nature REVIEWS NEUROSCIENCE

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 neural circuits and brain function. This Poster provides an overview of the actions of BDNF and its roles in normal brain function and in disease, and highlights the influence of this fascinating protein on human behaviour.

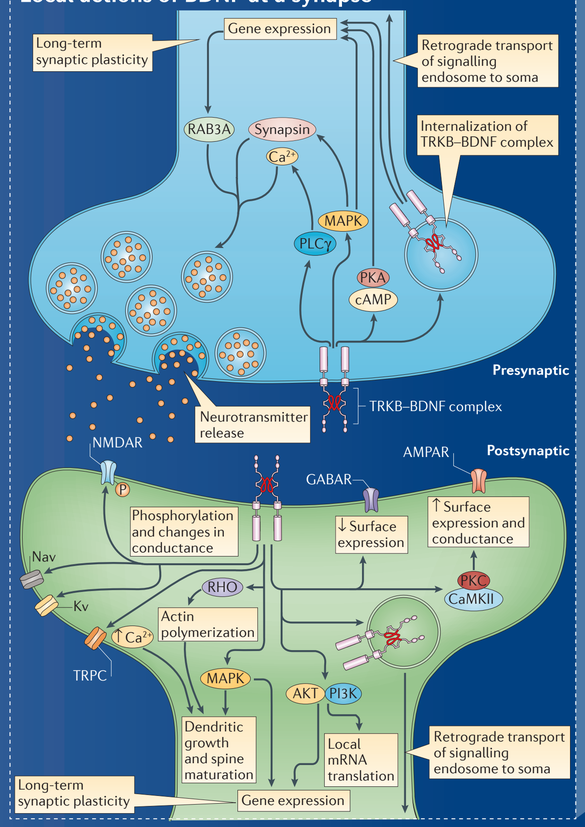
Physiological roles

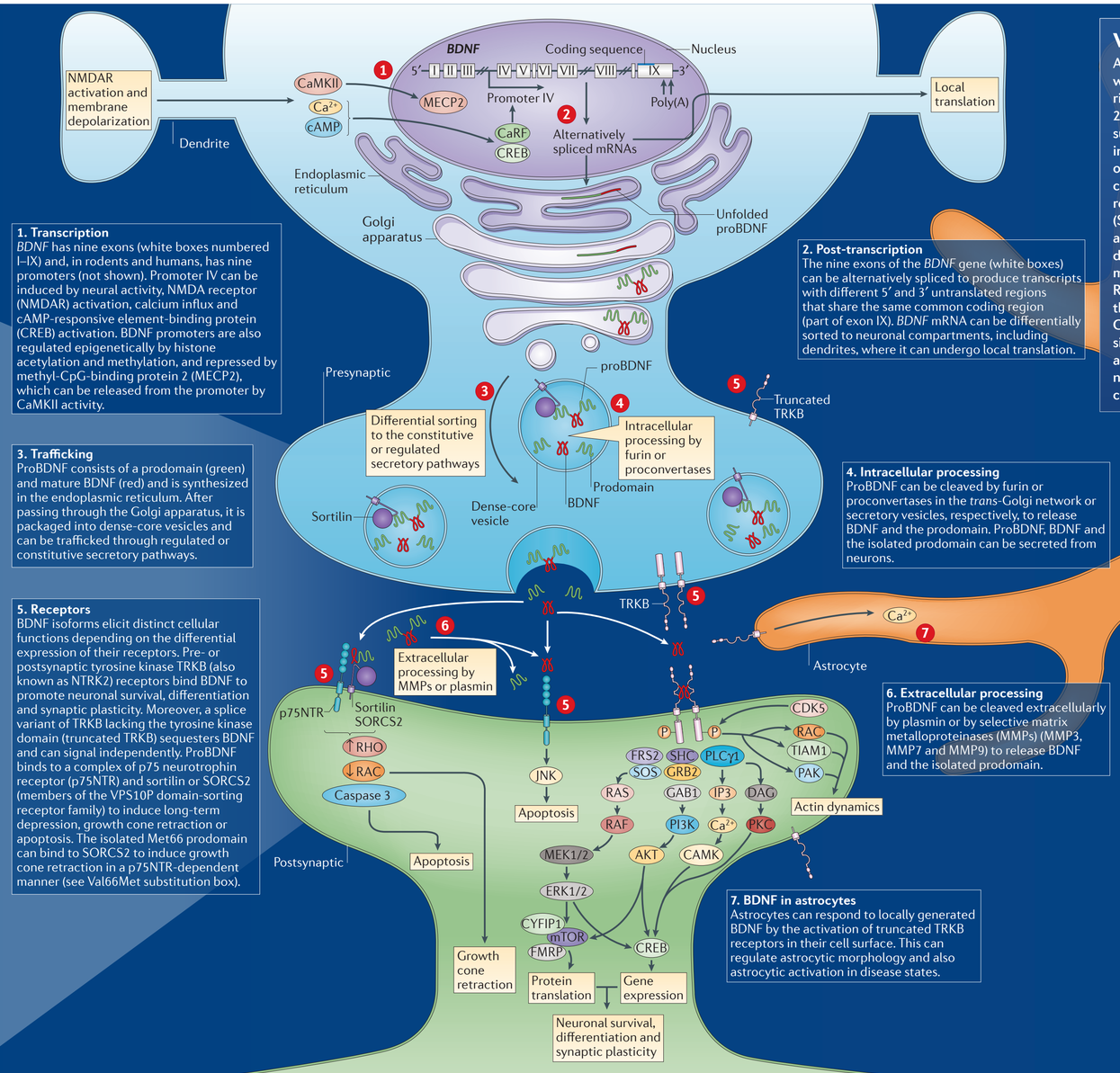
BDNF is crucially involved in nearly all stages of neural circuit development:

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

In the mature nervous system, BDNF promotes the elaboration and refinement of neuronal circuit structure, modulates synaptic plasticity and, consequently, regulates cognitive brain function (including learning and memory). 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 behaviour and suggests that it acts more as a differentiation and plasticity factor in the CNS.

Local actions of BDNF at a synapse





1. Transcription
BDNF has nine exons (white boxes numbered I–IX) and, in rodents and humans, has nine promoters (not shown). Promoter IV can be induced by neural activity, NMDA receptor (NMDAR) activation, calcium influx and cAMP-responsive element-binding protein (CREB) activation. BDNF promoters are also regulated epigenetically by histone acetylation and methylation, and repressed by methyl-CpG-binding protein 2 (MECP2), which can be released from the promoter by CaMKII activity.

2. Post-transcription
The nine exons of the *BDNF* gene (white boxes) can be alternatively spliced to produce transcripts with different 5′ and 3′ untranslated regions that share the same common coding region (part of exon IX). *BDNF* mRNA can be differentially sorted to neuronal compartments, including dendrites, where it can undergo local translation.

3. Trafficking
ProBDNF consists of a prodomain (green) and mature BDNF (red) and is synthesized in the endoplasmic reticulum. After passing through the Golgi apparatus, it is packaged into dense-core vesicles and can be trafficked through regulated or constitutive secretory pathways.

4. Intracellular processing
ProBDNF can be cleaved by furin or proconvertases in the *trans*-Golgi network or secretory vesicles, respectively, to release BDNF and the prodomain. ProBDNF, BDNF and the isolated prodomain can be secreted from neurons.

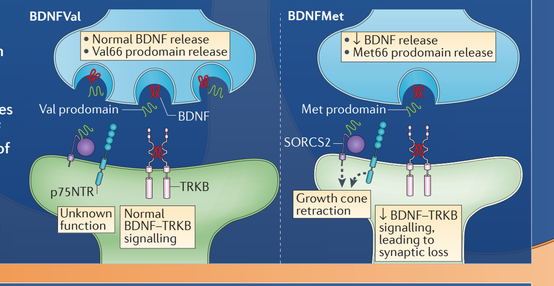
5. Receptors
BDNF isoforms elicit distinct cellular functions depending on the differential expression of their receptors. Pre- or postsynaptic tyrosine kinase TRKB (also known as NTRK2) receptors bind BDNF to promote neuronal survival, differentiation and synaptic plasticity. Moreover, a splice variant of TRKB lacking the tyrosine kinase domain (truncated TRKB) sequesters BDNF and can signal independently. ProBDNF binds to a complex of p75 neurotrophin receptor (p75NTR) and sortilin or SORCS2 (members of the VPS10P domain-sorting receptor family) to induce long-term depression, growth cone retraction or apoptosis. The isolated Met66 prodomain can bind to SORCS2 to induce growth cone retraction in a p75NTR-dependent manner (see Val66Met substitution box).

6. Extracellular processing
ProBDNF can be cleaved extracellularly by plasmin or by selective matrix metalloproteinases (MMPs) (MMP3, MMP7 and MMP9) to release BDNF and the isolated prodomain.

7. BDNF in astrocytes
Astrocytes can respond to locally generated BDNF by the activation of truncated TRKB receptors in their cell surface. This can regulate astrocytic morphology and also astrocytic activation in disease states.

Val66Met substitution

A common single-nucleotide polymorphism (SNP) in the *BDNF* gene is strongly associated with abnormalities in episodic memory, a reduction in hippocampal volume and an enhanced risk of depression and anxiety disorders in humans. This SNP (rs6265) is observed in more than 25% of the human population (but not in other species) and results in a valine to methionine substitution at codon 66 (Val66Met) within the prodomain region. The Val66Met substitution impairs BDNF release from neurons (right). The Val66Met substitution changes the structure of the BDNF prodomain, which alters its interaction with sortilin-related VPS10 domain-containing receptor 2 (SORCS2) and, in a p75NTR-dependent manner, decreases RAC (member of the RHO family of GTPases) signalling and induces neuronal growth cone retraction.



Pathological roles and therapeutic challenges

Alterations in BDNF levels are associated with neurodegenerative disorders (including Alzheimer's disease, Huntington's disease and epilepsy), neuropsychiatric disorders (including depression, anxiety disorders, bipolar disorders, schizophrenia and addiction) and obesity. The hallmark of BDNF deficiency is synaptic degeneration, and increased levels of BDNF can promote synaptic repair in preclinical models. Moreover, BDNF could potentially be used to treat diseases in which alterations in its 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 highly charged protein that does not readily cross the blood–brain barrier (BBB), so effective CNS delivery is a challenge. Strategies under consideration include: protein infusion intranasally or directly to the CNS; gene delivery to the CNS; fusion of BDNF to proteins or nanoparticles that can cross the BBB (Trojan horse delivery); small TRKB agonist molecules (peptide mimetics), including TRKB transactivators, enhancers of endogenous BDNF synthesis or secretion and p75NTR inhibitors compounds; and physical exercise, which increases BDNF levels.

Potential therapeutic applications of BDNF

	Target region	Expected result
Alzheimer's disease	Hippocampus and entorhinal cortex	Synaptic restoration
Amyotrophic lateral sclerosis	Intrathecal	Prevention of motor neuron degeneration
Huntington's disease	Striatum	Striatal neuroprotection
Metabolic disorders, including obesity	Hypothalamus	Weight loss
Parkinson's disease	Striatum and/or substantia nigra	Survival of nigral dopaminergic neurons
Spinal cord injury	Spinal cord	Prevention of secondary damage and axon guidance
Stroke and/or ischaemia	Cortex	Prevention of secondary damage

EVER Neuro Pharma is an Austrian pharmaceutical company focused on the field of neuroscience and clinical emergency. Based on our experience and proprietary R&D technology platform we develop innovative therapies for neurological disorders including stroke, acquired brain injuries, different forms of dementia (including Alzheimer's disease and vascular dementia), Parkinson's disease, epilepsy and hypertensive emergencies.

At the core of our technologically mature and safe products is Cerebrolysin®, a neurotrophic peptide compound which mimics the actions of endogenous neurotrophic factors (NTFs) and which stimulates endogenous production of NTFs in the central nervous system. Cerebrolysin is indicated for treatment of dementia, stroke and acquired brain injuries and is considered an unique neurotrophic treatment available for clinical use in about 50 countries.The future development of therapies for neurological diseases will increasingly rely on the multimodal treatment/management approach. Recognizing this trend we keep to our endeavor for further refinement of the neurotrophic therapy concept, and for constant improvement of our patient oriented services.

Among other agents our product portfolio is strengthened with Dacepton® (apomorphine hydrochloride) for the treatment of disabling motor symptoms of Parkinson´s disease and Tachyben® (urapidil hydrochloride) for patients with hypertensive emergencies.

For more information

EVER Neuro Pharma GmbH, Oberburgau 3, 4866 Unterach, Austria. office@everpharma.com, www.everpharma.com

Abbreviations

AMPAR, AMPA receptor; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; cAMP, cyclic AMP; CaRF, Ca^{2+} response factor; CDK5, cyclin-dependent kinase 5; CYFIP1, cytoplasmic FMR1-interacting protein 1; DAG, diacylglycerol; ERK1/2, extracellular signal-regulated kinase 1 and 2; FMRP, fragile X mental retardation protein; FRS2, fibroblast growth factor receptor substrate 2; GAB1, GRB2-associated-binding protein 1; GABAR, GABA receptor; GRB2, growth factor receptor-bound protein 2; IP3, inositol trisphosphate; JNK, JUN N-terminal kinase; Kv, voltage-gated K^+ channel; MAPK, mitogen-activated protein kinase; MEK1/2, MAPK kinase 1 and 2; mTOR, mammalian target of rapamycin; Nav, voltage-gated Na^+ channel; PAK, p21-activated kinase; PI3K, phosphatidylinositide 3-kinase; PKC, protein kinase C; PLCγ1, phospholipase Cγ1; RAF, rapidly accelerated fibrosarcoma kinase; SHC, SH2 domain-containing transforming protein; SOS, son of sevenless; TIAM1, T-cell lymphoma invasion and metastasis-inducing protein 1; TRPC, transient receptor potential cation channel C.

Acknowledgements

The authors have received support from the US National Institutes of Health (grants NS030687, NS064114 and HD23315) and the Cure Huntington's Disease Initiative Foundation. Given the breadth of this field, it is difficult to include all contributions and oversights are unintended.

Affiliations

A.A. and B.L.H. are at the Department of Medicine, Weill Cornell Medical College of Cornell University, 1300 York Avenue, New York, New York 10065, USA. e-mail: blhempst@med.cornell.edu (B.L.H.)

Competing interests statement

B.L.H. is a co-inventor of a patent held by Cornell (US 2011/0207827 A1). A.A. declares no competing interests.

Edited by Sian Lewis; copyedited by Harsimran Flora; designed by Jennie Vallis.