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New avenues in PET imaging of multiple sclerosis
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Chapter

8

Summary

Multiple sclerosis (MS) is a neurodegenerative disease characterized by infiltration of inflammatory cells and the formation of demyelinated lesions in the central nervous system (CNS). Inflammation, demyelination and remyelination are dynamic processes that change over time in individual lesions within a single MS patient.

So far, magnetic resonance imaging (MRI) is the method of choice to detect ongoing changes in (the number of) lesions in MS patients. However, this technique does not allow distinction between inflammation and demyelination/remyelination processes.

Positron emission tomography (PET) is a non-invasive imaging technique that enables *in vivo* monitoring of molecular and biochemical processes, with the use of specific ligands labeled with positron emitter isotopes. This thesis describes our studies that aimed to evaluate the potential of PET imaging for detecting and monitoring changes in myelin content and inflammation in different animal models for MS.

The specific aims of this project were to evaluate: (1) the feasibility of several PET tracers for imaging demyelination and remyelination processes in animal models of MS and to select the tracer that has the best characteristics for PET imaging; (2) the feasibility of PET to detect changes in neuroinflammation in the brain and spinal cord during disease progression; (3) the potential of PET imaging to monitor the efficacy of anti-inflammatory treatment.

In chapter 1, this thesis kicks off with a general introduction about the characteristics of MS, followed by an overview of the animal models that are applied in preclinical research on MS and a description of the principles of PET imaging.

Chapter 2 reviews the use of PET imaging in clinical and pre-clinical MS research. In the majority of these studies, the application of PET is still limited to the evaluation of neuroinflammation and glucose metabolism. Since other processes play a pivotal role in MS as well, imaging methods for imaging biomarkers of these processes are urgently needed. And so, potential new imaging targets and their potential future applications in MS are forwarded and discussed in this chapter as well.

In Chapter 3, the ability of two myelin PET tracers ([^{11}C]CIC and [^{11}C]MeDAS) to detect demyelination and remyelination processes in the cuprizone mouse model is investigated. *Ex vivo* brain biodistribution studies indicated that both tracers appeared to be able to reveal demyelination in the animals after 5 weeks on a cuprizone diet. However, only [^{11}C]MeDAS allowed detection of complete remyelination 5 weeks after normal diet was restored. *In vivo* PET imaging data showed slow kinetics for [^{11}C]CIC and spinal cord uptake of [^{11}C]CIC was not detectable. [^{11}C]MeDAS, in contrast, had fast kinetics and clear spinal cord uptake. No correlation was found between *ex vivo* and *in vivo* data for [^{11}C]CIC, whereas [^{11}C]MeDAS showed a strong correlation. It was concluded that [^{11}C]MeDAS was superior for detecting demyelination and remyelination processes in the cuprizone model in comparison to [^{11}C]CIC. A disadvantage of the cuprizone model is that it does not show focal lesions, like in MS patients, but rather general changes in myelin density throughout the brain. Moreover, mice have a less amount of myelin in comparison to other species, such as rats and primates. Therefore, it is important to repeat our experiments in another species and in a model with focal lesions.

To mimic the focal inflammatory demyelinating lesions in the CNS of MS patients, the lysolecithin rat model was used in the PET experiments described in <u>chapter 4.</u> The aim of these experiments was to evaluate the potential of PET imaging in monitoring local lesions, using [^{11}C]MeDAS, [^{11}C]PK11195 and [^{18}F]FDG as PET tracers for myelin density, microglia activation and glucose metabolism, respectively. To induce an MS-like lesion in this rat model, lysolecithin was slowly injected stereotactically in the right corpus callosum and striatum. After optimization of the injection procedure, a small lesion with a size detectable by the small animal PET scanner (resolution of 1.35 mm) was reproducibly obtained. PET imaging was performed in this model to monitor glucose metabolism, neuroinflammation and changes in myelin content in the focal lesion. [^{18}F]FDG PET did not show any significant differences in glucose metabolism 3 days, 1 week and 4 weeks after lysolecithin injection, suggesting the absence of significant tissue damage. [^{11}C]PK11195 PET was used to analyze neuroinflammation. Increased uptake of this tracer was observed only at the injection site 3 days and 1 week after injection, whereas tracer uptake had returned almost to baseline level 4 weeks after injection. [^{11}C]MeDAS PET was used to evaluate demyelination and remyelination of the lesion. The lesion-to-contralateral brain uptake ratio showed a decrease in tracer uptake in the lesion 1 week after lysolecithin injection, which was still present 4 weeks after injection. Histochemical analysis demonstrated that only minimal remyelination had occurred 4 weeks after lysolecithin injection, which is in accordance with the PET data. It was concluded that PET imaging was able to detect temporal changes in characteristic processes in focal lesions of rat model for MS.

After having established a well optimized lysolecithin rat model for MS, the model was used to study the pharmacokinetic properties of three myelin tracers, as described in <u>chapter 5</u>. The two tracers used in the cuprizone mouse model ([11C]CIC and [11C]MeDAS) were compared in the lysolecithin rat model as well. Since, the widely used PET tracer for β-amyloid plaque imaging [11C]PIB was recently described as a potential tracer for imaging myelin content, it was also included in the comparison with the other myelin tracers. The kinetics of the three evaluated tracers could best be fitted by Logan graphical analysis or the reversible two-tissue compartment model. The volume of distribution could reliably be determined by Logan analysis or compartment modeling. The volume of distribution showed an excellent correlation with the standardized uptake value for [11C]MeDAS and [11CPIB. All evaluated tracers were able to detect the demyelinated lesions. The rate of remyelination showed a high variability, but PET images correlated well with histochemical data, indicating that this variability in remyelination was due to animal model variability and not to tracer specificity. Homogeneous brain uptake, lack of spinal cord uptake and slow kinetics made [11C]CIC the least promising tracer for imaging myelin content. [11C]MeDAS and [11C]PIB showed fast kinetics, a heterogeneous brain uptake, as well as uptake in spinal cord. However [11C]MeDAS exhibited a generally higher brain uptake and a significantly higher uptake in regions rich in myelin, such as brainstem and midbrain, than [11C]PIB. [11C]PIB had the lowest uptake in cerebellum, which is a region frequently containing lesions in MS patients, making this tracer less suitable for myelin PET imaging.

Proceeding on the results from the previous chapters, the PET tracers were further evaluated in another MS animal model that particularly mimics the

immunological characteristics of MS, the experimental autoimmune encephalomyelitis (EAE) model (chapter 6). The EAE model used in our study mimicked relapsing-remitting MS (RRMS) and was characterized by periods of clinical symptoms (e.g. hind limb paralysis) and periods of remission. The aim of this study was to evaluate the feasibility of PET to monitor treatment efficacy by imaging of inflammation and demyelination in the brain and spinal cord during disease progression. In this study, dexamethasone was selected as a typical anti-inflammatory drug. The experimental design did not allow imaging during the period of remission, because the remission was shorter and occurred later than anticipated based on literature data. However, it was possible to detect a significant increase of macrophage/microglia activation in the brainstem and spinal cord of animals treated with saline: the highest levels of inflammation were detected at the peak of the clinical score. About 50% of the rats treated with dexamethasone presented only mild clinical symptoms, but did not develop paralysis. Despite the absence of clinical symptoms in the dexamethasone treated rats at the time of the PET scan, a significant increase of [^{11}C]PK11195 uptake was detected in the brainstem and spinal cord in animals that had previously shown symptoms. The occurrence of neuroinflammation was confirmed by immunohistochemical analysis, demonstrating the sensitivity of [^{11}C]PK11195 PET. Demyelination was evaluated by [^{11}C]MeDAS, the myelin tracer that showed best results in the previous experiments. No significant indication of demyelination by [^{11}C]MeDAS PET could be found, likely due to the small size of the lesions (<0.5mm), as confirmed by histochemistry. Another characteristic investigated with PET imaging was the T cell infiltration into the CNS. The recently validated PET tracer [^{18}F]FB-IL2 was used for imaging T cell infiltration in the EAE model. The hydrophilic propriety of this tracer makes it difficult to penetrate the blood-brain

barrier (BBB), but since BBB permeability in EAE model is increased, [18F]FB-IL2 was still tested in the EAE rats. Unexpectedly, our results showed a decreased [18F]FB-IL2 binding potential in the whole brain at day 6 and day 15 after immunization and a normal uptake, as compared to baseline scan, at days 11 and 19. Based on the literature, the decreases in tracer uptake before disease onset and at the peak of the clinical symptoms correlate with peripheral lymphopenia, suggesting that the binding potentials measured in our images were related to lymphocytes present in brain blood vessels and not to infiltrated T cells in the CNS. In conclusion, [11C]PK11195 PET was shown to be a sensitive tool for monitoring ongoing neuroinflammation during disease progression and for monitoring the therapeutic effects of anti-inflammatory treatment. [11C]MeDAS PET encountered technical limitations in this model, while [18F]FB-IL2 requires further investigation before application in MS can be considered.

In conclusion, the work presented in this thesis showed the feasibility of PET imaging in monitoring MS characteristics. Further investigation remains necessary before the feasibility of myelin imaging with [11C]MeDAS can be investigated in MS patients. First, toxicological studies in animals have to be performed and then proof-of-concept has to be established in a small number of patients. A very interesting opportunity would be to assess the ability of the myelin tracer to detect lesions in grey matter, as MRI is not suitable for this application. Combination of different PET tracers ([18F]FDG, [11C]PK11195 and [11C]MeDAS) can contribute to characterization of individual lesions, monitoring of temporal changes in MS and evaluation of treatment response. Hybrid imaging approaches, such as PET-MRI, that combine the high specificity of PET and the high spatial

resolution of MRI, should be considered in MS as tool for disease characterization, progression monitoring and treatment evaluation.

To conclude this thesis, it is fair to say that interesting applications for PET imaging in MS are within grasp now.