The Multienzyme Systems of Fatty Acid Biosynthesis

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With 18 Figures

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The synthesis of long-chain fatty acids from acetyl-CoA is catalyzed by two enzyme systems. Both systems are multienzyme assemblies; the acetyl-CoA carboxylase with just two partial enzyme activities is one of the simplest, and the fatty acid synthetase with at least seven partial enzyme activities is one of the more complex multienzyme systems.

Acetyl-CoA carboxylase from yeast was isolated in homogeneous form and compared in its properties with pyruvate carboxylase from yeast. Both enzymes have very similar sedimentation coefficients and molecular weights. Both enzyme are composed of four protomers. Acetyl-CoA carboxylase and pyruvate carboxylase split under identical conditions into a variety of aggregates: besides the protomer, dimeric, trimeric and polymeric forms are found. Patterns of the dissociated enzymes obtained by sedimentation in sucrose density gradients and by electrophoresis in polyacrylamide are almost identical.

Within the limits of sensitivity of the immunochemical techniques used in this study, no cross-reaction could be observed between antiacetyl-CoA carboxylase and pyruvate carboxylase. This indicates that the substructures catalyzing the ATP-dependent carboxylation of biotin, common to both enzymes, are not based on identical primary structures. From these results it is proposed that the genes for acetyl-CoA carboxylase and pyruvate carboxylase may have been derived from a common ancestor.

Regarding the second multienzyme system involved in fatty acid biosynthesis, fatty acid synthetase, it has become possible to
gain a preliminary insight in the structural organization of the complex by means of a simple method recently found to promote reversible dissociation of the complex. The molecular weights of the subunit proteins are between 200,000 and 250,000 which may indicate that the dissociation did not result in single enzyme components. After dissociation, the activity of the condensing enzyme and both reductases disappeared, but the activity of all other component enzymes did not decrease. Reactivation occurs on decrease of ionic strength by dilution or dialysis, suggesting that the catalytically active conformation of the reductase enzymes requires some protein-protein interactions which occur only in more complex structures.

Fatty acid synthetase produces palmityl-CoA and stearyl-CoA in equal amounts under standard conditions. A model is proposed, based on the known enzymatic properties of the fatty acid synthetase, which rationalizes the chain termination at the level of C_{16} and C_{18}-acid. The model assumes that the fatty acyltransferase involved experiences hydrophobic interaction with the growing carbon chain, starting at the level of the C_{13}-acid. The intensity of this interaction increases by an energy increment of $-0.9$ kcal per additional CH$_2$ group. To calculate the probability of the product release at a particular chain length, an equation was derived from the model for the quantitative description of the observed product distribution. The formula suggests the conditions under which either short acyl-CoA derivatives or exclusively stearyl-CoA can be produced. Synthesis under these conditions was tested experimentally and results indicated that the formula can be applied to a wide range of experimental conditions.

Die Multienzymsysteme der Fettsäurebiosynthese

Ausgehend vom Acetyl-CoA wird die Synthese von langkettigen Fettsäuren durch zwei Enzymsysteme, nämlich die Acetyl-CoA-Carboxylase und die Fettsäuresynthetase, katalysiert. Beide Enzymsysteme gehören zu den Multienzymkomplexen, wobei die Acetyl-CoA-Carboxylase mit zwei enzymatischen Teilfunktionen zu den einfachsten, die Fettsäuresynthetase mit wenigstens sieben enzymatischen Teilfunktionen zu den komplizierten Multienzymkomplexen zu rechnen ist.