Protein and Amino Acid Synthesis

This lecture will cover mechanisms and signals of both protein synthesis and amino acid biosynthesis, for the non-essential amino acids. Protein building is important for growth as well as tissue repair. This lecture will also cover in more detail why some amino acids are essential or conditionally essential in our diet.

Contents

Learning Objectives

- Understand the mechanistic differences that explain the difference between dispensable and indispensable amino acids.
- Evaluate the roles of insulin, growth hormone, testosterone and cortisol on protein synthesis and degradation.
- Describe the central role of glutamate as a pool of nitrogen.
- Describe the relationships between the glycolytic and TCA cycle intermediates and amino acid biosynthesis.
- Explain why cysteine and tyrosine are dispensable only if precursors are available.
- Understand how amino acid biosynthetic rates are controlled by utilization and by negative feedback.
- Understand the role that the indispensable amino acids play in controlling protein synthesis.

Protein Synthesis is a Tigthly Regulated Process

The Rate of Protein Synthesis Depends on the Levels of Available Amino Acids

Several Endocrine Signals Regulate Protein Biosynthesis

Several of these hormonal signaling systems converge on mTORC1.

Protein Synthesis is Energetically Expensive

Synthesis of and Control of Amino Acids

Humans Have Lost the Ability to Synthesize Several Amino Acids

A good example is Glytamine synthesis from Glutamate.

Several Amino Acids are Synthethized from Essential Amino Acids

Non-Essential Amino Acids Are Derived from Glycolytic and TCA Cycle Intermediates.

Glutamate is a Key to Maintaining Nitrogen Atoms for Amino Acid Synthesis

Glutamate is a key part of several *transaminase* reactions. These are near-equillibrium reactions where an amino group is transfered fom glutamate to another amino acid, or vice versa. Some examples are below:

$$\alpha KG + Ala \rightleftharpoons Glu + Pyr \tag{1}$$

$$\alpha KG + Asp \rightleftharpoons Glu + OAA \tag{2}$$

$$\alpha KG + Val \rightleftharpoons Glu + \alpha Ketoisovalerate \tag{3}$$

Since these are easily reversible reactions, the directionality depends on the concentrations of products and substrates on each side. For example in equation 1, if there is high levels of Glutamate and Pyruvate, then Alanine and α-ketoglutarate will be produced. Because Glutamate and α-ketoglutarate are present on both sides of most transaminase reactions, this is one way in which TCA cycle intermediates (α-ketoglutarate) and amino acids (*i.e.* Glutamate) are kept in balance.

Glutamate is a non-toxic carrier of nitrogen. During amino acid breakdown[1], several amino acids can be converted to glutamate via transaminases, then glutamate releases its amino group via the functions of Glutamate Dehydrogenase:

[1] This will be covered in the next lecture

$$Glu + H_2O + NAD^+ \rightarrow \alpha KG + NH_3 + NADH + H^+ \tag{4}$$

In humans this is irreversible, as we cannot re-synthesize glutamate from ammonia. The ammonia released from this reaction is released into the Urea cycle[2].

[2] Also covered in the next lecture

Protein Requirements and Determination

As we just mentioned, when amino acids are being used, ammonia is generated. This can be measured by urinary nutrogen levels. If dietary nitrogen and urinary nitrogen are equal, then a person is said to be in *Nitrogen Balance*. During periods of protein catabolism,

urinary nitrogen is higher than intake. During periods of protein synthesis, urinary nitrogen is lower*This is because the dietary nitrogen containing amino acids are not being oxidized.*. This is one way by which dietary requirements are determined, since the lack of any essential amino acid causes proteins to be degraded to release the essential amino acids. Now there will be an excess of the non-limiting amino acid, which will then be oxidized and released as urea. Several other methods for determining protein requirements exist, briefly these include:

Nitrogen Balance. In this method nitrogen intake is compared to nitrogen release, protein synthesis being associated with positive nitrogen balance.

DIrect Amino Acid Oxidation. In this method, stable-isotope labelled Phenylalanine, Lysine, Leucine, Isoleucine of Valine are provided. These indispensible amino acids when catabolized release the label to the body's bicarbonate pool which is eventually released as $^{13}CO_2$. The oxidation and release of this amino acid will increase if that amino acid is in excess.

Indicator Amino Acid Oxidation. In this method a stable-isotope labelled amino acid is added. If in protein deficiency, that amino acid will be oxidized. As protein intake increases, oxidation will decrease. Therefore the detection of oxidized label (typically $^{13}CO_2$) is inversely proportional to protein levels. More details in this method can be found in Elango et al. [2008].

References

Rajavel Elango, Ronald O Ball, and Paul B Pencharz. Indicator amino acid oxidation: concept and application. *The Journal of Nutrition*, 138(2):243–246, 2008. ISSN 1541-6100.