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INVITED REVIEW

Deconstructing brain-derived neurotrophic factor actions in adult brain circuits to bridge an existing informational gap in neuro-cell biology

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Abstract

Brain-derived neurotrophic factor (BDNF) plays an important role in neurodevelopment, synaptic plasticity, learning and memory, and in preventing neurodegeneration. Despite decades of investigations into downstream signaling cascades and changes in cellular processes, the mechanisms of how BDNF reshapes circuits *in vivo* remain unclear. This informational gap partly arises from the fact that the bulk of studies into the molecular actions of BDNF have been performed in dissociated neuronal cultures, while the majority of studies on synaptic plasticity, learning and memory were performed in acute brain slices or *in vivo*. A recent study by Bowling-Bhattacharya et al., measured the proteomic changes in acute adult hippocampal slices following treatment and reported changes in proteins of neuronal and non-neuronal origin that may in concert modulate synaptic release and secretion in the slice. In this paper, we place these findings into the context of existing literature and discuss how they impact our understanding of how BDNF can reshape the brain.

Key Words: *BONLAC; BDNF; adult slice proteomics; neuroproteomics; SILAC; BONCAT; hippocampus; protein synthesis*

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Introduction

Brain-derived neurotrophic factor (BDNF) was first purified by Barde et al. (1982) and was quickly established as a key factor in neurodevelopment that influences the survival of cultured embryonic chick spinal sensory neurons. Subsequently, BDNF was shown to have important roles in learning and memory and synaptic plasticity. Specifically, BDNF is involved in the conversion of short-term memories to long-term memories in inhibitory avoidance training, reconsolidation of fear extinction (Alonso et al., 2002; Lu et al., 2011; Radiske et al., 2015) and the facilitation of long-term potentiation (LTP), a well-described electrophysiological correlate of learning and memory (Patterson et al., 1996; Lu et al, 2011). Preincubation of hippocampal slices from juvenile rats with BDNF led to LTP following theta-burst stimulation, suggesting that BDNF alters synaptic release properties (Figurov et al., 1996). BDNF treatment for 24 hours also increased the frequency of release in slice cultures from young rats, further suggesting changes in synaptic transmission following treatment with BDNF (Tyler and Pozzo-Miller, 2001). In parallel BDNF was shown to induce structural changes in neurons by increasing synapto- and dendridogenesis (Yoshii et al., 2007; Bednarek and Caroni 2011) which again correspond to changes in plasticity in response to various stimuli. Finally, *via* its protective influence on neural progenitors and promoting neuronal differentiation, BDNF is thought to be a major mediator of neurogenesis and cognition (Bath et al., 2012).

Conversely, dysregulated BDNF secretion and/or signaling have been shown to be awry in a plethora of disease conditions ranging from schizophrenia, depression, and anorexia to autism. The known human Val to Met single nucleotide polymorphism alters plasticity in a mouse compared to wild-type littermates. This polymorphism occurs at nucleotide 196, resulting in a valine to methionine substitution (Val66Met) and is associated with reduced episodic memory and reduced hippocampal fMRI response in humans (Egan et al., 2003). BDNFMet/Met mice that model this mutation have reduced NMDA-dependent EPSP amplitude and impaired LTP (Ninan et al., 2010). Taken together, these studies

strongly implicate that BDNF facilitates LTP and alters synaptic release as part of its mechanism of action and thus, that these functions of BDNF may be critical for healthy cognitive function.

Much work has also been performed on understanding the molecular consequences of BDNF exposure, such as the pro-translation action of BDNF, *i.e.*, in how it regulates the process and how it mediates local translation. BDNF binding to its cognate Tropomyosin-receptor kinase B (TrkB) or p75 neurotrophin receptor ($p75^{NTR}$) usually activates canonical receptor tyrosine kinase cascade signaling to Ras-MEK-ERK1/2 pathways. It induces the Akt-mTORC1 and PLC gamma pathways all of which either individually or in concert mediate the multiple cellular effects of BDNF including transcription, translation, degradation and trafficking (Chao, 2003).

Identification of proteins that are induced upon BDNF stimulation has been of particular interest, as they may lead to an understanding of the specificity of trophic factors that use similar signaling pathways and how they are altered in disease. It is here that one finds a rather large disconnect in the experimental systems that have been used to investigate the phenomenon. An overwhelming number of BDNF molecular studies have been performed in neuronal culture systems (Liao et al., 2007; Genheden et al., 2015). In contrast, the majority of the information on how BDNF modulates the synapse stems from experiments in slice electrophysiology where neurons have developed together in a spatially, temporally and molecularly restricted fashion (Kang et al., 1995; Scharfman et al., 1999). To name some of the difference between these two systems: 1) cultures form a single layer of largely homogenous cells that are separated from their developmental environment and re-plated as individual neurons that form random connections, while slices contain multiple layers that develop in a genetically-encoded spatial pattern. 2) Neurons in culture and mature brain slices are derived at dissimilar developmental time points (embryonic compared to adult). 3) Brain slices contain multiple cell-types, including neurons, glia, and endothelial cells, whereas neuronal cultures are largely made up of neurons. To date, over 15,000 studies have been performed on BDNF, and while these have increased knowledge on its role in development, learning and memory, and signaling cascades, the mechanism by which it modifies circuits to induce changes in plasticity and learning and memory in a mature circuit remains unclear. Hence there is a pressing need to investigate whether the BDNF translational response in a slice is identical or equivalent to that in a dish. Since BDNF is a large, very basic protein that does not readily penetrate tissues, the application of BDNF was problematic in clinical trials (Thoenen and Sendtner 2002).

In Bowling-Bhattacharya et al., 2016, we adapted existing technique for measuring global translation rates (BONCAT/FUNCAT) and proteomic dynamics (SILAC) to ask how does an adult hippocampal slice as whole respond to BDNF and which proteins were newly synthesized following 1 hour of BDNF treatment. This adaptation of the two techniques was needed since they were both tailored to and heretofore used in culture systems. BONLAC (BioOrthogonal Non-canonical Labeling of Amino acids in Circuits or Culture) allowed for the isolation of the *de novo* proteome (BONCAT) and the direct quantitation and comparison between the BDNF and control treated groups (SILAC). The most apparent and initial observation from just measuring the translation response in slices was that there was a gradation in response of the slice from the outside to inside layers. The BDNF-induced uptick in translation was previous noted in studies that used radioactive methionine labeling and BONCAT in cultured neurons and cortical homogenates (Takei et al., 2004; Dieterich et al., 2010). The application of FUNCAT allowed for the visualization of translation throughout layers of the slice, as well as soma and dendrites. Compared to CA1, the dentate gyrus (DG) showed a higher response to BDNF-mediated protein synthesis. Whether this response might be enhanced in newly generated neurons in the DG remains to be explored. Not shown in the paper was the observation we made that incubating slices for shorter times, caused a partial wave of protein synthesis to propagate in the cell layers which did not reach the center. Also, the way BDNF is applied to cell cultures and slices (slow or fast) has been found to influence downstream signal transduction differently (Ji et al., 2010). This has important consequence in interpreting the electrophysiological data gleaned from slices. Typically in an LTP experiment, BDNF is applied for 10–15 minutes and the cell populations responding in evoked field EPSC or miniature EPSPs are thought to be the layers immediately beneath the exterior of the slice and not the mid most layer. This is empirically measured at the response in mV that is considered acceptable for a given baseline. The fact that this correlates well with the cell layers where we see maximal BDNF evoked response is a cell biological correlate that is not possible when the experimental system is a monolayer of neurons. A noteworthy fact is that the high affinity of BDNF to existing TrkB and $p75^{NTR}$ on the hippocampal slice (Rodriguez-Tebar and Barde, 1988) precludes actual penetration of the ligand past the first 2–3 cell layers. As a result the response seen in the mid-most part of the slice is likely due to evoked signaling cascades or BDNF-induced BDNF release. The proteomic analyses in Bowling-Bhattacharya et al. (2016) does detect BDNF synthesis in slices within the time period of the experiment, which lends support to the notion.

A compelling finding of the work was for the first time visualizing components other than neurons responding to BDNF stimulation. While we did not use cell-type specific markers to isolate neuronal *vs.* glial cells (which can be performed in future studies using a new BONCAT techniques tom Dieck et al., 2015) we saw consistently structures that were either blood vessels or capillaries that were responding to BDNF in the hippocampal slice. The notion that BDNF impacts non-neuronal cells is not new, but work supporting this has been done in pure cultures of glia or pericytes. BDNF,

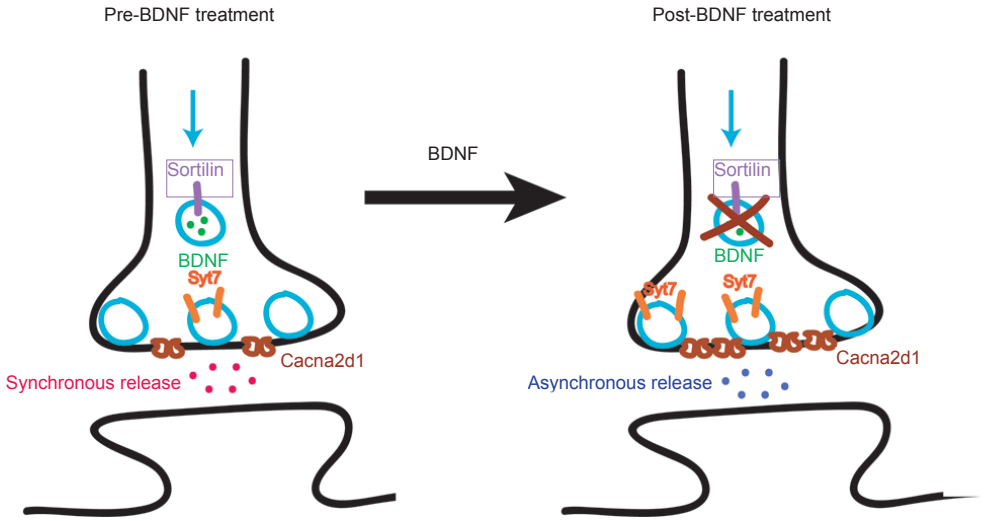

Figure 1 Schematic of proposed pre-synapse before and after brain-derived neurotrophic factor (BDNF) treatment.
Before BDNF treatment, Synaptotagmin-7 (Syt7), Voltage-Gated Calcium Channel Subunit Alpha-2/Delta-1 (Cacna2d1) and Sortilin-1 (Sort1) are expressed at normal levels. Following one hour of BDNF treatment, Syt7 and Cacna2d1 are upregulated and Sort1 is downregulated suggesting a potential shift in synaptic release.

Table 1 Proteins listed in blood-related Gene Ontology categories

Protein name	Gene name
Hemoglobin alpha, adult chain 1	*Hba-A1, Hba1*
Peroxiredoxin 1	*Prdx1, Prx1*
Ribosomal protein S6	*RpS6*
Ribosomal protein S19	*RpS19*
ATPase, H^+ transporting, lysosomal V0 subunit A1	*Atp6voa1*
Cysteine rich protein 2	*Crip2*
Protein phosphatase 3, catalytic subunit, beta isoform	*Ppp3cb*
Misshapen-like kinase 1	*Mink1*
Superoxide dismutase 2, mitochondrial	*Sod2*

Proteins identified as potential candidates from the BDNF BONLAC screen in Bowling et al. (2016) underwent Gene Ontology Analysis in DAVID. The following list indicates proteins that were altered with BDNF treatment that correspond to blood related processes (Methods discussed in Bowling et al., 2016). BNDF: Brain-derived neurotrophic factor; BONLAC: BioOrthogonal Non-canonical Labeling of Amino acids in Circuits or Culture; DAVID: The Database for Annotation, Visualization and Integrated Discovery.

a pro-angiogenic factor has been established by studies like Kermani and Hempstead (2007) and Kermani et al. (2005). However candidate proteins that are upregulated due to BDNF in an endothelial population in a slice were unknown.

BONLAC is a combination of BONCAT and SILAC proteomic techniques that enriches for candidates that are synthesized within a specific time window in response to a stimulus. In this paper, Bowling-Bhattacharya et al. (2016) have adapted it to the intact slice. This powerful technique identified over 200 protein candidates altered with BDNF treatment out of over 2,000 measured proteins, a feat that would have been prohibitively difficult without this combinatorial technique, as other techniques either do not allow for direct quantitation or for the isolation and live labeling of *de novo* protein synthesis. The most prominent gene ontology classes involved calcium signaling, neurotransmission and secretion with the validated candidates Synaptotagmin-7 (Syt7), Voltage-Gated Calcium Channel Subunit Alpha-2/Delta-1 (Cacna2d1), and Sortilin-1 (Sort1), featuring prominently in these categories. These three candidates had not been previously shown to be directly regulated by acute BDNF exposure, and were therefore, novel. Syt7 and Cacna2d1 are strongly associated with alterations in synaptic release, while Sort1 is associated with secretion across different cell types. Together, they may indicate a shift in synaptic release in the hippocampus following acute BDNF treatment (**Figure 1**). Genetic ablation studies have detailed a role for Syt7 in clamping synchronous release, vesicle replenishment and asynchronous release (Bacaj et al., 2013; Liu et al., 2014; Weber et al., 2014; Luo et al., 2015). Its upregulation following BDNF suggests a change in synaptic release properties may play a role in the mechanism of action of BDNF.

Changes in the abundance of Cacna2d1 also suggest changes in synaptic transmission. Because voltage-gated calcium channels reside in the active zone of the pre-synapse and regulate Calcium (Ca^{2+}) influx, it has long been hypothesized that they are involved in synaptic release. Cacna2d1 is a voltage-gated calcium channel subunit, and has been previously been shown to increase the probability of neurotransmitter release and to prevent negative regulation of this release by chelating Ca^{2+} (Arikkath and Campbell, 2003; Hoppa et al., 2012). In addition, mutations in the *CACNA2D1* gene in humans is associated with epilepsy and intellectual disability, further implicating Cacna2d1 as having an important role in regulating synaptic function. Together, these data strongly implicate that BDNF treatment-induced changes in Cacna2d1 may result in increased synaptic release and changes in Ca^{2+} dynamics.

Although the validation of candidates focused on those involved in synaptic release, we also obtained a highly enriched gene ontology class which included KEGG pathways for cardiac muscle contraction, hypertrophic cardiomyopathy,

dilated cardiomyopathy and arrythmogenic right ventricular cardiomyopathy (Supplementary Table S2 of Bowling and Bhattacharya et al., 2016) with an enrichment score of 4.32, which is higher than the regulation of actin cytoskeleton and calcium binding group at 3.95 and 3.87 respectively. Of the top 10 most regulated candidates from the screen only 3 are known to be expressed in neurons only. Interestingly proteins like CACNAG, Necab1/2, Mien1, Me1 are known to be highly expressed in the heart and muscles with protein forms known to express in the brain. Of the 3 validated candidates, Sortilin 1 is a known mediator of endocytosis in endothelial cells (Jin et al., 2008; Prabhakaran et al., 2012). Sort1 also indicates changes in neuronal secretion and synaptic plasticity, as it has been previously shown to control both BDNF trafficking throughout the cell and its activity-dependent secretion (Chen et al., 2005). However it is also of interest as it is an important protein in lysosomal degradation, and trafficking of receptors to the synapse, including Trks (reviewed in Lane et al., 2012). Although Sort1 has been heavily implicated in BDNF secretion and in response to synaptic actions, this is the first known demonstration of BDNF regulating Sort1 expression. Because Sort1 regulates activity-dependent BDNF secretion, its downregulation following BDNF treatment may indicate negative feedback of further BDNF release and alterations in Trk trafficking, however it bears further investigation.

In addition to proteins with synaptic plasticity and muscle associations, the gene ontology analysis indicated proteins associate with blood cell signaling and development (**Table 1**), consistent with the previously stated observation of increased FUNCAT in blood vessels. These data are interesting as the bulk of the studies of synaptic plasticity in the brain have centered on the effects of neurons in synaptic plasticity, very little attention has been paid to other cell types in the brain such as the different forms of glia and the blood vessels. For instance, it is well established that changes in blood flow and oxygen highly correlated to brain activity, as this is the basis of functional magnetic resonant imaging (fMRI) (reviewed in Logothetis, 2003). Therefore, despite the neuronal focus of synaptic plasticity, there do appear to be changes in blood that correspond to neuronal activity in the brain.

There are additional data suggesting a more direct relationship between the blood and synaptic plasticity in addition to a correlation between changes in the blood and neuronal activity in the brain. Blood and plasma from young mice has been shown to improve learning and memory performance and spine density in older mice, whereas denatured plasma did not (Villeda et al., 2014). This is consistent with other studies showing that poor blood flow in the hippocampus correlated with poor behavioral learning performance (Manschot et al., 2002). The evidence of interaction between blood flow and potentially important other protein-based factors and cognitive function has been heavily based upon fMRI and blood supplement and behavior studies. However, the precise role that BDNF may play in this function remains a question.

One way that BDNF interplays with the vascular system is through its receptors on blood vessels. BDNF can interact with multiple receptors, including its primary receptor TrkB, its truncated isoforms and $p75^{NTR}$. TrkB has been shown to be present in blood cells (genecards.org, Nassenstein et al., 2006), blood vessels (Wagner et al., 2005), and in pericytes that help form the blood-brain barrier (Anastasia et al., 2014). TrkB signaling is important for the development of vasculature as disruption of TrkB leads to improper and sparse development of blood vessels and that signaling through it can stabilize them (Wagner et al., 2005; Anastasia et al., 2014). Pericytes also perform a critical support function in the blood-brain barrier where they regulate endothelial cells, astrocytes, and blood-brain barrier permeability (Armulik et al., 2010). TrkB expression can also be found in other non-neuronal cells such as oligodendrocytes and astrocytes (Frisen et al., 1993), further suggesting a non-exclusive action on neurons following BDNF treatment. With the noted difference in BDNF-induced protein synthesis in the brain, and these previous studies, it begs the question of whether BDNF may play a role in the relationship between non-neuronal cells and synaptic activity.

Summary

The findings of Bowling and Bhattacharya et al. (2016) strongly suggest new molecular targets of BDNF action and suggest new hypotheses of the mechanism of BDNFs effect on synaptic plasticity (**Figure 1**). In addition, it was noted that non-neuronal associated proteins were altered with BDNF treatment suggesting that the circuit affected by BDNF does not only include neurons, but instead builds on previous evidence that interaction with the blood and other non-neuronal cells may also be important for synaptic plasticity. This study provides new data that is important in understanding the mechanisms of action of BDNF and shapes new research questions for the field to finally answer the question of how a small ligand such as BDNF can so profoundly alter circuits and be responsible for large-scale changes in learning and memory.

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