Neurotrophic Support of Midbrain Dopaminergic Neurons

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Abstract

In this chapter we review work on neurotrophic factors for midbrain dopaminergic neurons mainly from the past decade, with a focus on neurotrophins and fibroblast growth factors.

We summarize data obtained from animal models of Parkinson's disease, review analyses of neurotrophin, neurotrophin receptor and FGF-2 knockout mice and put these into context with data obtained from patients with Parkinson's disease and from postmortem studies. We provide a brief overview on several other factors (EGF, TGF-α, IGF, CNTF, PDGF, interleukins) and their capacity to promote survival and protect lesioned DAergic neurons. TGF-βs are reviewed in a separate chapter (Roussa et al, this volume).

Introduction

Neurotrophic factors are operationally defined as proteins, which are synthesized and released by neural and nonneural cells and required for the development, differentiation and maintenance of neurons in the developing and adult central nervous system (CNS). Considerable efforts have been invested over the years in the search for proteins and small molecule analogues that can promote the survival of embryonic neurons and protect postnatal neurons from lesion-mediated cells death, with the perspective to develop such factors into therapeutic tools for the treatment of neurodegenerative disorders. Parkinson's disease (PD) is the most frequent movement disorder. Its hallmark symptoms, bradykinesia, resting tremor and rigidity, are caused by losses of dopaminergic (DAergic) cell bodies in the substantia nigra pars compacta (SN) and their axonal projections to the striatum. The pathogenesis of PD is currently unknown, but both environmental and genetic factors have been implicated in the neurodegenerative process leading to neuron death. Currently, there is no treatment available to cure PD; all available therapies can only ameliorate the symptoms of PD. One therapeutic strategy aims at enhancing the survival of the remaining DAergic neurons in the diseased SN and promote axonal regeneration by applying "dopaminotrophic" factors, either by infusion or by grafting genetically engineered cells. Neurotrophic factors with well established survival promoting effects on DAergic neurons in vitro and in vivo include members of the neurotrophin, fibroblast-growth factor (FGF) ciliary neurotrophic factor (CNTF), epidermal growth factor (EGF), insulin-like growth factor (IGF) and interleukin families. Reviews on these factors and their applicability to lesioned nigrostriatal DAergic neurons have been published. The present review summarizes the most substantial findings with a focus on the past decade.

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Neurotrophins

This family of neurotrophic factors comprises the paradigmatic neurotrophic factor NGF, brain-derived neurotrophic factor (BDNF) and the neurotrophins (NT)-3, -4 and -6. TrkA is the functional receptor for NGF, TrkB serves as a receptor for BDNF and NT-4, whereas NT-3 signals primarily through TrkC. In addition, neurotrophins can act through p75NTR (p75 neurotrophin receptor, see Fig. 1) with approximately equal low affinity. BDNF and NT-3, along with their cognate receptors trkB and trkC, are expressed, inter alia, in the developing and adult SN and striatum, suggesting responsiveness of DAergic neurons in the nigrostriatal system to the corresponding trkB and trkC ligands.

BDNF and NT-3 have both been found to play a significant role in promoting survival and differentiation of SN DAergic neurons in vitro and in vivo. While NT-4 has also been shown to act as a survival factor for embryonic midbrain DAergic neurons, NGF is apparently not relevant in this system. Recently, it has also been demonstrated that BDNF is required for the establishment of the correct number of DAergic neurons in the SNpc.

Data from Animal Models of PD

Several animal models of PD replicate some, but not all features of human PD. Such models include, amongst others, unilateral 6-hydroxydopamine (6-OHDA) or systemic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesions. Lesions of the DAergic nigrostriatal system with 6-hydroxydopamine (6-OHDA) have been shown to reduce BDNF mRNA levels in the SN. 6-OHDA-injected animals treated with NT-3 or BDNF showed a reduction of 6-OHDA-induced behavioral deficits. Likewise, 6-OHDA-induced rotational behavior can be prevented by BDNF somatic gene transfer into neurons of the SN. Moreover, intrastriatal grafts of fibroblasts, genetically engineered to produce BDNF, prevent neurodegeneration of the 6-OHDA-lesioned nigrostriatal system.

Likewise, implantation of immortalized BDNF synthesizing fibroblasts largely prevents MPTP-induced DAergic neuronal degeneration and enhances DA levels. Together, these data suggest that BDNF is an important factor for the maintenance and survival of DAergic neurons and that dysfunctions in neurotrophin signaling may cause pathological alterations in the DAergic nigrostriatal system.

Figure 1. Schematic overview: Neurotrophins can act through specific receptors of the trk-family as well as through p75NTR receptors.