Effects of Chain Length and Tellurium Position on the Myocardial Uptake of Te-123m Fatty Acids

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A series of Te-123m-labeled fatty acids has been synthesized and studied in rats. In the series of compounds studied, the position of the Te-123m heteroatom was not as important as the total chain length, which dramatically affected the heart uptake. Five minutes after injection, significant heart uptake (1.7–2.3% of injected dose) was observed for agents with C_{15}, C_{17}, and C_{21} chain lengths, in which Te-123m replaced a methylene group in either the 6, 9, 11, or 17 positions, and the heart-to-blood ratios were high. An important observation was the prolonged retention of radioactivity for at least one hour after injection. In contrast, agents with shorter C_{13} chain lengths, with Te-123m in either the 6 or the 9 position, exhibited only low heart uptake (0.1–0.3% of injected dose).

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Since the beta oxidation of long-chain fatty acids supplies the major energy requirements for the normal myocardium, fatty acids radiolabeled with gamma-emitting nuclides are attractive agents for the concentration of sufficient levels of radioactivity for myocardial imaging (*1*). Although myocardial fatty-acid metabolism can be monitored noninvasively with carboxyl[C-11]-labeled palmitic acid (*2–4*), the 20-min physical half-life and relatively rapid washout limit the usefulness of this agent to only a small patient population near centers equipped with a cyclotron and positron-emission tomographic equipment.

Various ω-halogenated long-chain fatty acids radiolabeled with I-131 (*5*), F-18 (*6*), I-123 (*7–10*), Br-77 (*10*), and Cl-34m (*10*) show pronounced heart uptake. Iodine-123-labeled 17-iodoheptadecanoic acid has proven to be a clinically useful agent for the diagnosis of infarcted and ischemic tissue (*11*) but it shows significant in vivo deiodination. More recently, the pronounced heart uptake of terminal p-(bromo[Br-82]-phenyl)-substituted pentadecanoic acid has been reported and this agent shows little debromination (*12*). In contrast, α-halogenated long-chain fatty acids do not show significant heart uptake (*10*). In addition, Tc-99m-labeled thiol fatty acids (*13*), and fatty acids substituted with bulky chelating groups such as the ethylenediaminetetra-acetic acid moiety (*14*), do not show heart uptake.

Although these studies have demonstrated that drastic structural modifications significantly decrease or eliminate heart uptake, it has not been established what other structural features can be tolerated without destroying the cardiac specificity of long-chain fatty acids. Since the divalent tellurium heteroatom can be inserted chemically within the linear fatty-acid chain, this structural alteration was envisioned as a means of inhibiting catabolism of the fatty-acid analog. This could potentially be a means of "trapping" the Te-123m-labeled agent in the myocardium. We have demonstrated in rats the pronounced and prolonged heart uptake of Te-123m-labeled 9-telluraheptadecanoic acid (*15*), and more recently this agent has undergone extensive evaluation in normal and infarcted dogs (*16*). The goal of the present study was to determine the structural features required for heart uptake of Te-123m-labeled fatty acids by preparing and testing a series of compounds with variations of both the total chain length and the position of the tellurium heteroatom.

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TELLURIUM FATTY ACID	STRUCTURE	NOTATION
9-Telluraheptadecanoic Acid (Ib)	H_3C-$(CH_2)_7$-Te-$(CH_2)_7$-COOH	C_{17}-9-Te
11-Telluraheptadecanoic Acid (IIb)	H_3C-$(CH_2)_5$-Te-$(CH_2)_9$-COOH	C_{17}-11-Te
6-Telluraheptadecanoic Acid (IIIb)	H_3C-$(CH_2)_{10}$-Te-$(CH_2)_4$-COOH	C_{17}-6-Te
9-Tellurapentadecanoic Acid (IVb)	H_3C-$(CH_2)_5$-Te-$(CH_2)_7$-COOH	C_{15}-9-Te
6-Telluratridecanoic Acid (Vb)	H_3C-$(CH_2)_6$-Te-$(CH_2)_4$-COOH	C_{13}-6-Te
9-Telluratridecanoic Acid (VIb)	H_3C-$(CH_3)_3$-Te-$(CH_2)_7$-COOH	C_{13}-9-Te
17-Tellura-9-Heneicosenic Acid (VIIb)	H_3C-$(CH_3)_3$-Te-$(CH_2)_6$-CH=CH-$(CH_2)_7$-COOH	C_{21}-Δ^9-17-Te

FIG. 1. Structures of tellurium fatty acids.

EXPERIMENTAL

General. The Te-123m was produced in the Oak Ridge High Flux Isotope Reactor as previously described (*17*). The ω-bromo acids* were converted to the methyl esters by treatment with CH_2N_2. All other solvents and chemicals were analytical grade and were used without further purification. A gamma camera equipped with a medium-energy collimator was used for the dog's image. The Te-123m-**Ib** (Fig. 1) was complexed with a 6% bovine serum albumin solution (4 ml) and 400 μCi was injected into a cephalic vein.

Nomenclature. In accordance with the substitutive nomenclature adopted by the IUPAC (*18*) the tellurium fatty acids are named as analogs of the corresponding alkanoic acids in which the tellurium heteroatom (Te) has replaced a methylene group (-CH_2-) in the alkyl chain. The tellurium analog of heptadecanoic acid in which Te replaces the methylene group in the C_9 position (Fig. 1) is thus named 9-telluraheptadecanoic acid (**Ib**). In the shorthand notation for 9-telluraheptadecanoic acid (C_{17}-9-Te), the subscript denotes the total chain length of the carbon analog in which Te replaces the C_9 methylene group.

Synthesis of tellurium fatty acids. Several structurally modified tellurium fatty acids (Fig. 1) were prepared by the series of reactions outlined in the legend for Table 1. The unlabeled tellurium fatty-acid methyl esters (**Ia–VIIa**) and free acids (**Ib–VIIb**) exhibited chromatograhic, infrared, ultraviolet, low- and high-resolution mass spectral, and ^1H and ^{13}C nuclear magnetic resonance properties that were consistent with the proposed structures. The physical and chemical properties of these compounds will be described in detail in a subsequent report.

Synthesis of Te-123m-labeled compounds. The details for the preparation of the methyl esters of Te-123m-labeled fatty acids (**Ia–VIIa**) are summarized in Table 1. Syntheses were conducted on the one-millimolar scale for convenience and the general details are outlined below.

Sodium ditelluride (*Step 1*). The Te-123m was combined with carrier tellurium powder (45-micron) to give 127 mg (1 millimol), which was reacted with an equimolar amount of sodium metal (23 mg) in either liquid ammonia (20 ml) (*15,17*) or ethylenediamine (10 ml).

Dialkyl ditellurides (*Step 2*). These were prepared by alkylation of the Na_2Te_2 with the appropriate alkyl bromide or alkyl iodide. The NH_3 was evaporated and the orange-colored residue dissolved in C_6H_6, which was then filtered through a short silicic acid column. In the ethylenediamine system the reaction mixture was poured

TABLE 1. SUMMARY OF SYNTHETIC DETAILS AND RADIOCHEMICAL YIELDS FOR SYNTHESIS OF Te-123m-LABELED FATTY ACID METHYL ESTERS PREPARED BY THE FOLLOWING ROUTE:

$$Te \xrightarrow{\text{Step 1}} Na_2Te_2 + R\text{-}X \xrightarrow{\text{Step 2}} R_2Te_2 \xrightarrow[NaBH_4]{\text{Step 3}}$$

$$R\text{-}Te\text{-}Na + Br\text{-}R'\text{-}COOMe \xrightarrow{\text{Step 4}} R\text{-}Te\text{-}R'\text{-}COOMe \xrightarrow[NaOH]{\text{Step 5}} R\text{-}Te\text{-}R'\text{-}COOH$$

Tellurium fatty acid methyl ester	Alkyl halide R-X (Step 2)	ω-Bromo acid methyl ester substrate (Step 4)	% Radiochemical yield*	Specific activity (mCi/mmol)
Ia	n-Octyl Iodide	Methyl-8-bromooctanoate	68	31.3
IIa	n-Hexyl Iodide	Methyl-10-bromodecanoate	19	16.2
IIIa	n-Undecyl Bromide	Methyl-5-bromocaproate	51	9.7
IVa	n-Hexyl Iodide	Methyl-8-bromooctanoate	22	18.8
Va	n-Heptyl Iodide	Methyl-5-bromocaproate	36	30.9
VIa	n-Butyl Iodide	Methyl-8-bromooctanoate	45	10.4
VIIa	n-Butyl Iodide	Methyl-16-bromo-9-hexadecenoate†	10	20.2

* The radiochemical yields are based on the methyl bromo acid substrate (Step 4).

† The methyl-16-bromo-9-hexadecenoate substrate was a mixture of the olefinic cis and trans isomers.

into H_2O, extracted with ether, washed with H_2O, and evaporated to give the orange-colored ditelluride.

Sodium alkyl tellurols (Step 3). The ditelluride solutions were reduced with excess $NaBH_4$ under argon in a 30-ml mixture (1:1) of MeOH-C_6H_6 to give colorless solutions of the sodium alkyl tellurols (Na-Te-R).

Tellurium fatty acid methyl esters—the coupling reaction (Step 4). The ω-bromo fatty acid methyl ester substrates (Table 1) were added in MeOH to the Na-Te-R solutions and refluxed 30 min (Step 4). The reaction mixtures were cooled, poured into H_2O and the organic layers washed three times with H_2O. After drying over anhydrous Na_2SO_4 and concentration to a small volume, the benzene solutions were loaded onto silicic acid (acidic grade, 60–100 mesh)† columns (1 × 20 cm) packed in petroleum ether. Fractions (30 ml) were collected by elution with petroleum ether (Fractions 1–10) and 5% diethyl ether in petroleum ether (Fractions 11–25). The excess ditellurides were initially eluted (Fractions 2–5) and the tellurium fatty acid methyl ester products were eluted as homogeneous peaks in Fractions 13–20.

Tellurium fatty acids—basic hydrolysis reaction (Step 5). The methyl esters (**Ia–VIIa**) were converted to the free acids (**Ib–VIIb**) by refluxing in 20 ml of ethanol under argon for 30 min with 2 ml of 1 *N* NaOH. The hydrolysis mixtures were cooled, poured in H_2O, and the pH adjusted to 2–3 with 1 *N* HCl. The cloudy mixtures were then extracted twice with ethyl ether and the combined extracts washed three times with H_2O, dried with anhydrous Na_2SO_4, and the solvent evaporated under argon to give the free acids as light-yellow solids.

Chromatographic analysis. Radiochemical homogeneity was established by thin-layer radiochromatographic analyses on silica gel PF-254 plates.‡ The Te-123m methyl esters (**Ia–VIIa**) each showed a single radioactive spot that cochromatographed with the unlabeled standards in two solvent systems: C_6H_6 (R_f 0.60) and petroleum ether/ether/acetic acid, 70:30:1 (R_f 0.80). The Te-123m-labeled acids (**Ib–VIIb**) were analyzed in the latter solvent system (R_f 0.40) and MeOH:$CHCl_3$, 8:92 (R_f 0.50), and each showed a major radioactive component that chromatographed with the unlabeled standard. Unlabeled carrier material was added to minimize streaking that resulted from atmospheric oxidation.

Tissue distribution studies. The Te-123m-labeled fatty acids were evaluated in 160–180 g female Fischer 344

TABLE 2. DISTRIBUTION OF RADIOACTIVITY IN FEMALE RAT TISSUES AT 5, 30, AND 60 MIN AFTER I.V. ADMINISTRATION OF Te-123m-LABELED FATTY ACIDS

Fatty acid,	minutes after injection	% dose/g, range				
		Tissue				
		Heart	Blood	Liver	Lungs	Kidneys
Ib	5	2.47 (2.31–2.90)	0.49 (0.45–0.57)	13.27 (12.70–13.93)	1.06 (1.01–1.24)	1.65 (1.50–1.86)
	30	3.27 (2.29–4.06)	0.52 (0.47–0.65)	12.12 (11.47–13.12)	1.05 (0.95–1.12)	1.85 (1.61–2.06)
	60	5.50 (4.44–6.19)	0.62 (0.060–0.65)	8.55 (7.70–9.83)	0.90 (0.82–0.94)	2.01 (1.85–2.12)
IIb	5	3.79 (3.67–3.89)	0.13 (0.11–0.14)	11.23 (7.99–13.10)	0.78 (0.72–0.85)	1.22 (1.18–1.27)
	30	3.74 (3.45–4.28)	0.39 (0.31–0.45)	9.17 (7.76–10.07)	0.95 (0.94–0.96)	1.53 (1.36–1.70)
	60	2.73 (2.56–2.97)	0.65 (0.55–0.73)	9.51 (7.76–10.49)	1.04 (0.93–1.19)	1.44 (1.40–1.50)
IIIb	5	3.41 (1.06–6.12)	0.19 (0.14–0.26)	5.20 (4.93–5.60)	0.97 (0.88–1.13)	1.42 (1.35–1.53)
	30	2.82 (1.30–4.57)	0.32 (0.23–0.41)	5.57 (5.44–5.82)	0.98 (0.96–0.98)	1.58 (1.47–1.65)
	60	4.08	0.43	4.52	1.47	1.44
IVb	5	4.39 (2.41–6.11)	0.48 (0.45–0.52)	9.55 (7.99–11.02)	1.31 (1.02–1.66)	1.96 (1.80–2.15)
	30	2.97 (2.09–4.63)	0.63 (0.52–0.67)	7.91 (7.11–8.24)	0.92 (0.77–1.23)	1.60 (1.40–1.80)
	60	3.34 (2.68–4.22)	0.75 (0.69–0.78)	5.41 (4.37–6.09)	1.04 (0.97–1.13)	1.95 (1.67–2.23)
Vb	15	1.00 (0.61–1.60)	0.66 (0.51–0.78)	4.15 (3.77–4.62)	0.68 (0.68–0.69)	2.95 (2.60–3.23)
	30	1.20 (0.84–1.78)	1.24 (1.05–1.45)	3.44 (3.33–3.64)	0.87 (0.74–1.00)	2.73 (2.40–3.09)
	60	1.27 (1.00–1.73)	1.60 (1.56–1.64)	2.69 (2.54–2.83)	0.97 (0.83–1.06)	2.72 (2.51–2.93)
VIb	5	1.57 (1.14–1.89)	0.29 (0.24–0.36)	12.49 (9.83–14.10)	1.63 (1.33–2.63)	2.10 (1.90–2.30)
	30	1.02 (0.90–1.19)	1.14 (1.07–1.23)	5.27 (5.11–5.53)	3.56 (3.06–3.91)	1.26 (1.17–1.33)
	60	0.69 (0.58–0.81)	1.50 (1.38–1.62)	3.51 (3.02–4.01)	3.64 (3.28–3.99)	1.41 (1.28–1.54)
VIIb	5	2.74 (1.74–3.74)	0.24 (0.22–0.26)	5.08 (4.94–5.21)	1.27 (1.19–1.35)	0.93 (0.76–1.10)
	15	2.46 (2.01–2.75)	0.34 (0.30–0.38)	5.28 (4.89–5.58)	1.09 (0.97–1.20)	0.82 (0.76–0.87)
	120	1.84 (1.74–1.96)	1.12 (1.01–1.32)	3.59 (3.39–3.91)	1.04 (0.99–1.08)	1.10 (1.04–1.18)

* Percent dose/gram values are mean and range for three female rats. Radioactive contents of the following tissues were also analyzed: brain, large and small intestines, pancreas, and spleen.

rats that were allowed food and water *ad libitum*. The Te-123m-labeled fatty acids were freshly prepared for each experiment and dissolved in 200 μl of absolute ethanol. The ethanolic solutions were added dropwise to a stirred solution of delipidated 6% bovine serum albumin at 40°C. After filtration through 0.22-micron Millipore filters, the solutions were administered to the rats by injection into a lateral tail vein. Solutions from 0.5 to 1.0 ml in volume containing 5–10 μCi of the Te-123m-labeled fatty acid were administered. Groups of three rats were killed at each time period by decapitation under ether anesthesia. Blood was drained from the carcasses into beakers containing small volumes of sodium citrate solution. Organs were removed from the carcasses, rinsed with 0.9% saline solution, blotted dry, and counted in an autogamma counter. For excretion studies, animals were housed in metabolism cages and urine and feces collected daily.

RESULTS

The distribution of radioactivity in rat tissues following administration of Te-123m-labeled fatty acids (**Ib–VIIb**) is summarized in Table 2. Our earlier studies with rats (*15*) indicated that heart uptake of radioactivity was rapid and remained high for at least 60 min after administration of Te-123m (**Ib**). For this reason Te-123m-labeled fatty acids (**IIb–VIIb**) were studied at 5, 30, and 60 min after injection, since these time periods would allow a comparison with the parent compound **Ib**. The Te-123m-labeled telluraheptadecanoic acid isomers C_{17}-11-Te (**IIb**) and C_{17}-6-Te (**IIIb**) also showed pronounced heart uptake, suggesting that the position of the tellurium heteroatom was not a critical factor affecting heart uptake. Both 9-tellurapentadecanoic acid (C_{15}-9-Te, **IVb**) and a much longer chain fatty acid with the tellurium considerably further down the alkyl chain (C_{21}-Δ^9-17-Te, **VIIb**) also showed high heart uptake. In contrast to the long-chain acids, the shorter-chain Te-123m-labeled agents with tellurium in either the C-6 (C_{13}-6-Te, **Vb**) or C-9 (C_{13}-9-Te, **VIb**) positions showed much lower heart uptake. The absolute heart uptakes of radioactivity (% injected dose) for Te-123m fatty acids **Ib–VIIb** are compared in Fig. 2.

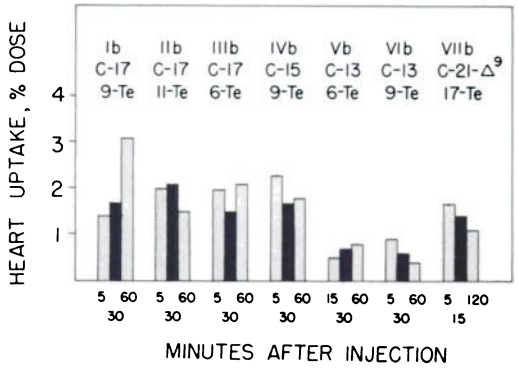

FIG. 2. Comparison of absolute heart uptake (mean percent injected dose) of radioactivity at various times after i.v. administration of Te-123m-labeled fatty acids **Ib–VIIb**. Three female rats were used for each time point. Notation for the various compounds includes position of Te heteroatom and chain length (see **Nomenclature** section for description of these abbreviations).

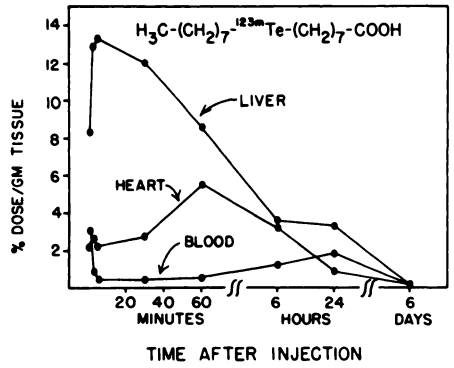

FIG. 3. Tissue distribution of radioactivity (mean percent injected dose/gram for three rats) in female rats at 2, 5, 10, 30, and 60 min, 6 and 24 hr, and 6 days following i.v. injection of 9-[^{123m}Te]telluraheptadecanoic acid (Te-123m-**Ib**).

The 9-[^{123m}Te]telluraheptadecanoic (C_{17}-9-Te, **Ib**) was chosen as a model agent for more detailed studies of tissue distribution and excretion. The distribution of radioactivity was determined in rat tissues for several time periods varying from 2 min to 6 days after injection of Te-123m-**Ib** (Fig. 3). The prolonged retention of radioactivity in the heart suggests that either the intact fatty acid or a catabolite is trapped in the myocardium. The results of excretion studies over a 20-day period (Fig. 4) indicate that significant amounts of radioactivity are excreted in both the urine and feces, and that 50% of the administered activity was not excreted until 5–6 days after injection. The left-ventricular myocardium of a dog was clearly visualized within a short period after administration of Te-123m-**Ib** (Fig. 5).

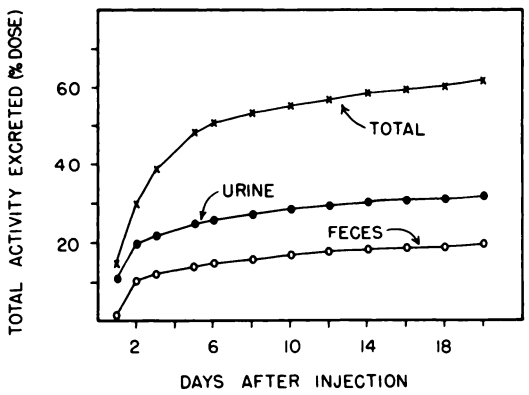

FIG. 4. Radioactive contents of urine and feces (mean cumulative dose excreted for three rats) from female rats following i.v. injection of 9-[^{123m}Te]telluraheptadecanoic acid (Te-123m-**Ib**).

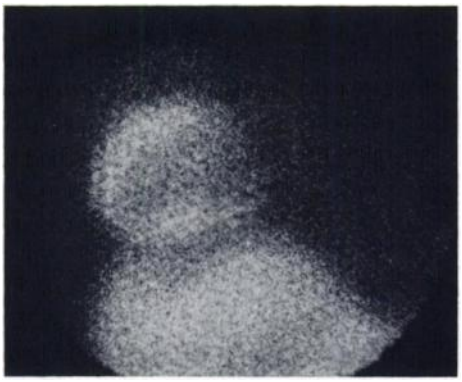

FIG. 5. Left anterior oblique gamma-camera image of 41-kg dog obtained 5–20 min after i.v. injection of 400 μCi of 9-[^{123m}Te]telluraheptadecanoic acid (Te-123m-Ib).

DISCUSSION

The results of tissue distribution studies with Te-123m-labeled fatty acids (**Ib–VIIb**) illustrate a striking relationship between heart uptake and the structure of these unique agents. The position of the Te-123m heteroatom appears to have less effect on heart uptake in comparison with the total chain length, which appears to be an important structural feature. The effects of total chain length on the heart uptake of these fatty acids are therefore consistent with the well-established structure-activity relationships described in the literature for myocardial extraction of simple alkanoic acids (*19*). Since our results demonstrate that the structural requirements (chain length) affecting the heart uptake of the Te-123m-labeled fatty acids resemble those features required for alkanoic acids, the Te-123m-labeled agents may be useful to monitor fatty-acid metabolism.

The radioactive contents of rat hearts remain high for at least 1 hr after injection of the longer-chain Te-123m fatty acids. This unexpected and important observation can be contrasted with the much more rapid washout of radioactivity from the heart observed after administration of C-11 palmitic acid (*2–4*) or radioiodinated fatty acids (*11*). The identification of structural features that would lead to an increase in the residence time of radiolabeled fatty acids in the heart could be of considerable importance, since redistribution of activity would be avoided and better counting statistics obtained. In addition, less radioactivity would be injected, which would lead to a smaller absorbed radiation dose.

The pronounced heart uptake that we have observed in rats with several Te-123m-labeled fatty acids such as 9-telluraheptadecanoic acid (Table 2) could be of considerable importance in the design of new myocardial imaging agents. It is very likely that the tellurium fatty acids showing pronounced and prolonged uptake are "trapped" in the myocardium as a consequence of some metabolic process that must result from the presence of the tellurium heteroatom within the alkyl chain (R-Te-R′-COOH). Even if beta oxidation of these unusual compounds were initiated, it seems improbable that this catabolic process could proceed any further than the immediate vicinity of the tellurium heteroatom. It seems quite probable that the alkyl substituent (R) is retained with the tellurium atom, and experiments to substantiate this possibility are being initiated in our laboratory using **Ib** labeled with C-14 in this region of the molecule. Since the alkyl region of **Ia** appears to be retained, introduction of radiohalogens such as I-123 into this region of **Ib** containing stable tellurium could be a unique and effective means of substantially increasing the myocardial residence time of such agents, thus eliminating the problems associated with rapid washout and high blood levels of radioactivity. The development of techniques for the synthesis of radioiodinated tellurium fatty acids is now being pursued.

FOOTNOTES

* K&K Laboratories.
† Sigma Chemical Company.
‡ Analtech.

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