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SUMMARY

In this report, an evaluation of the effects of albumin and albumin plus sodium palmitate in the phosphate buffer perfusate on the relative release of unmetabolized fatty acid and the unknown metabolite(s) from isolated rat hearts administered 15-(p-[I-125]iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) is described. Earlier studies had demonstrated the presence of a major unidentified polar radioactive component in the outflow of hearts injected with BMIPP and perfused with the traditional Krebs-Henseleit (KH) buffer, which does not contain albumin. The current studies were performed with KH buffer containing either albumin (BSA) or albumin and palmitate (BSA/PAL) to assess the relative loss of the metabolite and unmetabolized BMIPP from the perfused hearts. The results demonstrated that in the presence of albumin both the unidentified material and BMIPP are present in the outflow (i.e., 5 min perfusate buffer, % BMIPP: KH, 3%; KH + BSA, 10%; KH + BSA/PAL, 41%). These results demonstrate that BMIPP is a major radioactive component in the outflow of isolated hearts using a perfusate containing BSA and palmitate and, more importantly, suggest for the first time that the slow myocardial wash-out observed in humans after administration of [I-123]BMIPP probably represents loss of both unmetabolized BMIPP and the unidentified metabolite. Coronary sinus sampling studies with dogs are now in progress to relate the relative contribution of these two components to the release of radioactivity from the heart.

Also in this report, our production experience for several radioisotopes being used by the ORNL Nuclear Medicine Program is summarized. Production of osmium-191, platinum-195m, tungsten-188, copper-64, and copper-67 have been evaluated in the ORNL High Flux Isotope Reactor (HFIR), the High Flux Brookhaven Reactor (HFBR), and the Missouri University Research Reactor (MURR). With the "temporary" shut-down of the HFIR and HFBR, the MURR is currently the only production facility available.

METABOLISM OF RADIOIODINATED IODOPHENYL-SUBSTITUTED FATTY ACIDS IN ISOLATED RAT HEARTS – BACK-DIFFUSION OF UNMETABOLIZED FATTY ACIDS

The Langendorff-perfused rat heart system has provided an opportunity to study the metabolism of methyl-branched fatty acids in isolated hearts, thus eliminating the interference of release of metabolites from other tissues. Using this technique, we have described for the first time the release of what appears to be a major unidentified polar metabolite from isolated rat hearts administered 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) (ORNL/TM-10441 and -11043). The polar metabolite designated "X" was found to be the major component of the radioactivity present in the outflow from isolated hearts injected with BMIPP, accounting for approximately 80% of the "washout" within 5 min after injection. These initial results were obtained using the Krebs-Henseleit (KH) buffer specified in the Langendorff procedure – a buffer that contains glucose as the source for myocardial energy production and that does not contain albumin or fatty acids. These initial studies were conducted with the KH buffer for comparison with results from earlier studies performed with IPPA.

Investigations evaluating the metabolism of [C-11]-labeled palmitate in dog hearts has demonstrated that a significant fraction of the radioactivity lost from ischemic regions represent back-diffusion of the unmetabolized fatty acid. Because slow "washout" of BMIPP has been observed in both animal and clinical studies, it is important to demonstrate if such washout represents solely the metabolism of BMIPP or whether some back-diffusion of BMIPP might also occur. In order to evaluate this possibility in the isolated rat heart system, it was necessary to include albumin (0.4 mM bovine serum albumin, BSA) in the KH perfusate buffer to provide continuous availability of this carrier for the insoluble free fatty acids. In addition to the albumin effects, we were interested in determining the effects on BMIPP uptake (and possible back-diffusion) when a naturally-occurring fatty acid (palmitate) is available as an alternate energy source. Parallel studies were thus also conducted with 0.4 mM palmitate (PAL) combined with 0.4 mM BSA in the KH buffer (BSA/PAL).

The isolated heart technique has been described earlier (ORNL/TM-10441) and briefly involves administration of a mixture of [I-125]-BMIPP and [I-131]-IPPA to isolated rat hearts in a non-recirculating system. This single-pass system allows the collection of effluents from the hearts for counting, after which the lipids are extracted using an acidified Folch technique and then analyzed by thin-layer chromatography (TLC) using a petroleum ether:ethyl ether:acetic acid (70:30:1) solvent system. At the termination of the perfusion (i.e., 15 min after injection), the hearts are counted to determine the amount of radioactivity remaining at that time. The values calculated for the percent radioactivity remaining in the hearts are then added to the total radioactivity in perfusates collected at 3 to 15 min post-injection in order to approximate what we call the "extraction fraction" for the fatty acids under the various buffer conditions.

As expected, the presence BSA or palmitate and albumin (BSA/PAL) in the perfusate buffer affects the profiles of the radioactivity from the hearts for both BMIPP and IPPA as shown in Figure 1. In comparison to differences between the BMIPP and IPPA profiles observed with KH buffer, the release profiles of BMIPP and IPPA were quite similar to each other when albumin and palmitate were included in the buffer. Furthermore, the small peak of radioactivity characteristically observed between 5-7 min in the BMIPP profile with the KH buffer (ORNL/TM-10441) was not detected when BSA and palmitate were present.

Comparison of the "extraction fractions" of BMIPP and IPPA under the three buffer conditions demonstrate further differences in the handling of these analogues by the heart in the presence of palmitate and/or BSA (Table 1). When palmitate and/or BSA were present in the KH buffer, the values for total % dose extracted by the hearts were lower than those obtained with the KH buffer alone. This was true for both BMIPP and IPPA. Additionally, there were differences between the three buffer systems as to how much of the extracted BMIPP or IPPA was retained by the hearts at the termination of perfusion. With the KH buffer, 65% of the BMIPP extracted by the hearts was still in the heart tissue at the end of the perfusion, whereas only 29% of the IPPA activity remained. With the KH+BSA buffer and a lower % dose of BMIPP and IPPA extracted by the heart, only

40% of the extracted fraction of BMIPP and 36% of the IPPA was retained by the hearts. When palmitate was available as an energy source (KH+BSA/PAL), the extraction fraction of both analogues was the lowest observed, and there was no difference in the percentage of radioactivity remaining in the heart at the conclusion of perfusion (55% for BMIPP, 56% for IPPA).

When the lipids were extracted from selected perfusates (1, 3, 5, 7, 10, and 15 min) and the radioactivity analyzed by TLC, significant levels of unmetabolized BMIPP were found in the KH + BSA and the KH+BSA/PAL perfusates at later time points, when only the polar metabolite "X" was found in the KH perfusates (Table 2). When palmitate was present in the buffer, the proportion of BMIPP in the outflow was maximal. For all three buffer systems, however, significant levels of the unknown metabolite(s) was detected in perfusates, demonstrating some myocardial metabolism of BMIPP in all three buffer systems. The presence of palmitate and/or BSA in the buffer affected the metabolism of the straight chain analogue IPPA in a manner similar to BMIPP with back-diffusion as well as metabolism of this fatty acid occurring (data not presented).

Analysis of these data provides some interesting observations on the metabolism of the BMIPP methyl-branched fatty acid analogue. None of the three buffer conditions completely duplicates the *in vivo* environment, but that is not the purpose of these studies. Using the isolated heart system, it is possible to evaluate the specific effects of various components (i.e., BSA, palmitate) on the metabolism of the fatty acid analogues. These studies have shown that some back-diffusion of the extracted fatty acids can occur when albumin is present in the Langendorff system. It is likely that some back-diffusion of BMIPP occurs *in vivo*, and studies will soon be initiated in conjunction with Randy Patterson, M.D., and his colleagues at the Cardiology Department of Crawford Long Hospital in Atlanta, Georgia to evaluate this in an open chest canine model by sampling

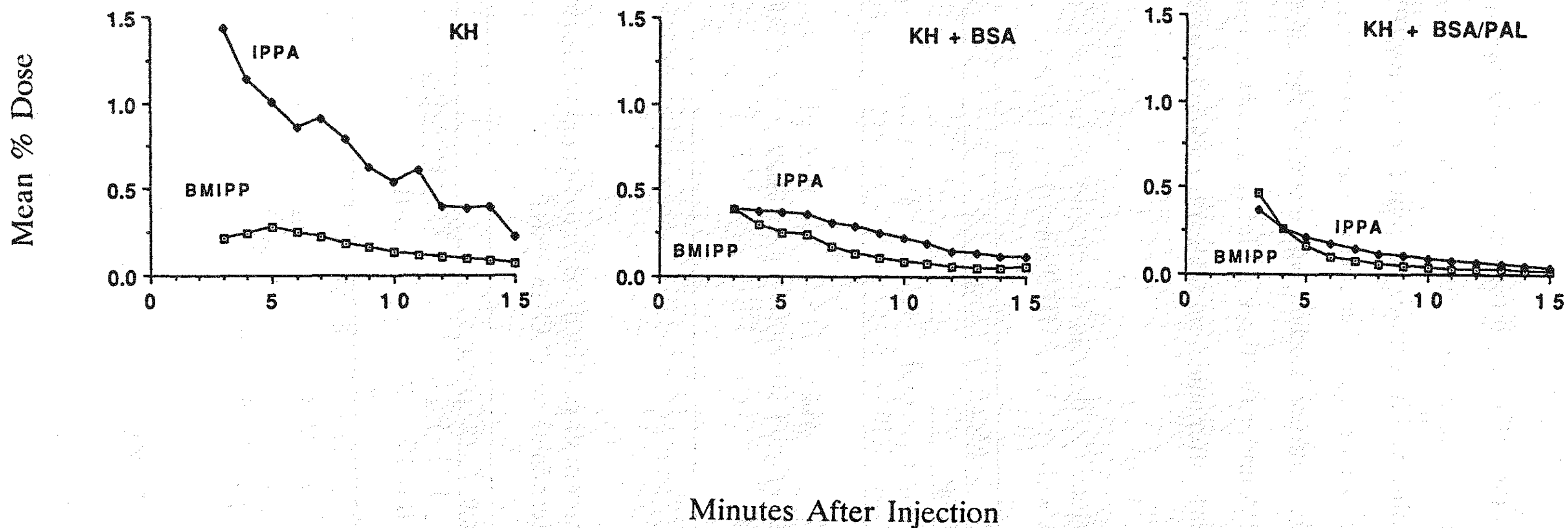

Figure 1. Levels (percent injected dose) of radioactivity from 15-(p-iodophenyl)pentadecanoic acid (IPPA) and 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) detected in the outflow of rat hearts administered a mixture of [I-131]IPPA + [I-125]BMIPP perfused with different buffer solutions.

the venous blood in the coronary sinus following intravenous administration of [I-123]-labeled BMIPP. When the perfusate buffer contains fatty acids, a natural nutrient for the heart, further differences are observed in a lower percent dose of BMIPP and IPPA extracted by the heart, but a higher percentage of extracted fatty acids retained by the heart, in comparison to BSA buffer. Future studies will evaluate the time course of myocardial storage of BMIPP and IPPA under the three buffer conditions by extracting and analyzing the isolated hearts lipids early after injection with the radioiodinated analogues.

Table 1. "Extraction fraction" values (% dose in hearts and perfusates 3-15) for isolated hearts injected with [I-125]-BMIPP and [I-131]-IPPA.[a]

	Mean % Dose					
	BMIPP			IPPA		
Buffer	Heart	Perfusate	Total	Hearts	Perfusate	Total
KH	4.04	2.17	6.21	3.84	9.33	13.17
KH+BSA	1.31	1.99	3.30	1.88	3.29	5.17
KH+BSA/PAL	1.66	1.34	3.00	2.31	1.78	4.09

[a]Values for four isolated hearts.

Table 2. Relative percent composition of Folch extracted components in the outflow determined by TLC analysis.[a]

	Mean % of Total					
Perfusate	KH		KH+BSA		KH+BSA/PAL	
(min)	BMIPP	"X"	BMIPP	"X"	BMIPP	"X"
1	80	4	69	12	82	4
3	12	48	33	44	76	9
5	3	78	10	70	41	27
7	2	78	7	77	35	34
10	3	68	10	64	34	33
15	4	67	7	80	31	29

[a]Values for perfusates from two isolated hearts.

SUMMARY OF PARAMETERS FOR REACTOR PRODUCTION OF RADIOISOTOPES FOR USE IN THE NUCLEAR MEDICINE PROGRAM

With the temporary shut-down of the ORNL High Flux Isotope Reactor in November 1986, alternative arrangements had to be made for production of radioisotopes to allow the continuation of a variety of important research products in the Nuclear Medicine Program. Staff at the High Flux Brookhaven Reactor (HFBR) have been very helpful in the production of osmium-191 to continue our work with the osmium-191/-iridium-191m radionuclide generator system and also have produced several samples of copper-67 by the (n,p) reaction on natural zinc and copper-64 by neutron irradiation of enriched copper-63. In addition, irradiations were initiated on a service irradiation basis with the Missouri University Research Reactor (MURR), which include tungsten-188 for the tungsten-188/rhenium-188 generator, copper-64 and platinum-195m for synthesis of the antitumor agent, *cis*-dichlorodiammineplatinum(II), for distribution through the ORNL Isotopes Distribution Office on a cost recovery basis. Since the temporary shut-down of the HFBR in December 1988, all irradiations for our program are now being conducted at the MURR. Table 3 provides a useful compilation of the yield and specific activity data based on our experience in producing these radioisotopes in the three facilities. The possibility of service irradiations through Nordion, Inc. at the Chalk River Canada facility, and at the Fast Flux Test Facility (FFTF) at Hanford, Washington, are also being pursued to ensure the continued availability of production sites during the hiatus of the HFIR and HFBR shut-down.

Table 3. Summary of Radioisotope Production Data for the ORNL Nuclear Medicine Program

		Production Facility					
		*Approximate Thermal Neutron Flux, neutrons/cm^2.sec					
		ORNL/HFIR 2×10^{15}		BNL/HFBR 8×10^{14}		MURR 5×10^{14}	
Radioisotope	Half-Life	Time (Days)	Spec. Act. (mCi/mg)	Time (Days)	Spec. Act. (mCi/mg)	Time (Days)	Spec. Act. (mCi/mg)
Osmium-191	15.4 d	3	300	25	230	21	165
Platinum-195m	4.02 d	1.5	1	...	...	21	0.7
Tungsten-188	69.4 d	21	3.5	...	...	75	0.3
Copper-64 –	12.7 h						
(n,)		1	1,200	2	760	...	...
(n,p)		...	...	...	...	7	0.3
Copper-67	61.9 h	...		7	0.3	...	...
Osmium-194**	6 y	365	3.59	...	...	...	...

*Irradiations have not been performed or yields calculated where values are not given.
**Calculated values.

Abbreviations:

ORNL/HFIR	=	Oak Ridge National Laboratory High Flux Isotope Reactor
BNL/HFBR	=	Brookhaven National Laboratory High Flux Brookhaven Reactor
MURR	=	Missouri University Research Reactor

AGENTS FOR MEDICAL COOPERATIVES

One shipment of [Os-191] potassium perosmate was made to Espoo, Finland (J. Hiltunen) for fabrication of osmium-191/iridium-191m generators for initiation of clinical trials with iridium-191m at the Helsinki University Hospital and the Kupio University Central Hospital. Several shipments of copper radioisotopes were made to the Oak Ridge Associated Universities, Oak Ridge, TN (J. Crook, M.D., Ph.D.), including copper-67, produced by the (n,p) reaction at the MURR. In addition, three shipments of copper-64-labeled antibodies were made for collaborative studies, one to the ORNL Biology Division, Oak Ridge, TN (S. Kennel, Ph.D.), and two to the Oak Ridge Associated Universities, Oak Ridge, TN (Dr. Crook).

One shipment of [I-131]IPPA was made to the Department of Cardiology at the Free University Hospital in Amsterdam, The Netherlands (F. Visser, M.D.). This collaborative program involves evaluation of the metabolism of radioiodinated fatty acid analogues in canine models. In addition, two shipments of [I-125]BMIPP were made to the Brookhaven National Laboratory (P. Som, D.V.M.), three to the Free University, Amsterdam, The Netherlands (Dr. Visser), and one to the University of Bonn, Bonn, West Germany (J. Kropp, M.D.). Two shipments of the thallated substrate for preparation of [I-123]IPPA were also made to Crawford Long Hospital, Atlanta, GA (Dr. Patterson) for the effects of reperfusion on fatty acid uptake in an open-chest canine model.

AGENTS PREPARED FOR COST-RECOVERY THROUGH THE ORNL ISOTOPES DISTRIBUTION OFFICE

On a cost recovery basis, five shipments of [Pt-195m]-*cis*-DDP were made: two to the University of California, San Diego, one to Durham, NC, one to Salt Lake City, UT, and one to Newark, NJ.

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Som, P., Oster, Z. H., Kubota, K., Goodman, M. M., Knapp, F. F., Jr., Sacker, D. F., and Weber, D. A. "Studies of a new Fatty acid Analogue (DMIVN) in Hypertensive Rats and the Effect of Verapamil Using ARG Microimaging," J. Nucl. Med. Biol., 16:483-490 (1989).

Srivastava, P. C., Hasan, A., Pratap, R., and Bhakuni, D. S. "An Unusual Iodine Monochloride Chlorination of an Imidazole Nucleoside," Nucleotides and Nucleosides, 8:1281-1285 (1989).

Visitors

On July 28, N. Schad, M.D., a nuclear cardiologist from Passau, West Germany, visited F. F. Knapp, Jr. to discuss the use of iridium-191m from the Os-191/Ir-191m generator for first-pass determination of ventricular function, in conjunction with iodine-123-labeled fatty acids for simultaneous evaluation of myocardial perfusion, function and metabolism. Dr. Schad was accompanied by Mr. Steven F. Basler, Technical Director of Scintillation Technologies Corporation in Maryville, Tennessee, who are interested in using iridium-191m with the modified Baird multi-crystal gamma camera. The status of approval for human use of iridium-191m from this generator in the U.S. was discussed.

Miscellaneous

D. W. McPherson presented a lecture entitled "Copper-64 Labeled TSC Bifunctional Chelates for Antibody Labeling" at the weekly seminar series at the Radiology Department at the University of Tennessee Hospital on July 27, 1989.

P. C. Srivastava presented an introductory lecture on "Nuclear Medicine Applications" in a Faculty Workshop for Nuclear Engineers held at the Oak Ridge

Associated Universities (ORAU) on August 15, 1989. The workshop was sponsored by the U.S. Department of Energy, and 30 college and university faculty members participated.

Representatives of Orbit, Inc. and General Electric Corporation visited to discuss the expertise and capabilities of the Nuclear Medicine Program for possible collaboration in the field of positron emission tomography (PET). Orbit is an Oak Ridge firm developing a new medical cyclotron design which was recently installed in the Medical Division at the Oak Ridge Associated Universities. General Electric has interest in the manufacture and marketing of a "complete" PET system, which will include the cyclotron, PET scanner and associated automated radiopharmaceutical synthesis apparatus. Opportunities at Orbit for the cyclotron design, and at ORNL and ORAU for radiochemical expertise and potential training capabilities were discussed during this initial meeting.

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