Nerve Growth Factor and Brain-Derived Neurotrophic Factor in Schizophrenia and Depression: Findings in Humans and in Animal Models

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Abstract: Depression and schizophrenia are major psychiatric disorders. Recently it has been documented that these diseases are characterized by deficits and/or loss of neurons in specific brain regions. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are endogenous biological mediators involved in neuronal survival and plasticity of dopaminergic, cholinergic, and serotonergic neurons in the central nervous system (CNS). Structural, biochemical, and molecular findings led to the hypothesis that these molecules play a role in the pathophysiology of psychiatric disorders and suggested that alterations in expression of neurotrophic factors could be responsible for neural maldevelopment and disturbed neural plasticity both in young, adult and aged subjects. Studies aimed at understanding the mechanisms regulating these events might be an important line of research for analyzing the etiopathogenesis of psychiatric disorders and eventually identifying new methods for diagnosis and new therapeutic strategies.

NEUROTROPHINS

Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) are supposed to derive from a common ancestral gene, and are therefore collectively called neurotrophins [48,89]. Neurotrophins (NTs) regulate development, maintenance, and function of the peripheral (PNS) and central (CNS) nervous systems. Neurotrophins also regulate many aspects of neural processes. In the mature nervous system, they control synaptic function and synaptic plasticity and modulate neuronal survival. All neurotrophins display a marked structural homology and a specific binding homology [reviewed in 107].

Nerve Growth Factor

Nerve growth factor (NGF) is the first neurotrophin to be discovered [reviewed in 132], and is a dimer of two identical polypeptide chains, each of 118 amino acid residues [144]. NGF was purified as a factor able to support survival of sympathetic and sensory spinal neurons in culture [132]. Injections with anti-NGF showed an important NGF role in maintaining the survival of sympathetic neurons in vivo and in vitro. In the PNS, NGF is synthesized and secreted by sympathetic and sensory target organs [reviewed in 126]. From these sources, it is captured in nerve terminals by receptor-mediated endocytosis and is transported through axons to neuronal cell bodies to promote neuronal survival and differentiation. The NGF expression in the CNS is much more restricted; NGF mRNA and protein are expressed in a number of brain regions, with the hippocampus providing the single largest source of NGF in the entire CNS [125]. In the hippocampus, NGF mRNA and protein are expressed by the principal excitatory (glutamate) neurons, as well as by a subset of γ-aminobutyric acid (GABA)-containing inhibitory neurons [171]. These hippocampal cells receive rich innervations from ascending neurons with their cell bodies in the basal forebrain.

Brain-Derived Neurotrophic Factor

BDNF was purified from the pig brain, for its effect on survival-promoting action on a subpopulation of dorsal root ganglion neurons [20]. The amino acid sequence of mature BDNF has a strong homology with that of NGF [131,172]. BDNF is necessary for survival of peripheral sensory neurons, notably those in the vestibular ganglia and nodose-petrous ganglia. Some trophic effects of BDNF in the PNS seem to depend on autocrine loops and paracrine interactions between adjacent neurons, since sensory neurons can express both BDNF and its high affinity receptor TrkB.

BDNF is more highly expressed and widely distributed than NGF in the CNS, and has survival promoting actions on a variety of CNS neurons including hippocampal and cortical neurons [82,133], cholinergic neurons [4], and nigral dopaminergic neurons [105]. Recent findings showed that BDNF is anterogradely transported in the CNS, a fact that could considerably expanded the concept of neuronal-derived trophic support, and sustained the hypothesis that BDNF act at the synaptic level [9] and might be a more multifunctional compound than thought before.

NEUROTROPHIN RECEPTORS

Two classes of membrane receptors mediate the biological actions of NTs [19,32,43,53]: the Trk family of receptor tyrosine kinases, and a protein called p75 a member of the TNF receptor superfamly. NTs bind with distinct selectivity to three highly related receptor protein-tyrosine kinases, known as high-affinity (Kd~10^-11 M) NT receptors