The endogenous repair capacity of the parkinsonian brain
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Citation for published version (APA):
van den Berge, S. A. (2011). The endogenous repair capacity of the parkinsonian brain

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Chapter 1

*Thesis scope and outline*

Parkinson’s disease (PD) is a neurodegenerative disorder, which clinically presents primarily with motor abnormalities such as tremor and postural instability, but also with autonomic nervous system impairments and neurological and psychiatric problems, such as dementia. The classical motor symptoms are caused by a loss of dopaminergic neurons in the substantia nigra, which leads to a dopamine deficiency in the caudate nucleus and the putamen.

The dopamine deficiency in PD may also affect the subventricular zone (SVZ), which is the main neurogenic zone of the adult brain, as it has been reported that the SVZ near the striatum is innervated by dopaminergic fibers. The SVZ is a source of newborn interneurons for the olfactory bulb (OB), which differentiate from neuroblasts that have migrated along the rostral migratory stream (RMS) into the olfactory bulb. The neuroblasts originate from transit-amplifying progenitors, which are the progeny of the neural stem cells of the SVZ. These neural stem cells are proliferative, self-renewing and multipotent cells. Furthermore, they can be classified as a subpopulation of astrocytes, as they express the astrocyte specific intermediate filament protein glial fibrillary acidic protein (GFAP). It is increasingly recognised that astrocytes also fulfill various other important functions in the brain, and are not only there to support neurons. They regulate microcirculation in the brain, provide energy metabolites to neurons, actively participate in synaptic transmission and plasticity and maintain the extracellular balance of ions, fluids and transmitters. In addition, astrocytes become reactive in response to central nervous system injury and during neurodegeneration. Depending on the context of the activation, reactive astrocytes are involved in neuronal survival and regeneration in either a protective or impedimental way.

In the present thesis, we investigate if different astrocyte populations are affected in the aging and parkinsonian human brain. We hypothesise that the pool of adult neural stem cells is affected in these conditions. In addition, we explore the possibility that reactive gliosis is correlated with dementia in PD, as has been described for Alzheimer’s disease. In chapter 1, we review the existing literature regarding adult neurogenesis in Parkinson’s disease. In chapter 2, we address the question whether a specific GFAP isoform, discovered by our group, GFAP-δ, is indeed a novel marker for neural stem cells in the human SVZ. Since only a few suitable markers for neural stem cells in the human brain are available, GFAP-δ antibodies could certainly contribute to identifying these cells. We employed extensive immunochemical studies to identify the GFAP-δ-expressing cell in the SVZ, RMS, and OB of the adult human brain. In addition, we have set up a unique system to culture human post mortem neurospheres. From these experiments, we concluded that GFAP-δ was indeed selectively expressed in neural stem cells in the adult human brain and can be used as an identifier protein for adult neural stem cells.

We then used GFAP-δ as a marker to study neural stem cells in Parkinson’s disease in chapter 3, to answer the question whether the stem cell population in the SVZ of PD patients is affected. It has been reported earlier that dopaminergic denervation, as observed in PD, causes a decrease in proliferation of neural precursor cells in the SVZ. We have investigated proliferation in the SVZ of a PD mouse model and in the human SVZ of PD patients and matched controls, and we studied the number of neural stem cells in the
human SVZ, using GFAP-δ. In addition, we investigated the effect of dopamine on human neural precursor cultures, which so far, has only been studied in rodent cultures. To this end, we added dopamine receptor agonists and antagonists to two different human neural stem cell lines and investigated the effect on cell proliferation and differentiation. Our findings show, in contrast to the literature, that the SVZ neurogenic niche in the brains of PD patients is not affected by the disease, with respect to cell proliferation and number of stem cells. Also, human neural precursor cells in culture are not affected by dopamine signaling.

In our studies on neural stem cells in the human SVZ, we encountered distinctive hypercellular structures in the wall of the lateral ventricles, which we describe in chapter 4. These so-called subventricular glial nodules have been described in the last three decades of the 20th century, but it is not fully understood what the phenotype of these cells is and how the nodules develop. We hypothesised that these nodules appear after damage to the brain-CSF barrier, for instance after infection of the ependyma by a virus, such as HIV. Furthermore, we suspected that the nodules contained either reactive astrocytes or SVZ neural stem cells. If the nodules are indeed stem cells we expected that the number might be reduced in PD brains, due to the lack of dopamine. We therefore investigated the occurrence of these nodules in a large cohort of control donors, HIV-infected donors and Parkinson’s disease patients. In addition, we have explored the possibility that these nodules contain neural stem cells and that they might shed these cells into the CSF. Our data show that the nodules consist of neural stem cells and are present in control donors of all ages, regardless of age. Also, we show that exposure to CSF after damage to the ependyma may influence nodule formation, since human neural stem cell cultures respond to CSF exposure by astrocytic differentiation.

In addition to neurogenic astrocytes, we also studied the occurrence of reactive astrocytes in Parkinson’s disease and the correlation with dementia in these patients. In Alzheimer’s disease, reactive gliosis is one of the main pathological hallmarks, besides amyloid plaques and intraneuronal tangles. It has previously been shown that the degree of reactive gliosis correlates with the cognitive state of the Alzheimer patient. In chapter 5, we investigated whether this correlation can also be found in Parkinson’s disease patients with and without dementia and in patients with Lewy Body dementia. We studied frontal cortex sections and CSF from the different patient groups, and did not find any correlation between astrogliosis and disease entity.

Finally, in chapter 6, we present an overview of the data we obtained about human neurogenic and reactive astrocytes in the aged and parkinsonian brain, and discuss these results in view of the current literature. We have not discovered changes in both these astrocyte populations, indicating that endogenous cells may be recruited for repair. In this section, we give a number of suggestions for future research in this field. In addition, we discuss the potential of novel therapeutic strategies for PD patients, aimed at stimulating neurogenic astrocytes.