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BDNF at the Synapse: Why Location Matters

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Abstract

Neurotrophic factors, a family of secreted proteins that support the growth, survival and differentiation of neurons, have been intensively studied for decades due to the powerful and diverse effects on neuronal physiology, as well as their therapeutic potential. Such efforts have led to detailed understanding on molecular mechanisms of neurotrophic factor signaling. One member, brain-derived neurotrophic factor (BDNF) has drawn much attention due to its pleiotropic role in the central nervous system (CNS) and implications in various brain disorders. In addition, recent advances linking the rapid-acting antidepressant, ketamine to BDNF translation and BDNF-dependent signaling, has re-emphasized the importance of understanding the precise details of BDNF biology at the synapse. While substantial knowledge related to the genetic, epigenetic, cell biological, and biochemical aspects of BDNF biology has now been established, certain aspects related to the precise localization and release of BDNF at the synapse have remained obscure. A recent series of genetic and cell biological studies have shed light on the question -- the site of BDNF release at the synapse. In this Perspectives article, these new insights will be placed in the context of previously unresolved issues related to BDNF biology, as well as how BDNF may function as a downstream mediator of newer pharmacological agents currently under investigation for treating psychiatric disorders.

Introduction

Over 25 years ago, Hans Thoenen, one of the scientists who, along with Yves Barde, discovered brain-derived neurotrophic factor (BDNF), concluded a review article with a set of future questions that needed to be addressed to fully understand the biological function of

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BDNF. He noted that a key issue was to identify the precise location of BDNF secretion at the level of the synapse - whether BDNF “was released by dendrites and/or axon terminals only. These problems, although extremely challenging experimentally, must be addressed in order to test current speculations in the involvement of neurotrophic molecules in synaptic plasticity and processes related to memory”.¹ While significant progress has been made in the subsequent decades on many aspects of BDNF-dependent molecular signaling pathways and biological functions, especially with relevance to neuropsychiatric disorders, this basic question about BDNF has not been fully clarified.

A remarkable series of studies over the past few years have shed light on this question -- the site of BDNF release at the synapse, which has now been established to comprise neuronal, astrocytic and microglial components.² In this Perspectives article, these recent genetic and cell biological studies³⁻⁶ will be placed in the context of what had been established about BDNF localization, and how these new insights can inform previously unresolved issues related to BDNF biology, as well as how BDNF may function as a downstream mediator of newer pharmacological agents currently under investigation for treating psychiatric disorders.

BDNF is a member of a unique family of polypeptide growth factors, neurotrophins, which influence the proliferation, differentiation, survival and death of neuronal and non-neuronal cells.^{7, 8} While the biological roles for neurotrophins were initially characterized during development of the nervous system, it is now clear that BDNF, in particular, has multiple roles in the adult nervous system, such as regulating synaptic connections, synapse structure, neurotransmitter release, and synaptic plasticity. BDNF is secreted into the synapse leading to the activation of tropomyosin receptor kinase B (TrkB) and its downstream signaling cascades that contribute to gene transcriptional events critical for synaptic plasticity and cognitive function.

It has been established that BDNF is initially synthesized in the endoplasmic reticulum as a precursor protein, a pre-proBDNF, which, in neurons is then selectively sorted to the regulated secretory pathway and ultimately packaged into dense core vesicles (DCV).⁹ Trafficking of BDNF into the biosynthetic pathway is a complex, highly regulated process, the precise mechanisms of which remain unclear. However, two sorting molecules have been identified as required for optimal sorting of newly synthesized BDNF to the regulatory secretory pathway - a VPS10 domain protein, sortilin, which has been demonstrated to interact with the BDNF prodomain, and carboxypeptidase E (CPE), which interacts with the BDNF mature domain.^{10, 11} At the presynaptic terminal, synaptotagmin-IV¹², and SNAREs, Syb2, SNAP25 and SNAP47¹³ have all been demonstrated to regulate the activity-dependent vesicular release of BDNF. Cleavage and processing of pre-proBDNF can occur at multiple sites including the Golgi apparatus by furin, the DCV by proconvertases, and extracellularly by plasmin generated by TPA or selective matrix metalloproteinases including MMP3 and MMP7.¹⁴

Thus, it has been traditionally assumed that BDNF synthesis and secretion occur from presynaptic neuronal sites. In vitro evidence for presynaptic storage and release had been shown in cultured neurons through co-localization of ectopically expressed and endogenous

BDNF with vesicular markers such as synaptotagmin and secretogranin II.^{10, 12, 15} However, localization of endogenous BDNF protein in the intact brain has been difficult to demonstrate due to the low basal levels of BDNF, the variability in the available peptide-based polyclonal BDNF antibodies, as well as lack of age-matched genetic knock-out (KO) controls (as the global BDNF KO mice die in early postnatal life) to validate the immunoreactivity. In vivo genetic evidence has supported the role of presynaptic BDNF when it was first demonstrated that conditional BDNF knock-out mice lacking cortical BDNF (*Emx-BDNF^{KO}*) displayed preferential neuronal loss in the striatum, a region that expresses minimal BDNF and had been assumed to receive neurotrophic support via anterograde delivery of BDNF from regions including the cortex.¹⁶

Presynaptic BDNF

A recent landmark study by Yves Barde utilized a series of newly developed reagents including a monoclonal BDNF antibody, an epitope-tagged BDNF knock-in mouse line (BDNF-Myc), as well as a conditional BDNF KO mouse line (cBDNF-ko) to identify its subcellular localization in the mature mouse brain.³ They focused on the hippocampal granule cell mossy fiber projections to the CA3 – one of the brain regions with the highest BDNF levels, as well as the CA3 Schaffer collaterals to the CA1. They determined using both immunohistochemical techniques and immuno-electron microscopy (EM) that BDNF was almost exclusively localized to presynaptic DCV. Strikingly, almost no BDNF immunoreactivity was observed in post-synaptic compartments. Interestingly, the DCV subtype that BDNF was stored in was distinct from those that contained other neuropeptides such as cholecystokinin and Met-enkephalin, suggestive of selective segregation of BDNF into a subpopulation of secretory vesicles. In addition, using separate antibodies for the prodomain and mature domains, they determined that mature BDNF and the cleaved BDNF prodomain co-localized in these DCV. They also reported co-secretion of the mature BDNF along with the cleaved prodomain, which has subsequently been confirmed by others.¹⁷

These findings are significant as they provide rigorous evidence supporting the notion that newly synthesized BDNF is localized to the presynaptic compartment. These findings also support the numerous electrophysiological studies implicating the requirement of presynaptic BDNF release in synaptic plasticity events, especially in hippocampal circuits. Of note, endogenous BDNF has been implicated in enhancing calcium transients in CA3 dendrites.¹⁸ In addition, it has also been shown that BDNF is necessary for LTP induction at hippocampal CA3-CA1 synapses.^{19, 20} In particular, region-specific BDNF KO mice also specifically implicated a requirement for presynaptic BDNF in LTP induction at the CA3-CA1 synapse.²¹

BDNF from other Synaptic Sites

However, recently, accumulating evidence has suggested that BDNF is capable of being synthesized and secreted from other components of the synapse including astrocytes²², microglia⁴, and post-synaptic dendrites⁹ (Figure 1). One of the key lines of support for additional sites of BDNF localization was subsequent immune-EM studies analyzing another epitope-tagged BDNF knock-in mouse line (BDNF-HA) that demonstrated

endogenous BDNF localization presynaptically (axons, terminals) and postsynaptically (dendrites, spines) in vesicular compartments in the mature hippocampus.⁵ One interpretation of these divergent results may be due to the higher sensitivity of the anti-HA antibody, as compared to the monoclonal BDNF antibody, allowing for detection of the lower levels of BDNF in the other compartments. In this context, while the predominant mode of BDNF secretion is from presynaptic sites, local effects at individual synapses may be modulated by lower levels of BDNF secreted from alternative sites.

It is now well accepted that glial cells are active components contributing to multiple aspects of synapse physiology, including clearance of extracellular ions and neurotransmitters, initial synapse formation and maintenance.² In response to neuronal activity, microglia, a population of brain resident macrophage, are activated and release so-called “gliotransmitters” to modulate neuronal communication. It had been previously been shown that BDNF is synthesized and secreted from microglia^{23–25}, and involved in pain modulation²⁶. A recent study by Wenbiao Gan demonstrated the direct contribution of BDNF secreted from microglia on synaptic remodeling associated with another function - learning and memory.⁴ The study showed that depletion of microglia leads to deficits in behavioral performance in multiple learning paradigms ranging from motor skill learning to fear conditioning and novel object recognition, as well as learning-induced remodeling of excitatory synapses. Using an epitope-tagged BDNF knock-in mouse line (BDNF-HA), they were able to detect endogenous BDNF in the microglia. Intriguingly, loss of microglial BDNF recapitulates the defects observed in microglia-depleted mice, suggesting that BDNF from non-neuronal sources regulates important functions related to learning and memory at the synapse.

With regards to BDNF synthesis and secretion from postsynaptic sites, there exists a long-standing series of studies suggesting its localization to this component of the synapse. For example, a number of *in vitro* studies in cultured neurons have demonstrated localization of ectopically expressed BDNF protein in dendrites.^{12, 13, 27–29} *In vitro* studies that overexpressed fluorescence-tagged BDNF constructs have also demonstrated activity-dependent BDNF secretion from dendrites utilizing similar regulators of vesicular secretion as used for presynaptic BDNF secretion (synaptotagmin-IV, Syb2, SNAP25 and SNAP47)^{12, 13}, as well as from post-synaptic endocytic compartments that were regulated by synaptotagmin-6 and complexin³⁰. In addition, *in situ* hybridization (ISH) studies have reliably detected endogenous *Bdnf* mRNA in neuronal dendrites in both cultured neurons and the intact brain; this expression increases following induction of neuronal activity.^{31, 32} The *Bdnf* gene has nine unique promoters that drive transcription of at least twenty different *Bdnf* transcripts that encode an identical BDNF protein.^{33–36} Each variant consists of a 5′ untranslated region (UTR) exon that is alternatively spliced to a downstream common coding exon. The existence of multiple *Bdnf* splice variants has led to the spatial code hypothesis, which posits that differential expression of *Bdnf* transcripts enables local spatial, temporal, and stimulus-specific BDNF production.³⁷ Indeed, *Bdnf* mRNA variants show activity-dependent targeting to dendrites, especially in the hippocampus.^{32, 34, 38, 39} Upon activation of both cortical and hippocampal neurons, exon 1 and 4-containing *Bdnf* transcripts are localized to the cell body and proximal dendrites, while exon 2 and 6-containing *Bdnf* transcripts are found in distal dendrites.^{40–42} Supporting these findings,

silencing exon 1 and 4-containing *Bdnf* transcripts in cultured hippocampal neurons reduces proximal dendrite number, while silencing exon 2 and 6-containing *Bdnf* transcripts alters distal dendrite morphology.⁴⁰ Recent studies confirmed that loss of exon 2 and 6-containing *Bdnf* splice variants impacts dendritic structure and spine morphology in CA1 and CA3 pyramidal cells of the intact hippocampus.⁴³ In addition to differential localization by the 5' UTR, *Bdnf* transcripts with short versus long 3' untranslated regions (3' UTRs) exhibit distinct subcellular localization to dendrites as well as cell bodies.⁴⁴ Alternative polyadenylation of *Bdnf* transcripts also differentially impacts spine morphology and synaptic plasticity in CA1 hippocampal neurons.⁴⁴ Existence of *Bdnf* transcripts in dendrites suggests local production of BDNF protein, and several lines of evidence support the existence of BDNF protein as well as a functional role for it in the dendritic compartment. Indeed, disruption of dendritic localization of *Bdnf* transcripts leads to deficiencies in dendritic spine morphology and long-term potentiation.⁴⁴ In addition, EM studies in intact brain localized endogenous BDNF to post-synaptic compartments^{5, 45}, although a caveat to the earlier EM studies was that appropriate age matched BDNF KO controls could not validate the specificity of the immunoreactivity. Finally, a series of electrophysiological studies in dissociated neuronal cultures, as well as hippocampal slices have implicated that postsynaptic BDNF release is required for certain synaptic events including enhancement of presynaptic glutamate release, as well as homeostatic synaptic plasticity.⁴⁶⁻⁴⁸

In this context, a recent study by James McNamara's and Ryohei Yasuda's laboratories elegantly demonstrated a role for newly synthesized BDNF in postsynaptic dendritic spines in a form of neuronal plasticity termed structural long-term potentiation (sLTP). While previously BDNF had been implicated in this form of structural plasticity involving rapid enlargement of dendritic spines, the source of BDNF was not specified.⁴⁹ Utilizing a series of live cell-imaging techniques, as well as a series of BDNF and TrkB receptor knock-in and knock-out mice, they were able to demonstrate the role of postsynaptically synthesized BDNF in eliciting autocrine BDNF/TrkB signaling in individual dendritic spines. They utilized two-photon fluorescence lifetime imaging combined with fluorescence resonance energy transfer (FRET)-based sensor for TrkB receptors to assess BDNF-dependent receptor activation after sLTP induction by single spine glutamate-uncaging.⁵ They detected, rapid onset of TrkB receptor activation, as well as BDNF release from spines utilizing BDNF that was fused to pH-sensitive fluorophore (superecliptic pHluorin; SEP). The study also directly demonstrated by immune-EM the existence of endogenous BDNF protein in an epitope-tagged BDNF knock-in mouse line (BDNF-HA) in the intact mature hippocampus. The HA-immunoreactivity was found both presynaptically (axons, terminals) and postsynaptically (dendrites, spines) in vesicular compartments. In addition, selectively knocking out BDNF in post-synaptic CA1 neurons, led to deficits in sLTP, which could be rescued by addition of BDNF.

These findings do come with caveats, such as that ectopic overexpression of pHluorin-fused BDNF has the limitation of possibly not representing endogenous conditions. Also, the subcellular localization findings are different than those reported from the previous BDNF EM study³, which did not detect BDNF immunoreactivity in dendrites or spines. As noted above, localization of endogenous BDNF to both pre and postsynaptic compartments may be due to differences in sensitivity of the antibodies utilized (anti-HA vs monoclonal anti-

BDNF). Even with these caveats, the latter study is noteworthy as it demonstrates the contribution of postsynaptic BDNF on structural and functional plasticity. It is intriguing to speculate that postsynaptically localized *Bdnf* transcripts would produce BDNF protein that would be packaged into vesicles for release from dendrites that were separate in class from presynaptic DCV's containing BDNF. In the hippocampus, it has been demonstrated that other neuropeptides, such as dynorphin can be secreted from postsynaptic sites in a manner distinct from presynaptic dynorphin secretion.^{50, 51} However, in neuronal dendrites there is sparse distribution of DCV's, suggesting that there may also be specialized structures for postsynaptic BDNF protein production, packaging, and release. Finally, another study from this same group demonstrated that the postsynaptically released BDNF from one dendritic spine is capable of priming neighboring dendritic spines for subsequent structural plasticity – a finding that suggests that postsynaptically released BDNF can have a different impact than presynaptically released BDNF on synaptic plasticity within a set of synapses.⁶

Clinical Implications

BDNF signaling has been linked to the etiology of depression and implicated in the action of traditional antidepressant therapies (including SSRIs, TCAs, and ECT). Importantly, several recent reports have established that BDNF plays a critical role in contributing to the synaptic plasticity mechanisms underlying the fast-acting antidepressant effects of ketamine and other NMDA receptor antagonists.^{52–54} Decreases in *BDNF* expression have been identified in a number of brain regions, including the prefrontal cortex and hippocampus, of individuals with mood disorders.^{55–59} Moreover, the expression of *BDNF* is increased in depressed patients after administration of antidepressants.^{57, 60} Deletion of the *Bdnf* gene in a number of mouse models attenuates behavioral responses to antidepressants and infusion of exogenous BDNF into the ventricles or the hippocampus has antidepressant effects.⁶¹

The recent studies discussed above highlight the possibility that BDNF biosynthesis and secretion occurs at different synaptic sites thereby allowing for multiple levels of regulation by a single growth factor. In this context, the precise subcellular localization of BDNF has significant implications for multiple classes of antidepressant treatments in which elevating BDNF levels is considered a main downstream mechanism of action.^{62–67} As such, these recent studies open up new questions about which pools of BDNF, and from which cell types, are being affected by different antidepressant treatments. For example, postsynaptic BDNF biosynthesis may be particularly noteworthy in the quest to elucidate the mechanism of action of the glutamatergic receptor modulator, ketamine, an NMDA receptor antagonist, which has been demonstrated to lead to rapid and sustained antidepressant responses. By blocking post-synaptic NMDA receptors, it has been shown that ketamine deactivates a kinase (eEF2 kinase), which alleviates a block on BDNF translation, resulting in rapid (within 30 minutes) BDNF protein synthesis.⁵² Of note, a recent preclinical study in mice showed that metabolites of ketamine have rapid antidepressant effects that are independent of the NMDA receptor. Specifically, they report that the (2*R*,6*R*)-hydroxynorketamine metabolite has antidepressant effects that do not require NMDARs, but do involve alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic (AMPA) receptor activation as well as rapid upregulation of BDNF expression.⁶⁸ However, whether the antidepressant activity of (2*R*,6*R*)-hydroxynorketamine *requires* BDNF has not yet been tested. Moreover, the

challenge to the view that the primary mechanism by which ketamine mediates its antidepressive qualities is via NMDAR antagonism, has fueled substantial debate in the field.^{69–71} Definitive answers to these important questions, including the extent to which BDNF is required for the behavioral effects of ketamine and its metabolites, will require further investigations.

Since it was traditionally assumed that ketamine acts on postsynaptic NMDA receptors, these recent BDNF studies discussed here suggest that pharmacological agents used to alleviate symptoms of depression, including ketamine, could also be selectively enhancing the rapid synthesis of a postsynaptic pool of BDNF. It is tempting to speculate that the rapid, yet sustained, effects of glutamatergic modulators, including ketamine, may differ from conventional antidepressants in that the pool (or pools) of BDNF that are being upregulated may lead to enhancement of BDNF-TrkB signaling at separate synaptic sites. Expression of dendritic BDNF may be particularly important in the context of mechanisms underlying rapid acting antidepressants because it has been demonstrated that BDNF application to isolated dendrites results in increased local translation in dendrites, a process which is critical for spine remodeling and synthesis, synaptogenesis and induction of synaptic plasticity.⁷² Thus, future antidepressant therapeutic development efforts may involve strategies to selectively elevate these separate pools of BDNF at the synapse (neuronal, astrocytic, microglia) that may lead to distinct functional outcomes. Given that individual *Bdnf* transcripts may differentially contribute to separate pools of BDNF at alternate synaptic sites, the unique *Bdnf* promoters as well as the 5' and 3' UTR sequences themselves are potentially promising candidates.

Conclusion

These recent series of studies highlight how BDNF biosynthesis and secretion can occur at different synaptic sites thereby allowing for multiple levels of regulation by a single growth factor. In particular, the studies highlight one theme in which even though the majority of BDNF that can be detected using current methodologies is stored and secreted from presynaptic sites, microglia, astrocytes and neuronal dendritic spines can produce and secrete BDNF at lower levels that can have qualitatively significant functional outcomes. Future studies undoubtedly will address the main questions in determining the precise mechanism on biosynthesis and release of BDNF, and relative impact of BDNF from these alternate synaptic sites in terms of in vivo consequences. Equally important will be a renewed focus on the downstream effects of secreted BDNF interacting with not only the selective populations of TrkB receptors, which are localized on the various constituents of the synapse (Figure 1), but also the array of other BDNF receptors and co-receptors (truncated TrkB, p75, SorCS2, and Slitrk5), which are also present at the synapse.^{17, 73–75} As example, as noted above, it has been shown that postsynaptically released BDNF from one dendritic spine can interact with postsynaptic TrkB receptors in neighboring dendritic spines to mediate heterosynaptic plasticity.⁶ Thus, understanding the basic cell biology of BDNF and its receptors at the synapse will continue to provide insights into the myriad of functions of this neurotrophin in both normal and pathological conditions.

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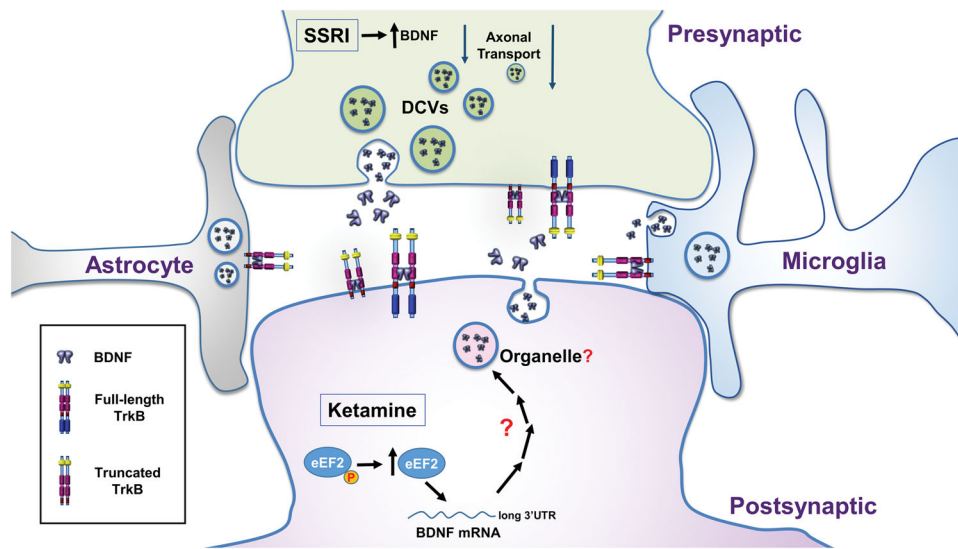


Figure 1. BDNF and its receptors at the mature synapse

Schematic of synapse showing localization of BDNF and its receptors in presynaptic, postsynaptic neuronal compartments, as well as from astrocytes and microglia. BDNF is stored in dense core vesicles (DCV) in the presynaptic compartment. The storage organelle for BDNF in the other synaptic components has not been identified. Conventional antidepressants (such as SSRI) elevate presynaptic BDNF, while ketamine has been postulated to enhance postsynaptic BDNF protein translation. While neurons express full-length TrkB as well as truncated TrkB with developmental and pathologically changing levels, non-neuronal cells mainly exhibit expression of truncated TrkB.^{76–78}