Isomeric fatty acids

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Fatty acids containing trans-unsaturation have attracted attention in recent years in regard to their nutritional properties and their influence on metabolism. trans-Unsaturation, however, is but one example of isomerism among the fatty acids. This paper aims briefly to review the chemistry, occurrence, metabolism and nutritional significance of isomeric fatty acids in relation to current dietary guidelines.

Chemistry

Isomers are different forms of a chemical substance with the same chemical formula. In this paper I shall consider only isomerism of the ethylenic double bond, either geometrical (cis and trans) or positional, in which the double bonds are at different locations in the hydrocarbon chain.

Unsaturated fatty acids are formed in living tissues by the removal of pairs of hydrogen atoms from adjacent methylene groups (Gurr & James, 1980). The resulting ethylenic double bond normally has the cis geometrical configuration (that is, the remaining two hydrogen atoms lie on the same side of the molecule). Generally, in higher animals, the double bond occurs between carbon atoms 9 and 10, and isomerism (cis and trans) or positional, in which the double bond is located between carbon atoms 9 and 10, and isomerism (cis and trans) is possible. The latter may have double bonds that are methylene-interrupted or conjugated. Polysaturated fatty acids may also have cis and trans-double bonds within the same molecule.

A characteristic of trans-fatty acids is that they have physical properties intermediate between saturated and cis-unsaturated acids. The trans-double bond creates a linear carbon chain compared with the kinked configuration of cis-acids. Thus trans-fatty acids can pack together in a crystalline assay and their melting points are higher than those of corresponding cis-acids (Gurr, 1986).

Qualitative and quantitative information about the trans-fatty acid content of fats can be obtained by infra-red spectroscopy, by separating out the different classes of fatty acids by argentation thin-layer chromatography or by separating individual acids by capillary gas–liquid chromatography. The determination of positional isomerism is more demanding and the accurate and comprehensive determination of all fatty acids isomers in a complex lipid mixture generally requires a combination of several or all of these techniques as well as mass spectrometric analysis (Christie, 1982).

Occurrence of isomeric forms of unsaturated fatty acids

Natural sources. cis-Unsaturation is most common in natural lipids and the double bonds normally occupy specific

they must be supplied from vegetable sources in the diet and are called essential fatty acids. Not all polysaturated fatty acids are essential since they may not have double bonds in appropriate positions or in the appropriate (cis) configuration.

Fatty acids with double bonds of the opposite (that is, trans) geometrical configuration are also found in nature, although in much less abundance. They may be mono-unsaturated or polyunsaturated. The latter may have double bonds that are methylene-interrupted or conjugated. Polysaturated fatty acids may also have cis and trans-double bonds within the same molecule.

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positions in the chain. trans-Unsaturation occurs naturally in short-lived intermediates in biochemical pathways (e.g. during the biosynthesis of saturated fatty acids) or as stable end products. An example of the latter, trans-3-hexadecenoic acid is an ubiquitous though minor constituent of photosynthetic tissue. Some seed oils (e.g. Tung oil) may contain up to 80% of trans-fatty acids such as a-eleostearic acid (cis-9, trans-11, trans 13-octadecatrienoic acid) although they are not generally important dietary sources.

trans-Unsaturated fatty acids are also produced by the process of biohydrogenation of dietary polyunsaturated fatty acids by micro-organisms in the rumen of ruminant animals. The tissues of ruminant animals are, therefore, richer in trans-fatty acids than are the tissues of monogastric animals fed a normal diet and so are food products derived from ruminants. During biohydrogenation, the cis-double bonds of the original all-cis-polyunsaturated fatty acids are isomerized. This may involve a shift in position along the carbon chain (positional isomerization) or a change of geometrical configuration or both. The more highly unsaturated the starting fatty acid, the greater the variety of isomers formed. In milk, the trans mono-unsaturated fatty acids are quantitatively the most important and may constitute up to 21% of the total mono-unsaturated acids. The cis-double bond is mainly found in position 9 whereas trans-unsaturation is present in positions 6–16 of octadecenoic acid with a predominance of the 11-trans-isomer.

Isomerization introduced by food processing. Highly unsaturated oils, such as those found in many seeds and fish, are unsuitable for many food fats because of their low melting points and ready susceptibility to oxidative deterioration. The objective of industrial hydrogenation is to reduce the degree of unsaturation, thereby raising the melting point of the oil. By careful choice of catalyst and temperature, the oil can be hydrogenated selectively so as to achieve a product with precisely the desired characteristics. Indeed, the process is seldom taken to completion, since completely saturated fats would have melting points that were too high. As in biohydrogenation a proportion of the cis-double bonds in natural oils are isomerized during the reaction to trans-double bonds and there is also a migration of double bonds along the chain.

The monoenoic acids represent the major fraction, with trans-unsaturation at positions 6–12, with a predominance at position 10. The trans-diene fraction ranges from 0 to 25% of the total diene fraction in different margarines. trans-Unsaturation in the dienoic acids is found in cis-9, trans-12-18; 2; trans-9, cis-12-18; 2 and cis-9, trans-13-18; 2.

Improvements in catalytic hydrogenation have reduced the amounts of trans, trans-diene in modern margarines often to zero.

Dietary intake of isomeric fatty acids. Estimates of consumption of trans-unsaturated acids in the U.K. diet vary between about 5 and 7 g per day (Burnt & Buss, 1984; Gurr, 1984). About half of these are derived from ruminant products, the remainder from industrially processed fats. Whereas a large proportion will be positional isomers of trans-oleic acids, predominately of chain length 18 carbon atoms, we have no detailed knowledge of the composition of these isomers in the dietary fat.

Digestion and absorption of fats containing isomeric fatty acids

Experiments designed to investigate the metabolic properties of isomeric fatty acids have employed either semisynthetic diets in which the lipid component contains a single isomeric fatty acid of defined structure, or in the majority of cases, an industrially produced fat, containing a complex mixture of fatty acids. The former yields results that are easier to interpret and more informative in biochemical terms. The latter may be more relevant to practical human nutrition but it is frequently impossible to relate effects to a specific structural feature of the dietary lipid.

There is no scientific evidence that the lipases catalysing the digestion of fat in the gut discriminate between fatty acids according to the geometry of the double bond. However, cis-isomers of octadecenoic acid in which the double bond occurs close to the carboxyl group are not well hydrolysed by pancreatic lipase (Holman, 1985). Very-long-chain fatty acids (C26 and above) are also more slowly hydrolysed from triacylglycerols than fatty acids of 18 carbon atoms or less (Sickinger, 1985). This is of significance for the digestion of some triacylglycerols found in fish oils and hardened fish oils, which are used as hardstock in some U.K. margarines, and has nothing to do with the isomeric composition of the oils or the process of hydrogenation. Likewise there is little evidence that isomeric fatty acids differ in their absorption. In reports that claim poorer absorption of trans-acids than cis-acids, there was also a higher content of long-chain saturated acids in the diet which might have accounted for the difference.

Incorporation into body tissues

When isomeric fatty acids are included in the diet, they can be found in the lipids of most tissues of the body (Beare-Rogers, 1983; Senti, 1985). The highest proportion of trans-fatty acids found in human biopsy and necropsy specimens have been in liver and adipose tissue (up to 14% of total fatty acids: Johnson et al., 1957). Amounts varying between 0.1 and 4.5% of total fatty acids have been found in human milk (Senti, 1985). There is some selectivity with regard to the complex lipids into which trans-fatty acids are incorporated. In general, there is preferential incorporation of trans-monoenoins into triacylglycerols because of the extensive deposition in body fats (Beare-Rogers, 1983). They occur mainly in position 1 of long-chain fatty acids; Johnston et al., 1957). In other tissues, such as isomeric position 3. Incorporation into position 1 or phospholipids (Moore et al., 1980). The trans-octadecenoic acids behave like saturated fatty acids and are preferentially incorporated into position 1 or phosphoglycerides in contrast to oleic acid which is randomly distributed. However, patterns of incorporation are extremely complex since there is selectivity both with respect to the geometry and the position of the double bond (Wood, 1979).

Catabolism

Catabolism of fatty acids, measured by the 14CO2 expired over a period of 51 h after 14C-labelled fatty acids had been administered to experimental animals, was similar whether the fatty acids were saturated or cis- or trans-monoen
unsaturated (Anderson & Coots, 1967). At a subcellular level, isolated rat heart mitochondria can utilize CoA esters of trans-monoenoic acids as substrates for β-oxidation but at a somewhat slower rate than the corresponding cis-isomers, the rate decreasing as the double bond approaches the carboxyl end of the molecule (Lawson & Kummerow, 1979). There is some evidence that the presence of isomeric fatty acids in diets can cause adaptive changes such as the induction of peroxisomal rather than mitochondrial oxidation (Christiansen et al., 1979). In their experiments the inducing diets were partially hydrogenated marine oil or high erucic rapeseed oil which would also have contained long-chain acids as well a mixture of isomers.

Interactions with essential fatty acid metabolism

When young animals are fed a diet that lacks essential fatty acids, signs of overt essential fatty acid deficiency are observed that can be reversed by feeding as little as 1% of dietary energy as linoleic acid. When the diet has only
marginally sufficient linoleic acid, the addition of non-
estential fatty acids can result in the appearance of defici-
ency signs even though the absolute amount of linoleic acid
has not been reduced. Under these conditions, Hill et al.
(1979) demonstrated that as the amount of dietary trans-
fatty acids was increased, the animals showed progressive
signs of essential fatty acid deficiency. The trans, trans-
isomer of linoleic acid appeared to be more potent than the
cis,trans-isomers (Privett et al., 1977).

Several reports provide evidence that one of the mech-
anism by which trans-acids influence the metabolism of
essential fatty acids is to inhibit desaturases. De Schrijver
& Privett (1982) showed that feeding trans-acids to rats
inhibited 6-desaturase but increased 9-desaturase. They
used a mixture of trans-9,12-18 : 1, trans-9,12-18 : 2 and
cis,trans-9,12-18 : 2 isomers. The work of Anderson
et al. (1975) indicates that the trans,trans-isomer is
more effective than the cis,trans-isomers. Shimp et al. (1982)
similarly demonstrated an effect of feeding trans, trans-18 : 2 on 6-desaturase activity. In vitro, this isomer specifically
inhibited 6-desaturase but not 5-desaturase activity in liver
microsomes. Studies with specific isomers are scientifically
satisfying, but in terms of practical human nutrition it
seems that trans-18 : 2 may not be important since it is
a very minor component of human diets.

Certain trans-fatty acids are themselves substrates for
desaturases, so that another possible mechanism for their
influence on essential fatty acid metabolism is to compete
with essential fatty acids for common desaturases. trans-
Monenes in which the trans-double bond is away from the
9-position are desaturated by the 9-desaturase to form a
series of cis-9, trans-x-18 : 2 isomers which are also
substrates for 6- and 5-desaturases in the further pathways
for essential fatty acid metabolism (Holman, 1985). Most
of these polyunsaturated acids are of unusual structure
and a whole range of new eicosanoids (prostaglandins and
prostaglandin-like products) and other oxidative products
may thus be formed from the octadecenoate isomers present
in partially hydrogenated vegetable and marine oils. The
metabolic effects of such potential autocoids cannot
be predicted and need further investigation. Hwang &
Kinsella (1979) showed that diets containing trans, trans-
18 : 2 or the corresponding cis,trans-isomers resulted in
lower concentrations of essential fatty acids in liver and
blood platelets and a lower rate of production of normal
prostaglandins by platelets. The diets did not, however,
relate closely to any practical human diet, and little is
known of what the physiological implications of modifying
prostaglandin production in such a way might be.

Yet another way in which isomeric fatty acids could
influence metabolism is by influencing the properties of
membranes into which they are incorporated. Several studies
of membrane fluidity lead to the conclusion that trans-fatty
acids generally substitute for saturated acids in animal
membranes with little change in membrane physical proper-
ties (e.g. see Senti, 1985). When the isomeric fatty acid can
become the predominant fatty acid in the membrane (as in
studies with certain micro-organisms, cells in culture or
model membranes) the trans-fatty acids can bring about
decreased fluidity, associated changes in permeability and
other metabolic parameters (e.g. De Kruyff et al., 1973;
Tsao & Lands (1980).

Dietary guidelines

When isomeric fatty acids can make a significant contri-
bution to dietary fat intake it is important to know whether
they can influence metabolism in ways that contribute to
disease and to make recommendations accordingly. In rela-
tion to vascular disease, much importance has been attached
to the role of dietary fats in regulating the types and concen-
trations of blood lipoproteins. trans-9-Octadecenoic acid,
like cis-9-octadecenoic acid, seems neither to raise nor lower
plasma cholesterol concentration. Experiments that have
apparently demonstrated a raising effect have been flawed
in some way, many have been conducted under conditions in
which dietary linoleic acid has been limiting (e.g. see Senti,
1985). Less is known about their effects on thrombogenesis,
although at least one author (Hornstra, 1982) has shown
trans-18 : 1 to be no more thrombogenic than cis-18 : 1. On
these grounds, it could be argued that trans-fatty acids
should not be regarded equivalent to saturated fatty acids
for the purposes of dietary recommendations. However,
some caution should be exercised until we know more about
the production and metabolic effects of eicosanoids formed
by the metabolism of dietary isomeric fatty acids in body
tissues. Whereas most people probably have a sufficiently
high intake of essential fatty acids to protect against the unwanted
effects of isomeric fatty acids, there will undoubtedly be
some individuals who are at risk from the effects of an
imbalance between essential and non-essential fatty acids.

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1987