New avenues in PET imaging of multiple sclerosis

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Chapter

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Concluding remarks and future perspectives

Positron emission tomography (PET) can monitor molecular and biochemical processes *in vivo*, offering a valuable tool for monitoring the evolution of specific aspects of multiple sclerosis (MS) and for evaluating the effects of (novel) therapies.

So far, magnetic resonance imaging (MRI) is the "gold standard" for detecting and monitoring changes in (the number of) lesions in MS. MRI has a high spatial resolution, but lacks specificity for characteristic processes in MS, as it does not discriminate between inflammation related processes and myelin changes (Filippi & Rocca, 2011). PET imaging with the use of specific radioligands could provide more specific information about temporal changes in MS focal lesions and enable discrimination between inflammation, demyelination and remyelination processes. However, PET lacks the high resolution of MRI.

To date, PET imaging studies in MS patients are still limited to the evaluation of two parameters: neuroinflammation and glucose metabolism. However, for monitoring other crucial aspects of MS, such as myelin changes and neurodegeneration, novel PET tracers still need to be validated. In this thesis, we have shown the relevance of PET imaging of neuroinflammation for evaluating disease progression and therapeutic efficacy and the feasibility of imaging myelin content to monitor demyelination and remyelination processes.

Neuroinflammation PET imaging

[^{11}C]PK11195 appeared to be an appropriate tracer to assess the temporal changes in neuroinflammation in brain and spinal cord in the lysolecithin and experimental autoimmune encephalomyelitis (EAE) animal models. This tracer has already been applied to investigate microglia activation in brain lesions in MS patients, but imaging of spinal cord lesions in MS patients has not been reported

so far. Lesions in spinal cord are correlated to movement disorders and they are common in primary-progressive MS (PPMS) patients, who have more walking disabilities than patients with relapsing type of MS (Miller & Leary, 2007). Although inflammatory lesions are less common in PPMS than in relapsing types of MS, monitoring spinal cord and brain lesions by [11C]PK11195 PET could help to better understand the temporal changes in the inflammation related processes in each type of MS and to correlate inflammation with clinical symptoms. In this respect, a hybrid system PET-MRI could be an interesting medical device, as it brings together the high spatial resolution of MRI and the specific functional information provided by PET.

Myelin PET imaging

We have demonstrated the feasibility of imaging myelin content *in vivo* with new myelin tracers in different MS animal models. Comparison of three myelin PET tracers led us to conclude that [11C]MeDAS can be considered the most promising PET tracer for imaging myelin content in the brain and spinal cord. Although, [11C]MeDAS showed promising results in MS animal models, further studies in humans need to be performed to prove feasibility of this tracer for PET imaging in MS patients. Before [11C]MeDAS can be used in MS patients, toxicological evaluation and assessment of the radiation burden of [11C]MeDAS in animals will first be required to prove the safety of clinical application of this tracer. Only after proven to be safe, [11C]MeDAS can be tested in healthy volunteers (clinical study phase I) and then in a limited group of MS patients (clinical study phase II).When successful results have been obtained, the tracer can be applied in large clinical studies, including intervention studies.

It is suggested that [11C]MeDAS binds to β-sheet structures, as present in the myelin basic protein (MBP), but the exact binding site of this tracer is not known

and needs to be elucidated to determine whether this tracer is truly specific for myelin content. Other binding sites that are specific for or restrict to myelination processes could be also considered for further development of PET imaging agents. We suggest oligodendrocytes and oligodendrocyte precursor cells as potential targets for PET tracer development, because these cells are responsible for the production of myelin in the brain and spinal cord and so directly involved in demyelination and remyelination processes. So far, no distinct biomarker on oligodendrocytic cells has been identified that could be targeted by a PET tracer. Specific demyelination biomarkers can be a target for PET imaging as well. For example, α*B*-Crystalline protein is over-expressed in the demyelination process, as compared to healthy myelin (Katsavos & Anagnostouli, 2013). A major advantage of imaging α*B*-Crystalline protein would be that it gives an increased uptake of a specific PET tracer during on-going demyelination, rather than a reduction in the imaging signal as is observed for tracers like [11C]MeDAS.

Neurodegeneration PET imaging

Degeneration of axons and the concomitant damage to neurons are responsible for the major disabling symptoms of MS. Recent new ideas about the pathogenesis of MS consider MS as a chronic, gradually aggravating neurodegenerative disease with oligodendrocytes and axons as primary affected targets. In this thesis, we investigated ongoing neurodegeneration in MS models by PET with the tracer for glucose metabolism: [18F]FDG. Absence of local accumulation of this tracer can be considered a sign of ongoing degeneration and loss of cells. [18F]FDG PET may help to discriminate between acute lesions and chronic lesions. In the [18F]FDG PET images, hyper-metabolism would indicate acute lesions (on-going inflammation) and hypo-metabolism would indicate

chronic lesions with possible axonal damage, which makes these chronic lesions less suitable for myelin repair therapies. Another application of [^{18}F]FDG PET may be the detection of focal cortical changes in glucose metabolism which could subsequently be correlated with evolution of clinical impairment. However, detection of changes in glucose metabolism in small focal lesions of the grey matter will be challenging due to the limited resolution and associated partial volume effects. Future technological advances in PET quantification and reconstruction will further enhance the potential of [^{18}F]FDG PET for focal lesion detection and quantification in MS.

Treatment monitoring

In view of the major impact of continuous neurodegeneration on disease progression and functional loss in all MS types, it is to be expected that a large portion of future therapeutic developments in MS will primarily be directed at protecting axons and neurons and preventing their loss. PET with appropriate radioligands that target neurodegeneration/neuroregeneration markers will be a crucial tool to establish the efficacy of these novel neuroprotective drugs. The best way to salvage axons, and so indirectly neurons, is to prevent demyelination and promote rapid remyelination of damaged and denuded axons by novel approaches. These may include stimulation of the endogenous remyelination potential or exogenous cell transplantation strategies. Monitoring the success of remyelination can potentially be done with PET imaging.

The progress in recent years in the development of immunomodulatory drugs (e.g. glatiramer acetate, nataluzimab, fingolimoid, etc) that suppress inflammation and delay or even prevent relapses will presumably continue in the coming years. The effectiveness of these novel drugs and the consequences for local neuroinflammation in the CNS can be monitored with PET and [^{11}C]PK11195 or

other appropriate tracers for neuroinflammation. Being a non-invasive technique, PET imaging can also be used as a tool for monitoring responses of individual patients to a specific drug, help early decision making and timely therapy changes. Labeling of therapeutic antibodies used in MS, such as natalizumab, alemtuzumab and rituximab, can be employed to better select the right treatment for each individual patient based on the *in vivo* information of the presence and affinity of each antibody target in each MS patient.

MS imaging development

A new challenge for the PET community will be to develop new tracers for detection of early lesions in grey matter (Geurtz et al, 2005). These lesions have limited inflammatory cell infiltration and show only minor blood-brain barrier damage, making them difficult to detect by gadolinium-enhancement MRI (Kipp et al, 2012). Since myelin levels obviously are very low in grey matter, it remains to be investigated whether $[^{11}C]$MeDAS PET can be successfully applied for the detection of grey matter lesions. More sensitive PET ligands for imaging of myelin (components) may need to be developed for this.

New developments in MRI are also trying to compensate the lack of specificity of the current MRI procedures in MS. For example, Magnetic Resonance Spectroscopy (MRS) has been developed to measure pathobiochemical processes and it has shown promising results in MS (Katsavos & Anagnostouli, 2013). MRS has shown a decrease in *N-acetylaspartate (NAA)* in lesions of relapsing-remitting MS patients, which can be used as a biomarker of neuronal and axonal loss. Moreover, choline could be a biomarker of myelin loss and glutamate a biomarker of acute inflammation. However, changes in NAA, choline or glutamate levels are not specific to MS. Diffusion Tensor Imaging (DTI) is another development in the

MRI field, which detects microstructure changes in white matter based on the anisotropic diffusion of the water molecules in the white matter fibers. Studies in MS patients have shown correlation of diffusion abnormalities and clinical condition (Sbardella et al, 2013) and DTI could detect abnormalities in corpus callosum before lesions could be seen by conventional MRI (Wahl et al, 2011). DTI seems to be a very sensitive technique to detect changes in the brain and spinal cord, however, common DTI does not differentiate axonal disruption from demyelination or focal edema (Lerner et al, 2013). The combination of DTI and [11C]PK11195 PET has been used in a patient after stroke. The results indicate that the combination of DTI and PET can be useful to correlate neuroinflammation and neuronal damage (Thiel et al, 2010), which could also been interesting for MS studies.

CONCLUSION

The combined use of PET tracers for evaluating neuroinflammation with tracers for neurodegeneration and for myelin changes can give new insights in the status of the lesions and thus improve our understanding in disease progression and therapy monitoring. Combination of different imaging approaches, such as PET and MRI may also be valuable in MS, since the specificity of PET imaging would complement the high spatial resolution and functional information of MRI and thus enable the fusion of morphologic localization of lesions with information about the physiologic changes in the lesions.

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