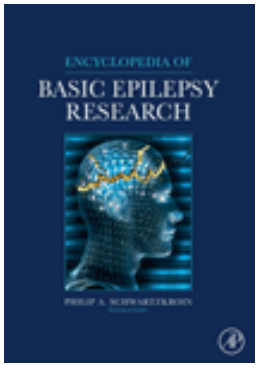

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Whatever the eventual neuroprotective approach taken in humans, be it growth factor-related or not, preserving the brain of the epileptic patient is a promising strategy for maintaining normal functioning. The success of neuroprotective approaches could lead to a substantial enhancement in the quality of life of epileptic patients.

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See also: **Epileptogenesis**: Epileptogenesis and Plasticity; **Inflammation**: Neurodegeneration, Neuroprotection and Inflammation in the Brain; **Neurotrophic Factors**: Activity-Regulated BDNF Expression: Contributions to Synaptic Plasticity and Neuroprotection; Role of BDNF in Animal Models of Epilepsy; The Influence of Neurotrophins on Excitability in Hippocampus and its Potential Relevance to Epilepsy.

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Role of BDNF in Animal Models of Epilepsy

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Introduction

Elucidating the cellular and molecular mechanisms of epileptogenesis could lead to novel therapeutic approaches aimed at the prevention or management of the disease. The discovery that limbic seizures increase nerve growth factor (NGF) mRNA levels led to the idea that seizure-induced expression of neurotrophic factors might contribute to the lasting structural and functional changes underlying epileptogenesis. Similarly, increases in neurotrophin expression that follow other insults (e.g., ischemia and traumatic brain injury) could also contribute to epileptogenesis. In the past decade, there has been an exciting confluence of in vitro and in vivo findings that strongly implicate the neurotrophin, brain-derived neurotrophic factor (BDNF), in particular, limbic circuits involved in the cascade of electrophysiological and behavioral changes underlying the development of the epileptic state.

In particular, seizure activity increases the expression of BDNF mRNA and protein, and interfering with BDNF signal transduction inhibits the development of the epileptic state in vivo. The purpose of this article is to summarize the evidence regarding a role of BDNF in epileptogenesis, and to examine the implications of BDNF's involvement in epileptogenesis for new therapeutic targets.

Background

Historical Background

In 1982, BDNF, the second member of the 'neurotrophin' family of neurotrophic factors, was shown to promote survival of a subpopulation of dorsal root ganglion neurons, and subsequently purified from pig brain. The amino acid sequence of BDNF has a strong homology with NGF, the neurotrophin first described because of its trophic (survival and growth-promoting) effects on sensory and sympathetic neurons. Since the discovery of NGF in the early 1950s by Rita Levi-Montalcini and Viktor Hamburger, and the discovery of BDNF by Yves Barde and colleagues in 1982, other members of the 'neurotrophin' family such as neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) have been described. Each appears to have a distinct profile of trophic effects on distinct subpopulations of peripheral nervous system (PNS) and central nervous system (CNS) neurons.

BDNF Structure

The gene for the mature form of human BDNF has been mapped to chromosome 11p. The protein shares about 50% amino acid identity with human NGF, NT-3, and NT-4/5. The structure of each neurotrophin protein molecule contains: (1) a signal peptide important for intracellular sorting of the protein; (2) a pro-region containing an N-linked glycosylation site and a proteolytic cleavage site for furin-like pro-protein convertases; (3) the mature BDNF protein sequence; and (4) a distinctive three-dimensional structure containing two pairs of antiparallel β-strands and cysteine residues in a cystine knot motif. Neurotrophins are initially produced as proneurotrophins; prohormone convertases, such as furin, cleave the proneurotrophins (MW ~30 kDa) to the mature neurotrophin protein. Proneurotrophins have altered binding characteristics and distinct biologic activity in comparison with mature neurotrophins. Mature neurotrophin molecules are noncovalently-linked homodimers, with molecular weight about 28 kDa. The BDNF gene has four 5′ exons (exons I–IV) that are associated with distinct promoters, and one 3′ exon (exon V) that encodes the mature BDNF protein. Eight distinct mRNAs are transcribed, with transcripts containing exons I–III expressed predominantly in brain and exon IV found in lung and heart.

BDNF Signal Transduction

Each neurotrophin binds one or more of the trk (tropomyosin-related kinase) receptors, members of the family of receptor tyrosine kinases (RTKs). Trk proteins are transmembrane RTKs homologous to other RTKs, such as the epidermal growth factor (EGF) receptor and insulin receptor family. Ligand-induced receptor dimerization results in kinase activation; subsequent receptor autophosphorylation on multiple tyrosine residues creates specific binding sites for intracellular target proteins, which bind to the activated receptor via SH2 domains. The intracellular proteins that bind to the activated receptor include PLCγ1 (phospholipase C), p85 (the noncatalytic subunit of PI-3 kinase), and Shc (SH2-containing sequence); activation of these target proteins can then lead to a variety of intracellular signaling cascades, such as the Ras-MAP (mitogen-activated protein) kinase cascade and phosphorylation of CREB (cyclic AMP-response element binding protein).

Binding specificity is conferred via the juxtamembrane Ig-like domain of the extracellular portion of the receptor in the following pattern: trkA binds NGF (with low-affinity binding by NT-3 in some systems); trkB binds BDNF and NT-4/5 (with lower-affinity binding by NT-3); and trkC binds NT-3. Trk receptors exist in both a full-length (trkB.FL) form as well as truncated (trkB.T1, trkB.T2) forms lacking the kinase domain. Although most functions attributed to BDNF are associated with trkB.FL, several roles have been suggested for truncated receptors, including growth and development and negative modulation of trkB receptor expression and function. Expression of truncated trk receptors on astrocytes is upregulated following injury, and may modulate neuronal vulnerability and sequestration of BDNF in astrocytes. Recent studies have shown that BDNF activates glial calcium signaling by truncated trk receptors.

In addition, all of the neurotrophins bind to the p75 receptor, designated $p75^{NTR}$. $p75^{NTR}$, related to proteins of the tumor necrosis factor (TNFR) superfamily, has a glycosylated extracellular region involved in ligand binding, a transmembrane region, and a short cytoplasmic sequence lacking intrinsic catalytic activity. Neurotrophin binding to $p75^{NTR}$ is linked to several intracellular signal transduction pathways, including nuclear factor-κB (NF-κB), Jun kinase, and sphingomyelin hydrolysis. $p75^{NTR}$ signaling mediates biologic actions distinct from those of the trk receptors, notably the initiation of programmed cell death (apoptosis). It has also been suggested that p75 may serve to determine neurotrophin binding specificity.

Localization, Transport, and Release of BDNF

BDNF mRNA has a widespread distribution in the central nervous system, including limbic forebrain and

neocortex, and is abundant in all principal neurons of the hippocampus. Like BDNF mRNA, constitutive BDNF protein expression is widespread, localized on neuronal cell bodies, axons, and dendrites. The mossy fiber axons of hippocampal dentate granule cells display especially intense BDNF immunoreactivity. TrkB mRNA and protein are widespread in hippocampus. Truncated trkB is also found in the ependymal cells lining the ventricular cavities, effectively limiting diffusion of intraventricularly administered BDNF.

Unlike the classical target-derived trophic factor model in which neurotrophins (such as NGF) are retrogradely transported, there is now abundant evidence that BDNF is also anterogradely transported in brain. First, BDNF protein is localized to nerve terminals, and pathway transection or axonal transport inhibition eliminates this terminal expression. Second, high-resolution microscopic studies have shown that BDNF is associated with dense-core vesicles, which are the primary site for neuropeptide storage and release from nerve terminals. Third, functional studies have supported the anterograde transport hypothesis. Fourth, pro-BDNF is shuttled from the trans-Golgi network into secretory granules, where it is cleaved by prohormone convertase 1 (PC1).

In addition, emerging evidence suggests that both BDNF and trk receptors may undergo regulated intracellular transport. For example, seizures lead to redistribution of BDNF mRNA from hippocampal CA3 cell bodies to their apical dendrites. Trk signaling is now thought to include retrograde transport of intact neurotrophin–trk complexes to the neuronal cell body.

Evidence also indicates that neurotrophins are released acutely following neuronal depolarization. In fact, direct activity-dependent pre- to postsynaptic transneuronal transfer of BDNF has been demonstrated using fluorescently-labeled BDNF. The released form of BDNF is thought to be pro-BDNF, raising the possibility of postsecretory proteolytic processing by membrane-associated or extracellular proteases in the modulation of BDNF action.

BDNF Gene Regulation

A multitude of stimuli have been described that alter BDNF gene expression in both physiologic and pathologic states. Physiologic stimuli are known to increase BDNF mRNA content. For example, light stimulation increases BDNF mRNA in visual cortex, osmotic stimulation increases BDNF mRNA in the hypothalamus, and whisker stimulation increases BDNF mRNA expression in somatosensory barrel cortex. Electrical stimuli that induce long-term potentiation (LTP) in the hippocampus (a cellular model of learning and memory) increase BDNF and NGF expression. Even physical exercise has been shown to increase NGF and BDNF expression in hippocampus. Interestingly, BDNF levels vary across the estrus cycle, with BDNF levels correlated with changes in neural excitability.

Distinct BDNF 5′ exons are differentially regulated by different stimuli (such as neural activity). For example, exons I–III, but not exon IV, increase after kainic acid-induced seizures or other stimuli that increase activity. Protein synthesis is required for the effects of activity on exon I and II, but not on III and IV, raising the possibility that the latter act as immediate-early genes. The transcription factor CaRF activates transcription of exon III under the control of a calcium-response element, CaRE1. CREB, which can be stimulated by diverse stimuli ranging from activity to chronic antidepressant treatment, also modulates exon III transcription. Recent evidence also indicates that neural activity triggers calcium-dependent phosphorylation and release of MeCP2 (methyl-CpG binding protein 2) from BDNF promoter III to de-repress transcription.

Effects of BDNF on Synaptic Transmission

BDNF has an enormous range of physiologic actions at both developing and mature synapses, overall enhancing synaptic transmission by both pre- and postsynaptic mechanisms. The first studies of BDNF effects on synaptic transmission showed that BDNF increased the frequency of miniature excitatory postsynaptic currents (mEPSCs) at neuromuscular synapses in *Xenopus*. Since then, numerous studies have examined the actions of BDNF. Overall, BDNF appears to strengthen excitatory (glutamatergic) synapses and weaken inhibitory (GABAergic) synapses. Exposure of adult rat hippocampal slices to BDNF leads to a long-lasting potentiation of synaptic strength at Schaffer collateral-CA1 synapses. Subsequent studies have supported a role of BDNF in long-term potentiation (LTP). For example, incubation of hippocampal or visual cortical slices with trkB inhibitors inhibits LTP, and hippocampal slices from $BDNF^{-/-}$ mice exhibit impaired LTP induction – which is restored by reintroduction of BDNF.

Whether BDNF-induced synaptic potentiation occurs primarily by a presynaptic action (e.g., through enhancement of glutamate release) or postsynaptically (e.g., via phosphorylation of neurotransmitter receptors) is intensely debated. A number of studies have provided evidence for a presynaptic locus, but evidence for postsynaptic actions has also been obtained. Both pre- and postsynaptic trkB receptors in the hippocampus may be important.

A role for BDNF in GABAergic synapses was first raised by studies showing that BDNF influences GABAergic neuronal phenotype. Subsequently, BDNF was shown to decrease inhibitory (GABAergic) synaptic transmission. Recent evidence shows that BDNF can modulate the

function of $GABA_A$ receptors via modulation of phosphorylation state. Interestingly, BDNF may also regulate the efficacy of GABAergic synapses by direct downregulation of the neuronal K^+–Cl^- cotransporter, which would impair neuronal Cl^- extrusion and weaken GABAergic inhibition. Indeed, BDNF selectively decreases the efficacy of inhibitory neurotransmission by downregulation of Cl^- transport.

Methods

BDNF gene regulation by seizure activity has been studied at both the mRNA and protein levels. Changes in mRNA induced by seizure activity have been studied by Northern blot and in situ hybridization analysis. In Northern blot analysis, total RNA is extracted from a tissue sample, run on an RNA gel, and a specific labeled antisense oligonucleotide probe is used to detect the RNA of interest. Similarly, in situ hybridization utilizes a specific radiolabeled or chemically labeled antisense RNA strand to detect specific genes (in this case BDNF) in ex vivo tissue sections. While it is less quantitative than Northern blot analysis, the advantage of in situ hybridization is that not only the level but the anatomic site(s) of BDNF mRNA regulation can be determined. Immunohistochemistry, Western blot analysis, and ELISA (enzyme-linked immunosorbent assay) have been used to examine BDNF protein regulation following seizures. Immunohistochemistry, using a specific antibody to BDNF, has shown levels and anatomic sites of BDNF protein upregulation by seizure activity. ELISA and Western blot can be used to evaluate, in a more quantitative manner, BDNF protein levels in tissue extracts.

Studies of the function of BDNF on synaptic transmission and epilepsy have used both in vitro and in vivo techniques. Potentiation of synaptic strength by BDNF has been most commonly studied in ex vivo slices of hippocampus. In these studies, specific hippocampal synaptic pathways (e.g., Schaffer collateral-CA1 synapses) are stimulated electrically and the responses recorded in the presence and absence of bath-applied BDNF. Likewise, inhibitors of BDNF transmission (such as trkB inhibitors) or studies of hippocampal slices from $BDNF^{-/-}$ mice have shown impaired induction of long-term potentiation, a common model of synaptic plasticity and learning and memory.

In vivo studies of the role of BDNF in epilepsy have used animal models of epilepsy, such as the pentylenetetrazol (PTZ) model, kainic acid (KA) model, and kindling model. In these studies, BDNF or BDNF inhibitors are given in the attempt to affect epileptogenesis. For example, trkB receptor bodies (which sequester endogenous BDNF) have been injected chronically via an intracerebroventricular route and have been shown to inhibit epileptogenesis in the kindling model.

Epilepsy-Relevant Results

Role of BDNF in Animal Models of Epilepsy

The discovery that limbic seizures increase NGF mRNA levels led to the idea that seizure-induced expression of neurotrophic factors may contribute to the lasting structural and functional changes underlying epileptogenesis. It is now clear that BDNF and trkB are markedly upregulated by seizures. A wide variety of seizure paradigms (kindling, kainic acid, pilocarpine, PTZ, electroconvulsive shock (ECS)) rapidly and markedly increase expression of BDNF mRNA in dentate gyrus as well as in other areas of the hippocampus and cortex. This mRNA increase is associated with a transient upregulation of BDNF protein. TrkB mRNA and protein in the dentate gyrus are also upregulated following various seizure protocols. TrkB mRNA expression is increased in dentate granule cells 2–6 hours after rapid electrical kindling, hippocampal afterdischarge, PTZ kindling, ECS, or pilocarpine status epilepticus. Subcellular studies have demonstrated targeting of BDNF and trkB mRNAs to dendrites in CA3 neurons following kindled seizures.

Studies using the kindling model of epilepsy have functionally implicated BDNF in epileptogenesis. In the kindling model, repeated, focal application of initially subconvulsive electrical stimuli eventually results in intense focal and tonic–clonic seizures. Once established, this enhanced sensitivity to electrical stimulation persists for the life of the animal. The kindling model has been an important tool, since it allows experimental control over seizures and precise quantitation of effects of experimental manipulation on epileptogenesis in vivo.

The development of kindling is partially inhibited in heterozygote knockout BDNF mice or mice with conditional BDNF gene deletion. Intraventricular infusion of trkB-Fc, a chimera of human IgG-Fc domain and the extracellular domain of the trkB receptor that would sequester and limit the activity of endogenous BDNF, inhibits kindling development. Mice overexpressing a truncated trkB display reduced seizure susceptibility. Interestingly, conditional homozygous deletion of trkB appears to prevent kindling. These results are consistent with studies demonstrating that increasing BDNF promotes excitability. For example, direct application of BDNF to hippocampal slices induces hyperexcitability in vitro; overexpression of BDNF in transgenic mice leads to spontaneous seizures; and intrahippocampal infusion of BDNF is sufficient to induce seizure activity in vivo.

A separate group of experiments has demonstrated that chronic BDNF infusion can inhibit kindling. These inhibitory effects appear to be due to trkB receptor downregulation following chronic BDNF administration, and hence are still consistent with the 'proepileptogenic BDNF' hypothesis. This interpretation is supported by

the observation that chronic exposure to BDNF in vitro leads to downregulation of trkB mRNA and protein. Similarly, continuous in vivo intrahippocampal BDNF infusion results in downregulation of trkB protein by as much as 80%. Thus, whereas chronic BDNF infusion inhibits kindling progression, acute microinjections of BDNF enhance epileptogenesis in the absence of effect on trkB expression. Furthermore, chronic infusions of BDNF may upregulate the inhibitory neuropeptide Y.

Whether BDNF has a significant effect on seizure-associated mossy fiber sprouting is not clear. Although mossy fiber sprouting has been reported in $BDNF^{+/-}$ mice and following BDNF infusion, there is no effect on mossy fiber sprouting in BDNF-overexpressing mice or following chronic infusion or bolus injection of BDNF in other studies. However, BDNF overexpression does increase dendritic length and complexity in the hippocampus. The relative role of BDNF in synaptic changes vs. larger-scale morphological changes during epileptogenesis remains to be clarified.

Trk Receptor Activation Following Seizure Activity

The ability to monitor trk receptor activation following seizures using phospho-specific trk antibodies has enabled investigators to identify the anatomical, time course, and threshold characteristics of trk receptor activation in the hippocampus following seizure activity. Following seizure activity, phospho-trk immunoreactivity is selectively increased in dentate hilus and CA3 stratum lucidum of hippocampus. This distribution precisely coincides with the 'mossy fiber' pathway of dentate granule cell axon terminals. In addition, this anatomic pattern coincides with the distribution of both basal and seizure-induced BDNF protein. Basal BDNF protein is also localized in hilus and CA3 stratum lucidum, and seizures increase levels of BDNF protein in dentate gyrus and CA3 (and BDNF immunoreactivity in hilus and CA3 stratum lucidum). This precise anatomic colocalization of increased phospho-trk immunoreactivity and increases in BDNF protein suggests that the phospho-trk immunoreactivity is caused by seizure-induced increases in BDNF. However, interesting recent evidence also demonstrates transactivation of trkB in the mossy fiber pathway by the divalent cation zinc, in a neurotrophin-independent manner.

Perspective and Goals for Future Research

Since the discovery of BDNF in the 1980s, a great deal of evidence has mounted for roles of BDNF in development, physiology, and pathology. BDNF appears essential to molecular mechanisms of synaptic plasticity and larger-scale structural rearrangements of axons and dendrites. Basic activity-related changes in the central nervous system are thought to depend on BDNF modulation of synaptic transmission. However, pathologic levels of BDNF-dependent synaptic plasticity appear to contribute to epileptogenesis in a variety of animal models. On the basis of distribution, regulation, and localization studies, the hippocampus and closely associated limbic structures are thought to be particularly important in the proepileptogenic effects of BDNF. Specimens from patients with temporal lobe epilepsy have also demonstrated BDNF upregulation. It is hoped that understanding of the hyperexcitability associated with BDNF in epilepsy animal models may lead to novel anticonvulsant or antiepileptic therapies.

New methods of regulation of neurotrophins have been developed to achieve therapeutic efficacy in diseases of neurotrophin deficiency. For example, 'ampakines' represent a new class of compounds that have been shown to upregulate BDNF over a long period of time. Determination of proper dosing protocols, so as not to trigger downregulation of important neurotrophin signaling pathways, will be critical to avoiding deleterious side effects of these potential new therapies. Nevertheless, these and similar compounds are under active clinical investigation as cognitive and memory-enhancing drugs.

Manipulating neurotrophin action by simple up- or downregulation may lead to many nonspecific effects. For ultimate clinical application in specific conditions such as epilepsy, it will be very helpful to elucidate downstream neurotrophin signaling pathways responsible for specific phenotypic effects. For example, BDNF activation of trkB downregulates hippocampal KCC2, a K^+–Cl^- cotransporter; this suppresses chloride-dependent fast GABAergic inhibition and may partially account for BDNF modulation of GABAergic synapses. In addition, BDNF phosphorylates specific subunits of both the NMDA receptor and the $GABA_A$ receptor, altering their function. Longer-term effects of BDNF must take into account the fact that it upregulates many other plasticity-related genes, such as neuropeptide Y. NPY, for example, may not only modulate excitability but also other phenomena such as neurogenesis. Targeting the downstream pathways specifically associated with epileptic hyperexcitability, in an anatomically and temporally restricted manner, will be necessary for optimal therapeutic effect.

See also: **Epileptogenesis**: Patterns of Gene Expression during Epileptogenesis: Micro-Array Studies in Rats; **Glia/Astrocytes**: Role of Astrocyte Dysfunction in Epilepsy; **Neurotrophic Factors**: Activity-Regulated BDNF Expression: Contributions to Synaptic Plasticity and Neuroprotection; Neuroprotective Strategies in Epilepsy; The Influence of Neurotrophins on Excitability in Hippocampus and its Potential Relevance to Epilepsy;

Plasticity: Dendritic Abnormalities in Epilepsy; LTP and Kindling: Phenomena of Activity-Dependent Plasticity Influencing Memory and Epilepsy.

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NON-SYNAPTIC MECHANISMS

Contents

Changes in Extracellular Ionic Composition

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Introduction

All neurons and glia maintain an electrical potential across the cell membrane, which is negative relative to the extracellular environment. This negative potential provides a driving force for charged particles to move across the membrane. Every nerve impulse is dependent on this movement of ions. Most of these ions move through ion channels, along concentration gradients generated by electrogenic pumps, but some ions move across membranes on transporters. Abnormalities in the control of ionic movement across membranes can result in abnormalities in neuronal excitability.

With neuronal activity, action potential firing results in movement of potassium out of the cell and sodium into it. A single action potential will result in little change in the ion concentrations in the extracellular space. During seizures (i.e., intense neuronal activity), however, the amount of potassium moving out of neurons exceeds the ability of the brain to regulate precisely the ion concentrations, and the extracellular potassium will increase from a resting level of around 3 to 10–12 mM.