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NEW TECHNIQUES FOR POSITRON EMISSION TOMOGRAPHY IN THE STUDY OF HUMAN NEUROLOGICAL DISORDERS

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Subproject 1

Methodological Developments for Improved Extraction of Quantitative Information from PET

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Progress:

During the past six months, we have continued work on the fronts of kinetic modeling of radioligands for studying neurotransmitter/receptor systems, iterative reconstruction techniques, and methodology for PET cerebral blood flow activation studies.

Initial human PET studies have been performed and analyzed with many different kinetic model formulations to determine the quantitative potential of the neurotransmitter/receptor ligand, [^{11}C]N-methyl piperidyl benzilate (NMPB), a muscarinic cholinergic antagonist. In addition, initial human studies using [^{11}C]tetrabenazine (TBZ), a marker for monoamine nerve terminal density. Results of the NMPB studies have indicated that this new agent yields better estimates of receptor density than previous muscarinic ligands developed at our facility, [^{11}C]-TRB and [^{11}C]scopolamine. TRB and scopolamine have previously been shown to be only partially successful ligands due to sub-optimal values of the individual rate constants, causing varying degrees of flow limitation. This is found to be much less of a problem for NMPB due to the 2.0-2.5 fold increase in ligand transport observed in the human studies (~60% first pass extraction). A 2-parameter 2-compartment simplification had previously been implemented for the benzodiazepine ligand, [C-11]FMZ, and a similar model appears to be suitable for TBZ based on the preliminary human data.

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.

We have been developing data analysis methods for PET O-15 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. [C-11]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.

Future Plans

The future work planned is primarily a continuation of the work (both on going and new) performed during the previous six month period. There is, however, a renewed effort to focus the various physics related sub-projects with a common goal of improving the quantitative extraction of data from PET imaging studies. Approximately half of the effort will go into studying particular problems that degrade PET images and potential approaches that reduce these problems effects. The major sources of image degradation that will be investigated include 1) limited system sensitivity (signal-to-noise), 2) subject motion during a study, and 3) photon attenuation by the body. Dr. Fessler is collaborating with Prof. Al Hero of ECS on methods for computing new versions of Cramer-Rao lower bounds that account for estimator bias. These bounds will be used to quantify the potential gains in quantitative accuracy obtainable using iterative reconstruction methods. We have also begun to investigate statistical methods for attenuation correction in PET. In particular, we will address issues dealing with 3-dimension PET data, both in data acquisition (as we will be obtaining a new 15cm FOV 47-slice scanner with retractable inter-plane septa) and image processing (treating all PET data as a single 3-D data set rather than merely a stack of 2-dimensional images). The remaining half of the overall effort will be directed towards the application of these potential advances to particular PET protocols, such as those studying brain activation in CBF studies or neurotransmitter/receptor function in radioligand studies. Three specific applications to be addressed include: 1) examining potential benefits of 3-D (septa out) vs. 2-D (septa in) acquisition for tracer kinetic studies, 2) designing better acquisition protocols for making the best use of the increased signal-to-noise obtainable in CBF activation studies using 3-D (septa out) conditions, and 3) optimizing CBF acquisition statistical analysis for single intra-individual (single subjects) studies.

Publications

Published Papers/Papers in press

1. Fessler, N. Clinthorne, and W. Rogers, "Regularized emission image reconstruction using imperfect side information," IEEE Transactions on Nuclear Science, Oct. 1992. (in press.)

2. Minoshima S, Berger KL, Lee KS, Mintun MA: An automated method for rotational correction and centering of three-dimensional functional brain images. J Nucl Med 1992;33(8):1579-1585

3. Minoshima S, Koeppe RA, Mintun MA, Berger KL, Taylor SF, Frey KA, Kuhl DE. Automated detection of the intercommissural (AC-PC) line for stereotactic localization of functional brain images. J Nucl Med (in press)

Papers Submitted for Publication

1. Fessler, "Improved {PET} quantification using penalized weighted least-squares image reconstruction," Submitted to IEEE Trans. Med. Imaging, 1992.

2. Koeppe RA, Frey KA, Mulholland GK, Kilbourn MR, Buck FL, Lee KS, Kuhl DE. [C-11]tropanyl benzilate binding to muscarinic cholinergic receptors: Methodology and kinetic modeling alternatives. Submitted to J Cereb Blood Flow Metab, Oct.1992.

Abstracts

1. JA Fessler, WL Rogers, NH Clinthorne, GD Hutchins, and RA Koeppe, "Quantification of the human basal ganglia via iterative reconstruction," Journal of Nuclear Medicine (Abstract Book), 33(5):878, May 1992.

2. NH Clinthorne, XH Wang, and JA Fessler, "Multi-energy maximum-likelihood reconstruction algorithms for SPECT and PET," Journal of Nuclear Medicine (Abstract Book), 33(5):831, 1992.

3. JA Fessler, "Hidden data spaces for maximum-likelihood PET reconstruction," Conference Record of the 1992 IEEE Nuclear Science Symposium and Medical Imaging Conference.

4. JA Fessler, "Segmented attenuation for PET using ICM," Conference Record of the 1992 IEEE Nuclear Science Symposium and Medical Imaging Conference.

5. AO Hero, JA Fessler, and WL Rogers, "A fast recursive algorithm for computing CR-type bounds for image reconstruction problems," Conference Record of the 1992 IEEE Nuclear Science Symposium and Medical Imaging Conference.

6. Minoshima S, Koeppe RA, Frey KA, Berger KL, Kuhl DE: Automated method for anatomical standardization of three-dimensional functional brain images. J Nucl Med 1992;33:1003

7. Minoshima S, Frey KA, Koeppe RA, Berger KL, Greenough R, Kuhl DE: Stereotactic metabolic atlas of the brain as a new diagnostic tool for functional brain imaging. J Nucl Med 1992;33:858

8. Minoshima S, Berger KL, Mintun MA, Taylor SF, Koeppe RA: Automated stereotactic transformation of functional brain PET images. J Nucl Med 1992;33:1007

9. Minoshima S, Kirk A. Frey, Robert A. Koeppe, Kevin L. Berger, Jeffrey A. Fessler, David E. Kuhl, Kenneth L. Casey: PET localization of response to thermal stimuli in human. JCBFM (submitted)

10. Minoshima S, Kirk A. Frey, Robert A. Koeppe, David E. Kuhl: Summation analysis of PET receptor images: assessment of age differences in [C-11]flumazenil distribution in the human brain. JCBFM (submitted)

Subproject 2

New Labeling Strategies for Short-Lived Positron Emitting Nuclides

G. Keith Mulholland, Ph.D., Subproject Leader
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Progress:

[^{11}C]Methyl triflate and related research.

We have equipped our three hot cells with the capability of producing high levels (approx.1000 mCi) of [^{11}C]methyl triflate at high specific activity.

We have applied [^{11}C]methyl triflate in the production three different radiopharmaceuticals which we are developing for clinical use at this facility - [^{11}C]epinephrine, [^{11}C]raclopride and [^{11}C]methionine. For all three agents the use of [^{11}C]methyl triflate instead of [^{11}C]methyl iodide has resulted in faster syntheses and simpler apparatus. This is because the reactions occur instantaneously without the need for heating the reactants under pressure. In the case of [^{11}C]epinephrine, switching to methyl triflate led to a 4-5 fold increase in yield (from about 20 mCi to about 100 mCi) making this agent for the first time practical for human studies.

Human use applications have been submitted for [^{11}C]raclopride and [^{11}C]epinephrine made with [^{11}C]methyl triflate, and the first human studies are expected before the end of the year. It is anticipated that most new carbon-11 radiopharmaceuticals under development at this facility will be made with methyl triflate.

Publications in Press:

1. Jewett, D. M., (1992) A simple synthesis of [^{11}C]methyl triflate. Appl. Radiat. Isot. , in press.

2. Jewett, D. M. (1992) Carbon-11. Chemtech 22: 592-6. (A review and overview setting how carbon-11 chemistry is poised to develop and how PET chemistry and basic C_1 chemistry stand to benefit mutually from new developments.)

[^{18}F]FEOBV

A simple and efficient one step labeling route to the new benzovesamicol analog [^{18}F]FEOBV has been developed which which makes this promising cholinergic neuron tracer readily available for anticipated human studies of Alzheimer's disease. The approach allows [^{18}F]FEOBV to be made with commercial FDG "black box" type synthesis units. A stable chiral tosylate precursor is labeled under standard solution phase nucleophilic conditions in high yield, and then purified by HPLC. Total synthesis time is about 1 hr and decay corrected yields average 60%.

Phosphazenium resins.

A new class of cation functionalized polystyrene resins with high thermal stability has been developed for applications in heterogeneous ("resin") nucleophilic radiolabeling reactions. The functional moiety of these materials is a phosphazenium (PZ) group: a central phosphorus(V) atom to which is bonded four dialkylamino groups. The thermal stability is conferred by the bulk of the dialkylamino groups and ability to distribute positive charge density by resonance among all N and P atoms. Three examples have been prepared with different dialkylamino groups and degree of loading, from 2-5% by weight phosphorus. The PZ resins examined so far have normal anion exchange properties, and the bicarbonate, carbonate and hydroxide forms absorb no-carrier-added [^{18}F]F^- ion from aqueous solution. The exchanged [^{18}F]F^- can be activated by removal of water, and participates in the same type of

nucleophilic labeling reactions as previously developed aminopyridinium (AP) resins, but whereas AP resins are stable only to ~100°C, the PZ resins continue to function up to ~145°. Furthermore, PZ materials appear to be more resistant to strong basic conditions than AP resins. These advantages can improve the speed of the resin labeling approach and extend its scope to more difficult reaction and potentially allow the resin columns to be reused in multiple syntheses.

Future Plans

Two new types of macroreticular ion exchange resin have developed commercially which are reported to have good kinetics and site accessibility in organic solvents. We will compare the performance of these to the existing Merrified type resins for the nucleophilic synthesis of [^{18}F]FDG. We will continue to develop the application of [^{11}C]methyl triflate to new radiopharmaceuticals, making an attempt to develop a systematic approach which others can follow in applying this new reagent. We will begin development of a microreactor, especially suited for radioalkylations with [^{11}C]methyl triflate which will allow direct interfacing with a preparative HPLC for purification.

PUBLICATIONS

PAPER IN PRESS

1. Mulholland GK, Jung Y-W, Kilbourn MR,. Wieland DM. Synthesis of [^{18}F]fluoroethoxybenzovesamicol, a radiotracer for cholinergic neurons 1992 (submitted).

ABSTRACTS

1. Mulholland GK, Jung Y-W, Sherman PS, Pisani TL, Kuhl DE, Wieland DM, Kilbourn MR. Efficient one-step synthesis of (-)-[^{18}F]fluoroethoxybenzovesamicol (FEOBV). A new tracer for mapping cholinergic neurons in vivo. Ninth Intnl Symposium on Radiopharmaceutical Chemistry 1992. J. Lab Compd Radiopharm. 1992(in press).

2. Mulholland GK, Kilbourn MR. 4-[^{18}F]fluoro-tert-butyl bicycloorthobenzoate (FTBOB). A potential tracer for the GABA$_A$ chloride channel. Ninth Intnl Symposium on Radiopharmaceutical Chemistry 1992. J. Lab Compd Radiopharm. 1992(in press).

3. Mulholland GK. New thermally stable ion exchange resin for heterogeneous nucleophilic radiofluorination. Society of Nuclear Medicine 39th Annual Meeting, 1992. J Nucl Med 33:984, 1992.

4. Mangner TJ, Mulholland GK, Toorongian SA, Jewett DM, Kilbourn MR. Purification of used O-18 target water by photochemical combustion. Society of Nuclear Medicine 39th Annual Meeting, 1992. J Nucl Med 33:982, 1992.

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