Challenges of Preclinical PET imaging

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Résumé

In vivo imaging techniques - such as PET, SPECT and MRI- are highly translational tools from bench to bedside and vice versa. PET and SPECT imaging benefit of higher sensitivities compared to MRI, rendering these imaging tools extremely suitable to study metabolism, receptor occupancies and drug distribution. Nevertheless, standardization of imaging protocols is highly important to control variability between- and within-subjects. Additionally, preclinical PET imaging on small or large animal models encounters divers and unique challenges compared to clinical PET imaging. Hefert and coworkers (Mol imaging Biol 2019) addressed different particularities of preclinical PET imaging in detail, and summarized these in four main categories: scanner technology, radiochemistry, methodology and biology.
Scanner Technology & Radiochemistry

Technological improvements of PET detectors have led to increased resolution of preclinical cameras allowing discrimination of different brain regions in small animal brains. The price to pay for this is a decreased sensitivity of the PET detectors. Consequently, the injected radioligand dose per body weight, in terms of radioactivity and the injected mass, can be up to 25 times higher in small rodents as compared to humans. Accurate receptor-binding quantification requires administration of radioligands at tracer doses in order to assure low occupancy of the receptor (around 5%) by the ligand. Therefore, and because of the low sensitivity of preclinical PET cameras, the optimal injected dose is a major challenge especially in small rodent PET imaging. To account for this, the radiochemistry has to aim for the highest possible tracer specific activity, corresponding to the ratio of radioactivity and the mass of compound.

Biology

In contrast to humans, animals are anesthetised during imaging. Physiological monitoring to maintain optimal biological conditions in terms of temperature, breathing- and hart rate, are primordial for reliable and reproducible imaging experiments. Additionally, the choice of anaesthesia must be carefully chosen such that it does not interfere with the receptor system being imaged, nor with physiology of the animal, which might affect the PET-outcome measure, such as for example, the impact of anaesthesia on blood glycaemia, which can interfere with 18F-FDG uptake.

Methodology

One of the advantages of preclinical imaging is the ease to acquire dynamic images up

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to several hours after radioligand injection. As animals are anesthetized and generally fixed with earplugs and a mouth bar, preclinical PET imaging does not suffer from head movement artefacts, as might be the case in human clinical imaging. In addition, arterial blood sampling is more accessible in animals whereas a burden in humans. Previously, arterial blood sampling during PET imaging was especially reserved for larger animal models, because of the limited blood volume of small rodents. Recent technical developments, allow now to measure the whole blood radioactivity concentration in rodents through an arterio-venous shunt, avoiding blood loss during PET imaging. The measure of the freely available plasma concentration of the intact ligand allows solving the pharmacokinetic model of the tracer and hence quantifying receptor binding or occupancy by the ligand. From these quantitative models, simpler quantification approaches without blood measurement, hence applicable in clinical context, can be validated.
Taken into account these issues, preclinical PET imaging is highly valuable to validate: (1) new radioligands in terms of specificity, selectivity and quantifiability; (2) new animal models using well-characterized and validated radioligands; (3) new therapeutic approaches on well-characterized animal models and validated radioligand.

Mots-Clés: Parkinson, imaging, PET