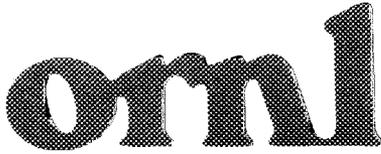




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**Nuclear Medicine Program
Progress Report for Quarter
Ending September 30, 1991**

F. F. Knapp, Jr.

- | | |
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| A. P. Callahan | C. R. Lambert |
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FOR QUARTER ENDING SEPTEMBER 30, 1991

F. F. Knapp, Jr., Group Leader

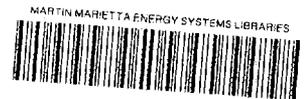
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SUMMARY

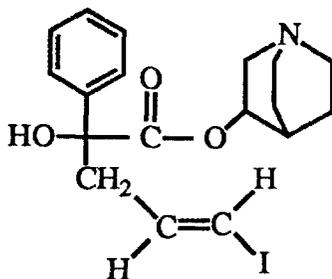
In this report the rat tissue distribution properties of "IQNP," a new radioiodinated cholinergic-muscarinic receptor antagonist, are described. IQNP is the acronym for 1-azabicyclo[2.2.2]oct-3-yl α -hydroxy- α -phenyl- α -(1-iodo-1-propen-3-yl)acetate, which is an analogue of the QNB muscarinic antagonist in which the p-iodophenyl moiety has been replaced with the 1-iodo-1-propen-3-yl moiety. The radioiodinated IQNP analogue is easier to prepare in much higher yields than QNB and is thus a candidate for the evaluation of muscarinic receptors by external imaging techniques.

Studies in rats demonstrated that IQNP shows high uptake in those cerebral regions rich in muscarinic receptors (at 6 h; cortex = 0.47% dose/gm; cortex/cerebellum = 7.83 and cortex/blood = 2.24). In addition, QNB-treatment of rats either 1 h before (pre) or 2 h after (post) administration of radioiodinated IQNP resulted in significant displacement or blocking of cerebral specific IQNP uptake (% dose/gm) in the cortex and striatum (at 3 h, striatum: control = 0.40, pre = 0.03, post = 0.10; cortex: control = 0.47, pre = 0.03, post = 0.14). Areas of non-specific uptake were not as greatly affected (at 3 h, cerebellum: control = 0.09, pre = 0.02, post = 0.03). Other blocking studies with ligands with established receptor specificity indicated that IQNP was only displaced by those ligands with established muscarinic receptor specificity (e.g., QNB and dextimide). These combined studies demonstrate that IQNP has specificity for the cholinergic-muscarinic receptor and is a good candidate for further studies.

Also during this period, several agents developed in the ORNL Nuclear Medicine Program were supplied to Medical Cooperative Programs for collaborative studies including the iodine-125-labeled BMIPP and DMIPP fatty acid analogues and the IPM antibody labeling agent. In addition, tin-117m and gold-199 were produced in the ORNL High Flux Isotope Reactor (HFIR) and supplied to the OHER-supported program in the Medical Department at Brookhaven National Laboratory to aid in their research until the re-start of the High Flux Brookhaven Reactor.

BIODISTRIBUTION STUDIES WITH 1-AZABICYCLO[2.2.2]OCT-3-YL
 α -HYDROXY- α -PHENYL- α -(1-IODO-1-PROPEN-3-YL)ACETATE (IQNP),
 A NEW LIGAND FOR THE STUDY OF MUSCARINIC RECEPTOR
 POPULATIONS

The muscarinic acetylcholine receptor system appears to play an important role in various physiological and behavioral processes, in addition to various dementias such as Alzheimer's disease. These observations have prompted the development of radiolabeled muscarinic receptor specific ligands for use in Computed Tomographic studies. We have previously reported the synthesis of a new ligand (ORNL/TM-11881), 1-azabicyclo[2.2.2]oct-3-yl α -hydroxy- α -phenyl- α -(1-iodo-1-propen-3-yl)acetate (IQNP) (1), an analogue of 1-azabicyclo[2.2.2]oct-3-yl α -hydroxy- α , α -diphenylacetate (QNB), a potent muscarinic antagonist.



Scheme I.

Biodistribution studies with ¹²⁵IQNP were performed using female Fisher VAF rats (~125 g) over a 6 h period. [I-125]QNP was dissolved in 0.1 ml of ethanol and 0.05 ml of 1N HCl was added. The solution was diluted to 10 ml with normal saline, passed through a 0.22 micron Millipore filter and injected through a tail vein into the metofane-anesthetized animals (1-2 mCi). The animals were killed by cervical fracture at the designated time points, and the various organs removed, rinsed with saline, blotted dry, and weighed in tared vials. The brains were immediately dissected into the various anatomical regions upon removal. Samples were counted in a Packard Minaxi 5000 sodium iodide auto gamma counter. The results are summarized in Table 1.

These data demonstrate that IQNP has a higher uptake in brain tissues that are rich in muscarinic receptors (cortex and striatum) with lower uptake in tissues that do not have a high concentration of these receptors (cerebellum). There is a modest uptake of radioactivity by the heart tissue, which also contains a high concentration of muscarinic receptors.

Table 1. Biodistribution of ^{125}I IQNP in Female Fisher VAF Rats (% dose/gm).*

Organ	Time (min)					
	15	30	60	120	240	360
Blood	0.85±0.15	0.62±0.05	0.38±0.05	0.38±0.03	0.27±0.04	0.21±0.02
Liver	1.46±0.18	1.10±0.05	0.80±0.06	0.95±0.04	0.75±0.08	0.65±0.07
Kidney	5.09±0.66	2.95±0.27	1.40±0.22	0.67±0.07	0.30±0.04	0.20±0.02
Heart	1.44±0.14	1.11±0.06	0.77±0.05	0.68±0.05	0.28±0.03	0.17±0.02
Lung	4.19±0.48	2.94±0.17	1.60±0.15	0.96±0.13	0.36±0.04	0.22±0.02
Cortex	0.99±0.09	0.80±0.09	0.86±0.05	0.64±0.02	0.54±0.04	0.47±0.06
Striatum	0.82±0.10	0.69±0.11	0.86±0.11	0.93±0.12	0.52±0.04	0.41±0.07
Cerebellum	0.54±0.05	0.36±0.02	0.30±0.02	0.24±0.01	0.09±0.01	0.06±0.01
Rest of Brain	0.72±0.06	0.53±0.04	0.58±0.07	0.41±0.03	0.32±0.02	0.27±0.03

*Mean ± standard deviation, 5 rats/time point.

A series of experiments were also conducted to determine if the uptake of IQNP could be blocked by QNB, a potent muscarinic antagonist. This experiment consisted of the preinjection of QNB (5 mg/kg) 1 h before the injection of ^{125}I IQNP to evaluate what effect the injection of a muscarinic antagonist would have on the uptake of IQNP. Another set of animals was injected with ^{125}I IQNP followed by injection of QNB (5 mg/kg) 2 h later to determine if the binding of IQNP to the receptor site was reversible. As a control, some animals received only the ^{125}I IQNP injection. Three hours after the injection of IQNP the animals were killed, the brain and heart removed, dissected into the various areas of interest, and counted. The results of this study are shown in Figure 1.

The results of this study demonstrate that the uptake of IQNP is blocked by the preinjection of a muscarinic antagonist, and that the uptake of IQNP is displaceable by muscarinic antagonist. These results suggest that IQNP demonstrates selectivity for the muscarinic receptor, and that this binding to the muscarinic receptor is reversible.

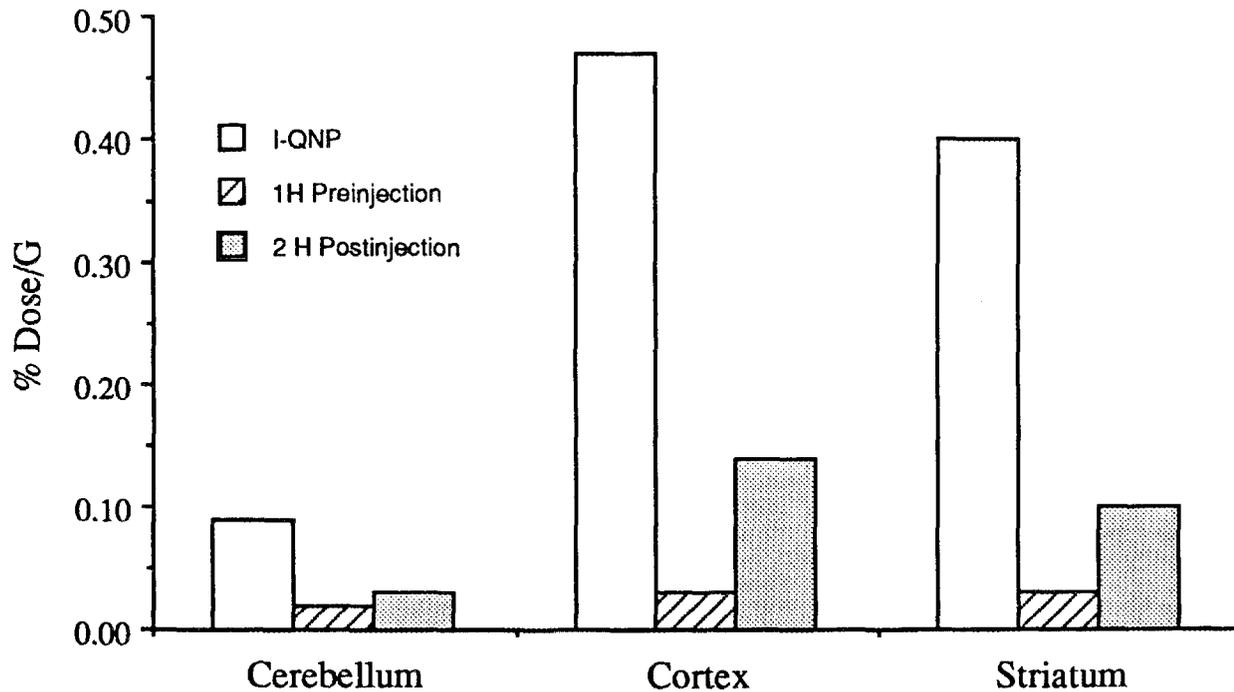


Figure 1. Comparison of the uptake of radioactivity in the cerebellum, cortex, and striatum after injection of iodine-125-QNP (control) with animals treated before or after with the QNB muscarinic antagonist.

A study to determine the specificity of IQNP binding for the muscarinic receptor was also performed using a series of blocking agents for different receptors (Figure 2). In this study, each challenge ligand (5 mg/kg) was injected into a set of animals and after 1 h a solution of ^{125}I IQNP was then injected. After 3 h, the animals were sacrificed, the various organs of interest removed and counted. The ligands and receptor specificity used for this study were: spiperone (D2 dopamine antagonist), (+)-butaclamol (D2/D1 dopamine antagonist), (-)-butaclamol (inactive enantiomer), QNB (muscarinic antagonist), dextetimide (muscarinic antagonist), and ketanserine (5HT₂ serotonin antagonist).

These results show that only QNB and dextetimide, both muscarinic antagonists, block the uptake of IQNP demonstrating that IQNP demonstrates specificity for the muscarinic receptor. The other blocking agents showed no effect on the uptake of IQNP into receptor

rich areas of the brain. Further studies utilizing IQNP as a muscarinic receptor imaging agent in larger animals utilizing imaging and autoradiographic techniques are in progress.

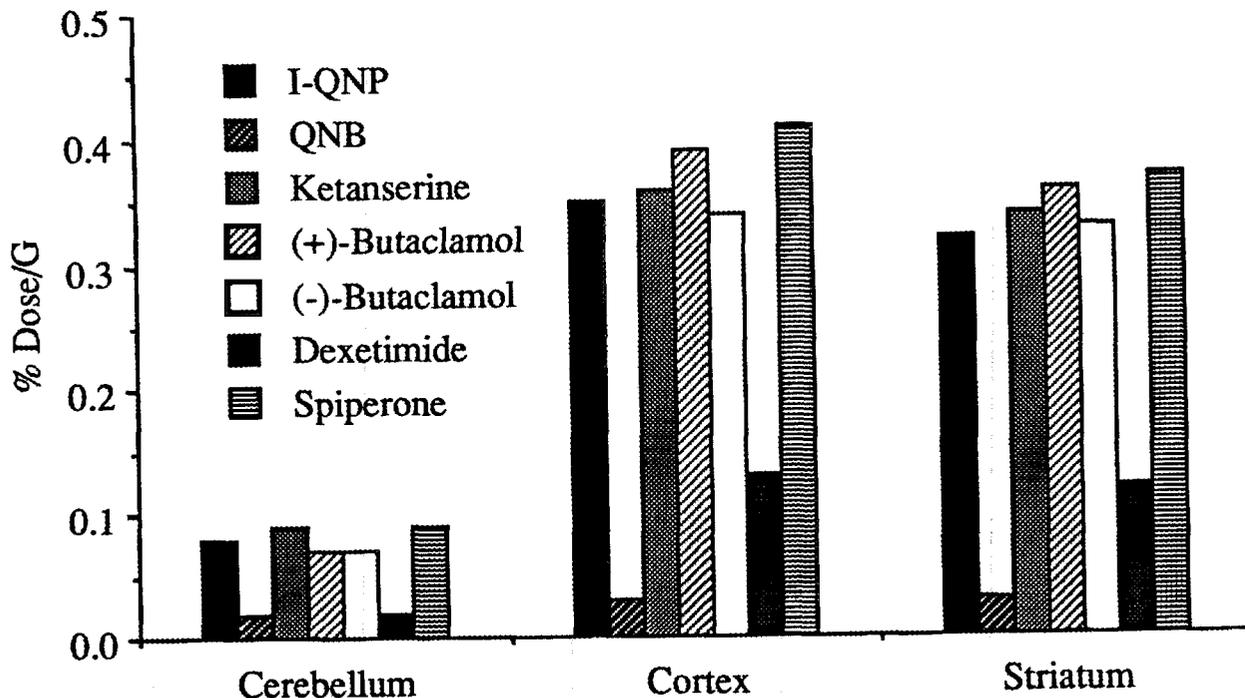


Figure 2.

AGENTS FOR MEDICAL COOPERATIVES

One shipment each of gold-199 and tin-117m were supplied to Brookhaven National Laboratory (L. Mausner, Ph.D.) to assist a continuation of BNL research topics until re-start of the High Flux Brookhaven Reactor (HFBR). A tungsten-188/rhenium-188 generator was shipped to the University of Bonn, Germany (J. Kropp, M.D. and F. F. Knapp, Jr., Ph.D.) for collaborative studies involving rhenium-188-labeled therapeutic agents. Samples of iodine-125-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) and the 3,3-dimethyl analogue (DMIPP) were shipped to the University of Bonn for continuing collaborative metabolic studies with an isolated rat heart preparation (J. Kropp, M.D.). Iodine-125-labeled BMIPP and DMIPP were also supplied to Brookhaven National Laboratory (P. Som, D.V.M.)

for collaborative studies of the effects of chronic and acute cocaine intoxication on myocardial fatty acid uptake.

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Franken, P., Dobbelier, A. A., Ham, H. R., Ranquin, R., Lieber, S., van den Branden, F., van den Heuvel, C., Brihaye, C., Guillaume, M., Vandevivre, J., and Knapp, F. F., Jr. "Discrepancy Between Myocardial Perfusion and Regional Wall Motion at Rest and During Exercise in Patients with Coronary Artery Disease," *Nucl. Med. Commun.*, 12:473-484 (1991).

Griffiths, G. L., Knapp, F. F., Jr., Callahan, A. P., Chang, H.-C., Hansen, H. J., and Goldenberg, D. M. "Direct Radiolabeling of Monoclonal Antibodies with Generator-Produced Rhenium-188 for Radioimmunotherapy," *Cancer Research*, 51, 4594-4602 (1991).

Kropp, J., Kohler, U., Knapp, F. F., Jr., Thulfaut, A., Joergens, M., Briele, B., and Biersack, H.-J. "Initial Clinical Scintigraphic Experience with 15-(p-I-123-Iodophenyl)-3-R,S-Methylpentadecanoic Acid (BMIPP) for the Diagnosis of Coronary Heart Disease (CHD)," Annual Meeting of the German Society of Nuclear Medicine, University of Tuebingen, April 11-13, 1991, *Nuklearmedizin*, 2, A47 (1991).

Kropp, J., Likungu, J., Kirschhoff, P. G., Knapp, F. F., Jr., Reichmann, K., Reske, S. N., and Biersack, H.-J. "Single Photon Emission Tomographic Imaging of Myocardial Oxidative Metabolism with 15-(p-[I-123]-Iodophenyl)Pentadecanoic Acid in Patients with Coronary Artery Disease and Aorta-Coronary Bypass Graft Surgery," *Eur. J. Nucl. Med.*, 18(7), 467-474 (1991).

Lambert, S. J., Kabalka, G. W., Knapp, F. F., Jr., and Srivastava, P. C. "Inductive Effect of Positively Charged Nitrogen on the Addition of Iodine Monochloride to Alkynamine Hydrochlorides," *J. Org. Chem.*, 56, 3707-3711 (1991).

Srivastava, P. C., Tedjamulia, M. L., Owen, B. A., Knapp, F. F., Jr. "Synthesis and Myocardial Specificity of *p*-(*n*-alkyl)-[¹²⁵I]-Iodophenyl Fatty Acid Analogues," Indian Journal of Chemistry, 30B, 188-194 (1991).

Presentations

Members of the Nuclear Medicine Group presented and co-authored three papers at the recent European Association of Nuclear Medicine Congress held in Vienna, Austria on September 1-5, 1991.

Ambrose, K. R., Kropp, J., Lambert, C. R., Biersack, H.-J., and Knapp, F. F., Jr. "Back Diffusion (BD) and Release of Metabolites ("X") Contribute to Washout of Radioiodinated BMIPP from Isolated Rat Hearts (RH)."

Knapp, F. F., Jr., Lisic, E. C., Mirzadeh, S., Callahan, A. P., and Rice, D. E. "A New Clinical Prototype Tungsten-188/Rhenium-188 Generator to Provide High Levels of Carrier-Free Rhenium-188 for Radioimmunotherapy (RAIT)."

Kropp, J., Koehler, U., Knapp, F. F., Jr., and Biersack, H.-J. "15-(*p*-123-Iodophenyl)-3-*R,S*-methylpentadecanoic (BMIPP) to Evaluate Ischemia in Patients with Coronary Artery Disease (CAD)."

Miscellaneous

F. F. Knapp, Jr. served as an external expert member of the thesis committee at the Free University of Brussels on September 23, 1991, for the doctoral thesis of Phillippe R. Franken, M.D., from the Nuclear Medicine Department at Middelheim Hospital in Antwerp, Belgium. The thesis entitled "Functional Evaluation of Ischemic Heart Disease by Means of First-Pass Radionuclide Angiography," is based on the evaluation of a large number of patients with the ultra-short lived iridium-191m radioisotope from the osmium-191/-iridium-191m generator developed in the ORNL Nuclear Medicine Group.

P. C. Srivastava has been appointed as a professor adjunct, at the University of Tennessee Biomedical School, for a five-year term.

Members of the Nuclear Medicine Group (F. F. Knapp, Jr., S. Mirzadeh, A. P. Callahan) are organizing a symposium entitled "New Radionuclide Generator Systems for Nuclear Medicine Applications," under the auspices of the Division of Nuclear Chemistry and Technology of the American Chemical Society (ACS) for the National ACS Meeting to be held in Washington, D.C., August 23-28, 1992. The proceedings of this symposium are planned for publication in the "ACS Advances in Chemistry" series.

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60. A. Jones, HMS Radiology Dept., Shields Warren Radiation Laboratory, 50 Binney Street, Boston, MA 02115
61. G. Kirsch, Department of Chemistry, Universite de Metz, Metz, France
62. J. Kropp, M.D., Klinik fuer Nuklear Medizin, Der Universitat Bonn, Sigmund Freud Strasse 25, 5300 Bonn 1, West Germany
63. D. E. Kuhl, M.D., Division of Nuclear Medicine, University of Michigan Hospitals, University Hospital BIG 412/0028, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0028.
64. S. Larson, M.D., Sloan-Kettering Inst. for Cancer Research, New York, NY 10021
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