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Invited review

# Neurobiological actions by three distinct subtypes of brain-derived neurotrophic factor: Multi-ligand model of growth factor signaling

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is one of the most active members of the neurotrophin family. BDNF not only regulates neuronal survival and differentiation, but also functions in activity-dependent plasticity processes such as long-term potentiation (LTP), long-term depression (LTD), learning, and memory. Like other growth factors, BDNF is produced by molecular and cellular mechanisms including transcription and translation, and functions as a bioactive molecule in the nervous system. Among these mechanisms, a particular post-translational mechanism, namely the conversion of precursor BDNF into mature BDNF by proteolytic cleavage, was not fully understood. In this review, we discuss the manner through which this post-translational mechanism alters the biological actions of BDNF protein. In addition to the initially elucidated findings on BDNF, the biological roles of precursor BDNF and the BDNF pro-peptide, especially synaptic plasticity, will be extensively discussed. Recent findings on the BDNF pro-peptide will provide new insights for understanding the mechanisms of action of the pro-peptides of growth factors.



**Contents**



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## 1. The neurotrophin family

Neurotrophins (NTs), which historically emerged as trophic proteins for promoting neuronal survival and differentiation, were recently studied as a class of modulators of synaptic transmission and plasticity [1,2].

In the 1950s, Levi-Montalcini and Hamburger discovered that a mouse sarcoma tumor implanted near the spinal cord of the developing chicken released a protein that increased neurite outgrowth from sympathetic neurons [3]. Later, this factor was named nerve growth factor (NGF) [4–6]. Their discovery played a pioneering role in the research of developmental neurobiology, which provided a new notion that target-derived secreted proteins control neuronal numbers and neurite growth. Over 20 years after the discovery of NGF, Barde et al. [7] isolated a neuronal survival-eliciting factor from the pig brain, named brain-derived neurotrophic factor (BDNF). In 1989, the full primary structure of BDNF and its expression in brain was identified [8], and BDNF was found to be highly homologous to NGF at the level of the amino acid sequence. Using the new technology of polymerase chain reaction (PCR), neurotrophin-3 (NT-3) [9] and neurotrophin-4/5 (NT-4/5) [10], whose amino acid sequence is highly homologous to NGF and BDNF as well, were molecularly cloned. Lastly, the four NTs and their genes showed marked homology to each other in terms of sequence and structure [11].

The discoveries of NT family members provided important insights into the formation of neuronal communication during the development of the nervous system and into synaptic plasticity, memory, and learning in the adult brain. Moreover, specific neuronal populations require the presence of one or more NTs, and their roles are exerted spatially and temporally. Furthermore, there are long- and short-term actions of NTs. The long-term trophic actions depend on gene regulation, whereas short-term effects, including chemotrophic effects on developing neurons and synaptic transmissions, are controlled by the activation of cytoplasmic effectors by NTs.

## 2. NT receptors and their signaling

Like most growth factors, NTs are initially synthesized as precursors (pro-neurotrophins) composed of approximately 270 amino acids. The protein products of NTs are structurally composed of a signal sequence, a pro-domain, and the mature domain. To produce the mature and bioactive form, the N-terminal fragment of approximately 120 amino acids, or the “pro-domain”, is proteolytically processed by intracellular and/or extracellular proteolytic enzymes (*e.g.*, furin, pro-hormone convertase, and plasmin) [12–15]. Several reports explored the intracellular mechanisms of NT processing. In neurons, the N-terminal pro-domain is proteolytically processed, either in the trans-Golgi by furin or in secretory granules by intracellular proteinases, to generate the mature form of neurotrophins, while in non-neuronal cells, neurotrophins are constitutively secreted [12]. However, secretion of BDNF is controlled by both constitutive and activity-regulated secretion pathways in neurons [16], and the secretion of BDNF is controlled in a neuronal activity- and $Ca2^{+}$-dependent manner (reviewed by Ref. [17]). The activity-dependent secretion of BDNF may be a critical mechanistic step in controlling synaptic transmission and long-term synaptic plasticity.

## 3. NT receptors and their signaling

There are two distinct classes of NT receptors. The first receptor, the p75 neurotrophin receptor ($p75^{NTR}$), is a member of the tumor necrosis factor (TNF) receptor family [18]. Initially, $p75^{NTR}$ was discovered as a low-affinity NGF receptor, but was subsequently found to bind to BDNF, NT-3, and NT-4/5 with a similar affinity [18]. The extracellular domain of $p75^{NTR}$ has cysteine-rich motifs. The cytoplasmic domain includes a ‘death’ domain, which is also found in the cytoplasmic domain of other members of the TNF receptor family [19,20]. Although $p75^{NTR}$ does not contain a catalytic kinase motif, it interacts with many proteins that transmit signals important for the regulation of neuronal survival and differentiation [18,21]. The $p75^{NTR}$ receptor activates three major signaling pathways. First, NF-kappa B activation leads to transcription of multiple genes, including several that promote neuronal survival. Second, activation of the Jun kinase pathway similarly controls the activation of several genes, some of which promote neuronal apoptosis. Third, ligand engagement of $p75^{NTR}$, through the regulation of Rho activity, controls the motility of growth cone [22].

The second class of NT receptors is the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases (TrkA, TrkB, and TrkC) [22]. Each NT binds to a specific Trk receptor: NGF binds to TrkA, BDNF and NT-4/5 to TrkB, and NT-3 to TrkC. The Trk receptors have a trans-membrane region that spans the plasma membrane and a cytoplasmic domain that has tyrosine kinase activity. Binding of an NT to a specific Trk receptor activates its tyrosine kinase, leading to the activation of the phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and phospholipase C-γ (PLC-γ) pathways. Activation of Ras leads to activation of the MAP kinase-signaling cascade, which promotes neuronal differentiation, including neurite outgrowth. Activation of $PI_3$ kinase through Ras or Gab1 promotes survival and growth of neurons and other cells. Activation of PLC-γ results in activation of protein kinase C-controlled pathways that promote synaptic plasticity [22]. Many additional adaptors for $p75^{NTR}$ and Trk receptors have been reported. Information about the two types of NT receptors and their signaling mechanisms has been extensively reviewed by others (*e.g.*, see Refs. [18,22–25]) and will not be further discussed in this review.

## 4. Synaptic plasticity, long-term potentiation (LTP), and BDNF

Since BDNF mRNA is expressed in the brain, including the hippocampus and cortex [8], the role of BDNF in synapse function has been intensively investigated [2]. Synaptic plasticity is thought to be critical for the processing and encoding of information by neuronal networks, which is central to learning and memory [26]. LTP and long-term depression (LTD) are forms of activity-dependent synaptic plasticity that increase or decrease the strength of synaptic transmission, respectively (reviewed by Ref. [27]). LTP and LTD can be categorized into at least two distinct phases: early-LTP/LTD (E-LTP/LTD) and late-LTP/LTD (L-LTP/LTD). E-LTP and L-LTP are corresponded to short-term memory and long-term memory, respectively. E-LTP occurs during the first hour or two of LTP and can be induced by a high-frequency tetanus stimulation (100 pulses at 100 Hz), increasing the strength of synaptic transmission and activating signaling molecules such as protein kinases, while L-LTP persists for longer and involves *de novo* synthesis of plasticity-related proteins (PRPs) [28,29]. E-LTD is usually induced by low-frequency stimulation (LFS; 1 Hz, 900 pulses, 15 min).

Although NTs were originally identified as a family of protein factors that regulate neuronal survival and differentiation, a number of studies show that neurotrophins play roles in the development and function of synapses (reviewed by Ref. [2]). The function of BDNF in synaptic transmission and plasticity in the hippocampus has been extensively investigated. Both expression and secretion of BDNF are controlled by neuronal activity and excitatory transmission [30–35]. Acute application of exogenous BDNF increases neuronal activity and synaptic transmission in primary