino acids have multiple and important functions, so their homeostasis has to be finely maintained. However, the amino acidemia can be affected by certain nutritional conditions or various forms of aggression. It follows that mammals have to adjust several of their physiological functions involved in the adaptation to amino acid availability by regulating expression of numerous genes. The aim of this review is to examine the role of amino acids in regulating mammalian gene expression and physiological functions.

A limitation for several amino acids strongly increases the expression of target genes such as IGFBP-1, CHOP and asparagine synthetase (AS) genes. The molecular mechanisms involved in the regulation of CHOP and AS gene transcription in response to amino acid starvation have been partly identified. Particularly, a signalling pathway requiring the protein kinase GCN2 and the transcription factor ATF4 has been described to sense the amino acid limitation. In case of an amino acid imbalanced food source, this pathway has been shown to decrease food intake by activating a neuronal circuit. Taken together, the results discussed in this review demonstrate that amino acids by themselves can act as "signal" molecules with important roles in the control of gene expression and physiological functions.

Keys words: amino acid, gene expression, signalling pathway, GCN2, ATF4, nutrition, protein.

(1) Unité de Nutrition Humaine, Institut National de la Recherche Agronomique de Theix, 63122 Saint-Genès-Champanelle, France
To whom correspondence should be addressed : Tél. : (33) 4 73 62 45 62 / FAX : (33) 4 73 62 45 70 / e-mail: fpierre@clermont.inra.fr

RÉSUMÉ

Bien que l'étude du rôle des nutriments dans la régulation de l'expression des gènes chez les Mammifères soit devenue un domaine de recherche important, les mécanismes impliquant les acides aminés sont encore peu connus. Du fait de l'importance de leurs rôles physiologiques, l'homéostasie des acides aminés doit être finement régulée. Cependant, les concentrations plasmatiques des acides aminés peuvent être affectées par certaines conditions nutritionnelles ou différentes formes d'agression. En régulant l'expression d'un grand nombre de gènes, l'organisme a la capacité d'ajuster certaines de ses fonctions impliquées dans l'adaptation à la disponibilité en acides aminés. Cette revue vise à rassembler les données actuelles concernant le rôle des acides aminés dans la régulation de l'expression des gènes et des fonctions physiologiques chez les Mammifères.

Pour plusieurs acides aminés dits « indispensables », une diminution de leur concentration entraîne la stimulation de l'expression de gènes cibles spécifiques tels que les gènes codant pour IGFBP-1, CHOP et l'asparagine synthétase (AS). Les mécanismes moléculaires impliqués dans l'activation transcriptionnelle de CHOP et AS en réponse à une carence en acide aminé ont été en partie identifiés. En particulier, une voie de signalisation faisant intervenir la protéine kinase GCN2 et le facteur de transcription ATF4 joue le rôle de senseur des déficits en acides aminés. Au niveau physiologique, des travaux récents montrent que l'activation de cette voie permet, par le biais d'un circuit neuronal, d'inhiber la prise alimentaire lorsque l'apport nutritionnel en acides aminés est déséquilibré.

L'ensemble des données présentées dans cette revue montre que les acides aminés peuvent agir comme des molécules « signal » contrôlant l'expression de gènes afin de réguler certaines fonctions physiologiques.

Mots-clés : acide aminé, expression des gènes, voie de signalisation, GCN2, ATF4, nutrition, protéine.

ABBREVIATIONS

AARE	Amino Acid Regulatory Element
APC	Anterior Piriform Cortex
ASNS	Asparagine Synthetase
ATF	Activating transcription Factor
C/EBP	CCAAT/Enhancer Binding Protein
CHOP	C/EBP Homologous Protein
eIF2α	eukaryotic Initiation Factor 2α
HRI	Heme-regulated eIF2α kinase
IGF1	Insulin Like Growth Factor 1
IGF2	Insulin Like Growth Factor 2
IGFBP1	Insulin Like Growth Factor Binding Protein1
mTOR	Mammalian Target of Rapamycin
NSRE-1	Nutrient Sensing Response Element 1
PERK	PKR-like Endoplasmic Reticulum kinase
PKR	double stranded RNA regulated Protein Kinase

Regulation of metabolism is achieved by coordinated actions between cells and tissues and also by mechanisms operating at the cellular level. These mechanisms involve the conditional regulation of specific genes in the presence or absence of appropriate nutrients. In multicellular organisms, the control of gene expression involves complex interactions of hormonal, neuronal and nutritional factors. Although not as widely appreciated, 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 (Towle 1995; Foufelle *et al.* 1998; Pegorier 1998; Duplus *et al*. 2000; Vaulont *et al*. 2000; Grimaldi 2001). However, the mechanisms involved in the amino acid control of gene expression have just begun to be understood in mammalian cells (Kilberg *et al*. 1994; Fafournoux *et al*. 2000; Bruhat & Fafournoux, 2001). This review summarizes recent work on the effect of amino acid availability in the regulation of biological functions. On the basis of the physiological concepts of amino acids homeostasis, we will discuss specific examples of the role of amino acids in the regulation of physiological functions, particularly focusing on the mechanisms involved in the amino acid regulation of gene expression.

REGULATION OF AMINO ACID METABOLISM AND HOMEOSTASIS IN THE WHOLE ANIMAL

Amino acids exhibit two important characteristics compared with other macronutrients (lipids or sugars). First, in healthy adult humans, 9 amino acids (valine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, histidine and tryptophan) are indispensable (or essential). In addition, under a particular set of conditions certain dispensable (non-essential) amino acids may become indispensable. These amino acids are termed "conditionally indispensable". For example, enough argi-

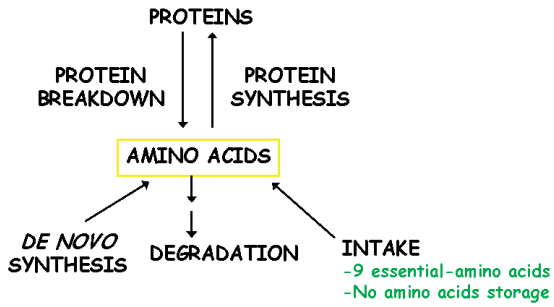

Figure 1 : *Biochemical systems involved in the homeostasis of proteins and amino acids.*

nine is synthesised by the urea cycle to meet the needs of an adult but not those of a growing child. Secondly, there are no large stores of amino acids. Consequently, when necessary, an organism has to hydrolyse muscle proteins to produce free amino acids. This loss of protein will be at the expense of essential elements. Therefore, complex mechanisms that take into account these amino acid characteristics are needed for maintaining the free amino acid pools.

Free amino acids pool

The size of the pool of each amino acid is the result of a balance between input and removal ***(figure 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, a protein-containing meal given to an animal or a human subject has been reported to increase both the nitrogen balance and the level of amino acids in the plasma. Particularly, the concentration of leucine and certain other amino acids approximately doubles in peripheric blood following a protein rich meal (Aoki *et al*. 1976) and reaches much higher concentrations within the portal vein (Fafournoux *et al*. 1990). It is now well established that the effect of a protein-rich meal on protein turnover is due to postprandial increases in the concentrations of circulating amino acids (Yoshizawa *et al*. 1995; Svanberg *et al*. 1997).

Another example of the nitrogen balance adjustment is the adaptation to an amino acid deficient diet. A dramatic decrease in the plasma concentrations of certain essential amino acids has been shown to occur following a dietary imbalance, a deficiency of any one of the essential amino acids or a deficient intake of protein (Grimble & Whitehead, 1970; Peng & Harper, 1970; Ozalp *et al*. 1972; Baertl *et al*. 1974). Long term feeding with such diets can lead to a negative nitrogen balance and clinical symptoms.

The examples cited above show that amino acid metabolism can be affected by various nutritional and/or pathological situations, with two major consequences: a large variation in blood amino acid concentrations and a negative nitrogen balance. In these situations, individuals have to adjust several of their physiological functions involved in the defence/adaptation to amino acid limitation by regulating numerous genes. In the next section the specific role of amino acids in the adaptation to amino acids deficient diets will be considered.

SPECIFIC EXAMPLES OF THE ROLE OF AMINO ACIDS IN THE ADAPTATION TO PROTEIN DEFICIENCY

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. For example, leucine and methionine concentrations can be reduced from about 100-150 µM and 18-30 µM to 20 µM and 5 µM, respectively, in plasma of children affected by kwashiorkor (Grimble & Whitehead, 1970; Baertl *et al*. 1974). It follows that individuals have to adjust several physiological functions in order to adapt to this amino acid deficiency. One of the main consequences of feeding a low protein diet is the dramatic inhibition of growth. 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 the IGFs are modulated by the IGF-binding proteins (IGFBPs) that specifically bind IGF-I and IGF-II (Lee *et al.*, 1993; Straus, 1994). Straus *et al*. (1993) demonstrated that a dramatic overexpression of IGFBP-1 was responsible for growth inhibition in response to prolonged feeding on a low protein diet. Known regulators of IGFBP-1 expression are GH, insulin or 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 the amino acid concentration was directly responsible for IGFBP-1 induction (Straus *et al*. 1993; Jousse *et al*. 1998). Therefore, amino acid limitation, as occuring during dietary protein deficiency, participates in the down-regulation of growth through the induction of IGFBP-1.

Imbalanced diet

The ability to synthesise protein is essential for survival, and protein synthesis is dependent on the simultaneous supply of the 20 precursor amino acids. Because mammals cannot synthesise all of the amino acids, the diet must provide the remaining ones. Thus, in the event of a deficiency of one of the indispensable amino acids body proteins are broken down to provide the limiting amino acid and the remaining amino acids are catabolised and lost (Munro 1976). It follows that mammals (with the exception of the ruminants) need mechanisms that provide for selection of a balanced diet. The capacity to distinguish balance from imbalance among the amino acids in the diet and to select for the growth-limiting essential amino acid provides an adaptive advantage to animals.

After eating an amino-acid imbalanced diet, animals first recognise the amino acid deficiency and then respond by reducing their food intake. Recognition and anorexia resulting from an

amino-acid imbalanced diet take place very rapidly (Harper *et al.* 1970; Rogers & Leung, 1977; Gietzen 1993). The mechanisms that underlie the recognition of protein quality must act by way of the free amino acids resulting from intestinal digestion of proteins. The decrease in the blood concentration of the limiting amino acid becomes apparent as early as a few hours after feeding an imbalanced diet and depends on the extent of deficiency. 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. Gietzen (1993, 2000) reviews the evidence that a specific brain area, the anterior piriform cortex (APC), can sense the variations in the amino acid concentrations. This recognition phase is associated with a localised decrease in the concentration of the limiting amino acid and changes in protein synthesis rate and gene expression. Subsequent to recognition of the deficiency, the second step – development of anorexia – involves another part of the brain.

These two examples demonstrate that a variation in blood amino acid concentration can activate several control processes in target cells that can specifically regulate the expression of target genes. Although the role of the amino acids that are considered to be regulators of gene expression is understood in only a few nutritional situations, progress has recently been made in understanding the mechanisms by which amino acid limitation controls the expression of several genes.

AMINO ACID CONTROL OF GENE EXPRESSION IN MAMMALIAN CELLS

Amino acids as "signal" molecules

- *Genes up-regulated by amino acids*

Genes that are specifically up-regulated in response to supra-physiological concentrations of amino acids have been described. For example, a high concentration of L-tryptophan enhances the expression of collagenase and of tissue inhibitors of metalloproteinase. In rat hepatocytes, Na+- cotransported amino acids like glutamine, alanine or proline stimulate acetyl-coA carboxylase, glycogen synthetase and arginino succinate synthetase activity. It has been demonstrated that the swelling resulting from the addition of amino acid could be involved in the regulation of gene expression (Watford 1990; Haussinger 1996), although the molecular mechanisms involved in these processes are poorly understood.

- *Genes up-regulated by amino acid starvation*

Specific mRNAs that are induced following amino acid deprivation have been reported (Marten *et al.* 1994) in mammalian cells. Most molecular mechanisms involved in the amino acid regulation of gene expression have been obtained by studying the up-regulation of C/EBP homologous protein (CHOP), Asparagine synthetase (ASNS) and the cationic amino acid transporter (Cat-1) genes.

MOLECULAR MECHANISMS INVOLVED IN THE MAMMALIAN REGULATION OF GENE EXPRESSION BY AMINO ACID LIMITATION

Transcriptional activation of mammalian genes by amino acid starvation

It has been established that the increase in CHOP or ASNS mRNA following amino acid starvation is mainly due to an increased transcription (Hutson & Kilberg, 1994; Bruhat *et al.* 1997). By first identifying the genomic cis-elements and then the corresponding transcription factors responsible for regulating these specific target genes, it is anticipated that one can progress backwards up the signal transduction pathway to gain an understanding of the individual steps required.

- *Regulation of the human CHOP gene by amino acid starvation*

CHOP encodes a ubiquitous transcription factor that heterodimerises avidly with the other members of the C/EBP (Fawcett *et al.* 1996) and jun/fos (Ubeda *et al.* 1999) family. The CHOP gene is tightly regulated by a wide variety of stresses in mammalian cells (Luethy & Holbrook, 1992; Sylvester *et al.* 1994; Wang *et al.* 1996). Leucine limitation in human cell lines leads to induction of CHOP mRNA and protein in a dose dependent manner (Bruhat *et al.*, 1997).

We identified a cis-positive element in the CHOP promoter located between –313 and –295 that is essential for amino acid regulation of the gene transcription (Bruhat *et al.* 2000) ***(figure 2)***. This short sequence can regulate a basal promoter in response to starvation of several individual amino acids, which is then termed an amino acid regulatory element (AARE). The sequence of the CHOP AARE region exhibits some homology with the specific binding sites of the C/EBP and ATF/CREB transcription factor families. Using gel shift experiments and chromatin immunoprecipitation, we have shown that ATF2, ATF3, ATF4 and CCAAT/enhancer-binding protein , (C/EBP,) that belong to the ATF or C/EBP family have the ability to bind to the CHOP AARE. Among these factors ATF2 and ATF4 are involved in the amino acid control of CHOP expression: when knockout cell line for these two proteins were tested, amino acid regulation of CHOP expression was abolished (Bruhat *et al.* 2000; Averous *et al.* 2004). This work was broadened to the regulation of other amino acid regulated genes and confirmed that ATF4 and ATF2 are key components in the amino acid control of gene expression (Averous *et al.* 2004).

Amino acid signalling pathway

It appears that more than one amino acid signalling pathway exists in mammalian cells (Jousse *et al.* 2000; Bain *et al.* 2002). However, the individual steps required for these pathways are not well understood.

• *ATF4 and the amino acid signalling pathways*

D. Ron's group has identified a signalling pathway for regulating gene expression in mammals that is homologous to the well-characterised yeast general control response to amino acid deprivation (Harding *et al.* 2000). Its components include ***(figure 3)*** the mammalian homologue of the GCN2 kinase, the initiation factor eIF2α and ATF4. Like GCN4 transcript, the ATF4 mRNA contains uORF in its 5'UTR that allows translation when the cap-dependent translation is inhibited. The authors showed that GCN2 activation, phosphorylation of eIF2α and translational activation of ATF4 are necessary but not sufficient for the induction of CHOP expression in response to leucine starvation. These data are in good agreement with the analysis of the CHOP and ASNS promoters showing that ATF4 can bind to the promoter sequences involved in the response to amino acid starvation.

• *ATF2 and the amino acid signalling pathways*

Transactivating capacity of ATF2 is activated via phosphorylation of N-terminal residues Thr-69, Thr-71 and Ser-90 (Gupta *et al.* 1995; Livingstone *et al.* 1995). There are two lines of evidence suggesting that ATF2 phosphorylation belongs to the amino acid response pathway leading to the transcriptional activation of CHOP by amino acids: (i) Leucine starvation induces ATF2 phosphorylation in human cell lines (Averous *et al.* 2004) and (ii) an ATF2 dominant negative mutant (Sano *et al.* 1999) in which the three residues cannot be phosphorylated inhibits the CHOP promoter activity enhanced by leucine starvation (Bruhat *et al.* 2000). These data suggest that a specific amino acid regulated pathway that leads to the transcriptional activation of CHOP may involve a phosphorylation of prebound ATF2 rather than an increase in ATF2 binding. However, the identity of any kinases involved in ATF2 phosphorylation by amino acid starvation remains to be discovered ***(see figure 2)***.

It appears that at least two different pathways that lead to ATF2 phosphorylation and to ATF4 expression are necessary to induce CHOP expression in response to one stimulus (amino acid starvation). In addition, ATF4 and ATF2 belong to the b-ZIP transcription factor family. These proteins have the ability to interact with several transcription factors to bind the target DNA sequence. In the case of amino acid regulation of CHOP expression, we have no evidence that ATF2 and ATF4 form a dimer that bind the AARE sequence but they could be included in a larger regulatory protein complex. However, it has been shown that ATF2 is able to interact with the coactivator of transcription p300 which has histone acetyltransferase activity (Kawasaki *et al.* 1998) and also with JDP2, a repressor that recruits a histone deacetylase complex (Jin *et al.* 2002), suggesting that this transcription factor could modulate transcription by interacting directly or indirectly with the chromatin structure.

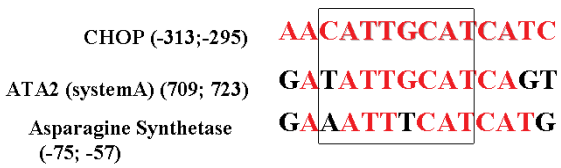

Figure 2: Cis-acting elements required for induction of CHOP, ATA2 and ASNS genes following amino acid starvation

Sequence comparison of the CHOP AARE with the ASNS NSRE-1 and the ATA2 AARE. The positions of sequences from the transcription start site are shown in brackets. The minimum sequence (core sequence) required for the response to amino acid starvation is in boxes. Identical nucleotides to the CHOP sequence are in red.

ROLE OF THE GCN2/ATF4 PATHWAY IN NUTRITION: AMINO ACID DEFICIENCY SENSING BY GCN2 TRIGGERS FOOD AVERSION

Food intake results from a complex behavioural pattern in which innate factors play an important role, particularly in the case of omnivores. A remarkable example of an innate mechanism governing food choice is presented by the fact that omnivorous animals will consume substantially less of an otherwise identical experimental meal lacking a single essential amino acid (Harper *et al.* 1970; Gietzen *et al.* 1993). Although it seems likely that the signalling pathway leading to this response comprises the sensing of amino acid variations, the basis for this innate aversive response is poorly understood. As described above, previous studies have implicated the anterior piriform cortex (APC) in controlling food intake according to amino acid levels (Leung & Rogers, 1971; Gietzen 1993). Furthermore, it has been recently reported that consumption of an amino acid imbalanced diet rapidly elevates levels of phosphorylated eIF2α in APC neurons (Gietzen *et al.* 2004).

Blood concentration of an essential amino acid decreases rapidly when this amino acid is missing in the diet. As a consequence, the protein kinase GCN2, which is ubiquitously expressed, could be activated in most tissues. Its only known substrate is the serine 51 of the a subunit of eIF2. Therefore GCN2 could be an important sensor of amino acid homeostasis

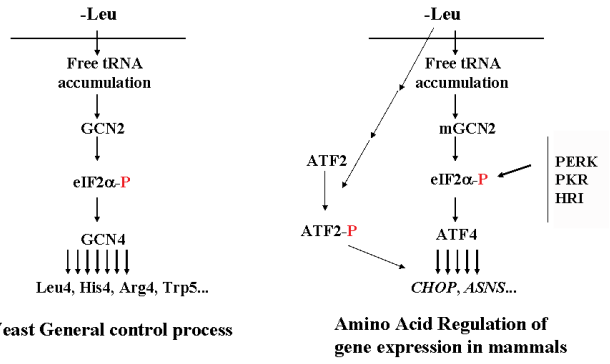

Figure 3 : Comparison between the general control process of gene expression by amino acid availability in yeast and the amino acid regulation of CHOP or ASNS expression in mammals

The mammalian pathway appears to be more complex than the yeast pathway; for example, ATF2 needs to be phosphorylated to allow CHOP transcriptional induction in response to leucine starvation. In addition, eIF2a can be phosphorylated by 4 different kinases (GCN2, PERK, PKR, and HRI).

inside cells and could activate downstream rectifying responses mediated by phosphorylated eIF2α. The latter affect gene expression programs at the level of mRNA translation and transcription (Hinnebusch 1994; Harding *et al*. 2000; this review).

Recent results (Maurin *et al*. 2005; Hao *et al*. 2005) establish that the aversive response of wild-type mice to a diet deficient in one essential amino acid is likewise blunted in GCN2-/- mice whereas serum amino acid levels are decreased to similar levels by the imbalanced diet in both genotypes ***(figure 4)***. These results indicate an altered response to amino acid deficiency in mice lacking GCN2 activity. Moreover, we confirmed the previously described increase in phosphorylated eIF2α levels in the APC of wild-type animals after consumption of an imbalanced meal, and further showed that no such signal occurs in the GCN2-/-. This observation indicates a role for GCN2 in mediating eIF2α phosphorylation in the APC of mice fed an imbalanced diet. Using conditional GCN2 knockout mice, we further demonstrated that GCN2 ablation specifically in the brain also impairs the aversive response to an imbalanced diet. Thus, even if the consumption of an imbalanced meal also activates GCN2 and promotes eIF2α in peripheral tissues, particularly in the liver, our observation implicates brain GCN2 signalling in initiating the aversive response. This example highlights the need to rely on physiological observations of molecular events described in vitro to improve our knowledge on physiological consequences of nutritional status.

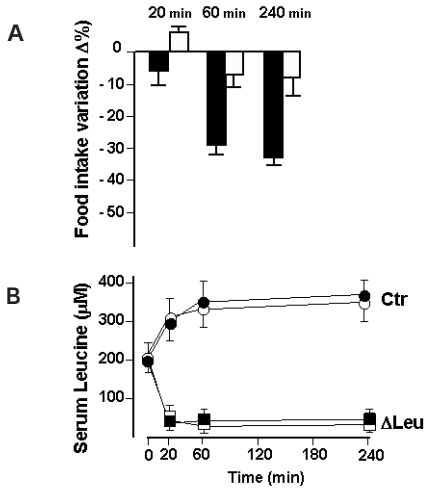

Figure 4: Mice lacking the GCN2 kinase are impaired in their aversive response to amino acid imbalanced food

(A) *Relative consumption of balanced diet (Ctr) and diet lacking leucine (ΔLeu) for 20, 60 or 240 minutes after the beginning of the meal. Results from GCN2+/+ mice are shown as dark bars and mutant GCN2-/- mice as open bars. Results are expressed as the ratio of consumption (Δ% ±SEM) of the ΔLeu diet versus the consumption of the Ctr by the same animal. For example, 60 minutes after the beginning of the meal, wild type mice consumed 30% less of the ΔLeu diet compared to the Ctr diet, whereas the GCN2-/- mice consumed equally both diets.*

(B) *Plasma leucine levels (μM) of mice fed the indicated diet (circles: control diet and squares: leucine devoid diet). Results from GCN2+/+ mice are shown as dark symbols and mutant GCN2-/- mice as open symbols.*

CONCLUSION

The idea that amino acids can regulate gene expression is now well established. Amino acids by themselves can play an important role in the control of gene expression, in concert with hormones, but the underlying processes are only now being discovered. Amino acid availability can modify the expression of target genes at the level of transcription, mRNA stability and translation.

Defining the precise cascade of molecular events by which the cellular concentration of an individual amino acid regulates gene expression will be an important contribution to our understanding of metabolite control in mammalian cells. These studies will provide insight into the role of amino acids in the regulation of cellular functions such as cell division, protein synthesis or proteolysis.

BIBLIOGRAPHY

- Aoki, T.T., Brennan, M.F., Muller, W.A., Soeldner, J.S., Alpert, J.S., Saltz, S.B., Kaufmann, R.L., Tan, M.H., Cahill, G.F. Jr. 1976. Amino acid levels across normal forearm muscle and splanchnic bed after a protein meal. Am J Clin Nutr. 29(4) : 340-350.
- Averous, J. , Bruhat, A., Jousse, C., Carraro, V., Thiel, G., Fafournoux, P. 2004. Induction of CHOP expression by amino acid limitation requires both ATF4 expression and ATF2 phosphorylation. J Biol Chem. 279(7): 5288-5297.
- Baertl, J.M., Placko, R.P., Graham, G.G. 1974. Serum proteins and plasma free amino acids in severe malnutrition. Am J Clin Nutr. 27(7): 733-742.
- Bain, P.J., Leblanc-Chaffin, R., Chen, H., Palii, S.S., Leach, K.M., Kilberg, M.S. 2002. The mechanism for transcriptional activation of the human ATA2 transporter gene by amino acid deprivation is different than that for asparagine synthetase. J Nutr. 132(10): 3023-3029.
- Bruhat, A. & Fafournoux, P. 2001. Recent advances on molecular mechanisms involved in amino acid control of gene expression. Curr Opin Clin Nutr Metab Care 4(5): 439-443.
- Bruhat, A Jousse, C Carraro, V Reimold, A.M., Ferrara, M., Fafournoux, P. 2000. Amino acids control mammalian gene transcription: activating transcription factor 2 is essential for the amino acid responsiveness of the CHOP promoter. Mol Cell Biol. 20(19): 7192-7204.
- Bruhat , A., Jousse, C., Wang, X.Z., Ron, D., Ferrara, M., Fafournoux, P. 1997. Amino acid limitation induces expression of CHOP, a CCAAT/enhancer binding protein-related gene, at both transcriptional and post- transcriptional levels. J Biol Chem. 272(28):17588-17593.
- Duplus, E Glorian, M., Forest, C. 2000. Fatty acid regulation of gene transcription. J Biol Chem. 275(40): 30749-30752.
- Fafournoux, P., Bruhat, A., Jousse, C. 2000. Amino acid regulation of gene expression. Biochem J. 351(Pt 1):1-12.
- Fafournoux , P., Remesy, C., Demigne, C. 1990. Fluxes and membrane transport of amino acids in rat liver under different protein diets. Am J Physiol. 259(5 Pt 1): E614-E625.
- Fawcett, T.W., Eastman, H.B., Martindale, J.L., Holbrook, N.J. 1996. Physical and functional association between GADD153 and CCAAT/enhancer- binding protein beta during cellular stress. J Biol Chem. 271(24): 14285-14289.
- Foufelle, F., Girard, J., Ferre, P. 1998. Glucose regulation of gene expression. Curr Opin Clin Nutr Metab Care 1(4): 323-328.
- Gietzen, D.W. (1993). Neural mechanisms in the responses to amino acid deficiency. J Nutr. 123(4): 610-625.
- Gietzen, D.W. 2000. Amino acid recognition in the central nervous system. In BERTHOUD H.R., SEELEY R.J., editors. pp 339-357: CRC press, Boca-Raton London, New York, Washington.
- Grimaldi, P.A. 2001. Fatty acid regulation of gene expression. Curr Opin Clin Nutr Metab Care, 4(5): 433-437.
- Grimble, R.F. & Whitehead R.G. 1970. Fasting serum-aminoacid patterns in kwashiorkor and after administration of different levels of protein. Lancet 1(7653): 918-920.
- Gupta, S., Campbell, D., Derijard, B., Davis, R.J. 1995. Transcription factor ATF2 regulation by the JNK signal transduction pathway. Science 267(5196): 389-393.
- Hao, S. Sharp, J.W., Ross-Inta, C.M., McDaniel, B.J., Anthony, T.G., Wek, R.C., Cavener, D.R., Mcgrath, B.C., Rudell, J.B., Koehnle, T.J., Gietzen, D.W. 2005. Uncharged tRNA and sensing of amino acid deficiency in mammalian piriform cortex. Science 307(5716): 1776-1778.
- Harding, H.P., Novoa, I.I., Zhang, Y., Zeng, H., Wek, R., Schapira, M., Ron, D. 2000. Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol Cell. 6(5): 1099-1108.
- Harper, A.E., Benevenga, N.J., Wohlhueter, R.M. 1970. Effects of ingestion of disproportionate amounts of amino acids. Physiol Rev. 50(3): 428-558.
- Haussinger, D. 1996. The role of cellular hydration in the regulation of cell function. Biochem J. 313 (Pt 3): 697-710.
- Hutson, R.G. & Kilberg M.S. 1994. Cloning of rat asparagine synthetase and specificity of the amino acid- dependent control of its mRNA content. Biochem J. 304(Pt 3): 745-750.
- Jin,C., Li,H., Murata,T., Sun,K., Horikoshi, M., Chiu,R., Yokoyama, K.K. 2002. JDP2, a repressor of AP-1, recruits a histone deacetylase 3 complex to inhibit the retinoic acid-induced differentiation of F9 cells. Mol Cell Biol. 22(13): 4815-4826.
- Jousse, C., Bruhat, A., Ferrara, M., Fafournoux, P. 1998. Physiological concentration of amino acids regulates insulin-like- growth-factor-binding protein 1 expression. Biochem J. 334(Pt 1): 147-153.
- Jousse, C., Bruhat, A., Ferrara, M., Fafournoux, P. 2000. Evidence for multiple signaling pathways in the regulation of gene expression by amino acids in human cell lines. J Nutr. 130(6): 1555-1560.
- Kawasaki, H., Song, J., Eckner, R., Ugai, H., Chiu, R., Taira, K., Shi, Y., Jones, N., Yokoyama, K.K. 1998. p300 and ATF-2 are components of the DRF complex, which regulates retinoic acid- and E1A-mediated transcription of the c-jun gene in F9 cells. Genes Dev. 12(2): 233-245.
- Kilberg, M.S., Hutson, R.G., Laine, R.O. (1994). Amino acid-regulated gene expression in eukaryotic cells. Faseb J. 8(1): 13-19.
- Lee, P.D., Conover, C.A., Powell, D.R. 1993. Regulation and function of insulin-like growth factor-binding protein-1. Proc Soc Exp Biol Med. 204(1): 4-29.
- Livingstone, C., Patel, G., Jones, N. 1995. ATF-2 contains a phosphorylation-dependent transcriptional activation domain. Embo J. 14(8): 1785-1797.
- Luethy J.D.& Holbrook N.J. 1992. Activation of the gadd153 promoter by genotoxic agents: a rapid and specific response to DNA damage. Cancer Res. 52(1): 5-10.
- Marten, N.W., Burke, E.J., Hayden, J.M., Straus, D.S. 1994. Effect of amino acid limitation on the expression of 19 genes in rat hepatoma cells. Faseb J. 8(8): 538-544.
- Maurin, A.C., Jousse, C., Averous, J., Parry, L., Bruhat, A., Cherasse, Y., Zeng, H., Zhang, Y., Harding, H.P., Ron, D., Fafournoux, P. 2005. The GCN2 kinase biases feeding behavior to maintain amino acid homeostasis in omnivores. Cell Metab. 1(4): 273-277.
- Munro, H.N. 1976. Second Boyd Orr Memorial Lecture. Regulation of body protein metabolism in relation to diet. Proc Nutr Soc. 35(3): 297-308.
- Ozalp, I., Young, V.R., Nagchaudhuri, J., Tontisirin, K., Scrimshaw, N.S. 1972. Plasma amino acid response in young men given diets devoid of single essential amino acids. J Nutr. 102(9): 1147-1158.
- Pegorier, J.P. 1998. Regulation of gene expression by fatty acids. Curr Opin Clin Nutr Metab Care 1(4): 329-334.
- Peng, Y. & Harper, A.E. 1970. Amino acid balance and food intake: effect of different dietary amino acid patterns on the plasma amino acid pattern of rats. J Nutr. 100(4): 429-437.
- Rogers, Q.R.& Leung, P.M.B. 1977. The control of food intake:when and how are amino acids involved? In KARE, M.R.& MALLER, O., editors. Academic press, New york. 213 p.
- Sano, Y., Harada, J., Tashiro, S., Gotoh-Mandeville R., Maekawa, T., Ishii, S. 1999. AF-2 is a common nuclear target of Smad and TAK1 pathways in transforming growth factor-beta signaling. J Biol Chem. 274(13): 8949-8957.

- Straus, D.S. 1994. Nutritional regulation of hormones and growth factors that control mammalian growth. Faseb J. 8(1): 6-12.
- Straus, D.S., Burke, E.J., Marten, N.W. 1993. Induction of insulin-like growth factor binding protein-1 gene expression in liver of protein-restricted rats and in rat hepatoma cells limited for a single amino acid. Endocrinology 132(3): 1090-1100.
- Svanberg, E., Jefferson, L.S., Lundholm, K., Kimball, S.R. 1997. Postprandial stimulation of muscle protein synthesis is independent of changes in insulin. Am J Physiol. 272(5 Pt 1): E841-E847.
- Sylvester, S.L., ap Rhys, C.M., Luethy-Martindale, J.D., Holbrook, N.J. (1994). Induction of GADD153, a CCAAT/enhancer-binding protein (C/EBP)-related gene, during the acute phase response in rats. Evidence for the involvement of C/EBPs in regulating its expression [published erratum appears in J Biol Chem 1995 Jun 16, 270(24): 14842]. J Biol Chem. 269(31): 20119-20125.
- Towle, H.C. (1995). Metabolic regulation of gene transcription in mammals. J Biol Chem. 270(40): 23235-23238.
- Ubeda, M., Vallejo, M., Habener, J.F. 1999. CHOP enhancement of gene transcription by interactions with Jun/Fos AP- 1 complex proteins [In Process Citation]. Mol Cell Biol. 19(11): 7589-7599.
- Vaulont, S., Vasseur-Cognet, M., Kahn, A. 2000. Glucose regulation of gene transcription. J Biol Chem. 275(41): 31555-31558.
- Wang, X.Z., Lawson, B., Brewer, J.W., Zinszner, H., Sanjay, A., Mi, L.J., Boorstein, R., Kreibich, G., Hendershot, L.M., Ron, D. 1996. Signals from the stressed endoplasmic reticulum induce C/EBP-homologous protein (CHOP/GADD153). Mol Cell Biol. 16(8): 4273-4280.
- Watford, M. 1990 A 'swell' way to regulate metabolism. Trends Biochem Sci. 15(9): 329-330.
- Yoshizawa, F, Endo, H, Ide, H, Yagasaki, K, Funabiki, R 1995. Translational regulation of protein synthesis in the liver and sketal muscle of mice in response to refeeding. Nutr Biochem. 6:130 - 136.