Conf-9405213--2

Invited Talk, For, "Proceedings of the Fourth Mediterranean Symposium on Nuclear Medicine and Radiopharmaceuticals - Nuclear Cardiology," Athens, Greece May 24-29, 1994. *In Press.*

Fatty Acids Labeled with Positron-Emitting Radioisotopes for Myocardial PET Imaging

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Research at ORNL supported by the Office of Health and Environmental Research (OHER), U.S. Department of Energy (DOE), under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc.

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ABSTRACT

The use of [1-^{11}C]-palmitate for generation of myocardial time-activity curves in conjunction with positron emission tomography (PET) has played an important role in the understanding of myocardial fatty acid substrate utilization and changes which occur in various cardiac diseases. Because the palmitate model is difficult to interpret and involves assumptions which may not be valid in ischemic regions (i.e. "back diffusion") myocardial metabolic studies with PET have more recently focussed on the use of [1-^{11}C]-acetate. For studies of fatty acid utilization an alternative strategy has been pursued using analogues containing beta-methyl-substitution as a means of delaying myocardial tracer clearance. Studies with 3-R,S-methyl-[1-^{11}C]heptadecanoic acid (BMHA) have demonstrated that introduction of β-methyl-substitution significantly delays myocardial clearance kinetics. While BMHA has a considerably increased myocardial retention, the corresponding straight-chain analogue shows rapid metabolism and tracer clearance. Because of its short 20 minute half-life, however, carbon-11-labeled fatty acids are currently not widely used and research interest in fatty acids for PET currently focuses on the use of [^{18}F]-labeled fatty acid analogues. As a result of the longer half-life of ^{18}F in comparison to ^{11}C (110 min versus 20 min), [^{18}F]-labeled fatty acid analogues can be available several hours after preparation and can be distributed to other sites. The various [^{18}F]-labeled fatty acid analogues which have been studied include mono-fluorine-18 for hydrogen substitution at the 2-, 6-, 7-, and terminal positions, and difluoro-substitution at the 10,11-positions. Methyl-substitution and introduction of the sulfur heteroatom in the fatty acid chain of various [^{18}F]-labeled analogues have also been evaluated as approaches to delay myocardial clearance. The goals of this paper are to briefly review the development and use of ^{11}C- and ^{18}F-labeled fatty acids for myocardial PET imaging.

INTRODUCTION

Since long chain fatty acids provide the principal energy requirements for myocardial metabolism under normoxic conditions, interest in the use of radiolabeled fatty acids was first pursued with [^{131}I]-iodooleic acid.[1] For PET studies, [1-^{11}C]-palmitic acid was an early choice because introduction of the ^{11}C radioisotope as the carboxyl carbon (i.e. -^{11}COOH) would not change the fatty acid structure. [2-4] In addition, loss of the carboxyl carbon through oxidative catabolism could be monitored non-invasively and the inherent advantages of PET for high resolution, high sensitivity and rapid repeat acquisitions could be used to evaluate changes in palmitate metabolism in carefully controlled animal models and in patients.

DEVELOPMENT OF [1-^{11}C]-PALMITIC ACID

The synthesis and animal studies with [1-^{11}C]-palmitic acid (Figure 1) were reported during the late 1970's and early 1980's. [5-9] Both open and closed chest canine experiments evaluated a variety of physiological factors affecting the clearance kinetics of palmitate, and these studies have been reviewed. [3-4] Because of the difficulties in developing and interpreting kinetic models for [1-^{11}C]-palmitic acid metabolism and the problems with "back diffusion", [10] over the last few years both basic and clinical research in this area has evolved with the use of [1-^{11}C]-acetic acid[11] since the metabolism of this important carbon source has been elucidated in detail by biochemists and physiologists. The intermediary metabolism of acetate has been elucidated and is well understood and the essential steps of interest for cardiac metabolism can be traced with this tracer using the appropriate kinetic models.

There is still interest in the use of palmitate, however, and one recent paper described the development of an semi-automated system for the "On-Line" preparation of [1-^{11}C]-palmitate from ^{11}C-carbon dioxide using a dry column for the Grignard reaction step.[11] The product is extracted and purified by passage through a silica gel Sep-Pak. One of the most interesting and potentially important animal studies with palmitate involved occlusion-reperfusion studies in an closed-chest canine model.[13] In this study, following coronary artery occlusion and reperfusion, [^{15}O]-water and then [1-^{11}C]-palmitate were sequentially administered to evaluate regional perfusion and metabolism, respectively. Static PET imaging was was performed soon after reperfusion and 1, 2 and 4 weeks later. The regional uptake patterns of both tracers were compared in serial static images. Perfusion of post-ischemic segments had returned to about 66 % of normal after 1 week and uptake of palmitate was parallel with perfusion alterations during ischemia and early post-ischemic reperfusion. After 4 weeks, flow and fatty acid uptake were not related to collateral flow during ischemia or the extent of initial reperfusion. The uptake observed with palmitate in the jeopardized zones one hour after reperfusion was found to be a good indicator of palmitate uptake 4 weeks after reperfusion. Because of the potential relevance of the results of these studies to patient management following thrombolysis, such early static imaging with fatty acids following reflow may be a predictor of return of normal contraction in post-ischemic segments, precluding the use of complex kinetic measurements.

METHYL-BRANCHED [^{11}C]-LABELED FATTY ACID ANALOGUES

Because of the rapid metabolism of palmitate acid in oxygenated tissue, one approach to slow catabolism was by the introduction of a 3-methyl group in [1-^{11}C]-3-R,S-methylheptadecanoic acid ("BMHA", Figure 2).[14-17] A number of studies in dogs[14, 18-20] have demonstrated that this

approach is successful. The metabolism of BMHA has been studied in some detail and proceeds via pathways different than those encountered with terminal iodophenyl-substituted fatty acids represented by 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP), which is discussed in detail in the accompanying paper on methyl-branched fatty acids for SPECT.

While BMIPP is evidently not metabolized by terminal ω-oxidation, which would not be expected because of the impediment imposed by the bulky p-iodophenyl moiety, the apparent myocardial metabolism results from either α- or β-oxidation (Figure 1). [21] In contrast, BMHA is primarily metabolized (66 %) by ω-oxidation in rat hearts, and β-oxidation plays only a small role (< 1 %) under normoxic conditions.[20] These studies also demonstrated that in rat liver, however, BMHA is metabolized to a large extent (53 %) by α-oxidation.

It was not until quite recently, however, that a quantitative model has been reported to assess the differences in regional uptake and clearance of this agent.[22] In these canine studies a mathematical model using arterial-venous measurements was developed to determine the net extraction fraction (E_n) values for BMHA in comparison with similar values for natural fatty acids. A normal group of dogs (n=6-8) and a group of dogs infused with glucose-insulin were studied. Myocardial blood flow and utilization of glucose, oxygen and lactate substrates were also measured. In the basal state, the E_n value for natural fatty acids in normal dogs was 0.335, while this value fell to 0.195 in dogs infused with glucose. Parallel studies with 1-[^{11}C]-BMHA gave similar E_n values of 0.220 for normals and 0.100 for the glucose group. The authors concluded that these studies demonstrate that the rates of myocardial fatty acid metabolism can be determined from the steady-state concentration values of the 1-[^{11}C]-BMHA. Evidently, similar studies in humans with this agent have not yet been reported.

Other studies have evaluated the effects of geminal dimethyl-substitution in the myocardial extraction and clearance kinetics of the [1-^{11}C]-3,3-dimethylheptadecanoic acid analogue.[23] This dimethyl analogue showed considerably lower heart uptake in fasted rats after 30 min (0.42 % injected dose/gram) in comparison to BMHA (2.94 % ID/gram). In addition, the kinetics of myocardial washout of activity from the dimethyl analogue were much more rapid. After 30 min the value for the dimethyl analogue was 0.42 % ID/gm, versus 2.94 % ID/gm for BMHA. These results demonstrated that in this series of fatty acid analogues dimethyl substitution is detrimental. In another study, the effects of total fatty acid chain length on the biological properties of several [1-^{11}C]-3-R,S-methyl alkanoic acid esters were investigated in rats.[24] In comparison, BMHA had the highest heart uptake, while the myocardial specificity of the 11-carbon-, 16-carbon- (palmitic acid), 18-carbon- (stearic acid) and 21-carbon-chain isomers were considerably decreased, demonstrating the importance of total chain length on myocardial uptake. These data are consistent with results of similar studies with natural alkanoic acids and other "modified" fatty acids illustrating that total chain length is an important factor affecting myocardial uptake and clearanec kinetics. The release of [^{11}C]-carbon dioxide from rats administered all of these compounds demonstrated that catabolism involves in part from β-oxidation.

DEVELOPMENT OF [^{18}F]-LABELED FATTY ACIDS

Although there is evidently not current widespread interest in the use of carbon-11-labeled fatty acids for the reasons described above, a number of investigators have explored the synthesis and animal evaluation of various ^{18}F-labeled fatty acid analogues. The 110 minute half-life of fluorine-18 offers a major advantage in comparison to the use of 20 minute half-life carbon-11, since single large batches of [^{18}F]-labeled fatty acid analogues can be prepared and used for several hours, while

use of carbon-11 necessitates repeated tracer production and fatty acid synthesis. Also, offsite preparation and distribution of fluorine-18-labeled agents is very feasible and currently conducted in several countries. In addition, the wide use of proton irradiation of oxygen-18-enriched water targets using medical cyclotrons now routinely provides large amounts of fluorine-18 on a routine basis. In terms of the expected physiological factors affecting the metabolism of fluorinated fatty acids, however, one would expect to encounter similar anomalies with significant "back diffusion" from highly ischemic regions which would interfere with kinetic modeling. Although these questions concerning the use of [^{18}F]-labeled fatty acid analogues presumably have not yet been evaluated in animal models, several groups have explored the synthesis of various fatty acid analogues because of the attractive properties of fluorine-18.

Because of the ease of synthesis, early studies assessed the synthesis and biological properties of various fluorine-18-labeled 2-fluoro (i.e. alpha-substituted) fatty acid analogues,[25-27] which demonstrated that substitution at this position significantly decreases myocardial uptake. Analogues with fluorine introduced into the terminal position such as 6- and 7-fluoropalmitic acid[28-31] and more recently, [^{18}F]-labeled 16-fluoroheptadecanoic acid[32] (Figure 2), show myocardial uptake and clearance patterns similar to palmitic acid, but these agents have not gained favor and have not been studied in humans. Difluorinated analogues have also been prepared (Figure 2)[27] from fluorine ($^{18}F_2$) addition across an olefin, but this approach is now impractical since a variety of methods and extensive experience has been gained over the last decade for fluoride (i.e. F^-) substitution, due to the ready availability of fluorine-18 produced in large amounts from medical cyclotrons using [^{18}O]-enriched water targets, as described earlier.

The concept of introduction of methyl groups into the chain of [^{18}F]-labeled fatty acids as a

means of prolonging myocardial residence has been extended in this series[33] by preparation of the 5-methyl-[34] and the 3-methyl analogues[35-36] of 17-fluoroheptadecanoic acid (Figure 2). Although these analogues showed increased myocardial retention in rats compared to the corresponding straight-chain [illegible] myocardial uptake is considerably less demonstrating unexpected effects of methyl-substitution at the 3- and 5-positions. In addition, significant bone localization of fluoride in these studies indicated *in vivo* defluorination of the 3- and 5-methyl analogues.

CURRENT STATUS OF THE USE OF [^{18}F]-LABELED FATTY ACIDS

The most recent studies reported with ^{18}F-labeled fatty acids have focussed on a "bifunctional" approach with the synthesis and evaluation of 14-(R,S)-methyl-[^{18}F]-fluoro-6-thiaheptadecanoic acid ("FTHA") analogue (Figure 2), where the sulfur heteroatom has been introduced into the fatty acid chain as a means of inhibiting fatty acid metabolism. Sulfur is a member of the same chemical group as selenium and tellurium, and these studies are similar to the development of radioiodinated fatty acid analogues containing the tellurium heteroatom in the chain to inhibit metabolism described in the accompanying paper[37] (See Knapp and Kropp, accompanying SPECT paper).

Animal Studies with [F-18]-FTHA. Studies with this analogue in mice demonstrated that introduction of the sulfur in the carbon chain does not decrease myocardial uptake but significantly delays clearance kinetics, with a half-time of about 2 hours[38-39]. The position of the sulfur atom plays an important role, however, since a similar 3-thia analogue with a sixteen carbon chain length showed low myocardial uptake and poor retention. Biodistribution studies demonstrated good heart uptake and high heart/blood ratios, and little skeletal uptake of free fluoride with the FTHA analogue (Figure 4). Analysis of organic phases of tissue extracts demonstrated that radioactivity following the

administration of the FTHA analogue is found in both the organic and aqueous extracts of blood and liver, but primarily in the organic fraction of heart extracts. Chromatographic analysis of the organic [illegible] heart and liver extracts was also evaluated and showed FTHA incorporation primarily into the triglyceride fraction from heart tissue from normal mice. In a parallel series of experiments myocardial uptake of FTHA in mice treated with an inhibitor (POCA"; 2[5(4-chlorophenyl)pentyl]oxirane-2-carboxylate) of the carnitine palmitoyltransferase (i.e. required for transport of fatty acids through the mitochondrial membrane) was significantly decreased by 81 %. These combined results suggest that the myocardial trapping observed with FTHA occurs before transport into the mitochondria.

Since treatment with the POCA inhibitor resulted in a 80-90% decrease in myocardial accumulation of radioactivity after intravenous administration of the FTHA analogue in mice, these data demonstrate that the expected reduction of fatty acid oxidation with FTHA parallels results of similar studies carried out with natural fatty acids. In contrast to many other fatty acids which have been studied, FTHA is incorporated primarily into phospholipids rather than triglycerides. These authors have suggested that measurement of the uni-directional uptake of FTHA can be used to approximate the "utilization" rate of long chain fatty acids, since initial intracellular activation is required *a priori* for both oxidation and esterification. Accumulation of metabolic products beyond this activation step should be directly related to the utilization rate. Thus, direct measurement of uptake could reflect utilization and such measurements would be much easier than with fatty acid analogues which are oxidized.

Clinical Studies with [F-18]-FTHA. One report describes initial human trials in two fasting, normal volunteers[40]. PET acquisitions were conducted for 30 minutes on three different days at rest, during

submaximal exercise and after administration of dipyridamole to increase myocardial blood flow independent of metabolic demand. The myocardium was well visualized in all studies and PET time-activity curves generated and evaluated after correction for metabolites by HPLC analysis of plasma samples. The data validated that accumulation rate of FTHA was dependent upon on metabolic demand and not solely on perfusion.

SUMMARY

Although there is still interest in the use of fatty acids analogues labeled with positron-emitting radioisotopes for PET evaluation of cardiac metabolism, research in this area is now limited to only a few centers with emphasis on selected fluorine-18-labeled analogues. As more patient data is available, the potential wider use of agents such as FHTA can be assessed.

ACKNOWLEDGEMENTS

Research at ORNL supported by the Office of Health and Environmental Research (OHER), U.S. Department of Energy (DOE), under contract DE-AC05-84OR21400 with the Martin Marietta Energy Systems, Inc.

REFERENCES

1. Evans JR, Gunton RW, Naker RG, et al. Use of radioiodinated fatty acids for photoscans of the heart. Circ Res 16:1-10, 1965.

2. Goldstein RA, Klein MS, Welch MJ, et al. External assessment of myocardial metabolism with C-11 palmitate in vivo. J Nucl Med 21:342-348, 1980.

3. Schelbert HR, Henze E, Keen R, et al. C-11 palmitate nonivasive evaluation of regional fatty acid metabolism with positron-computed tomography. IV. In vivo evaluation of acute demand-induced iscehmia in dogs. Am Heart J 106:736-750, 1983.

4. Schelbert H, Schwaiger M: PET studies of the heart. Positron emission tomography and autoradiography. Principles and applications for the brain and heart:581-661, 1986.

5. Weiss ES, Siegel BA, Sobel BE, et al. Evaluation of myocardial metabolism and perfusion with positron-emtting radionuclides. Prog Cardiovasc Dis 20:191-206, 1977.

6. Machulla H, Stocklin G, Kupfernagel C, Freundlieb C, Hock A, Vyska K, Feinendegen K: Comparative evaluation of fatty acids labeled with C-11, C1-34m, Br-77, and I-123 for metabolic studies of the myocardium. Commun Eur J Nucl Med 13:298-302, 1978

7. Klein MS, Goldstein RA, Welch MJ. External assessment of myocardial metabolism with [^{11}C]-palmitate in rabbit hearts. Am J Physiol 237: H51-H58, 1979.

8. Lerch RA, Ambos HD, Bergmann SR, et al., Localization of viable, ischemic myocardium by positron emission tomography with ^{11}C-palmitate. Circ 64:689-699, 1981.

10. Fox K, Abendschein D, Ambos, H, Sobel B, Bergmann, S: Effects of metabolized and nonmetabolized fatty acid from canine myocardium: implications for quantifying myocardial metabolism tomographically. Circ Res 57:232-43, 1985.

11. Brown M, Marshall D, Sobel B, Bergmann S: Delineation of myocardial oxygen utilization with carbon-11-labeled acetate. Circulation 76:687-96, 1987.

12. Iwata R, Ido T, Takahashi T, Tada M: On-line preparation of ^{11}C-labelled acetate and palmitate by column extraction. Meeting Proceedings, 10th International Symposium on Radiopharmaceutical Chemistry:134-35, 1993.

13. Knabb RM, Bergmann SR, Fox KAA, et al. The temporal pattern of recovery of myocardial perfusion and metabolism delineated by positron emission tomography after coronary thrombolysis. J Nucl Med 28:1563-1570, 1987.

14. Elmaleh D, Livni E, Levy S, Varnum D, Strauss H, Brownell G: Comparison of ^{11}C and ^{14}C-labeled fatty acids and their ß-methyl analogues. Int J Nucl Med Biol 10:181-87, 1983.

15. Livni E, Elmaleh DR, Levy S, et al. Beat-methyl-[1-^{11}C]-heptadecanoic acid: A new myocardial metabolic tracer for positron emission tomography. J Nucl Med 23:169-175, 1989.

16. Strauss HW, Livni E, Brill B, et al. *In vivo* studies of branched-chain fatty acids. In, Regional Myocardial Metabolism by Positron Tomography, Advances in Clinical Pharmacology Series, Vol. III, H. W Heiss, editor; Foundation for Advances in Clinical Medicine, Mahwah, New Jersey, USA, pp 102-105, 1987.

17. Yamada K, Matsuzawa T, Abe Y, et al. Experimental studies on myocardial metabolism with β-methyl-[1-^{11}C]-heptadecanoic acid. CYRIC Annual Report, 225-228, 1983.

18. Abendschein D, Fox K, Ambos H, Sobel B, Bergmann, S: Metabolism of beta-methyl[1-^{11}C]heptadecanoic acid in canine myocardium. Nucl Med Biol 14:579-85, 1987.

19. Rosamond T, Abendschein, D, Sobel, B, Bergmann, S, Fox K: Metabolic fate of radiolabeled palmitate in ischemic canine myocardium: implications for positron emission tomography. J Nucl Med 28:1322-29, 1987.

20. Fink G, Montgomery J, Garneau M, Livni E, Elmaleh D, Strauss H, Brunengraber H: Metabolism of ß-methyl-heptadecanoic acid in the perfused rat heart and liver. J Nucl Med 31:1823-30, 1990.

21. Knapp FF Jr. Kropp J. Goodman MM. et al. The development of iodine-123 methyl-branched fatty acids and their applications in nucler cardiology. Ann Nucl Med 7, S-II: 1-14, 1993.

22. Elmaleh DR, Livni E, Aoki MM, Strauss HW, Buxton R and Fleman AJ. Myocardial extraction of 1-[^{11}C]betamethylheptadecanoic acid. J Nucl Med 35:496-503, 1994.

23. Nishimura S, Takahashi T, Ido T, Ishiwata K, Iwata R: Development of branched-chain [^{18}F]fluorofatty acids for evaluating regional ß-oxidation in the heart. J Nucl Med 31:901, 1990.

23. Jones GS, Livni E, Strauss HW, et al. Synthesis and biological evaluation of 1-[C-11]-3,3-dimethylheptadecanoic acid (DMHDA). J Nucl Med ? :728, 1982.

24. Livni E, Elmaleh DR, Strauss HW, et al. Structure localization relationship of different chain length 1-[C-11]-labeled betamethyl fatty acids. J Nucl Med 25: P-125-126 (1984) (abstract).

25. Knust E, Schuller M, Stocklin G: Synthesis and quality control of long-chain ^{18}F-fatty acids. J Lab Com 17:353-63, 1978.

26. Knust E, Kopfernagel C, Stocklin G: Long-chain F-18 fatty acids for the study of regional metabolism in heart and liver; odd-even effects of metabolism in mice. J Nucl Med 20: 1170-75, 1979.

27. Machulla H-J. Laufer P. Stoecklin G. Radioanalytical control of C-11, F-18 and I-123-labeled compounds and radiopharmaceuticals. J Radioanal Chem 32:381-400, 1987.

28. Ehrenkaufer R. Rapid synthesis of high specific activity, biologically active ^{18}F-fluoroaliphatic analog compounds. J Nucl Med 14: 446, 1973.

29. Berridge M, Tewson T, Welch M: Synthesis of ^{18}F-labeled 6- and 7- fluoropalmitic acids. Int J. Appl Radiat Isot 34: 727-30, 1983.

30. Bosch A, DeGrado T, Gatley S: Preparation of no carrier added fluorine-18 labeled 16-fluorohexadecanoic and fluoroacetic acids from highly reactive tetraethylammonium [^{18}F]fluoride. Appl Radiat Isot 37: 305-08, 1986.

31. Gatley S: Rapid production and trapping of F-18 fluorotrimethylsilane and its use in labeling 16-fluoropalmitic acid without an aqueous evaporation solvent. J Nuc Med 29: 930, 1988.

32. Coenen H, Klatte B, Knochel A, Schuller M, Stocklin G: Preparation of n.c.a [17-^{18}F]fluoroheptadecanoic acid in high yields via aminopolyether supported, nucleophilic fluorination. J Lab Compd Radiopharm 23:455-66, 1986.

33. Nishimura S. Takahashi T, Ido T, Ishiwata K, Iwata R: Development of branched-chain [^{18}F]fluoro fatty acids for evaluating regional β-oxidation in the heart. J Nucl Med 31:901, 199.

34. Takahashi T, Ido I, Iwate R, Ishiwata K: Preparation of methyl-branched (w-^{18}F)fluorofatty acids and their tissue distributions. J. Labl Cmpd Radiopharm 26:445-47, 1989.

35. Lim E, Emran D. Synthesis of 16-[^{18}F]fluoro-beta-methylhexadecanoic acid ([^{18}F]FBMHA and 16-[^{18}F]fluorohexadecanoic acid ([^{18}F]FHA) from the corresponding triflates. J Labl Cmpd Radiopharm 26:231-32, 1989.

36. Takahashi T, Ido T, Iwate R: Study of leaving groups for the preparation of [ω-^{18}F] Fluorofatty acids via nucleophilic fluorination and its application to the synthesis of 17-[^{18}F]fluoro-3-methylheptdecanoic acid. Appl Radiat. Isot 42:801-09, 1991.

37. Knapp JR FF, Butler TA, Ambrose KR, et al. New Myocardial Imaging Agents - The Influence of Chain Length on the Heart Uptake of Se-75-Labeled Fatty Acids. In, Proceedings, International Symposium on Practical Applications of Nuclear and Radiochemistry; American Chemical Society Meeting, Las Vegas, NE, US, August 25-29, 1980; Chapter 28, pp 347-358, Pergamon Press, New York, 1982.

38. DeGrado T R, Coenen H H and Stoeklin G. 14-(R,S)-Fluoro-6-thiaheptadecanoic acid (FTHA): evaluation in mouse of a new probe of myocardial utilization of long chain fatty acids. J Nucl Med 32:1888-1896, 1991.

39. De Grado T: Synthesis of 14-(R,S)-[^{18}F]fluoro-6-thiaheptadecanoic acid (FTHA). J Lab Comp Radiopharm 9:989-95, 1991.

40. Ebert A, Henrich M, DeGrado T, Herzog H, Coenen HH and Stoeklin G. 14-(R,S)-[F-18]-fluoro-6-thiaheptadecanoic acid kinetics in normal human heart. Eur J Nucl Med 19:595, 1992 (abstract # 212-3)

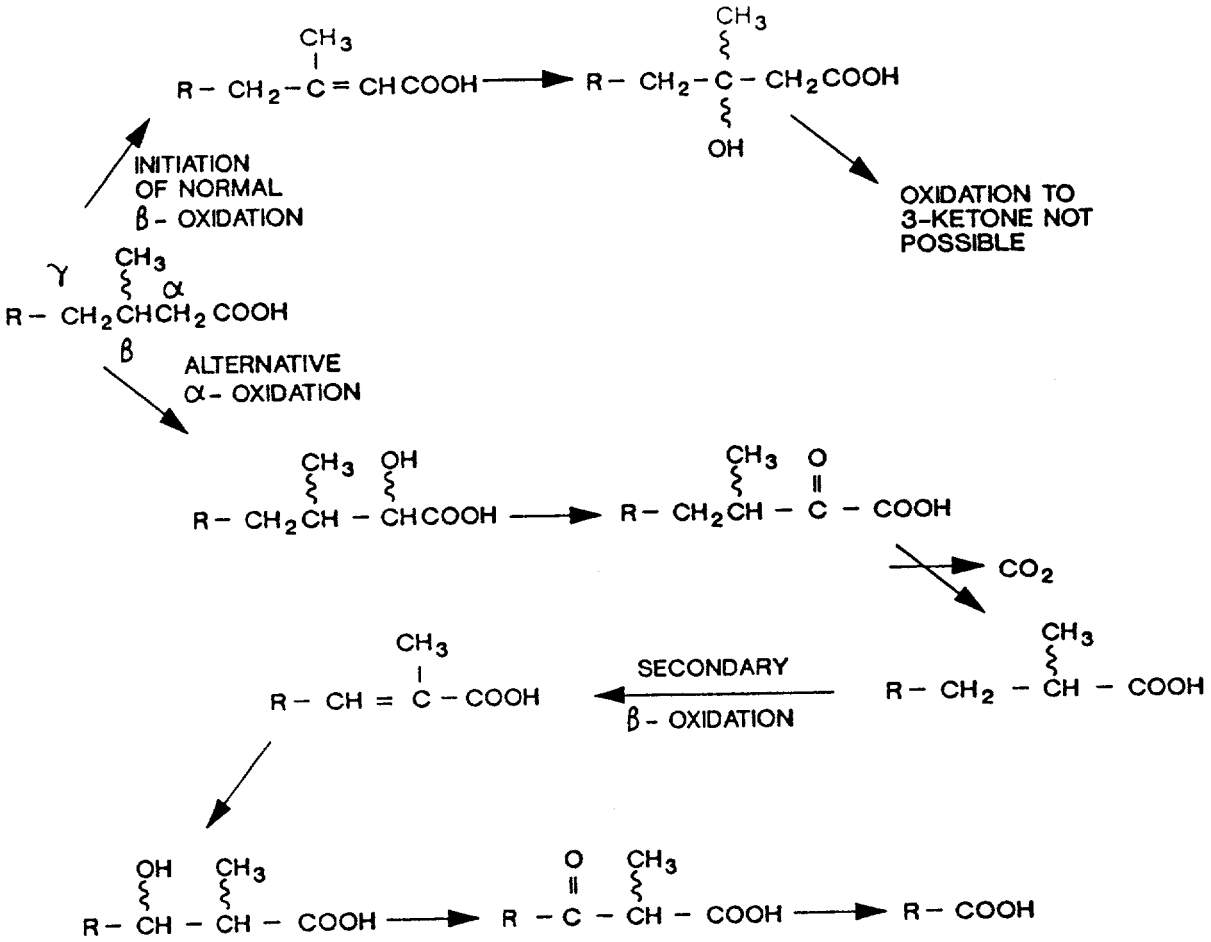
FIGURE LEGENDS

Figure 1. Metabolism of long-chain fatty acids by beta-oxidation.

Figure 2. Examples of radiolabeled long-chain fatty acids which have been used for PET.

Figure 3. Hypothetical time-activity curves demonstrating the influence of chemical changes such as methyl-branching to delay myocardial tracer clearance (Curves are exaggerated to show more clearly the biphasic clearance).

Figure 4. Biodistribution of 14-(R,S)-[^{18}F]fluoro-6-thiaheptadecanoic acid (FTHA) in in selected tissues from mouse studies (Data taken from DeGrado, et al., 1991).



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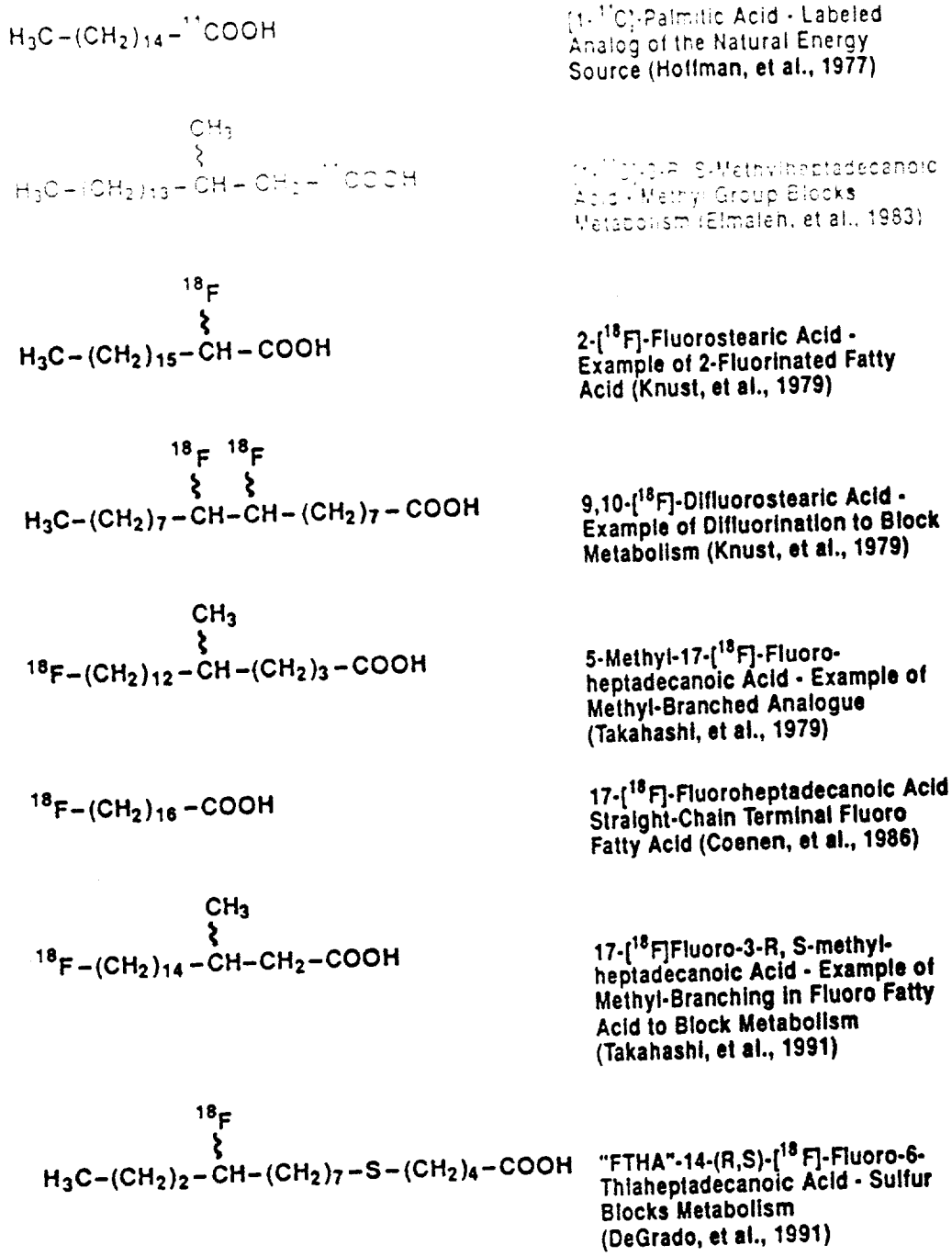
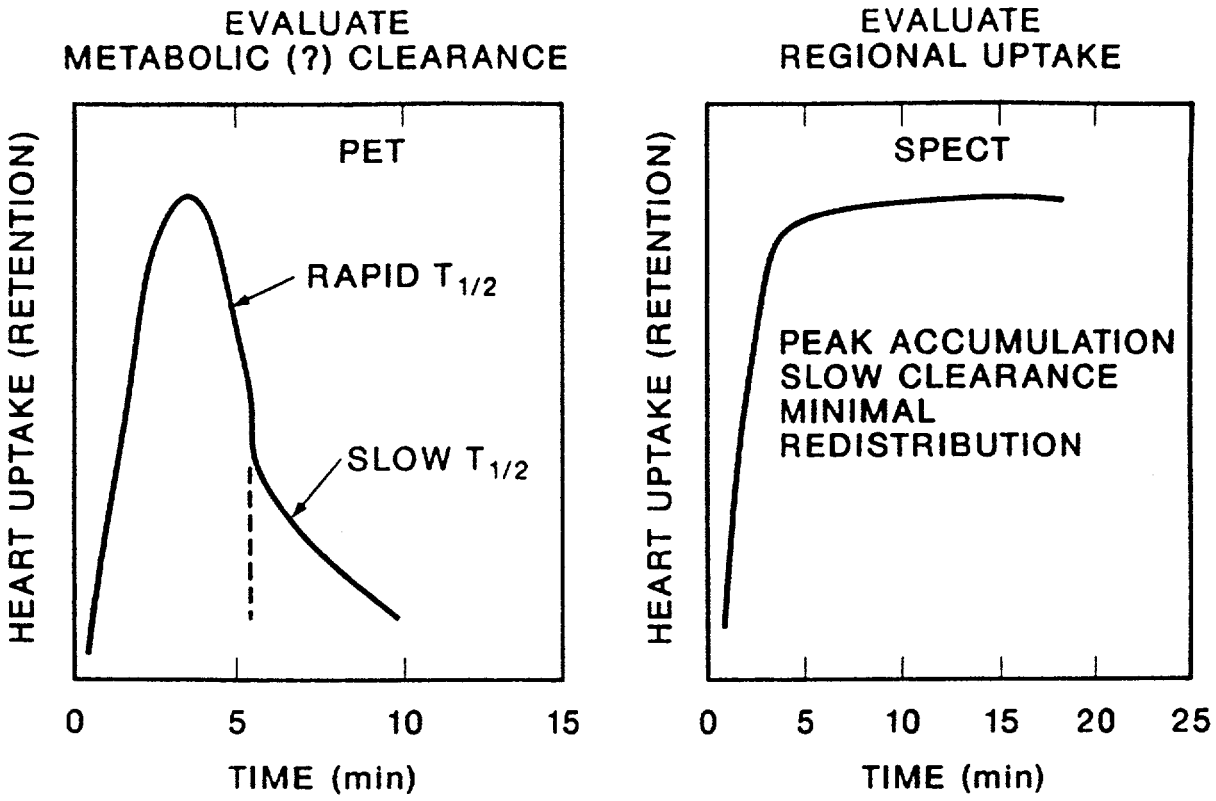


Figure 2. Examples of radiolabeled long-chain fatty acids which have been used for PET.



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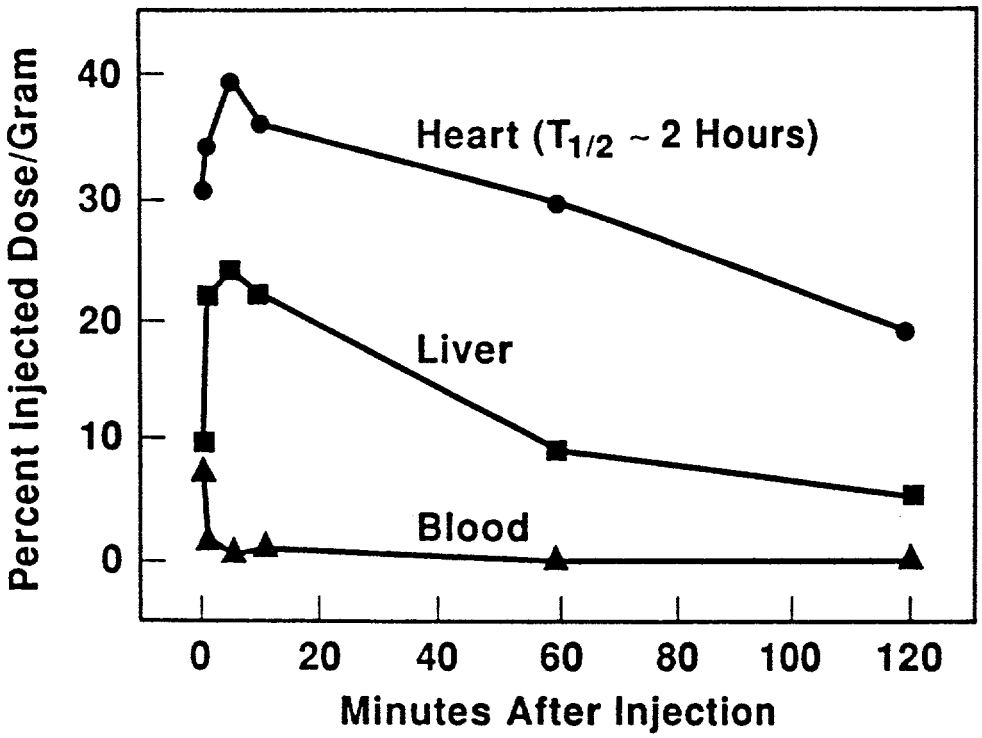

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