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Mapping alteration of dopaminergic neurons in a rat model of Parkinson Disease through the comparison of the presynaptic PET tracers, [18F]-LBT999 and 6-[18F]fluoro-L-m-tyrosine

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Introduction

The pathological features of Parkinson's Disease (PD) are mainly driven by the loss of the dopaminergic projection neurons in the substantia nigra (SN) resulting in a dopamine (DA) deficiency in the striatum [1]. We developed a pathologically relevant rodent PD model; overexpressing the mutant (A53T) human alpha-synuclein protein in the SN [2]. Our aims are triple: 1- map neuronal loss and DA deficiency over time using two different presynaptic PET tracers, 2- evaluate the respective sensitivity of each radioligand, and 3- correlate individual PET data to behavioural and histological results.

Materials & Methods

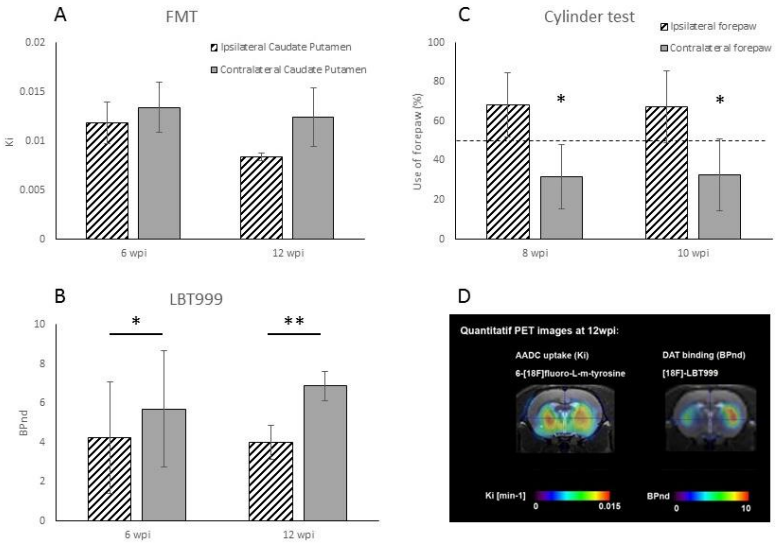
A total of ten rats were unilaterally injected in the SN with a viral vector (AAV2/6) overexpressing mutated (A53T) human alpha-synuclein, and were studied either at 6 weeks post-injection (6wpi, n=6, 543±36g) or 12wpi (n=4, 573±40g). PET imaging was performed using a ligand substrate for AADC, 6-[18F]fluoro-L-m-tyrosine ("FMT", 60min acquisition, 31.3-60.8MBq; pre-treatment by IP injection of 10mg/kg benserazide 30' before imaging [3]), or a ligand for DA transporter (DAT), [18F]-LBT999 [4] ("LBT", 90min acquisition, 40.3-63.0MBq). For behaviour, rats were subjected for 5 minutes to the cylinder test, in which contralateral and ipsilateral paw use was compared. After the *in vivo* studies rats were sacrificed for histological studies using tyrosine hydroxylase immunohistochemistry. From LBT and FMT PET scans, quantitative uptake images (BPnd and Ki, respectively) were calculated using Logan and Patlak graphical methods, with the cerebellum as a reference. Unilateral AAV injections allowed the contralateral striatum to serve as internal control. Paired student

t-test were used to compare the contra- and ipsilateral sides in imaging studies, while an ANOVA was used to compare contralateral paw use to a control group.

Results

Injection of benserazide was not effective in 42% of the animals, thus Ki values could not reasonably be estimated for FMT. Additionally, Ki images showed more non-specific binding than LBT BPnd images. At 6wpi we did not observe any asymmetry in the Ki of quantifiable scans (n=5, p=0.084, Fig 1A, D), however LBT data show decreased BPnd in the ipsilateral caudate putamen (n=6, p=0.027; Fig 1B, D). At 12wpi we observed a similar pattern (Ki, n=2, p=0.336; BPnd, n=4, p=0.003; Fig 1A, B, D). These results are in concordance with the behavioural observations, showing roughly only 30% use of the contralateral forepaw at 8wpi (n=7, p=0.044) and 12wpi (n=8, p=0.045; Fig 1C). No significant correlations between PET data and behaviour were observed. Histological comparisons are still ongoing.

Fig 1: Positron emission tomography and behavioural studies. PET scans were obtained from α-syn-A53T rats at 6wpi and 10/12wpi, using a tracer substrate of AADC (18F-FMTyr) (A), or a dopamine transporter ligand (DAT, 18F-LBT999) (B). (A) Neither at 6wpi (n=5) nor at 12wpi (n=2) a difference was observed in AADC metabolism (FMT). (B) In contrast the DAT tracer (LBT999) showed a significant difference at 6wpi (n=6) and 12wpi (n=4). (C) Cylinder tests at 8wpi (n=7) and 10wpi (n=8) detected motor deficits in α-syn-A53T overexpressing rats. (D) Representative PET images of both tracers.



Discussion/Conclusion

We created an AAV rat model of PD that shows progressive DA deficiency and neuronal loss detectable by FMT and LBT PET imaging. Our parametric data suggest that the DAT tracer is more sensitive to detect a mild PD phenotype as compared to the AADC tracer. This phenomenon has previously been described, and is possibly due to a combination of reduced nerve terminal DAT binding sites and downregulation of DAT in surviving neurons, in an attempt to increase DA availability [5]. More FMT scans will have to be done to increase numbers and compensate for ineffective benserazide blocking. Further analysis of PET data will allow correlating PET data to behavioural and histological measurements.

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