PROGRESS REPORT
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"New Techniques for Positron Emission Tomography in the Study of Human Neurological Disorders"

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TABLE OF CONTENTS

Progress Report: Radiochemistry

Subproject 1 Faster, simpler processing of positron-emitting precursors: new physiochemical approaches (Douglas M. Jewett, Subproject Leader)

Subproject 2 Novel solid phase reagents and methods to improve radiosynthesis and isotope production (G. Keith Mulholland, Subproject Leader)

During the past grant period, we have made considerable progress in the development of new techniques for the production of radionuclides and synthesis of radiolabeled organic molecules, as well as in the development of specific new radiopharmaceuticals for PET studies in vivo.

Radionuclide production.

We have continued exploration of new target configurations and irradiation conditions which might simplify the production of the important PET radionuclides. To allow simultaneous production of a very short lived radionuclide, oxygen-15 (half-life 2 min) and longer lived radionuclides, such as nitrogen-13 or fluorine-18, we have developed tandem water targets. Using such targets and a medium energy cyclotron, such as our own, we have demonstrated that it is feasible to produce [15O]water for repeated blood flow studies (as per CNS activation protocols) without interfering with the required production of other radionuclides for PET.

Radiopharmaceutical chemistry: [18F]fluoride ion.

This grant has provided significant progress in the handling of small precursors for PET, development of new labeling strategies, and introduction of new reactive precursors for radiolabeling of organic radiopharmaceuticals.

As part of this project, we have introduced and continued to refine the use of solid supports for the collection and reaction of no-carrier-added [18F]fluoride ion. The majority of the work has been done using specific anion exchange resins synthesized in these laboratories. These resins are used for the collection of [18F]fluoride ion from [18O]water (allowing recycling of the [18O]water), and then used for chemical synthesis of organic molecules directly on the resin. The most important application has been to the synthesis of [18F]FDG, a process which has now been duplicated by at least two other institutions and two manufacturers; a commercial apparatus developed around this concept will be marketed shortly by one cyclotron manufacturer. We have continued research into better, more stable resins for use in such reactions, and have developed and evaluated new phosphazenium functionalized resins suitable for nucleophilic substitutions with [18F]fluoride ion.

We have also evaluated several alternative methods for the collection and isolation of [18F]fluoride ion. These have included the evaluation of fibrous anion exchange resins, which present different and potentially superior flow properties over conventional resins, as well as the use of a novel elution media aqueous carbonic acid for the elution of [18F]fluoride ion from anion exchange resins. Elution of [18F]fluoride ion from a resin can also be accomplished by passing through solutions of aryl trimethylammonium triflates; heating of the solution of eluted aryltrimethylammonium [18F]fluorides provides formation of the aryl[18F]fluorides via nucleophilic aromatic substitution, providing a novel method for the synthesis of aryl[18F]fluorides in the complete absence of cations, crown ethers or resins. Finally, a novel surface, oxidized carbon, was evaluated as a means of [18F]fluoride ion collection from target water. Such surfaces are rigid and thermally stable, and the collection of [18F]fluoride ion, elution with aqueous base, and subsequent conversion to [18F]FDG was demonstrated.

In conjunction with our methods for [18F]fluorinations on solid surfaces, we have developed two additional useful techniques for maximizing efficiency of our operation. First, we have developed a method utilizing UV irradiation for the purification and recycling of our [18O]water; this has been in continual use for more than two years. Second, we have developed a method for the recovery of unreacted [18F]fluoride ion from surfaces and resins, using purification via the trimethylsilyl[18F]fluoride intermediate. These techniques have allowed us to maximize our efficiency in the use of the relatively precious [18O]water for our targets.

Radiopharmaceutical chemistry: carbon-11.

We have also made considerable progress in developing novel methods and precursors for carbon-11 labeling of radiopharmaceuticals. Our goals, as in the area of fluorine-18 radiochemictry, have been to simplify and speed up the synthesis of carbon-11 labeled compounds.

We have utilized captive solvent methods for a number of radiopharmaceutical preparations. In this method, a thin film of reagent in organic solution is absorbed on a solid surface, and reacted with a [11C]precursor. We have demonstrated this technique to be useful in a number of alkylation reactions using [11C]methyl iodide, as well as in the production of [11C]acetate via a Grignard reagent and [11C]carbon dioxide.

To speed the synthesis of various [11C]labeled compounds, we have developed chromatographic methods for the separation of precursor from product which do not involve the use of expensive and hard-to-maintain HPLC equipment. By judicious choosing of solid phases, sometimes even the solid phase on which the labeling reaction is performed, it is possible to elute only the desired radiolabeled product, free of chemical impurities. This technique, combined with the captive solvent approaches developed in this laboratory, allow us to routinely and quickly prepare large batches of high specific activity, carbon-11 labeled radiopharmaceuticals (e.g., 690 mCi of [11C]flumazenil at end-of-synthesis). To provide maximum yields of [11C]methylation reactions, thus minimizing irradiation times and radiation exposures, we have also developed a rapid colorimetric test for methyl iodide; this allows simple testing of reaction conditions that might be used in the preparation of a new radiopharmaceutical.

Finally, we have most importantly introduced a new one-carbon precursor, [11C]methyl triflate, into use for [11C]methylations of new radiopharmaceuticals. This compound is much more reactive then [11C]methyl iodide, allowing reactions to proceed faster and under more mild conditions than are commonly used with [11C]methyl iodide. The synthesis of this precursor is accomplished simply by incorporation of an on-line catalytic furnace, thus it adds no time to the synthesis, and very little added complexity. This precursor has already found important applications in out laboratories, in the synthesis of [11C]raclopride and [11C]epinephrine for human use, and in the potential synthesis of [11C]methionine.

Radiopharmaceutical development.

As part of this project, we have made considerable progress in the synthesis and evalaution of several new PET radiopharmaceuticals.

Muscarinic acetylcholinergic receptor antagonists. Over the entire duration of this grant, we have been involved in the synthesis and evalaution, and eventual clinical use, of radiotracers for the muscarinic cholinergic receptor. We have previously reported the synthesis and in vivo human evaluation of [11C]scopolamine. In the last grant period, we have evaluated [11C]tropanyl benzilate in humans, and even more recently have introduced [11C]N-methylpiperidyl benzilate as an improved, third-generation imaging agent. Evalaution of this radiotracer in humans is underway.

Cholinergic markers: Vesicular uptake. We have developed numerous potential imaging agents based on the vesamicol structure; vesamicol is a high affinity inhibitor of the vesicular transport of acetylcholine. Derivatives with a variety of carbon-11 and fluorine-18 labeled moieties have been synthesized and evaluated in rodents, dogs and monkeys. Many of these compounds hold great potential as in vivo markers of cholinergic neurons in the brain and heart. We are currently obtaining in vivo data and toxicology data for two of these candidate compounds in preparation for the submission of an IND for their use in humans.

GABA chloride channel markers. In the newest area undertaken as part of our radiopharmaceutical development program, we have synthesized and begun to evaluate the in vivo behaviour of fluorine-18 labeled bicycloorthobenzoates. These compounds are high affinity ligands for the GABA/benzodiazepine receptor chloride ion channels. Potentially, these agents would form an alternative method for the study of GABA receptors, particularly the functional aspects of this ion channel and its relationship to normal or abnormal functioning of the GABA system

Progress Report: Physics

Subproject 3 Quantitative evaluation of the extraction of information from PET images (Gary, D. Hutchins, Ph.D., Subproject leader)

Subproject 4 Optimization of tracer kinetic methods for radioligand studies in PET (Robert A. Koeppe, Ph.D., Subproject leader)

This project (R.A. Koeppe, Project Director) has been one of two projects (the other with G.D. Hutchins as Project Director) related to the physics and data analysis aspects of quantitative neurological PET scanning within this DOE program for the past 6 years. The project under Dr. Hutchins' direction dealt with improvements in the measurements of both the tomographic data (reconstruction) and the arterial input function data (on-line detection). Dr. Koeppe's project has been focussed in tracer kinetic modeling, in particular the development and implementation of rapid pixel-by-pixel estimation schemes for the creation of functional imaging. More recently there has been an increased emphasis on the development of practical modeling approaches for neurotransmitter/receptor studies of the brain. Over the past three years we have developed and implemented useful tracer kinetic modeling approaches for several new radioligands.

In July of 1992, Dr. Hutchins left the group at University of Michigan to become the Director of a new PET facility at Indiana University Medical School. Prior to his departure, we have reorganized and consolidated the physics and data analysis efforts into a single project under the direction of Dr. Koeppe. Three new co-investigators joined the project (Drs. Clinthorne, Fessler, and Minoshima) and have devoted effort to this project for the past six months. The new group has emphasis in both the very basic aspects of nuclear medicine instrumentation (Clinthorne) and theoretical and practical statistical aspects related to image reconstruction from projections (Fessler) in addition to expertise in tracer kinetic modeling (Koeppe) and considerable experience in the measurement of cerebral blood flow and the performing of activation studies of the brain (Minoshima and Koeppe).

Tracer Kinetic Modeling

Computer simulations and human PET studies were performed to analyze the quantitative potential of the neurotransmitter/receptor ligands, [^{11}C]tropanyl benzilate (TRB) and [^{11}C]N-methyl piperidyl benzilate (NMPB), two new muscarinic cholinergic antagonists, [^{11}C]flumazenil (FMZ), a central benzodiazepine antagonist, and [^{18}F]GBR a pre-synaptic dopamine uptake ligand. Simulations have indicated that parameter sensitivity when performing kinetic analysis in conjunction with a three-compartment model yields estimates with a high degree a variability for each of these three PET agents. Results from the human studies, described in the following paragraphs, further indicate the difficulty in employing this complex a model. Thus, potential simplifications in the kinetic model (a past specific aim of this project) were investigated. Appropriate simplifications appear promising for the muscarinic agents, TRB, NMPB (Koeppe et al., 1992a,b). A two parameter two compartment simplification has been implemented for the benzodiazepine ligand, FMZ (Koeppe et al., 1991). We have recently begun analyzing a radioligand, [^{11}C]tetrabenazine, that binds to monoamine uptake sites (DaSilva et al, 1992; Kilbourn et al, 1992). Very preliminary results from the first two human studies show this to be a promising agent with favorable kinetics for compartmental modeling, similar to those observed for [^{11}C]flumazenil.

[^{11}C]-FMZ studies were carried out initially in eighteen normal volunteers (and by this time in over 30 volunteers and 75 patient subjects). Kinetic data in the initial studies was acquired for 90 minutes, and arterial blood samples were obtained and corrected for radiolabeled metabolites. Kinetic analysis alternatives, including a 2-compartment 2-parameter, a 3-compartment 3-parameter, and a 3-compartment 4-parameter estimation, were examined. The goodness-of-fit for a 2-parameter estimation (transport and total distribution volume) was best for the high receptor density regions (cortex) and worst for the low receptor density regions (pons). A 4-parameter analysis yielded stable results only in the pons. Other

regions were ill-conditioned, with variability in the receptor related parameters, k_3 and k_4, of 50-100% (s.d./mean). The only suitable approaches for dynamic analysis of FMZ data appear to be a 2-parameter analysis for transport and distribution volume, or a 3 parameter analysis (K_1, k_3, and k_4) where the free plus non-specific distribution volume is fixed to that found from a 4-parameter analysis of the pons. This analysis makes the assumption that there are no specific binding sites in the pons. Currently, more normal controls are being studied to examine the difference in performance between the current bolus injection/2-compartment analysis approach and an equilibrium or steady-state approach for estimating the distribution volume following a continuous infusion of [^{11}C]FMZ as performed at other institutions.

[^{11}C]TRB studies were carried out in six normal volunteers. Kinetic data was acquired for 110 minutes, and arterial blood samples were obtained and corrected for radiolabeled metabolites. Data were analyzed by a variety of kinetic approaches with a range of complexities in order to be able to derive an analysis technique with the optimal degree of model complexity, balancing the levels of variability and bias in the parameter estimates. Analysis schemes included 1) a simple single scan approach, using tissue concentration measurements late in the study (70-90 minutes post-injection), 2) a graphical approach (Patlak plot method), 3) a 2-compartment 2-parameter technique for estimating K_1 and distribution volume (DV), that uses DV as a receptor measure, 4) a dual scan approach, using a single early scan to estimate the transport parameter K_1, and a single late scan to estimate the binding parameter k_3, and by assuming a value for the free plus non-specific distribution volume, 5) a 3-compartment 2-parameter estimation of K_1 and k_3 using an assumed value for the free plus non-specific distribution volume, and 6) a 3-compartment, 3-parameter estimation of K_1, DV, and k_3. Results have indicated that the single scan and graphical approaches oversimplify the model and cause considerable biases in the results, while the full 3-compartment, 3-parameter analysis is not sufficiently stable, yielding estimates with a high degree of variability. The two-parameter K_1 and DV method, or either of the 2-parameter K_1 and k_3 approaches provide the best trade-off between bias and variability in the parameter estimates. These approaches have the additional advantage that
they can be performed pixel-by-pixel, therefore yielding maps of both ligand transport and receptor density parameters.

[^{11}C]NMPB studies were carried out in seven young normal volunteers during the past six months. Kinetic data was acquired for 110 minutes, and arterial blood samples were obtained and corrected for radiolabeled metabolites. Data have been analyzed by a variety of kinetic approaches with a range of complexities, as with TRB. Analysis schemes from a simple single scan or a graphical approaches to a more complex 3-compartment, 4-parameter estimation of the ligand's transport rate, free plus non-specific distribution volume, and the combined forward rate constant, representing the product for the ligand-receptor association rate and the receptor density. Preliminary results indicate that this new agent yields better estimates of receptor density than does the previous muscarinic receptor ligand, [^{11}C]TRB. Simulations indicate that problems associated with flow-limitation (Koeppe et al., 1990) should not be as great a problem for NMPB because of the 2-2.5 fold increase in ligand transport observed in the human studies (~60% first pass extraction) Simulation studies and the initial modeling efforts support this conclusion.

[^{18}F]GBR studies have been carried out in two normal volunteers. Kinetic data was acquired for 120 minutes and arterial blood samples were obtained and corrected for radiolabeled metabolites. Data were analyzed using a 3-compartment 4-parameter model. It was determined that neither a 2-compartment 2-parameter model nor a 3-compartment 3-parameter model with the dissociation rate constant assumed to be negligible during the course of the experiment (k_4=0), adequately describe the temporal behavior of GBR. The estimates of the rate constants for the two subjects were very similar to those for FDG (K_1 = 0.07-0.08 ml g^{-1}min^{-1}, k_2 =0.15-0.2 min^{-1}, k_3 =0.05-0.09 min^{-1}) except that k_4 is approximately 0.03-0.05 min^{-1}, a factor of 5-10 times higher than in FDG. Since this agent is for quantifying pre-synaptic dopamine reuptake sites, basal ganglia regions-of-interest (ROIs) were compared to cortical and cerebellar ROIs. Estimates for K_1, k_2 and k_4 were very similar between regions. The estimates for k_3 the receptor binding related parameter were different, however, ratio of k_3

values between basal ganglia and other regions was only about 1.5 to 1. To improve stability of the estimate, the ratio k_3/k_4 (which equals B_{max}/K_D) was calculated, and it too showed a difference between basal ganglia and other regions of only about 1.5 to 1. Thus, preliminary results from studies employing this PET ligand are not promising since the degree of non-specific binding is so high (approximately two thirds of the total binding).

Statistical Methods using Penalized-Likelihood

We have implemented and evaluated a new statistical image reconstruction method based on a penalized, weighted least-squares (PWLS) objective function. This method has several advantages over alternative methods: 1) it can accommodate (non-Poisson) PET scans that are pre-corrected for accidental coincidence events, unlike the ML-EM method, 2) by using an iterative coordinate descent algorithm, we can easily enforce the non-negativity constraint, unlike in WLS-CG methods, and 3) the convergence of the algorithm is very fast when initialized with a FBP reconstructed image, typically only requiring about 20 iterations for convergence. We have demonstrated through simulations and preliminary human PET studies that the weighting scheme is central to this approach: different detector pairs have significantly different variances, which the statistical approach can account for, unlike FBP.

We presented preliminary results from this method at the 1992 Society of Nuclear Medicine Meeting (see below). We performed simulations to compare quantification of the human basal ganglia using both conventional FBP and the iterative PWLS method. These results showed that quantification of regional uptake within the globus pallidus and putamen could be improved (reduced root mean-square (RMS) error) by compromising between variance and bias. We have submitted a manuscript to the IEEE Transactions on Medical Imaging on this reconstruction method (see below).

During this project period, a new multi-energy maximum-likelihood scatter correction method was developed that is applicable to PET. Briefly, the method integrates our knowledge concerning both the spatial and energy distributions of the direct and scattered coincidence intensities allowing separate constraints (e.g. spatial smoothness, non-negativity, support) to be placed on each. This method may be highly relevant to volume PET because of recent Monte Carlo investigations suggestion that there is not enough information in a simple dual energy-window scan to correct for Compton-scatter. Indeed, our own preliminary measurements appear to indicate that multi-energy methods may also be insufficient when applied in a simple, point-wise fashion to the projection data. Out integrated approach, however, which combines both spatial and energy information (and can be combined with model-based approaches), may yield improved corrections especially in heterogeneous scattering media.

CBF Activation Studies

We have been developing data analysis methods for PET [^{15}O]water activation studies. We have finalized an automated method for detection of the intercommissural (AC-PC) line which is a fundamental part of the stereotactic localization approach. We have integrated those anatomical registration methods and a statistical analysis method. The stochastic model in two dimensions reported by Friston et al. has been adapted into three dimensions. Preliminary validations were done for this model using computer generated simulation data. Pain stimulation studies analyzed by the automated and integrated method showed excellent demonstration of cortical and sub-cortical activation due to thermal pains.

We have also applied three dimensional anatomical standardization techniques to PET receptor images. A purpose of this application is a group-by-group comparison of PET data without a priori regional hypothesis. [^{11}C]flumazenil images from 28 normal subjects were analyzed with the standardization and summation techniques. We have found that there is increased receptor distribution in the cerebellar hemispheres with aging. Further development of statistical assessment on a pixel-by-pixel basis is necessary.

In both approaches, a co-registration technique between two PET scans from the same subject was used. We have developed our own criterion and have been validating the accuracy using a three-dimensional brain phantom and human data.

GRADUATE AND POSTDOCTORAL TENURES

The following graduate students have participate in this research project as part of their education and training:

Ping Chiao, B.S.	(1987-1991)
Ray Raylman, B.S.	(1989-1991)
Kevin Berger, B.S.	(1991-1992)

The following postdoctoral students have participate in this research project as part of their education and training:

Fred Buck, M.D.	(1989-1990)
Robert Greenough, M.B., B.S.	(1991-1992)
Vjera Holthoff, M.D.	(1989-1990)
Yong-Woon Jung, Ph.D.	(1988-1990)
Kien Lee, M.B., B.S.	(1989-1991)
Stephen Taylor, M.D.	(1989-present)
Satoshi Minoshima, M.D.	(1991-1992)
Jeffrey A. Fessler, Ph.D.	(1991-1992)
Michael Meyer, M.D.	(1991-1992)
Ping Chiao, Ph.D.	(1991-1992)
Ray Raylman, Ph.D.	(1991-present)
Jon Zubieta, M.D.	(1991-present)

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