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Protein Metabolism



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Protein Biosynthesis

- Proteins are assembled from amino acids using information encoded in genes
- Each protein has its own unique amino acid sequence that is specified by nucleotide sequence of the gene coding
- Genetic code is a set of three nucleotide sets called codon and each three nucleotide combination designates an amino acid
 - AUG (Adenine-uracil-guanine) is the code for methionine



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Transcription

- DNA contains four nucleotides and the total number of possible codons is 64
- Redundancy in genetic code with some amino acids specified by more than one
- Genes encoded in DNA are first transcribed into messenger RNA (mRNA) by enzymes such as RNA polymerase
- mRNA is used as a template for protein synthesis by the ribosome



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Transcription

- The DNA template opens, and RNA polymerase moves down one strand in the 3' → 5' direction inserting nucleotides into a growing strand of RNA
- Ribonucleotides come from ATP, CTP, GTP, UTP and follow base pairing
- Synthesis of RNA proceeds in the 5' → 3' direction



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Protein Biosynthesis

- Process of synthesizing a protein from mRNA template is known as translation
- mRNA is loaded onto ribosome and is read three nucleotides at a time by matching each codon to its base pairing anticodon located on a transfer RNA molecule (tRNA)
- tRNA molecule carries amino acid corresponding to the codon it recognizes



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Translation

- Enzyme aminoacyl tRNA synthetase charges the tRNA molecule with the correct amino acid
- Proteins are always biosynthesized from N- terminus to C-terminus



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Protein Breakdown

- Key physiological process in all forms of life wherein proteins are converted to amino acids and then catabolised
- Complete hydrolysis of polypeptide requires mixture of peptidases (Exopeptidases and endopeptidases)
- In normal human beings about 90% of energy requirement is met by oxidation of carbohydrates and fats and 10% is met by oxidation of carbon skeletons of amino acids



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Amino Acid Catabolism

- Removal of α amino group is important reaction in the breakdown
- Important reactions involved are:
 - Deamination
 - Transamination
 - Oxidative deamination
 - Nonoxidative deamination



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Amino Acid Catabolism

- **Transamination** – is the starting point for amino acid metabolism (shuffling of amino groups from amino acids)
- Involves transfer of an amino group from an amino acid to a keto acid
- Involves the inter-conversion of a pair of amino acids and a pair of keto acids catalyzed by transaminases (transferases)



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Transamination

- Transaminases require pyridoxal phosphate (PLP – coenzyme derived from vitamin B6)
- Aspartate and alanine transaminases make a significant contribution
- Transamination is reversible and diverts the excess amino acids to energy
- Lysine, threonine, proline, and hydroxyproline do not participate



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Amino Acid Catabolism

- Amino transferase reactions occurs in two stages:
 - Pyridoxal phosphate is covalently attached to amino transferases by a Schiff's base linkage resulting in formation of pyridoxamine phosphate
 - The amino group attached to pyridoxamine phosphate is transferred to a different keto acid yielding a new amino acid and releases pyridoxal phosphate



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Deamination

- **Removal of amino group from amino acids as ammonia is deamination**
- **Carbon skeleton of amino acids is converted to keto acids**
- **Deamination may be either oxidative or non-oxidative**
- **Deamination and transamination occur simultaneously involving glutamate as the central molecule**



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Oxidative Deamination

- Is the liberation of free ammonia from the amino group of amino acids coupled with oxidation that occurs in liver and kidney
- In transamination, the amino groups of most amino acids are transferred to α keto glutarate to produce glutamate
- Glutamate rapidly undergoes oxidative deamination catalysed by glutamate dehydrogenase (GDH) to liberate NH_3



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Oxidative Deamination

- GDH utilizes either NAD^+ or NADP^+ as a coenzyme
- Conversion of glutamate to α -ketoglutarate occurs through the formation of intermediate α -iminoglutarate
- L-amino acid oxidase and D-amino acid oxidase are flavoproteins, possessing FMN and FAD respectively



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Oxidative Deamination

- FMN and FAD act on corresponding amino acids (L or D) to produce α -keto acids and NH_3
- Oxygen is reduced to H_2O_2
- Keto acids may be oxidized to generate energy or serve as precursors for glucose and fat synthesis



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Non-Oxidative Deamination

- Serine, threonine, and homoserine are hydroxy amino acids that undergo non-oxidative deamination catalysed by PLP-dependent dehydrases producing respective α -keto acids liberating NH_3
- Cysteine and homocysteine undergo deamination coupled with desulfhydration to give keto acids, liberating NH_3 and H_2S



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Urea Cycle

- Also known as ornithine cycle that occurs in ureotelic organisms
- Converts highly toxic ammonia to urea
- First metabolic cycle to be discovered by Hans Krebs and Kurt Henseleit
- The urea cycle primarily takes place in liver and to a lesser extent in kidneys



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Function of urea cycle

- Amino acid catabolism results in ammonia production
- In species including birds and most insects, ammonia is converted into uric acid or its urate salt that is excreted in solid form
- In humans, ammonia is converted to urea in liver, that enters the bloodstream and finally excreted by kidneys



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Urea Cycle

- Citrulline is synthesized from carbamoyl phosphate and ornithine by ornithine transcarbamoylase
- Citrulline is transported to cytosol
- Arginosuccinate synthase condenses citrulline with aspartate to produce arginosuccinate with utilization of ATP
- Arginosuccinase cleaves arginosuccinate to give arginine and fumarate



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Urea Cycle

- Arginase cleaves arginine to yield urea and ornithine; ornithine enters mitochondria for reuse in urea cycle
- Urea cycle is irreversible and consumes 4 ATP (2 ATP for synthesis of carbamoyl phosphate, 1 ATP for synthesis of Arginosuccinate which equals 2 ATP)
- **Overall equation:**

