Dietary fatty acids with small differences in structure may have large differences in their metabolic effects. By the late 1950s and 60s Keys and Hegsted among others had already shown that the effects of dietary fatty acids on serum cholesterol varied according to their structure. Myristic acid (14:0) was the most potent cholesterol-increasing fatty acid, and much more so than palmitic acid (16:0). Stearic acid, with two C atoms more than palmitic acid, and also the monounsaturated oleic acid (cis-18:1), had no effect on serum cholesterol while linoleic acid (cis-18:2) was found to lead to a decrease. No good explanation has so far been found as to the mechanisms behind these different effects. The regulation of LDL-receptor activity by fatty acids and cellular free cholesterol mediated through the sterol regulatory element binding protein (SREBP) has been proposed (Dietschy, 1998), but it is difficult to see how this model can account for the specificity of effects of the different fatty acids.

The early findings by Keys and others on the influence of dietary fatty acids on serum cholesterol formed the basis for all subsequent and still generally accepted dietary guidelines for the prevention of CHD (American Heart Association, 1988). Trans fatty acids formed during the partial hydrogenation of edible oils or by bacterial activity in ruminants were not taken into account in these guidelines. Without any firm evidence, they were for decades considered to have insignificant effects on serum cholesterol. In terms of food labelling and in food tables they are considered to have insignificant effects on serum cholesterol while linoleic acid (cis-18:2) was found to lead to a decrease. No good explanation has so far been found as to the mechanisms behind these different effects. The regulation of LDL-receptor activity by fatty acids and cellular free cholesterol mediated through the sterol regulatory element binding protein (SREBP) has been proposed (Dietschy, 1998), but it is difficult to see how this model can account for the specificity of effects of the different fatty acids.

The important question as to the mechanisms involved in the diversity of metabolic effects of isomeric fatty acids is unanswered. The results obtained in studies with trans isomers of conjugated linoleic acid (CLA) may give a clue to an answer. In experimental animals CLA has been shown...
to have marked effects on energy metabolism, to inhibit carcinogenesis and atherosclerotic plaque formation and delay the onset of diabetes. The two main isomers of CLA, cis-9,trans-11 and trans-10,cis-12, have very different metabolic and biochemical effects and the reason for these differences has become an intriguing question. Both isomers are strong ligands to peroxisome proliferator activated receptors (PPAR), nuclear receptors involved in the regulation of several cellular processes (Moya-Camarena et al. 1999). Functional PPAR response elements have been identified in several genes involved in lipid and energy metabolism and it is probable that part of the answer to the question of the mechanisms of action of CLA isomers will be found in their different potencies to regulate gene expression. In addition, other natural and synthetic fatty acids such as thia-fatty acids are ligands to these receptors. In general, ligands to PPAR are lipophilic compounds with an acidic and a hydrophobic part that is difficult or impossible to be oxidized by the β-oxidation system. The existence of trans double bonds in a fatty acid molecule may require the presence of isomerase enzymes able to convert the trans bonds to cis in addition to shifting the position of the double bond in order for the β-oxidation enzymes to degrade the molecule. It is conceivable that such auxiliary enzymes may be rate limiting, thereby imposing some hindrance towards oxidation. This may lead to the activation of PPAR and/or other transcription factors which in turn set up a number of regulatory cellular processes. Such PPAR-activated processes are now under investigation. 

Except for CLA, no reports have so far appeared as to the effects of other trans fatty acids as ligands to transcription factors. It is probable that in the time to come we will see a diversity of effects of different isomeric fatty acids and interesting new examples of what can be characterized as ‘bioactive fatty acids’.

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References


