Phenytoin–Lipid Conjugates: Chemical, Plasma Esterase-Mediated, and Pancreatic Lipase-Mediated Hydrolysis *in Vitro*

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Phenytoin–lipid conjugates obtained by covalent binding of hydroxymethylphenytoin to diacylglycerides and to 3-acyloxy-2-acyloxymethylpropionic acids formed dispersions with a particle size of 10–200 μm when briefly sonicated in a sodium taurodeoxycholate-containing ethanol–water mixture. In contrast to the corresponding *bis*-deacyl derivatives, the lipids were not significantly hydrolyzed in aqueous buffers and in plasma. Incubation with pancreatic lipase yielded primarily the *bis*-deacyl compounds, which are comparable to monoglycerides, and subsequently liberated phenytoin. The glyceride-derived prodrugs were better substrates for the enzyme than the 3-acyloxy-2-acyloxymethyl-propionic acid derivatives. It is concluded that the phenytoin lipid conjugates are hydrolyzed by pancreatic lipase in a similar manner as natural triglycerides.

KEY WORDS: phenytoin; prodrugs; prodrug hydrolysis; pancreatic lipase; lipolysis.

INTRODUCTION

Prodrug formation can improve the physicochemical properties of a variety of drugs (1). Phenytoin (1), a low water-soluble, low lipid-soluble drug, has shown erratic bioavailability when administered orally (2,3). Superior availability was obtained by ester prodrugs of 3-hydroxymethylphenytoin (2) (4,5) or by coadministration of lipids (6).

Mixed triglycerides formed by coupling of drugs to diglycerides exhibited physicochemical properties (7,8) and absorption characteristics (9,10) similar to those of natural triglycerides, resulting in a different pharmacokinetic and/or pharmacodynamic profile compared to that of the parent drug. Compounds which lack carboxyl groups, allowing direct formation of an ester bond with a diglyceride, can be bound to the glycerides via spacers such as succinic acid (7).

Two classes of phenytoin–lipid conjugates have recently been synthesized as potential prodrugs of phenytoin in an attempt to improve the oral bioavailability of the drug (11). The first group of compounds included triglycerides with 3-hydroxymethylphenytoin bound to position 2 (Fig. 1, **5a–f**) or position 1 (Fig. 1, 7) of a glyceride via succinic acid. In the second series of compounds the glycerol moiety has been replaced by 3-hydroxy-2-hydroxymethylpropionic acid, which allows the direct formation of an ester bond with the alcoholic function of drugs without incorporating a spacer (Fig. 1, **9a–f**). Hydroxymethylphenytoin is itself a prodrug which decomposes spontaneously in aqueous media at physiological pH to give phenytoin and formaldehyde (4,12).

Because of the structural similarity to triglycerides, drug–lipid conjugates are likely to be good substrates for pancreatic lipase upon oral administration. Thus, the present *in vitro* study was conducted in order to estimate the chemical, plasma esterase-catalyzed, and lipase-mediated hydrolysis of phenytoin–lipid conjugates prior to *in vivo* experiments. The deacyl derivatives **4**, **6**, and **8** and the monosuccinate **3** were expected to be intermediates of the hydrolysis of the lipid conjugates and have, therefore, been included in the study.

MATERIALS AND METHODS

Chemicals

The chemicals were obtained from the following sources: phenytoin (1) from Caelo (Hilden, FRG); sodium taurodeoxycholate and porcine pancreatic lipase (type II, crude preparation containing colipase), from Sigma Chemical Co. (Deisenhofen, FRG). 3-Hydroxymethylphenytoin (2) and 3-hydroxymethylphenytoin monosuccinate (3) were prepared according to Varia *et al.* (4). Phenytoin-2-monoglyceride (4), phenytoin-2-triglycerides (**5a–f**), phenytoin-1-monoglyceride (6), phenytoin-1-triglyceride (7), phenytoin dihydroxypropionic acid ester (8), and phenytoin diacyloxypropionic acid esters (**9a–f**) were synthesized as described (11). The compounds were characterized by their spectral data and are at least 98% pure. All other chemicals were obtained from commercial sources at the highest purity available. Buffer solutions were prepared in double-distilled, deionized water.

Analytical Methods

The HPLC system consisted of a Shimadzu LC 6A solvent delivery module, a Shimadzu SPD 6A UV detector operated at 254 nm, and a Shimadzu C-R6A integrator (Shimadzu AG, Duisburg, FRG). The chromatographic separation was obtained on a LiChrospher 100 RP-18 column (125 × 4.6 mm, 5 μm) (Merck, Darmstadt, FRG) equipped with a guard column (25 × 4.6 mm, 5 μm) filled with the same adsorbent. For the analysis of the deacyl derivatives, the mobile phase consisted of 0.05 *M* phosphate buffer, pH 5.8, containing 25% acetonitrile (v/v). The lipid conjugates were chromatographed using acetonitrile/water (95:5, v/v). The flow rate was always 1.5 mL/min. Phenytoin and prodrug concentrations were calculated from calibration curves obtained by analysis of the pure compounds under identical chromatographic conditions.

Solubilities

The solubilities of the esters were determined by vigorously stirring a saturated solution of the compounds in water or *n*-hexane at 25 ± 0.2°C for 48 hr. Following centrifugation at 2500*g* for 10 min, aliquots of the clear supernatant were analyzed by HPLC.

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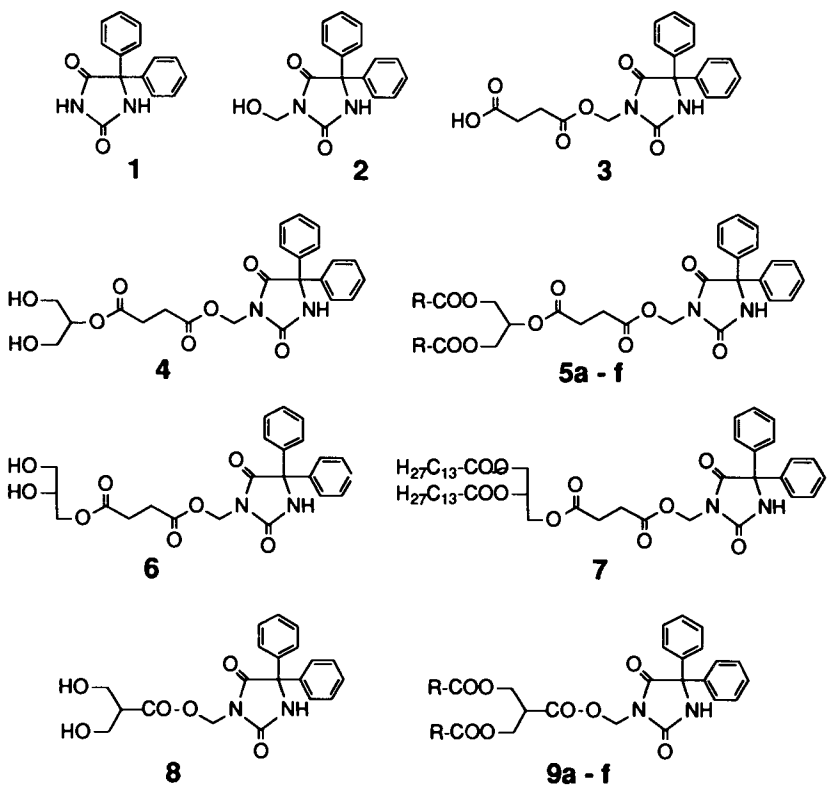

	R	fatty acid	mp 5a - f	mp 9a - f
a	C_7H_{15}	caprylic acid	oil	29 - 31°C
b	$C_{10}H_{21}$	undecanoic acid	34 - 36°C	oil
c	$C_{11}H_{23}$	lauric acid	46 - 48°C	34 - 37°C
d	$C_{13}H_{27}$	myristic acid	52 - 54°C	38 - 41°C
e	$C_{17}H_{35}$	stearic acid	44 - 45°C	37 - 40°C
f	$C_{17}H_{33}$	oleic acid	oil	oil

Fig. 1. Structures of the compounds.

Kinetics

Chemical hydrolysis was studied at 37 ± 0.2°C in 0.05 *M* glycine/HCl, sodium citrate/HCl, phosphate, borate, and glycine/NaOH buffers adjusted to an ionic strength of μ = 0.5 by the addition of the calculated amount of potassium chloride, in heparinized human and rat plasma, and in the presence of porcine pancreatic lipase. The incubations with lipase were performed with an activity of 375 or 37.5 U/mL of lipase (assayed by Sigma using triacetin as substrate, pH 7.4) in 0.1 *M* Pipes (pH 6.5) or Tris buffers (pH 7.4 and 8.5) containing 25 m*M* calcium chloride. Stock solutions of the compounds in water/acetonitrile (70:30, v/v) or dispersions of the lipids were added to the prewarmed incubation mixtures to give a final concentration of 1 m*M*. The dispersions were prepared as follows: 1 part of a solution of the lipids in ethanol was added to 4 parts of a 25 m*M* solution of sodium taurodeoxycholate in water and sonicated briefly. The reaction mixtures were vigorously stirred during the kinetic run. Aliquots (100 μL) were withdrawn at selected time intervals, diluted with water/acetonitrile (70:30, v/v) and analyzed by HPLC. Plasma and lipase samples were quenched by addition to 50 μL ice-cold 0.5 *M* perchloric acid followed by dilution with 850 μL water/acetonitrile (70:30, v/v) and centrifugation at 2500*g* for 10 min. Aliquots of the clear supernatant were assayed by HPLC. The recoveries of compounds **1**, **3**, **4**, **6**, and **8** from the incubations with lipase or plasma were at least 96%.

RESULTS AND DISCUSSION

The phenytoin–lipid conjugates were obtained as low-melting point waxes or oils (Fig. 1). The solubilities of selected compounds in water and *n*-hexane have been summarized in Table I. The lipids proved to be insoluble in water, while the deacyl derivatives **4**, **6**, and **8** exhibited increased aqueous solubility compared to phenytoin. The solubility of the myristic acid esters in *n*-hexane increased in the order **5d** < **7** < **9d**.

Brief sonication of the conjugates in ethanol–water mixtures containing taurodeoxycholate as one of the natural emulsifiers of lipid digestion gave "milky" dispersions. Oily, emulsion-like droplets with a particle size of 10–200 μm were observed by microscopy. However, the preparations were unstable. Considerable coalescence of the droplets was observed after about 30 min. The exact nature of these preparations was not further investigated.

No degradation of the lipid conjugates could be detected

Table I. Aqueous and *n*-Hexane Solubilities of Esters of 3-Hydroxymethylphenytoin at 25°C

Ester	mp (°C)	Phenytoin equivalent	Solubility (mg/mL)	
			Water	*n*-Hexane
Phenytoin (1)	295	1	0.03[b]	0.005
4	—[a]	0.55	2.26	0.045
6	—[a]	0.55	2.16	0.047
8	116–117	0.66	2.38	0.064
5d	52–54	0.29	—[c]	8.3
7	35–37	0.29	—[c]	54.8
9d	38–41	0.31	—[c]	295

[a] Compounds 4 and 6 were obtained as hygroscopic foams that could not be crystallized.
[b] Literature values vary from 0.01 to 0.04 mg/mL (4,12,13).
[c] Undetectable concentrations.

in the incubations of the prodrugs in aqueous buffers after 48 hr at 37°C either as taurodeoxycholate preparations or as suspensions. This can be attributed to the insolubility of the lipids in aqueous media. The deacyl derivatives 4, 6, and 8 and the monosuccinate 3 were expected intermediates of the degradation of the lipid conjugates. Therefore, the hydrolysis in aqueous buffers was studied. The pH–rate profiles are shown in Fig. 2. The compounds displayed pseudo-first-order kinetics at pH 1.2 and between pH 7 and pH 10 or were assumed pseudo-first-order kinetics between pH 2 and pH 6 where less than 10% were found to be hydrolyzed after the maximum incubation period of 120 hr at 37°C. Except for the monosuccinate 3 the slopes of linear regressions of the pH–rate profiles above pH 6 to 7 were between 0.93 and 0.98, indicating hydroxide ion catalysis. This is typical for the hydrolysis of esters in general (14).

At pH 1.2 considerable acyl migration of the succinate residue from position 2 of the glycerol (2-monoglyceride 4) to position 1 (1-monoglyceride 6) was observed. This isomerization is known to occur easily under strongly acidic and alkaline conditions, resulting in an equilibrium of approximately 90% of 1-monoglyceride and 10% of 2-monoglyceride (15). The rate of the isomerization is dependent on the nature of the acyl functionality. In the present study, the monoglycerides 4 and 6 could not be separated completely by HPLC. Therefore, the kinetics of the isomerization could not be quantified but appeared to be complete within 48 hr.

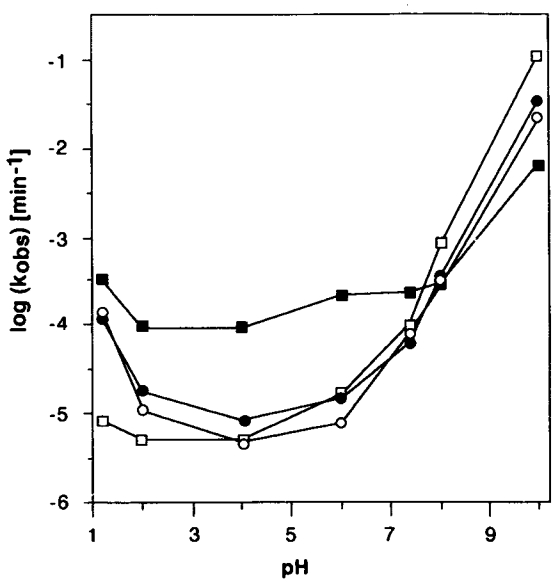

Fig. 2. The pH–rate profiles for the hydrolysis of ester 3 (■), ester 4 (○), ester 6 (●), and ester 8 (□) in 0.05 *M* aqueous buffers, μ = 0.5, at 37°C.

In rat and human plasma only slow degradation was observed upon incubations of the lipids as suspensions or taurodeoxycholate preparations. For example, less than 4% of phenytoin was released from lipid conjugates 5d or 9d after an incubation period of 6 hr at 37°C in rat plasma. These results can be attributed to the extremely low water solubility of the lipids and/or to the fact that triglycerides are poor substrates for plasma esterases *in vivo* but are hydrolyzed by lipoprotein lipase and related enzymes in the endothelium (16). In contrast, rat plasma esterases quickly liberated phenytoin from compounds 3, 4, 6, and 8 (Table II). In human plasma the phenytoin esters were cleaved at a lower rate but in the same order. The monoglycerides 4 and 6 were the best substrates for the enzymes of the compounds tested, both yielding predominantly phenytoin. No significant difference in their rates of hydrolysis was observed. Phenytoin monosuccinate (3) exhibited only a poor rate of hydrolysis. It has generally been observed that monosuccinate esters are poor substrates for a variety of esterases (17–20).

Upon incubation of the lipid conjugates 5a–f, 7, and 9a–f with pancreatic lipase, the compounds 4, 3, and 8, respectively, were primarily formed and subsequently liberated phenytoin. Although the pH optimum of lipase is about 8, the incubations were performed at pH 6.5, the approximate pH of the upper small intestine. Figure 3 illustrates the hydrolysis of the myristoyl derivatives 5d, 7, and 9d, respectively. Only low levels (5–9%) of the succinic acid ester 3 were observed in incubations of 5a–f (Figs. 3A and B). However, when phenytoin was attached to position 1 of the triglyceride 7, the succinic acid ester 3 was the primary product of the lipase-mediated hydrolysis (Fig. 3C). The monoglyceride 6 could not be detected in these incubations. The rate of hydrolysis was dependent on the enzyme activity (Figs. 3A and B) and increased with the pH of the incubation medium (data not shown). The degradation rates decreased in the order 5a–f > 7 > 9a–f. In agreement with the fact that the specificity of lipase is known to be independent of the nature of the fatty acids (16), no significant difference of the rate of hydrolysis depending on the chain length of the fatty acids was observed under the incubation conditions applied. Minor differences found for the 3-hydroxy-2-hydroxymethylpropionic acid ester prodrugs 9a–f can be explained by a varying particle size of the bile acid–lipid preparations. The activity of lipase is known to depend on the interfacial area of lipid droplets (16). On the other hand, differences in the lipase-catalyzed rate of hydrolysis of esters have been observed (21,22).

Pancreatic lipase also catalyzed the hydrolysis of phenytoin from the *bis*-deacyl compounds 4, 6, and 8 as well as the succinic acid ester 3 (Table III). The monoglyceride 4 was the best substrate for the enzyme. In contrast to the other esters, the apparent rate constant of the lipase-mediated hydrolysis of the monosuccinate 3 decreased with increasing pH of the incubation mixtures.

Table II. Apparent Pseudo-First-Order Rate Constants, k, and Half-Lives, $t_{1/2}$, of the Hydrolysis of the Esters 3, 4, 6, and 8 in Rat and Human Plasma

	Human plasma		Rat plasma		20% rat plasma[a]	
Ester[b]	$k \times 10^2$	$t_{1/2}$ (min)	$k \times 10^2$	$t_{1/2}$ (min)	$k \times 10^2$	$t_{1/2}$ (min)
3	0.19 ± 0.01	371 ± 2	6.96 ± 0.52	9.99 ± 0.76	—	—
4	2.58 ± 0.03	26.9 ± 0.3	>1100	<4 sec	155.1 ± 9.5	0.45 ± 0.07
6	—	—	—	—	168.2 ± 5.8	0.41 ± 0.11
8	0.62 ± 0.02	111.5 ± 3.3	146.8 ± 1.1	0.47 ± 0.02	—	—

[a] Plasma diluted with phosphate-buffered saline.
[b] Concentration of the esters, 1 m*M*; 37°C; n = 3 ± SD.

Pancreatic lipase cleaves with a high positional specificity the ester bonds in positions 1 and 3 of triglycerides. This was also observed for the glyceride prodrugs **5a–f** and 7 as well as the "glyceride mimics" **9a–f**. The taurodeoxycholate–lipid conjugate preparations appeared to provide a suitable interface for the binding of the lipase–colipase complex and subsequent hydrolysis of the fatty acid esters by the enzyme. Thus, the 2-monoglyceride **4** and the dihydroxy ester **8** were the primary products of the lipolysis of **5a–f** and **9a–f**, respectively, whereas the monosuccinate **3** was detected primarily in the incubations of glyceride 7. The low levels of monosuccinate **3** observed in the incubations of the triglycerides **5a–f** might be attributed to the hydrolysis of the succinic acid ester bond in position 1 of a glyceride following intramolecular acyl migration rather than direct cleavage of the ester bond in position 2. This intramolecular acyl migration is known to occur also *in vivo* during fat digestion (16). The differences between the rates of hydrolysis of the three series of prodrugs suggest that lipase is able to discriminate between the substrates depending on their structures and physicochemical properties, an observation reported also for simple esters of phenytoin (21). However, as the exact nature of the bile acid–lipid preparations was not determined, it cannot be totally ruled out that the release rates might also reflect different physical states of the lipids in the dispersions.

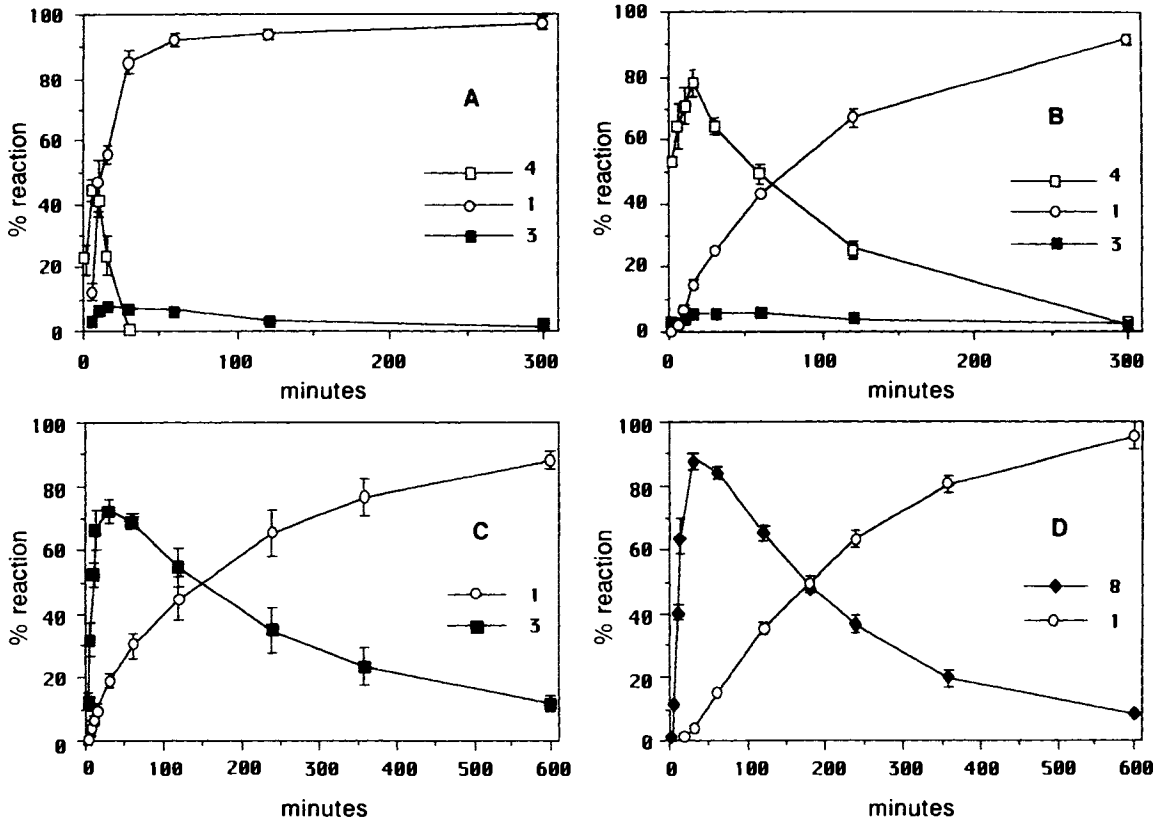

Fig. 3. Representative time courses of the lipase-catalyzed hydrolysis of the phenytoin–lipids. Phenytoin-2-triglyceride **5d** (A,B), phenytoin-1-triglyceride 7 (C), and 3-acyloxy-2-acyloxymethylpropionate **9d** (D) were incubated at 37°C in the presence of 375 U/mL (A, C, D) or 37.5 U/mL (B) porcine pancreatic lipase in 0.1 *M* Pipes buffer, pH 6.5, as described under Materials and Methods. The appearance of phenytoin 1 (○), monosuccinate 3 (■), ester 4 (□), and ester 8 (◆) was monitored. The values are expressed as mean ± SD (n = 3).

Table III. Apparent Pseudo-First-Order Rate Constants, k, and Half-Lives, $t_{1/2}$, of the Pancreatic Lipase-Catalyzed Hydrolysis of Esters 3, 4, 6, and 8

		Ester 3[a]		Ester 4[a]		Ester 6[a]		Ester 8[a]	
pH[b]	n	$k \times 10^3$	$t_{1/2}$ (min)	$k \times 10^3$	$t_{1/2}$ (min)	$k \times 10^3$	$t_{1/2}$ (min)	$k \times 10^3$	$t_{1/2}$ (min)
6.5	2	0.54	1.3×10^3	0.016	4.3×10^4	0.017	4.1×10^4	0.03	2.3×10^4
6.5, lipase[c]	3	4.67 ± 0.2	148 ± 6	104 ± 3	6.7 ± 0.2	27.2 ± 1.3	25.4 ± 1.4	3.9 ± 0.3	179 ± 15
7.4	2	0.51	1.4×10^3	0.37	1.9 ± 10^3	—	—	0.50	1.4×10^3
7.4, lipase[c]	3	1.81 ± 0.11	381 ± 22	202 ± 7	3.4 ± 0.2	—	—	6.0 ± 0.2	116 ± 5
8.5	3	1.52 ± 0.06	458 ± 20	2.08 ± 0.08	333 ± 13	—	—	3.4 ± 0.1	202 ± 5
8.5, lipase[c]	3	1.62 ± 0.10	427 ± 17	203 ± 14	3.4 ± 0.2	—	—	7.6 ± 1.0	91 ± 2

[a] Concentration of the esters, 1 m*M*; $n \pm$ SD.
[b] 0.1 *M* Pipes (pH 6.5) or 0.1 *M* Tris buffers (pH 7.4 and 8.5) containing 25 m*M* Ca^{2+} and 2.5 m*M* sodium taurodeoxycholate, 37°C.
[c] Porcine pancreatic lipase, 375 U/mL buffer.

Further hydrolysis of the esters 3, 4, and 8 eventually yielded phenytoin (Fig. 3 and Table II). Although lipase has been shown to hydrolyze esters nonspecifically including esters of phenytoin (21), this cleavage was unexpected because pancreatic lipase acts primarily at the oil/water interface of emulsions, and not on compounds dissolved in aqueous media. However, the lipase–colipase complex is also active toward esters in bile acid micellar solution (21,23) and even suspended solid prodrugs (21,22). On the other hand, only a crude preparation of pancreatic lipase was used in the present study. Thus, it cannot be excluded that the enzyme is contaminated with nonspecific esterases which hydrolyzed the phenytoin esters.

The rate of hydrolysis of the fatty acid ester bond always exceeded the rate of the cleavage of the hydroxymethylphenytoin ester bond. This preferential hydrolysis results, besides the positional specificity of lipase, from a higher affinity and/or V_{max} for the fatty acid esters as substrate for the enzyme. Thus, the lipase-catalyzed *in vitro* hydrolysis of the phenytoin–lipid conjugates appears to occur as depicted in Fig. 4.

In conclusion, the results obtained show that the phenytoin-triglyceride conjugates as well as the "inverse" lipids derived from 3-hydroxy-2-hydroxymethylpropionic acid are degraded by pancreatic lipase *in vitro* similar to natural triglycerides. If triglyceride prodrugs bearing spacers such as succinic acid are designed for oral administration, it appears desirable to attach the drug to position 2 of the glyceride. Otherwise, lipolysis of the succinyl moiety in position 1 will yield a monosuccinic acid ester which is a known poor substrate for hydrolytic enzymes. The pharmacokinetics and the pharmacological activity of the phenytoin–lipid conjugates are currently being investigated.

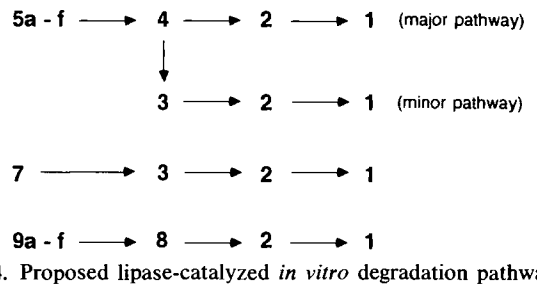

Fig. 4. Proposed lipase-catalyzed *in vitro* degradation pathway of the phenytoin–lipid esters.

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