The endogenous repair capacity of the parkinsonian brain
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The research described in the present thesis is focused on neurogenic astrocytes, which are neural stem cells (NSCs) in the main neurogenic niche, the subventricular zone (SVZ), and on reactive astrocytes in both the aging and parkinsonian brain. The human adult SVZ contains multipotent NSCs, which are astrocytic in nature, as they express glial fibrillary acidic protein (GFAP). The NSCs normally produce new interneurons for the olfactory bulb. The discovery of proliferating precursor cells in the adult human SVZ has sparked an interest in these cells as potential therapeutic targets, especially in Parkinson’s disease (PD). In PD, the striatum is deprived of dopaminergic innervation, which causes the well known motor problems of the disease. The striatum is a potential target for endogenous NSC therapy, because it is lined by the NSC-containing SVZ. If it would be possible to stimulate SVZ precursor cells to proliferate, migrate into the striatum and differentiate into dopaminergic neurons, the levels of dopamine in the striatum could be restored, thereby alleviating the motor symptoms of PD. There are indications that proliferation in the SVZ is stimulated by dopamine. This has been shown in in vitro models and in rodents. The dopaminergic deficit in PD, then, results in a decrease in proliferation rate in the SVZ. This effect has been proven in different animal models for PD and in one study in the human brain. We have summarised these results in chapter 1. If the SVZ is really affected in PD patients, this would have negative implications for the development of new therapeutic strategies using endogenous NSCs. Therefore, we have extensively investigated, in this thesis, the SVZ of PD patients, as well as of aged ‘control’ individuals without a neurological disease.

We have identified and characterised, in chapter 2, a new marker for NSCs in the SVZ, i.e. GFAP-δ, which is a splice variant of the astrocyte-specific intermediate filament protein glial fibrillary acidic protein. We have shown that it is specifically expressed in the astrocyte-like NSCs in the adult human SVZ. For this purpose, we have extensively phenotyped these cells by immunohistochemistry and we have set up neurosphere cultures from the SVZ of post mortem human brain to confirm the presence of NSCs. All our data show that the GFAP-δ expressing cells in the SVZ of aged individuals are indeed NSCs, as the GFAP-δ staining co-localised with markers for proliferating cells and for NSCs, and the post mortem neurosphere cultures expressed GFAP-δ. In addition, we have shown that GFAP-δ is expressed in the glial net of the rostral migratory stream and in the putative precursor cells of the olfactory bulb. In chapter 3, we studied whether the SVZ of Parkinson’s disease (PD) patients was indeed affected, as had been reported before by others. In contrast with these earlier reports, we found an equal number of GFAP-δ-positive NSCs and an equal level of precursor proliferation in both the PD and control SVZ, disproving the earlier literature that the SVZ is affected by the loss of dopamine. We replicated this finding in a mouse model for PD, and in human NSC cultures, indicating that dopamine is not an important regulator of NSC proliferation.

While investigating the human SVZ, we encountered distinct structures, the subventricular glial nodules (SGNs), which are denuded of ependyma and protrude into the ventricles. These structures have been described before, but were never investigated in detail, which we have done in chapter 4. It was generally assumed that SGNs are related to viral infections, and consist of reactive astrocytes. We hypothesised that the SGNs might contain NSCs, because of their shape and localisation. We describe that SGNs occur in about two thirds of control brains, also in young cases, indicating that they arise
already during early life. The incidence of SGNs was not different in brains of HIV-infected donors, excluding that viral infections in later life contribute to SGN formation. We also studied SGNs in PD donors, because these patients may, according to the literature, have a decrease in NSCs in the SVZ, but we saw no difference in SGN incidence. This is in concordance with our data that in PD patients the number of NSCs in the SVZ is not diminished. In addition, we examined SGNs using different cell markers and showed that SGNs contain neural stem and precursor cells. We hypothesised that these NSCs may be influenced by the exposure to cerebrospinal fluid (CSF), since the ependymal layer is lost on SGNs, and tested this in culture. After exposure to CSF, human foetal NSCs showed indeed an increase in astrocytic differentiation.

In chapter 5, we studied the potential role of reactive gliosis in the cognitive decline in PD patients. We have examined whether astrogliosis occurs in the cortex of PD patients, and whether this process was correlated with dementia, as has been described for Alzheimer’s disease. We did not detect changes in the amount of cortical astrocytes in PD, PD with dementia (PDD), or dementia with Lewy bodies (DLB). In addition, we have examined the use of astrocytic proteins as marker for PD and/or PDD and DLB in CSF. We were able to detect astrocytic proteins in CSF, but the levels did not change in PD, PDD, or DLB. We did identify a positive correlation between the presence of cortical Lewy bodies and dementia in PD.

In the final chapter, chapter 6, we discuss our results and their relevance for future therapeutic approaches in PD. The presence of NSCs in the SVZ of PD patients provides hope that these could be stimulated to produce new dopaminergic neurons in the striatum, which may give therapeutic benefits. However, there are still many steps that need to be taken to reach this goal, the most important being dopaminergic differentiation of NSCs. Our discovery of GFAP-δ as a NSC marker and our human neurosphere culture system can be very useful in this process, as they will allow testing of differentiation protocols on human NSCs.