



G. Berding

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### Current research

Brain imaging using radioactive tracers allows to obtain in vivo measurements of functional parameters, such as cerebral blood flow or receptor availability, in absolute units. Since in brain diseases functional changes often precede morphologic changes, radiotracers provide unique possibilities for early diagnosis and evaluation of new neuroprotective and restorative treatment strategies. Furthermore, pathological changes in neurochemical systems (e.g. changes in transmitter synthesis or release - or in enzyme activity) can be targeted to elucidate pathophysiology or in a clinical context contribute to differential diagnosis. Our research focuses on the development or improvement of radiotracer methods for diagnosis, treatment monitoring and pathophysiologic evaluation of brain diseases. This includes the evaluation of new radiotracers and software for data analysis. In particular we study: (1) radiotracer methods for the diagnosis of Parkinson syndromes and dementia, (2) investigations of regional brain activity for indication and monitoring of surgical procedures to restore/improve brain functions, (3) the availability of serotonin transporters in brain diseases with evidence for a pathophysiologic involvement of the serotonin system and (4) the optimization and application of CB<sub>1</sub>-receptor imaging to improve insight in the pathophysiology of brain diseases with involvement of the cannabinoid system.

### 1. Radiotracer methods for diagnosis of Parkinson syndromes and dementia

The differential diagnosis of Parkinson syndromes is important, since typical and atypical forms have different prognosis and invasive treatment options. To improve the differentiation we evaluate two procedures: (1) The dopamine D<sub>2</sub>-receptor ligand I-123-iodobenzamide (IBZM) is frequently applied to differentiate Parkinson syndromes. Nevertheless, reliable assessment of such studies is frequently hampered by subjective techniques of data analysis. Therefore, we evaluate a new software (IBZM-Tool) allowing a completely user independent assessment. This is based on an automated extraction of distribution volumes and comparison to reference data. (2) In Parkinson's disease orthostatic symptoms are common and as neuropathological correlate Lewy bodies have been demonstrated in the cardiac plexus. We employed the "false transmitter" C-11-hydroxyephedrine and positron emission tomography (PET) to image adrenergic myocardial innervation. Preliminary data indicates a potential of the method to differentiate Parkinson's disease from atypical syndromes and a correlation between the degree of denervation and the severity of orthostatic hypotension (Figure 1). With respect to dementia we evaluate: (1) the value of an absolute determination of the cerebral metabolic rate of glucose and statistical parametric mapping for early and differential diagnosis and (2) the usefulness of the cocaine analogue I-123-FP-CIT, that binds to striatal dopamine transporters, to differentiate dementia with Lewy bodies from other types of dementia.

### 2. Investigations of regional brain activity for indication and monitoring of surgical procedures to restore/improve brain functions

In some brain diseases surgical procedures hold the potential to improve/restore brain functions. Examples are ventriculoperitoneal shunting in normal pressure hydrocephalus, deep brain stimulation in Parkinson's disease (PD) and cochlear implantation in sensorineural deafness. We used F-18-fluorodeoxyglucose or O-15-water to study brain activity at rest or in comparison to stimulated state (e.g. stimulation via electrodes placed in subthalamic nucleus (STN) or promontorium). Special care was applied to optimize procedures of data acquisition (3-dimensional) and analysis (statistical parametric mapping). We were able to show in hydrocephalus patients that the severity of symptoms and the reduction of symptoms after ventriculoperitoneal shunting can be related to hypoperfusion / reversed hypoperfusion in the mesial frontal cortex. In Parkinson's disease we revealed STN-stimulation induced hypometabolism as a sign for reduced activity in abnormal PD-related networks. With respect to cochlear implantation we began to validate statistical parametric mapping as a procedure to reliably verify the intactness of the retro-cochlear auditory pathway and furthermore as a tool to detect neuronal plasticity of the auditory system.

### 3. Availability of serotonin transporters in brain diseases with evidence for a pathophysiologic involvement of the serotonin system

Changes of serotonin transporter (SERT) availability are of particular interest in several neuropsychiatric diseases, due to the possibility of treatment with serotonin reuptake inhibitors (SRI) that bind on these structures. We studied different groups of patients with evidence for an involvement of the serotonergic system (due to symptomatology, neuroendocrine testing, cerebrospinal fluid investigations, responsiveness to SRI, etc.). We detected reduced SERT availability in patients with hepatitis C infection induced fatigue syndrome, Tourette syndrome with obsessive compulsive behaviour, Parkinson's disease and multiple system atrophy. In hepatitis induced fatigue impaired SERT availability correlated to attention deficits, in Tourette syndrome to concomitant obsessive compulsive behaviour. Up to now we studied SERT using I-123- $\beta$ -CIT, a tropan derivative that binds even with a higher affinity to dopamine transporters than to SERT. In further investigations we will use I-123-ADAM, a ligand that binds with high selectivity and affinity to SERT. Studies will include healthy control subjects and patients with obsessive compulsive disorder investigated before and during treatment with SRI. With respect to methodology, SPECT (single-photon emission computed tomography) and MRI will be obtained in parallel and coregistered with the use of fiducial markers. Software for automated determination of binding parameters will be developed.

### 4. Optimization and application of CB<sub>1</sub>-receptor imaging to improve insight in the pathophysiology of brain diseases with involvement of the cannabinoid system

The gene coding for the central cannabinoid CB<sub>1</sub> receptor has been cloned in 1990. Cannabinoid receptors occur with a high density – similar to that of striatal dopamine receptors – in the substantia nigra, globus pallidus, striatum, cerebellum and -hippocampal and cingulate cortices. This distribution suggest already a pathophysiologic relevance in movement disorders and schizophrenia. This is further supported by beneficial effects of cannabinoids on tics in Tourette syndrome as well as levodopa-induced dyskinesia in Parkinson's disease and by the following observations made with respect to schizophrenia: (1) an increased prevalence of schizophrenia in cannabis users, (2) cannabinoid induced perceptual abnormalities in healthy volunteers similar to those found in schizophrenia, (3) changes in receptor density in schizophrenics observed at post mortem and (4) an elevation of endogenous cannabinoids in the cerebrospinal fluid of schizophrenic patients. As potentially useful ligands for CB<sub>1</sub>-receptor imaging classical cannabinoids, pyrazole derivatives and aminoalkylindoles have been evaluated in animal studies. So far only the pyrazole derivate AM281 showed appropriate properties for in vivo imaging of CB<sub>1</sub>-receptors and appeared to be suitable for imaging of these receptors in the human brain. In a pilot study we used AM281, labelled it with Iodine-123 and SPECT to investigate CB<sub>1</sub>-receptors in patients with Tourette syndrome before and during treatment with cannabinoids. We were able to demonstrate a maximal brain uptake of about 2% of the injected dose and a

specific over non-specific binding around 30% in the putamen / globus pallidus region (Figure 2). In one clear responder to cannabinoids a clear decline of radioligand binding compared to baseline was observed. Further investigations will be directed to radioligand displacement studies, the application of radioligands labelled with positron emitting nuclides and a comparison of receptor status between schizophrenic patients with a low or high probability of cannabinoid induced psychosis.

### Future Projects and Goals

We aim to expand the possibilities to answer the clinicians questions regarding improved diagnosis and pathophysiologic understanding of brain diseases by providing new methods of radiotracer imaging. One example could be the implementation of imaging neuroinflammatory changes in the brain using the peripheral benzodiazepine receptor ligand PK11195 that binds to activated microglia. In the long run the above aim might require the implementation of preclinical radiotracer studies in animals.

### Selected Publications

- [1] Berding G, Müller-Vahl K, Schneider U, Gielow P, Fitschen J, Stuhmann M, Harke H, Buchert R, Donnerstag F, Hofmann M, Knoop BO, Brooks DJ, Emrich HM, Knapp WH. [<sup>123</sup>I]AM281 single-photon emission computed tomography of central cannabinoid CB<sub>1</sub> receptors before and after  $\Delta^9$ -Tetrahydrocannabinol therapy and whole-body scanning for assessment of radiation dose in Tourette patients. *Biol Psychiatry* 2004; 55: 904-15.
- [2] Berding G, Brücke F, Odin P, Brooks DJ, Kolbe H, Gielow P, Harke H, Knoop BO, Dengler R, Knapp WH. [<sup>123</sup>I] $\beta$ -CIT SPECT imaging of dopamine and serotonin transporters in Parkinson's disease and multiple system atrophy. *Nuklearmedizin* 2003; 42: 31-8
- [3] Berding G, Schrader CH, Peschel T, Van den Hoff J, Kolbe H, Meyer GJ, Dengler R, Knapp WH. [N-methyl <sup>11</sup>C]meta-Hydroxyephedrine positron emission tomography in Parkinson's disease and multiple system atrophy. *Eur J Nucl Med Mol Imaging* 2003; 30: 127-31.
- [4] Berding G, Odin P, Brooks DJ, Nikkiah G, Matthies C, Peschel T, Shing M, Kolbe H, van den Hoff J, Fricke H, Dengler R, Samii M, Knapp WH. Resting regional cerebral glucose metabolism in advanced Parkinson's disease studied in the off and on conditions with [<sup>18</sup>F]FDG-PET. *Mov Disord* 2001; 16: 1014-22
- [5] Klinge P, Berding G, Brinker T, Knapp W, Samii M. A positron emission tomography study of cerebrovascular reserve before and after shunt surgery in patients with idiopathic chronic hydrocephalus. *J Neurosurg* 1999; 91: 605-9.

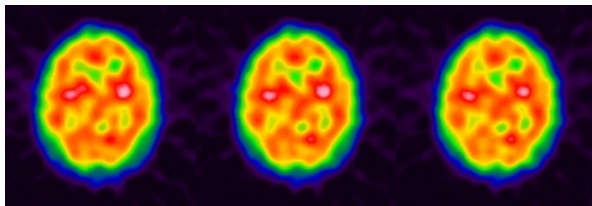
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*Figure 1: Single-photon emission computed tomography (SPECT) images obtained in patient with Tourette syndrome. Pronounced uptake of the cannabinoid CB<sub>1</sub>-receptor radioligand I-123-AM281 can be seen in both lentiform nuclei, where receptor density is known to be high according to post mortem studies.*



*Figure 2: Positron emission tomography (PET) images of postganglionic sympathetic transmission in the heart obtained using the “false transmitter” of the adrenergic system C-11-hydroxyephedrine in patients with multiple system atrophy (A) and Parkinson’s disease (B). Orthostatic hypotension was present in both patients. This symptom is likely to be caused by postganglionic sympathetic denervation of the myocardium in Parkinson’s disease (low uptake of the radiotracer in comparison to the liver), while it is presumably caused by preganglionic/central denervation in multiple system atrophy (normal uptake in postganglionic adrenergic neurons in the heart). This difference can be used for differential diagnosis.*

