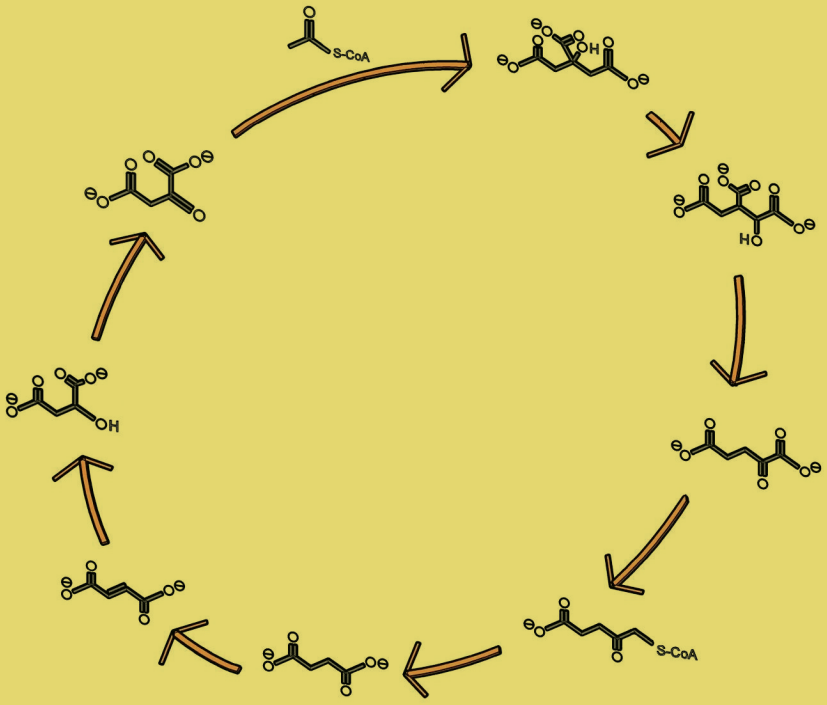
Enzymes Involved in Glycolysis, Fatty Acid and Amino Acid Biosynthesis: Active Site Mechanisms and Inhibition



Marco Brito-Arias

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PREFACE

The present book entitled "***Enzymes Involved in Glycolysis, Fatty Acid and Amino Acid Biosynthesis: Active Site Mechanism and Inhibition***" comprehends a thorough revision about the known reaction mechanism occurring between the enzymes related to the mentioned biosynthetic pathways with their substrates, cofactors and residues. Different disciplines provide a wealth of knowledge including crystallographic studies, kinetic studies, docking, genetic mutagenesis and biochemistry. The knowledge about the reaction mechanism is primordial to understand in a better way the normal functioning of the cell process, which is used as a starting point for preventing or to correct pathologies. Currently, the drug design relies strongly on the understanding of the interaction between the substrates or ligands with the amino acid residues and derived from these studies, a wealth of potent inhibitors have emerged for the treatment of several diseases such as cancer, tuberculosis, anti-parasitic, and also importantly metabolic syndrome alterations such as diabetes and obesity.

The enzymatic reaction mechanism includes aldolase, isomerase, kinase, mutase, synthase, dehydrogenase, reductase, transferase, hydrolase, lyase *etc.*, all of them widespread in all biochemical transformations.

This book pretends to serve as a tool for professionals involved in pharmaceutical, health, food and other related disciplines, providing well known, and key insights of the reaction mechanism occurring at the molecular level between the biological catalyst and the chemical ligands and how the transformation occurs within the cell.

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The authors confirm that this chapter contents have no conflict of interest.

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CHAPTER 1

Glycolysis

Abstract: The biochemical process known as glycolysis is a fundamental pathway, which allow the glucose to be transformed into energy (ATP) and pyruvate. During this process the glucose is first phosphorylated at the 6th position, then converted to fructose by the phosphoglucose isomerase and phosphorylated to fructose 1,6-biphosphate. The next steps involve the bond cleavage by the enzyme fructose biphosphate aldolase to dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, which can be converted from the keto to the aldehyde by the enzyme triose phosphate isomerase. A second phosphorylation of glyceraldehyde 3-phosphate takes place by the enzyme glyceraldehyde-3-phosphate dehydrogenase in the presence of NAD+ and Pi providing 1,3-bisphosphoglycerate. The next step was mediated by the enzyme phosphoglycerate kinase to produce ATP and 3-phosphoglycerate which undergoes phosphate migration producing 2-phosphoglycerate. Further dehydration mediated by the enzyme enolase produce phosphoenolpyruvate which is finally converted by the enzyme pyruvate kinase to pyruvate and the release of a second ATP molecule.

Keywords: ATP molecules, Biphosphate, Dehydration.

The biochemical process known as glycolysis is a fundamental pathway, which allows the glucose to be transformed into energy (ATP) and pyruvate. The glycolytic pathway occurs in either prokaryotic and eukaryotic cells, however in bacteria, the common pathway is known as the Entner-Doudoroff pathway (ED) while in eukaryotes, the glycolysis follows the Embden-Meyerhoff-Parnas (EMP) pathway (Fig. **1**) [1].

In cancer cells, the glycolytic pathway is affected significantly since tumor cells consume much higher amounts of glucose than normal cells, which is known as the Warburg effect [2]. The Embden-Meyerhof-Parnas pathway is the glycolytic pathway used by mammals, consisting of the initial phosphorylation of glucose at the 6^{th} position, consuming the first ATP molecule to produce glucose-6-phosphate (G6P), being catalysed by the enzyme hexokinase (HK). Next, an isomerization process takes place under the catalysis of phosphoglucose isomerase (PGI) converting the pyranose into a furanose ring, resulting in the formation of fructose 6-phosphate (F6P). Then, a second phosphorylation reaction at position 1 occurs, requiring an ATP molecule, and catalysed by the enzyme ph-

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osphofructokinase (PFK), to provide fructose 1,6-diphosphate (F1,6DP) which is cleaved into dihydroxyacetone (DHAP) and glyceraldehyde 3-phospate (G3P) by the catalysis of fructose biphosphate aldolase (FBP).

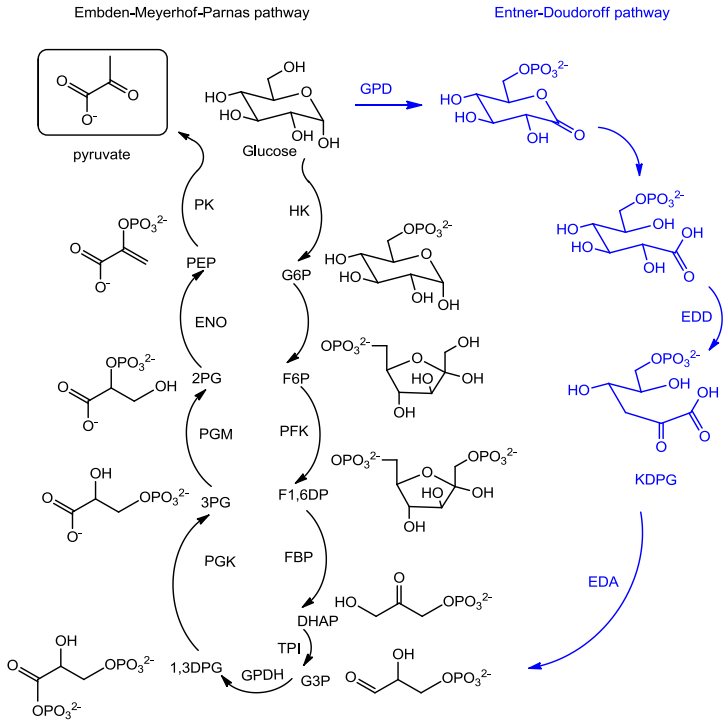


Fig. (1). The Embden-Meyerhof-Parnas and Entner-Doudoroff as the main glycolytic pathways in prokaryote and eukaryote cells.

The next steps involve inter-conversion from DHAP to the G3P by the enzyme triose phosphate isomerase (TPI). Second phosphorylation of glyceraldehyde 3-phosphate proceeds by the enzyme glyceraldehyde-3-phosphate dehydrogenase (G3P) in the presence of NAD^+ and Pi providing 1,3 diphosphoglycerate (1,3DPG). The next step is mediated by the enzyme phosphoglycerate kinase to produce the first ATP molecule and 3-phosphoglycerate which undergoes phosphate migration producing 2-phosphoglycerate. Further, dehydration mediated by the enzyme enolase produces phosphoenolpyruvate which is finally converted by the enzyme pyruvate kinase to pyruvate, leading to the generation of a second ATP molecule. It is important to notice that the overall energy yield is two ATPs, considering that one glucose consumes two ATPs to form fructose-1,6-diphosphate (F1,6DP), and then the cleavage of each F1,6DP produces two three-carbon molecules G3P and DHAP, each of them producing two ATP molecules (Fig. **2**).

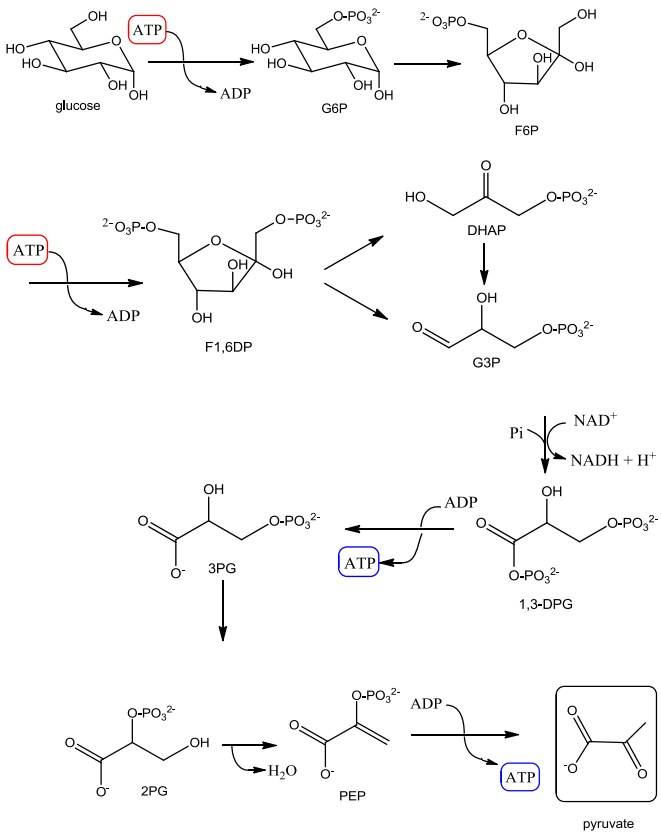


Fig. (2). The Embden-Meyerhof-Parnas pathway showing the intermediates and the steps where ATP is consumed and produced.

CHAPTER 2

Citric Acid Cycle (Krebs)

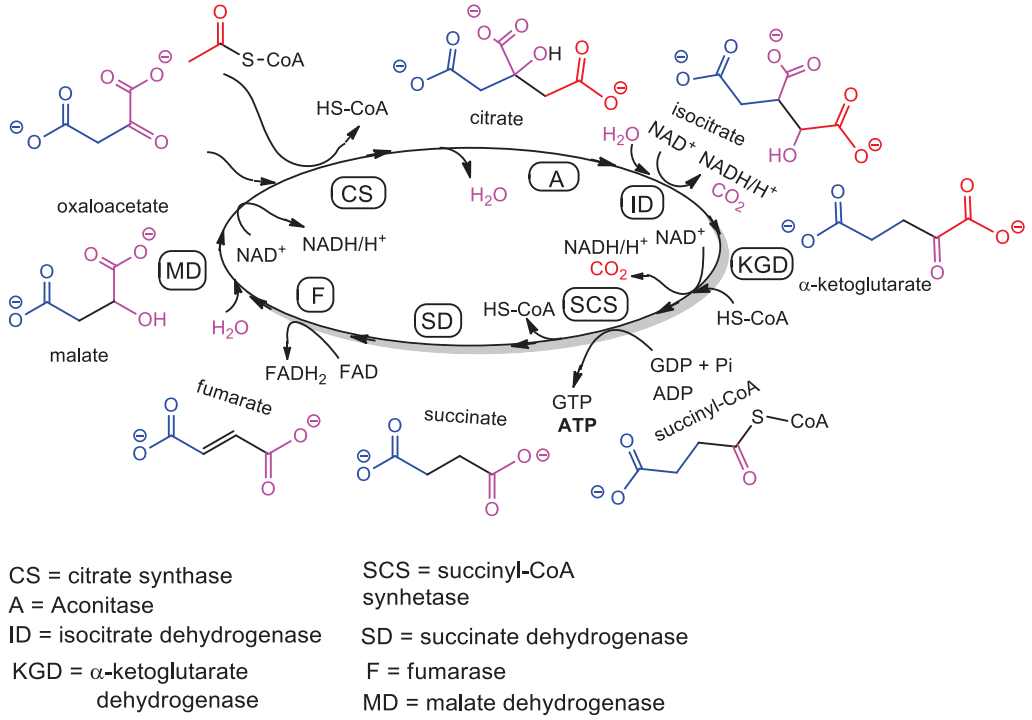
This is an essential process considered a second step on the respiratory chain, consisting of a series of eight reactions that will produce 8 electrons transported by 3 $NADH/H^+$ and 1 $FADH_2$ molecules, aside from an ATP molecule.

The cycle begins with the condensation of acetyl-CoA with oxaloacetate catalysed by citrate synthase to form citrate, a six-carbon molecule and CoA. Next, a dehydration reaction by aconitase occurs to produce cis-aconitate, which by the addition of a water molecule is converted to D-isocitrate. This citrate isomer is oxidized by NAD^+ and transformed to α-ketoglutarate by isocitrate dehydrogenase, along with the formation of a second molecule of $NADH/H^+$ and CO_2. A condensing reaction between α-ketoglutarate and CoA catalysed by α-ketoglutarate dehydrogenase resulted in the formation of succinyl-CoA, $NADH/H^+$ and CO_2. The succinyl-CoA is hydrolysed by succinyl-CoA synthase to give succinate, CoA, and one ATP or GTP molecule. The succinate is oxidized to fumarate by succinate dehydrogenase in the presence of FAD as an electron acceptor to produce $FADH_2$. Then, fumarate is converted to malate by the enzyme fumarase, and finally, oxidation of the hydroxyl group to the ketone by malate dehydrogenase to provide oxaloacetate and the third molecule of $NADH/H^+$, completing the cycle (Fig. **51**).

1. ENZYMES INVOLVED IN THE CITRIC ACID CYCLE

1.1. Citrate Synthase (CS)

The first step of the citric acid cycle consisting of the Claisen condensation between acetyl-CoA with oxaloacetate catalysed by citrate synthase to give the intermediate citryl CoA which is hydrolysed to citrate and coenzyme A (Fig. **52**) [48].



CS = citrate synthase
A = Aconitase
ID = isocitrate dehydrogenase
KGD = α-ketoglutarate dehydrogenase
SCS = succinyl-CoA synhetase
SD = succinate dehydrogenase
F = fumarase
MD = malate dehydrogenase

Fig. (51). The citric acid cycle.

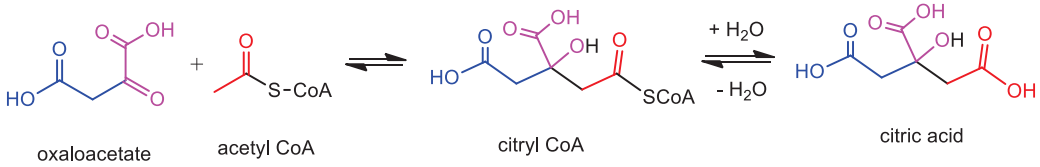


Fig. (52). The citrate synthase reaction.

The crystal structure of CS from different species such as pig, chicken, eukaryotes, bacteria gram-positive, and archaea have been solved as dimeric structures, except from gram-negative bacteria characterized as hexameric structure. The citrate synthase from *Antarctic bacterium* strain DS2-3R (*Ds*CS) was compared with Hyperthermophilic archaeon *Pyrococcus furiosus* (*Pf*CS) showing 40% identity. At the binding site, *Pf*CS citrate ligand is bound to His223, His262, and Arg271, Arg337, Arg356), while the binding of CoA to Lys254, Lys256, Lys305, Ile257, Ala260, Gly259, Asn310, Arg263, Arg353 [49]. The surface representation of the active site for *Ds*CS with citrate and CoA in the active site are represented in Fig. (**53**) [50].

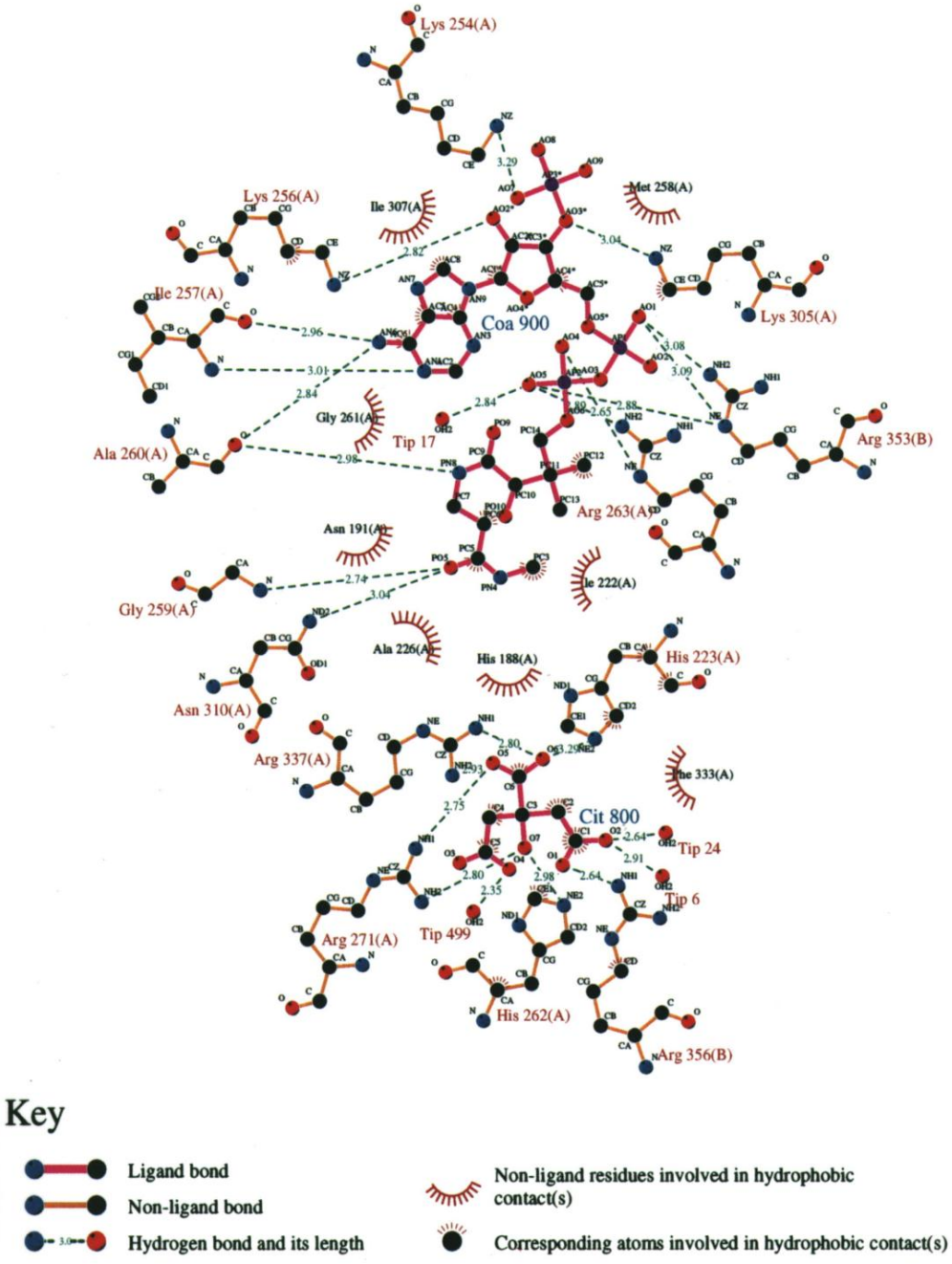

Lys 254(A)
Lys 256(A)
Ile 307(A)
Met 258(A)
Ile 257(A)
Coa 900
Lys 305(A)
Gly 261(A)
Tip 17
Ala 260(A)
Arg 353(B)
Asn 191(A)
Arg 263(A)
Gly 259(A)
Ile 222(A)
Ala 226(A)
His 188(A)
His 223(A)
Asn 310(A)
Arg 337(A)
Ile 333(A)
Cit 800
Tip 24
Tip 6
Tip 499
Arg 271(A)
His 262(A)
Arg 356(B)
Key
Ligand bond
Non-ligand bond
Hydrogen bond and its length
Non-ligand residues involved in hydrophobic contact(s)
Corresponding atoms involved in hydrophobic contact(s)

Fig. 53 cont.....

CHAPTER 3

Fatty Acid Biosynthesis

The fatty acid biosynthesis, also known as lipogenesis, is a process that occurs in the cytosol and its role is the production of the fatty acid palmitate from acetyl-CoA as a starting material. In humans, the process for the *de novo* biosynthesis of long-chain fatty acids is assigned to the cytosolic enzyme human fatty acid synthase (FAS) responsible for the catalysis of palmitate C16 from acetyl-coenzyme A and malonyl-coenzyme A in the presence of NADPH. During the elongation process, the chain is attached to the acyl carrier protein (ACP) and transported to the active site by enzymes known as malonyl-CoA transacylase (MAT or acetyl-CoA being used), β-ketoacyl synthase (KS), β-ketoacyl reductase (KR), dehydratase (DH) and β-enoyl reductase (ER) (Fig. **85**).

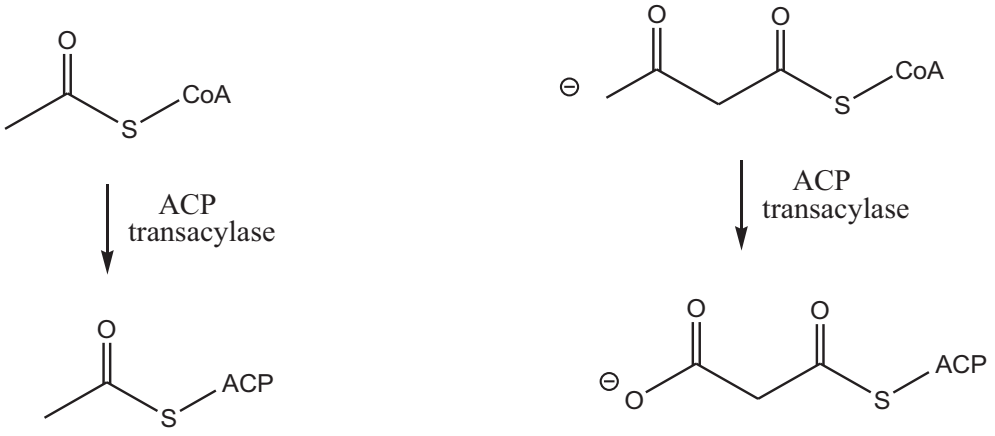


Fig. (85). Transacylation reaction by the acyl carrier protein (ACP)

The initiation process involves the parallel conversion of acetyl-CoA into acetyl-S-ACP, and malonyl-CoA to malonyl-S-ACP by the acyl carrier protein (ACP).

The phosphoryl transfer reaction to convert acetyl-CoA to acetyl-S-ACP involves the post-translational addition of the phosphopantetheine prosthetic group bearing the acyl group to the ACP through a serine residue (Fig. **86**) [88].

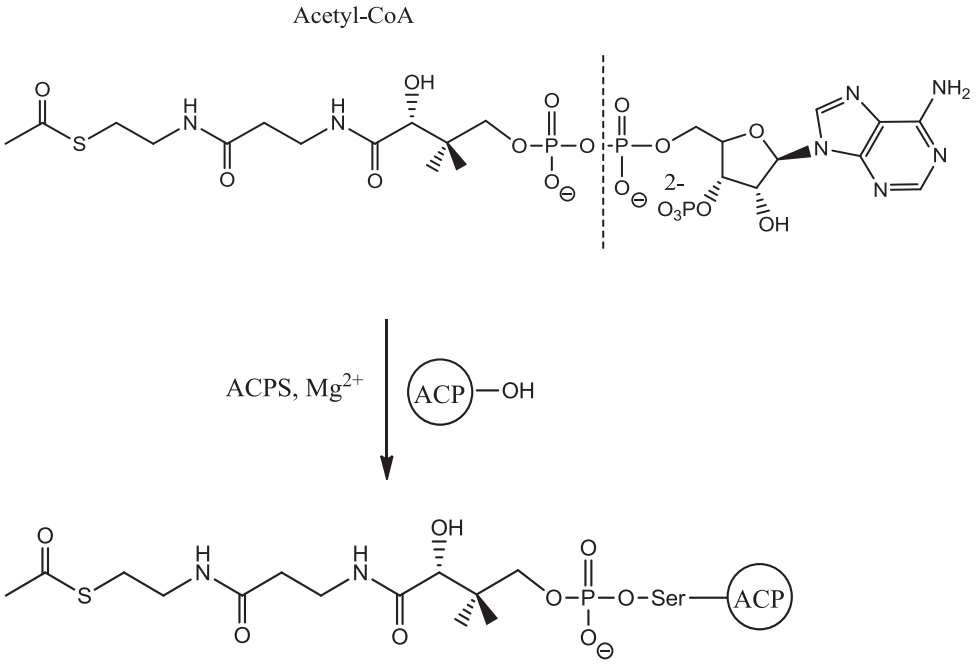


Fig. (86). The phosphoryl transfer reaction to convert acetyl-CoA to acetyl-S-ACP.

The transfer of malony-CoA to malonyl-ACP is mediated by the malonyl-CoA:ACP transacylase enzyme (MAT) according to the cycle shown in Fig. (**87**), involving histidine and serine residues, the later attacking the thioester carbonyl, forming a tetrahedral intermediate, which undergoes proton exchange followed by the attack of ACP-SH to furnish a second tetrahedral intermediate which upon releasing the serine residue provides malonyl-ACP [89].

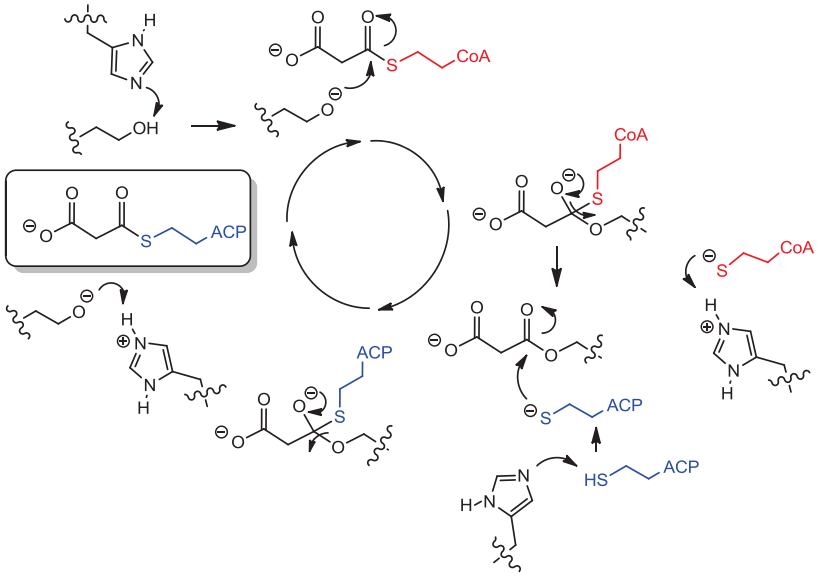


Fig. (87). Full cycle to convert malony-CoA to malonyl-ACP.

Malonyl-CoA transacylase (MAT) is a monomer composed of two subdomains, containing at the catalytic site Phe200, Thr56, Gln9, Met126, Arg122, His201, Ser97, Gln60, Val98, Ser97 residues (Fig. **88**).

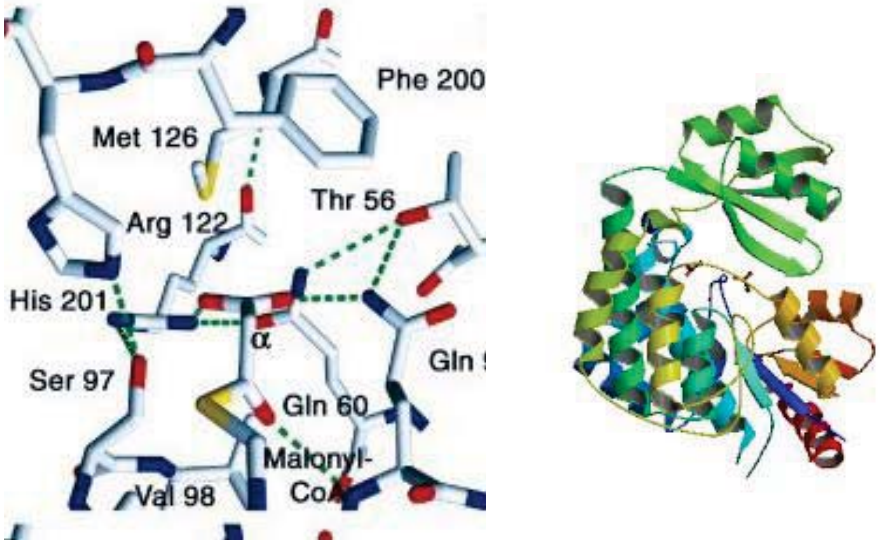


Fig. (88). Crystal structure of malonyl-CoA transacylase and the catalytic site (PDB: 1NM2).

CHAPTER 4

Aminoacid Biosynthesis

Amino acids are biomolecules composed of an amino group and carboxylic acid as common features and different R substituents attached to a chiral carbon with L-configuration for the biologically active enantiomer in humans except for glycine devoid of chirality (Fig. **129**). Biosynthetically, the amino acids are derived from glycolysis, Krebs cycle or the pentose phosphate pathway.

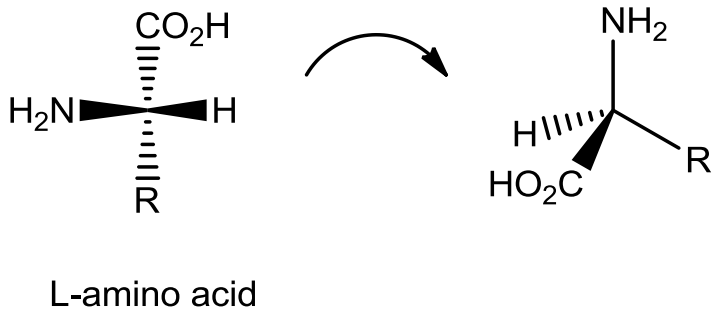
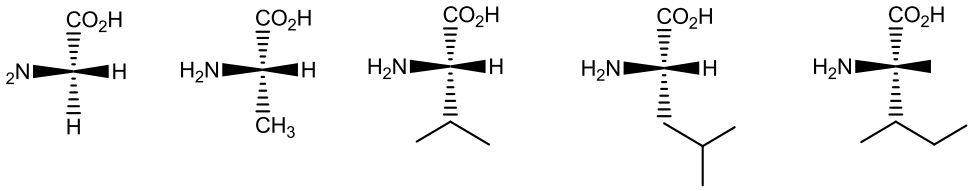


Fig. (129). Tetrahedral projection of amino acids.

Based on additional functionalities present in the amino acids, they can be classified in aliphatic, aromatic, polar (hydroxyl and thiol groups), cationic, anionic, and heterocyclic groups (Fig. **130**).

1. GLYCINE BIOSYNTHESIS

Glycine is the simplest amino acid having hydrogen as R substituent, and therefore not presenting chirality. It is an amino acid with important implications in brain excitatory and inhibitory activities, and in the synthesis of other essential molecules such as muscle supplement creatine, antioxidant glutathione, and as an abundant component in the structural protein collagen. This amino acid is synthesized from amino acids serine, threonine or nutrient choline, and its detailed biosynthesis is described in the following sections (Fig. **131**).



Glycine
Gly/G

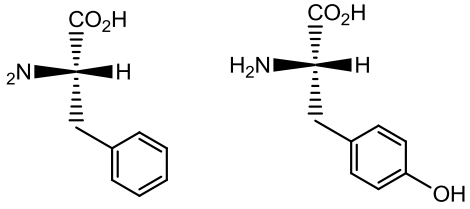
Alanine
Ala/A

Valine
Val/V

Leucine
Leu/L

Isoleuci
Ile/I

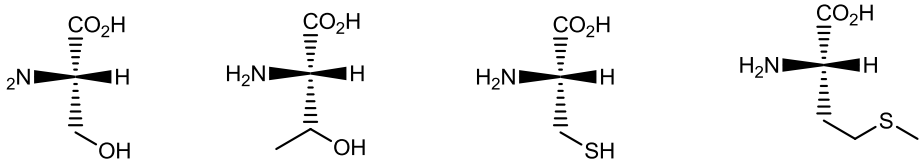
Aromatic



Phenylalanine
Phe/F

Tyrosine
Tyr/Y

Polar



Serine
Ser/S

Threonine
Thr/T

Cysteine
Cys/C

Methionine
Met/M

Heterocyclic

Fig. 130 cont.....

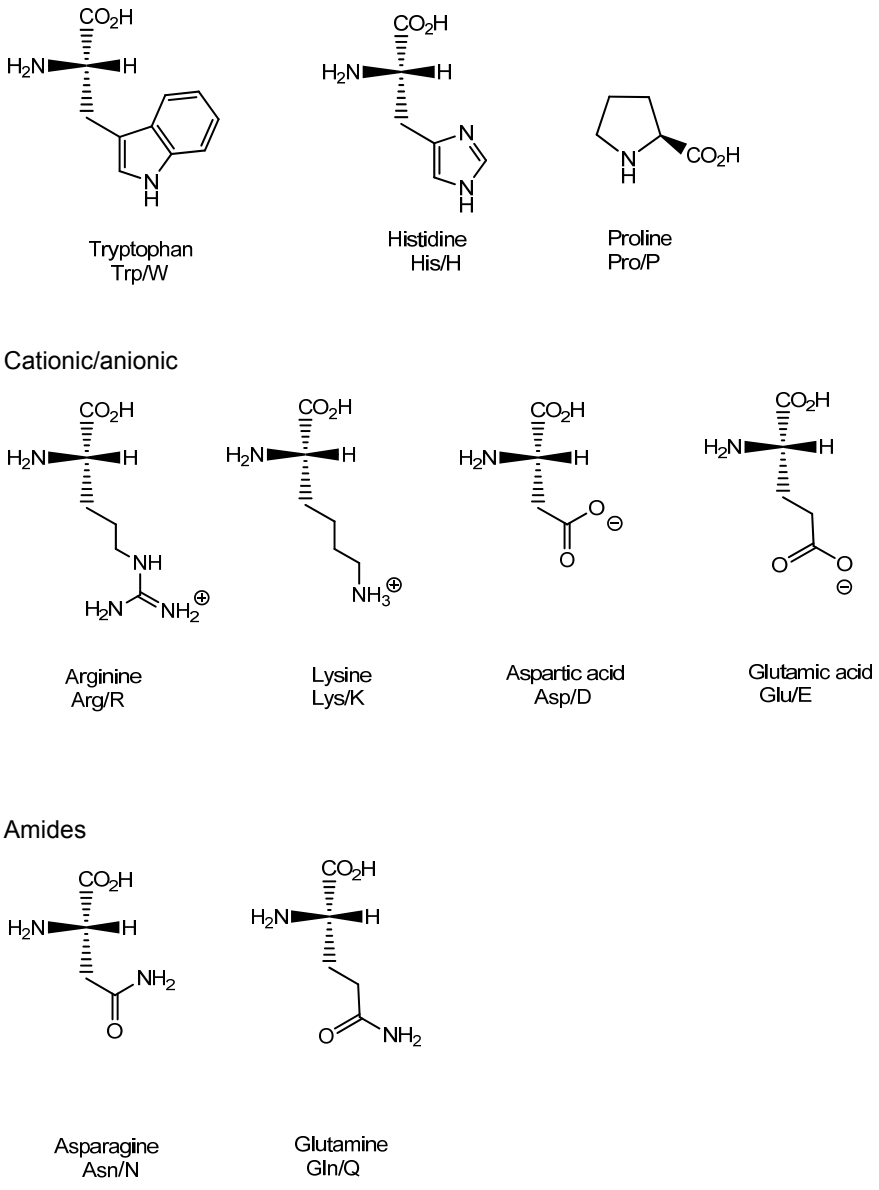


Fig. (130). Classification and structure of amino acids.

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MARCO BRITO-ARIAS

Marco Brito-Arias carried out his bachelor studies at the National Polytechnic Institute of México, obtaining the degree as a pharmaceutical industrial chemist, followed by masters in science courses of bioorganic chemistry. After a short period working in a pharmaceutical company, he decided to continue his PhD studies at the University of Gent Belgium, from 1988 to 1993, on the synthesis of hypermodified nucleotides, and substrates for enzymatic detection in the group of Marc Van Montagu, obtaining the title with Magna cum Laude distinction. The results of this research were published in The Plant Cell, 1993, 5, 1761 (Cover page) and Plant Cell Reports, 2000, 19, 966.

After finishing his PhD studies, he joined the chemistry institute at the National University of México, for conducting research on heterocyclic chemistry in 1993 till 1995 and after that period, he got a position as professor of chemistry at the Biotechnology Unit of the National Polytechnic Institute where he is currently teaching subjects, namely, bioorganic chemistry, drug design and heterocyclic chemistry.

In 2002, he spent a year as a postdoc at the University of California Berkeley researching the first synthesis of glycoresin, tricolorin F at the laboratory of Professor Clayton Heathcock. The result of this research was published in the Journal of Organic Chemistry, 2004, 69, 4567 (Cover page).