Depboylu, C; Höllerhage, M; Schnurrbusch, S; Brundin, P; Oertel, WH; Schrattenholz, A; Höglinger, GU

Neuregulin-1 receptor tyrosine kinase ErbB4 is upregulated in midbrain dopaminergic neurons in Parkinson disease.

Previously we demonstrated that systemically administered neuregulin-1-?1, a nerve growth and differentiation factor, passed the blood-brain barrier and accumulated in brain areas with expression of its receptor ErbB4. In substantia nigra (SN), neuregulin-1-?1 phosphorylated ErbB4 and protected dopaminergic neurons in a toxin-based mouse model of Parkinson disease (PD). We studied ErbB4 in the context of human midbrain dopaminergic degeneration in vivo and in vitro. Post-mortem ventral midbrain tissue sections of neuropsychiatric healthy individuals and PD patients (matched for age, gender and post-mortem delay) were immunostained for ErbB4. Cultured Lund human mesencephalic (LUHMES) post-mitotic dopaminergic neurons were treated with dopaminergic toxins and analyzed for ErbB4 expression. In control individuals, 85.0±5.0% of dopaminergic neurons, containing cytoplasmic neuromelanin, expressed ErbB4 in the SN. In PD cases, the percentage of ErbB4-positive nigral dopaminergic neurons was increased to 94.9±2.5%. The mean ErbB4 immunoreactivity of melanized neurons was higher in PD than controls. LUHMES neurons upregulated ErbB4 when exposed to toxins 1-methyl-4-phenylpyridinium and 6-hydroxydopamine. Increased rate of ErbB4-positive dopaminergic neurons in PD may either reflect a
better survival of ErbB4-positive neurons or an increased expression of ErbB4 by remaining neurons to seek trophic support. Enhanced ErbB4 expression in human in vitro toxin-based PD models supports the latter interpretation. Thus, dopaminergic neurons in SN might be susceptible to neuregulin-1 treatment in PD.