Textbook Error

The gluconeogenicity of fatty acids in mammals

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Although excess glucose can be readily converted to fatty acids in mammals, most textbooks state that glucose cannot be formed from fatty acids. Whilst this remains largely true, several pathways have now been discovered in mammals in which fatty acids are potentially gluconeogenic.

The standard dogma in most textbooks is that mammals are unable to convert fatty acids to glucose. The β-oxidation of fatty acids produces two-carbon units of acetyl-CoA which are completely oxidized by the Krebs cycle: the entry of the C_2 acetyl units is balanced by the loss of two carbon atoms through decarboxylations. This is in contrast to the metabolism of amino acids, for example, where conversion to intermediates of the citric acid cycle results in incomplete oxidation; the remaining carbon skeletons are potentially gluconeogenic[1]. This article lists the metabolic pathways theoretically capable of converting a part of a fatty acid carbon skeleton to succinate and therefore to glucose. It should be stressed that these pathways are at present considered to be of limited physiological importance[2]. There is little evidence that fatty acids make more than a minor contribution to the supply of glucose precursors. Nonetheless, the pathways described below demonstrate the capacity for gluconeogenesis from fatty acid substrates in mammals.

Odd numbered fatty acids, occasionally present in diet[3,4], can be β-oxidized to generate one succinyl-CoA per oxidized molecule, with propionyl-CoA as an intermediate (see Fig. 1). In contrast to acetyl units, succinyl units and other Krebs cycle intermediates are well known precursors of glucose[1]. Succinyl-CoA can also be produced, via the formation of both propionyl- and isobutyryl-CoA[5], from branched chain fatty acids (see Fig. 1). An example is phytanic acid[6], a branched chain C_{20} fatty acid which may be ingested as such or in the form of its precursor, phytol[7].

The most abundant fatty acids in mammals are long straight chain fatty acids with an even number of carbon atoms and these do not yield either propionyl-CoA or isobutyryl-CoA by direct β-oxidation. Some of these fatty acids are metabolized by ω-oxidation[8–11], although estimates of the proportion involved vary (between 4 and 15% with one extreme of 40%, see Mortensen, P. B. [1983] PhD thesis, University Department of Clinical Chemistry, Aarhus, Denmark). In a first step, the monocarboxylate (fatty acid) is hydroxylated at the ω-position[12,22]. The resulting ω-hydroxymonocarboxylate

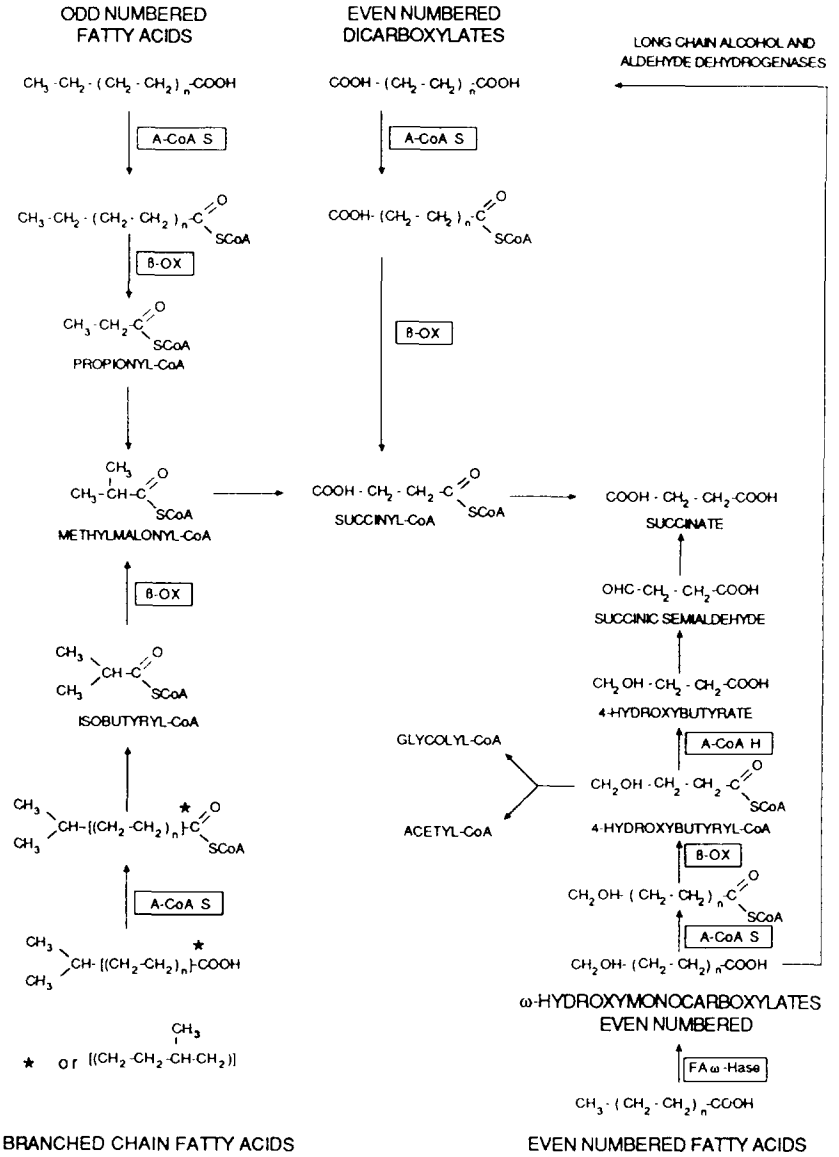

Fig. 1. Partial conversion of fatty acid skeletons to succinate in mammals. Abbreviations: A-CoAS, *acyl-CoA synthesis*; β-OX, *acyl-CoA β-oxidation*; A-CoAH, *acyl-CoA hydrolase*; FAω-Hase, *fatty acid ω-hydroxylase.*

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is further oxidized to form a dicarboxylate[13]. In contrast to β-oxidation, the ω-oxidation system utilizes unesterified fatty acids, does not require coenzyme A as cofactor, and occurs in the microsomal and cytosolic compartments (β-oxidation takes place in mitochondria and peroxisomes)[8–13]. The subsequent metabolism of ω-hydroxymonocarboxylates and dicarboxylates via β-oxidation generates gluconeogenic intermediates and products (see Ref. 14). The β-oxidation of the long chain ω-hydroxymonocarboxylates is likely to occur predominantly in mitochondria (where they are precursors of 4-hydroxybutyryl-CoA) and proceeds at the same rates as those of the fatty acids[15]. Theoretically, 4-hydroxybutyryl-CoA can undergo two types of conversion: either its β-oxidation to acetyl-CoA and glycolyl-CoA (the fate of which remains unknown) or its hydrolysis to CoA and 4-hydroxybutyrate. The terminal alcohol residue of the latter metabolite can be oxidized (see Refs 16 and 17), so that succinate is produced from the ω-hydroxymonocarboxylates. The overall oxidation rates recorded for long chain dicarboxylates may be similar to, or very different from, those for fatty acids, depending on the tissue studied[18]. There is now accumulating evidence to show that long and medium chain dicarboxylates are indeed precursors of succinate. *In vivo* experiments demonstrate that, in rats, (1) the incorporation of radioactivity into glucose from [1-^{14}C]- and [U-^{14}C]hexadecanedioate is considerably higher than from the corresponding radiolabelled palmitate[19], (2) that the administration of the C_6 dicarboxylate gives rise to an increase in the excretion of succinate[19] and (3) that about 70% of the infused C_{12} dicarboxylate is oxidized by mitochondria[20]. *In vitro* experiments indicate that the mitochondrial oxidation of long and medium chain dicarboxylates generates succinate in liver[21] and apparently in extra-hepatic tissues[18].

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