Application of reduction and refinement principles in the evaluation of prodromal markers of Parkinson's disease in a progressive neurotoxic mouse model using multi-tracer PET imaging

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Positron Emission Tomography (PET) is a non-invasive technique used to image metabolic processes *in vivo* with different radiotracers, allowing repeated measurements over time in the same animal. One of the advantages of PET in preclinical research is the possibility to follow the 3Rs principle, especially Reduction and Refinement. Indeed, by setting up longitudinal studies, it is possible to reduce the number of animals by using the same experimental subject for each time point and process investigated. Refinement is ensured by the use of small animal-dedicated instruments that allow the translation to preclinical research of non-invasive diagnostic imaging procedures already in use in clinical practice. Here, we characterized the prodromal stage of Parkinson's disease using a mouse model obtained by treatment with the neurotoxin MPTP and the clearance inhibitor probenecid (MPTPp), by combining *in vivo* PET imaging and immunohistochemistry.

A group of 10 mice were injected with 100 mg/kg of probenecid followed by 25 mg/kg of MPTP, twice a week, for a total of 5 weeks. They were monitored longitudinally with PET before treatment and after 1, 3 and 10 MPTPp injections using two radiotracers: [18F]-FP-CIT, a marker of Dopamine Transporter (DAT) and [18F]-FDG to assess brain glucose metabolism. They were then sacrificed and brains collected for post-mortem immunohistochemical analysis.

We found that both striatal DAT-binding *in vivo* assessed with [18F]-FP-CIT PET and the density of striatal DAT-positive fibers observed post-mortem started to decrease significantly after 3 MPTPp injections. [18F]-FDG uptake was significantly decreased in the striatum and thalamus already at the first administration, while at 10 MPTPp injections [18F]-FDG uptake was increased in the somatosensory and somatomotor cortex. Our results suggest that glucose metabolism is an earlier marker than DAT-binding in detecting neurodegeneration.

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