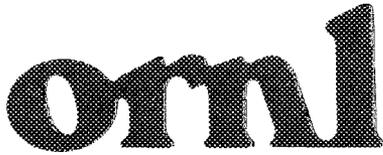




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**Nuclear Medicine Program
Progress Report for
Quarter Ending March 31, 1990**

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Health and Safety Research Division

NUCLEAR MEDICINE PROGRAM PROGRESS REPORT
FOR QUARTER ENDING MARCH 31, 1990

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SUMMARY

The evaluation of the effects of albumin and albumin plus sodium palmitate in the phosphate buffer perfusate on the relative incorporation of 15-(p-[I-125]iodophenyl-3-(R,S)-methylpentadecanoic acid (BMIPP) into endogenous lipids of isolated rat hearts has been studied. In earlier studies, the outflow of isolated hearts administered [I-125]BMIPP in the presence of palmitate and albumin was found to contain unmetabolized BMIPP as well as the unidentified, previously described polar component "X." Thus, "back diffusion" of unmetabolized BMIPP contributes to the loss of radioactivity observed in isolated hearts, and probably also occurs *in vivo*. These follow-up studies show that despite the relative decrease in the percent [I-125]BMIPP extracted by hearts in the presence of palmitate and/or albumin, there is relatively high incorporation into triglycerides when compared to isolated hearts perfused without palmitate and/or albumin.

The effects of eluant salt character and concentration on the elution of [Re-188]perrhenate from the alumina-based tungsten-188/rhenium-188 generator system have also been investigated. By decreasing the NaCl concentration from 0.155 M to 0.010 M, the volume of eluant required to elute the Re-188 bolus is greatly increased. Since the eluted Re-188 is reduced for attachment to various ligands after elution, the use of physiological (0.155 M) saline is not required. Preliminary studies of the effects of elution with different salt solutions has demonstrated that low concentrations (0.01 M) of other salts elute the Re-188 in a sharp bolus in the order CsCl > RbCl > KCl > LiCl > NaCl > NaBr >>> HCl. Thus, low concentrations of KCl or CsCl, etc., can be used to provide radioactive Re-188 in a more concentrated solution.

During this period several agents were supplied to Medical Cooperative investigators, including [I-123]-labeled and [I-131]-labeled fatty acid analogues for studies at the Brookhaven National Laboratory and the Cardiology Department at the Free University of Amsterdam. Tungsten-188/rhenium-188 generators were supplied to the University of Massachusetts and the Center for Molecular Medicine and Immunology, in Newark, New Jersey. Osmium-191 was supplied for fabrication of generators for patient studies in Finland.

INCORPORATION OF RADIOIODINATED IODOPHENYL-SUBSTITUTED
FATTY ACIDS OF ISOLATED RAT HEARTS INTO
ENDOGENOUS LIPIDS

In previous reports, we have described the use of the Langendorff-perfused rat heart system to study the metabolism of the methyl-branched fatty acids. Several of these reports contained descriptions of the radioactive components of the outflow of the isolated hearts injected with 15-(p-[I-125]iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) (ORNL/TM-10441, -10531, and -11043). Additionally, we have described the incorporation of BMIPP into the endogenous lipid pools of the rat hearts under both normoxic and hypoxic conditions (ORNL/TM-10839 and -11014). In these studies with the Langendorff rat hearts, the straight-chain 15-(p-iodophenyl)pentadecanoic acid (IPPA) analogue was labeled with I-131 and was administered simultaneously with [I-125]BMIPP as a control.

More recently we have used the Langendorff system to evaluate the effects of albumin, a carrier for insoluble fatty acids, with or without an exogenous fatty acid, palmitate, in the perfusate buffer on the metabolism of BMIPP. In ORNL/TM-11377, we reported the first demonstration of "back-diffusion" of unmetabolized BMIPP in the outflow of the perfused hearts when bovine serum albumin (BSA) or BSA and sodium palmitate (BSA/PAL) were present in the perfusate buffer. Under these two conditions, both BMIPP as well as the unidentified radioactive material previously designated "X" were present in the outflow, suggesting that the slow washout of radioiodinated BMIPP observed *in vivo* probably also represents both "back diffusion" and loss of metabolites. These results suggested for the first time that the slow myocardial washout observed in humans after the administration of [I-123]BMIPP is due to the loss of both metabolized and unmetabolized BMIPP.

In a further effort to delineate the metabolism of BMIPP, studies were initiated to evaluate the incorporation of BMIPP into endogenous lipids of isolated hearts in the presence of BSA or BSA/PAL. The concentration of BSA or BSA/PAL in the Krebs-Henseleit (KH) buffer was 0.4 mM for these studies, and the isolated rat hearts were

perfused in a retrograde fashion with the [I-125]BMIPP/[I-131]IPPA mixture administered in a non-recirculating system. At 5, 7, 10, and 15 min after injection of the radioiodinated fatty acids, the perfusion was terminated, and the hearts removed and immediately weighed and counted prior to homogenization in 10 mL of cold chloroform:methanol (2:1) solution. Care was taken to minimize the interval between the termination of perfusion and the extraction of lipids in order to avoid lipolysis; all hearts were homogenized within 2 min of the end of the experiment.

The lipids were extracted from the acidified chloroform:methanol homogenates and analyzed by silica gel thin-layer chromatography (TLC) using a petroleum ether:ether:acetic acid (70:30:1) solvent system with the following standards: triglycerides (TG), the free fatty acids BMIPP and IPPA (FFA), diglycerides (DG), p-iodobenzoic acid (IBA) and β -OH BMIPP. The developed TLC strips were cut into 20 sections, and the radioactivity determined by an autogamma counter. The endogenous lipid profiles are expressed as the percent of the total activity on the TLC strip that co-chromatographed with a particular standard. Once the percent of total activity/fraction (lipid class) was determined, this value was then used with the percent injected dose/heart value, which had been determined for each heart, to obtain percent injected dose/fraction values for each heart at the specified time points under the different buffer conditions.

A comparison of the percent injected dose values in the isolated hearts at the specified time points under the different buffer conditions (Figure 1) demonstrated that approximately four times more BMIPP was extracted by the hearts when there was no albumin or palmitate present in the KH buffer. By 15 min post-injection, however, this difference had diminished to only two-fold with the greater loss of radioactivity from the hearts that did not have access to albumin or palmitate. By contrast, in the (KH + BSA) and the (KH + BSA/PAL) buffer groups, there was a relatively small loss of the extracted BMIPP from the hearts over the 15 min time period; the profiles of extraction and retention were very similar for these two groups.

TLC analyses of the lipids extracted from the hearts showed evidence of BMIPP incorporation into several endogenous lipid classes (e.g., phospholipids, triglycerides, and possibly diglycerides) under all buffer conditions; however, for simplicity of comparison, we have presented only the profiles of BMIPP incorporation into triglycerides and BMIPP flux through the free fatty acid pool. Comparison of the percent total activity/fraction values of the three buffer groups (Table 1) shows that the (KH + BSA/PAL) group has the greatest relative percentage incorporation of BMIPP into triglycerides, with a proportional increase of activity in this pool. Radioactivity in the free fatty acid pool was essentially undetectable at the latter time points in this group of hearts. In the (KH + BSA) group, there was also a proportional increase in the triglyceride incorporation of BMIPP; however there was still detectable activity in the free fatty acid pools of these hearts at 15 min. Only in the KH buffer group was there a decrease observed in the proportional distribution of radioactivity in the triglyceride pools.

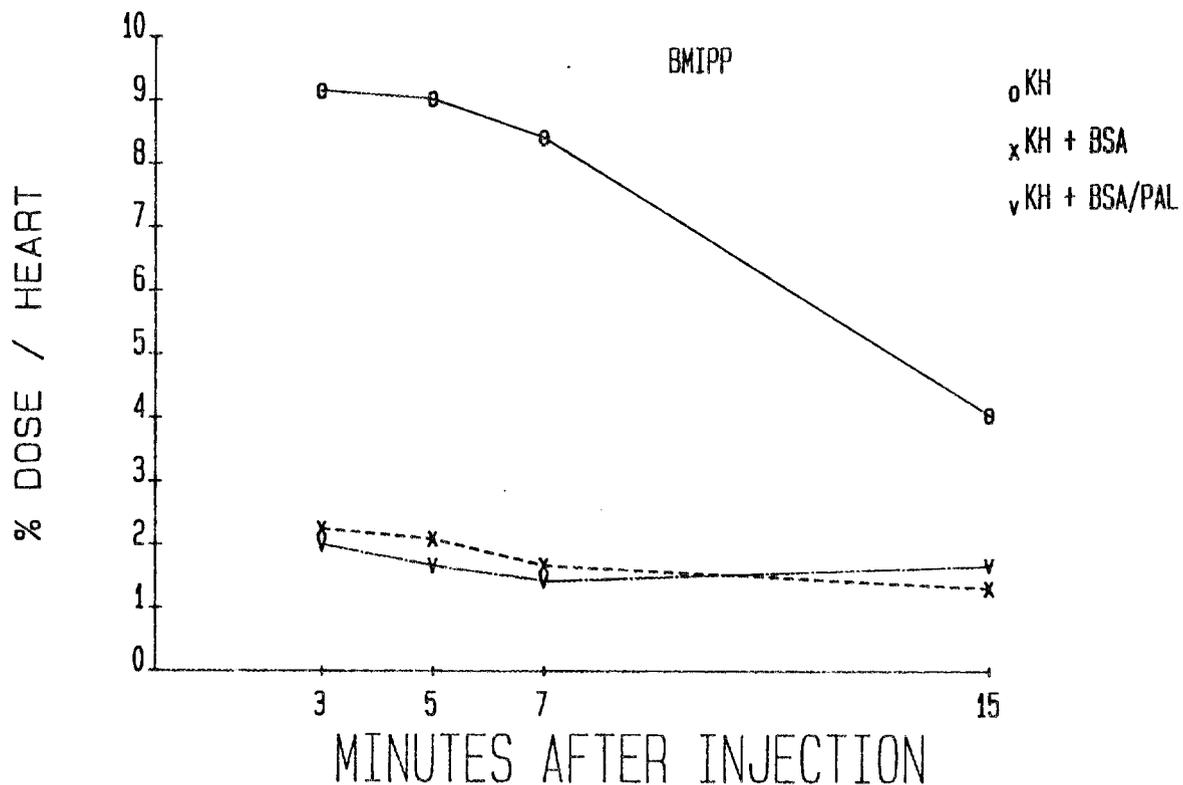


Figure 1. Effects of buffer solution composition on the global retention of [I-125]BMIPP.

Table 1. Relative percent activity in triglyceride (TG) and free fatty acid (FFA) for isolated hearts injected with [I-125]BMIPP.

Time (min)	Mean % Total Activity (\pm S.D.) Buffer					
	KH		KH+BSA		KH+BSA/PAL	
	TG	FFA	TG	FFA	TG	FFA
3	54 \pm 3	14 \pm 2	37 \pm 5	18 \pm 3	60 \pm 6	8 \pm 1
5	50 \pm 3	14 \pm 1	41 \pm 8	15 \pm 3	66 \pm 4	4 \pm 1
7	50 \pm 2	13 \pm 2	45 \pm 7	13 \pm 3	72*	<2*
15	42 \pm 5	9 \pm 4	53 \pm 9	11 \pm 1	72 \pm 3	<2

*Only two hearts; remainder is mean of four hearts per time point.

Because of the differences observed in the percent injected dose of BMIPP extracted or retained by the isolated hearts under the three buffer conditions, a comparison of the relative distribution of the radioactivity within the hearts, such as presented in Table 1, provides only part of the picture. Comparison of the percent injected dose/fraction values provides further insight into the effects of buffer composition on the relative incorporation of [I-125]BMIPP into the FFA and TG lipid pools. Comparison of these values (Figure 2) shows that the loss of BMIPP radioactivity from hearts perfused with KH buffer occurs from both triglyceride and free fatty acid pools, but predominantly from triglycerides. In contrast, the (KH + BSA) and (KH + BSA/PAL) hearts show little change in the triglyceride levels of radioactivity during the 15 min assay period.

In the TLC distribution of the lipids extracted from the isolated hearts under the various buffer conditions, there are 1-2 polar radioactive fractions which are as yet unidentified. One component may represent the endogenous diglycerides. Differences in the relative distribution of radioactivity in these polar fractions of hearts in the presence and absence of albumin and palmitate are also observed (data not shown). With the identification of these polar endogenous components, more information concerning the metabolism of methyl-branched fatty acids can be obtained.

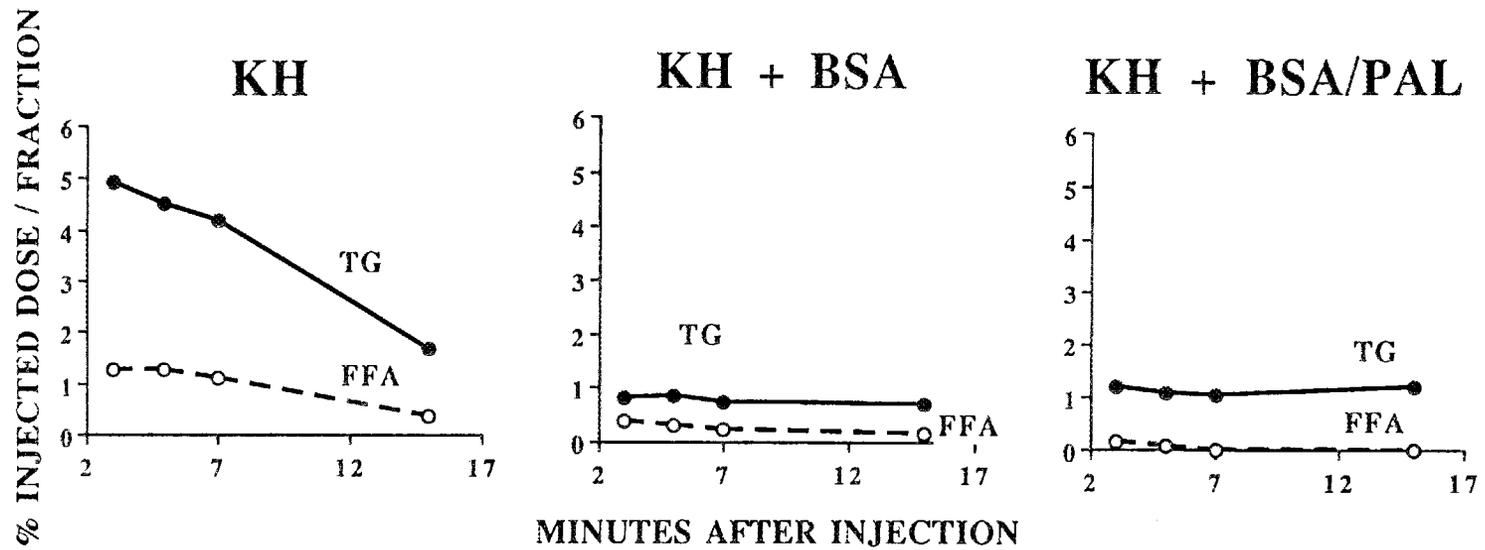


Figure 2. Comparison of the effects of buffer composition on the incorporation of [I-125]BMIPP into the FFA and TG fractions of Langendorff-perfused rat hearts.

EFFECTS OF CATIONS ON ELUTION OF RHENIUM-188 FROM THE ALUMINA-BASED W-188/Re-188 GENERATOR SYSTEM

There is widespread interest in the availability of rhenium-188 for various therapeutic applications, particularly for attachment to tumor-specific monoclonal antibodies for radioimmunotherapy. Rhenium-188 can be conveniently obtained from our W-188/Re-188 alumina generator system described earlier (ORNL/TM-10531) by elution with normal saline (0.155 M NaCl).¹ High-performance liquid chromatography has demonstrated that sodium perrhenate ($\text{Na}^{188}\text{ReO}_4$) is the principal radioactive species eluted from the parent sodium tungstate ($\text{Na}_2^{188}\text{WO}_4$) (unpublished data through collaborative studies with NeoRex, Inc., Seattle, WA). Normal saline was originally chosen as the eluant in comparison with the Mo-99/Tc-99m generator and since it is compatible with biological systems. Similar to ^{99m}Tc-pertechnetate (NaTcO_4), Re-188 is usually not used directly in the perrhenate chemical form, but is chemically modified after elution for radiolabeling an appropriate intermediary substrate or ligand which is part of a tissue-specific agent. Since both the nature of the cation and the radioactivity concentration (mCi/mL) are important factors, the effects of other eluants on the elution performance of the W-188/Re-188 generator have now been evaluated.

These studies were performed in collaboration with E. C. Lisic, a post-doctoral fellow during the November 1987-1989 period. Dr. Lisic is now an assistant professor at Tennessee Technological University, and these collaborative studies are continuing. In analogy with the Mo-99/Tc-99 generator, water does not elute either the Re-188 daughter or W-188 parent from the alumina-based W-188/Re-188 generators. We have shown that the concentration of NaCl required to elute Re-188 from $\text{Na}^{188}\text{ReO}_4$ can be much lower than physiological saline (0.155 M). In fact, by decreasing the NaCl concentration from 0.155 M NaCl to 0.01 M NaCl, Re-188 is still eluted from the generator in theoretical yield. Unfortunately, decreasing the concentration to 0.01 M NaCl significantly increases the volume required for elution of $\text{Na}^{188}\text{ReO}_4$ by at least a factor of two.

The effects of alkali metal chlorides on the elution of Re-188 are shown in Table 2. The elution volume decreases and elution profile becomes more narrow when larger (heavier) Group IA alkali metal cations (Cs^+ or Rb^+) are used in place of Na^+ . One generator was used for these studies and was equilibrated with the salt solution before elution at the same flow-rate. Changing the anion of the salt from Cl^- to Br^- , by using NaBr , increases the elution volume.

Table 2. Effect of eluant composition on elution of rhenium-188 on the % yield of Re-188 eluted per 10 mL fraction as a function of eluant.

10 mL Fraction	Fraction of Re-188 Eluted, %				
	Elution Salt (0.010 M)				
	LiCl	NaCl	KCl	RbCl	CsCl
1	0.90	0	0.50	0.70	1.3
2	2.3	1.2	2.4	2.0	2.9
3	27.2	9.7	29.1	39.6	48.2
4	62.8	51.4	60.9	51.3	42.2
5	6.0	35.3	6.3	5.1	4.0
6	0.80	2.4	0.80	1.3	1.4

Our preliminary results showed that elution of $^{188}\text{ReO}_4^-$ from an alumina column using a 0.010 M salt eluant increases in the order (from fastest to slowest) of $\text{CsCl} > \text{RbCl} > \text{KCl} > \text{LiCl} > \text{NaCl} > \text{NaBr} \gg \gg \text{HCl}$. Thus, a 0.01 M CsCl solution will elute $^{188}\text{ReO}_4^-$ from an alumina column generator in essentially the same volume as a 0.155 M NaCl solution. The advantages are a lower salt concentration and a high radioactivity concentration (mCi/mL).

LITERATURE CITED

1. Callahan, A. P., Rice, D. E., and Knapp, F. F., Jr. "Rhenium-188 for Therapeutic Applications from an Alumina Based Tungsten-188/Rhenium-188 Radionuclide Generator," NucCompact - European/American Comm. in Nuclear Medicine, 20, 3-6 (1989).

AGENTS FOR MEDICAL COOPERATIVES

Four samples of iodine-125-labeled fatty acids were supplied to the Cardiology Department, Free University, Amsterdam, the Netherlands (F. Visser, M.D.), as well as three shipments of iodine-131-fatty acids. One shipment each of iodine-125-BMIPP and iodine-123-BMIPP were made to Brookhaven National Laboratory, Upton, New York (P. Som, D.V.M.). In this collaborative program, the effects of cocaine intoxication on myocardial metabolism are being evaluated by SPECT using the methyl-branched BMIPP. One shipment of iodine-125-BMIPP was made to the University of Bonn, Bonn, West Germany (Dr. J. Kropp).

Tungsten-188/rhenium-188 generators were supplied to collaborators at the University of Massachusetts, Worcester, Massachusetts (A. B. Brill, M.D., Ph.D.) and also to the Center for Molecular Medicine and Immunology (CMMI) in Newark, New Jersey (D. Goldenberg, M.D., et al.).

One shipment of osmium-191 for fabrication of osmium-191/iridium-191m generators for Phase I patient studies with iridium-191m was made to the VIT Reactor Laboratory, in Espoo, Finland (J. Hiltunen). In addition, fabrication of a nonsterile generator was supplied to Syncor, Inc., in Metairie, Louisiana, for initial testing of elution procedures in anticipation of Phase I patient studies at the Houma Heart Clinic in Houma, Louisiana (G. Murray, M.D.).

Copper-64 was produced by the (n,p) reaction at the Missouri University Research Reactor (MURR), and following processing at ORNL, was supplied as cupric chloride to the Oak Ridge Associated Universities, Oak Ridge, Tennessee (L. C. Washburn, Ph.D.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Staff Publications

Audia, V. Y., McPherson, D. W., Weitzbert, M., Rzeszotarski, W. J., Sturm, B., Kachur, J. F., Abreu, M., and Kaiser, C. "Synthesis of Some 3-(1-Azabicyclo[2.2.2]octyl) 3-Amino-2-hydroxy-2-phenylpropionates: Profile of Antimuscarinic Efficacy and Selectivity," J. Med. Chem., 33:307-310 (1990).

Goodman, M. M., Neff, K. H., Ambrose, K. R., and Knapp, F. F., Jr. "Effect of 3-Methyl-Branching on the Myocardial Retention of Radioiodinated 19-Iodo-18-Nonadecenoic Acid Analogues," J. Nucl. Med. Biol., 16(8):813-819 (1989).

Mirzadeh, S., Brechbiel, M. W., Atcher, R. W. and Gansow, O. A., "Radiometal Labeling of Immunoproteins: Covalent Linkage of 2-(4-Isothiocyanatobenzyl)diethylenediaminepentaacetic Acid Ligands to Immunoglobulin," Bioconjugate Chemistry, 1:59-65 (1990).

Presentations

D. W. McPherson presented an invited lecture on March 22, 1990, entitled "Specialized Aspects of Radiolabeling - Copper-64 Labeled Antibodies" at the training course on Radiolabeling Antibodies at the Medical Division of the Oak Ridge Associated Universities.

Patents

M. M. Goodman and F. F. Knapp, Jr. "Radiohalogenated Thienylethylamine Derivatives for Evaluating Local Cerebral Blood Flow," U.S. Patent 4,900,539, Patent Gazette, February 13, 1990.

Visitors

Dr. Bert M. Coursey, Group Leader of the Radiation Interactions and Dosimetry Group at the Center for Radiation Research, National Institute of Standards and Technology, Gaithersburg, Maryland, visited on January 8 to discuss areas of collaboration with the Nuclear Medicine Group.

Miscellaneous

F. F. Knapp, Jr., was an invited speaker at the 30th Commemorative Meeting of the Finnish Society of Nuclear Medicine held in Helsinki on March 2-3, and presented a talk entitled "Development and Initial Clinical Applications of the Activated Carbon Osmium-191/Iridium-191m Generator System." He presented seminars in the nuclear medicine departments at the university hospitals in Kupio on March 1 and Turku on March 5 describing clinical applications of iridium-191m from the generator for the evaluation of cardiac function and the use of iodine-123-labeled fatty acids for evaluation of cardiac metabolism. He also met with research groups in Helsinki and Espoo to coordinate collaborative studies and to offer guidance on the synthesis and applications of various radiopharmaceuticals. Following these visits in Finland, he visited the Clinic for Nuclear Medicine at the University of Bonn, West Germany, and the Cyclotron Research Center at Sart Tilman University in Liege, Belgium, to coordinate collaborative projects on both the preclinical and clinical evaluation of radiopharmaceuticals.

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