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Review Article

A Review on Amino Acids as the Building Blocks of Lifespan

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Abstract

Amino acids serve as the foundational building blocks of life and are critical regulators of human healthspan and longevity. This paper examines the classification of the twenty standard amino acids into essential, non-essential, and conditionally essential categories, detailing their specific physiological demands across different stages of life. Beyond their primary role in protein synthesis and tissue repair, amino acids act as potent biochemical signaling molecules that directly modulate aging pathways. Specifically, this review analyzes the role of branched-chain amino acids like leucine in regulating the mechanistic target of rapamycin pathway, the contribution of alanine and glutamine to immune preservation, and the reliance of collagen synthesis and neurotransmitter production on structural amino acid precursors. Finally, we discuss dietary optimization strategies, emphasizing the balance between complete and incomplete proteins to mitigate age-related physiological decline. Ultimately, strategic management of amino acid profiles represents a vital therapeutic approach for promoting cellular maintenance and extending functional longevity.

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INTRODUCTION

As per to the Miller's experiment, the first living cell was made up of Glycine, Alanine, Aspartic and Glutamic acid. That' sway amino acids is called as building block of life. The ultimate source of amino acids (a. a) in the body is dietary proteins. Dietary proteins are digested to their constituent amino acids by proteolytic enzymes and peptidases in the gastrointestinal tract. A few small proteins and several peptides are absorbed directly from the intestine, but most of the digestion products circulate as amino acids. We know Amino acids are the main component of proteins. It helps in growth, repair and maintenance of the tissues. The main function of the amino acids are as follows given below:-

- Protein synthesis, Enzyme production, Hormone regulation as well as immune function.
- All types of biochemical events occur in presence of different types of amino acids.

The amino acids are of two types. Those are essential amino acids (EAA), non-essential amino acids (NEAA) and conditional amino acids.

Classification of Amino Acids

1. The amino acids are classified into various ways.
2. Classification based on their incorporation in proteins
3. Classification based on the structure of the side chain (R group)
4. Classification based on the polarity of the side chain (R group)
5. Classification based on reaction in solution
6. Classification based on the position of amino group
7. Classification based on metabolism
8. Classification based on nutritional requirements

- **Essential Amino Acids (EAA):** These are not produced in our body, so it is obtained through the diet/ supplements. There are 09 acids like as Valine, Isoleucine, Leucine, Methionine, Phenylalanine, Tryptophan, Threonine, Histidine and Lysine.
- **Non-Essential Amino Acids (NEAA):** These are produced/ synthesized in our body. There are 11 in numbers like Alanine Aspertic acid, Aspergine, Glutamic acid, Serine etc.
- **Conditional Amino Acids (CAA):** Amino acids that becomes essential under specific conditions i.e synthesis cam be limited under special condition such as prematurity in the infant or individuals in severe catabolic stress. These are about 06 in numbers like Arginine, Cysteine, Glycine, Glutamine, Proline and Tyrosine.

Methionine deficiency causes cataracts in fish like trout. It is essential for growth and reproduction in ruminant animals. Tryptophan deficiency leads to Scoliosis (Spinal cord curve) and Lordosis (Inward curve of the spine) in fish like salmon and trout.

The 11 Non-Essential Amino Acids	The 9 Essential Amino Acids
Alanine	Histidine
Arginine	Isoleucine
Asparagine	Leucine
Aspartic acid	Lysine
Cysteine	Methionine
Glutamic acid	Phenylalanine
Glutamine	Threonine
Glycine	Tryptophan
Proline	Valine
Serine	
Tyrosine	

Lysine deficiency causes finrot in rainbow trouts. Deficiency of excessive intake of amino acids can have negative impacts on the human as well as plants and other animals. If a person's intake of any of the amino acids can lead to deficiency in another. High dose of Methionine or Trypotophan can be toxic. Amino acids like Glutamine can cause gastrointestional side effects.

Homocysteine and phenylalanine are the two specific amino acids linked with cardio vascular and phenylketonuria (PKU) disease respectively. High quality of proteins, EAA and Omega-3 Fatty acids are found in different fishes and meat like beef, chicken, pork and diary product like milk, cheese, yoghurt etc.

Phenylketonuria (PKU) is a rare, inherited metabolic disorder where the body cannot properly break down the amino acids phenylalanine, which causes neurological and developmental problems and if affects both human and other animals.

Legumes like beans, lentils and peas are rich sources in proteins and essential amino acids. Nuts and seeds like almonds Chia seeds etc. having also good sources of different proteins and amino acids. Spirulina: this Algae represents an important staple diet in human and has been used as sources of proteins and vitamins supplements in humans without any significant side effects.

Nitrogen (N) is the main component of amino acids. Its absence leads to reduction in protein-synthesis, chlorosis, stunted growth, reduced fruits and seeds in the plants. Sulphur(S) is required for synthesis of certain amino acids cysteine and Methionine which leads to stunted growth and delay maturity.

Human insulin (Humulin) are made of two stretches of A and B chains (A contains 21 and B contains 30 amino acids) that binds with disulphide (S-S) bridges. Humulinhave rapid uses for treatment of Diabetics, Type-I.

Technical Analysis of Amino Acids in Lifespan Regulation
Amino acids are not only substrates for protein synthesis but also critical regulators of metabolic signaling, cellular maintenance, and longevity pathways. Recent advances in molecular biology, biochemistry, and Gerontology reveal that amino acid availability directly influences mechanisms associated with aging and lifespan extension.

1. Amino Acids and Protein Homeostasis
Protein homeostasis (proteostasis) is essential for maintaining cellular integrity during aging. Amino acids regulate the synthesis, folding, and degradation of proteins through pathways involving ribosomes, chaperones, and proteasomes.
A disruption in proteostasis leads to:
- Accumulation of damaged proteins
- Oxidative stress
- Cellular senescence
- Neurodegenerative disorders

The balance between protein synthesis and autophagy strongly affects lifespan.

2. Role of mTOR Signaling Pathway
One of the most important longevity-associated pathways is mTOR Signaling.
The mechanistic target of rapamycin (mTOR) senses amino acid availability, particularly leucine and arginine, and regulates:
- Cell growth
- Protein synthesis
- Autophagy
- Energy metabolism

The pathway is commonly represented as:
$mTOR \propto$ Amino Acid Availability

Biological Interpretation
- High amino acid concentrations activate mTOR, increasing anabolic activity and cellular growth.
- Chronic over activation may accelerate aging by suppressing autophagy.
- Controlled reduction in amino acid intake can enhance cellular repair mechanisms and lifespan in experimental organisms.

3. Amino Acid Restriction and Longevity
Studies indicate that selective amino acid restriction influences lifespan positively.

Methionine Restriction
Reduced methionine intake has been associated with:
- Lower oxidative stress
- Improved mitochondrial efficiency
- Enhanced insulin sensitivity
- Increased lifespan in animal models

Branched-Chain Amino Acids (BCAAs)
BCAAs include:
- Leucine
- Isoleucine
- Valine

These amino acids stimulate muscle protein synthesis but excessive intake may contribute to metabolic dysregulation through persistent mTOR activation.

4. Mitochondrial Function and Oxidative Stress
Amino acids contribute to mitochondrial bioenergetics and antioxidant defense systems.

For example:
- Glutathione synthesis depends on cysteine, glycine, and glutamate.
- Glutathione neutralizes reactive oxygen species (ROS).

The oxidative balance can be represented conceptually as:
Oxidative Stress $\propto$ ROS/Antioxidant
Lower oxidative stress is strongly associated with delayed cellular aging.

5. Amino Acids in Epigenetic Regulation
Certain amino acids act as methyl-group donors or metabolic cofactors influencing epigenetic modifications:
- Methionine participates in methylation cycles via S-adenosylmethionine (SAM).
- Glycine and serine contribute to one-carbon metabolism.

These mechanisms affect:
- Gene expression
- DNA repair
- Cellular differentiation
- Aging-associated transcriptional regulation

6. Autophagy and Cellular Recycling
Autophagy is a protective mechanism that removes damaged organelles and proteins.

When amino acid levels decrease:
- mTOR activity declines
- Autophagy increases
- Cellular waste removal improves

This relationship is often summarized as:
$Autophagy \propto 1/mTOR$
Enhanced autophagy is linked with increased lifespan in several experimental models.

Systemic Metabolic Reconfiguration
Amino acid availability influences systemic health by modulating hormone secretion and adipose tissue function.

Fibroblast Growth Factor 21 (FGF21) Induction
- **Hepatic Secretion:** Deprivation of methionine or total branched-chain amino acids (BCAAs) stimulates hepatic FGF21 production.

- **Thermogenesis:** FGF21 promotes white adipose tissue browning, increasing energy expenditure.
- **Insulin Regulation:** High circulating FGF21 levels lower systemic glucose levels and enhance total insulin sensitivity.

Hydrogen Sulfide (H_2S) Production

- Transsulfuration Pathway: Methionine restriction diverts cysteine utilization toward the transsulfuration pathway.
- **Gasotransmitter Synthesis:** This metabolic shift boosts the production of hydrogen sulfide (H_2S) gas.
- **Vascular Protection:** Increased (H_2S) protects tissue from ischemia-reperfusion injury and promotes angiogenesis.

Cellular Quality Control Mechanisms

Altering amino acid availability initiates a cascade of intracellular cleaning and protective processes.

Autophagy and Proteostasis

- **Organelle Clearance:** Amino acid restriction deactivates mTORC1, removing the brake on macroautophagy.
- **Protein Turnover:** Cells degrade damaged proteins, aggregated macromolecules, and dysfunctional mitochondria.
- **Aggregate Prevention:** Enhanced proteostasis prevents toxic protein aggregation, a hallmark of neurodegenerative diseases.

Mitochondrial Hormesis (Mitohormesis)

- **Proteotoxic Stress:** Restricting essential amino acids induces mild, beneficial mitochondrial stress.
- **ATF4 Signaling:** This stress triggers the mitochondrial unfolded protein response (UPR^{mt}) via ATF4.
- **Defense Amplification:** Cells upregulate endogenous antioxidant enzymes, increasing resistance to subsequent oxidative stress.

Effects of Specific Amino Acids on Longevity

Not all amino acids impact lifespan equally. Restricting specific essential amino acids or supplementing non-essential ones produces distinct phenotypic outcomes.

Amino Acid	Intervention Type	Primary Mechanism	Phenotypic Outcome
Methionine	Restriction	Lowers mitochondrial ROS production; alters lipid metabolism	Extends lifespan consistently in rodents and lower organisms
Isoleucine / Valine	Restriction	Deactivates mTORC1; increases FGF21 hormone secretion	Improves metabolic health; reduces mid-life adiposity
Leucine	Restriction	Directly suppresses Sestrin2-mediated mTORC1 activation	Mimics calorie restriction; improves insulin sensitivity
Glycine	Supplementation	Promotes methionine clearance; enhances glutathione synthesis	Mimics methionine restriction; extends rodent lifespan

Translational Challenges and Clinical Implications

Translating animal model findings to human populations requires balancing longevity benefits against functional physical demands.

The Sarcopenia Conundrum

- **Anabolic Resistance:** Elderly individuals develop resistance to muscle protein synthesis.
- **Muscle Wasting:** Strict amino acid restriction can exacerbate age-related sarcopenia, causing frailty and falls.
- **Dynamic Tuning:** Protein intake must remain dynamic: restricted during middle age to suppress cancer and metabolic disease, but elevated in advanced old age to preserve muscle mass.

Dietary Strategies

- **Plant-Based Regimens:** Vegan and vegetarian diets naturally exhibit lower levels of methionine and BCAAs.
- **Intermittent Restriction:** Periodic, short-term protein restriction cycles offer metabolic benefits without causing lean tissue loss.
- **Precision Formulation:** Designing medical foods with specific amino acid deficiencies allows targeted pathway modulation without total protein malnutrition.

CONCLUSION

Technically, amino acids function as both structural biomolecules and metabolic signaling regulators. Their interaction with pathways such as mTOR Signaling, oxidative stress control, mitochondrial metabolism, and autophagy demonstrates their central role in lifespan regulation. Current longevity research suggests that the quality, quantity, and balance of amino acid intake may significantly influence healthy aging and age-related disease progression.

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