Published in final edited form as:

AAPS J. ; 20(1): 15. doi:10.1208/s12248-017-0157-6.

Pharmacoimaging of Blood-Brain Barrier Permeable (FDG) and Impermeable (FLT) Substrates After Intranasal (IN) Administration

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Abstract

Purpose—To illustrate the use of imaging to quantify the transfer of materials from the nasal cavity to other anatomical compartments, specifically, transfer to the brain using the thymidine analogue, [¹⁸F]fluorothymidine (FLT), and the glucose analogue, [¹⁸F]fluorodeoxyglucose (FDG).

Methods—Anesthetized rats were administered FLT or FDG by intranasal instillation (IN) or tail-vein injection (IV). PET/CT imaging was performed for up to 60 minutes. Volumes-of-interest (VOIs) for the olfactory bulb (OB) and the remaining brain were created on the CT and transferred to the co-registered dynamic PET. Time-activity curves (TACs) were generated and compared.

Results—The disposition patterns were successfully visualized and quantified and differences in brain distribution patterns were observed. For FDG, the concentration was substantially higher in the OB than the brain only after IN administration. For FLT, the concentration was higher in the OB than the brain after both IN and IV and higher after IN than after IV administration at all times, whereas, the concentration in the brain was higher after IN than after IV administration at early times only. Approximately 50% and 9% of the IN FDG and FLT doses, respectively, remained in the nasal cavity at 20 minutes post-administration. The initial phase of clearance was similar for both agents ($t_{1/2}$ =2.53 and 3.36 minutes) but the slow clearance phase was more rapid for FLT than FDG ($t_{1/2}$ =32.1 and 85.2 minutes, respectively).

Conclusion—Pharmacoimaging techniques employing PET/CT can be successfully implemented to quantitatively investigate and compare the disposition of radiolabeled agents administered by a variety of routes.

Keywords

nasal absorption; preclinical pharmacokinetics; site-specific absorption pharmacimaging; [^{18}F]fluorothymidine (FLT); [^{18}F]fluorodeoxyglucose (FDG)

Introduction

Pharmacimaging provides a means to not only visualize but to quantitate the disposition (absorption, distribution, excretion) of labeled compounds. Positron emission tomography (PET) quantitatively images the distribution of radiopharmaceuticals whereas computed tomography (CT) provides information about anatomical structure. Hybrid modalities like PET/CT can provide the combination of distributional information co-registered to structure thereby allowing the investigation of the disposition of radiolabeled materials to be both visualized as well as quantified in discrete anatomical regions, many of which cannot be sampled directly.

Direct material transfer from the nasal cavity to the brain has been reported for a number of drugs and protein-based therapeutics.(1–3) However, quantitation of the time-course of the influx and efflux of materials into and out of the brain non-invasively is currently only possible with the use of imaging, and specifically a quantitative methodology such as PET. The purpose of this investigation was to develop pharmacimaging techniques to facilitate the exploration of the mechanisms controlling absorption across the mucosal tissues within the nasal cavity and to examine the role of substrate permeability characteristics in the distribution of materials from the nasal cavity directly to the brain.

[^{18}F]Fluorodeoxyglucose (FDG), a glucose analogue, is utilized clinically to map glucose metabolism in the brain,(4, 5) heart and tumors and readily crosses the blood brain barrier (BBB) from the systemic circulation. [^{18}F]Fluorothymidine (FLT), a thymidine analogue, is utilized on an investigational basis in humans and animals to map proliferation in tumors(6) and bone marrow.(7–10) FLT is known to only minimally cross the intact BBB,(11) and when used to image gliomas after IV administration, uptake has been related to the breakdown in the BBB(11, 12) which is frequently seen in these rapidly growing tumors.

The comparison of the nose-to-brain distribution of FDG, a highly permeable and BBB permeable substrate, to FLT, a low permeability and BBB impermeable substrate, enables the further investigation of the proposed direct nose-to-brain pathways that are not dependent on material access to the systemic circulation prior to entrance into the CNS. Typically, substances used to investigate these pathways have access to both the systemic circulation with some, although potentially limited, permeability across the BBB. The low permeability of FLT, along with the high sensitivity of PET quantitation, provides a unique opportunity to study distribution pathways accessible directly from the nasal cavity without confounding distribution resulting from substrate present in the systemic circulation. To this end, the distribution between the nasal cavity and the brain following IN administration was quantified for FDG, a well-absorbed and BBB-permeable compound,, and FLT, a compound with essentially no BBB permeability.

Imaging techniques have been used to study nasal drug delivery previously, and in many cases these investigations have focused on nasal deposition or clearance patterns. Shingaki, et al. (13) investigated the volumetric and mucociliary clearance of FDG over a 30 minute period after nasal instillation to rats in the prone position using PET. They reported a rapid removal of the FDG tracer from the nasal cavity with the percent of administered activity in the nasal cavity reduced by approximately 50% at the end of the imaging period. The balance of the FDG dose (approximately 50%) was swallowed and, therefore, available for absorption into the systemic circulation from the gastrointestinal tract. Since the PET images obtained in the current studies also allowed for the evaluation of volumetric and mucociliary clearance from the nasal cavity, similar measures of the initial clearance rates from the nasal cavity were made for both the FDG and FLT markers.

Materials and Methods

Radiopharmaceutical dose preparation

Radiopharmaceutical doses prepared for intravenous administration to humans frequently require alterations to their formulation in order to be safely and effectively administered to small animals, including mice and rats. Administered volumes are generally restricted to 200 μ L for IV administration to mice, 500 μ L for IV administration to rats, 5–10 μ L for intranasal administration to mice and 25–50 μ L for IN administration to rats. Therefore, the radiopharmaceutical dose frequently requires concentration as well as the removal of solvents (e.g., alcohol) that would endanger the animal. For the current investigation, FDG was produced in a manner equivalent to that employed for the production of clinical human doses, and because of the relatively high radioactivity concentration shortly after preparation, the FDG product could be used unchanged. On the other hand, FLT was produced in a manner equivalent to that employed for research human doses as described in IND # 101023 (Dr. Michael Graham, MD, PhD, PI)¹ and then further processed as described in Appendix A to reduce the approximately 9% ethanol content to less than 1%.

Animal preparation and imaging

Anesthetized Sprague-Dawley rats (~250–400g) were administered FLT or FDG by intranasal instillation (IN) (volume = 20–25 μ L) or tail-vein injection (IV) (volume ~100 μ L). Sedation consisted of 50 mg/kg pentobarbital intraperitoneally (IP) rather than an inhalation anesthetic (e.g., isoflurane). The inhalation agents are more commonly used in small animal imaging but were not used in this case because of the potential for inhalation agents to alter nasal physiology (e.g., tissue response to gas flows, drying of nasal passages). In order to minimize the potential for breathing difficulties, IN administration was made to a single nostril only with the same nostril used for each rat. Prior to FDG imaging, rats were fasted (with access to water) for a minimum of 12 hours, and measurements of the blood glucose levels were made from a 0.3 microliter blood sample acquired from the tail and analyzed using a Freestyle glucometer (Abbott Labs, Abbott Park, Illinois).

¹The University of Iowa's IND for FLT is essentially equivalent to that utilized in the FLT Demonstration Project of the Clinical Trials Network of the Society of Nuclear Medicine and Molecular Imaging (SNMMI CTN). For further information on specifications for FLT, see the Centralized Biomarker INDs, <http://www.snm.org/index.cfm?PageID=8819>.

All doses were administered with the animal on the camera by positioning the rat on a specially constructed sled that could be moved into the gantry immediately post-administration. Contrary to the position used by Shingaki, et al.(13), the rat was positioned in a supine position with the head at a 40 degree angle to the bed. For IN studies, the dose was drawn up into a Hamilton syringe equipped with a short piece of PE50 tubing and injected slowly into a single nostril (same nostril for every rat). After instillation or injection of the radiopharmaceutical, the rat was immediately transferred to the field-of-view of an Inveon Docked PET-SPECT-CT system (Siemens Medical, USA), kept in the supine position with the head at an approximately 40 degree angle to the bed (which was equipped with an internal heater) and imaged using a list-mode acquisition for up to 90 minutes. The majority of animals were imaged for 45–60 minutes. The time between start of administration and start of imaging was accounted for in the quantitation. There was no observed leakage of the dose outside of the nasal cavity either visually or on the images. A CT image was obtained for attenuation correction and anatomical co-registration with the PET image immediately after dynamic emission imaging. PET data were histogrammed into a dynamic sequence and reconstructed using filtered back-projection and a ramp filter to create a dynamic series of images. In select animals, the tracer and route of administration were repeated to investigate intra-animal variability. All procedures were approved and conducted in accordance with the University of Iowa Institutional Animal Care and Use Committee (IACUC).

Image and data analyses

In general, PET imaging provides a means to visualize the distribution, location and quantity of drug during the imaging period. The data can be evaluated as a series of static (i.e., snapshot) images in one or more orthogonal planes (transaxial, coronal or sagittal) or as a three-dimensional cine image (see supplementary data). Time-activity curves (TACs) can be generated for the dose (as the total amount and as concentration values) at the site of administration as well as for any organ or structure within the field-of-view for the duration of imaging.

All image analyses were performed using the view, volume-of-interest and co-registration (fusion) tools of the PMOD Biomedical Quantification Package (version 3.3, PMOD Technologies, Ltd., Zurich, Switzerland). Three-dimensional volume images were created using the 3D Tool of PMOD (version 3.5). Volumes-of-interest (VOIs) for the olfactory bulb (OB) and rest of the brain (brain) were created by manually drawing regions on the inside surface of the skull on all relevant CT slices (Figure 1A & B). The OB and brain VOIs were digitally transferred to the co-registered dynamic PET images. In addition, the VOI containing the IN administered dose was created using a 10% maximum pixel value threshold over the nasal cavity on the initial time frame of the PET dynamic image. Time-activity curves (TACs) were generated for the OB, brain and nasal cavity for the IN administered dose VOIs. The TACs were scaled in normalized concentration units (i.e., $SUV = \text{standardized uptake values (g/mL)} = \text{concentration (kBq/mL)}/\text{dose (kBq)}/\text{animal's weight (g)}$) and in normalized quantity units (i.e., fraction of administered dose) for each VOI. For comparison purposes between the small volume OB tissue and the larger volume brain

tissue, the concentration was also parameterized as fraction of the administered dose per cc of tissue.

Results

Visualization of Dose Migration

Figures 2 and 3 present the visual time-course of disposition of FDG and FLT from the nasal cavity VOI, respectively. For both tracers, a significant portion of the dose was cleared rapidly to the oropharynx and was swallowed. For agents like FDG that can be absorbed from the GI tract this presents an alternative route for systemic availability. In comparison, agents such as FLT with little or no GI absorption simply result in the swallowed dose being excreted unchanged.

The imaging sequence for FLT (Figure 3) provides an excellent visual display of the clearance behavior of the tracer from the nasal cavity. There is significant “bulk” clearance of the instilled dose within the first few minutes following administration followed by a slower clearance over the next ~20 min. The remaining dose in the nasal cavity cleared very slowly and some signal was still measurable at the last sampling time (60 min). The clearance results for FDG, however, are not a simple reflection of the clearance of the unabsorbed tracer as was the case with FLT. FDG is able to be taken up into the nasal tissues, and following the likely phosphorylation and sequestration of a fraction of the absorbed dose within those tissues, the FDG signal remains strong in the main nasal cavity region for an extended period of time.

Non-invasive Determination of Tissue Concentration in the Nasal Cavity

The concentration of the labeled drug, e.g., FDG or FLT, within defined, anatomically distinct tissue and volume spaces can be determined over the time-course of imaging (see TACs). Figure 4 illustrates TACs of the dose in the nasal passages. The resulting 60 minute TACs (Figure 4) could all be well-described by bi-exponential functions and quantitatively showed that most of the FLT was cleared within 20 minutes in each of the animals. (Table 1). These results are in excellent agreement with mucociliary clearance behavior reported previously for rats (13, 14) and for humans (15). In both species, the nasal cavity residence time of an instilled dose is typically in the range of 15–30 minutes. The bi-phasic behavior has been attributed to an initial volumetric clearance (< 2 minutes) of the quantity of the dose unable to be retained or associated with the mucosal surfaces followed by a slower clearance attributed to mucociliary clearance resulting in a nasal residence time of 15–30 minutes for the remainder of the instilled dose. An extremely slow clearance is observed from the anterior, non-ciliated region of the nasal cavity where the dose was initially instilled. Although the limited timeframe of the imaging session did not provide for the quantification of the extremely slow clearance phase, the images illustrate the presence of a reservoir of tracer in the anterior regions at 1 hour which will continue to be slowly cleared from the region

Non-invasive Determination of OB and Brain Concentrations

The concentration in the nasal cavity, OB and in the rest of the brain after the IN administration of FDG, the glucose analogue, and FLT, the thymidine analogue, are presented in Figure 5. For FDG (panels A & C), the concentration in the nasal cavity and the OB exhibit parallel declining time courses after the initial phase (panel A) whereas the concentration in the brain increased over time although the magnitude was approximately 1/20 of the OB concentration even at the latter times (panel C). Whereas, for FLT (panels B & D), although a concentration similar to the initial FDG concentration in the nasal cavity was observed, the concentration in the OB was much lower than for FDG (panel B) although it also paralleled the decrease in the nasal cavity concentration over time. Unlike the inverse relationship between OB and brain concentrations over time seen with FDG, the OB and brain reached stable FLT concentrations by approximately 25 – 30 minutes with the brain concentration measured to be approximately 1/3 of that observed in the OB. The differences in the OB and brain concentration patterns are likely due to FDG uptake from the nasal cavity as well as from the systemic circulation derived from the systemic nasal absorption and oral absorption of the swallowed dose. Whereas, FLT does not undergo substantial oral absorption of the swallowed dose, resulting in delivery to the brain solely from the nasal cavity.

In preliminary control experiments (data not shown), following intravenous FDG administration, the SUV measurement at approximately 2 hours post-administration was very low in the nasal cavity and essentially equal in both the brain and the olfactory bulb (5.2 and 5.3 SUV units, respectively) reflecting the systemic distribution pattern of FDG and the relative consistency in the glucose metabolic rates of these tissues. There was no significant signal observed within the nasal cavity region indicating that the affinity of the nasal tissues for FDG was not different than expected for other non-glucose-avid tissues. In comparison, since the brain is a non-proliferative tissue, brain tissue has very low affinity for FLT. Figure 6 illustrates the OB (upper panel) and brain (lower panel) TACs derived from IN compared to IV administration for FLT. The elevated FLT OB and brain concentrations after IN administration rapidly decreased and reached levels similar to those obtained following IV administration after approximately 25 minutes. As illustrated in Figure 7, the brain concentrations of FLT differed from the concentrations of FDG after IN administration after approximately 10 minutes, indicative of the differing metabolic and cellular processes underlying the distribution of each agent.

Discussion

The direct transfer of materials from the nose to the brain has been investigated for a wide variety of materials, including drugs(1–3), environmental toxins(16–18) and viruses(19). All of these investigations have utilized invasive methods for concentration measurements (direct CSF sampling, microdialysis, tissue harvesting) or have involved post-mortem analyses. Each of these interventions may result in unintended effects on the distribution patterns being measured.

Pharmacoinaging approaches provide a means to not only non-invasively quantify kinetic behavior but to also visually observe the distribution of labeled compounds. The advantages

of the pharmacoinaging approach, especially using PET imaging (in contrast to SPECT or optical imaging), are that quantitative measures of tissue concentrations can be determined non-invasively, simultaneously, and repeatedly with high sensitivity providing the means to make intra-animal and inter-animal comparisons. For intranasal administration, imaging also provides an improved method to non-invasively monitor and quantify volumetric and mucociliary clearance along with distribution patterns of the administered dose.

Human olfacto-scintigraphy using [^{201}Tl] SPECT imaging has been previously reported by Shiga and colleagues as a method to assess the reported direct pathway between the nose and brain.(20–22) Higher migration rates to the OB were found in subjects with normal olfactory thresholds compared to patients with impaired olfaction because the tracer migration was associated with intact olfactory nerve fibers. Although these studies do not report on the use of imaging, and specifically PET imaging, as a tool for the evaluation of the PK properties of IN dosage forms, they support the feasibility and tolerability of human imaging after IN administration of radiotracers and suggest the direct role of the olfactory neurons in the transfer of materials within the nasal mucosa.

Investigation of the behaviors of FDG and FLT, two tracers with significantly different distribution properties, provide examples of the types of comparisons and conclusions that can be drawn using pharmacoinaging approaches. For these agents, it was observed that the clearance of the dose from the nasal mucosa as well as the tracer transport into and retention in the olfactory bulb (OB) and the rest of the brain differed between the glucose analogue, FDG, and the thymidine analogue, FLT. These comparisons strongly suggest that administration via the nasal cavity provides the opportunity for substrates to distribute into the nasal tissues and further distribute into the brain without the need to be first absorbed into the systemic circulation. FDG concentrations in the brain continued to increase with time due to uptake from both the nasal mucosa and the systemic circulation driven by the high glucose metabolic rate of brain cells which facilitates cellular uptake and phosphorylation with resulting intracellular retention of FDG, whereas, FLT concentrations fell to a plateau level because of the lack of proliferative activity of normal brain cells.

Although FDG absorption after oral administration is significantly lower than that of glucose(23) potentially because it does not appear to be a substrate for the sodium-dependent glucose transporter (SGLT)(24), FDG is still readily absorbed from the GI tract with clinically useful images achieved in humans after 60 minutes post-oral administration. (25) Since the FDG concentrations in the olfactory bulb measured in the current study paralleled the concentration remaining in the nasal cavity over time, this provides additional evidence that continued absorption of unphosphorylated FDG from the nasal cavity took place throughout the imaging interval as well as delivery from the systemic circulation resulting in the increasing brain concentrations over time.

Higher FLT concentrations observed in the OB and the rest of the brain following IN compared to IV administration were indicative of FLT distribution into the brain via non-circulatory pathways. Due to the lack of proliferative activity in the brain tissues, there was limited cellular uptake and phosphorylation of FLT in the brain, resulting in rapid clearance with low residual brain concentrations following both intranasal (IN) and systemic (IV)

administration. These findings are consistent with the evidence that thymidine kinase-1 (TK1) activity, an enzyme up-regulated during S-phase and decreased in cells that do not undergo division,(12) is needed for the accumulation of FLT.(26–28)

As powerful a tool as pharmacimaging can potentially be, there are some important limitations to these techniques to be considered. First, for the use of PET, the compound of interest must be labeled with a positron emitting radionuclide (e.g., [^{11}C], [^{18}F], [^{13}N], [^{15}O] or [^{68}Ga]). Inherent to the use of these types of labels, the ability to detect the compound and therefore, the timeframe of the kinetic investigation will be limited by the half-life of the radionuclide (e.g., 20 minutes, 109.8 minutes, 10 minutes, 2.03 minutes (122 seconds) or 68 minutes, respectively) and the metabolic stability of the label. In the current study, the relatively long half-life of [^{18}F], the metabolic stability of the label for both FDG and FLT coupled with the rapid time frame of the distributional processes after IN administration allowed for the assessment of the kinetic behavior within a reasonable imaging acquisition period (< 2 h) both from a physiological and physicochemical perspective. This set of conditions may not be applicable for other types of compounds and/or kinetic processes, so careful study design is crucial to effective utilization pharmacimaging techniques.

Second, the spatial and temporal resolution of the modality in general and the scanner in particular will limit the data sampling protocol. For example, the spatial resolution of PET is approximately 2 mm(29) and is poorer than CT or MRI. Ex vivo techniques such as autoradiography can overcome a portion of the spatial limitations but will not achieve the resolution of high dose CT or high field-strength MRI. And, by necessity, ex vivo tissue analyses involve destructive sampling and, therefore, only a single time point is provided per animal. Temporally, list-mode acquisitions provide for the potential binning of data into frames as short as 1–2 seconds in length, however, adequate count-statistics must be available to create frames of such short duration. Therefore, data is frequently binned into shorter frames initially and then longer intervals at later time periods and with list-mode data, re-binning of the data to optimize information content can be performed post facto. In the current study the spatial and temporal resolution adequately characterized the kinetics of both FDG and FLT in the nasal cavity, OB and the rest of the brain after IN and IV administration.

Third, partial volume and spillover effects may alter measured concentration values. Partial volume effects result in a lower measured concentrations compared to the actual concentration present in small (relative to the resolution of the scanner) regions or volumes due to smearing out of the activity due to the limits in resolution inherent to the modality. Spillover, as the name implies, involves signals “spilling” from high activity regions to lower activity regions or the contribution of blood in the tissue to the measured activity in the region or volume. Because the physical volume of the tracer dose resided immediately adjacent to the OB, spillover contributed to a portion of the signal measured in the OB VOI; this effect was much less likely to be an issue for the brain VOI due to the anatomical location of the brain relative to the nasal cavity in rats. On the other hand, the OB VOI was smaller than the brain VOI, and therefore, subject to a greater partial volume effect. The conflicting nature of these two effects made weighting potential corrections difficult, so no corrections were made for either partial volume or spillover effects in the analyses.

Partial volume and spillover effects should not differ between FDG and FLT IN administrations and should result in equivalently reliable SUV measurements for both compounds. Yet as evidenced from Figures 5 and 7, the differences observed between the tracers suggest that partial volume and spillover effects do not systematically alter the results. Although the initial nasal concentrations of FDG and FLT were nearly identical, theoretically providing the same degree of spillover into the OB VOI, the OB concentrations differed between the two agents in magnitude and time course. The “gold standards” for the assessment of spillover and partial volume effects are comparisons of imaging-based results with measurements derived from ex vivo tissue analyses. In a follow-up study(30), ex vivo findings are presented that support the reliability of the imaging-based results to accurately determine the OB and brain radiotracer concentrations. Concentrations of FLT in specific anatomical brain regions provided parallel results to imaging studies and provided further evidence for the direct nose-to-brain transfer of FLT to the olfactory bulb.

Conclusions

PET/CT imaging is a powerful tool that allows for visualization and quantification of the distribution of drugs within the body. The technique can be applied to characterize pathways and rates of absorption; tissue distribution patterns, retention and clearance; and perform pharmacokinetic analyses not possible from static blood or tissue samples. Pharmacoinaging of the dynamics of absorption and distribution following intranasal drug administration confirms that standard *in vivo* techniques utilizing rats provide highly reproducible patterns of absorption and clearance from the nasal cavity. Pharmacoinaging of FLT disposition clearly demonstrates an enhanced distribution of FLT into the brain compared to that following intravenous administration with significantly higher concentrations measured in the olfactory bulb region following intranasal administration. This enhanced distribution occurs nearly immediately after administration, but rapid clearance from the tissues returned the concentrations to values similar to those obtained following IV administration within 30 – 45 minutes. In comparison, FDG is transferred to the brain both directly from the nasal cavity and via the systemic circulation. Due to its phosphorylation within the brain (and nasal tissues), concentrations of ^{18}F are detected within these tissues for extended time periods. Both the FLT and FDG results show that nasal administration may provide a short-term distribution advantage for substances to enter the brain, but their subsequent pharmacologic or toxicologic activities are the result of both the initial disposition profile and the metabolism and elimination of the material from the tissue compartment. Pharmacoinaging represents a powerful tool to investigate all of these ADME-based activities, yet continued improvements in the resolution of the measurement systems and the broader availability of appropriate, PET-labeled ligands are needed to expand the use of these techniques.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by National Institute on Deafness and Other Communication Disorders of the National Institutes of Health under award number R01DC008374-03S1. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Appendix A: Preparation of [¹⁸F]Fluorothymidine (FLT) for Small Animal and Cell Culture Studies

Final sterile [¹⁸F]Fluorothymidine (FLT) product, prepared according to IND # 101023 (Dr. Michael Graham, MD, PhD, PI) typically contains 80 – 120 mCi in 14 – 17 mL with approximately 9% ethanol content. This product is modified to meet the requirements for administration to small animals. A 1.5 – 2.0 mL sample is withdrawn from the product vial

into a clean 13mm × 100mm borosilicate tube. The tube is then transferred to a stirred oil bath that has been pre-equilibrated to 90° – 95° C. The sample is heated under a steady stream of dry nitrogen for 12 minutes. A 3 1/2 inch sterile arterial needle is used to direct the stream of nitrogen close to the surface of the FLT solution. At approximately 10 minutes, the needle is gradually withdrawn in order to blow off ethanol that may have condensed on the wall of the tube. Water condensate is always observed during this processing. The tube is withdrawn from the oil bath, rapidly wiped free of oil, and the top covered with Parafilm™ to avoid ingress of microbial agents. This material, when cooled, is apportioned to sterile plastic microfuge tubes as requested by the imaging facility using sterile pipet tips. Samples are removed for the analysis of ethanol content by gas chromatography and for final product quality control in a manner identical to the original human product using HPLC.

Figure 1.

Volumes-of-interest (VOI), created and superimposed on co-registered CT images, for measurement of olfactory bulb (fuschia) and residual brain (blue) concentrations in the PET images ((A) dorsal view and (B) sagittal view). Rainbow colors represent the initial distribution of the concentration of radioactivity from the IN administered dose in the nasal passages (concentration: red > green > blue).

Figure 2. Visualization of an FDG dose in the nasal cavity (sagittal views). Note a portion of the instilled FDG remained within the absorptive region of the nasal cavity but the concentration appeared to decrease (red to yellow to blue transition) with time. Increasing amounts of swallowed FDG were observed in the oropharynx (arrow) with increasing time post-administration.

Figure 3.

Visualization of an FLT dose in the nasal cavity (sagittal views). Note the instilled FLT remained near the absorptive region within the nasal cavity for less than 15 minutes. After this time, the residual signal from the nasal cavity resided primarily in the anterior region near the nostrils. Decreasing amounts of FLT were observed in the oropharynx (arrow) over time.

Figure 4.

Fraction of the administered dose of FDG and FLT remaining in the nasal cavity over a 1 hour period from the start of instillation. Note the greater retention of the FDG compared to the FLT (approximately 50% of the FDG in nasal cavity at 20 minutes compared to 9% of the FLT) and the intra- and inter-animal consistency across the entire time period of imaging. The measured FDG signal is likely a combination of FDG mucosal uptake and residual unabsorbed FDG.

Figure 5. Concentration (in standardized uptake value units (SUV)) of FDG (Rat A) (panels A and C) and FLT (mean of Rats A, B, C, D) (panels B and D) in the nasal cavity (administered dose) and olfactory bulb (OB) (panels A and B) and olfactory bulb and rest of brain (panels C and D) versus time. The plots for FDG and FLT are scaled equivalently for the concentration in the nasal cavity, OB and brain. Note the parallel relationship between the OB concentration and that in the nasal cavity after the initial phase (panel A) and the possible re-distribution from the OB to the brain proper over time (panel C).

Figure 6.

Fraction of the administered FLT dose (expressed as percent) in the olfactory bulb (upper panel) and rest of the brain (lower panel) (see Figure 1 for VOI) after intravenous (IV) (red) and intranasal (IN) (blue) administration versus time. Note that for both regions there is greater uptake after IN administration than after IV administration.

Figure 7. Comparison of fraction of administered dose (percent,%) in brain VOI after intranasal (IN) [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]fluorothymidine (FLT) in the same animal (Rat A). Note the similar initial time-course and then the divergence between the two agents.

Table 1

Fitting Parameters for a Bi-exponential* Model for the Clearance of FLT and FDG from the Nasal Cavity (mean value with 95% confidence interval (CI) of estimate)

[¹⁸F]Fluorothymidine (FLT)			
Parameter	Estimate (95% CI)	Half-life (min) (95% CI)	
A (percent dose)	78.9 (76.6–81.2)	-	
alpha (fast phase)(min ⁻¹)	0.206 (0.192 – 0.220)	3.36 (3.16 – 3.61)	
B (percent dose)	11.6 (9.5 – 13.7)	-	
beta (slow phase)(min ⁻¹)	0.0216 (0.016 – 0.027)	32.1 (25.5 – 42.9)	
[¹⁸F]Fluorodeoxyglucose (FDG)			
Parameter	Estimate (95% CI)	Half-life (min) (95% CI)	Clearance values (min⁻¹) reported by Shingaki, et al., 2016 (13)
A (percent dose)	16.3 (12.2 – 20.3)	-	
alpha (fast phase)(min ⁻¹)	0.273 (0.178 – 0.369)	2.53 (1.88 – 3.92)	
B (percent dose)	60.7 (59.6 – 61.9)	-	
beta (slow phase)(min ⁻¹)	0.00813 (0.00754 – 0.00872)	85.2 (79.5 – 91.7)	5 µL dose volume: 0.0076 ± 0.0034 15 µL dose volume: 0.0111 ± 0.0071 25 µL dose volume: 0.0055 ± 0.0054

* Model: Percent of Administered Dose = $A \times \exp(-\alpha t) + B \times \exp(-\beta t)$ where t = time (minutes) from start of instillation.