RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Long-Chain F-18 Fatty Acids for the Study of Regional Metabolism in Heart and Liver; Odd–Even Effects of Metabolism in Mice

E. J. Knust, Ch. Kupfernagel, and G. Stöcklin

Institut fur Chemie 1 (Nuklearchemie) der KFA Julich GmbH, D-5170 Julich, FRG (West Germany)

In view of the potential usefulness of fluorine-tagged fatty acids in the study of regional metabolism in the heart and liver, the time courses of uptake and release of 9,10-[^{18}F]fluorostearic acid, 2-[^{18}F]fluorostearic acid, 16-[^{18}F]fluorohexadecanoic acid, 17-[^{18}F]fluoroheptadecanoic acid have been investigated in several organs of NMRI mice. Whereas 2-[^{18}F]fluorostearic acid shows very little uptake in the heart muscle but an increasing accumulation in the liver, the fatty acids with the F-18 label in the middle or at the end of the carbon chain exhibit uptake and elimination behavior similar to that of the analogous C-11-labeled compounds. After rapid concentration in the heart within 1 min, clearance takes place with fast and slow components. 16-[^{18}F]fluorohexadecanoic acid and 17-[^{18}F]fluoroheptadecanoic acid have different half-times of elimination. These differences are also reflected by the fact that nearly all the activity present in the heart can be recovered as fluoride(F-18) in the case of 17-[^{18}F]fluoroheptadecanoic acid, whereas practically no fluoride was found among the metabolites of 16-[^{18}F]fluorohexadecanoic acid. Similar differences were observed for the F-18 activity in bone. The results can be interpreted in terms of the odd-even rule: β oxidation of even-numbered fatty acids ends up with [^{18}F]fluoroacetic acid, whereas the odd-numbered fatty acids give rise to β-[^{18}F]fluoropropionic acid. Only in the latter case does dehalogenation take place leading to free fluoride, whereas fluoroacetic acid undergoes further reactions in the citric acid cycle.

J Nucl Med 20:1170–1175, 1979

Recently an increasing interest in the biochemistry of fluoro-organic compounds has led to many investigations concerning their kinetics and metabolism in the cell. Since 1944, when Marais (*1*) discovered that the toxic agent of the South African plant "*Dichapetalum cymosum*" is 2-fluoroacetate, the application of other fluorine-containing aliphatic and aromatic molecules has given interesting insights into their pharmacological behavior.

In general it is not possible to predict the biological behavior of a compound after the introduction of either a single fluorine atom or the CF_3^- group. Given proximity to the reaction site, however, the presence of the tag can alter the biological behavior of the parent molecule. An example is the blocking of β oxidation after introduction of fluorine in the α position of a fatty acid (*2*), an effect that can be described as "obstructive halogenation" (*3*).

In past years the suitability of labeled fatty acids for cardiac imaging and the measuring of myocardial uptake has been demonstrated by several authors (*4–9*). In previous studies in our laboratory (*8,9*), various α- and ω-halogenated fatty acids labeled with Cl-34m, Br-77, and I-123 were prepared for comparative measurements of myocardial extraction and elimination rates. It was found that the ω-halofatty acids show a behavior similar to that of 1-[^{11}C]palmitic acid, whereas the α-halogen-

Received Jan. 29, 1979; revision accepted May 17, 1979.

For reprints contact: G. Stöcklin, Institüt für Chemie 1 (Nuklearchemie) der Kernforschungsanlage Jülich GmbH, Postfach 1913, D-5170 Jülich 1, Federal Republic of Germany.

ated compounds were extracted less effectively. This led us to the clinical evaluation of ω-[^{123}I]iodofatty acids for the diagnosis of coronary insufficiency (*10,11*). In the present work we extend these investigations to the analogous F-18-labeled fatty acids. Considering the high energy of the C–F bond and the higher electronegativity compared with the other halogens, specific features could be expected. The toxicity of even-numbered ω-fluorofatty acids is caused by the metabolite fluoroacetic acid, whereas odd-numbered acids end up with the nontoxic β-fluoropropionic acid (for a review see ref. (*12*)).

The radionuclide F-18, which can be produced in a nuclear reactor or in a cyclotron by several reactions, combines the advantages of positron emission (which permits positron tomography) with the relatively long half-life of 110 min. In contrast to C-11 ($T_{1/2}$ = 20 min), F-18 radiopharmaceuticals can be distributed within a radius of a few hundred kilometers from the site of production. Among the "organic" positron emitters, the β^+ particles of F-18 have the lowest energy and hence the shortest range; this gives the F-18-labeled compounds a potential higher resolution in emission tomography.

MATERIALS AND METHODS

Synthesis and purification. The F-18-labeled products were prepared by nucleophilic F-for-Br exchange in acetamide melt, starting with the corresponding bromofatty acid methylesters. Fluorine-18 was produced via the reaction $^{16}O(^3He,p)^{18}F$, by irradiating 10 ml of H_2O in a water target with a He-3 beam (36 MeV, 10 μA). After adding KF carrier and evaporating the water to dryness in an ampoule, acetamide and the bromofatty acid methylester were added. The ampoule was then sealed under vacuum and heated in an oil bath. Finally the F-18-labeled fatty acid ester was hydrolyzed and extracted with n-heptane. The experimental procedure is described in more detail elsewhere (*13*). Purification of the products was performed with Reverse Phase HPLC using the following separation conditions.

1. 2-[^{18}F]stearic acid: NH_2 column 30 cm long, 0.4 cm i.d.; n-heptane:diethyl ether:acetic acid (58:40:2) at 3 ml/min.
2. 16-[^{18}F]hexadecanoic acid, 17-[^{18}F]heptadecanoic acid, and 9,10-[^{18}F]stearic acid: NH_2 column 30 cm long, 0.4 cm i.d.; n-heptane:acetic acid (998:2) at 3 ml/min.

Starting with a F-18-activity of 40 mCi, specific activities of 4 mCi/mg were available about one half-life after e.o.b.; this, of course, can be increased by a factor of at least ten by use of a higher F-18 starting activity.

Animal experiments. After the purification of the fatty acid by HPLC, the eluent was completely removed by vacuum evaporation. With the following general procedure it was possible to prepare an injectable solution of labeled fatty acids without decomposition. The fatty acid (specific activity as above) was dissolved in 100–150 μl of 96% ethanol and slowly added dropwise, with shaking, to 1.5–2 ml of a 4% solution of human serum albumin (HSA). Sterilization was performed by Millipore filtration (pores 0.22 μm). Thus, extraction yields of 30–70% of the F-18-labeled fatty acid could be obtained in the filtered solution. Aliquots of about 0.1 ml were injected into the tail vein of female NMRI-mice.

Analysis of the heart. This was performed at maximum uptake, as follows. The heart (blotted dry of blood) was crushed in a homogenizer with 2 ml of chloroform: methanol (2:1) (*14*). The product was transferred into a glass tube, with 0.65 ml of 0.02 *N* H_2SO_4 and 0.65 ml of a 40% aqueous solution of urea added and the tube shaken for 1 min. After centrifugation, the phases were separated and the tissue extracted a second time. The organic, inorganic, and tissue activity were measured in a gamma counter and the percentage of F-18 activity relative to the injected activity was determined.

The organic phase was concentrated on a water bath to about 0.5 ml and separated by thin layer chromatography (*15*) on silica gel F254 Al foil (20 × 18 cm, thickness 0.2 mm) with n-heptane:diethyl ether:acetic acid (90:10:1). Thirty to fifty microliters of the solution were separated together with added 17-Br-heptadecanoic acid, peanut oil DAB 7, and lecithin as standard compounds for the fatty acids, as well as triglycerides and phospholipids. After treatment with a 0.05% solution of Rhodamin B in ethanol, the fatty acid, triglycerides, and lecithin could be observed under uv light of 366 nm. R_f values: fatty acids, 0.22 ± 0.041; triglycerides, 0.43 ± 0.049; lecithin 0. The spots were cut out, and the radioactivity was measured and compared with an aliquot of the starting solution. On the average 84 ± 11% of the F-18 activity in the heart was extracted.

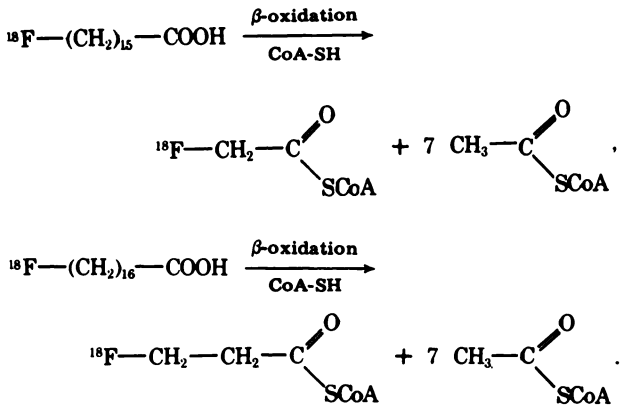
The determination of free F-18 in the inorganic phase was carried out by HPLC (column: stainless steel 20 cm long, 4 mm i.d., filled with Aminex A-27/CH_3COO^- form; eluent: 0.1 *N* aqueous CH_3COONa at 2.4 ml/min).

RESULTS AND DISCUSSION

Figure 1 shows the time courses of myocardial uptake and release for the four F-18-labeled fatty acids after i.v. injection. It is seen that a maximum is rapidly reached within about 1 min. In contrast to 2-[^{18}F]stearic acid, which shows little accumulation in the heart muscle, high uptake is observed for the other three fluorofatty acids. In all cases, elimination from the myocardium exhibits a biexponential behavior, depending on the nature of the fatty acid. The results are summarized in Table 1. The data are similar to those found for the corresponding fatty acids labeled with C-11, Cl-34m, Br-77, and I-123 (*8*). Differences are observed, however, when comparing liver and myocardial uptake of the various halofatty

acids labeled in the α- and ω-positions.

β-Oxidation of ω-labeled fluorofatty acids; odd–even effect. An interesting effect is observed when comparing the clearance data from heart muscle of 16-[^{18}F]hexadecanoic and 17-[^{18}F]heptadecanoic acid (Table 1). The half-times of elimination show significant differences. This odd-even effect can be explained on the basis of the β oxidation of ω-fluorofatty acids. Since the lengths of the carbon chain in the two compounds differ by one CH_2 group, β oxidation results in [^{18}F]fluoroacetic and β-[^{18}F]fluoropropionic acids, respectively, as can be seen in the following reaction scheme:



Because of the difference in toxic behavior between fluoroacetic acid or other even-numbered ω-fluorofatty acid (whose final metabolites are fluoroacetic acid) and odd-numbered acids (whose LD_{50} values are considerably higher), differences should also be expected in the clearance behavior. These findings are confirmed by the analysis of the heart at maximum accumulation. The results are summarized in Table 2. The F-18 distribution between the inorganic phase, the organic phase, and the tissue of the heart is similar for both acids. An apparent difference, however, can be observed for the free F-18. Whereas 16-[^{18}F]hexadecanoic acid shows very little free F-18 activity, the odd-numbered acid is completely catabolized to the inorganic halide. The reason appears in the two equations showing the final reaction products after β oxidation. β-[^{18}F]fluoropropionic acid seems to

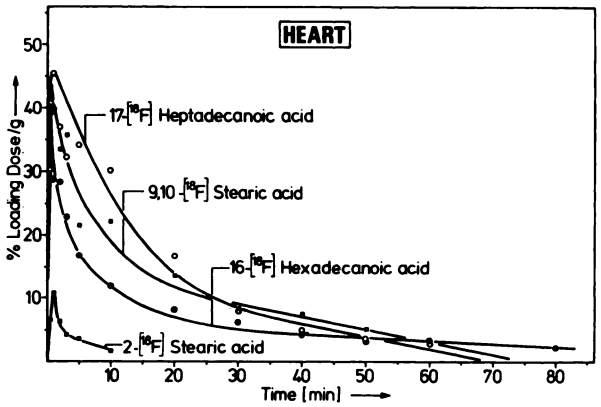


FIG. 1. Time course of radioactivity in heart muscle of mice after i.v. injection of 16-[^{18}F]hexadecanoic acid, 17-[^{18}F]heptadecanoic acid, 2-[^{18}F]stearic acid, and 9,10-[^{18}F]stearic acid (100 μl of a 4% HSA solution containing 1 μCi with about 0.2 μg fluorofatty acid as carrier). Average deviations are within ±15–20% of indicated values.

be unstable under the physiological conditions in the mitochondria, and will be further catabolized via dehydrofluorination, thus giving rise to free F-18. Strong evidence for this mechanism is provided by studies on 3-fluoro-1,2-propanediol in the presence of propanediol dehydrase (*16*). The results indicate that the primary product of the reaction is 3-fluoropropionaldehyde, which spontaneously loses hydrogen fluoride to yield acrolein. On the other hand, comparable dehalogenation can hardly be expected for fluoroacetic acid because of its relative chemical stability. Furthermore, it reacts (as fluoroacetyl-CoA) with oxaloacetate to fluorocitrate which, in the presence of the enzyme aconitase, leads to cis-aconitic acid by elimination of H_2O and yields isocitric acid after addition of H_2O to the double bond. With acetyl-CoA this is an equilibrium reaction containing about 91% citrate, 6% isocitrate, and 3% cis-aconitate. With fluoroacetyl-CoA, however, formation of fluorocitric acid takes place which, in an irreversible reaction, blocks aconitase, thus interrupting the citric acid cycle at this stage, a process that has been called "lethal synthesis" (*17*). This obviously leads to a different elimination half-time compared with the odd-

TABLE 1. UPTAKE AND ELIMINATION OF RADIOACTIVITY IN HEART MUSCLE AFTER i.v. INJECTION OF 16-[^{18}F]HEXADECANOIC ACID, 17-[^{18}F]HEPTADECANOIC ACID, 2-[^{18}F]STEARIC ACID, AND 9,10-[^{18}F]STEARIC ACID*

Fatty acid	t_{max} (min)	% Loading dose/g heart at t_{max}	Half-time of elimination (min) T_{fast}	T_{slow}
16-[^{18}F]Hexadecanoic acid	0.25	41 ± 11	3 ± 0.8	44 ± 11
17-[^{18}F]Heptadecanoic acid	1	46 ± 3	6 ± 1.5	18 ± 6
2-[^{18}F]Stearic acid	1	11 ± 3	0.5 ± 0.1	5 ± 1.5
9,10-[^{18}F]-Stearic acid	0.5	43 ± 10	4 ± 1	24 ± 7

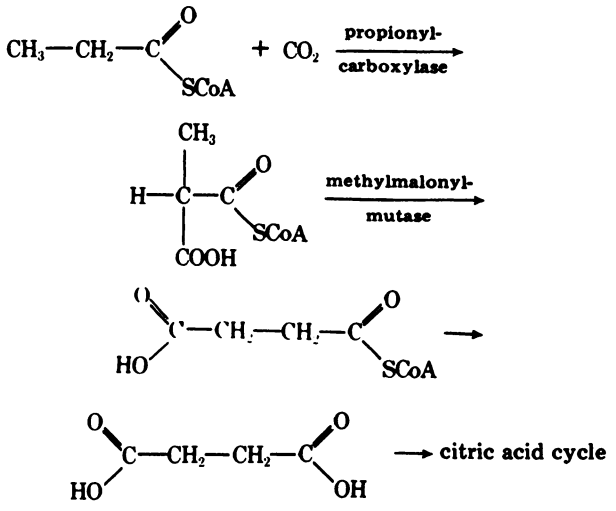
* 100 μl of a 4% HSA solution containing 1 μCi with about 0.2 μg fluorofatty acid as carrier.

TABLE 2. ANALYSIS OF THE HEART AT t_{max} AFTER I.V. INJECTION OF 16-[^{18}F]HEXADECANOIC ACID AND 17-[^{18}F]HEPTADECANOIC ACID [TOTAL F-18 ACTIVITY IN HEART ≙ 100%]*

	Inorganic phase		Organic phase			
Fatty acid	$^{18}F^-$	Not identified	Total	Glycerides	Fatty acid	Rest in tissue
16-[^{18}F]hexadecanoic acid	4	73	—	10	1	12
17-[^{18}F]heptadecanoic acid	62	1	16	—	—	21

* 100 μl of a 4% HSA solution containing 1 μCi with about 0.2 μg fluorofatty acid as carrier. Average deviations are within ±20–30% of indicated values.

numbered acid, and to a higher content of water-soluble organic F-18 activity (see Table 2). However, the elimination mechanism of the last reaction step pointed out for 17-[^{18}F]heptadecanoic acid has no validity for unsubstituted odd-numbered fatty acids. After β oxidation these compounds end up as propionic acid which (as propionyl-CoA) will be carboxylated to methylmalonyl-CoA. In the next reaction step, isomerization to succinyl-CoA takes place followed by transformation to free succinate, which can enter the citric acid cycle:



Bone activity and blood clearance. The postulated defluorination reaction in the case of an odd-numbered fatty acid is also reflected in the analysis of the bone activity. The results are shown in Fig. 2. It can be seen that the highest F-18 accumulation is reached in the case of 17-[^{18}F]heptadecanoic acid. Since the bone-seeking properties of fluoride are well known, this finding can be explained only by a defluorination of β-[^{18}F]fluoropropionic acid as mentioned above, again reflecting the odd-even effect. The low bone activity for 2-[^{18}F]stearic acid is in agreement with the relative stability of the α-labeled compound, whereas [^{18}F]citric acid, resulting from the metabolism of 16-[^{18}F]hexadecanoic acid and the further reactions of [^{18}F]fluoroacetic acid, obviously releases free F-18 to a smaller extent than does β-[^{18}F]fluoropropionic acid. The bone activity from the isomeric mixture 9,10-[^{18}F]stearic acid, lying as it does between these values, reflects the fact that 9-[^{18}F]stearic acid, as one compound of the isomeric mixture, is metabolized to β-[^{18}F]dodecanoic acid by β oxidation, whereas the other, 10-[^{18}F]stearic acid, ends up as 2-[^{18}F]decanoic acid. β oxidation of the former compound would lead to dehydrofluorination, but metabolism of the latter will be blocked (see 2-[^{18}F]stearic acid).

With respect to a desired low blood background for in vivo application of F-18-labeled fatty acids, we followed the radioactivity in blood for the four compounds, together with that of the free F-18, as shown in Fig. 3. We note that 16-[^{18}F]hexadecanoic acid, 17-[^{18}F]heptadecanoic acid, 2-[^{18}F]- and 9,10-[^{18}F]stearic acids exhibit similar behavior. After a rapid decrease of activity within the first minutes, a slow release proceeds with a longer half-time.

Metabolism of halofatty acids in the liver; accumulation of 2-[^{18}F]stearic acid. Whereas this acid shows an

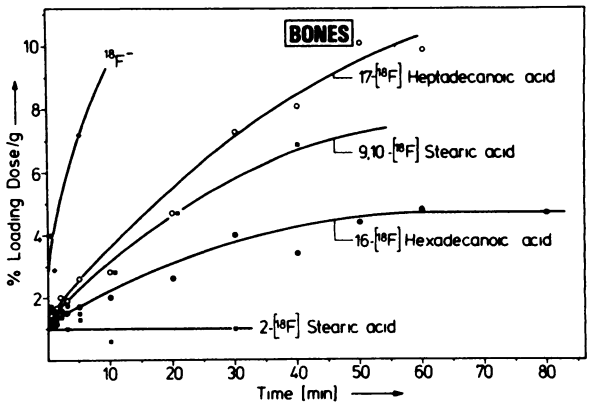


FIG. 2. Time course of radioactivity in bones of mice after i.v. injection of 16-[^{18}F]hexadecanoic acid, 17-[^{18}F]heptadecanoic acid, 2-[^{18}F]stearic acid, 9,10-[^{18}F]stearic acid, and ionic F-18 (100 μl of a 4% HSA solution containing 1 μCi with about 0.2 μg fluorofatty acid or halide as carrier). Average deviations are within ±20–30% of indicated values.

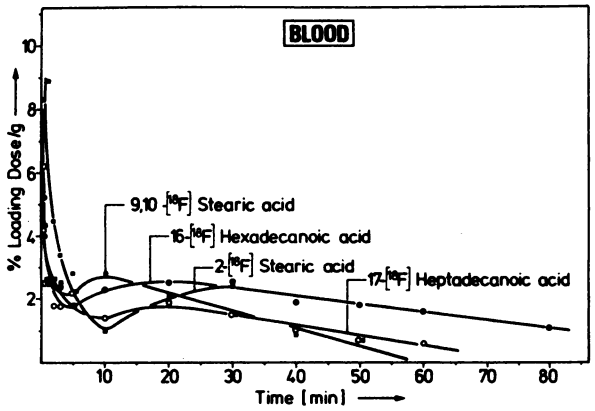


FIG. 3. Time course of radioactivity in blood of mice after i.v. injection of 16-[^{18}F]hexadecanoic acid, 17-[^{18}F]heptadecanoic acid, 2-[^{18}F]stearic acid, 9,10-[^{18}F]stearic acid, and ionic F-18 (100 μl of a 4% HSA solution containing 1 μCi with about 0.2 μg fluorofatty acid or halide as carrier). Average deviations are within ±20–30% of indicated values.

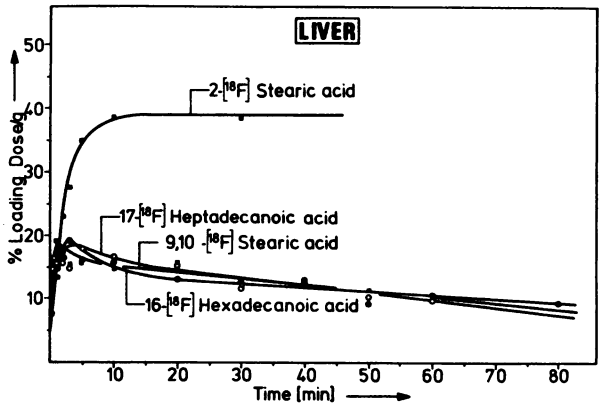


FIG. 4. Time course of radioactivity in liver of mice after i.v. injection of 16-[^{18}F]hexadecanoic acid, 17-[^{18}F]heptadecanoic acid, 2-[^{18}F]stearic acid, and 9,10-[^{18}F]stearic acid (100 μl of a 4% HSA solution containing 1 μCi with about 0.2 μg fluorofatty acid as carrier). Average deviations are within 20–25% of indicated values.

even smaller uptake in the heart than do other α-halofatty acids (*18*), a slow increase of liver activity, up to about 40 %/g, is observed within 30 min after injection. This behavior, which is not exhibited by any of the other fatty acids studied so far (*18*), is shown in Fig. 4. Since fatty acids are also metabolized in the mitochondria of the liver, the application for measuring regional metabolism in this organ seems obvious (*19*). It has been demonstrated recently in our laboratory (*18*) that 1-[^{11}C]palmitic acid and ω-halofatty acids (Cl-34m, Br-77, and I-123) exhibit a similar time course of uptake and elimination from the liver as ω-[^{18}F]fatty acids and [9,10-^{18}F]stearic acid, all showing rather slow clearance half-times. In the case of α-halofatty acids, however, a drastic decrease of activity takes place within 5 min, as was demonstrated for 2-[^{77}Br]stearic acid and 2-[^{123}I]stearic acid (*18*). These behavior differences may be interpreted in either of two ways.

1. According to the investigation of Pande et al. (*20*) the activation rate for the formation of the coenzyme-A ester in heart and liver after Br- or OH-substitution in the α-position of a fatty acid is only 1/20 of the rate for the unsubstituted compounds.

2. Rat livers contain glutathione-S-alkyltransferases, catalyzing the formation of S-alkylglutathione by dehalogenation of alkylbromides and alkyliodides (*21*). However, no similar reaction could be observed with the corresponding alkylchlorides (*22*). Thus, the observed rapid decrease of liver activity may be the result of debromination and deiodination, respectively, rather than of esterification, a reaction that is improbable for 2-[^{34m}Cl]stearic acid due to the lack of reactivity of alkyltransferases with chlorocompounds. Concerning inductive effects in the molecule, the introduction of a fluorine atom in the α position of a fatty acid will strongly alter the properties of the carboxylic group. Thus the drastic change of polarity will inhibit esterification with coenzyme-A and carnitine and thereby reduce the ease of passage through the mitochondrial membrane. Deposition of the fatty acid in the liver presumably takes place after its transformation into glycerides, phospolipids, or cholesterol esters.

CONCLUSION

Fluorine-18-labeled ω-fluorofatty acids are well suited to the probing of regional myocardial metabolism in vivo. Their high and rapid uptake is similar to that of C-11-labeled palmitic acid. The observed odd-even effect may provide an additional parameter for metabolic function studies in the healthy and diseased heart. [^{18}F]fluorofatty acids are also potentially useful for measuring regional metabolism in the liver. The characteristic differences between the α- and ω-fluorofatty acids may again permit application of two different approaches: namely trapping against β oxidation. The relatively long half-life of F-18 allows a wider geographical distribution than in the case of C-11. In addition, the lower β^+ energy is potentially advantageous with respect to resolution in emission tomography. Applications in humans, however, would require an increase of specific activity by a factor of at least ten, particularly in the case of the toxic even-numbered fatty acids. This is possible in principle, as pointed out in the experimental part, but it necessitates an automated synthesis due to the high starting activity.

ACKNOWLEDGMENT

The authors thank Mr. Gerrit Blessing and Mr. Manfred Schüller for valuable experimental assistance.

REFERENCES

1. MARAIS JSC: Monofluoroacetic acid, the toxic principle of

"Gifblaar" *Dichapetalum cymosum* (Hook) Engl. *Ond J Vet Sci Animal Ind* 20: 67-73, 1944

2. PATTISON FLM, BUCHANAN RL, DEAN FH: The synthesis of α-monofluoroalkanoic acids. *Can J Chem* 43: 1700-1713, 1965
3. CHENOWETH MB, MCCARTY LP: On the mechanisms of the pharmacophoric effect of halogenation. *Pharmacol Rev* 15: 673-707, 1963
4. EVANS JR, GUNTON RW, BAKER RG, et al: Use of radioiodinated fatty acid for photoscans of the heart. *Circ Res* 16: 1-10, 1965
5. POE ND, ROBINSON GD JR, MACDONALD NS: Myocardial extraction of labeled long-chain fatty acid analogs. *Proc Soc Exp Biol Med* 148: 215-218, 1975
6. WEISS ES, HOFFMANN EJ, PHELPS ME, et al: External detection and visualisation of myocardial ischemia with ^{11}C-substrates in vitro and in vivo. *Circ Res* 39: 24-32, 1976
7. POE ND, ROBINSON GD JR, GRAHAM LS, et al: Experimental basis for myocardial imaging with ^{123}I-labeled hexadecenoic acid. *J Nucl Med* 17: 1077-1082, 1976
8. MACHULLA H-J, STÖCKLIN G, KUPFERNAGEL CH, et al: Comparative evaluation of fatty acids labeled with C-11, Cl-34m, Br-77, and I-123 for metabolic studies of the myocardium:concise communication. *J Nucl Med* 19: 298-302, 1978
9. MACHULLA H-J, KUPFERNAGEL CH, STÖCKLIN G: Preparation, quality control, and stability of ^{11}C-, ^{34m}Cl-, ^{77}Br-, and ^{123}I-labelled fatty acids for heart muscle metabolism studies. Proc. XIV. International Annual Meeting of the Society of Nuclear Medicine, Berlin, Sept. 15-18, 1976, p 2420
10. FREUNDLIEB CH, HÖCK A, VYSKA K, et al: Use of 17-^{123}I-heptadecanoic acid for non-invasively measuring myocardiac metabolism. Proc. XV. International Annual Meeting of the Society of Nuclear Medicine, Groningen, Sept. 13-16, 1977, p 216
11. FEINENDEGEN LE, VYSKA K, MACHULLA H-J, et al: Advances in myocardial images and functional studies using labeled fatty acid. World Federation of Nuclear Medicine and Biology, Second International Congress, Sept. 17-21, 1978, Washington, DC, p 92 (abst)
12. PATTISON FLM, PETERS RA: Monofluoro aliphatic compounds. In *Handbook of Experimental Pharmacology*, Eichler O, Farah A, Herken H, et al. eds., Vol. XX, part 1, chapter 8. Berlin/Heidelberg/New York, Springer-Verlag, 1966, pp 387-458
13. KNUST EJ, SCHÜLLER M, STÖCKLIN G: Synthesis and quality control of long-chain ^{18}F-fatty acids. *J Lab Comp Radiopharm:* (in press)
14. FOLCH J, LEES M, STANLEY GHS: A simple method for the isolation and purification of total lipids from animal tissues. *J Biol Chem* 226: 497-509, 1957
15. MALINS DC, MANGOLD HK: Analysis of complex lipid mixtures by thin-layer chromatography and complementary methods. *J Am Oil Chem Soc* 37: 576-578, 1960
16. EAGAR RG, BACHOVCHIN WW, RICHARDS JH: Mechanism of action of adenosylcobalamin: 3-fluoro-1,2-propanediol as substrate for propanediol dehydrase-mechanistic implications. *Biochemistry* 14: 5523-5528, 1975
17. PETERS RA: Lethal synthesis. *Proc Roy Soc Biol* 139: 143-170, 1952
18. KUPFERNAGEL CH: Qualitätskontrolle und Pharmakokinetik ^{11}C-, ^{18}F-, ^{34m}Cl-, ^{77}Br- und ^{123}I-markierter Fettsäuren, PhD Thesis, University of Bonn, 1978; Jül-1551-NC (1978)
19. VYSKA K, HÖCK A, FREUNDLIEB CH, et al: Liver scanning and hepatocellular function analysis with radioiodinated fatty acids. Proc. XVI. International Annual Meeting of the Society of Nuclear Medicine, Madrid, Oct. 24-27, 1978, p 137
20. PANDE SV, SIDDIQUI AW, GATTEREAU A: Inhibition of long-chain fatty acid activation by α-bromopalmitate and phytanate. *Biochim Biophys Acta* 248: 156-166, 1971
21. JOHNSON MK: Studies on gluthathione S-alkyltransferase of the rat. *Biochem J* 98: 44-56, 1966
22. GRENBY TH, YOUNG L: Biochemical studies of toxic agents. 12. The biosynthesis of n-propylmercapturic acid from n-propyl halides. *Biochem J* 75: 28-33, 1960

THE FLEISHNER SOCIETY MEETING

February 22-28, 1980 **New Orleans Hilton** **New Orleans, Louisiana**

The Fleishner Society Meeting will be held February 22-28, 1980 in the New Orleans Hilton Hotel.

The 10th Annual Symposium on Chest Disease will be offered to all interested persons February 23-27, 1980 in the New Orleans Hilton. For information regarding the course contact:

Jan Carr
New Orleans Convention Center
2621 Trytania St.
New Orleans, LA 70130

The Annual George Simon Memorial Fellowship Award, which is in honor of Dr. Simon to perpetuate his interest in and encourage original investigation of radiologic or other imaging of the respiratory system, will be offered. Applicants should be under 40 years of age and should submit original, unpublished information before November 1, 1979. For further information contact:

Richard H. Greenspan
Dept. of Radiology
Yale Univ. School of Medicine
333 Cedar St.
New Haven, CT 06510

The recipient will be presented at the Scientific Meeting and will present his findings.