Normal Lipid Metabolism

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Very striking advances have been made recently in our understanding of lipid metabolism. Much of this has come about because biochemists have learned how to prepare cell-free preparations without producing too extensive destruction of intracellular enzyme systems. The tremendous advantages of this type of technic are obvious. Once a cell-free preparation is available, the various particulate fractions of the cell can be separately studied for enzymatic activity. If, in addition to this, it becomes possible to extract from these particles the water-soluble enzymes capable of performing a series of metabolic reactions, then the way is open for a final attack. Every energy of the chemist is devoted to obtaining aqueous solutions of such enzyme mixtures since this permits him to fractionate and separate individual enzymes. Once this has been achieved, it becomes possible to study single reactions of an otherwise complex series of metabolic reactions. With a single enzyme, the reaction product accumulates; in a mixture of enzymes, the reaction product is metabolized further and does not accumulate. It is obvious that studies with the whole animal or with a whole organ can provide answers concerning starting material and end-products. Almost never can such studies yield direct evidence of the nature of the intervening reactions.

It is a source of great satisfaction that both the oxidation of fatty acids as well as their synthesis have now been accomplished in aqueous particle-free enzyme solutions. Such studies have demonstrated conclusively that the initial oxidative attack upon fats involves the formation of activated fatty acids. Such activated acids have now been shown to be combined through their acid groups with coenzyme A (a pantothenic acid derivative containing a sulfhydryl group). The resulting activated product is a thiol ester (figure 1) which is now capable of undergoing the classical beta oxidation process. The important point to remember is that, although this involves the usual beta-hydroxy and beta-keto acids as intermediates, the coenzyme A group still remains firmly

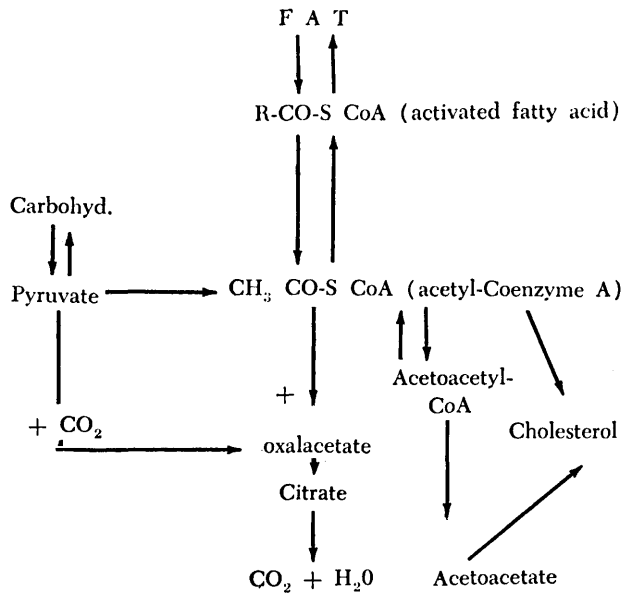

FIG. 1

attached to the carboxyl or acid radical. When a two-carbon fragment is finally broken off, it is released not as acetic acid but as acetyl coenzyme A. The remaining fatty acid is now shorter by two carbons, but is still attached to a second coenzyme A molecule which was introduced when the acetyl coenzyme A fragment was split off. The process can now be repeated a number of times until the fatty acid coenzyme A complex has been completely broken down to acetyl coenzyme A. The major product of fatty acid oxidation in all cells is therefore acetyl coenzyme A. Incidentally the major product resulting from the decarboxylation of pyruvate (derived from carbohydrate) is also acetyl coenzyme A. This coenzyme A derivative of acetate is therefore the important metabolic intermediate common to both carbohydrate and lipid catabolism. The fate of this substance is accordingly of paramount importance for an understanding of the metabolism of fats, carbohydrates and, to some extent, protein.

Utilizing purified enzyme systems it has now been established that acetyl coenzyme A can act as follows:
1. It can condense with oxalacetate to form citrate.
2. It can condense with itself to form acetoacetyl co-

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enzyme A (ketone bodies). 3. It can condense with itself and with short-chain fatty acid coenzyme A derivatives to form long-chain fatty acids. 4. It is capable of condensing with acetoacetate to form the major building stones for cholesterol synthesis. 5. It is an important biological acetylating agent.

Reaction 1 clarifies the way in which fatty acids and carbohydrate are oxidized to carbon dioxide and water. Both give rise to acetyl coenzyme A which can promptly condense with oxalacetate to form citrate which is oxidized efficiently by way of the Krebs citric acid (tricarboxylic) cycle. Although this cycle regenerates oxalacetate which should therefore be required only in catalytic amounts, situations may arise where the available amount of this substance may be inadequate. If, for example, fat is mobilized and transported to the liver in abnormal quantities, and if excessive amounts of acetyl coenzyme A result from an accelerated breakdown of fatty acids in the liver, such conditions might prevail. If the amount of oxalacetate available then becomes insufficient, the excess of acetyl coenzyme A must be channeled into other pathways. Condensation of two molecules of acetyl coenzyme A will yield one molecule of acetoacetyl coenzyme A. This is a reversible reaction.

$$2\ CH_3\ CO\text{-}S\ CoA \rightleftharpoons CH_3\ CO\ CH_2\ CO\text{-}S\ CoA + CoA$$

$$CH_3\ CO\ CH_2\ CO\text{-}S\ CoA \longrightarrow CH_3\ CO\ CH_2\ COOH + CoA$$

and acetoacetyl coenzyme A is therefore capable of being readily oxidized by liver to carbon dioxide and water. In liver, however, the coenzyme A can also be readily removed from acetoacetyl coenzyme A yielding acetoacetate. Since liver is relatively incapable of reactivating acetoacetate (cannot make acetoacetyl coenzyme A from acetoacetate) we can understand why the ketone bodies are inert in liver. They must therefore be transported to extra-hepatic tissues where there are available enzyme systems capable of once again forming acetoacetyl coenzyme A from acetoacetate. One other point needs to be made. Although pyruvate readily gives rise to acetyl coenzyme A, it can also react with carbon dioxide to form oxalacetate or its equivalent, malate. Whether or not the diabetic state is associated with a relative lack of oxalacetate (since pyruvate is derived from glucose) is not clear. Whatever the reasons, it is clear that when carbohydrate utilization is impaired, overwhelming amounts of acetyl coenzyme A are produced in the liver. If oxalacetate becomes limiting, then ketone body formation must increase. Since such conditions are associated with increased quantities of acetoacetate and acetyl coenzyme A, it is not surprising that accelerated cholesterol synthesis may also frequently occur. It has previously been pointed out that these two substances are important precursors of cholesterol.

Another channel open to acetyl coenzyme A is the resynthesis of fatty acids. It is now clear that acetyl coenzyme units can condense to form long-chain fatty acids; the conversion of carbohydrate to fat involves therefore preliminary glycolysis of carbohydrate to pyruvate which is subsequently decarboxylated to acetyl coenzyme A. In vitro experiments with acetyl coenzyme A indicate that it can form all of the carbon atoms of fatty acids. Strangely enough, this synthesis of fat from acetyl coenzyme A appears to require the simultaneous participation of rapid glycolysis. Liver tissue from a previously fasted or alloxanized rat (or depancreatized cat) appears to be unable to synthesize fat from acetyl coenzyme A. In diabetes therefore, another channel for the utilization of acetyl coenzyme A is closed off, and this provides still more reason for the ketosis of diabetes.

It may well be asked why pyruvate is antiketogenic even though it is a ready source of acetyl coenzyme A. A ready answer could be made that pyruvate not only can yield acetyl coenzyme A but can also provide its own oxalacetate by fixation of carbon dioxide. This, at least, provides a reasonable explanation for the antiketogenic action of carbohydrate. It could also be argued, of course, that anything operating to reduce the amount of fat pouring into the liver would have a similar effect.

I mention these points to make it obvious that there are a few unsolved problems left. Even the most skeptical must now, I think, admit that studies with isolated enzyme systems have yielded significant results. The difficulties arise when the attempt is made to interpret such findings in the light of the known physiological behavior of the intact cell, tissues or whole animal. This is undoubtedly the most difficult task of all, but is one that the mammalian biochemist always must keep in mind.

SUMMARIO IN INTERLINGUA

Normal Metabolismo de Lipidos

Progresso in le comprension del metabolismo de lipidos ha essite effectuate per le utilisation de purificate systemas enzymic. Il ha essite possibile demonstrar que le major producto del oxydation de acidos grasse in omne cellulas es acetylcoenzyma A. Isto es etiam le major producto del discarboxylation de pyruvato (derivate de hydratos de carbon). Assi illo es le importante intermediario metabolic commun al catabolismo de e hydratos de carbon e lipidos. Su varie actiones metabolic es discutite.