BDNF function in health and disease
Agustin Anastasia and Barbara L. Hempstead

Brain-derived neurotrophic factor (BDNF) is the most widely expressed and well-characterized member of the neurotrophin family in the mammalian brain. It is translated as a precursor protein (proBDNF), which consists of an N-terminal prodomain and a C-terminal mature domain. Mature BDNF consists of dimers of the mature domain, and its effects are tightly regulated. BDNF can exert its functions in a highly localized manner and also at a distance by anterograde or retrograde transport. Modest changes in BDNF levels affect the development and regulation of neurites in a cell-autonomous manner, and BDNF plays a key role in the development and maintenance of nervous system circuitry. This Review provides an overview of the actions of BDNF and its roles in neural brain function and disease, and highlights the influence of the interacting factors on human behavior.

**Physiological roles**
BDNF is crucially involved in nearly all stages of neural circuit development:

- **Survival of stem cells and progenitors**
- **Neurogenesis and neuronal differentiation**
- **Neuronal polarization and guidance**
- **Branching and survival of different types of neurons**
- **Formation and maturation of spines and synapses**

In the mature nervous system, BDNF promotes plasticity and refinement of neuronal circuitry, modulates synaptic plasticity, and consequently regulates learning and memory formation. Although BDNF does not seem to be essential for the survival of most CNS neurons, it does modulate dendritic complexity and spine density, which markedly affects behavior and suggests that it acts more as a differentiation and plasticity factor in the CNS.

**Local mechanisms**

1. **Extracellular**
   - BDNF has two forms (white box indicates N- and C-termini labeled); however, the mature form (red) is the one that is secreted. The extracellular signal-regulated kinase (ERK) family kinases are involved in the activation of BDNF. BDNF can act on the plasma membrane, which can be trafficked through regulated or constitutive secretion.

2. **Neuronal signals**
   - BDNF can bind to TrkB receptors on neurons and promote neuronal survival, differentiation, and plasticity. BDNF can act at a distance through extracellular signals, which can be mediated by soluble BDNF or by TrkB receptors that share the same common signaling pathways. The TrkB receptor family includes TrkB, p75NTR, and sortilin.

3. **Cytoskeleton**
   - BDNF regulates cytoskeletal changes, including actin dynamics and microtubules, affecting neuronal morphology and plasticity.

4. **Gene expression**
   - BDNF promotes neuronal survival, differentiation, and plasticity by regulating gene expression. BDNF can bind to transcription factors, such as CREB, and activate gene expression in target cells.

**Val66Met substitution**

A common single-nucleotide polymorphism (SNP) in the BDNF gene is strongly associated with alterations in synaptic plasticity, a reduction in hippocampal volume, and an enhanced risk of mood and anxiety disorders in humans. This SNP (Val66Met) is observed in more than 25% of the human population but not in other species and results in a valine to methionine substitution at Val66. This SNP has been associated with changes in the expression and function of BDNF, which results in altered neuronal plasticity.

**Pathological roles and therapeutic challenges**

Alterations in BDNF levels are associated with neurodegenerative disorders (including Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis, or ALS), and psychiatric disorders (including depression, anxiety disorders, bipolar disorders, schizophrenia, and autism spectrum disorders). Moreover, BDNF could potentially be used to treat diseases in which alterations in BDNF levels are not directly involved in the pathogenesis (for instance, in Parkinson's disease, amyotrophic lateral sclerosis, stroke and spinal cord injury). BDNF is a known neuromodulator and does not merely cross the blood–brain barrier, so an effective CNS delivery is a challenge. Strategies under consideration include: promoting infusion directly or indirectly to the CNS, delivery to the CNS, fusion of BDNF to proteins or nanoparticles that can cross the BBB (tropic horse delivery), and small molecule enhancers of endogenous BDNF synthesis or secretion and p75NTR inhibitors. These and other physical exercises, which increase BDNF levels.

**Potential therapeutic applications of BDNF**

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**Abbreviations**

- AMPAR: AMPA receptor
- AAV: AAV vector
- ACC: anterior cingulate cortex
- APP: amyloid precursor protein
- CaMKII: calcium/calmodulin-dependent protein kinase II
- CREB: cAMP response element-binding protein
- CREB: cAMP response element-binding protein
- DRP1: dynamin-related protein 1
- DREADDs: designer receptor–activated designer drugs
- ERK1/2: extracellular signal-regulated kinase 1 and 2
- FMRP: fragile X mental retardation protein
- GRB2: growth factor receptor-bound protein 2
- HGF: hepatocyte growth factor
- HIV: human immunodeficiency virus
- JAK: Janus kinase
- KAIN: kainic acid
- MEK1/2: MAPK kinase 1 and 2
- mTOR: mammalian target of rapamycin
- Munc13-1: a vesicle-associated membrane protein
- PI3K: phosphatidylinositide 3-kinase
- p75NTR: p75 nerve growth factor receptor
- RhoA: Ras homolog gene family member A
- SFK: Src family kinase
- VEGF: vascular endothelial growth factor
- VGLUT2: vesicular glutamate transporter 2
- zeta-2: a subunit of the AMPA receptor

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