

previously reported. However, in the acute phase, FDG uptake is highly demonstrated on the infarcted and periinfarcted area whether viable or not. These results suggest that cell infiltration and membranous damage may be related to FDG uptake in acute MI. Therefore, these findings should be considered in the evaluation of FDG uptake as a gold standard for myocardial viability.

Neurology Basic I: New Ligands

3:30-5:00 Session 16 Room: 104 C and D

Co-moderator: Robert B. Innis, MD, PhD

Co-moderator: Robert M. Kessler, MD

No. 90

THE IN-VIVO BEHAVIOR OF D- AND L- [C-11]-N-METHYLNORFENFLURAMINE AS SEROTONIN REUPTAKE LIGANDS IN RATS AND MONKEYS. D.R. Elmaleh, X.-J. Meng, T.M. Shoup, A.-L. Brownell, A.J. Fischman. Massachusetts General Hospital, Boston, MA.

Fenfluramine (N-ethyl- β -methyl-3-trifluoromethylphenethylamine) is a useful anorectic and antidepressant drug. Its pharmacologic activity is associated predominantly with its D-enantiomer. Although the drug is a substituted amphetamine, its neurochemical effects are markedly different from those of the D-amphetamines. D-fenfluramine inhibits serotonin presynaptic reuptake and enhances 5-HT (serotonin) release.

We have synthesized norfenfluramine and resolved its D and L optical enantiomers. We have prepared the [C-11]methyl analogs and evaluated their biodistribution in rats and their brain imaging characteristics in monkeys. Both C-11-labeled fenfluramine analogs showed high brain uptake in regions rich with serotonin terminals (cortex, caudate-putamen, hypothalamus and thalamus). Although the L-enantiomer had higher initial uptake than the D-enantiomer, the L-isomer cleared with time while the D-isomer activity remained unchanged. Monkey imaging studies indicated high brain activity in frontal cortex, caudate, putamen and thalamus regions with striatum to frontal cortex ratios of 1 to 1.2, as expected for a presynaptic serotonin ligand. The selectivity of the tracer was monitored by following the drug activity in different brain regions as a function of time and by chasing or preloading with fluoxetine. In contrast to C-11-fluoxetine, the dimethyl derivative of fenfluramine demonstrated selectivity to the serotonin reuptake system.

Some of these analogs are potentially useful tracers for monitoring with PET depression and its treatment.

No. 91

IMAGING SEROTONIN UPTAKE SITES WITH (+)[C-11]McN. Z. Szabo, U. Scheffel, M. Suehiro, R.F. Dannals, H.T. Ravert, G.A. Ricaurte, and J. Wagner Jr. The Johns Hopkins Medical Institutions, Baltimore, MD.

Presynaptic serotonergic (5-HT) dysfunction has been implicated in several psychiatric diseases. The purpose of the study was to investigate the recently developed ligand (+)[C-11]McN (trans-1,2,3,5,6,10 β -hexahydro-6-[4-(methylthio)phenyl]-pyrrolo-[2,1-a]-isoquinoline) (Suehiro et al: J Label Comp Radiopharm 31:841, 1992; Suehiro et al: J Nucl Med 34:120, 1993) as a tracer for imaging presynaptic 5-HT uptake sites using PET.

PET imaging was carried out in anesthetized baboons after injection of 20 mCi of (+)[C-11]McN (n=3), its pharmacologically inactive (-) enantiomer (n=3) and after blocking 5-HT uptake with 5 mg/kg fluoxetine (n=1). In addition, the distribution of (+)[C-11]McN was quantitated by both PET and ex vivo counting in a green monkey. PET images were obtained 100-120 minutes post injection. 5-HT uptake site densities were assessed by the difference in the regional uptake of (+) and (-)[C-11]McN and were compared to known densities of antidepressant binding sites in human brain (Cortes et al: Neurosci 27:473, 1988) by rank correlation.

There was a significant correlation between the cerebral distribution of (+)[C-11]McN measured in vivo and ex vivo ($r_s=0.8$, $p=0.025$). 5-HT

transport blocker caused an average reduction of radioactivity of 29%. The average uptake difference obtained with (+) and (-) [C-11]McN showed the following rank order: midbrain (26%)>pons>thalamus>occipital cortex>temporal cortex>cerebellum (4%), which is in agreement with the regional densities of antidepressant uptake sites ($r_s=0.94$, $p=0.002$).

The results indicate that (+)[C-11]McN labels 5-HT uptake sites in the baboon brain. Subtraction of (-)[C-11]McN from (+)[C-11]McN images on a pixel by pixel basis may afford quantitation of specifically bound tracer. Thus, (+)[C-11]McN may be useful for imaging 5-HT uptake sites in the human brain.

No. 92

IN VIVO HUMAN IMAGING OF MONOAMINERGIC NERVE TERMINALS USING [C-11]TETRABENAZINE ([C-11]TBZ) AND POSITRON EMISSION TOMOGRAPHY. M.R. Kilbourn, K.A. Frey, R.A. Koeppe, J.N. DaSilva, T.J. Mangner, and D.E. Kuhl, Division of Nuclear Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI

Synaptic vesicular amine transporters (SVAT) are specific components of presynaptic monoaminergic neurons, and losses of SVAT have been demonstrated in post-mortem Parkinson's disease brains. In vivo imaging of these sites would form a new approach to the quantitative measurement of monoaminergic nerve terminal densities in neurodegenerative diseases and hyperkinetic movement disorders. We have performed the first in vivo PET imaging of SVAT in human brain using PET and [C-11]tetrabenazine ([C-11]TBZ), a high affinity inhibitor ($K_i = 3$ nM) of synaptic monoamine transport. Studies were done in young normals using injections of no-carrier-added, high specific activity [C-11]TBZ. [C-11]TBZ shows excellent brain uptake after i.v. injection, rapid egress from the brain, and different pharmacokinetics in various brain regions (striatum, cortex, thalamus, cerebellum). Longer retention of [C-11]TBZ in the monoaminergic terminal-rich striatum results in clear visualization of this structure at early time points (striatum/cortex ratio of 1.9 after 20 min). PET imaging of [C-11]TBZ thus forms a new method for assessment of nerve terminal loss in neurodegenerative disorders such as Parkinson's disease.

No. 93

IN VIVO MAPPING OF CHOLINERGIC NEURONS IN THE HUMAN BRAIN USING SPECT AND (-)-5-[I-123] IODOBENZOVESAMICOL (IBVM). D.E. Kuhl, R.A. Koeppe, J.A. Fessler, S. Minoshima, R.J. Ackermann, J.E. Carey, K.A. Frey, and D.M. Wieland. University of Michigan, Ann Arbor, MI

In search for an in vivo marker of cholinergic neuronal integrity, we extended to human use the tracer (-)-5-[I-123] Iodobenzovesamicol (IBVM). IBVM is an analog of vesamicol, which binds to the acetylcholine transporter in synaptic vesicles (Rogers, 1989). In mouse brain, IBVM is a stereo specific (-), regionally specific, signal which marks the presynaptic cholinergic vesicle site (Jung, 1990).

IBVM was prepared with a specific activity of 21,000 to 70,000 Ci/mmol (Van Dort, in press). Five normal human subjects, aged 22-29 years, received IBVM (10 mCi) intravenously. Radial arterial blood was sampled and corrected for metabolites in order to determine the cerebral input function. SPECT (Picker Prism 3000) images of the brain were collected sequentially over the first four hours and again at 22 hours. In all image frames, head movement was corrected using fiducial markers, an automated method (Minoshima, in press) realigned and transformed data to a stereotactic coordinate system, voxels-of-interest were localized stereotactically in selected brain structures, and corresponding activity values for the first four hours were extracted for tracer kinetic estimations.

The best data fit was for a three compartment model fitting K_1 , DV' , k_3' , and blood volume, (i.e., $k_4=0$). For the fitted parameters K_1 (transport) (0.060 to 0.075 ml/gm/min) and k_3 (binding site density)(cortex 0.0077, striatum 0.0499 ml/gm/min), coefficients of variation were 15%-22% in regions of interest. Striatum/cortex ratios corresponded well for postmortem immunohistochemical values reported (Araujo 1988) for the acetylcholine-