PN 1322

Interconversion of long-chain fatty acids in the rat

Nonadeca-10,13-dienoic acid has no[1,2] or only little[3] curative effect on symptoms of essential fatty acid deficiency in rats. The essentiality of linoleic acid appears to be correlated with its conversion into arachidonic or higher acids. Therefore, it is of interest to check for an equivalent conversion of nonadeca-10,13-dienoic into higher acids.

Methyl nonadeca-10,13-dienoate was prepared from linoleic acid[4,5]. It was free of linoleate according to gas-liquid chromatography but was contaminated with about 1% of a chlorinated C_{19} compound. Methyl linoleate or nonadeca-10,13-dienoate (1 g per animal per day), was incorporated into a restricted daily ration of fat-deficient rats. Each of the compounds was given in this manner to two animals for 5 days. The lipids were extracted from the pooled hearts, livers, kidneys and spleens from each group. After saponification, the fatty acids were analyzed by gas–liquid chromatography[6] as methyl esters (see Table I).

TABLE I

FATTY ACIDS IN ORGANS OF FAT-DEFICIENT RATS BEFORE AND AFTER FEEDING OF LINOLEATE AND NONADECA-10,13-DIENOATE

Figures are area percentages of methyl esters in gas–liquid chromatography recorder tracings. There were two rats per diet group.

Diet	*Fatty acids*									
	14	*16*	*16:1*	*17:2*	*18*	*18:1*	*18:2*	*19:2*	*20:3*	*20:4*
Fat-free	1.1	26.9	12.7	—	8.8	40.6	1.6	—	8.1	trace
Linoleate	0.6	22.0	5.3	—	12.1	24.9	21.5	—	1.6	11.8
Nonadeca-10,13-dienoate	0.5	21.6	4.6	5.2	12.0	32.3	0.4	16.0	4.9	2.3

Feeding of linoleate resulted in a high content of arachidonic acid, but neither a 19:3 nor a 21:4 acid was detected in the animals which had received 19:2 acid. The unsaturated portion of the esters was enriched by crystallization from acetone at −18° and −52°, but again trienoic or tetraenoic odd-numbered acids could not be detected. Similarly, no heneicosanoate was found in the hydrogenated esters.

In these experiments nonadeca-10,13-dienoate was fed at high level for a short period. In concurrent experiments, RAHM AND HOLMAN[2] fed another preparation of this ester at low level for a long period and found no conversion into higher acids.

Several conclusions and hypotheses may be derived from the data of Table I and from other experiments:

(a) Nonadeca-10,13-dienoic acid is metabolized since an appreciable amount of the most likely partial degradation product, heptadeca-8,11-dienoic acid, has been found. A similar partial degradation was encountered also with heptadecanoic and nonadec-10-enoic acids[7].

(b) The increase of 20:4 acid after administering 19:2 is surprising. A one-carbon transition is unexpected but may be possible with the chlorinated contaminant. It is of interest in this connection that, according to THOMASSON[3], nonadeca-10,13-dienoic acid has 9% of the biological activity of linoleic acid.

(c) Amounts of fatty acids smaller than employed here may be used in screening

for interconversion by feeding at a relatively high level for a few days. Amount and time can, of course, be further reduced when radioactive acids are employed.

(d) The biological inefficiency of nonadeca-10,13-dienoic acid is connected with the failure of the animal body to convert it into higher unsaturated fatty acids according to the usual pattern of elongation and desaturation.

(e) Quite generally, the carboxyl moiety of an unsaturated acid is as important as the terminal moiety for the usual conversions into highly unsaturated fatty acids.

A double bond in position 9 of a C_{18} chain is the most efficient combination of the two variables for further conversions which may involve the plant-type desaturation towards the methyl or the vertebrate-type desaturation towards the carboxyl group. The distinct function of a double bond in position 9 for further desaturation has been postulated already by BREUSCH[8].

KLENK *et al.*[9] showed that $\Delta^{9,12}$-, $\Delta^{6,9,12}$- and $\Delta^{6,9,12,15}$-C_{16} acids when given to fat-deficient rats did not markedly change the composition of highly unsaturated C_{20} and C_{22} acids. However, $\Delta^{4,7,10,13}$-C_{16} pronouncedly increased the C_{20} and C_{22} acids of the linolenic family[10]. The difference may be due to the fact that the latter tetraenoate belongs to the linolenic acid family while the former C_{16} acids do not belong to one of the common types of acids.

An alternate explanation may be as follows. Assuming elongation for these acids, $\Delta^{4,7,10,13}$-C_{16} can be converted into $\Delta^{6,9,12,15}$-C_{18}, and fulfills then the preferred combination of a Δ^{9} double bond in a C_{18} chain. When the other C_{16} acids are elongated, their double bonds are not at a favorable distance from the carboxyl group.

FULCO AND MEAD[11] tested Δ^{12}-C_{18} acid for possible formation of linoleic acid and found very inefficient conversion, if any.

TABLE II

CORRELATIONS OF ISOMERIC ACIDS FOUND IN RAT LIPIDS

(a) The correlation of these monoenes has been established with ^{14}C-labeled acids[7,12]. (b) Isomeric monoenes were pronounced in weanling rats. (c) Isomeric dienes became pronounced with increasing fat deficiency. (d) Not found here, but identified by FULCO AND MEAD[11,13]. (e) Not found here, but identified by KLENK AND OETTE[14].

(a) ↕	Δ^{7}-C_{16} (b)	(a) ↓	Δ^{9}-C_{16} (b)	Δ^{6}-C_{16} (b) ↓
	Δ^{9}-C_{18} (b)		Δ^{11}-C_{18} (b)	Δ^{8}-C_{18} (b)
	$\Delta^{6,9}$-C_{18} (c)		$\Delta^{8,11}$-C_{18} (c)	$\Delta^{5,8}$-C_{18} (c)
			$\Delta^{5,8,11}$-C_{18} (d)	
	$\Delta^{5,8,11}$-C_{20}		$\Delta^{7,10,13}$-C_{20}	
			$\Delta^{4,7,10,13}$-C_{20} (e)	

Isomeric unsaturated acids in fat-deficient rats were investigated by the same authors[11] and in this laboratory[12]. Δ^{6}-, Δ^{7}- and Δ^{9}-C_{16} acids were identified and the scheme in Table II gives the most likely correlations with other acids that have been isolated and characterized.

The Δ^{6}-C_{16} isomer seems to be least suitable to form eicosatrienoic and higher acids although a structure, $\Delta^{4,7,10}$-C_{20}, would be feasible. Whereas the relative amounts

of Δ^{6}-C_{16}, Δ^{7}-C_{16}, Δ^{8}-C_{18} and Δ^{11}-C_{18} may be between 0.5 % and 10 % of the isomers, it is striking that Δ^{10}-C_{16} and Δ^{10}-C_{18} have not been encountered in the rat nor have they been reported from lipids of higher animals and plants. On the other hand, it appears that a first double bond in position 10 is prohibitive to further elongation and desaturation. When the artificial nonadeca-10,13-dienoic acid is given to the animal, it is not converted. One might reason that the second double bond should promote the process, since linoleic acid is more readily converted into highly unsaturated acids than is oleic acid. Such reasoning does not apply to the 19:2 acid although it has the terminal structure of linoleic acid.

Mullet (*Mugilus cephalus*) oil contains more than 25% of odd-numbered acids and numerous unsaturated acids have been isolated from this oil and identified[12]. Among them were $\Delta^{9,12}$-C_{15}, -C_{16}, -C_{17}, -C_{18}; $\Delta^{6,9,12}$-C_{15}, -C_{16}, -C_{17}, -C_{18}; $\Delta^{5,8,11,14}$-C_{19}, -C_{20}; $\Delta^{6,9,12,15}$-C_{17} and -C_{18} acids. The present concept of oleic, linoleic, etc., families is not valid for any of the odd-numbered acids. Three nonadecadienoic acids have been identified but $\Delta^{10,13}$-C_{19} is not among them. This lack is in agreement with the non-convertibility of the synthetic 19:2 acid into higher acids.

The specificity of the enzyme systems which synthesize polyunsaturated acids is not as rigorous in regard to linoleic and linolenic terminal structures as has been often assumed; it appears necessary to consider also the proximal moiety.

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