Molecular Neurobiology

ISSN0893-7648/06/33(1): 017–032/$30.00

What Is the Biological Significance of BDNF mRNA Targeting in the Dendrites?

Clues From Epilepsy and Cortical Development

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Abstract

The neurotrophin brain-derived neurotrophic factor (BDNF) is a regulatory factor of several, partially contrasting, aspects of the biology of neural cells, including survival, growth, differentiation, and cell death. Regulation of the local availability of BDNF at distinct subcellular domains such as the cell soma, dendrites, axons, and spines appears to be the key to conferring spatial and temporal specificity of the different effects elicited by this neurotrophin. This article reviews recent findings in the context of epileptogenesis and visual cortex maturation that showed that different BDNF messenger RNA (mRNA) transcripts are localized at different subcellular locations in hippocampal and cortical neurons. It also reviews findings demonstrating that strong depolarizing stimuli, both in vitro and in vivo, elicit accumulation of BDNF mRNA and protein in the distal dendrites through a signaling pathway involving the activation of the *N*-methyl-D-aspartate and tyrosine kinase B receptors and an intracellular increase in Ca^{2+} concentration. Finally, this article proposes that the regulation of the delivery of BDNF mRNA and protein to the different subcellular domains—particularly the dendritic compartment—may represent a fundamental aspect of the processes of cellular and synaptic morphological rearrangements underlying epileptogenesis and postnatal development of the visual cortex.

Index Entries: Neurotrophins; BDNF isoforms; mRNA dendritic targeting; cellular mRNA trafficking; local protein synthesis; visual cortex; hippocampus; synaptogenesis; epileptogenesis; temporal lobe epilepsy; synaptic maturation.

Received January 3, 2005; Accepted June 2, 2005.
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Introduction

The neurotrophin brain-derived neurotrophic factor (BDNF) was first isolated as a soluble protein with neurotrophic properties by Barde and collaborators *(1)* in 1982, but was cloned only in 1989 *(2)*. In analogy with the other neurotrophins, BDNF is a regulatory factor of several, and partially contrasting, aspects of the biology of neural cells, including survival, growth, differentiation, and cell death *(3–5)*. Besides acting as a growth and trophic factor, BDNF can also have synaptic effects that potentiate active excitatory synapses and depress inhibitory ones *(6–8)*. BDNF exerts its functions upon secretion in the extracellular space and subsequent binding to two types of cell surface receptors: its high-affinity tyrosine kinase (Trk) receptor, TrkB, and the p75 neurotrophin receptor p75NTR *(9–11)*.

Activated receptors initiate several signal transduction cascades, including mitogen-activated protein kinase pathways, the phosphatidylinositol 3-kinase pathway, and the phospholipase C-γ pathway *(9,11)*. These signaling pathways culminate in the activation of transcription factors that alter gene expression, leading to long-lasting plastic changes *(4,7)*. Recent studies suggest that neurons can selectively activate one or more of these intracellular pathways, depending on the cellular location of the activated Trk receptor *(12)*. The prediction of this model is that activation of TrkB receptors on cell soma, dendrites, or axons may induce different cellular effects. Another important implication is that compartmentalization of TrkB and/or BDNF is an essential requisite for proper regulation of the cell biology of a neuron. This concept raises two questions: how is local availability of BDNF and TrkB regulated and what are the functional consequences of errors in the regulation of the local availability of these two molecules? Possible answers to these questions, arising particularly from studies on BDNF expression during epileptogenesis and cortical development, are the topic of this article.

Dendritic Targeting of mRNAs and Local Protein Synthesis

In recent decades, it has become clear that an important aspect of gene expression is the targeting of messenger RNAs (mRNAs) to different intracellular locations where the local translational machinery allows the synthesis of selected proteins within restricted subcellular domains *(13–15)*. This process occurs in cell types ranging from oocytes to the most complex and highly polarized cells of the body, the neurons. One possible explanation for the evolutionary advantage of mRNA targeting in neurons is that it greatly simplifies the task for targeting proteins required for plasticity to activated synapses. By keeping the protein machinery nearby, each synapse may operate as an autonomous entity and can change its transmission efficacy independently of the others *(14,16)*. At least three lines of evidence support this view. First, dendrites and subsynaptic compartments are equipped with the essential elements required for protein synthesis and posttranslational modifications, including glycosylation *(17–20)*. Second, a growing number of mRNAs (estimated to be about 400) have been found in dendrites of mature neurons *(21–23)*. Finally, long-lasting synaptic potentiation in the hippocampus requires local protein synthesis in dendrites, and most importantly, potentiation persists even after the cell bodies of pre- and postsynaptic neurons are severed from their dendrites *(24)*.

The mechanisms allowing mRNAs to be targeted to dendrites are not clear and are probably multiple *(25)*. For example, certain mRNAs are known to contain sequences (such as the cytoplasmic polyadenylation element) that facilitate mRNA transport to the dendrites; often, but not always, these "targeting elements" are situated in the 3'-untranslated region (3'UTR) of the mRNA *(26)*. Identification of these targeting elements has proven difficult because most of these sequences are poorly conserved among different dendritic mRNAs, and a single mRNA may contain several of them

(25). Thanks to early studies in *Drosophila* embryos and *Xenopus* oocytes, targeting sequences are known to be recognized by specific RNA-binding proteins *(27),* which are directly involved in RNA targeting and asymmetric distribution. Mammalian homologs of the *Drosophila* and *Xenopus* RNA-binding proteins have recently been identified *(28).* One such molecule is staufen *(29),* which is present in hippocampal neurons, where it localizes into mRNA-containing granules moving along microtubules in the dendrites *(30,31).* Indeed, the forward, somatodendritic transport of these granules has been shown to be mediated by microtubules, and it has been proposed to depend on kinesins plus-end (i.e., from the soma to the dendrites) directed motors *(32,33).* However, how mRNAs interact with the microtubule motors is unclear. In neurons, granules are formed by large mRNA-containing ribonuclear particles, which contain transacting factors responsible for RNA transportation *(30,34–39)* as well as many—if not all—components of the translational machinery *(39–43).*

BDNF mRNA Cellular Localization Under Basal Conditions In Vitro and In Vivo

BDNF and TrkB are among those genes whose mRNA is targeted into the dendritic processes. The first clear evidence of this feature was found in primary cultures of rat hippocampal neurons. Under basal conditions in these hippocampal neurons, BDNF and TrkB mRNAs are localized in the proximal dendritic compartment (≤80 μm from the cell soma) but, in response to tetanic electrical activity, they also extend in the distal dendrites (≥100 μm; ref. *44*). Accumulation in distal dendrites is mediated by activation of glutamate receptors, intracellular Ca^{2+} influx, and activation of the TrkB-mediated phosphatidylinositol-3-kinase intracellular signaling cascade *(44,45).* Moreover, BDNF and TrkB mRNAs localized to the distal dendrites in vitro appear to be locally translated into protein *(44).*

Through high-resolution *in situ* hybridization and electron microscopy analyses of rat brain sections, BDNF mRNA was also found constitutively in dendrites in vivo up to a distance of 70 μm from the soma *(46).* In the dendritic compartment, it was associated with polyribosomes *(46),* suggesting active translation *(47).* Under basal conditions, TrkB mRNA is also localized in the proximal somatodendritic compartment of hippocampal neurons in vitro *(44)* and of basal forebrain neurons in vivo, whereas the mRNAs for the other neurotrophin receptors (TrkA, TrkC, and p75) are restricted to the cell soma *(48).* Consistent with these findings, BDNF and TrkB mRNAs have been amplified from dendritic mRNA prepared from synaptoneurosomes *(33).* Therefore, it is conceivable that, in dendrites, the local availability of both BDNF and TrkB is controlled through regulation of the targeting of their mRNAs and/or their local translation into protein. Evidence for this has come from our recent studies on epileptogenesis and visual cortex maturation.

BDNF and Epilepsy

The phenomenon by which a normal tissue is transformed into an epileptic tissue is termed "epileptogenesis." An "epileptogenic insult" (e.g., a trauma, a stroke, a prolonged nonepileptic seizure) can be followed by the occurrence of spontaneous seizures (i.e., epilepsy) after a latent period of weeks to years. A cascade of cellular events, including neuronal death, microgliosis, astrogliosis, neurogenesis, and axonal sprouting, occurs during the latent period *(49,50).* These events are believed to produce extensive reorganization of cellular processes as well as synaptic connections; ultimately, they lead to the epileptic condition of latent hyperexcitability. It can be hypothesized that critical mediators capable of priming the cellular phenomena mentioned earlier are produced following an

epileptogenic stimulus as well as during the latent period. Indeed, complex changes in gene expression, including changes in expression levels of both *bdnf* and *trkB*, have been observed under these conditions *(51).*

BDNF is a very strong candidate as a "plasticity" gene for epileptogenesis. Limbic seizures increase *bdnf* gene expression *(52–57)* and TrkB receptor activation *(58).* These phenomena appear to play a pro-epileptic role, because epileptogenesis is reduced in (a) $BDNF^{+/-}$ mutant mice, in whom elimination of one allele causes a reduction in BDNF protein levels in the brain *(59);* (b) rats infused with TrkB bodies that scavenge the ligand and limit TrkB activation *(60);* and (c) mice overexpressing truncated TrkB, a dominant negative BDNF receptor *(61).* Conversely, transgenic mice overexpressing BDNF show increased seizure severity in response to kainic acid *(62),* and multiple bolus micro-injections of BDNF (a paradigm that, at variance with the continuous infusion, does not downregulate TrkB receptors) accelerate epileptogenesis *(63).* Finally, epileptogenesis is completely abolished in Synapsin-Cre conditional $TrkB^{-/-}$ mice, in whom TrkB was ablated in multiple neuronal populations of the forebrain, including hippocampal granule cells and CA3 pyramidal neurons *(64).* These data argue that TrkB activation plays an essential, and not merely regulatory, role in epileptogenesis.

However, the mechanism of this pro-epileptic effect remains uncertain. One attractive hypothesis is that it relates to the synaptic effects of BDNF. Neurotrophins have been proposed to participate in activity-induced persistent modification of synaptic transmission, with potentiation of glutamatergic, excitatory synapses and depression of γ-aminobutyric acid (GABA)-ergic, inhibitory synapses *(65).* The idea that the synaptic effects of BDNF are epileptogenic is also supported by data suggesting that other cellular actions of BDNF are not implicated in its epileptogenic effects: occlusion of the signaling pathway activated by the Shc site of TrkB implicated in survival, differentiation, and neurite outgrowth, but not in synaptic potentiation *(66),* does not affect epileptogenesis *(67).*

If BDNF plays a pro-epileptic role by potentiating excitatory synapses, then the mechanism by which it is delivered to these synapses comes into question. One possibility is that BDNF is synthesized in the cell body, anterogradely transported along the axons, and stored in the presynaptic terminals, from which it will be released in an activity-dependent manner. This appears to be the case for hippocampal granule cells: BDNF produced in the cell bodies of these cells may travel along the mossy fibers and reach their terminals in the CA3 stratum lucidum *(68–73).* However, in the hippocampus no evidence exists to support the finding that such an anterograde mechanism occurs at other synapses. Alternatively, BDNF may be retrogradely transported to the active synapses in two ways: (a) the protein may be synthesized in the soma and transported in the dendrites or (b) BDNF mRNA may be targeted to the dendrites, and local protein synthesis may occur at postsynaptic sites. Evidence supporting the latter possibility is examined in greater detail in the following section.

Epileptogenic Stimuli Trigger Accumulation of Dendritic BDNF mRNA

We found that epileptogenic limbic seizures cause a dramatic accumulation of BDNF mRNA in the dendrites *(46,74).* BDNF mRNA dramatically accumulates in the distal dendrites of all principal hippocampal neurons following pilocarpine administration in the rat, with a peak at 3 h after onset of status epilepticus. Accumulation of BDNF mRNA was also observed in two other models of temporal lobe epilepsy (kainate and kindling) and occurred during epileptogenesis (i.e., following pilocarpine- and kainate-induced status epilepticus or the initial seizures induced by kindling stimulation) but not after epileptic seizures in chronic animals. This suggests that the phenomenon is associated with the development, and not with the maintenance, of epilepsy.

Nonepileptogenic stimuli (i.e., stimuli not followed by spontaneous seizures or by a decreased seizure threshold, such as single maximal electroshock seizures and perforant path stimulation) did not induce accumulation of BDNF mRNA into the dendritic compartment *(46).*

Several features of the pilocarpine seizure-induced accumulation of BDNF mRNA in the dendrites have been identified *(46).* First, epileptogenic seizures cause BDNF mRNA to localize selectively at particular sets of synapses. For example, after pilocarpine-induced seizures, BDNF mRNA localizes in laminae corresponding to the terminal fields of either the mossy fibers (originating from the granule cells) or the associational-commissural projection system (originating from CA3 pyramidal neurons and neurons in the hilus of the dentate gyrus). These neurons are highly activated during the seizures, and, therefore, the selective targeting of BDNF mRNA to the sites of their terminations coincides with the set of synapses that are most active. Second, dendritic accumulation of BDNF mRNA appears to be coordinately regulated with TrkB mRNA, because the expression pattern *(75)* and the dendritic localization *(74)* of both mRNAs is similar in all of the epilepsy models tested to date. Third, dendritic BDNF mRNA may be locally translated into protein. BDNF protein is preferentially localized in cell bodies and axons under basal conditions *(69,70,76),* but it accumulates in dendrites after pilocarpine-induced seizures, with a distribution and a time-course that match those of its mRNA *(46).*

What might be the mechanism of the dendritic accumulation of BDNF mRNA during epileptogenesis? The first step in the cascade of events leading to this phenomenon might be the activation of *N*-methyl-D-aspartate (NMDA) receptors. In vitro and in vivo evidence support this idea: (a) in culture, the electrical-activity-dependent dendritic targeting of both BDNF and TrkB mRNA can be completely abolished by blockers of glutamate receptors *(44);* (b) in vivo, NMDA receptor antagonists (MK801) block pilocarpine-seizure-induced dendritic targeting of BDNF mRNA *(46).* Therefore, through NMDA receptor activation, the massive release of glutamate occurring during status epilepticus is likely to trigger the strong dendritic accumulation of BDNF *(46)* and TrkB mRNAs *(74)* in hippocampal neurons. This phenomenon does not appear to depend on an increase in gene transcription, because NMDA receptor agonists do not induce BDNF mRNA expression *(76,77),* and activity-dependent BDNF and TrkB mRNA targeting in vitro occurs without new mRNA transcription *(44).* Additionally, it appears that the activation of the NMDA receptor *per se,* and not the seizure, is the trigger for mRNA targeting, both because MK801 prevents BDNF mRNA targeting but not pharmacologically induced status epilepticus or kindled seizures *(78,79)* and because electroshock seizures do not cause dendritic targeting *(46).*

The signaling pathways (and the synaptic tagging mechanism) that link NMDA receptor activation with the accumulation of BDNF at the active synapses remain unknown. Nonetheless, NMDA receptor activation appears to be a critical step in the epileptogenic process. In fact, blockade of NMDA receptors prevents pilocarpine-induced epileptogenesis *(80)* and kindling development *(78).* Conversely, an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid antagonist (NBQX) only prevents accumulation of BDNF mRNA in the dendrites in animals in which it prevents seizures *(46).* As discussed earlier, TrkB receptor activation also seems to be critical (or even essential) for epileptogenesis. How then may dendritic BDNF favor the development of epilepsy?

Dendritic BDNF and Epileptogenesis

The fate of seizure-induced dendritic BDNF protein has not been investigated: it may produce intracellular effects, or, more likely, it may be released and exert pre- and/or postsynaptic effects. The principal consequence of the latter scenario is that neurons, activated by an epileptogenic stimulus, are exposed to BDNF released locally from the postsynaptic dendrites located

at specific sets of active synapses. On the other hand, epileptogenic stimuli can also increase the synthesis of BDNF in the soma of granule cells, its transport along the mossy fibers, and its release from presynaptic terminals at the mossy fiber–CA3 synapse *(81).* These two possibilities are not mutually exclusive but actually raise the interesting possibility that TrkB receptors in the CA3 area are activated by BDNF secreted by both pre- and postsynaptic elements. It appears likely that the effect of secreted BDNF is primarily local, because BDNF is a sticky, poorly diffusible molecule, and both neurons and glia express high amounts of truncated TrkB receptor, which are believed to limit BDNF diffusion *(82–84).* The possibility exists that part of this secreted BDNF, binding presynaptic, full-length TrkB receptors, is internalized and in retrogradely transported to the cell soma, conveying signaling to the nucleus *(73,85).* However, this article does not discuss this possibility but focuses on the former (local, synaptic effects).

In the hippocampus, as well as in the cortex (*see* below), BDNF exerts complex effects on excitatory glutamateric and inhibitory GABA-ergic synapses. Studies in cultures of hippocampal neurons have indicated that the acute treatment with BDNF facilitates excitatory neurotransmission in a long-lasting manner *(86,87)* but reduces inhibitory neurotransmission *(88).* Observations in mature synapses of the adult hippocampus are consistent with these data. Under basal conditions, BDNF increases the glutamatergic transmission at the Schaffer collateral–CA1 synapse in slices *(89,90,91)* and at the perforant path–granule cells connection in vivo *(92),* whereas it depresses the GABA-ergic transmission in CA1 *(93,94).* The stimulatory effect of BDNF on basal glutamatergic transmission in the hippocampus has not been confirmed in other studies *(93–97).* However, solid evidence implicates BDNF in activity-dependent excitatory transmission (reviewed in ref. *65*). BDNF is a very potent excitatory agent because it produces changes in synaptic activity at concentrations three orders of magnitude lower than those necessary for glutamate *(98,99).* Interestingly, the effects described in this paragraph are target-specific: in glutamatergic neurons, BDNF increases the amplitude of excitatory postsynaptic currents but slightly decreases that of inhibitory postsynaptic currents; in GABA-ergic neurons, it increases inhibitory postsynaptic current amplitude *(88).* Therefore, excitatory effects are conveyed onto glutamatergic neurons, and inhibitory effects are conveyed onto GABA-ergic neurons.

In hippocampal synapses, TrkB receptors are present both presynaptically (on the nerve terminals) and postsynaptically (at the postsynaptic density) *(82,84).* Therefore, BDNF may exert effects at both sides of the synapse. Presynaptically, BDNF increases glutamate release *(98,100–103)* and decreases GABA release *(94).* Postsynaptically, it increases NMDA receptor function by phosphorylating its 2B subunit *(104,105)* and decreases $GABA_A$ receptor function by downregulating its α2-, α2,3-, and α2-subunits *(106).*

In summary, BDNF increases glutamatergic transmission and depresses GABA-ergic transmission in the hippocampus under both basal conditions and, more so, conditions of increased activity, such as in the course of an epileptogenic insult. These effects appear to be long-lasting and, therefore, may account for increased network excitability. Thus, it can be hypothesized that an epileptogenic insult might produce the pathological activation of a feed-forward circuit, including increased glutamate release, NMDA receptor activation, dendritic accumulation of BDNF mRNA and protein, release of this newly synthesized BDNF, activation of local TrkB receptors, further glutamate release, NMDA receptor activation, and so on.

The idea that the effect of BDNF on excitatory synaptic responses depends on the stimulation frequency is extremely pertinent to a possible role in epileptogenesis. In fact, the effect of BDNF on synaptic responses to repetitive stimulation in the hippocampus has been reported to be present only *(96),* or mainly *(107),* when presynaptic neurons are stimulated at high frequency and, thus, undergo severe synaptic fatigue. Therefore, BDNF could selectively modulate synapses undergoing high fre-

quency transmission during an epileptogenic insult *(108,109).* Similarly, decreased efficiency of GABA-ergic inhibition may build up. The net result of these phenomena is an escalating increase in excitability that eventually leads to the epileptic condition.

Consistent with this view, the synapse between mossy fibers and CA3 pyramidal cells is particularly potentiated in kindled animals*(110);* this synapse is one at which (a) dendritic accumulation of BDNF mRNA was detected during kindling development *(46);* (b) BDNF may also be secreted presynaptically *(81);* and (c) activation of TrkB receptors has been reported to occur in anatomical and chronological coincidence with the accumulation of dendritic BDNF *(46,58).*

Relevance for Human Epilepsy

The emerging role of BDNF single-point mutations in frequent human neurological pathologies (such as Alzheimer's disease and impaired memory, bipolar affective disorders, Parkinson's disease, and partial epilepsy) opens new questions related to the pathological mechanisms underlying these disorders. Two distinct human BDNF polymorphisms have been identified that, based on initial studies, support the idea that BDNF may be causally related to human epilepsy—particularly to temporal lobe epilepsy (TLE), one of the most common epileptic syndromes. The first polymorphism, a valine to methionine substitution at position 66 in the BDNF prodomain (val66met), has been associated with a loss of function, decreased intracellular trafficking from the cell body to the processes (dendrites and axon), and decreased regulated, activity-dependent secretion of BDNF *(111,112).* This polymorphism does not associate with TLE *(113)* or febrile seizures *(114).* Conversely, another human BDNF polymorphism (cys270thr, or C270T) has been associated with idiopathic TLE *(113).* The C270T substitution occurs in one of the alternatively spliced 5'-UTR noncoding exons (human exon V; ref. *115*) containing an internal ribosomal entry site (IRES). Several mRNAs targeted to the dendritic compartment use CAP-independent translation based on specific IRES sequences *(116).* The human BDNF also contains two such IRES sequences in exon V and exon VIII, respectively, and the T allele of the C270T polymorphism alters the IRES-dependent translation of the human exon V, which induces increased production of BDNF *(115,117).* Therefore, the pathological mechanism of the C270T mutation appears to be a gain-of-function mechanism related to an increased translatability of BDNF in dendrites, which is consistent with our finding that epileptogenesis is accompanied by a dramatic dendritic accumulation of BDNF mRNA and protein.

The studies mentioned so far strongly suggest that a dramatic accumulation of BDNF and TrkB mRNAs in the distal dendrites of hippocampal neurons occurs and may play an important role in a pathological event—that is, epileptogenesis. Therefore, an important question arises: is the trafficking of BDNF and TrkB mRNAs also regulated under physiological conditions? A clue to answering this question comes from studies on BDNF expression during the postnatal maturation of the rat visual cortex, another example of cellular and synaptic rearrangements induced by a complex interplay between neuronal activity and gene expression.

BDNF and the Postnatal Maturation of the Visual Cortex

In mammals, cortical maturation represents a dynamic process involving the formation, establishment, and refinement of synaptic connectivity. In the visual cortex, this process leads to maturation of several functional properties underlying vision, such as receptive field organization, selectivity of the neuronal response to the orientation and direction of a visual stimulus, enhancement of the visual acuity, and formation of ocular dominance columns (i.e., groups of cortical neurons organized in columnar anatomical structures responding only to

visual stimuli coming from either the left or the right eye). During a period of postnatal development known as the critical period, the visual cortex is highly sensitive to manipulation of visual experience, and if pups do not receive equivalent visual stimulation from the two eyes, then the ocular dominance columns and the capacity of cortical neurons to respond to either eye become altered *(118–120).*

Evidence for a role of BDNF in maturation and plasticity of the visual cortex has been suggested by studies showing that (a) in cocultures of cortical cells *(121)* and in organotypic cortical slices *(122),* BDNF enhances the maturation of dendrites in inhibitory neurons and (b) BDNF supply promotes in vitro the dendritic arborization of pyramidal neurons in organotypic cortical slices *(123,124).* Remarkably, the effects of BDNF are layer-specific, and BDNF released from cortical cells affects the dynamic of dendritic spine formation in neighboring neurons, suggesting that this neurotrophin may contribute to remodeling the spatial distribution of synapses along the neuronal processes *(124).*

In addition to affecting dendritic arborization, BDNF appears to modulate long-term synaptic plasticity, stabilizing specific connections during postnatal development *(125).* Several lines of evidence support this conclusion First, exogenously supplied BDNF disrupts ocular dominance columns during development in vivo *(126,127)* and modulates the effects of monocular deprivation *(128).* Second, BDNF overexpression in vivo shortens the critical period for monocular deprivation that accelerates the maturation of the GABA-ergic circuitry *(129)* and prevents the effects induced by dark-rearing *(130).* Third, BDNF acutely enhances excitatory synaptic transmission and long-term potentiation in visual cortex slices *(131,132).* In contrast, blockade of TrkB ligands by TrkB fusion proteins reduces long-term potentiation expression *(133).* Long-term depression is also modulated by BDNF: the induction of long-term depression by low-frequency stimulation is prevented by pretreatment with BDNF (ref. *134; see also* ref. *135*). Finally, BDNF restores the capacity of synapses to be depressed and then potentiated at a late stage of postnatal development, when this form of synaptic plasticity is lost *(125).*

Visual Experience Induces BDNF mRNA Targeting in the Visual Cortex

Similarly to the hippocampus, we have shown that in the visual cortex, BDNF mRNA is expressed in the soma of pyramidal-like cells as well as in their dendrites *(136).* This is particularly visible in layer V neurons of adult rats *(137)* during an early stage of postnatal development when BDNF mRNA is localized in a few cell perykaria but not in dendrites *(138).* Therefore, not only the cellular expression throughout cortical layers but also the subcellular localization of BDNF mRNA is modified during postnatal development.

Visual experience also regulates the subcellular distribution of BDNF mRNA, because BDNF mRNA targeting in pyramidal cell dendrites is abolished by dark-rearing but resumes after 2 h of exposure to normal light *(136,137).* Similarly, in rat primary cortical cultures, decrease of neuronal activity (as obtained by tetrodotoxin) induces a restriction of BDNF mRNA to cell bodies, whereas an increase of neuronal activity after treatment with potassium chloride augments dendritic targeting of BDNF mRNA *(138).* Because protein synthesis can occur in neuronal dendrites, visual experience, in addition to displacing BDNF mRNA toward distal dendrites, might also regulate the efficiency of its translation. Indeed, we showed that protein expression is decreased in dark-reared rats and that 2 h of light is sufficient time to restore a normal BDNF expression pattern *(139).* Notably, the translational efficiency of the mRNA for α-Ca^{2+}calmodulin-dependent kinase (α-CaMKII), which is abundant in dendrites, has been shown to be increased by visual experience *(140).* This enhancement of translational competence is

achieved through elongation of the poly-A tail mediated by the RNA-binding protein cytoplasm polyadenylation element binding protein, following association with the cytoplasm polyadenylation element, a *cis*-acting sequence present in the 3′-UTR of α-CaMKII *(140).* Interestingly, this sequence was also found in the 3′-UTR of BDNF (Tongiorgi, unpublished observations, 2005).

The rat BDNF gene consists of one 3′-exon encoding the BDNF protein and at least four different 5′-exons, each of which is linked to a different promoter *(141).* Previous studies have shown that these different 5′-regions are necessary to express BDNF in a tissue-specific manner and are differentially expressed in different brain regions *(141–144).* Recent results *(138)* showed that the different transcripts containing exons I, II, III, and IV are all present in the rat visual cortex and are regulated differently during postnatal development. Remarkably, different isoforms of BDNF are expressed in different subcellular compartments: exon IV-containing mRNAs have been detected both in the soma and dendrites, whereas exon III expression is restricted to the cell body *(138).* Neuronal activity regulates the cellular expression of different BDNF transcripts. Dark-rearing in vivo *(136)* and blockade of spiking activity in vivo and in vitro prevents translocation of BDNF mRNAs to the dendrites—specifically of those encoded by exon IV *(138),* resulting in their accumulation in the soma. What is the functional meaning of the different cellular localization of BDNF transcripts in the context of activity-dependent maturation of the visual cortex?

Dendritic BDNF and Visual Cortex Maturation

One attractive hypothesis is that the different BDNF mRNA isoforms may contribute to the local expression of BDNF in different cellular compartments at different times during postnatal life. Activity-dependent transcription, distinct turnover properties, or translational competence of the different BDNF isoforms may account for differences in the availability of BDNF at specific subcellular districts. More specifically, exon III transcripts, which are present only in the soma, may be involved in maturation of interneurons through a transsynaptic route; indeed, a subset of cortical inhibitory neurons known as the basket parvalbuminergic cells make synapses almost exclusively with the soma of the pyramidal neurons *(145–147)* and express TrkB *(148,149).* On the other hand, there are other neurons (mainly excitatory) that form synapses with dendrites whose synaptic maturation might be regulated by local release of BDNF produced by translation of exon IV-containing mRNAs targeted to dendrites. Importantly, researchers recently reported that dendritic release of BDNF can act on a local scale, affecting only nearby dendrites of recipient cells *(150).*

Therefore, targeting of BDNF mRNA in different districts of cortical neurons may be necessary for local release of BDNF to confer spatial and temporal specificity to the process of synaptic strengthening/depression.

Closing the Circle: BDNF Regulates mRNA Targeting and Local Synthesis of BDNF

Dendritic mRNAs can be locally accumulated and translated not only as a result of synaptic activity but also following neurotrophin stimulation *(31).* For example, BDNF can enhance the dendritic localization of TrkB and its own mRNA through activation of a TrkB signaling cascade that involves the phosphoinositol-3-phosphate kinase *(151).* Additionally, the synaptic enhancement induced by BDNF in hippocampal slices requires the local synthesis of new (unknown) proteins in activated dendrites *(152–154).* BDNF appears to be able to activate the dendritic local protein machinery by inducing translocation of the eukaryotic initiation factor 4E to an mRNA granule-rich cytoskeletal fraction *(155).*

In conclusion, in vivo and in vitro studies point to a fundamental role of BDNF in activity-dependent plasticity and circuit re-organization. The idea is that BDNF released under the control of neuronal activity acts locally, within restricted cellular domains, to regulate synaptic transmission and plasticity, spine distribution, dendrite maturation, and maintenance. If local availability is key for conferring spatial and temporal specificity to the different effects of BDNF, then regulation of its delivery to the different subcellular domains should represent a fundamental aspect of BDNF biology.

For example, BDNF transcripts with different translational competence may localize in different subcellular compartments and produce the BDNF protein at different rates and/or in response to different signals coming from segregated synaptic inputs. On the other hand, locally synthesized BDNF might regulate synaptic plasticity in a site-specific manner by modulating both the presynaptic (neurotransmitter release) and the postsynaptic component (efficiency of the local protein synthesis machinery at postsynaptic sites) with a self-perpetuating mechanism. Enhancement of this local circular feedback system may explain long-lasting effects on plasticity associated with neuronal network maturation and epileptogenesis. Conversely, decreased efficiency of this mechanism may explain phenomena of cognitive impairment and neuronal vulnerability.

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