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NUCLEAR MEDICINE AND IMAGING RESEARCH
(Quantitative Studies in Radiopharmaceutical Science)

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**THE
FRANKLIN McLEAN MEMORIAL RESEARCH INSTITUTE
DEPARTMENT OF RADIOLOGY

PROGRAM OF
NUCLEAR MEDICINE AND QUANTITATIVE IMAGING RESEARCH**

**THE
UNIVERSITY OF CHICAGO**

QUANTITATIVE STUDIES
IN
RADIOPHARMACEUTICAL SCIENCE

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Section I
Radiochemistry
(Jogeshwar Mukherjee, Ph.D., Section Leader)

Radiotracers for Metabolic Studies. Tracers for the study of glucose metabolic rates and alterations in blood flow are produced on a routine basis in the FMI Radiochemistry Research Laboratories. Fluorine-18, which is produced by the UC CS-15 cyclotron in an O-18 (p,n) F-18 reaction, is used for preparation of [F-18]-labeled 2-fluorodeoxyglucose (FDG). Oxygen-15-labeled water is produced by an N-14 (d,n) O-15 reaction in a nitrogen-hydrogen gas mixture.

Radiopharmaceutical Design. Based on available information on pharmaceuticals, a structure-activity relationship study was conducted by the radiochemistry group in order to optimize properties of tracers for use *in vivo*. Such studies were enhanced by the use of small-molecule modeling approaches, which allowed correlations of the energy-minimized structures of various analogs. Fluorine-18-labeled fallypride with its excellent properties for imaging dopamine D-2 receptors resulted from this approach.

Radiopharmaceuticals for Dopamine D-1 Receptors. High affinity and selective fluorinated derivatives of SCH 38548 were developed in the Radiochemistry Research Laboratories as potential selective PET radiotracers for dopamine D-1 receptors. The table shows *in vitro* binding affinities (nM) in rat membranes for D-1 and D-2 receptor sites. Preliminary biodistribution of [F-18]fluoropropyl derivative in rats and monkeys shows specific uptake in striata.

	R	D-1	D-2
1 H	0.53±0.46	3100
	2 (CH ₂) ₂ ¹⁸ F	4.02±2.10	2.5x10 ⁴
	3 (CH ₂) ₃ ¹⁸ F	4.80±3.60	10 ⁶
	4 CH ₂ C ₆ H ₄ ¹⁸ F	1.53±0.81	1.6x10 ⁴
	5 COC ₆ H ₄ ¹⁸ F	0.55±0.33	270

Radiopharmaceuticals for Dopamine D-2 Receptors. The first-generation dopamine D-2 tracer FPMB was modified and structurally optimized for high brain uptake and binding affinity. This was done by placing highly lipophilic groups at the pyrrolidine nitrogen of the ethyl group of FDPMB. Fallypride has the desired optimal properties. The development of labeled fallypride was followed by that of ZYY-107, an agent for potential studies of fluctuations in endogenous dopamine levels.

Compd	R	R'	K _i (nM)
FPMB	OCH ₃	CH ₂ CH ₃	0.26
ZYY-104 (Fallypride)	OCH ₃	CH ₂ CH=CH ₂	0.03
ZYY-107	H	CH ₂ CH=CH ₂	0.85

Radiopharmaceuticals for Serotonin Transmitter-Receptor Systems. Fluoxetine or Prozac is a clinically used potent antidepressant. Radiosynthesis of [F-18]fluoxetine involves coupling of 4-nitro- α,α -difluoro- α [F-18]fluorotoluene with sodium alkoxide of (S)-3-(methylamino)-1-phenyl-1-propanol. The yield of HPLC-purified [F-18]fluoxetine is 1-2%. Specific activity of the product is 1480 GBq/mM. Shown is HPLC chromatogram of reaction mixture containing [F-18]fluoxetine.

Competition Experiments Using PET and [F-18]fallypride in Rhesus Monkeys. Uptake images of [F-18]fallypride shown at four time-points (top); corresponding images of specifically bound [F-18]fallypride following displacement by haloperidol (middle) (haldol was injected 17 minutes post injection of fallypride); and corresponding images of specifically bound [F-18]fallypride following displacement by endogenous dopamine (bottom) (*d*-amphetamine was injected 18 minutes post injection of fallypride).

Rhesus Monkey Brain Scan Obtained Using the PETT VI Tomograph. The image shows uptake levels of 0.04 to 0.06% injected dose per cc with [F-18]fallypride. The tracer accumulates in the striata (bilateral dark areas) and clears quite rapidly from non-specifically bound regions. Ratios of [F-18]fallypride binding in striata to cerebellum have been shown to be 3.0 at 14 minutes, 5.0 at 35 minutes, and 8.0 at 70 minutes; they have been shown to plateau at a maximum of 9.6 at 100 minutes post-injection.

***In Vivo* Selectivity of [F-18]fallypride vs Ketanserin and Raclopride in Rhesus Monkeys.** Shown are PET data on the competition of ketanserin and raclopride with [F-18]fallypride binding in striata and cerebellum in rhesus monkey brain. Specific binding was obtained as the difference of striata and cerebellum uptakes. Inset is plot of $\ln X/X_0$ versus time (X_0 = specific binding of fallypride 101 minutes post injection--the time of raclopride injection; X = specific binding of fallypride post X_0).

Section II
PET Studies
(John T. Metz, Ph.D., Section Leader)

Contours of PET and MRI Data During Image Registration. PET Center investigators routinely perform surface fitting of MRI and PET data using techniques developed with researchers in the Department of Radiation and Cellular Oncology. In 1993, PETT VI data collection and analysis were simplified significantly as a new processing platform for PETT VI was acquired, new hardware and software interfaces for acquisition were developed, and new graphic interfaces to analysis software were written.

A PET Image That Has Areas of Increased Metabolic Activity (White) and Decreased Metabolic Activity (Black) Integrated with an MRI Image. Effects of drugs on the metabolism of glucose in different areas of the brain were investigated. Some studies involve drugs with abuse potential--alcohol and amphetamine; others involve drugs with therapeutic potential--fluoxetine (Prozac). The studies combine measurements of glucose metabolism and controlled subject behavior.

PET Images Registered with MRI Images Demonstrating Activation of Brain Areas (Dark Patches) Over Time as a Result of Performance of a Motoric Memory Task. These studies were part of a series designed to identify brain areas involved in memory. Findings so far, which may be important to understanding diseases such as Alzheimer's, indicate that different areas of the brain are involved in different kinds of memory and at different times in the development of a memory.

Section III Quantitative Image Analysis (Chin-Tu Chen, Ph.D., Section Leader)

Factor Analysis of an Opiate Receptor (Diprenorphine) PET Study. FCIA and PET Center investigators use statistical methods to study temporal characteristics of dynamic images. For example, factor analysis is applied to image sequences and is used to improve the images by reducing them to functional images and physiological time functions. Results that characterize neuroreceptor binding, glomerular filtration rate, cerebral glucose metabolism, and ventricular function were achieved in 1993.

Three-dimensional Maximum Intensity Projections (MIP) Rendering of Data of a Heart. Although research in 3D techniques was initiated to develop visualization software, the research has resulted in 3D techniques for other image processing tasks as well. Methods that have been developed include techniques for 3D image segmentation (interactive-snake-based and split-and-merge), interpolation (surface and intensity), and classification (interactive, neural-network, and fuzzy-Kohonen-clustering).

Three-dimensional (3D) Volume Rendering of Computed Tomography Data of a Skull. Three-dimensional (and higher) representations and analyses of medical imaging data provide information that results in more accurate diagnoses. FCIA investigators are engaged in research in analysis of 3D dynamic data and in development of clinical software for 3D data. Visualization tools that have been developed include surface-rendering, volume-rendering, and multi-modality image-fusion software.

Posterior and Anterior Views of 3D Volume Renderings of a Liver and Its Vascular Tree. Images of the liver and its vascular tree can be displayed individually or in 3D registration. FCIA investigators have developed techniques that make it possible for radiologists and surgeons to interact with a 3D data set on a computer monitor so that organs can be viewed from arbitrary directions and at arbitrary depths. The work requires expertise in both image processing and graphical display.

Reconstructions of [F-18]fallypride Uptake in a Rhesus Monkey Brain Using Principal Component Analysis (PCA), Projections Onto Convex Sets (POCS), and a Hybrid Method Involving Both Techniques. Investigators in the FCIA developed and used techniques for improving the quantitative accuracy of PET images. PCA is applied to projection data as a preconditioner that reduces noise. Application of POCS to the preconditioned data results in improved spatial resolution.

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