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The Development of Radioiodinated Fatty Acids for Myocardial Imaging

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Since free fatty acids are the principal energy source for the normally oxygenated myocardium, the use of iodine-123-labeled fatty acid analogues is an attractive approach for myocardial imaging[1]. Interest in the use of these substances results from divergent fatty acid metabolic pathways in ischemic (triglyceride storage) versus normoxic tissue (ß-oxidative clearance), following flow-dependent delivery. Iodine-123-labeled fatty acids may offer a unique opportunity to identify myocardial viability using single photon emission tomography (SPECT). The development of structurally-modified fatty acids became of interest because of the relatively long acquisition periods required for SPECT. The significant time required by early generation single- or dual-head SPECT systems for data acquisition (e.g. 15-30 minutes) requires minimal redistribution during the acquisition period to ensure accurate evaluation of the regional fatty acid distribution pattern after re-construction. Research at several institutions in the U.S., Western Europe and Japan has focussed on the evaluation of structural modifications which can be introduced into the fatty acid chain which would inhibit the subsequent ß-oxidative catabolism which normally results in rapid myocardial clearance. Introduction of a methyl group in position-3 (ß) of the fatty acid carbon chain has been shown to significantly delay myocardial clearance and iodine-123-labeled 15-(p-iodophenyl)-3- R,S-methylpentadecanoic acid ("BMIPP") is a new tracer based on this strategy (Figure 1). Several recent publications which have reviewed the development and use of radioiodinated fatty acids include the Proceedings of the First[2], Second[3] and Third[4] International Workshops on Radioiodinated Free Fatty Acids and a recent book.[5]

The increased myocardial retention required for SPECT imaging, especially with the early camera systems, stimulated the development of the concept of "metabolic trapping," where fatty acids would be concentrated in the myocardium as a means of overcoming rapid myocardial washout. Our initial research in the Nuclear Medicine Program at the Oak Ridge National Laboratory (ORNL) involved the synthesis of unique fatty acid analogues in which the divalent

tellurium heteroatom (Te) was introduced into the fatty acid chain. These studies represented the first demonstration that such a drastic modification could be made without interfering with the myocardial extraction of these fatty acids.[6-9] The first such analogue investigated was 9-[^{123m}Te]-telluraheptadecanoic acid (9-THDA) and these studies demonstrated that the modified fatty acids could be extracted similar to natural fatty acids. The development of these analogues thus represented an important foundation for further development of the concept of metabolic blocking using radioiodinated fatty acids for cardiac imaging. The tellurium analogues easily decompose, however, and care is required in their handling because of the chemical susceptibility of tellurium to oxidation. The tellurium-substituted fatty acids thus played an important role in demonstrating that rather unusual structural modifications could be introduced into the fatty acid chain without decreasing myocardial targeting and high extraction.

The strategy of metabolic trapping was thus further extended by the preparation of radioiodinated ß-methyl-branched fatty acids (Figure 1). We choose the development of the 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid analogue (BMIPP),[10-13] as an analogue of the linear 15-(p-iodophenyl)pentadecanoic acid (IPPA) agent which demonstrated metabolism similar to natural fatty acids. Radioiodide was readily stablized by attachment to the *para*-position of the terminal phenyl ring. Thus, the only structural difference between IPPA and BMIPP is the presence of the 3-methyl group in BMIPP. Animal studies with radioiodinated BMIPP evaluated the regional myocardial distribution of this tracer in various cardiac disease models, paving the way for subsequent human studies. An important early observation was the demonstration of a "mismatch" between flow tracer (thallium-201) and methyl-branched fatty acid distribution in the free wall of the left ventricle and septal regions of hearts from rat and hamster models with hypertrophic and cardiomypathic heart disease.[14] An example of this discordance in regional myocardial distribution between flow and fatty acid metabolic marker distribution, is illustrated in

the autoradiographic studies (ARG) shown in Figure 2. A dramatic illustration of the effects of 3-methyl-branching on myocardial retention in rat hearts *in vivo* is shown in Figure 3.

The first clinical studies with [I-123]-BMIPP by Dudczack and co-workers demonstrated that this agent exhibited the expected prolonged myocardial retention and provided excellent delineation of the myocardium by planar imaging.[15] More recently, several SPECT protocols have been described.[16-21] Excellent images of the left ventricular myocardium are obtained with SPECT imaging after injection with as low as 3-5 mCi of [I-123]-BMIPP. As discussed by several groups at the New Town Conference, there are currently various clinical protocols which are being pursued in Japan for patient use with [I-123]-BMIPP. SPECT studies include evaluation of [I-123]-BMIPP in patients with hypertrophic cardiomyopathy.[19] An evaluation of regional myocardial uptake and clearance of [I-123]-BMIPP in patients with myocardial infarction has also recently been reported.[20] An important observation from these studies was the mismatch observed between BMIPP uptake and perfusion tracer distribution more often in areas which had suffered an acute myocardial infarction and areas which were supplied by revascularized vessels compared with nonrevascularized areas. Most importantly, lower BMIPP uptake was more often observed in segments which exhibited wall motion scores lower than perfusion scores in comparison to segments showing a concordant decrease in both wall motion and perfusion scores.

Iodine-123-labeled BMIPP is also being studied at several institutions in Western Europe. One approach currently used by J. Kropp, M.D., and colleagues at the Clinic for Nuclear Medicine at the University of Bonn, Germany with [I-123]-BMIPP, utilizes a submaximal exercise to promote ischemia prior to tracer administration.[16-17] The initial SPECT-I acquisition is obtained after administration of 5 mCi [I-123]-BMIPP following sub-maximal exercise, with a second acquisition (SPECT-II) 3 hours later at rest. SPECT-III is then acquired at rest following a second

tracer injection of 2 mCi of [I-123]-BMIPP. In this initial patient group, 98% of infarctions could be detected as persistent defects. The sensitivity and specificity to detect ischemia were 89% and 91%, respectively. A total of 94% of non-infarcted segments exhibited reduced or absent uptake of BMIPP in SPECTs I and II and regularly showed no major differences in activity distribution. These segments had normal BMIPP uptake after re-injection in SPECT III, demonstrating the attractive properties of BMIPP for differentiation between irreversibly damaged and ischemic, but still viable, myocardium.

An additional recent example is a study protocol being conducted by P. Franken, M.D.. and colleagues at the Nuclear Medicine Department at the Free University Hospital in Brussels (VUB), Belgium, involving administration of [I-123]-BMIPP at rest and comparison with the myocardial distribution of [Tc-99m]-Sestamibi (MIBI).[21] These studies are also being complemented with two-dimensional echocardiography and ECG-gated magnetic resonance imaging (MRI) to provide information on the evolution of wall motion during heart contraction. The goal is to correlate functional changes with changes in tracer distribution observed in the radionuclide studies and to determine if such differences can identify ischemic but viable myocardium.

The issue of myocardial viability will continue to be an important factor in determining patient therapy and it would appear that radiolabeled agents such as [I-123]-BMIPP will be required to provide information which cannot be obtained with flow tracers. It is still unclear, however, how the deficits in regional BMIPP uptake observed in the SPECT cross sectional images correlate with some aspect of aberrations in the mechanism of fatty acid uptake or metabolism. Low BMIPP uptake and aberrations in contractile function in myocardial regions which have adequate perfusion demonstrated with flow tracers indicates that factors which are currently unknown or not well understood affect myocyte fatty acid uptake. Factors which could result in significantly decreased extraction of exogenous fatty acids in viable myocardial regions

may include alterations in ATP levels[22] or alterations in the fatty acid binding protein(s)[23] involved in the transfer of fatty acids.

In comparison with earlier studies of ischemic myocardium, myocardial segments which are viable but have decreased contraction would presumably be expected to concentrate 3-fluorodeoxglucose (3-FDG), which is the generally accepted "gold standard" for viability. Approaches include studies of radioiodinated fatty acid uptake, ventricular function and [F-18]-labeled-3-FDG uptake in myocardial segments that have adequate perfusion but demonstrate significantly decreased contractile function. Other studies which would be expected to provide additional insight from the results of animal models would include a biochemical and histological analysis of biopsy segments removed from the myocardial regions which have decreased fatty acid uptake. Since the washout of BMIPP is considerably delayed in comparison to the IPPA straight-chain analogue, the measurement of differences in washout between normal and ischemic myocardial segments, for instance, could be studied by construction of regional time-activity curves of normal versus abnormal regions using the new three-head SPECT systems which have a rapid acquisition capability.

The commercial availability of [I-123]-BMIPP from Nihon Medi-Physics Co., Inc., will be an important milestone in providing this agent for routine clinical use. In addition, continued basic studies of the mechanism of myocardial uptake, and metabolism, and the other factors affecting washout of BMIPP would be expected to provide important information in advancing our understanding of the physiological factors affecting the regional myocardial pharmacokinetics of this important cardiac imaging agent. These basic studies will complement the expected significantly increased clinical studies now that [I-123]-BMIPP is commercially available as a new radiopharmaceutical for cardiac imaging.

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FIGURE LEGENDS

Figure 1. Structures of radioiodinated methyl-branched fatty acids.

Figure 2. Comparison of "mismatch" between distribution of [I-131]-BMIPP and [T1-201]-thallous chloride in cross-sectional slices of hearts from normal and cardiomyopathic hamsters determined by autoradiography. Upper panel, normal hamsters; left, BMIPP; right, thallous chloride. Lower panel, cardiomyopathic hamsters; left, BMIPP; right thallous chloride. (Courtesy of Dr. P. Som, Medical Department, Brookhaven National Laboratory).

Figure 3. Triple-label study comparing myocardial uptake and retention of radioactivity after simultaneous intravenous administration of a mixture of [I-131]-IPPA, [I-125]-BMIPP and [I-123]-DMIPP to fasted rats. Although global myocardial extraction is not significantly altered, the effects of methyl-substitution on myocardial retention are quite dramatic.

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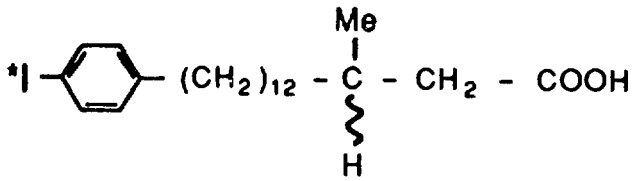

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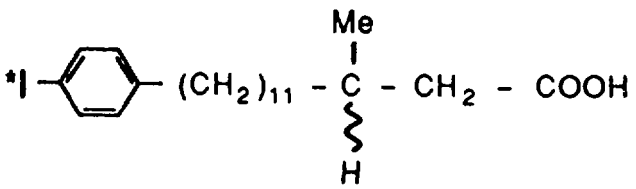

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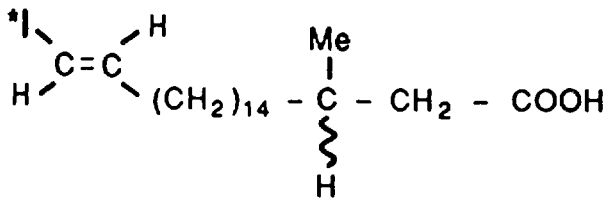

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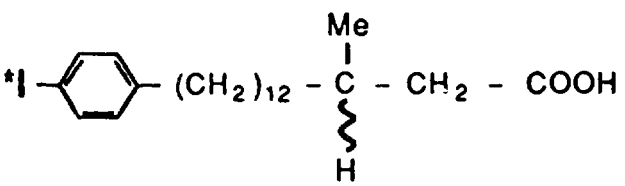

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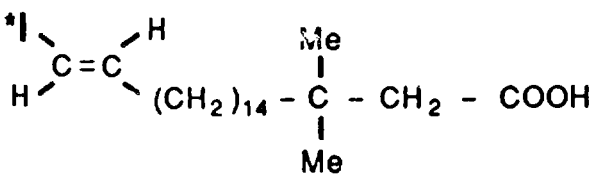

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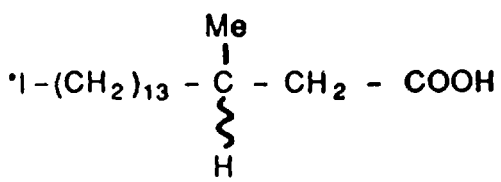

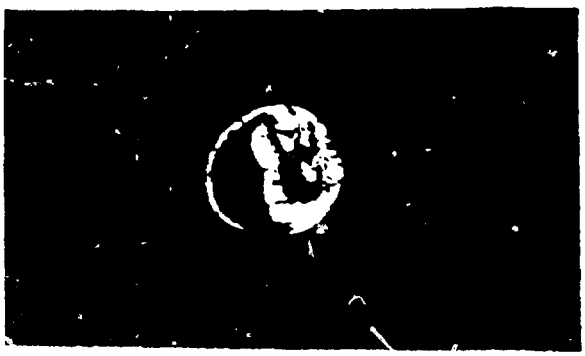

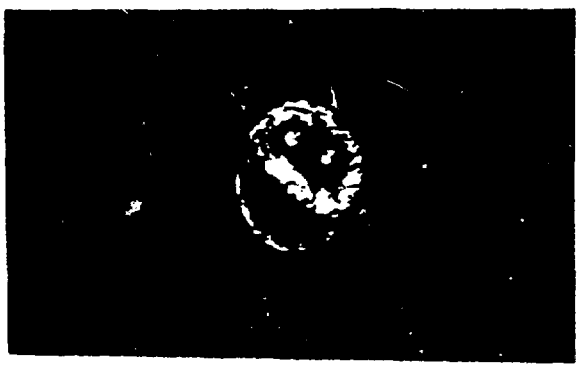

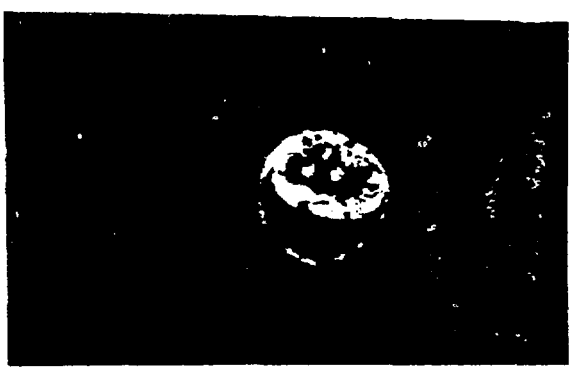

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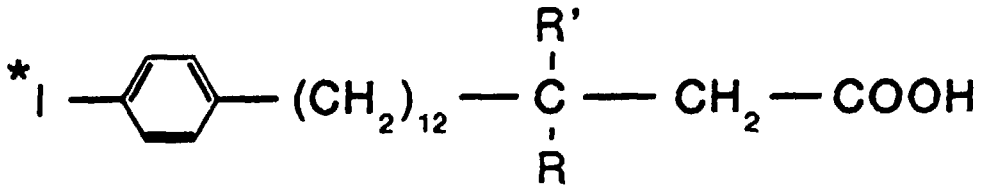
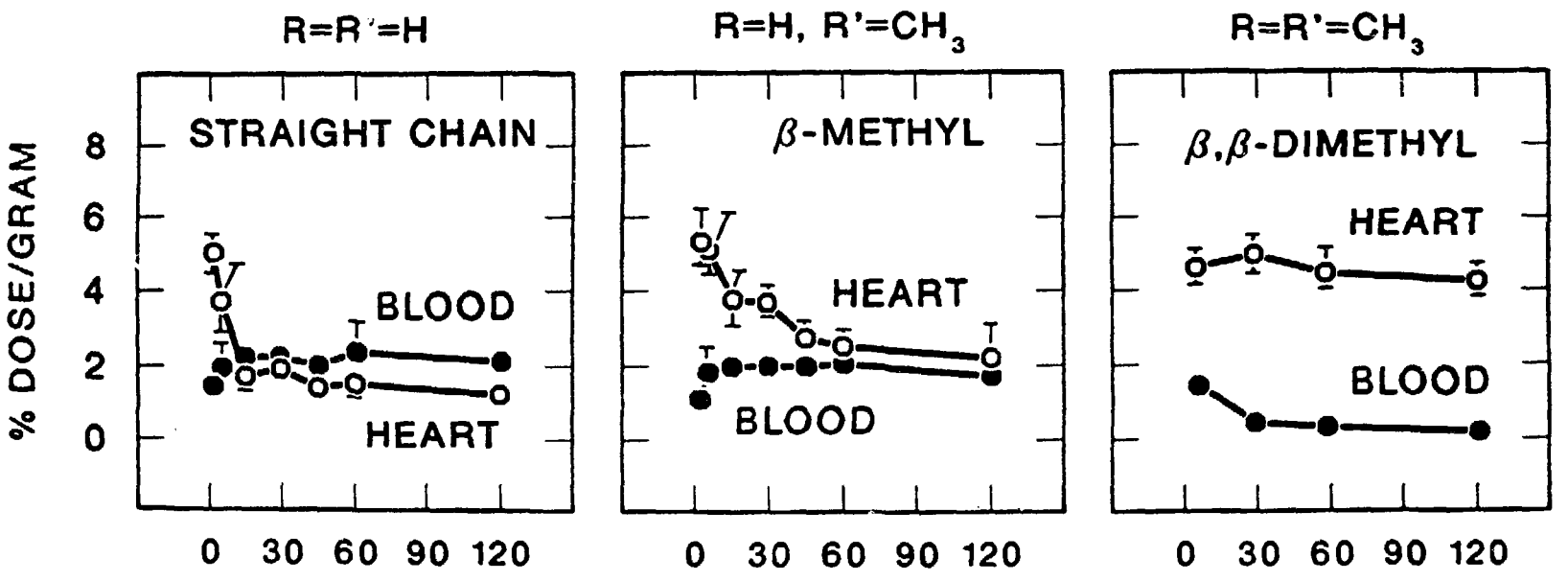
FASTED RATS





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