ON THE MECHANISM OF FATTY ACID BIOSYNTHESIS

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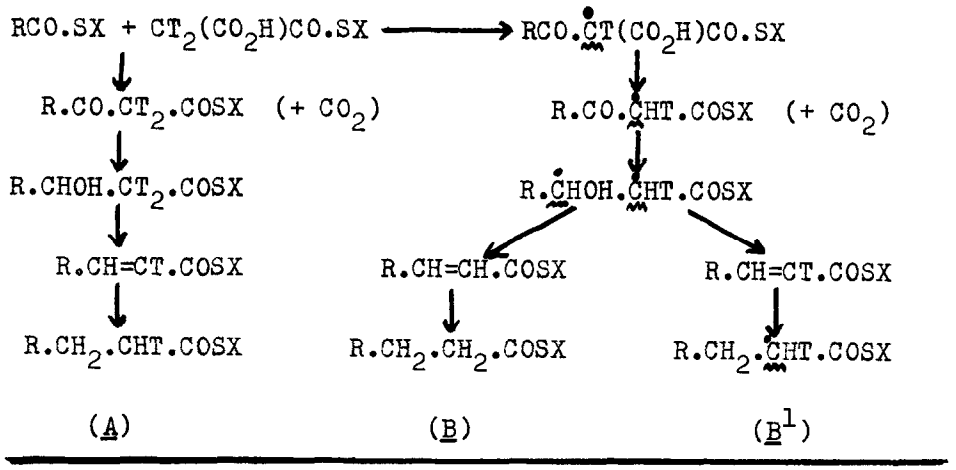
In their important paper on the biosynthesis of palmitic acid from acetyl-coenzyme A (acetyl-CoA) and malonyl-CoA, Bressler and Wakil (1961) note that tritium-labelled malonyl-CoA, $CT_2(CO_2H)CO.CoA$, contributes approximately one-half of its radioactivity to the palmitic acid, and conclude that in the chain-extending condensation, decarboxylation occurs synchronously, as in scheme (A) here. This conclusion, which has won general acceptance, appears to follow from consideration of the subsequent steps in which the carbon chain is reduced and oxygen is eliminated. However, it is abundantly clear from studies of the enzymology of similar reaction sequences that processes like those shown in (A) will occur in a fully stereospecific manner. From this it follows that a reaction in which condensation and decarboxylation are not concerted is by no means excluded by the experimental data. As shown in (B), an acylmalonyl derivative containing one-half of the tritium of the original malonyl-CoA will afford, by stereospecific reduction and dehydration steps, a fatty acid containing <u>either</u> no tritium at all (sequence B) <u>or</u> the same amount of tritium (sequence B^1). This is so whether the reduction and dehydration steps take place before further chain-extension, as shown here, or after a chain of several $-CO.CHT-$ groups has been assembled.

Alternative Reaction Schemes

(XSH = Coenzyme A or enzyme; $\overset{\bullet}{C}$ = asymmetric centre)



This conclusion, that a sequence such as (B^1) is not ruled out by the experimental data, is relevant not only to the pathway of fatty acid biosynthesis but also to considerations of the type of intermediate involved in other biosyntheses, particularly of the many secondary metabolites which seem to arise by variations of the fatty acid pathway.

REFERENCE

Bressler, R., and Wakil, S.J., J.Biol.Chem., 236, 1643 (1961).