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Invited commentary

More on *trans* fatty acids

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 were included among the monoene fatty acids, thus giving the erroneous impression of a fairly favourable nutritional quality. Only sporadic epidemiological studies alluded to a possible unfavourable influence of dietary *trans* fatty acids on CHD risk (Thomas, 1975). This situation changed completely after publication of the important controlled dietary study of Mensink & Katan (1990) which convincingly demonstrated that monoene *trans* fatty acids (18:1*trans*) increase both total- and LDL-cholesterol and decrease HDL-cholesterol, thus causing an unfavourable LDL-cholesterol:HDL-cholesterol ratio. Subsequent studies have confirmed their findings and also shown them to be true not only for partially hydrogenated vegetable oils but also for partially hydrogenated fish oils (Almendingen *et al.* 1995). These studies have also disclosed that *trans* fatty acids increase serum lipoprotein (a): this is an unusual effect since this lipoprotein, which is strongly related to CHD risk, has not been considered to be influenced by diet. Subsequent to the publication of several epidemiological studies indicating that the intake of *trans* fatty acids is related to the risk of CHD to the same extent (if not more so) as that of saturated fatty acids (Hu *et al.* 1997), partially hydrogenated fat has gradually been removed from most margarines in European countries.

Partial hydrogenation is not, however, the only process that results in the formation of *trans* fatty acids. Deodorization is a necessary step in the refining of edible oils. During this process a not insignificant proportion of the *cis* bonds in polyunsaturated fatty acids, in particular in α-linolenic acid, are converted to the *trans* configuration. Thus, up to 40 % α-linolenic acid may be converted to isomers of *trans* α-linolenic acid if special precautions are not taken. It has been suggested that as much as 50 % ingested α-linolenic acid may be *trans* isoforms. In addition to reducing any favourable health effects of dietary α-linolenic acid, the question may be raised as to whether these isomers may have unfavourable metabolic effects similar to those of *trans* monoenes. Part of the answer to this question is given in the study published by Vermunt *et al.* (2001) for the *Trans*LineE project in this issue of the *British Journal of Nutrition*. The results of the study show that even small amounts of these *trans* isomers have measurable unfavourable effects on blood lipids and lipoproteins with an increase in the total cholesterol and LDL-cholesterol:HDL-cholesterol ratios. For the moment it is not possible to evaluate any possible health effects of the small amount of *trans* α-linolenic acid present in the diet. It is, however, possible to reduce the content to a negligible amount by selecting proper conditions for deodorization (Hénon *et al.* 1999). To avoid possible risks, and in view of recent recommendations to increase the amount of α-linolenic acid relative to linoleic acid (de Deckere *et al.* 1998), it is desirable that the food industry selects processes that maintain as much as possible of the initial content of α-linolenic acid intact.

It is of interest that in a previous study from the same group it was found that of the three possible isomers only *cis*-9, *cis*-12, *trans*-15-α-linolenic acid was incorporated into phospholipids (Sébédio *et al.* 2000). This particular isomer is thus seen as linoleic acid by the enzyme responsible for incorporation of this fatty acid into phospholipids. It may be inferred that the metabolic effects of the different *trans* fatty acids will depend both on the number and on the position of the *trans* bonds. Considering that the number of possible isomers is almost unlimited, a whole array of metabolic effects from dietary *trans* fatty acids is to be expected.

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 auxilliary 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 intensive study.

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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