[^{123}I]-β-Methyl iodophenyl-pentadecanoic acid

[^{123}I]-BMIPP

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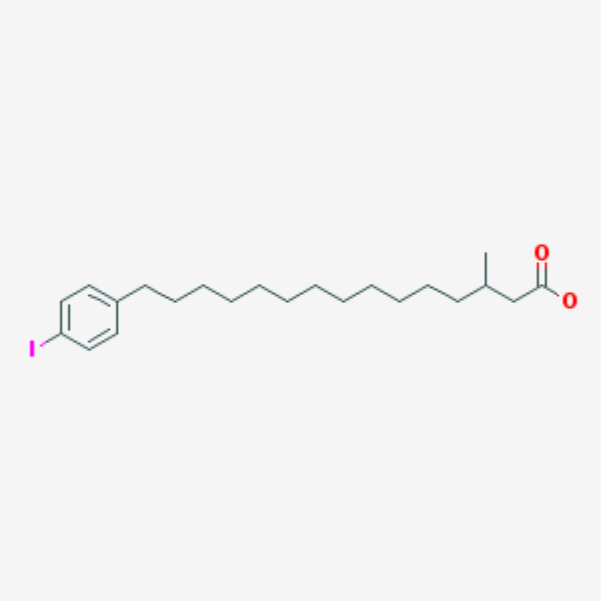
Chemical name:	[^{123}I]-β-Methyl iodophenyl-pentadecanoic acid
Abbreviated name:	[^{123}I]-BMIPP
Synonym:	15-(*p*-[^{123}I]iodophenyl)-3(*R*,*S*)-methylpentadecanoic acid; [^{125}I]-3(*R*,*S*)-BMIPP
Agent Category:	Compound
Target:	Myocardial tissue fatty acid metabolism
Target Category:	Uptake
Method of detection:	Single-photon emission computed tomography (SPECT) or gamma planar imaging
Source of Signal/ Contrast:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

Under normal conditions the myocardium can metabolize several different types of substrates for energy. Although fatty acids supply almost 66% of the energy requirements of this tissue, the myocardium can also metabolize glucose (the second most preferred substrate), lactate, amino acids, and ketone bodies (1). Either through β-oxidation or glycolysis the fatty acids and glucose are, respectively, broken down to acetyl-coenzyme A (CoA), which is further oxidized through the tricarboxylic acid cycle to produce energy. Certain pathological conditions, such as ischemia, are known to alter myocardial metabolism, and the reduced availability of oxygen shifts the myocardium into an anaerobic mode that leads to an increased utilization of glucose for energy because glycolysis requires less oxygen in comparison to β-oxidation (2). Therefore, different imaging agents are used to assess myocardial changes observed during heart disease. For example, radioactive fluorodeoxyglucose ([^{18}F]-FDG) is often used to evaluate glucose metabolism, labeled acetate is used to assess oxygen consumption, and fatty acids labeled with iodine (^{123}I) are used for single-photon emission computed tomography (SPECT) of the heart (1).

Among the fatty acids, [^{123}I]-β-methyl iodophenyl-pentadecanoic acid ([^{123}I]-BMIPP), used as a racemic mixture ([^{125}I]-3(*R,S*)-BMIPP), is used most frequently for SPECT imaging of the heart because the methyl group at the β position of the molecule slows β-oxidation of the fatty acid, which results in prolonged retention and improved quantitative imaging of the organ (3). Animal and clinical studies have shown that the CD36 molecule on the cell membrane plays an important role in the transport of BMIPP into the cell (4). It is then converted to BMIPP-CoA and rapidly incorporated into triglycerides (5). Using a dual mixture of [^{125}I]-3(R)-BMIPP and [^{131}I]-3(S)-BMIPP as surrogate molecules for [^{123}I]-BMIPP to study the effect of BMIPP molecular configuration on its uptake and metabolism in the rat myocardium, it was shown that uptake of the 3(R)-BMIPP isomer was higher compared to 3(S)-BMIPP but the two isomers were metabolized in the same manner in the rat myocardium (6, 7). Morishita et al. proved that BMIPP was metabolized in the mitochondria of the tissue (8). Other investigators studying the metabolism of branched-chain fatty acids in the myocardium of rats with streptozotocin-induced acute or chronic diabetes mellitus concluded that the uptake of BMIPP was reduced in rats with chronic diabetes mellitus because the mitochondrial function was not normal in the myocardium of these animals (9).

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In humans, [^{123}I]-BMIPP was shown to be a superior cardiac SPECT imaging agent compared to its dimethyl analog, and it has been used extensively for this purpose in Japan and Europe (1, 7, 10). Akashi et al. investigated the significance of [^{123}I]-BMIPP imaging in cardiac patients and concluded that this radiochemical enhanced the assessment of fatty acid metabolism disorders in the myocardium both under normal and diseased conditions (11). Nishimura and colleagues have shown that [^{123}I]-BMIPP scintigraphy can be used to detect asymptomatic coronary artery disease and predict cardiac death and coronary artery stenosis in hemodialysis patients (12-14). In the United States, [^{123}I]-BMIPP has been used for the imaging of ischemic heart and coronary artery disease as well as acute coronary syndrome in clinical trials approved by the U.S. Food and Drug Administration. The use of [^{123}I]-BMIPP for diagnostic imaging has been patented in the United States (15).

Synthesis

[PubMed]

The synthesis of BMIPP has been described by Goodmen et al. (16). Briefly, a mixture of 3-methylglutaric anhydride and methanol was stirred at 100°C for 90 min, and the resulting clear, viscous oil (crude half-ester) was vacuum-distilled at 30°C for 30 min. The crude half-ester was then mixed with thionyl chloride and stirred at room temperature for 14 h. After removing excess thionyl chloride, the crude acid chloride was mixed with a solution of 2-(6-phenylhexyl)thiophene in dichloromethane (DCM) and cooled to 0^{o}C; anhydrous tin chloride was then slowly added to it. After purification, the product was chromatographed on silica gel to obtain a crude product (i.e., a keto ester) with a yield of 83%.

The keto ester was suspended in diethylene glycol containing potassium hydroxide and hydrazine hydrate. The mixture was distilled until the temperature reached 200°C, and then it was refluxed for 3 h. The mixture was then cooled to 90°C, poured into water, and acidified to a pH between 2 and 3 with 12-N HCl. The acidified mixture was then extracted thoroughly with ether, washed with water, and dried over anhydrous sodium sulfate to obtain 2-(3-(*R,S*)-methyl-4-carboxybutyl)-5-(6-phenylhexyl)-thiophene, an acid. The yield of this reaction was 90%.

A Raney nickel suspension was added to the thiophene product and mixed with ethanol and sodium carbonate. The mixture was stirred vigorously under reflux for 16 h and filtered. The filtrate was cooled, acidified, and extracted with ether. The ether extract was washed four times with water and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum to obtain 15-phenyl-3-(*R,S*)-methylpentadecanoic acid. The acid was chromatographed on silicic acid, and the appropriate fractions were dried under vacuum to obtain a white solid with a yield of 67%. The methyl ester was prepared using diazomethane. After purification on a silicic acid column, the methyl ester was dissolved in trifluoroacetic acid with thallium trifluoroacetate. This mixture was stirred in the dark at room temperature for 48 h, and an intermediate compound obtained after distillation

was mixed with a solution of DCM containing isoamyl nitrate under red light. A solution of 12 N HCl and glacial acetic acid was added, and the mixture was stirred for 10 min. To this mixture, 1 N HCl was added, and the mixture was stirred for another 10 min and filtered through Celite to obtain a green-colored DCM layer. This extract was washed several times with 0.1 N HCl and water and dried over sodium sulfate. A green-colored oil, left behind after the solvent was evaporated under vacuum, was chromatographed on silicic acid, and a nitroso intermediate, methyl 15-(*p*-nitrosophenyl)-3-(*R,S*)-methyl-pentadecanoate, was obtained with a yield of 48% that was determined to be a single component by thin-layer chromatography (TLC).

A suspension of the nitroso intermediate was prepared in methanol containing palladium on charcoal, and it was stirred under argon at room temperature and followed by the addition of sodium borohydride in methanol. A chloroform extract was washed with water and dried over anhydrous sodium sulfate to obtain an amine, methyl 15-(*p*-aminophenyl)-3(*R,S*)-methyl-pentadecanoate, which was an orange-colored oil, after the evaporation of chloroform. The amine was purified on a silica gel column as a yellow oil with a yield of 90%.

The amine from above was suspended in 0.5 N HCl, and the mixture was cooled to 0–5^{o}C, followed by the addition of a sodium nitrite solution and 5 min of stirring. Subsequently, piperidine was added to the reaction mixture over 20 min while the temperature was maintained, and the mixture was poured into water, extracted with chloroform, washed with water, dried over anhydrous sodium sulfate, and evaporated under vacuum to obtain a crude triazine, 1-[4-(13(*R,S*)-methyl-14-carbomethoxytetradecyl)-phenyl]3,3-(1,5-pentanediyl)triazine. This crude triazine was chromatographed on silica gel to obtain a yellow oil with a yield of 62%.

The above compound was refluxed in ethanol containing NaOH for 60 min, cooled, poured into water, and acidified to pH 3 with 1 N HCl. The mixture was extracted with ethyl ether, and the extract was washed with water. It was then dried over anhydrous sodium sulfate, and the solvent was removed to obtain a tan solid that was recrystallized from methanol-water as a light solid powder, 1-[4-(13(*R,S*)-methyl-14-carboxytetradecyl)-phenyl]3,3-(1,5-pentanediyl)triazine. The yield of this reaction was 53%.

This light solid powder was dissolved in acetone and added dropwise with stirring to a mixture of trifluoroacetic acid and sodium iodide at 0–5^{o}C. An ethanol extract was washed with sodium sulphite and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the resulting product, BMIPP (yield 65%), was crystallized from petroleum ether.

An alternate method for the synthesis of BMIPP and labeling with radioactive iodine (^{131}I) was also described elsewhere (17).

Radioiodination of BMIPP with iodine (^{123}I) was described by Sloof et al. (18) and performed with the use of the copper-assisted nucleophilic exchange method of Mertens

et al. (19). Purification of [^{123}I]-BMIPP was performed with a Sep-Pak RP-18 Light cartridge. Purified [^{123}I]-BMIPP in ethanol was formulated in 5% human serum albumin, and the final solution was sterilized by filtration. Purity of [^{123}I]-BMIPP was determined with high-performance liquid chromatography (HPLC). Radiochemical purity of [^{123}I]-BMIPP was determined to be >99% with a specific activity of 5.14–5.7 mCi/μmol (190–210 MBq/μmol). The radiochemical yield and stability of the formulated product was not provided by the investigators (18).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Yamamichi et al. studied the metabolism of BMIPP in isolated rat hearts (20). The rat hearts were initially perfused with HEPES buffer containing various energy substrates in bovine serum albumin (BSA), and this was followed by recirculation of the buffer for 4 h after a bolus injection of [^{123}I]-BMIPP. The various metabolites in the buffer were subsequently analyzed with HPLC and TLC. More than eight BMIPP metabolites were identified when oleate served as the energy substrate, and the metabolites changed with the type of energy substrate (oleate, glucose + insulin, acetate, or BMIPP alone) in the buffer. This study showed that the metabolism of [^{123}I]-BMIPP in the myocardium was closely related to the carbohydrate metabolic activity in the tissue (20).

Kropp et al studied the metabolism of [^{123}I]-BMIPP in rat hearts perfused with Krebs-Henseleit buffer (pH 7.4) either with or without BSA or palmitate (21). The radioactive metabolites were determined with HPLCA and TLC analyses, and the primary metabolites of BMIPP were further characterized by electrospray mass spectrometry. The major metabolite of [^{123}I]-BMIPP in the perfusion buffer was identified to be 2-(p-iodophenyl)acetic acid, and the addition of BSA or palmitate to the perfusion buffer reduced the uptake and metabolism of BMIPP. The rat heart tissue was found to contain α-methyl-14-(p-iodophenyl)tetradecanoic acid, 12-(p-iodophenyl)-substituted-dodecanoic acid, -hexanoic acid, and IPC2, in addition to [^{123}I]-BMIPP. From these results the investigators concluded that [^{123}I]-BMIPP was metabolized through the α- and subsequently through the β-oxidation pathways in these animals (21).

Animal Studies

Rodents

[PubMed]

Myocardial perfusion and fatty acid metabolism was determined with the use of SPECT imaging with thallium-201 (^{201}Tl) and [^{123}I]-BMIPP to investigate the effect of exercise on the left ventricle (LV) metabolic and functional recovery in rats with myocardial transient ischemia (22). A significantly lower severity score was reported ($P < 0.05$) with both radiochemicals after exercise in the ischemic animals; no such change was observed in the sedentary controls. Plasma levels of the free fatty acids were reported to normalize

in the ischemic trained rats, but these levels remained elevated in the ischemic, sedentary, control rats. In addition, the exercised rats had a significant increase in the LV stroke volume ($P < 0.05$) and hypertrophy. The investigators concluded that the myocardial perfusion, fatty acid metabolism, and LV function improved in the animals as a result of exercise training after transient ischemia (22).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

Dormehl et al. compared the use of ortho- and para-[^{123}I]-15-(iodophenyl)pentadecanoic acid (oPPA and pPPA, respectively) and [^{123}I]-BMIPP for planar myocardial imaging in baboons (23). From this study the investigators concluded that these radiochemicals could be used to study the myocardial metabolism. Among these labeled compounds, [^{123}I]-BMIPP produced the best images and primarily reflected the tracer incorporation in the neutral lipids.

Human Studies

[PubMed]

It is pertinent to mention that a large number of human studies that deal with myocardial imaging with [^{123}I]-BMIPP are available. Because it is out of the scope of this chapter to cover all studies, only a select few recent studies are presented in this section. Interested readers are encouraged to visit the PubMed site for an exhaustive list of studies available on [^{123}I]-BMIPP imaging.

Inoue et al. used [^{123}I]-BMIPP and ^{201}TI myocardial scintigraphy to study cardiac events in 33 patients with dilated cardiomyopathy (24). Among these patients, 9 patients had a cardiac event (event group) whereas the other 24 patients were event-free (event-free group). Images obtained with [^{123}I]-BMIPP and ^{201}TI were divided into 17 segments, and the total defect score was calculated for each. Compared with ^{201}TI, the total defect score was significantly higher ($P < 0.05$) with [^{123}I]-BMIPP for individuals in the event group compared with those in the event-free group. With results from this study the investigators concluded that [^{123}I]BMIPP was a good predictor of cardiac events in patients with dilated cardiomyopathy (24).

The relationship of [^{123}I]-BMIPP uptake to rest myocardial blood flow (MBF), hyperemic MBF, and myocardial reserve flow (MRF) was assessed with radioactive oxygen [^{15}O]-water positron emission tomography (PET) (25). For the study, 21 patients with chronic stable angina and no previous infarction were enrolled, and all underwent imaging with

[^{123}I]-BMIPP and [^{15}O]-water. The investigators observed that, as the [^{123}I]-BMIPP uptake decreased, the MBF and the MRF were also reduced. The investigators concluded that, in patients with chronic stable angina and no previous infarction, a lower [^{123}I]-BMIPP uptake indicated a decreased cardiac MRF (25).

The use of a combination of tetrofosmin radiolabeled with meta-stable technetium ([^{99m}Tc]-TF) and [^{123}I]-BMIPP SPECT, a combination of [^{18}F]-FDG PET and [^{123}I]-BMIPP SPECT, or a combination of [^{18}F]-FDG PET and [^{99m}Tc]-TF SPECT were compared to predict functional improvement of ischemic myocardium in 10 patients <3 weeks after a large acute myocardial infarction (26). The sensitivity, specificity, and accuracy of the various combinations are shown in the table below.

Combination	Sensitivity (%)	Specificity (%)	Accuracy (%)
[^{99m}Tc]-TF + [^{123}I]-BMIPP	61	83	70
[^{18}F]-FDG + [^{123}I]-BMIPP	94	40	71
[^{18}F]-FDG + [^{99m}Tc]-TF	76	49	63

With results obtained from this study, the investigators concluded that the use of [^{99m}Tc]-TF and [^{123}I]-BMIPP for SPECT was suitable to predict functional improvements of ischemic myocardium after a large acute myocardial infarction (26).

The myocardial creatine (CR) concentration and changes in cardiac fatty acid metabolism were investigated in 34 patients with different heart diseases (27). Gated 1H magnetic resonance spectroscopy, applying point-resolved spectroscopy, was used to measure the CR concentration of the septum in the patients. Of these patients, only 14 patients underwent [^{123}I]-BMIPP myocardial scintigraphy to evaluate myocardial fatty acid metabolism. The heart/mediastinum count ratio was used to determine the uptake of [^{123}I]-BMIPP. The myocardial CR concentration was reported to correlate positively with the LV ejection fraction by echocardiography ($R = 0.61$, $P < 0.001$) for all of the patients. A similar correlation was observed between [^{123}I]-BMIPP uptake and LV ejection fraction ($R = 0.60$, $P < 0.05$ for initial imaging; $R = 0.63$, $P < 0.05$ for delayed imaging). The investigators concluded that there was an association between CR depletion and reduced fatty acid metabolism in patients with cardiac disease (27).

Supplemental Information

[Disclaimers]

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