Appendix K

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synthesis cannot be specified.

Many organs had significant ^{14}C activity in one or more fatty acids having retention times equal to those for 20:5, 22:2, 22:3, 22:4, 22:5 and 22:6. In the case of fatty acids from lungs and from brain, two of these were shown to be 22:2 and 22:4. In brain tissue about 40% of the ^{14}C activity was in fatty acids other than 20:4 and of this about half was in a fraction tentatively identified as 18:2. Though the chemical identity of this compound was not established further, it may be $\Delta^{8,12}$ octadecadienoic acid, synthesized from Δ^{9} 16:1, or $\Delta^{6,9}$ octadecadienoic acid. The presence of the latter isomer in pig brain tissue has been reported by Kishimoto and Radin (15). Formation of $\Delta^{6,9}$ octadecadienoic acid from ^{14}C-oleic acid by rat liver microsomes was shown by Holloway et al. (16). An 18:2 fatty acid (presumably the same isomer) was shown to be synthesized from 1-^{14}C-acetyl CoA by subcellular particles of rat liver by Harlan and Wakil (17). We have previously also observed biosynthesis of this isomer by rat liver microsomes incubated with ^{14}C-acetyl CoA (18).

ACKNOWLEDGMENTS

This work was supported by Grant No. GB-5114 from the National Science Foundation and Institutional Grant No. IN-25H from the American Cancer Society.

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[Received April 19, 1967]

Resistance of Certain Long-Chain Polyunsaturated Fatty Acids of Marine Oils to Pancreatic Lipase Hydrolysis

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ABSTRACT

When whale oil triglycerides were subjected to pancreatic lipase hydrolysis, eicosapentaenoic and docosahexaenoic acids were found mainly in the di- and triglyceride products, suggesting that they are in the 1,3-positions but resistant to the action of the lipase. Their presence in the 1,3-positions was confirmed. Their resistance to pancreatic lipase hydrolysis was demonstrated by analysis of the products of the enzyme action on: (a) a concentrate of highly unsaturated whale oil triglycerides; (b) the latter after randomization; and (c) synthetic 1,2-di-octadecenoyl-3-eicosapentaenoyl glycerol.

Docosapentaenoic acid was also shown to be present in the 1,3-position of whale oil triglycerides but was not lipase resistant. It is postulated that the presence of a double bond near the carboxyl group exercises an inhibitory effect, or that the location of the double bonds in the resistant acids places their terminal methyl groups close to the carboxyl, producing a steric hindrance effect.

INTRODUCTION

IN A STUDY OF THE STRUCTURE of marine mammal oils by the use of pancreatic lipase, the distribution of fatty acids in the hydrolytic products of whale oil suggested that eicosapentaenoic (20:5) and docosahexaenoic (22:6) acids, but not docosapentaenoic (22:5) acid, are resistant to the action of that hydrolytic enzyme. The results of the present study confirm the resistance of those acids to pancreatic lipase action, even though the acids are located in the 1,3-positions of whale oil triglycerides. A preliminary report of this work has been presented (1).

EXPERIMENTAL

The location of the 20:5, 22:5, and 22:6 acids in the whale glyceride molecules and the resistance of these acids to the activity of pancreatic lipase were determined by analyses of the products of the enzyme action on: (a) unmodified whale oil; (b) a concentrate of highly unsaturated whale oil triglycerides; (c) the latter after randomization; and (d) synthetic 1,2-di-octadecenoyl-3-eicosapentaenoyl glycerol.

Methods

The triglycerides of two samples of whale oil[1] were purified by preparative thin-layer chromatography (TLC). A highly unsaturated fraction was prepared from one of them by crystallization at –60C (2). Menhaden oil was provided by the Department of Oceanography, Texas A&M University. Lipase (EC 3.1.1.3) from hog pancreas, PL-III, was purchased from Worthington Biochemical Corporation, Freehold, N. J. Lipase hydrolyses were performed in vitro by the procedure of Luddy et al. (3), including the determination of the fatty acid composition of the free fatty acids and of the mono-, di-, and triglyceride products.

Randomization of the highly unsaturated concentrate of whale oil was achieved by treatment with 0.1 M lithium secondary butylate in dimethyl formamide (4). The reaction mixture was kept under nitrogen at room temperature for 3 days. The rearranged triglycerides were purified by preparative TLC.

Purification of triglycerides by TLC was achieved on 0.25-mm thick layers of silica gel (Adsorbosil-1, Applied Science Laboratories, State College, Pa.) on 20 x 20 cm glass plates. The developing solvent system was a mixture of petroleum ether (30-60C bp)-ethyl ether-acetic acid (60:40:1.6, v/v/v).

Gas-liquid chromatography (GLC) was performed in a Research Specialties Model 600 gas chromatograph (Warner-Chilcott Laboratories Division, Richmond, Calif.). The chromatograph was equipped with an argon ionization detector and a 6 ft x 1/4 in. column packed with 15% diethylene glycol succinate on 60-80 mesh Chromosorb W. The column was operated isothermally at 195C. The identities of the quantitatively more important peaks were ascertained by comparing their relative retention times with those of known standards.

[1] One of the samples of whale oil was from the Arista Company, New York. The other was obtained through the courtesy of H. S. Olcott.

Infrared spectra were obtained in a IR8 Beckman infrared spectrophotometer between sodium chloride pellets.

1,2-Di-octadecenoyl-3-eicosapentaenoyl glycerol was synthesized from 1,2-diolein and eicosapentaenoyl chloride and purified by TLC. A manuscript describing this synthesis is in preparation. Eicosapentaenoic acid, 91% pure, isolated from menhaden oil, was purchased from the Hormel Institute, Austin, Minn.

RESULTS AND DISCUSSION

Evidences of Resistance

After 50% pancreatic lipase hydrolysis of the whale oil triglycerides, the concentrations of the 20:5 and 22:6 acids were lower in both the fatty acid and the monoglyceride fractions, but higher in the diglyceride and triglyceride fractions of the resultant mixture than in the original oil (Table I). This suggests that these two polyunsaturated fatty acids are in the 1- and 3- positions but are resistant to the action of the lipase. That the 20:5, 22:5, and 22:6 acids of the whale oil are in the 1,3-positions has been reported by Brockerhoff and Hoyle (5). The accumulation of long-chain polyunsaturated fatty acids in the diglycerides after lipase hydrolysis of marine oils has also been reported by others (4, 6, 7).

Not all the polyunsaturated acids of whale oil behave as the 20:5 and 22:6 acids. The 22:5 acid was present in the free fatty acids and was not enriched in the di- and triglycerides, although like the 20:5 and 22:6 acids it was in low concentration in the monoglyceride products of hydrolysis (Table I). Therefore, the 22:5 acid must be considered as also present in the 1,3-positions; but, in contrast to the 20:5 and 22:6 acids, susceptible to the action of pancreatic lipase.

TABLE I

Major Fatty Acid Components of Whale Oil Triglycerides and Its Lipase Hydrolysis Products

Acid[a]	Sample	Whale oils: Original TG	Products of hydrolysis[b]: FA	MG	DG	TG
		percentage				
14:0	I[c]	8.7	8.1	9.3	9.2	7.1
	II	4.6	3.4	7.7	3.9	2.4
16:0	I	14.8	20.1	5.5	9.9	12.5
	II	14.9	21.1	10.0	7.9	7.3
16:1	I	16.7	11.3	28.9	17.8	12.0
	II	14.4	9.2	24.1	16.6	8.6
18:1	I	32.2	37.5	40.9	29.4	23.7
	II	33.6	38.7	45.0	30.1	19.0
20:1	I	2.6	5.3	0.3	1.1	1.9
	II	2.1	2.3	1.1	2.1	2.8
20:5	I	6.6	2.0	2.1	11.8	13.8
	II	8.1	3.0	2.4	17.7	26.0
22:5	I	3.9	2.9	0.5	2.2	2.9
	II	5.2	5.9	tr	3.9	6.8
22:6	I	4.9	2.6	0.8	5.3	10.1
	II	5.8	3.9	tr	8.1	17.3

[a] Chain length: number of double bonds.

[b] FA = Fatty Acids; M = Monoglycerides; DG = Diglycerides; TG = Triglycerides.

[c] Average of duplicate analyses.

Since the concentration of some of the polyunsaturated acids were low in the original whale oil, a highly unsaturated concentrate was obtained by removal of the more saturated glycerides by crystallization from acetone at −60C (2). The concentrate was then subjected to pancreatic lipase hydrolysis. The results are presented in Table II-A. It can be seen that, as compared to a level of about 22% in the concentrate, there were only 7% and 8% of the 20:5 acid in the free fatty acid and monoglyceride fractions, respectively. There were 26% in the diglycerides and 30% in the triglycerides. The results from the concentrate thus reinforce previous indications of resistance. The distribution of the 22:6 acid in the hydrolysis products also indicates resistance but to a somewhat lesser degree. The 22:5 acid was hydrolzed normally as shown by its relatively high level in the fatty acid fraction.

TABLE II

The Effect of Randomization on the Products of Pancreatic Lipase Action on a Highly Unsaturated Fraction from Whale Oil Triglycerides (major fatty acids only)

Acid[b]	(A) Whale oil highly unsaturated TG[a]: Concentrate (original TG)	Products of hydrolysis: FA	MG	DG	TG	(B) Randomized whale oil highly unsaturated TG: Randomized TG	Products of hydrolysis: FA	MG	DG	TG	(C) Recalculation of (B) omitting 20:5 and 22:6: Randomized TG	Products of hydrolysis: FA	MG	DG	TG
	percentage					percentage					percentage				
14:0	4.9	4.1	6.3	4.1	4.7	4.6	8.5	7.3	4.6	4.3	6.9	9.0	9.5	7.7	7.6
16:0	2.4	4.6	1.1	1.3	2.4	2.3	5.1	3.0	2.0	2.0	3.5	5.4	3.9	3.4	3.5
16:1	15.6	16.9	34.5	20.3	12.1	14.1	24.0	18.6	14.6	12.9	21.3	25.5	24.2	24.5	22.8
18:1	25.5	38.0	27.0	20.0	19.4	25.3	35.1	26.8	17.1	17.8	38.2	37.3	34.9	28.7	31.5
20:1	3.5	2.3	3.2	3.6	3.1	3.1	1.5	2.7	4.5	3.9	4.7	1.6	3.5	7.6	6.9
20:5	22.3	7.0	8.2	26.4	30.1	22.4	3.2	16.4	29.7	29.6					
22:5	4.6	8.0	0.9	3.1	4.3	4.8	3.6	4.5	5.2	5.1	7.2	3.8	5.9	8.7	9.0
22:6	12.6	8.5	2.0	11.4	15.9	11.3	2.8	6.8	10.8	13.9					

[a] FA = Fatty Acids; MG = Monoglycerides; DG = Diglycerides; TG = Triglycerides.

[b] Chain length: number of double bonds.

TABLE III

Major Fatty Acid Components of Menhaden Oil Triglycerides and Its Lipase Hydrolysis Products

Acid[a]	Original TG	Products of hydrolysis[b]: FA	MG	DG	TG
	percentage				
14:0	11.1	11.0	14.2	7.7	6.3
16:0	19.4	27.2	24.9	14.7	17.4
16:1	16.1	17.6	13.6	9.1	8.1
18:0	5.6	7.6	3.2	3.4	3.7
18:1	16.2	20.1	5.7	4.7	5.0
20:1	3.8	1.6	2.8	6.6	6.0
20:5	10.5	2.0	11.4	22.8	25.5
22:5	1.4	0.6	2.5	2.2	tr
22:6	7.3	1.5	15.1	15.0	16.0

[a] Chain length: number of double bonds.

[b] FA = Fatty Acids; MG = Monoglycerides; DG = Diglycerides; TG = Triglycerides.

In order to rule out position in the triglyceride molecule as the determining factor in the low degree of hydrolysis of the 20:5 and 22:6 acids, an aliquot of the highly unsaturated concentrate was randomized by chemical treatment. Whale oil offers unusual resistance to rearrangement by the use of standard procedures. Several combinations of catalysts, solvents and different times of treatment were tested before satisfactory results could be obtained. Sodium methoxide in methanol solution produced methyl esters difficult to separate from the randomized triglycerides. A xylene suspension of the same catalyst (8) was only partially effective. Lithium secondary butylate in dimethyl formamide solution (4) was found to be effective when the reaction period was prolonged for 3 days at room temperature. This procedure was therefore used. The randomized triglyceride products, purified by TLC, were analyzed by GLC and subjected to pancreatic lipase hydrolysis. The results are presented in Table IIB. Since the fatty acid compositions of the four products of hydrolysis are not similar, one might conclude that the randomization is incomplete. However, this criterion would only be valid if all the acids were equally susceptible to the lipase, a condition which is not met due to the presence of the resistant 20:5 and 22:6 acids. If the data are recalculated omitting the 20:5 and 22:6 acids or, in other words, making the nonresistant acids equal to 100%, the figures shown in Table IIC are obtained. The quite similar concentrations of the six major acids in all four fractions indicates effective randomization.

The presence of significant amounts of 20:5, 22:5, and 22:6 acids in the monoglycerides after, but not before randomization (Table IIB), indicates that they were not originally located in the 2-position in the whale oil triglycerides. Finally, the very low levels of 20:5 and 22:6 acids in the free fatty acid fraction of the pancreatic lipase hydrolysis products of the randomized oil indicate that the reduced degree of hydrolysis of those acids is not due to the positional specificity of the enzyme, but is due to a characteristic of the fatty acid molecule itself.

In order to compare the behavior of the 20:5 and 22:6 acids in the pancreatic lipase hydrolysis of whale oil with their behavior when located mainly in the 2-position as in fish oils, menhaden oil triglycerides were subjected to pancreatic lipase hydrolysis (Table III). The distribution of the 20:5 and 22:6 acids in the hydrolysis products of menhaden oil is different from that in whale oil products (Table I), although their concentrations in the two oils are quite similar. This is further evidence that the distribution of these acids in the two oils is different and that in whale oil hydrolysis their resistance to pancreatic lipase is independent of their position.

It required about 2 min to attain 50% hydrolysis of the untreated whale oils under the conditions used. An extended reaction time should increase the general degree of hydrolysis but leave higher concentrations of the resistant 20:5 and 22:6 acids in the unhydrolyzed di- or triglycerides. This was found to be true only for 20:5, whose concentrations after 2, 3, and 5 min of hydrolysis were 11.8, 14.4 and 18.2% respectively in diglycerides and 13.8, 13.3, and 19.7% respectively in triglycerides. The concentration of 22:6 after 2, 3, and 5 min of hydrolysis was 5.9, 5.3, and 5.4% respectively in diglycerides and 11.0, 7.2, and 6.7% respectively in triglycerides. The lack of increase in percentage of 22:6 in the di- and triglycerides with time might be due to its having approached maximum levels at the 2-min period.

It was also found that the rate of hydrolysis decreased appreciably after half the triglyceride acids were released. This is a logical consequence of distribution in the 1,3-position of the 20:5 and 22:6 acids, their resistance to hydrolysis, and the reported presence of the

C_{20} and C_{22} acids in only 50% of whale oil triglycerides (2).

Proof of Resistance

Proof of the resistance of the 20:5 acid (and by inference of the 22:6 acid) was obtained by study of the action of pancreatic lipase on synthetic 1,2-di-octadecenoyl-3-eicosapentaenoyl glycerol. The results are presented in Table IV. The fatty acid compositions of the triglycerides before lipase hydrolysis and of the monoglyceride and triglyceride products of hydrolysis show that the substance synthesized is, in fact, 1,2-di-octadecenoyl-3-eicosapentaenoyl glycerol, with some contamination due to impurities in the starting materials.

The experimental values for the composition of the fatty acid and diglyceride fractions are closer to the values calculated on the assumption of resistance than on the assumption of nonresistance. The small amount of monoglycerides produced is another indication of resistance. The presence of 17% 20:5 acid in the fatty acid fraction indicates that some hydrolysis of that acid took place. This could be due to the resistance to the enzyme not being absolute, to the presence of a hydrolyzable isomer of the 20:5 acid in the starting material, or to an alteration in the structure of the all *cis* 20:5 acid during the chemical synthesis of the triglyceride. Analyses of the starting material showed that there were 9% impurities as ascertained by GLC and that only 75% of the theoretical amount of glutaric acid was produced by $KMnO_4$ oxidation in acetic acid medium (9). Examination of the original 20:5 acid and the 1,2-di-octadecenoyl-3-eicosapentaenoyl glycerol by infrared spectrometry showed that only traces of *trans* isomerization occurred during the synthesis.

TABLE IV

Products of the Action of Pancreatic Lipase on 1,2-Di-octadecenoyl-3-eicosapentaenoyl Glycerol

Acid[b]	Original TG	Products of hydrolysis[a] FA	MG	DG	TG
		Mole percent[c]			
		Theoretical (nonresistance)			
18:1 + impur.[d]	69.7	54.6	100	77.7	69.3
20:5	30.3	45.4	0	22.3	30.3
		Theoretical (absolute resistance)			
18:1 + impur.	69.7	100	[e]	54.5	69.7
20:5	30:3	0	[e]	45.5	30.3
		Experimental			
18:1 + impur.	71.5	83.0	99.1[f]	60.8	73.0
20:5	28.5	17.0	0.9[f]	39.2	27.0

[a] FA = Fatty Acids; MG = Monoglycerides; DG = Diglycerides; TG = Triglycerides.

[b] Chain length: double bond.

[c] The detector response to the 20:5 acid was found to be 0.88 times that of the 18.1. However, no correction was applied since it would have had no significant effect on the conclusions.

[d] The preparation of 20:5 acid used had 8.9% impurities of other fatty acids. Since they are not expected to be lipase resistant, their percentages are added to that of oleic acid.

[e] No MG should be obtained.

[f] Very small amount of MG obtained.

Mechanism of Resistance

It is evident that in spite of being located at the 1,3-positions of the whale oil triglycerides, the 20:5 and 22:6 acids resist pancreatic lipase hydrolysis while the 22:5 acid is hydrolyzed without difficulty. The explanation for this phenomenon may lie in differences in their molecular structures:

20:5 $CH_3CH_2(CH{=}CHCH_2)_5 - CH_2CH_2COOH$

22:5 $CH_3CH_2(CH{=}CHCH_2)_5 - CH_2CH_2CH_2CH_2COOH$

22:6 $CH_3CH_2(CH{=}CHCH_2)_5 - CH{=}CHCH_2CH_2CO^3OH$

In view of the evidence presented by others (10) the ω3 structure is assumed for these three acids. Since their terminal 17 carbon chains are identical, any differences in behavior must be assumed to be caused by differences in their structure at the carboxyl end of the chain. The responsible factor could be the proximity of the double bond to the carboxyl group, since the first double bond of the resistant 20:5 and 22:6 acids lies closer to the carboxyl group than does that of the nonresistant 22:5 acid. This view is strengthened by the demonstration by Kleiman et al. (11) that the *trans*-3-enoic acids of *Grindelia oxylepis* seed oil are also resistant to lipase hydrolysis. The presence of methyl groups in a position close to the carboxyl end has also been shown to hinder hydrolysis by the lipase (12).

Another difference in structure between the resistant and the susceptible polyunsaturated acids lies in the space relations of their terminal methyl to their carboxyl groups. As shown in the photographs of the molecular models (Figure 1) the terminal methyl groups of the resistant acids lie close to their carboxyl groups. This proximity may cause a steric hindrance effect on the hydrolysis by the lipase.

Metabolic Implications

The resistance of some of the polyunsaturated fatty acids of whale oil to pancreatic lipase hydrolysis provides an explanation for the finding by Garton et al. (13) that whale

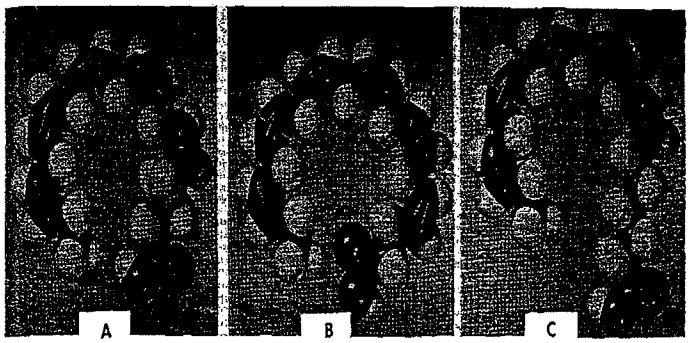

FIG. 1. Molecular models of the 20:5 (A), 22:6 (B), and 22:5 (C) acids of marine oils.

oil can be crystallized almost unchanged from the depot tissues of pigs fed high doses of the oil for a prolonged period of time. In preliminary experiments in this laboratory, however, neither the triglycerides, nor the phospholipids of thoracic duct lymph of rats administered by stomach tube one dose of the highly unsaturated concentrate of whale oil, contained the marine long-chain polyunsaturated acids. The presence of whale glycerides in the tissues of Garton's pigs may have been the product of a low degree of intestinal absorption over a long period of ingestion.

ACKNOWLEDGMENT

Supported in part by a grant from the National Institute of Health (AM-06011).

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[Received June 12, 1967]

Appendix L

Hernell et al., "Does the Bile Salt-Stimulated Lipase of Human Milk Have a Role in the Use of the Milk Long-Chain Polyunsaturated Fatty Acids?" J Pediatr Gastroenterol Nutr 16: 426-31(1993)

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