NEUROTROPHIC FACTORS AS NOVEL THERAPEUTIC TARGETS

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1 INTRODUCTION

In mammals and other vertebrates, soluble peptide growth factors play essential roles in intercellular communication. They exert their effects by signaling through surface membrane receptors that interact with diverse types of intracellular second-messenger systems. In a sometimes surprising manner, many growth factors have been found to subserve a wide variety of functions by acting on many cell types at different stages of development or in adult life. One of the major advances of cellular neuroscience has been to recognize that much of the cellular damage resulting from such central nervous system (CNS) insults as stroke, trauma, and neurodegenerative disease may be caused by a limited number of endogenously generated molecules with neurotoxic activities. Less well developed is the idea that endogenous mechanisms exist to provide neuroprotection and that endogenous molecules may be produced specifically to service neuroprotective signaling functions.

Neurotrophic factors are secreted proteins that promote neurite outgrowth, neuronal cell differentiation, and survival both in vivo and in vitro. Since their discovery in the 1950s, neurotrophic factors have raised expectations that their clinical application to neurodegenerative diseases might provide an effective therapy for what are now untreatable conditions. There is a large volume of evidence for neuroprotective effects of neurotrophic factors in animal models of neurodegerative diseases. These applications include abolishing cell loss in the septum following fimbria-fornix transection, a cholinergic model for Alzheimer's disease [1, 2], recovery from chemically induced parkinsonism [3, 4], motor neuron disease [5, 6], and spinal cord injury [7–9]. While showing great promise for the treatment of such dirorders, the poor pharmacokinetics and bioavailability of these protein factors have limited the use of polypeptides as drugs. The development of nonpeptidyl small-molecule neurotrophic factor mimetics would obviate the need for protein factors and the potential problems associated with them. This chapter will discuss various strategies whereby a small molecule can influence neurotrophic signaling.

2 NEUROTROPHINS AND THEIR RECEPTORS

Neurotrophins were identified as promoters of neuronal survival, but it is appreciated that they regulate many aspects of neuronal development and function, including synapse formation and synaptic plasticity [10–13]. The first neurotrophin, nerve growth factor (NGF), was discovered during a search for survival factors that could explain the deleterious effects of deletion of target tissues on the subsequent survival of motor and sensory neurons [14]. NGF is part of the neurotrophin

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