Acetyl CoA Carboxylase: By: Acacia White

Metabolism is often defined as the sum of biochemical processes that occur within a living organism. More specifically metabolism is the building and breaking down of substances, usually foods, and converting them into usable sources of energy for the body [1]. The metabolism of biomolecules; proteins, lipids, carbohydrates and nucleic acids are essential to the rate at which biochemical pathways occur by providing cells with usable energy [2]. Lipids or fatty acids have four main functions in the body. They are the building blocks of phospholipids and glycolipids are fatty acids. Secondly, fatty acids act as targeting molecules for integral and transmembrane proteins in the cell membrane. Fatty acids also serve as fueling molecules, in which energy is stored in the form of triacylglycerols after esterification and these neutral fats or triglycerides serve as major storage molecules [6]. Lastly, fatty acids can serve as messenger molecules: hormones, intracellular messenger molecules, and steroids for example are products of the metabolism of fatty acids [3]. Metabolism of fatty acids is controlled, to maintain the physiological responsiveness of the synthesis and degradation {of fatty acids} responsive to the physical needs of the body [4]. The carboxylation reaction of acetyl-CoA to produce malonyl-CoA requires 1 ATP, and this reaction is catalyzed by the biotin-dependent (biotin is the cofactor) enzyme Acetyl-CoA carboxylase (ACC), this is the beginning of the biosynthesis for a fatty acid [5].

 The initial step of the fatty acid synthesis pathway is the conversion of acetyl- CoA to malonyl-CoA, which is catalyzed by the enzyme ACC binds with biotin as the cofactor [3]. The gain of energy stored in the bonds of fatty acid molecules occurs because the fatty acid synthase reaction (see Figure 1), which allows for the anabolism of malonyl CoA. In this reaction acetyl CoA is synthesized 2 carbon molecules at a time by ACC which does so by adding a $CO\_{2}$ group to each acetyl group, beginning with the methyl end of the fatty acid molecule down to the carboxylic acid end [6]. The final step of fatty acid synthesis consists of the 5 step elongation process; condensation, reduction, dehydration, and reduction yielding the final product of fatty acid synthesis palmitoyl CoA [7].

The reaction which converts acetyl-CoA to malonyl CoA by adding$ CO\_{2}$, is a ATP dependent irreversible process, that is limited by the availability of acetyl-CoA. The spontaneous carboxylation of acetyl- CoA, the 2 carbon molecule to become the 3 carbon molecule, requires 1 ATP molecule to activate malonyl CoA. The process is also, irreversible reaction because The process is an irreversible reaction because $CO\_{2}$ becomes incorporated into the produced 3 carbon molecule but not the final fatty acid. Therefore, the rate at which fatty acid synthesis produces palmitoyl CoA, the 16 carbon molecule, is limited by the abundance of acetyl CoA. ADP is produced from the hydration of ATP used during the reaction involving ACC [5]. The carboxylation of acetyl CoA yields no energy but, this regulates the rate of fatty acid biosynthesis by producing malonyl CoA [8].

ACC requires a non-protein cofactor, biotin, for enzymatic activity. Biotin is an organic compound that also serves as a carrier [6]. Biotin, binds to the enzyme creating an amide link to an amino acid within the enzymes primary structure, serves as the prosthetic group by adding a $CO\_{2}$ group from bicarbonate ($HCO\_{3-}$) to the acetyl group of the fatty acid. Although biotin is an essential nutrient to a human’s fatty acid synthesis, humans cannot synthesis biotin [9]. Vitamin B7, formerly known as biotin, is the only indicator of biochemical energy reserves, keeps the ACC enzyme reactions efficient without affecting other metabolic reactions [10]. Since biotin is a prosthetic to the enzyme it can relocate between two active sites [6].

ACC is regulated by feedback inhibition and allosteric restriction of two local metabolites: palmitoyl CoA and Citrate, creating both an active and inactive form of the enzyme [6]. This enzyme in the active form is represented as a polymer, while the inactive form of the enzyme is a single monomeric unit. The metabolite Citrate influences the polymer or active conformation of the ACC enzyme, while the inactive or monomer formation is influenced by palmitoyl CoA. Palmitoyl CoA, the product of fatty acid synthase often gives the greater influence, by feedback inhibition palmitoyl CoA which stops the production of malonyl CoA and ultimately the ACC enzyme. Another pathway of regulation for the enzyme are hormones such as: glucagon, epinephrine, and norepinephrine. These hormones activate cAMP dependent and AMP-dependent protein kinases leading to the phosphorylation of the enzyme. This step-wise reaction causes a shift in the equilibrium towards inactive formation of the enzyme. The active form of the enzyme is subjective to insulin as well, which in turn, stimulates the desphosphorylation, of ACC [11].

It is necessary to regulate the enzyme activity of ACC to maintain homeostasis as it relates to the amount of energy produced from the biosynthesis of fatty acids. As previously stated, ACC is regulated by certain hormones, citrate, and the product of fatty acid synthase, palmitoyl CoA [12]. These regulators can generate both an active form of ACC that is needed when the body is low on energy and the first form of energy for the body to metabolize are fats. The biosynthesis of fats can only begin after ACC has added a carboxyl group to acetyl- CoA producing malonyl CoA. Induced regulation of the enzyme can also lead to the inhibition of metabolic syndrome, which is a cluster of cardiovascular risk factors that lead to heart disease [13].

The role of ACC is very important to the biosynthesis of fatty acids. Fats contain more amounts of energy than all the biomolecules including carbohydrates because they contain more electrons. Fats, more specifically lipids contain long hydrocarbon chains filled with electrons or energy, but fatty acids have to become useable forms of energy [3]. Esterification of fatty acids produce acetyl-CoA which can then be converted to malonyl CoA by the binding of the biotin and ATP to the enzyme ACC. This molecule is regulated by hormones (insulin glucagon, epinephrine, and norepinephrine), citrate and palmiotyl CoA [2]. These regulators can inhibit and activate ACC, which produces malonyl CoA, and regulate the biosynthesis of fatty acids. ACC can also be therapeutic to individuals with metabolic syndrome.

Figure 1: The Conversion of Acetyl-CoA to malonyl CoA by carboxylation (of Acetyl-CoA)



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