Diprenorphine (mu delta kappa antagonist) at two, seven and 24 hours post drug. To optimize the quantification we employed various region of interest (time activity curves) and parametric (using SRTM) reference region modeling methods (REFM) employing the occipital cortex as the reference region. Occupancy measures during the two, seven and 24 hours post drug demonstrated a peak of 90% declining to 85% occupancy with no significant difference between the REFM measures at each time point. To confirm using the more traditional approach with a radial arterial input, various one and two tissue compartment models were considered. Occupancy estimated by arterial methods compared to REFM methods was within 10% for the two methods measured at two and seven hours post drug. This demonstrates the approach of serial measures of opiate receptor occupancies of initial dosing and washout for potential future therapeutic dose selection with opiate drugs. It emphasizes the importance of verifying the appropriate mathematical models for quantification of the outcome measures depending on whether methodological accuracy (e.g. using arterial input and specific compartment models) or simpler logistics (e.g. with REFM techniques) are required for drug development decisions.

No. 117

SYNTHESIS, RADIOLABELING AND EVALUATION OF 4-METHOXY-1H-INDOLE-3-CARBOXYLIC ACID-(4-[4-(2,4-DICHLORO-PHENYL)PIPERAZIN-1-YL]BUTY))AMIDE ([11C]WLD3.001) AS DEVELOPMENT OF POTENTIAL SELECTIVE DOPAMINE D3 POSITRON EMISSION TOMOGRAPHY TRACER

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Introduction: Antagonism of the dopamine D3 receptor was suggested to be important to the therapeutic effects of antipsychotic drugs. To date the vast majority of dopamine receptor radiotracers are nonselective binding to both D2 and D3 subtypes, complicating interpretation of results. To address this issue, we synthesized [C-11]WLD3.001 and performed an initial assessment of its potential as a selective D3 receptor positron emission tomography (PET) tracer. Methods: WLD3.001 and its corresponding phenol precursor WLD3.002 were synthesized. The Log P value of WLD3.001 was assessed by an HPLC method, and *in vitro* binding assays performed. [C-11]WLD3.001 was synthesized by reacting WLD3.002 with [C-11]CH3I at 40 C for two minutes. Regional brain biodistribution and blocking studies were performed in conscious male Sprague - Dawley rats (225-300g). Results: The affinities (Ki) of WLD3.001 for dopamine D2, D3, D4 and D5 subtypes were 1,650 nM, 2.4 nM, 2,818 nM and >1000 nM, respectively. The log P value was 2.92. The regional brain biodistribution data revealed that peak uptake (%ID/g +/- SD) at 15 minutes post-injection were highest in the thalamus (0.96 +/- 0.10) > frontal cortex (0.84 +/- 0.07) > striatum (0.67 +/- 0.10) > cerebellum (0.49 +/- 0.03), with clearance of activity from all regions thereafter. Blocking studies (15 minutes) revealed ~45% saturable binding in the thalamus and frontal cortex, and ~25% specific binding in other regions. Conclusions: [C-11]WLD3.001 is a high affinity selective ligand for dopamine D3 receptors that exhibited saturable binding in the rodent brain. Further characterization of this tracer is warranted.

No. 118

DCE MAGNETIC RESONANCE IMAGING DETECTED DIFFERENTIAL RESPONSE OF METASTATIC VERSUS INDOLENT HUMAN MELANOMA TO ZD6126 TREATMENT

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It has been previously demonstrated that two melanoma cell lines obtained from a surgically excised tumor of the same patient have different phenotype: C6181cells form a metastatic tumor *in vivo* when xenografted in nude mice; microscopic necrosis or a necrotic center is common in this tumor; it even forms blood vessels through a unique mechanism called vasculogenic mimicry. On the other hand, the indolent line (A375P) is not metastatic. ZD6126, which targets the microtubular cytoskeleton of endothelial cells, is shown to induce vascular shutdown leading to tumor necrosis. We hypothesized that metastatic melanoma may have more immature vasculature, which can be blocked by ZD6126 treatment. We utilized dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) to study the acute response (within one hour after treatment). The pretreatment Ktrans values (first order rate constant for transfer of contrast agent from vasculature to tumor interstitium) of C8161 and A375P are 0.45 (±0.29, n=5) min-1 and 0.15 (±0.11, n=4) respectively. Immunostaining for CD31 shows that C8161 has higher vessel fraction than the A375P tumor (4.5% vs 2.2%, $P<0.05$). A significant reduction of Ktrans (0.16 min-1 compared to the pretreatment value of 0.45 min-1, $P<0.05$) in C tumors was observed within an hour after injection of ZD6126 (200 mg/kg), whereas Ktrans was reduced only slightly in A tumors ($P=0.1$) in response to ZD6126 treatment. Our results suggest that a radical difference in vasculature between the two melanomas could be the mechanism behind this differential response and DCE MRI could play a critical role in probing this difference.

Poster Presentations

Basic Science Poster Presentations

No. 119

EFFECT OF SINOGRAM FILTERING IN THE QUALITY OF POSITRON EMISSION TOMOGRAPHY RECONSTRUCTIONS

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Introduction and rationale: In the reconstruction of positron emission tomography (PET) studies, list mode data are usually aggregated into sinograms. This step is necessary for filtered backprojection algorithms and also for some statistical methods. Several effects, such as randomness of the positron emission, scatter, positron range and non-colinearity, degrade these sinograms. The subsequent reconstruction process propagates these errors to the final images. Since filtering in the angular direction introduces non-uniform tangential blurring, sinograms are generally filtered only in the radial direction for noise reduction. This filtering, however, also degrades resolution. Several methods have been proposed to face this problem, for instance filtering in the Wavelet or Stackgram domains. Fourier transform of a sinogram is known to show a particular shape of the spectral energy distribution. In this work, this property has been exploited to perform an adapted filtering, comparing the results with previously reported methods. Materials and methods: Data from phantoms and rodents obtained from a real PET system (rPET, SUINSA) have been used to compare different sinogram filtering techniques and to evaluate the enhancement achieved. Results and conclusions: A comparison of different methods for noise reduction in sinograms is presented. The proposed method for filtering in the Fourier domain provided the best results in terms of efficiency, noise reduction and simplicity. It achieved a SNR increase of up to 30% with no FWHM degradation. Furthermore, this correction improves the sinogram leading a visual enhancement similar to that of scatter correction methods.

No. 120

EFFECT OF MISALIGNMENTS IN SMALL ANIMAL POSITRON EMISSION TOMOGRAPHY SCANNERS BASED ON ROTATING PLANAR DETECTORS

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Introduction: Technological advances have improved the assembly process of positron emission tomography (PET) devices, resulting in quite exact geometric parameters. However, in high sensitivity and high spatial resolution systems, even minimum misalignments (submillimetric) of the