Dopaminergic differentiation induction of neural stem cells

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Neural stem cells (NSC's) are multipotent stem cells that have the capacity for indefinite self-renewal and for differentiation into the major cell types of the nervous system, i.e. neurons, astrocytes and oligodendrocytes. NSC's may become a potential source of dopaminergic cellgrafts for restorative treatment in Parkinson's disease, however efficient generation of functional, mature dopaminergic neurons from NSC's is still a great challenge. Dopaminergic neuronal differentiation *in-vitro* may be induced by extrinsic factors such as Sonic Hedgehog (Shh) and fibroblast growth factor 8 (FGF8). So far this has resulted in only a limited number of dopaminergic neurons. Alternatively, direct stimulation of the gene transcription program for dopaminergic differentiation may be provoked via the forced expression of transcription factors such as Nurr1 (and Ptx3?) known to be crucial for the initiation of dopaminergic differentiation during embryogenesis. Moreover, inhibiting histone deacetylase activity may eventually facilitate dopaminergic gene transcription. In this study we have characterised NSC's isolated from mouse embryonic whole brain and investigated the effects of trichostatin-A (TSA), an inhibitor of histone deacetylases, on the *in-vitro* differentiation induction processes of mouse NSC's initiated by Shh and FGF8. Our results show that short (24 hrs) exposure to TSA significantly stimulates the *in-vitro* differentiation of NSC's into fully grown neurones with elaborate neurites while completely suppressing the induction of astroglial differentiation. TSA had no specific stimulatory effect on dopaminergic differentiation by Shh and FGF8. Transient expression of the transcription factor Nurr1 in NSC's, induced via nonviral gene transfection, appeared to be able to trigger the transcription cascade that leads to dopaminergic differentiation. Ongoing studies will further elucidate the regulation of dopaminergic differentiation of NSC's *in-vitro*. The functionality and stability of the NSC-derived dopaminergic neurons will be tested in an animal model for Parkinson's disease.

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