Preclinical PET Imaging of CNS Diseases in Rodent Models

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1 SUMMARY

Small animal PET imaging is an important tool for preclinical drug research. It can provide valuable information of disease progression and treatment effects longitudinally. Furthermore, PET is a translational imaging technique which can provide information about receptor density, brain metabolism, and receptor occupancy.

In this study, we have utilized several PET-tracers to visualize changes, in neuroinflammation, dopaminergic receptor levels, beta-amyloid plaque burden using different preclinical CNS models. Additionally, we present technique to obtain metabolite corrected arterial input function (AIF) from rats without hypovolemia. Dynamic PET imaging of rodents is usually limited to tracers with reference tissue available. Image derived input functions are limited to small size of arteries and the inherent resolution of PET imaging. Moreover, traditional techniques for blood sampling to generate full arterial input function are not feasible due to limited blood volume of rodents. Hypovolemia may also bias the tracer pharmacokinetics. Furthermore, multiple blood sampling can be conducted only as a terminal procedure preventing longitudinal studies within individual. With arteriovenous shunt and coincidence counter blood input function can be obtained during dynamic PET scan without blood loss. Correction for plasma activity and parent fraction can be achieved from minimal blood volume samples collected from the shunt during the scan allowing longitudinal imaging of same individuals.

As a summary, PET imaging provides a powerful and translational research tool together with CNS disease animal models allowing comprehensive evaluation of disease progression and treatment interventions for in vivo studies. Metabolite corrected AIF can be obtained from rats enabling the use of multiple compartment models and longitudinal imaging without reference tissue.

2 IMAGING

All animal experiments were carried out according to the National Institute of Health (NIH) guidelines for the care and use of laboratory animals, and approved by National Animal Experiment Board. Animal facility has been accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), International. Prior imaging (BioPET, Sedecal) the animals were anesthetized using isoflurane and cannulated in the lateral tail vein. Radiotracer was administrated as bolus and the animals were scanned in list mode. The images were reconstructed with 3D OSEM and corrected for attenuation. Image analysis was performed with PMOD (v. 3.7).

3 NEUROINFLAMMATION

Neuroinflammation after intrastriatal lipopolysaccharide (LPS) infusion, was followed longitudinally in male SD rats 1, 8 and 15 days post operation with translocator protein (TSPO) ligand ^{18}F-FEPPA . To obtain blood input function, the tail artery and vein were cannulated and connected to a coincidence counter (Twilite, SwissTrace) and a peristaltic pump with a constant flow rate (0.32 ml/min). During the PET scan blood samples for plasma fraction and parent fraction were collected at 3, 6, 9, 12, 15, 20, 30, 45, 60 and 85 min. The radioactivity was measured in blood and plasma samples (á 10 µl) with gamma counter and unmetabolized tracer in plasma with thin layer chromatography (á 30 – 50 µl). Individual blood input curve was corrected with individual plasma fraction- (Figure 1, A) and parent fraction (B) functions to generate metabolite corrected AIF (C). Total volume of distribution (VT) values were calculated with 2-tissue compartment model.

In the following two weeks after LPS infusion the same individual rat (n=2) was imaged three times including blood sampling for input function. Tracer retention is visible on the injection site suggesting focal neuroinflammation (Figure 2A). Highest V_T values are seen 8 and 15 days post LPS infusion (Figure 2B). The method described here allows longitudinal imaging or same rat with full metabolite corrected arterial input function.

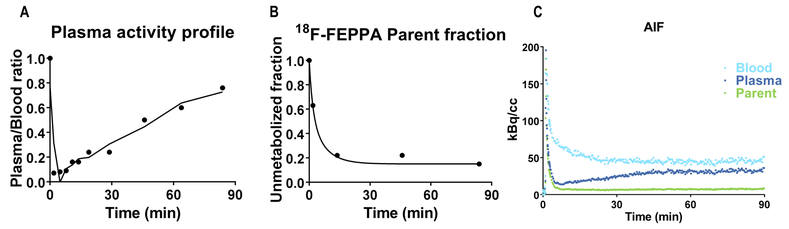


Figure 1. A) Radioactivity distribution between whole blood and plasma during the PET scan in LPS induced rats. B) Fraction of unmetabolized ^{18}F-FEPPA in plasma during the PET scan. C) Generation of AIF from the measured blood input curve corrected with plasma fraction- and parent fraction functions.

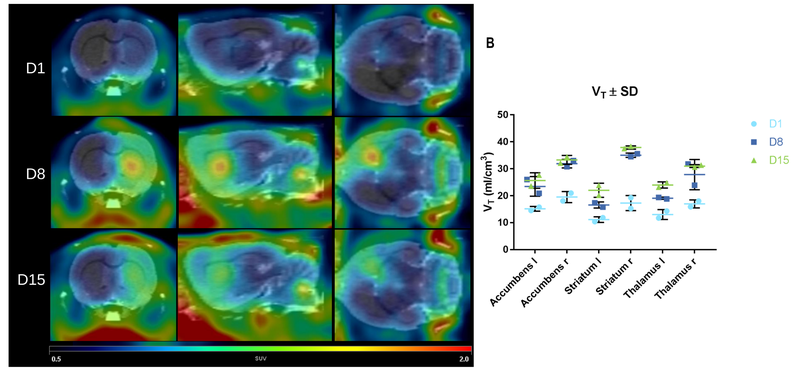


Figure 2. A) Individual rat imaged 1, 8 and 15 days after instrastiatal LPS infusion with TSPO tracer ^{18}F-FEPPA. Metabolite corrected AIF was generated for each scan. Higher tracer accumulation was seen to the injection site. The PET images (averaged frames 30 – 90 min) were aligned with rat MRI template. Sections shown as coronal, sagittal and horizontal view. B) V_T-values of ^{18}F-FEPPA in nucleus accumbensis, striatum and thalamus of both hemispheres. V_T was low on D1, increased thereafter and remained elevated between D8 and D15. Individual data points are plotted in the graphs with mean ±SD.

4 HUNTINGTON'S DISEASE

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion. Dopamine receptors are involved in the pathophysiology of neuropsychiatric diseases, such as Huntington's disease, Parkinson's disease, Alzheimer's disease, and schizophrenia.

In this study mouse model of HD, z175Q KI DN, was imaged at the age of 9 – 10 and 12 months with D2/3R radioligand, ^{18}F-Fallypride. Significant ($p<0.05$) reduction in the striatal BP_{ND} was observed in comparison to wild type mice at the age of 9 months (n=12). Moreover, disease progression with aging was observed as the BP_{ND} of z175Q KI DN was reduced further at the age of 12 months (Figure 3).

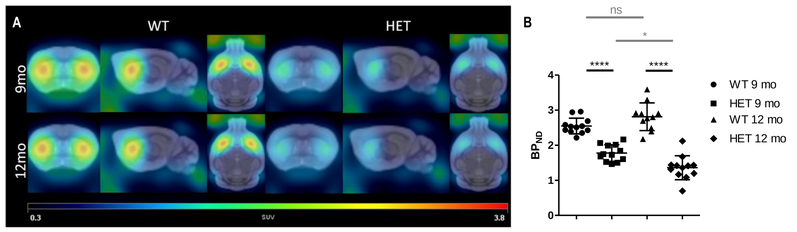


Figure 3. A) Mean PET images 45 – 90 min post injection shows higher ^{18}F-Fallypride uptake in the striatum of WT mice compared to HET both at 9 and 12 mo. The PET-images were aligned with in-house created MRI template for Q175 mice. Sections shown as coronal, sagittal and horizontal view. B) BP_{ND} of 9 and 12 mo WT and HET zQ175KI DN mice (n=12/genotype). HET showed 30.2% and 51.6% decrease in BP_{ND} compared to WT at the age of 9 and 12 months, respectively. The PET scans were performed from the same individuals at both time points. Statistical significance within genotype during aging was performed as paired two-tailed T-test (grey) and comparison between genotypes at the same age using unpaired two-tailed T-test (black, ns = non significant, *** $p = 0.005$, **** $p < 0.0001$).

5 PARKINSON'S DISEASE

Loss of dopaminergic cells in striatum of Parkinson's disease (PD) can be modelled with MPTP challenge. Dopamine transporter availability and glucose metabolism were studied by using ^{18}F-FE-PE2I and ^{18}F-FDG, respectively (Figure 4). Significant decreases in the BP_{ND} of DAT ligand and glucose metabolism in MPTP exposed mice were observed suggesting dopaminergic neuronal death characteristic to Parkinson's disease.

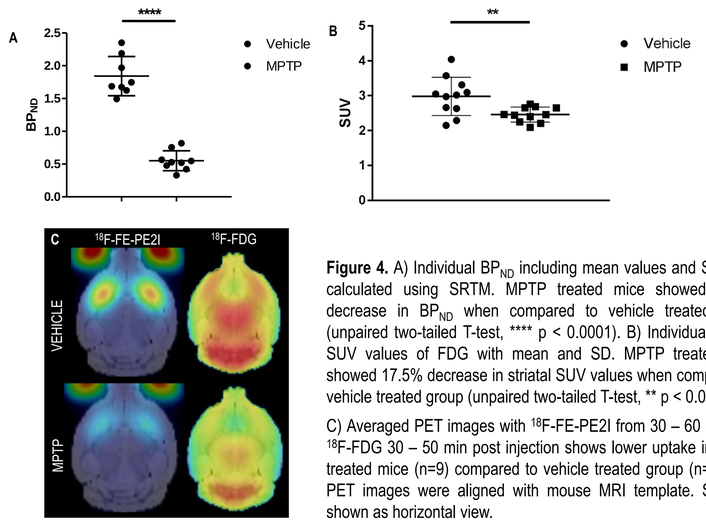
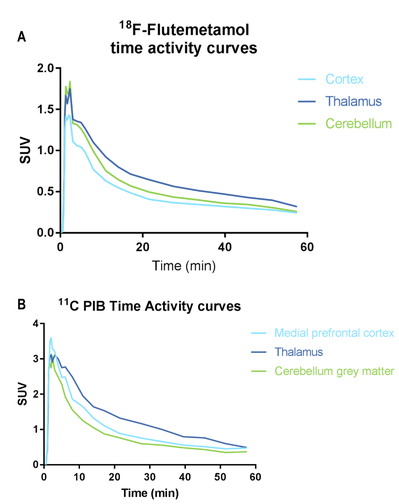


Figure 4. A) Individual BP_{ND} including mean values and SD were calculated using SRTM. MPTP treated mice showed 70.1% decrease in BP_{ND} when compared to vehicle treated group (unpaired two-tailed T-test, **** $p < 0.0001$). B) Individual striatal SUV values of FDG with mean and SD. MPTP treated mice showed 17.5% decrease in striatal SUV values when compared to vehicle treated group (unpaired two-tailed T-test, ** $p < 0.01$).

C) Averaged PET images with ^{18}F-FE-PE2I from 30 – 60 min and ^{18}F-FDG 30 – 50 min post injection shows lower uptake in MPTP treated mice (n=9) compared to vehicle treated group (n=8). The PET images were aligned with mouse MRI template. Sections shown as horizontal view.

6 ALZHEIMER'S DISEASE

Beta-amyloid plaque imaging was performed in CVN mouse (APPSDI/NOS2 KO) with ^{18}F-Flutemetamol and analogous tracer ^{11}C-labelled Pittsburg compound B (^{11}C-PiB) in naïve CD rat (Figure 5). Both tracers showed similar retention profiles. ^{18}F-Flutemetamol had higher extracranial uptake and non specific uptake in nasal epithelia.



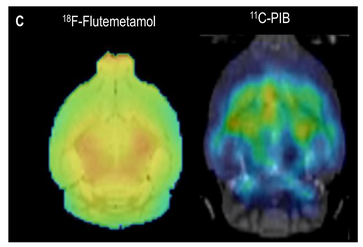


Figure 5. A, B) Similar profile in time activity curves of ^{18}F-Flutemetamol and ^{11}C-PIB from frontal cortex, thalamus and cerebellum grey area were seen. C) PET images of ^{18}F-Flutemetamol (mouse) and ^{11}C-PIB (rat) from 30–60 min post injection. PET images are co-registered with corresponding MRI templates. Sections shown in horizontal view.

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