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Chapter

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Summary

Synaptogenesis is encoded by multiple genes that program the assembly of neural networks in the immature brain during development and later in life, in the experienced brain that must respond to changes of the external world and of proprioception. Processing of neural network activity cannot solely rely on the activity of established synapses as their plasticity can saturate. For this reason, synaptogenesis is reversible. Assembly and disassembly of synapses depend on the exchange of signals between the pre- and post-synaptic terminals. Synaptic trophic factors are paramount for neural network remodeling, homeostasis and survival because they are present in limited supply. Neurotrophins present the necessary attributes to operate as synaptic trophin. It is speculated that many diverse and pleiotropic actions of neurotrophins on the synapse depend on the sources of neurotrophin ligands, its modes of secretion and signaling, all influenced by their locations at the synapse. What information is encoded when synaptic neurotrophin signaling is retrograde or anterograde, paracrine or autocrine? Answers emerged from the characterization of the cells that secrete neurotrophins, the cells that respond to neurotrophins, the various modes of secretion, receptor-signaling pathways, and the temporal constraints imposed by synaptic transmission. Failure to communicate the appropriate synaptic trophic signals impairs neuronal networks maintenance and updated wiring.

Keywords:

BDNF, Autocrine-paracrine, anterograde-retrograde signaling, P75NTR, Sortilin-related receptors, TrkB, LTP-LTD, mTOR, Actin, Val66met polymorphism

I. Introduction

Exchanges of anterograde and retrograde signals between synaptic connections serve to adjust input-to-output. In the absence of bi-directional trans-synaptic signaling, the changes of synaptic strength would decay and information lost (Harris, 2008). As a result, the anterograde signaling in target post-synaptic cells should be consolidated by back-propagating signals in the target pre-synaptic cells. To be efficient, trans-synaptic signals shall present specific features: (i) it shall be produced in a limited amount; (ii) it shall be dependent on synaptic activity; (iii) it shall be poorly diffusible; (iv) it shall be emitted when pre- and post-synaptic activities are correlated; (v) receptors shall emit specific signaling on every sides of the synapse via anterograde and retrograde pathways.

For decades, evidence were collected to demonstrate that neurotrophins operate in a trans-synaptic and bi-directional fashion for regulating synaptic plasticity and strength within active but not resting neuronal networks (Autry and Monteggia, 2012; Bennett and Lagopoulos, 2014; Castren and Antila, 2017; Choi, 2018; Cohen-Cory et al., 2010; Hao et al., 2018; Lessmann, 1998; Lu and Chow, 1999; Panja and Bramham, 2014; Park and Poo, 2013; Poo, 2001; Tyler et al., 2002). Two examples: (i) anterograde spread of the trans-synaptic neurotrophin rescued the lack of input activity on post-synaptic cells (Chen et al., 2016; Du et al., 2009), and (ii) retrograde transport of target-derived neurotrophin via signaling endosomes can extend from axon terminals to dendrites where it instructs molecular composition of postsynaptic densities (Sharma et al., 2010). Of all the neurotrophins, brain derived neurotrophic factor (BDNF) is best characterized. BDNF is available in limited supply at the synapse. Bulk BDNF is extrasynaptic (Swanwick et al., 2004), secreted upon synaptic activity (Nagappan and Lu, 2005), and captured by receptors lacking the tyrosine kinase domain on astrocytes upmost and neurons (Bergami et al., 2008; Biffo et al., 1995; Stahlberg et al.). Yet, the synapse is its primary site of actions on neurons (Song et al., 2017). BDNF packed in dense core vesicles of the pre-synapse ensures anterograde signaling (Dieni et al., 2012) whereas dendritic BDNF in the post-synapse and in microglia contribute to the anterograde signaling (Hedrick et al., 2016; Parkhurst et al., 2013).

The paucity of neurotrophins results from an active process with temporal and spatial resolutions that permits synaptogenesis and competition between synapses of

different projecting axons (Cohen-Cory et al., 2010; Snider and Lichtman, 1996). This is essential for synaptic scaling of both excitatory and inhibitory neurons to maintain homeostasis (Gottmann et al., 2009) but also for synaptic potentiation, including the induction, maintenance and consolidation phases (Poo, 2001). Therefore, it is interesting that synaptic priming with BDNF can convert weak synaptic activity into robust potentiation by post-synaptic mechanisms (Figurov et al., 1996; Kovalchuk et al., 2002; Wierenga et al., 2005).

One way to restrict neurotrophin responsiveness to active synapses is to pair neurotrophin signaling with neuronal activity (Boulanger and Poo, 1999; Tanaka et al., 2008). Neuronal activity originating from both pre- and post-synaptic sides can stimulate the secretion of neurotrophins, which may result in strengthening and maintenance of active synapses (Castren and Antila, 2017; Jakawich et al., 2010). In contrast, synapses with unsynchronized activity between the pre-and post-synaptic terminals do not receive neurotrophin support and are weakened (Jakawich et al., 2010; Poo, 2001; Snider and Lichtman, 1996).

This chapter will enumerate the attributes that permit BDNF to instruct circuit-specific responses devised to enforce circuit adaptation to changing environment (*e.g.* behavior, perception-anticipation, drugs, diseases). Neurotrophin responses rely on a trans-synaptic molecular system consisting of multiple ligands and receptors, which specificity, sensitivity and location matter (Song et al., 2017).

II. One neurotrophin, three ligands at the synapse

Neurotrophins are synthetized as precursors (proneurotrophins) with a N-terminal prodomain and a C-terminal mature domain. Classically, neurotrophins must be cleaved off their prodomains to be operational. That is to promote synaptic and non-synaptic growth and differentiation via rapid signaling routes and long lasting changes in gene transcription (see other reviews (Gonzalez et al., 2016; Hempstead, 2006; Woo et al., 2005). This view came with the assumption that the proforms of all neurotrophins are inactive. But proforms are signaling molecules as well (Hempstead, 2015; Mizui et al., 2017).

II.1 Pro-BDNF

Like all neurotrophins, BDNF is synthetized as a large precursor called proBDNF. This precursor is approximately a 32kDa peptide that is glycosylated in the N-terminal prodomain region (Mowla et al., 2001; Mowla et al., 1999). Following synthesis in the endoplasmic reticulum (ER), proBDNF is directed to the secretory pathway. ProBDNF can be cleaved to prodomain and mature BDNF in the Golgi apparatus or in secretion vesicles but, during early development, substantial amounts of proBDNF can escape processing. Trafficking occurs in the trans Golgi network (TGN) where proBDNF interact with the type 1 receptor sortilin (Chen et al., 2005b). Sortilin is a member of a group of receptors containing a vacuolar sorting protein 10 (VPS10) domain that acts like chaperones to target their cargo protein to different cellular compartments (Nykjaer and Willnow, 2012). By interacting with the prodomain, sortilin acts as a chaperone for intracellular trafficking and directs proBDNF into dense-core vesicles destined to the activity dependent secretory pathway (Dieni et al., 2012; Mowla et al., 1999).

Yet, an interaction with sortilin is also necessary to engage BDNF toward the lysosomal pathway (Evans et al., 2011). Two mechanistic frameworks explain how proBDNF is sorted toward secretory or degradation routes. First, targeting of sortilin and its proBDNF cargo to the lysosomal pathway relies on the cleavage of sortilin by ADAM 10 (Evans et al., 2011). Second, targeting of sortilin and its proBDNF cargo to the secretory pathway required physical interaction with the huntingtin interacting protein 1 (HAP1) (Yang et al., 2011).

A separate mechanism involves a common human single nucleotide polymorphism (SNP) on the prodomain of BDNF. The Val66Met polymorphism is the result of a nucleotide change from a guanine to an adenine at position 196 (G196A) substituting a valine (Val) to methionine (Met) at codon 66. The SNP was reported to alter the transport of BDNF mRNA transcripts to dendrites for local synthesis of BDNF (Chiaruttini et al., 2009). The Val66Met substitution also disrupts the interaction between the proBDNF and sortilin, resulting in defects of transport, maturation and subcellular sorting (Chen et al., 2005b; Egan et al., 2003; Sasi et al., 2017).

II.2 Cleavage of proBDNF

Mature BDNF is a 14KDa peptide with well-characterized trophic and plasticity abilities that have been extensively reviewed elsewhere (Binder and Scharfman, 2004; McAllister et al., 1999). Mature BDNF results from proteolytic cleavage of proBDNF. Following synthesis in the ER, proBDNF can undergo processing directly in the Golgi apparatus by furin or within secretory vesicles of the regulated pathway by other proconvertases (Mowla et al., 1999). The cleavage of proneurotrophins by furin occurs at the consensus sequence R–X–K/R–R, (RVRR in proBDNF) to produce mature neurotrophins and prodomains. Furin cleaves proBDNF at Arg 128 of the consensus site. The mutation of this consensus site from RVRR to RVAA (Yang et al., 2014) or MVLR (Koshimizu et al., 2009) has been instrumental to produce a cleavage resistant proBDNF insensitive to furin and plasmin, and has been exploited to produce recombinant uncleavable proBDNF to demonstrate its biological activity in vitro and in vivo (Koshimizu et al., 2009; Pang et al., 2004; Teng et al., 2005; Yang et al., 2014). Other proconvertases, such as PACE4, PC5, and PC7, have been shown to process proBDNF in mature BDNF and prodomain utilizing the same RVRR site (Marcinkiewicz et al., 1998; Seidah et al., 1996; Wetsel et al., 2013).

When proBDNF escape intracellular cleavage by furin or other proconvertases, it can be found in the dense-core vesicles destined to the secretory pathway. The existence of secreted proBDNF was the subject of an intense debate that we will discuss later in this chapter, but if secreted, proBDNF can be converted into mature BDNF and prodomain by extracellular proteases. The most prominent of these proteases is plasmin, which is the product of the activation of the inactive plasminogen by tissue-type plasminogen activator (tPA). The specific plasmin cleavage site of proBDNF was identified and found it to be located within the consensus furin-cleavage sequence of BDNF, but occurring after Arg^{125} rather than Arg^{128} of the RVRR sequence (Gray and Ellis, 2008). Interestingly, a SNP has been identified at position 125, which induces an arginine substitution for a methionine that would potentially prevent plasmin processing of proBDNF (Koshimizu et al., 2009). Multiple regulatory steps are implicated in this reaction as conversion of plasminogen to plasmin is antagonized by Plasminogen activator inhibitor (PAI1), and PAI1 depends on vitronectin to remain active (Mou et al., 2009). Furthermore tPA is an extracellular serine protease which secretion is stimulated

by neuronal activity (Shin et al., 2004). The fact that both proBDNF/BDNF/prodomain containing vesicles and tPA are secreted in an activity dependent fashion raises questions about regulation of bio-available tPA. For instance, a reduction of tPA secretion may be enough to favor proBDNF signaling and vice and versa. ProBDNF can be processed by selected matrix metalloproteinases (MMPs) such as MMP-3 and MMP-7 (Lee et al., 2001). Moreover, it has been shown that MMP-9 converts proBDNF into mature BDNF after kindled seizures in the hippocampus (Mizoguchi et al., 2011).

All these intra- and extracellular enzymes cleave proBDNF at distinct but interdependent sites, all generating biochemically undistinguishable mature BDNF and prodomain species. No distinct biological functions of the mature BDNF cleaved by one or the other proteases have ever been reported to our knowledge.

II.3 The prodomain

The prodomain is a 15.5kDa protein recently found to be very abundant in the hippocampus and results from the proteolytic cleavage of pro-BDNF at the site that also produce mature BDNF (Anastasia et al., 2013; Dieni et al., 2012). The BDNF prodomain is detected in dense core vesicles in vivo and found to be secreted as ligand (Anastasia et al., 2013; Mizui et al., 2015) independent of mature BDNF and proBDNF. BDNF prodomain facilitates hippocampal long-term depression (LTD) by a mechanism involving the internalization of AMPA receptors from the synapse (Mizui et al., 2015). Interestingly, the Val66met polymorphism of BDNF positioned in the prodomain alters the reported structural conformation (Anastasia et al., 2013; Wang et al., 2018), subcellular sorting and transport (Arango-Lievano et al., 2015a; Zanin et al., 2017), as well as activities of the prodomain: (i) Met66 carriers impaired the expression of LTD (Mizui et al., 2015), (ii) Met66 carriers elicited growth cone collapse (Anastasia et al., 2013) and (iii) Met66 carriers promoted dendritic spine elimination (Giza et al., 2018) as opposed to its counterpart the val66 carriers that facilitated LTD with no effects on axonal growth cones or dendritic spine turnover.

III. Which side of the synapse produce neurotrophins?

Neurotrophin ligands are expressed by a multitude of neuronal cells, for the most part excitatory (*e.g.* glutamatergic) and neuromodulatory (*e.g.* dopaminergic, serotoninergic, adrenergic…), and non-neuronal cells supporting synaptic functions (*e.g.* glia, vascular cells…). Most neuronal cell types in brain are able to produce some neurotrophin isoforms with the exception of cortical interneurons and striatal medium spiny neurons among others that rely upon paracrine secretion (Kohara et al., 2003). See table 1 for an inventory of single cell types expressing and cells not expressing BDNF mRNA transcripts based on based on the mouse brain atlas of single cell RNA sequencing (http://mousebrain.org/ (Zeisel et al., 2018)).

One issue is that BDNF expression is variable, depending on cues from the internal and external world (Jeanneteau and Chao, 2013). Multiple promoters drive its transcription in specific cell types and upon various stimuli (Aid et al., 2007; Cattaneo et al., 2016). Transcription of BDNF is also susceptible to epigenetic marks that are specific to individuals, possibly transmitted to progeny associated with transgenerational impact on individuals' health (Cattaneo et al., 2016; Kundakovic et al., 2015; Roth et al., 2009; Roth and Sweatt, 2011). One consequence is that BDNF expression pattern may be unique to each individual as it reflects gender, history of living conditions and experiences (Bath et al., 2013).

Expression of the BDNF gene is a reflection of synaptic activity in selective networks of neurons and circuits. That is, BDNF expression is very responsive to neuronal activity from sensory inputs and behavioral conditioning. Therefore, it is specific for neural circuits engaged in excitation and inhibition (Hill and Martinowich, 2016). For example, stimulation of a single whisker increases *Bdnf* genomic expression in the cortical barrel corresponding to that whisker (Genoud et al., 2004). Other stimuli such as physical exercise, experimental seizure, olfaction, fear conditioning, food restriction, auditory and visual cues affect BDNF expression (reviewed by (Hill and Martinowich, 2016; Lu, 2003)). Mechanistically, activity-dependent expression of BDNF is mediated by promoter I and IV, which conditions the amount of BDNF available for vesicular release (Rattiner et al., 2004; Tao et al., 2002). BDNF transcripts containing the exon-I or IV are abundant in soma whereas BDNF transcripts harboring the exon-II or VI are found in distal dendrites (Baj et al., 2011; Chiaruttini et al., 2008). The 3'-UTR of *bdnf* gene

carries information regarding polarized localization for dendritic translation, which is lacking in the somatic shorter isoform (An et al., 2008). As a result the many splice isoforms of BDNF, which encode the same protein, possess alternative regulatory elements necessary for the precise control of its expression in space and time (Tongiorgi et al., 2006). Yet, the vast majority of BDNF mRNA is located in the soma, barely detected in dendrites that advocates for a clear dominance for the anterograde mode of secretion over the retrograde (Will et al., 2013). The source of neurotrophins is important to determine the local effects since neurotrophins diffuse poorly (Wang et al., 1998).

III.1. Presynaptic source of BDNF

Most synaptic BDNF protein is detected in presynaptic dense core vesicles using immuno-electron microscopy with epitope-tagged BDNF expressed with its endogenous promoter in knockin mouse lines (Dieni et al., 2012). In dense core vesicles, all three ligands can be packed with other peptides like cholecystokinin and met-enkephalin (Dieni et al., 2012). This is particularly evident in the mossy fibers projecting from the dentate gyrus to CA3 region of the hippocampus. Elsewhere, BDNF levels are scarces and its protein is detectable mostly in the soma of neurons in the amygdala, cortex, hippocampus, and hypothalamus (Lambert et al., 2013; Lessmann and Brigadski, 2009; Salio et al., 2007; Sasi et al., 2017). It is interesting that BDNF is poorly detectable in the striatum, evidently not expressed in striatal cells, and yet BDNF signaling is essential to the synaptic function and plasticity of medium spiny neurons (Humbert and Saudou, 2005). Reduced BDNF levels in the striatum produce motor defects in Huntington's disease due to a lack of anterograde transport from the cortex (Gauthier et al., 2004; Samadi et al., 2013). Presynaptic storage of BDNF ligands results from anterograde vesicular transport (Gauthier et al., 2004) as well as from local production (Lessmann and Brigadski, 2009) using axonal BDNF mRNA as template given some BDNF isoforms can be transported to the axon terminals (Jung et al., 2012). Remarkably, the highest stocks of BDNF are located at the presynapses of glutamatergic hippocampal neurons (Andreska et al., 2014). This argues strongly for presynaptic BDNF coming from excitatory synapses as a major source. However, the BDNF content is very variable

between individual presynaptic varicosities (Andreska et al., 2014), as it is perhaps recruited to some specific synaptic networks.

Whether presynaptic BDNF is produced in soma and transported or locally at the presynapse could explain how pro-BDNF can escape cleavage (Yang et al., 2009). The source of BDNF stocks could determine the combinations of ligands released in the synaptic cleft.

III.2. Postsynaptic source of BDNF

BDNF is also synthetized in dendrites from which it can be secreted to impact synaptic plasticity (Lessmann and Brigadski, 2009). The source of BDNF necessary to promote pre-synaptic terminal maturation and innervation was investigated using knockdown-rescue experiments. Complete knockdown of BDNF during embryonic development impaired innervation of trigeminal axons, which was rescued when target post-synaptic tissue was replaced with ectopic grafts expressing BDNF (Huang et al., 2007). Therefore, both retro- and post-synaptic BDNF signaling from a post-synaptic source of BDNF are central contributors of pre-synaptic differentiation of both excitatory and inhibitory neurons consistently with the classical hypothesis of target-derived neurotrophic support (Oppenheim, 1989). In dendrites, exogenous BDNF is can be recycled and stored in endosome-like vesicles. Recycling of BDNF in post-synaptic compartment involved synaptotagmin 6, which is distinct from those involved in secretion from dense core vesicles (Wong et al., 2015). Studies in cultured neurons indicate that secretory granules in dendrites and post-synaptic spines are the prime vesicular routes for retrograde secretion of BDNF (Lessmann and Brigadski, 2009).

A quantitative estimate of BDNF content in the synapse using high resolution microscopy dSTORM revealed that 90% of all BDNF synaptic immunoreactivity located in the presynapse (Andreska et al., 2014). Solely 10% overlapped in the post-synapse, again arguing that the retrograde route isn't the principal source for synaptic release of BDNF. One way to explain this 1:9 ratio is by the reuptake of presynaptic BDNF released quanta by the post-synaptic compartment (Santi et al., 2006). However, it is striking that dendritic trafficking of BDNF mRNA is blocked by the Val66Met mutation (Chiaruttini et al., 2009). Therefore, whether produced locally or taken from elsewhere,

post-synaptic derived BDNF content is likely important for synaptic physiology related to the Val66Met polymorphism. Electrophysiological studies indicated that postsynaptic BDNF release is required for the enhancement of presynaptic glutamate release and synaptic plasticity (Harward et al., 2016; Jakawich et al., 2010; Magby et al., 2006). BDNF released optically from one postsynaptic spine can prime the neighboring spines for subsequent structural remodeling (Hedrick et al., 2016). This spreading effect of postsynaptic BDNF is different from that of the presynaptic BDNF, and suggests that BDNF can have different impact depending on its source.

III.3. Non-neuronal source of synaptic BDNF

Other source of BDNF synaptic quantum originates from the astrocytes and microglia (Chung et al., 2015). Microglia produce and secrete low levels of BDNF (Gomes et al., 2013; Trang et al., 2009). This source of BDNF is essential for the maintenance of learning-associated new dendritic spines (Parkhurst et al., 2013). The proportion of glial-derived BDNF with respect to the pre-synaptic source is considered small, but its conditional genetic deletion leads to severe deficits in behavioral performance. This argues that non-neuronal source of BDNF regulates synaptic functions.

One post-synaptic source of BDNF release from non-neuronal cells could come from the recycling of synaptic BDNF by astrocytes. For example, peri-synaptic glia recycles BDNF for LTP stabilization (Vignoli et al., 2016). Engagement of BDNF recycling by astrocytes corresponded with TrkB phosphorylation localized on adjacent neurons, a process required to sustain LTP. Additionally, astrocytes can uptake pro-BDNF via an endocytic compartment competent for pro-BDNF recycling (Bergami et al., 2008). This astrocytic-derived BDNF is important for transmitter-induced secretion and suggests a specialized form of bidirectional communication between neurons and glia.

IV. What are the modes of neurotrophin synaptic release?

Contrary to the neurotrophins NGF (nerve growth factor), NT3 (neurotrophin 3) and NT4 (neurotrophin 4) that are secreted in a constitutive manner, BDNF employs both a regulated and constitutive pathways (Mowla et al., 1999). Electron microscopy indicated that BDNF is not located in the active zone of the presynapse, raising the

possibility that it might be secreted from the sides of the synapse (Lessmann and Brigadski, 2009). Secretion of neurotrophins from both pre- and post-synaptic terminals (referred to as bi-directional release) has been reported upon neuronal activation and back-propagating action potentials (Kuczewski et al., 2008; Magby et al., 2006). Pre-synaptic release of BDNF and NT3 depends on intracellular Ca^{2+} sensor proteins like CASP2 (Sadakata et al., 2007). Vesicular release of BDNF dense core vesicles depends on SNARE complex at least in callosal presynaptic terminals (Shimojo et al., 2015). Post-synaptic release of BDNF and NT3 depends on glutamate neurotransmission via NMDA receptor signaling but is independent of pre-synaptic neurotrophins (Kolarow et al., 2007). Additional mechanisms controlling the secretion of BDNF have been identified. Synaptotagmin-4 and -6 function as retention factors for BDNF-containing vesicles to ensures appropriate quantal release. Indeed, lack of pre-synaptic Synaptotagmin-4 increases spontaneous exocytosis of BDNF whereas loss of post-synaptic Synaptotagmin-4 increases neurotransmitter amplitude due in part to trans-synaptic trigger of neurotransmitter release by BDNF (Dean et al., 2009). Similarly, lack of Synaptotagmin-6 in postsynaptic neurons impaired activity-dependent release of endosomal BDNF from postsynaptic dendrites, which can contribute for activity-dependent synaptic modulation (Wong et al., 2015).

Trans-synaptic quantal scaling, local translation and reuptake of BDNF are consensus mechanisms for explaining the retrograde actions of BDNF (Cohen-Cory et al., 2010). The anterograde actions of BDNF in brain can be autocrine and paracrine (Harward et al., 2016; Hedrick et al., 2016). Remarkably, the Val66met polymorphism of BDNF impairs the regulated secretion by interfering with the binding of sortilin, a trans-Golgi trafficking protein (Chen et al., 2005b; Chen et al., 2006b). This would alter both the autocrine and paracrine effects of BDNF release. Consequently, homozygous carriers of the Met allele have 20% less total BDNF and poorer synaptic functions and hippocampal-dependent memory than Val carriers (Dincheva et al., 2012; Egan et al., 2003; Ninan et al., 2010).

IV.1. Secretion of pro-BDNF

Whether proBDNF can be secreted as a signaling molecule has been the subject of a very intense debate. Observing proBDNF directly in the extracellular milieu of mice is difficult due to the nanomolar concentrations of BDNF and the lack of antibodies that are specific and sensitive enough to identify proBDNF in such quantities. The first evidence of proBDNF secretion was obtained from a pituitary derived cell line (ATt20) infected with a rabies virus expressing recombinant human BDNF. In these conditions proBDNF as well as mature BDNF were found on the culture media of cells (Mowla et al., 1999). These conditions were useful to demonstrate that it is possible for cells to secrete proBDNF, but were very far from physiological as they rely on overexpression, and did not answer whether endogenous proBDNF could be secreted by neurons. Other cell lines including HEK293 and endothelial cell lines infected with adenovirus encoding for BDNF were used to demonstrate that proBDNF is released in the culture media and readily cleavable extracellularly when exposed to recombinant plasmin. On the contrary, the quantities of extracellular proBDNF increased after treatment of cells with the protease inhibitor aprotinin (Lee et al., 2001). Interestingly, high frequency neuronal activity was capable of inducing the secretion of proBDNF alongside with the mature BDNF on hippocampal neurons transduced with a lentivirus for the overexpression of BDNF (Nagappan et al., 2009).

Despite the demonstration of activity-dependent secretion, the yield of extracellular proBDNF remained low compared to the mature BDNF. The results suggested that (i) extracellular proBDNF is unstable, readily cleavable by activity-dependent extracellular proteases (Nagappan et al., 2009) and that (ii) extracellular proBDNF could have escaped intracellular cleavage due to the overexpression experimental approach. This controversy was supported by evidence arguing against the neuronal secretion of endogenous proBDNF (Matsumoto et al., 2008). To avoid overexpression, neuronal cultures were obtained from a knock-in mouse featuring a BDNF gene fused to a Myc tag at the N terminus. This allowed the expression of the BDNF gene under the endogenous promoters and detection of proBDNF and BDNF by very sensitive reagents against the Myc tag.

Although endogenous levels of mature BDNF and proBDNF were detectable in neuronal cell lysates, only the mature BDNF was observed in the extracellular space after

neuronal activation via NMDA receptors (Matsumoto et al., 2008). In this study, inhibitors against plasmin or matrix metalloproteinases to preserve secreted proBDNF were not included in the culture media. Also, mitotic inhibitors were not utilized to avoid glial cell growth, which could have been a source of extracellular proteases. A subsequent study addressed this issue combining a different knock-in mouse to label mature BDNF and proBDNF with a C-terminal HA tag and an antibody raised specifically against proBDNF. Endogenous levels of proBDNF were detected in the conditioned media of hippocampal neuronal cultures in the absence of glial cells, and treated with a plasmin inhibitor (Yang et al., 2009). In cultures, at least part of proBDNF secretion was activity dependent (Yang et al., 2009).

Secretion of pro-neurotrophins *in vivo* suggests there is a mode of escape from intracellular vesicular cleavage by proteases. Pro-BDNF is a proteolytic substrate of the protease tPA (tissue plasminogen activator), which activity-dependent synaptic release (Pang et al., 2004) offers two functional outcomes: (1) under high frequency stimulation of nerve terminals, pro-BDNF detected at active synapses should be cleaved into mature BDNF. In contrast, when low frequency stimulation is applied, pro-BDNF released into the synaptic cleft isn't cleaved, thus producing long-term depression and synaptic destabilization (Woo et al., 2005).

Finally, cortical astrocytes can uptake and recycle proBDNF for subsequent synaptic release in an activity-dependent fashion (Bergami et al., 2008). The release from astrocytes of neuron-derived synaptically uptaken proBDNF can be rapidly re-relased (Bergami et al., 2008).

IV.2. Secretion of the mature BDNF

Several proteases have been shown to cleave proBDNF both in the intracellular and in the extracellular milieu. In some culture conditions, the latter seems to be less prominent than the intracellular cleavage. Indeed, inhibition of the main extracellular proteolytic enzymes did not affect the levels of the secreted prodomain, suggesting that most of the processing occurs within the cells (Anastasia et al., 2013). On the other hand, it has been shown that neuronal activity controls the ratio of extracellular

proBDNF/mature BDNF by regulating the secretion of extracellular proteases, like tPA (Woo et al., 2005).

It is postulated that mature BDNF are secreted only at active synapses (Tanaka et al., 2008). Indeed, pre-synaptic stimulation alone by 1-Hz spike train cannot trigger BDNF release, even though it induces a robust elevation of post-synaptic $[Ca^{2+}]_i$ (> 10 mM) via NMDA receptors. The secretion of mature BDNF in *ex vivo* preparations is possible only when pre- and post-synaptic activities are synchronized (Tanaka et al., 2008). Given that such synchronous spiking activity results in short-lasting Ca^{2+} influx (< 2 mM) in spines, mature BDNF secretion is possible within a select $[Ca^{2+}]_i$ range that is afforded by synchronous activity of the pre- and post-synaptic terminals.

The combination of its poor diffusion with its activity-dependent secretion suggests BDNF synaptic release follows a model of coincidence detection of pre-synaptic input activity and a post-synaptic spike. For example, dendritic spine enlargement by photolysis of caged glutamate is more efficient when paired with post-synaptic spike activity because it promotes local protein synthesis and synaptic release of mature BDNF (Tanaka et al., 2008). In this experiment, it is assumed that spike-timing plasticity induced BDNF synaptic release. Remarkably, fusion of BDNF with the pH-sensitive GFP, the pHluorin combined with ultrafast microscopy revealed secretion of BDNF post-synaptic stocks within the range of milliseconds to seconds in correlation with local photostimulated uncaging of glutamate (Harward et al., 2016; Hedrick et al., 2016).

IV.3. Secretion of the prodomain

According to the sorting and cleavage events of BDNF described before, the prodomain of BDNF is predicted to be released from neurons. A careful electron microscopy study of the adult hippocampus revealed that the prodomain is indeed present in presynaptic secretory dense-core vesicles along with the mature form of BDNF (Dieni et al., 2012). This finding suggests that the prodomain is likely to be released in the synaptic cleft, co-secreted with mature BDNF and unprocessed proBDNF. A recent report confirmed that the prodomain in isolation is detected extracellularly (Anastasia et al., 2013). The experimental approach of this report utilized cultured hippocampal neurons in conditions to reduce glia contamination, collected the conditioned media, and

detected the endogenous prodomain secreted utilizing specific monoclonal antibodies. In this study, the prodomain was secreted in an activity-dependent manner after depolarization of the cultured neurons. Incubation of the hippocampal neuron cultures with a plasmin inhibitor and/or MMP inhibitor II (which inhibits MMP1, 3, 7 and 9) to prevent extracellular cleavage of secreted proBDNF did not alter significantly the levels of the secreted prodomain in the media, in basal conditions or after depolarization (Anastasia et al., 2013).

Interestingly, both the Val66 and Met66 prodomains can be secreted after depolarization with potassium chloride; however, the levels of secreted Met66 prodomain are significantly lower as compared with the Val66 prodomain. This finding is in agreement with previous studies, which showed that the Val66Met polymorphism leads to a decrease in the trafficking of BDNF to secretory vesicles and the subsequent impairment of activity-dependent release of mature BDNF (Chen et al., 2005b; Chen et al., 2006b; Egan et al., 2003).

V. Receptors for neurotrophin ligands

Neurotrophins utilize the tropomyosin related kinase (Trk) and $p75^{NTR}$ as their main receptors. Other receptor systems such as sortilin family members (SorCS1, SorCS2, SorCS3) also cooperate to propagate responses. Receptors for NGF were originally defined by the binding characteristics of high and low affinity-binding sites (Sutter et al., 1979). When the p75 neurotrophin receptor ($p75^{NTR}$) and TrkA receptors were identified by molecular cloning, it was assumed that the $p75^{NTR}$ receptor encoded the low affinity site and that TrkA (tropomyosin receptor kinase) receptor represented high affinity sites. However, this model was incorrect, since Trk receptors bind with an equilibrium binding constant of 10^{-9} to 10^{-10} M (Dechant et al., 1993; Hempstead et al., 1991; Schropel et al., 1995), which is lower in affinity than the high affinity site Kd of 10^{-11} M detected on sensory and sympathetic neurons. Moreover, sympathetic neurons with little expression of TrkC mRNA still possess high affinity NT3 binding sites with a Kd of 10^{-11} M, which were blocked by neutralizing antibodies against $p75^{NTR}$ (Dechant et al., 1997). Hence $p75^{NTR}$ display multiple affinities with different neurotrophin ligands.

Surface-plasmon resonance measurements confirmed that NGF bound TrkA with nM affinity, not pM affinity (Chao and Hempstead, 1995; Nykjaer et al., 2004). The use of the high versus low affinity nomenclature is not accurate for neurotrophins since the pro-neurotrophins can bind to $p75^{NTR}$ with a relatively higher affinity than mature neurotrophins (Lee et al., 2001). Contrary to $p75^{NTR}$, which equally bind to all neurotrophins, the Trk receptor is more selective. When combined as co-receptor, Trk-$p75^{NTR}$ complexes display a higher affinity toward neurotrophins. This change in affinity is due to a relatively fast on-rate and a slow off-rate of NGF binding (Mahadeo et al., 1994).

The different affinity constants of pro- and mature neurotrophins for their receptors strongly suggest that mature neurotrophin prefers Trk whereas pro-neurotrophins prefer $p75^{NTR}$ (Lee et al., 2001). Therefore, the neurotrophin ligands in its proform, mature form and/or the prodomain should elicit a multitude of responses depending on the combination of cognate receptors expression in target cells. For example, striatal medium spiny neurons are much more sensitive than neocortical neurons to the knockout of BDNF for maintaining synapse number because they express different levels of Trk receptors (Baquet et al., 2004; Rauskolb et al., 2010). Cortical interneurons, which do not synthesize neurotrophins (Gorba and Wahle, 1999), rely on paracrine sources to regulate inhibitory synapse density and functional inhibition using the anterograde signaling pathway that requires TrkB (Kohara et al., 2007; Liu et al., 2007). See table 2 for TrkB and $p75^{NTR}$ expression in single cell types based on the mouse brain atlas of single cell RNA sequencing (http://mousebrain.org/ (Zeisel et al., 2018)).

V.1. Receptors for Pro-neurotrophins

ProNGF binds to $p75^{NTR}$ with an equilibrium binding constant Kd of 1 nM. Mature NGF has similar equilibrium dissociation constant for both TrkA (Kd 1nM) and $p75^{NTR}$ (Kd 2 nM). On the other hand, proNGF has a weaker affinity for TrkA but binds to $p75^{NTR}$ (Kd of 0.2 nM), suggesting proNGF could have an independent signaling mechanisms through $p75^{NTR}$ (Lee et al., 2001).

Sortilin was found to be essential for proNGF/$p75^{NTR}$ activation making this sortilin a 3rd receptor to be identified for proneurotrophins (Nykjaer et al., 2004). Sortilin binds specifically to the prodomain region of proNGF with an equilibrium binding constant of Kd= 5 nM. When sortilin and $p75^{NTR}$ are co-expressed they exhibit a synergetic effect on proNGF internalization rather than a simple additive effect (Nykjaer et al., 2004). Complexes of sortilin, $p75^{NTR}$ and proNGF were detected after crosslinking suggesting the possibility that proNGF could bind to sortilin and $p75^{NTR}$ at the same time (Nykjaer et al., 2004). Such a dual receptor system was later replicated for proBDNF which can bind to $p75^{NTR}$ utilizing its mature moiety and to sortilin by its prodomain region (Teng et al., 2010). The affinities of proBDNF for its receptors were determined using purified recombinant proBDNF and immobilized sortilin. Sortilin binds with high affinity (Kd of 0.4 nM) to the prodomain region of proBDNF whereas $p75^{NTR}$ affinity for proBDNF showed a Kd of 20 nM. Interestingly, ProBDNF does not bind to the TrkB receptor (Teng et al., 2005). The sortilin-$p75^{NTR}$ co-receptor system appears to be functionally relevant as binding of proBDNF to sortilin was necessary for $p75^{NTR}$ mediated cell death induced by this ligand. Abundant in the nervous system (Petersen et al., 1997), sortilin is predominantly present on intracellular membranes (Nielsen et al., 2001), which limits its capacity to transduce proBDNF signal with $p75^{NTR}$. Therefore, it is important to understand how sortilin localization to the plasma membrane is regulated.

The mammalian homologue of $p75^{NTR}$, NRH2 (PLAIDD or NRADD) also interact with sortilin. This interaction reduces its lysosomal degradation, thus favoring the proportion of surface to intracellular sortilin and its association with $p75^{NTR}$ and proBDNF (Kim and Hempstead, 2009). It is important to note that while the first co-receptor to be identified for proneurotrophin signaling through $p75^{NTR}$ was sortilin, other members of the VSP10 family such as SorCS2 can also act as co-receptors (Deinhardt et al., 2011). An independent report confirmed these findings demonstrating that SorCS2 binds to the prodomain region of NGF, BDNF and NT3, as well as to $p75^{NTR}$ (Glerup et al., 2014). Loss-of-function of $p75^{NTR}$ increases the number of post-synaptic filopodia when compared to wild-type littermates whereas overexpression of $p75^{NTR}$ reduced the density of spines in CA1 hippocampal neurons (Zagrebelsky et al., 2005).

Importantly, the expression of $p75^{NTR}$ receptor is abundant during early development but is significantly reduced after birth. It is found in both the pre- and post-synaptic terminals. It is expressed in selective neuronal and many non-neuronal cells (see Table 2).

V.2. Receptors for mature neurotrophins

Mature BDNF binds with an equilibrium binding dissociation constant 10^{-11} M to the TrkB receptor (Rodriguez-Tebar and Barde, 1988). The binding of BDNF to TrkB is essential for synaptic strength and plasticity (Aicardi et al., 2004; Figurov et al., 1996; Gartner et al., 2006; Harward et al., 2016; Korte et al., 1995; Minichiello et al., 2002; Patterson et al., 1996). Part of this effect of BDNF is due to anterograde signaling (Zakharenko et al., 2003). But pre- and post-synaptic localization of Trk receptors indicate that neurotrophins can convey both retro- and anterograde signaling. Complete deletion of TrkB revealed a stronger synaptic phenotype than ablation of BDNF. TrkB -/- mice harbor reduced spines number (Luikart et al., 2005). Despite the reserve pool of neurotransmitter vesicles is intact, the density of neurotransmitter vesicles near the active zone and docked to the active zone is significantly decreased in TrkB -/- and TrkC -/- mice. As a result, the quantal release of neurotransmitter (glutamate or GABA) is reduced producing impaired synaptic efficacy (Genoud et al., 2004; Martinez et al., 1998). Loss-of-function of TrkB produces a more robust impairment of synapses than BDNF knockout because other TrkB ligands like NT4 and transactivation mechanisms exist (Chao, 2003; Jeanneteau et al., 2008; Lee and Chao, 2001).

The three Trk receptors are encoded by independent genes affording selectivity among neurotrophins with NGF and NT3 binding to TrkA, BDNF and NT4 binding to TrkB and NT3 binding to TrkC (Chao, 1992). Neurotrophin binding promotes homodimerization of Trk receptors, which in turn initiates intracellular phosphorylation cascades. There are several functional splice variants of Trk receptors that lack the intracellular kinase domain (Chao, 2003; Poo, 2001). These truncated receptors (TrkB.T1, TrkB.T2, TrkB.T3 and TrkB.T4) are often presented as dominant negative forms of the full-length Trk receptors (Sasi et al., 2017). The alternative view is that the truncated receptors are involved in signal transduction. Indeed, the removal of TrkB.T1

rescued the aggressive and obesity phenotypes resulting from BDNF haplo-insufficiency (Carim-Todd et al., 2009). However, specific neurotrophic signaling via the truncated TrkB receptors has been demonstrated (Carim-Todd et al., 2009; Ohira et al., 2006; Rose et al., 2003). For example, TrkB.T1 activation induces rapid intracellular Ca2+ release transients in glial cells (Rose et al., 2003).

The expression of BDNF and TrkB.T1 during development coincides well with the period of elimination of excessive axons and synaptogenesis. In the adult, neuronal TrkB.T1 is concentrated in the pre-synaptic site, whereas TrkB full-length is localized in both pre- and postsynaptic regions, suggesting a major role for pre-synaptic TrkB signaling. Overexpression of the truncated TrkB.T1 isoform increases the density of filopodia in organotypic slices (Chakravarthy et al., 2006; Hartmann et al., 2004).

V.3. Receptors for the prodomain

The BDNF prodomain binds independently to Sortilin and related Sortilin family members (SorCS) with a Kd of 0.4 nM and to $p75^{NTR}$ with a lower affinity (Kd of 20 nM) (Anastasia et al., 2013). Thus, preferential receptor for the BDNF prodomain is Sortilin and SorCS. But Sortilin and SorCS are not specific for the BDNF prodomain as it binds to other ligands like NGF prodomain, NT3 prodomain and neurotensin (Hempstead, 2015). Deletion of $p75^{NTR}$ abrogated the effect of the prodomain in several preparations (Anastasia et al., 2013; Mizui et al., 2015). This could be explained by the fact that sortilin and $p75^{NTR}$ heterodimerize and operate as co-receptors (Bronfman and Fainzilber, 2004; Jansen et al., 2007; Nykjaer and Willnow, 2012; Skeldal et al., 2012). $P75^{NTR}$ is expressed on both sides of the synapses, in presynaptic terminals and postsynaptic spines (Brito et al., 2014; Deinhardt et al., 2011; Woo et al., 2005). SorCS1 and SorCS3 are located at the synapse (Guo et al., 2016; Savas et al., 2015) and all are regulated by neuronal activity (Hermey et al., 2004). Questions remain to be answered regarding the roles of sortilin and SorCS either as co-receptor or dominant negative receptors that could regulate synaptic availability of the prodomain for $P75^{NTR}$ –mediated synaptic responses.

VI. Signaling mechanisms of Trk and $p75^{NTR}$

Several mechanisms have been proposed to coordinate neurotrophin receptor-to-ligand availability (see Table 3). First, incorporation of Trk receptor to the cell surface is promoted within seconds of neurotrophin exposure or neuronal activity (Du et al., 2000; Haapasalo et al., 2002). Second, only competent cells with permissive intracellular cAMP signaling increase Trk surface expression and chances to meet with the ligand (Ji et al., 2005). Third, another important mechanism for extrasynaptic Trk receptors is the translocation into lipid rafts, which may enhance responsiveness (Assaife-Lopes et al., 2010; Pereira and Chao, 2007). Local post-synaptic synthesis of BDNF and TrkB may regulate the directionality of neurotrophin signaling at the synapse (anterograde versus retrograde).

Recruitment of selective adaptor molecules discriminates signaling between the $p75^{NTR}$ and Trk receptors (Chao, 2003). For instance, neurotrophins activate the RhoA-JNK pathway by the $p75^{NTR}$ pathway that impairs the clustering of MAGUK in he postsynaptic density, elicits growth cone collapse, long-term depression and synapse elimination (Deinhardt et al., 2011; Nagerl et al., 2004; Sharma et al., 2010; Woo et al., 2005). However, Trk activates signaling pathways common to most receptor tyrosine kinases resulting from the dimerization and trans-autophosphorylation by the tyrosine kinase domains (Deinhardt and Chao, 2014; Kaplan and Miller, 2000; Reichardt, 2006).

The wave of second messengers involves PLCγ, which raises intracellular Ca^{2+}, the Ras-Erk and PI3-kinase/Akt pathways (see table 4 for a simplified web of intracellular signaling routes). In brief, phosphorylation of TrkB-Y515 serves as docking site for the SHC1-SOS-GRB2-RAS complex that permits the activation of Pi3K/Akt-mTOR pathway for the control of protein synthesis and MAPK-CREB pathway for the control of gene transcription (Panja and Bramham, 2014; Panja et al., 2014). Phosphorylation of TrkB-Y816 serves as docking site for the PLCγ, which modulates intracellular Ca2+ level and subsequent CAMKII or PKC as effectors (Minichiello, 2009). Phosphorylation of TrkB-S478 serves as docking site for TIAM1, which activates Rac1 to promote spine growth (Lai et al., 2012).

Of all these pathways, The TrkB-Y816-PLCγ pathway seems the most important for the maintenance of long term synaptic potentiation (Minichiello et al., 2002). But the TrkB-Y515-Erk pathway is important for regulating the synaptic

responses of the glucocorticoid receptor in conditions of stress (Arango-Lievano and Jeanneteau, 2016; Arango-Lievano et al., 2015b). Very fast signaling pathway through TrkB can also mediate sodium influx that subsequently triggers fast calcium influx through voltage gated channels (Lang et al., 2007; Sasi et al., 2017).

It has been proposed that $p75^{NTR}$ signaling prunes silent synapses that compete with active synapses that use TrkB-mediated facilitation of synaptic plasticity and strength in a BDNF-dependent fashion (Singh et al., 2008). Therefore, mature neurotrophins may represent a synaptotrophic support whereas pro-neurotrophins may be seen as punishing signals to balance the synaptic plasticity and the resulting maintenance of competing synaptic terminals (Lu et al., 2008; Woo et al., 2005). This dual system for controlling the efficacy of the synaptic network opposes proBDNF and/or prodomain signaling via the $p75^{NTR}$ pathway to the mature BDNF signaling via the TrkB pathway (Giza et al., 2018; Harward et al., 2016; Tanaka et al., 2008; Yang et al., 2014). Importantly, the directionality of the signaling (anterograde versus retrograde) is not completely understood but compelling arguments suggests it could be an important determinant to modulate a synaptic engram within a specific neural network (Harward et al., 2016; Hedrick et al., 2016).

VI.1. Pre-synaptic responses

Neurotrophin ligands modulate developmental maturation of synapses by a pre-synaptic mechanism (Collin et al., 2001). Pre-synaptic maturation involves the reduction of the pre-synaptic kainate receptors activity, which inhibits glutamate release (Lauri et al., 2006). Selective inhibition of TrkB receptors using a chemical-genetic approach impedes the downregulation of pre-synaptic kainate receptors activity that controls pre-synaptic efficacy and therefore, the formation of functional synapses (Sallert et al., 2009). Consistently, the genetic ablation of BDNF is associated with delayed synaptic maturation and persistent pre-synaptic kainate receptors activity (Sallert et al., 2009).

Application of mature BDNF alters the number of synaptic vesicles, the number of docked vesicles at the active zones without affecting the reserve pool of vesicles. As a result of structural maturation, BDNF can raise the quantal release of neurotransmitters by increasing the release probability and the size of a rapidly recycling vesicle pool

(Tyler and Pozzo-Miller, 2001; Tyler et al., 2006). In contrast, fewer vesicles and docked vesicles are observed in the BDNF knockout mice. Therefore, BDNF might help mobilize vesicles for immediate release at existing synapse through a myosin motor mechanism (Yano et al., 2006). One of the mechanisms by which BDNF mobilizes synaptic vesicles depends on a TrkB-dependent dissociation of the cadherin-βcatenin adhesion complex (Bamji et al., 2006). Pre-synaptic structural parameters are impaired when TrkB is removed from the pre-synaptic side only or from both sides (Luikart et al., 2005). Remarkably, pre-synaptic TrkB deficiency increases the probability to contact with two or more post-synaptic densities due to the atrophy of axon terminals (Luikart et al., 2005).

Several studies have addressed the role of neurotrophin signaling in synapse stabilization. One approach is to promote destabilization of existing synapses by acute pharmacological blockade of glutamate neurotransmission (Hering and Sheng, 2001). Application of mature BDNF in the presence of APV, an inhibitor of NMDA receptors, recues the number of clusters of GFP-synaptobrevin, a marker for pre-synaptic terminals, by stabilization of existing clusters and addition of novel clusters (Hu et al., 2005). Mechanisms that translate extracellular signals into cytoskeletal rearrangements underlie morphological remodeling. The cytoskeleton is composed of actin and microtubules as well as a vast array of associated regulatory proteins. Neurotrophins may impact dynamics of filopodia, branching and synaptogenesis by local effect on cytoskeletal dynamics via cyclic nucleotides like cGMP and phosphorylation, which are used as molecular switches to regulate many of the structural proteins. For example, BDNF-induced phosphorylation of synapsin-I and Eps8 by Erk1/2 lead to actin remodeling and development of axonal terminals (Jovanovic et al., 1996; Menna et al., 2009). On the contrary, proneurotrophin causes growth cone collapse by using the $p75^{NTR}$-SorCS2-rac1 pathway (Deinhardt et al., 2011). Additional experiments showed that the BDNF prodomain harboring the Met66 variation is sufficient to produce growth cone collapse by using the $p75^{NTR}$-SorCS2-rac1 pathway (Anastasia et al., 2013). This means that the Met66 variation present in 25% of the general population confers a gain of function.

Structural changes in neurons often give rise to physiological consequences. Neurotrophins increase the frequency of AMPA miniature excitatory post-synaptic

currents (mEPSCs) within minutes with minimal effect on amplitude. These observations are usually attributed to a pre-synaptic change in the probability of neurotransmitter release (Tyler and Pozzo-Miller, 2001). In accordance, inactivation of pre-synaptic TrkB signaling using the truncated TrkB isoform, TrkB.T1 impaired BDNF-elicited synaptic potentiation, thus confirming a role for synaptic neurotrophin signaling (Li et al., 1998). Similar pre-synaptic effects have been observed in inhibitory neurons. For instance, BDNF increases the expression of GAD65, a GABA synthetic enzyme, as well as mIPSCs frequency without affecting amplitude (Huang et al., 1999; Ohba et al., 2005).

VI.2. Post-synaptic responses

Neurotrophins increase dendritic arbor complexity and the number of spines in several preparations (Alonso et al., 2004; McAllister et al., 1995; Sanchez et al., 2006). Knockout of BDNF does not affect spine density significantly in the hippocampus of P10-16 animals (Martinez et al., 1998). However, no addition of new spines was possible in the barrel cortex of BDNF -/- mice after sensory stimulation in contrast to the experience-dependent synaptogenesis observed in the wild-type littermates (Genoud et al., 2004). Consistently, there is an overall reduction in spine density in the hippocampus of conditional TrkB knockout mice (Luikart et al., 2005). Application of the mature BDNF or NT3 to embryonic E16 hippocampal neurons, grown in culture, can trigger the conversion of silent synapses into functional ones (Vicario-Abejon et al., 1998). Also, acute thalamocortical slices from BDNF knockout mice revealed silent synapses that are unmasked after rescuing BDNF levels back to normal (Itami et al., 2003).

Neurotrophins enhance local protein synthesis that is required for long term structural and functional synaptic plasticity (Lu et al., 2008; Tanaka et al., 2008). The post-synaptic BDNF-TrkB pathway mediates the enlargement of spine heads following synchronized pre- and post-synaptic spiking activities (Tanaka et al., 2008). The post-synaptic BDNF-TrkB pathway also regulates the protein content in post-synaptic density notably the NMDA and GABA receptor subunits (Elmariah et al., 2004; Slipczuk et al., 2009; Yamada et al., 2002). Because BDNF action is selective to active spines, it is postulated that BDNF may act as a structural tag for the selective trapping of the protein synthesis machinery necessary to stabilize spine head volume overtime.

Neurotrophins alter spine morphogenesis by changing the cytoskeleton using small GTPases to modify the dynamics of actin polymerization/depolymerization (Hedrick et al., 2016). That is, activation of Rac1/Cdc42 and inhibition of RhoA is involved in spine formation, and vice versa in spine retraction (Fu and Ip, 2007). Regulation of the small GTPase family of proteins (Rho, Rac, cdc42) by Trk and $p75^{NTR}$ is proposed as a mechanism to impact the dynamic structure of synapses. Indeed, the Rac1 activator, TIAM1 is directly regulated by BDNF, TrkB, PI3K and NMDA-dependent calcium levels (Miyamoto et al., 2006). Similarly, $p75^{NTR}$ stimulates Rac1 but dampens RhoA activity resulting in lengthening of filopodia (Gallo and Letourneau, 2004). In fact, neurotophins affects several GTPases at the same time by different receptors to impact synaptic morphology (Chen et al., 2006a; Esteban et al., 2006; Shen et al., 2006). Another signaling pathway recruited by BDNF and central to the regulation of the cellular cytoskeleton is CDK5. Several substrates of CDK5 including the WAVE proteins are known to regulate actin polymerization and dendritic spine morphology (Cheung et al., 2007; Kim et al., 2006). Post-synaptic morphology is affected by the loss of post-synaptic TrkB but not by the loss of pre-synaptic TrkB (Luikart et al., 2005). Chemical-genetic inactivation of TrkB-F616A mutant (Chen et al., 2005a) substituted for the endogenous TrkB specifically on the post-synaptic cells, is sufficient to decrease the number of dendritic spines in vivo, recapitulating the impact of chronic unpredictable mild stress and chronic corticosterone administration with no further effects when paired (Arango-Lievano et al., 2015b; Arango-Lievano et al., 2016). These observations support a cell autonomous effect of TrkB signaling on the post-synaptic architecture. Moreover, elevation of Ca^{2+} within spines within minutes of synchronized pre- and post-synaptic activity elicits BDNF-TrkB signaling that mediates enlargement of spine head volume (Tanaka et al., 2008). In contrast, BDNF signaling cannot shape spine head volume in absence of synchronized pre- and post-synaptic activity. Therefore, BDNF signaling orchestrates Ca^{2+} sensors, kinases and small GTPases to elicit structural changes of synaptic terminals.

The source of BDNF required for synaptic potentiation differed from that required for pre-synaptic differentiation. In fact, deletion of only the 3'UTR sequence of the *bdnf* gene, which targets BDNF mRNA to the dendrites, is sufficient to reduce spine

head volume in hippocampus, suggesting an autocrine post-synaptic pathway (An et al., 2008). This is consistent with the autocrine TrkB activation on the same spines that is crucial for structural and functional plasticity (Harward et al., 2016). Post-synaptic TrkB allows robust synaptic potentiation only when paired to a weak burst stimulation of pre-synaptic terminal (Kovalchuk et al., 2002). However, others have reported that pre-synaptic BDNF released from CA3 neurons but not post-synaptic CA1 neurons, so a paracrine pathway was essential for synaptic potentiation at these synapses (Zakharenko et al., 2003).

Neurotrophins promote stabilization of post-synaptic terminals in several preparations. Infusion of mature NGF in the septum revealed a robust potentiation of cholinergic synaptic efficacy in the septo-hippocampal neural circuit whereas infusion of NGF blocking antibodies diminished hippocampal LTP and impaired spatial memory (Conner et al., 2009). The role of BDNF in the maintenance of synapses has also been studied. For instance, blocking BDNF signaling by using anti-BDNF antibodies or overexpressing a dominant negative TrkB construct reduces mushroom spine maintenance and synaptic efficacy, accompanied by an increase in long and thin spines and filopodia (Chakravarthy et al., 2006; Sanchez et al., 2006). In agreement, the inactivation of TrkB signaling may prevent the formation of new synapses and promote the destabilization of existing spines through the post-synaptic TrkB-PI3-K pathway (Luikart et al., 2005; Luikart et al., 2008).

Contrasting with the effects of mature BDNF, the BDNF pro-peptide decreases the number of dendritic spines via a mitochondrial caspase-3 pathway (Guo et al., 2016). Prodomain of BDNF but not of NGF facilitates LFS-induced LTD, an effect that also depends on $p75^{NTR}$ (Mizui et al., 2015). Interestingly, the Met66 prodomain shows the opposite effect and inhibits LFS-induced LTD.. These results are consistent with a previous study describing a deficit on LFS-induced LTD in hippocampal slices of $BDNF^{met/met}$ mice (Ninan et al., 2010), which suggest that the prodomain could be responsible for this effect. The LFS protocol elicits NMDA dependent LTD that relies, in part, on trafficking of AMPA receptor subunits. Mizui et al demonstrated that the Val66 prodomain facilitates LTD by promoting the surface expression of GluN2B NMDA receptor subunit and the endocytosis of AMPA receptors, while the Met66

prodomain blocks it. These results imply a general effect of the Met66 prodomain on NMDA signaling (Mizui et al., 2015). The deficient NMDA-dependent LTP of the $BDNF^{met/met}$ (Ninan et al., 2010) mice supports also this hypothesis. Unfortunately the effect on the Met66 prodomain in hippocampal LTP has not yet been reported.

This is consistent with the impact of a cleavage resistant proBDNF knockin mouse, which displayed decreased spine number, impaired LTP due to the lack of mature BDNF mediated TrkB signaling, and enhanced LTD mediated by the $p75^{NTR}$ pathway (Yang et al., 2014). Also, the application of proBDNF causes synaptic depression (Woo et al., 2005), which was previously associated with spine shrinkage and elimination (Nagerl et al., 2004). Removal of $p75^{NTR}$ by genetic methods reduces the elimination of silent pre- and post-synaptic terminals in several preparations (Cao et al., 2007; Lim et al., 2008; Singh et al., 2008; Zagrebelsky et al., 2005). Overexpression of $p75^{NTR}$ decreases the overall number of spines in hippocampal neurons *in vivo* (Zagrebelsky et al., 2005). It is assumed that the post-synaptic proBDNF-$P75^{NTR}$-SorCS pathway is preferred for negative plasticity but other studies indicated that inactivation of the post-synaptic mature BDNF-TrkB pathway could do the same. In Purkinje cells, the loss of TrkB, which does not affect dendritic differentiation and synaptogenesis, impairs the developmental elimination of redundant GABAergic climbing fibers (Bosman et al., 2006). One hypothesis is that the conversion of pro-BDNF to mature BDNF could determine the nature of the response (Woo et al., 2005).

VI.3. Rapid and slow responses

Several observations of rapid synaptic neurotrophin signaling have been reported. Blocking BDNF signaling using a caged photo-activable quenching antibody revealed instructive role as synaptic potentiator within minutes (Kossel et al., 2001). Neurotrophic signaling has been shown to affect synaptic transmission within minutes by modulation of ion channel properties. Indeed, voltage-gated sodium channels, potassium channels as well as glutamate and GABA receptors have been proposed to be downstream targets of BDNF-TrkB signaling (Blum et al., 2002; Jovanovic et al., 2004; Kramar et al., 2004; Levine et al., 1998). How does rapid neurotrophic signaling translate into modifications of synapses? *In vitro*, high BDNF level produces repulsion

whereas low BDNF induces attraction of growth cones (Mai et al., 2009). Responses to bound BDNF gradient depend on the absolute difference rather than the relative difference in the BDNF density across the neuron. *In vivo*, BDNF signaling via the $p75^{NTR}$ results in the elimination of silent synapses whereas TrkB signaling provides a mechanism for the preservation of functional synapses (Singh et al., 2008). Moreover, fast and slow increases in BDNF concentration can differentially affect TrkB signaling (transient versus sustained) such that spine head enlargement and spine neck elongation are affected (Ji et al., 2010).

Rapid modulation of synaptic function by BDNF is attributed to both pre- and post-synaptic mechanisms. To unravel the cell autonomous mechanisms of BDNF-mediated enhancement of synaptic plasticity, TrkB signaling in the pre-synaptic sides was impaired by removal of the synaptic vesicle protein Rab3A. Knockout mice, which lack a pre-synaptic response to BDNF (miniature EPSC frequency), still display normal post-synaptic sensitivity to BDNF because Rab3a is required for the initial (<10 min) but not for the later (>10 min) phase of BDNF-enhanced transmission (Alder et al., 2005). Indeed, BDNF enhancement of postsynaptic glutamate-induced current did not differ in the mutant neurons compared to the wild type (Alder et al., 2005). One possible post-synaptic mechanism of synaptic potentiation by BDNF signaling is that neurotrophins induce within minutes the phosphorylation of a variety of synaptic substrates such as ion channels.

For example, NMDA and GABA receptors are phosphorylated by BDNF signaling via Erk1/2 and PKC, respectively, to regulate the probability of channel opening (Jovanovic et al., 2004; Levine and Kolb, 2000; Suen et al., 1997). In addition, BDNF induces rapid intracellular calcium transients via the Trk-PI3-K pathway and surface expression of TrpC channels (Amaral and Pozzo-Miller, 2007; Li et al., 2005). Blocking endogenous TrkB signaling decreases the frequency of spontaneous Ca^{2+} rises at post-synaptic sites (Lang et al., 2007). Rapid elevation of intracellular Ca^{2+} via Trk-PLCγ-IP3 pathway was also reported (Du and Poo, 2004). Moreover, deletion of the Y785 docking site in TrkB knock-in mice revealed the importance of the PLCγ over the ERK and PI3K pathways for the maintenance of synaptic function and the rapid pre-synaptic effects of BDNF (Gartner et al., 2006; Minichiello et al., 2002). Finally, BDNF

signaling has been shown to be dependent on gradient of second messengers like cAMP to allow functional and structural synaptic responses (Ji et al., 2005; Mai et al., 2009).

Robust stimulation evoking long-term potentiation (lasting >180 min) elicits a large increase in BDNF secretion persisting 5-12 min beyond the stimulation period. Weaker stimulation patterns leading only to the initial phase of synaptic potentiation (about 35 min) are accompanied by a smaller increase in BDNF secretion lasting <1 min (Aicardi et al., 2004). Prolonged BDNF signaling triggered by robust synchronized pre- and post-synaptic activities allows synapse-specific potentiation and structural stabilization changes that are dependent on protein synthesis (Aicardi et al., 2004; Tanaka et al., 2008). To be specific, the newly synthesized plasticity-related proteins must be captured only at the active sites by a transient synaptic tag. TrkB signaling endosomes has been proposed to be a synaptic tag (Lu et al., 2008). Many BDNF-regulated genes are newly synthesized plasticity-related genes (Glorioso et al., 2006). The functions of several activity-regulated genes have been investigated in the context of synaptic potentiation: (i) *Arc* mRNA, which expression is sustained in active spines, participates in structural changes of spines associated to the consolidation of synaptic potentiation by the remodeling of actin cytoskeleton (Bramham, 2008); (ii) *Homer-1* mRNA is captured only in active spines and regulates the stability of synaptic function (Okada et al., 2009; Szumlinski et al., 2006); (iii) *bdnf* exon IV mRNA modulates the shape and potency of neuronal networks (Barco et al., 2005; Hong et al., 2008).

Proteomic approaches have revealed that BDNF induces widespread changes in synaptic protein content and up-regulates components of the translation machinery, which requires hours (Liao et al., 2007). Several mechanisms can account for this effect. On one hand, BDNF relieves the inhibitory control of the microRNA miR-134 on synaptogenesis (Schratt et al., 2006). On the other hand, BDNF employs the post-synaptic TrkB-PI3K-mTOR pathway to regulate the local synaptic translation of a select group of mRNAs (GLUR1, Arc, BDNF, TrkB, Homer and CamKII…) (Schratt et al., 2004; Slipczuk et al., 2009; Wang et al., 2010). Therefore, rapid and slow signaling may serve a dual function. Promoting transcription of plasticity-dependent genes and the capture of their mRNA products where TrkB signaling endosomes persist as putative

synaptic tags may strengthen and maintain existing synapses (Lu et al., 2011; Sajikumar and Korte, 2011; Shivarama Shetty and Sajikumar, 2017).

The activity controlled production and release of BDNF at the synapse define spatio-temporal constraints for the location of TrkB and $p75^{NTR}$ receptors at active synapses. Because some of the neurotrophic factors, like BDNF are secreted in two distinct modes (constitutive and regulated), signaling responses may thus be interpreted accordingly. Indeed, an acute increase in BDNF concentration in cultured hippocampal neurons mimicking the regulated secretion produces distinct signaling outcome when compared to a gradual increase modeling constitutive secretion. Fast and slow increases in extracellular BDNF produce transient and sustained TrkB signaling, respectively. As a result, transient TrkB activation produced neurite elongation and spine head enlargement whereas sustained TrkB activation facilitated neurite branch and spine elongation (Ji et al., 2010). Slow delivery of BDNF facilitates LTP, whereas fast application of BDNF enhances basal synaptic transmission. Interestingly, high-frequency stimulation of neurons converts BDNF-induced TrkB signaling from a transient to a sustained mode (Guo et al., 2014; Guo et al., 2018). Therefore, the mode of secretion and the source of BDNF underlying its availability within the synaptic cleft are critical for cell signaling and function.

VI.4. Balancing act on excitation and inhibition

The ratio of excitation/inhibition is adjustable to the level of neuronal activity by homeostatic mechanisms of metaplasticity that depend on BDNF signaling. It is particularly well documented in the maturation of the visual cortex (Maffei, 2002). (i) BDNF impacts the strength of neuronal networks by regulating the balance of inhibition and excitation (Nelson and Valakh, 2015; Oh et al., 2016); (ii) BDNF plays an important role in promoting the maturation and number of inhibitory and excitatory synapses (Huang et al., 1999); (iii) activity-dependent enhancement of inhibitory input also requires release of BDNF from the postsynaptic neuron and BDNF uptake by GABAergic synaptic terminals (Liu et al., 2007; Peng et al., 2010).

Neurotrophins adjust synaptic strength by regulating the quantal release of neurotransmitters on both excitatory and inhibitory neurons (Tyler and Pozzo-Miller,

2001; Tyler et al., 2006). As a result, neurotrophins adjust neuronal ouput activity based on the overall network demands. This is partly due to the strength of parvalbumin (PV) neuron mediated inhibition in response to changes of excitatory inputs regulated by BDNF (Bloodgood et al., 2013). Neurotrophins increase the number of interneurons and the density ratio of inhibitory to excitatory synapses (Rutherford et al., 1997; Seil and Drake-Baumann, 2000). Both NGF and BDNF increased the number of medial septum GABAergic and cholinergic neurons projecting to the cortex and hippocampus. BDNF also affects distinct class of synapses in opposite fashion accordingly to the level of neuronal activity. For instance, upon chronic activity blockade, BDNF scales down synaptic responses between excitatory neurons whereas BDNF scales up glutamatergic synaptic responses onto interneurons and vice-versa upon blockade of inhibition (Rutherford et al., 1998; Seil, 2003). Because BDNF regulates the strength of glutamatergic synapses onto interneurons at higher concentrations than between excitatory neurons suggests a negative feedback mechanism for the recruitment of additional inhibition under very high activity regimes.

BDNF contributes to half of the effect of NPAS4 as master regulator of the activity-dependent transcriptional epigenetic program that controls inhibitory synapse formation (Lin et al., 2008). In the visual cortex, BDNF accelerates the maturation of GABAergic synapses and the establishment of the inhibitory neural network (Huang et al., 1999). In contrast, decrease of BDNF signaling by genetic methods reduces the efficacy of GABAergic synapses (Abidin et al., 2008). In the hippocampus, experimental seizure upregulates BDNF and a collapse of the balanced excitation and inhibition (Koyama and Ikegaya, 2005). Overexpression of BDNF in excitatory hippocampal neurons from $BDNF^{-/-}$ mice increases the number of glutamatergic synapses and concomitantly decreases the density of GABAergic synapses (Singh et al., 2006). Moreover, both BDNF and NT4 decrease the expression of the chloride transporter KCC2, which allows GABA to be depolarizing rather than hyperpolarizing in order to increase the activity and density of the neuronal network (Cancedda et al., 2007; Rivera et al., 2002). Therefore, BDNF balances the number of functional inhibitory and excitatory synapses to keep overall firing rate of the neuronal network within an operational range (Gottmann et al., 2009; Ibata et al., 2008; Turrigiano, 2007).

VII. Specificity of neurotrophin actions at the synapse

Neurotrophins have similar properties but can signal through different receptors subtypes that share similar signaling cascades. What are the specific functions of individual neurotrophins in the process of synaptogenesis? Can one neurotrophin substitute for the lack of others? BDNF and NT4, which are both TrkB ligands accelerate the differentiation and maturation of cortical neurons but with distinction (McAllister et al., 1997; McAllister et al., 1995). In addition, BDNF and NT4 increase both inhibitory and excitatory synapses whereas NT3 only impacts excitatory synapse formation (Cotrufo et al., 2003; Vicario-Abejon et al., 1998). TrkC is expressed on both pre- and post-synaptic sides and NT3 increases the number of dendrites and spines on the post-synaptic side. But NT3 has no structural effects on the pre-synaptic side (Vicario-Abejon et al., 1998). Therefore, TrkB ligands seem to promote inhibitory synapse formation and stabilization. The role of NGF and NT3 in the process of synaptogenesis in the central nervous system needs further characterization. Interestingly, neuronal expression of NT3 and NT4 is not regulated by activity contrary to some isoforms of BDNF (Poo, 2001).

Because both BDNF and NT4 are TrkB ligands, one study examined whether NT4 can substitute for BDNF functions by knocking NT4 into the BDNF gene locus. The substitution of NT4 for BDNF accelerates the formation of functional excitatory synapses in hippocampal neurons (Fan et al., 2000). Exogenous NT4 is more potent than BDNF in increasing excitatory hippocampal synapses. One possible mechanism is that NT4 activates more robust TrkB signaling than BDNF. Similarly, another study examined whether NT3, which is not a TrkB ligand can substitute for BDNF by knocking NT3 into the BDNF gene locus. The substitution of NT3 for BDNF impaired pre-synaptic differentiation and target innervation of peripheral neurons in the vestibular and gustatory systems like in $BDNF^{-/-}$ mice (Agerman et al., 2003). If NT3 and BDNF share redundant function as survival factor for peripheral neurons, they show striking differences in the process of synaptogenesis.

Visual deprivation dramatically impairs the development of neuronal networks in the visual cortex, which is reversed upon light exposure. Infusion of neurotrophins in the

visual cortex mimics light exposure by restoring some level of plasticity in a specific manner. For instance, NGF selectively restores the expression of components of the NMDA system whereas both BDNF and NT4 restore the expression of components of the AMPA system as well as the GABAergic system (Cotrufo et al., 2003). For instance, the expression of the voltage-gated potassium channels that allow fast repolarization and facilitate high frequency firing of cortical interneurons is distinct after exposure treatment with BDNF or NT4 (Grabert and Wahle, 2008). Differential effects of neurotrophins on synaptogenesis *in vivo* may also reflect the overall firing rate of the neuronal network because synaptogenesis is an activity-dependent process and BDNF recruits interneurons to adjust neuronal activity.

VIII. Conclusion and Perspectives

Neurotrophins affect virtually all steps of synaptic differentiation and function. There is a general consensus that neurotrophins can scale the overall synaptic activity within homeostatic range by a complex combination of mechanisms including maturation of existing synapses and the recruitment of new synapses from inhibitory and excitatory neurons to update neural network activity.

Neurotrophins acts both pre- and post-synaptically. Post-synaptic neurotrophin signaling seems dispensable for the differentiation and topographic innervation of axon terminals. A pre-synaptic mechanism elicited by a post-synaptic source of neurotrophins is likely sufficient to regulate the early steps of pre-synaptic differentiation. In contrast, both pre- and post-synaptic neurotrophic signals, which are cell autonomous and temporally distinct, are required for the functional maturation of synapses. A post-synaptic source of BDNF is crucial to strengthen the pre-synaptic sides whereas a pre-synaptic source of BDNF contributes to the structural maturation of spines and synaptic potentiation.

BDNF is a well-suited trophic factor to modulate neuronal networks. Because (i) the signaling through Trk receptors is dependent on neuronal activity; (ii) post-synaptic secretion of BDNF is sensitive to synchronized activation of both pre- and post-synaptic terminals; (iii) neurotrophic signals can be retrogradely and anterogradely transported to modify and strengthen synapses; (iv) the potential BDNF and TrkB to behave as a

synaptic tag provide a means to regulate synapse-specific changes driven by neuronal activity; (v) inactive synapses may be eliminated by a pro-BDNF-$P75^{NTR}$ mechanism.

Substantial evidence described in this chapter, supports the idea that proBDNF function goes beyond being a synthesis precursor for mature BDNF. The concomitant expression of proBDNF and $p75^{NTR}$ during early post-natal periods and its subsequent decrease in adulthood is a good example of developmental shift between functions of the proBDNF, mature BDNF and its prodomain.

Since neurotrophins contribute to the establishment and refinement of neuronal networks, impaired neurotrophin signaling has been linked to several neurodegenerative and psychiatric disorders. It is intriguing that human carriers of the Met66 polymorphism of BDNF gene are more vulnerable to develop early onset or more severe forms of these diseases. Until now, the effect of the Val66Met polymorphism was mainly explained by a loss of function of mature BDNF (Chen et al., 2006b). But recent publications exploring the biological functions of the BDNF prodomain (independently of mature BDNF and proBDNF) describe gains of functions for the Met66 variant, raising the question of which BDNF ligands are contributing more to the phenotypic characteristics of the Met66 human carriers. Future studies implicating the BDNF prodomain in pathological states are warranted.

Tables

Cell types expressing BDNF	Cell types not expressing BDNF
Excitatory neuron, cerebral cortex	Medium spiny neurons, striatum
Excitatory neuron, hippocampus CA1, CA2, CA3	Neuroblast-like, habenula
Granule neurons, dentate gyrus	Inhibitory neurons, thalamus
Basket cells (parvalbumin), cerebral cortex/ hippocampus	Inhibitory interneurons, hippocampus
Adrenergic neurons, medulla	Cholinergic interneuron, telencephalon
Dopaminergic neurons, VTA, SN, periaductal grey	Cck interneuron, cerebral cortex / hippocampus
Orexin neurons, hypothalamus	Inhibitory neurons, telencephalon
Serotoninergic neurons, hindbrain	Vasopressinergic neurons, hypothalamus
Peptidergic neurons, hypothalamus	Oxytocinergic neurons, hypothalamus
Inhibitory neurons, hypothalamus	Epithelial cells, choroid plexus
Excitatory neuron, hindbrain	Radial glia
Excitatory neuron, midbrain	Schwann cells
Excitatory neuron, hypothalamus	Oligodendrocytes
Excitatory neuron, thalamus	pericytes
Excitatory neuron, amygdala	
Excitatory neuron, habenula	
Inhibitory neurons, midbrain	
Neuroblast, septum	
Granular layer interneuron, Cerebellum	
Molecular layer interneurons, cerebellum	
Purkinje cells, cerebellum	
Granule neurons, cerebellum	
Microglia	
Astrocytes	
Vascular endothelial cells	

Table 1: BDNF-producing cells (mRNA) in brain are putative sources of pro-BDNF, mature BDNF and pro-peptide ligand.

Cell types expressing TrkB	Cell types expressing $P75^{NTR}$
Excitatory neuron, cerebral cortex	Excitatory neuron, cerebral cortex
Excitatory neuron, hippocampus CA1, CA2, CA3	Excitatory neuron, hippocampus CA3
Granule neurons, dentate gyrus	Inhibitory neurons, thalamus
Basket cells (parvalbumin), cerebral cortex/ hippocampus	Cck interneurons, cerebral cortex / hippocampus
Adrenergic neurons, medulla	Cholinergic interneurons, telencephalon
Dopaminergic neurons, VTA, SN, periaductal grey	Cholinergic neurons, Meissnert nucleus, septum
Orexin neurons, hypothalamus	Adrenergic cells, medulla
Serotoninergic neurons, hindbrain	Dopaminergic neurons, VTA, SNC
Peptidergic neurons, hypothalamus	Serotoninergic neurons, hindbrain
Inhibitory neurons, hypothalamus	Peptidergic neurons, hypothalamus
Excitatory neuron, hindbrain	Inhibitory neurons, hypothalamus
Excitatory neuron, midbrain	Vasopressinergic neurons, hypothalamus
Excitatory neuron, hypothalamus	Oxytocinergic neurons, hypothalamus
Excitatory neuron, thalamus	Inhibitory neurons, hindbrain
Excitatory neuron, amygdala	Cholinergic neurons, midbrain
Excitatory neuron, habenula	Inhibitory neurons, midbrain
Inhibitory neurons, midbrain	Purkinje cells, cerebellum
Inhibitory neurons, septum	Excitatory neuron, midbrain
Neuroblast, septum	Noradrenergic neurons, sympathetic
Granular layer interneuron, Cerebellum	Cholinergic neurons, sympathetic
Molecular layer interneurons, cerebellum	Astrocytes
Purkinje cells, cerebellum	Vascular leptomeningeal cells
Granule neurons, cerebellum	Pericytes
Microglia	Vascular endothelial cells
Astrocytes	Schwann cells
Vascular endothelial cells	Oligodendrocytes
Oligodendrocytes	Microglia
Medium spiny neurons, striatum	
pericytes	
Vascular endothelial cells	

Table 2: BDNF-responding cells (with mRNA for receptors) in brain are putative effectors of the pleiotropic actions. Based on the single cells RNA sequencing atlas of the mouse nervous system

Ligands	Source	Secretion	Receptor	Synaptic effect
mature BDNF	Autocrine or paracrine	Constitutive	TrkB full length	Formation, maintenance
mature BDNF	Autocrine or paracrine	Activity-dependent	TrkB full length	Formation, maintenance, plasticity, strength
mature BDNF	Autocrine or paracrine	Constitutive	TrkB truncated isoforms	Formation, maintenance, plasticity, strength
mature BDNF	Autocrine or paracrine	Activity-dependent	TrkB truncated isoforms	Formation, maintenance, plasticity, strength
Pro-BDNF	Autocrine or paracrine	Constitutive	$P75^{NTR}$	Elimination, plasticity, strength
Pro-BDNF	Autocrine or paracrine	Activity-dependent	$P75^{NTR}$	Elimination, plasticity, strength
Pro-peptide	Autocrine or paracrine	Constitutive	Sortilin and SorCS 1-3	Elimination, plasticity, strength
Pro-peptide	Autocrine or paracrine	Activity-dependent	Sortilin and SorCS 1-3	Elimination, plasticity, strength
Pro-peptide	Autocrine or paracrine	Constitutive	$P75^{NTR}$	Elimination, plasticity, strength
Pro-peptide	Autocrine or paracrine	Activity-dependent	$P75^{NTR}$	Elimination, plasticity, strength

Table 3: Putative responses of trans-synaptic BDNF ligands.

Receptors	Docking effector	Signaling pathway	Synaptic effect
TrkB Y701/Y705/Y706 phosphorylation	TrkB Tyrosine kinase	Trans-phosphorylation of TrkB	Mandatory
TrkB Y515-phosphorylation	SHC1	MAPK-synapsin1	Synapse maintenance, plasticity
TrkB Y515-phosphorylation	SHC1	MAPK-CREB-gene transcription	Synaptogenesis
TrkB Y515-phosphorylation	SHC1	MAPK-BAD-BCL2-mitochondria	Spine remodeling and maintenance
TrkB Y515-phosphorylation	SHC1	MAPK-glucocorticoid receptor	Spine remodeling and maintenance
TrkB Y515-phosphorylation	SHC1	AKT-mTOR- protein synthesis	Synaptogenesis
TrkB S478-phosphorylation	Tiam1	Rho -Actin cytoskeleton	Spine growth
TrkB Y816-phosphorylation	PLCgamma	Ca2+ -CaMK-CREB-gene transcription	Synaptic plasticity
TrkB Y816-phosphorylation	PLCgamma	PKC	Synaptic plasticity
TrkB Truncated T1 isoform	RhoGDI	Rho – actin cytoskeleton	Filopodia remodeling
TrkB Truncated T1 isoform		IP3 receptors- Ca2+	
TrkB Truncated T1 isoform	TrkB full length	Dominant negative action on trans-phosphorylation of TrkB	
$P75^{NTR}$ Death domain	TRAF4/6	JNK - NFKB	
$P75^{NTR}$ Death domain	NRIF	JNK	
$P75^{NTR}$ Death domain	RIP2	JNK - NFKB	
$P75^{NTR}$ Death domain	NRAGE	JNK - caspases	Spine pruning
$P75^{NTR}$ ICD	RhoA	Actin cytoskeleton	Growth cone remodeling
$P75^{NTR}$ ICD	Rac1	Actin cytoskeleton	Growth cone remodeling
$P75^{NTR}$ ICD	RhoGDI	Rho – actin cytoskeleton	Filopodia, spine, axon remodeling
$P75^{NTR}$ Transmembrane domain	Gamma-secretase	ICD- gene transcription regulation	
$P75^{NTR}$ ICD	SC1	Regulation of gene transcription	
$P75^{NTR}$ SPV, PDZ ligand can be phosphorylated	PDZ domain proteins	PDLIM1- actin cytoskeleton	
$P75^{NTR}$ ICD serine, phosphorylation	PKA	Subcellular trafficking to lipid raft	
$P75^{NTR}$ ICD cysteine, palmitoylation		Subcellular trafficking to lipid raft	
Sortilin	$P75^{NTR}$	$P75^{NTR}$ – mediated pathways	
Sortilin related receptors SorCS (1-3)	$P75^{NTR}$	$P75^{NTR}$ – mediated pathways	Synaptic depression, spine elimination

Table 4: Receptor signaling pathways on the synapse.

Refererences

Abidin, I., Eysel, U.T., Lessmann, V., and Mittmann, T. (2008). Impaired GABAergic inhibition in the visual cortex of brain-derived neurotrophic factor heterozygous knockout mice. J Physiol *586*, 1885-1901.

Agerman, K., Hjerling-Leffler, J., Blanchard, M.P., Scarfone, E., Canlon, B., Nosrat, C., and Ernfors, P. (2003). BDNF gene replacement reveals multiple mechanisms for establishing neurotrophin specificity during sensory nervous system development. Development *130*, 1479-1491.

Aicardi, G., Argilli, E., Cappello, S., Santi, S., Riccio, M., Thoenen, H., and Canossa, M. (2004). Induction of long-term potentiation and depression is reflected by corresponding changes in secretion of endogenous brain-derived neurotrophic factor. Proc Natl Acad Sci U S A *101*, 15788-15792.

Aid, T., Kazantseva, A., Piirsoo, M., Palm, K., and Timmusk, T. (2007). Mouse and rat BDNF gene structure and expression revisited. J Neurosci Res *85*, 525-535.

Alder, J., Thakker-Varia, S., Crozier, R.A., Shaheen, A., Plummer, M.R., and Black, I.B. (2005). Early presynaptic and late postsynaptic components contribute independently to brain-derived neurotrophic factor-induced synaptic plasticity. J Neurosci *25*, 3080-3085.

Alonso, M., Medina, J.H., and Pozzo-Miller, L. (2004). ERK1/2 activation is necessary for BDNF to increase dendritic spine density in hippocampal CA1 pyramidal neurons. Learn Mem *11*, 172-178.

Amaral, M.D., and Pozzo-Miller, L. (2007). TRPC3 channels are necessary for brain-derived neurotrophic factor to activate a nonselective cationic current and to induce dendritic spine formation. J Neurosci *27*, 5179-5189.

An, J.J., Gharami, K., Liao, G.Y., Woo, N.H., Lau, A.G., Vanevski, F., Torre, E.R., Jones, K.R., Feng, Y., Lu, B.*, et al.* (2008). Distinct role of long 3' UTR BDNF mRNA in spine morphology and synaptic plasticity in hippocampal neurons. Cell *134*, 175-187.

Anastasia, A., Deinhardt, K., Chao, M.V., Will, N.E., Irmady, K., Lee, F.S., Hempstead, B.L., and Bracken, C. (2013). Val66Met polymorphism of BDNF alters prodomain structure to induce neuronal growth cone retraction. Nature communications *4*, 2490.

Andreska, T., Aufmkolk, S., Sauer, M., and Blum, R. (2014). High abundance of BDNF within glutamatergic presynapses of cultured hippocampal neurons. Front Cell Neurosci *8*, 107.

Arango-Lievano, M., Anastasia, A., and JEANNETEAU, F. (2015a). ProBDNF Biology and Emerging Roles in the CNS. In Brain-Derived Neurotrophic Factor (BDNF): Therapeutic Approaches, Role in Neuronal Development and Effects on Cognitive Health (Nova Biomedical).

Arango-Lievano, M., and Jeanneteau, F. (2016). Timing and crosstalk of glucocorticoid signaling with cytokines, neurotransmitters and growth factors. Pharmacol Res *113*, 1-17.

Arango-Lievano, M., Lambert, W.M., Bath, K.G., Garabedian, M.J., Chao, M.V., and Jeanneteau, F. (2015b). Neurotrophic-priming of glucocorticoid receptor signaling is essential for neuronal plasticity to stress and antidepressant treatment. Proc Natl Acad Sci U S A *112*, 15737-15742.

Arango-Lievano, M., Peguet, C., Catteau, M., Parmentier, M.L., Wu, S., Chao, M.V., Ginsberg, S.D., and Jeanneteau, F. (2016). Deletion of Neurotrophin Signaling through the Glucocorticoid Receptor Pathway Causes Tau Neuropathology. Sci Rep *6*, 37231.
Assaife-Lopes, N., Sousa, V.C., Pereira, D.B., Ribeiro, J.A., Chao, M.V., and Sebastiao, A.M. (2010). Activation of adenosine A2A receptors induces TrkB translocation and increases BDNF-mediated phospho-TrkB localization in lipid rafts: implications for neuromodulation. J Neurosci *30*, 8468-8480.
Autry, A.E., and Monteggia, L.M. (2012). Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev *64*, 238-258.
Baj, G., Leone, E., Chao, M.V., and Tongiorgi, E. (2011). Spatial segregation of BDNF transcripts enables BDNF to differentially shape distinct dendritic compartments. Proc Natl Acad Sci U S A *108*, 16813-16818.
Bamji, S.X., Rico, B., Kimes, N., and Reichardt, L.F. (2006). BDNF mobilizes synaptic vesicles and enhances synapse formation by disrupting cadherin-beta-catenin interactions. J Cell Biol *174*, 289-299.
Baquet, Z.C., Gorski, J.A., and Jones, K.R. (2004). Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor. J Neurosci *24*, 4250-4258.
Barco, A., Patterson, S., Alarcon, J.M., Gromova, P., Mata-Roig, M., Morozov, A., and Kandel, E.R. (2005). Gene expression profiling of facilitated L-LTP in VP16-CREB mice reveals that BDNF is critical for the maintenance of LTP and its synaptic capture. Neuron *48*, 123-137.
Bath, K.G., Schilit, A., and Lee, F.S. (2013). Stress effects on BDNF expression: effects of age, sex, and form of stress. Neuroscience *239*, 149-156.
Bennett, M.R., and Lagopoulos, J. (2014). Stress and trauma: BDNF control of dendritic-spine formation and regression. Prog Neurobiol *112*, 80-99.
Bergami, M., Santi, S., Formaggio, E., Cagnoli, C., Verderio, C., Blum, R., Berninger, B., Matteoli, M., and Canossa, M. (2008). Uptake and recycling of pro-BDNF for transmitter-induced secretion by cortical astrocytes. J Cell Biol *183*, 213-221.
Biffo, S., Offenhauser, N., Carter, B.D., and Barde, Y.A. (1995). Selective binding and internalisation by truncated receptors restrict the availability of BDNF during development. Development *121*, 2461-2470.
Binder, D.K., and Scharfman, H.E. (2004). Brain-derived neurotrophic factor. Growth Factors *22*, 123-131.
Bloodgood, B.L., Sharma, N., Browne, H.A., Trepman, A.Z., and Greenberg, M.E. (2013). The activity-dependent transcription factor NPAS4 regulates domain-specific inhibition. Nature *503*, 121-125.
Blum, R., Kafitz, K.W., and Konnerth, A. (2002). Neurotrophin-evoked depolarization requires the sodium channel Na(V)1.9. Nature *419*, 687-693.
Bosman, L.W., Hartmann, J., Barski, J.J., Lepier, A., Noll-Hussong, M., Reichardt, L.F., and Konnerth, A. (2006). Requirement of TrkB for synapse elimination in developing cerebellar Purkinje cells. Brain Cell Biol *35*, 87-101.
Boulanger, L., and Poo, M.M. (1999). Gating of BDNF-induced synaptic potentiation by cAMP. Science *284*, 1982-1984.
Bramham, C.R. (2008). Local protein synthesis, actin dynamics, and LTP consolidation. Curr Opin Neurobiol *18*, 524-531.

Brito, V., Giralt, A., Enriquez-Barreto, L., Puigdellivol, M., Suelves, N., Zamora-Moratalla, A., Ballesteros, J.J., Martin, E.D., Dominguez-Iturza, N., Morales, M.*, et al.* (2014). Neurotrophin receptor p75(NTR) mediates Huntington's disease-associated synaptic and memory dysfunction. J Clin Invest *124*, 4411-4428.
Bronfman, F.C., and Fainzilber, M. (2004). Multi-tasking by the p75 neurotrophin receptor: sortilin things out? EMBO Rep *5*, 867-871.
Cancedda, L., Fiumelli, H., Chen, K., and Poo, M.M. (2007). Excitatory GABA action is essential for morphological maturation of cortical neurons in vivo. J Neurosci *27*, 5224-5235.
Cao, L., Dhilla, A., Mukai, J., Blazeski, R., Lodovichi, C., Mason, C.A., and Gogos, J.A. (2007). Genetic modulation of BDNF signaling affects the outcome of axonal competition in vivo. Curr Biol *17*, 911-921.
Carim-Todd, L., Bath, K.G., Fulgenzi, G., Yanpallewar, S., Jing, D., Barrick, C.A., Becker, J., Buckley, H., Dorsey, S.G., Lee, F.S.*, et al.* (2009). Endogenous truncated TrkB.T1 receptor regulates neuronal complexity and TrkB kinase receptor function in vivo. J Neurosci *29*, 678-685.
Castren, E., and Antila, H. (2017). Neuronal plasticity and neurotrophic factors in drug responses. Mol Psychiatry *22*, 1085-1095.
Cattaneo, A., Cattane, N., Begni, V., Pariante, C.M., and Riva, M.A. (2016). The human BDNF gene: peripheral gene expression and protein levels as biomarkers for psychiatric disorders. Transl Psychiatry *6*, e958.
Chakravarthy, S., Saiepour, M.H., Bence, M., Perry, S., Hartman, R., Couey, J.J., Mansvelder, H.D., and Levelt, C.N. (2006). Postsynaptic TrkB signaling has distinct roles in spine maintenance in adult visual cortex and hippocampus. Proc Natl Acad Sci U S A *103*, 1071-1076.
Chao, M.V. (1992). Neurotrophin receptors: a window into neuronal differentiation. Neuron *9*, 583-593.
Chao, M.V. (2003). Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci *4*, 299-309.
Chao, M.V., and Hempstead, B.L. (1995). p75 and Trk: a two-receptor system. Trends Neurosci *18*, 321-326.
Chen, A.I., Zang, K., Masliah, E., and Reichardt, L.F. (2016). Glutamatergic axon-derived BDNF controls GABAergic synaptic differentiation in the cerebellum. Sci Rep *6*, 20201.
Chen, T.J., Gehler, S., Shaw, A.E., Bamburg, J.R., and Letourneau, P.C. (2006a). Cdc42 participates in the regulation of ADF/cofilin and retinal growth cone filopodia by brain derived neurotrophic factor. J Neurobiol *66*, 103-114.
Chen, X., Ye, H., Kuruvilla, R., Ramanan, N., Scangos, K.W., Zhang, C., Johnson, N.M., England, P.M., Shokat, K.M., and Ginty, D.D. (2005a). A chemical-genetic approach to studying neurotrophin signaling. Neuron *46*, 13-21.
Chen, Z.Y., Ieraci, A., Teng, H., Dall, H., Meng, C.X., Herrera, D.G., Nykjaer, A., Hempstead, B.L., and Lee, F.S. (2005b). Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. J Neurosci *25*, 6156-6166.

Chen, Z.Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S.*, et al.* (2006b). Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science *314*, 140-143.
Cheung, Z.H., Chin, W.H., Chen, Y., Ng, Y.P., and Ip, N.Y. (2007). Cdk5 is involved in BDNF-stimulated dendritic growth in hippocampal neurons. PLoS Biol *5*, e63.
Chiaruttini, C., Sonego, M., Baj, G., Simonato, M., and Tongiorgi, E. (2008). BDNF mRNA splice variants display activity-dependent targeting to distinct hippocampal laminae. Mol Cell Neurosci *37*, 11-19.
Chiaruttini, C., Vicario, A., Li, Z., Baj, G., Braiuca, P., Wu, Y., Lee, F.S., Gardossi, L., Baraban, J.M., and Tongiorgi, E. (2009). Dendritic trafficking of BDNF mRNA is mediated by translin and blocked by the G196A (Val66Met) mutation. Proc Natl Acad Sci U S A *106*, 16481-16486.
Choi, S.Y. (2018). Synaptic and circuit development of the primary sensory cortex. Exp Mol Med *50*, 13.
Chung, W.S., Welsh, C.A., Barres, B.A., and Stevens, B. (2015). Do glia drive synaptic and cognitive impairment in disease? Nat Neurosci *18*, 1539-1545.
Cohen-Cory, S., Kidane, A.H., Shirkey, N.J., and Marshak, S. (2010). Brain-derived neurotrophic factor and the development of structural neuronal connectivity. Dev Neurobiol *70*, 271-288.
Collin, C., Vicario-Abejon, C., Rubio, M.E., Wenthold, R.J., McKay, R.D., and Segal, M. (2001). Neurotrophins act at presynaptic terminals to activate synapses among cultured hippocampal neurons. Eur J Neurosci *13*, 1273-1282.
Conner, J.M., Franks, K.M., Titterness, A.K., Russell, K., Merrill, D.A., Christie, B.R., Sejnowski, T.J., and Tuszynski, M.H. (2009). NGF is essential for hippocampal plasticity and learning. J Neurosci *29*, 10883-10889.
Cotrufo, T., Viegi, A., Berardi, N., Bozzi, Y., Mascia, L., and Maffei, L. (2003). Effects of neurotrophins on synaptic protein expression in the visual cortex of dark-reared rats. J Neurosci *23*, 3566-3571.
Dean, C., Liu, H., Dunning, F.M., Chang, P.Y., Jackson, M.B., and Chapman, E.R. (2009). Synaptotagmin-IV modulates synaptic function and long-term potentiation by regulating BDNF release. Nat Neurosci *12*, 767-776.
Dechant, G., Rodriguez-Tebar, A., Kolbeck, R., and Barde, Y.A. (1993). Specific high-affinity receptors for neurotrophin-3 on sympathetic neurons. J Neurosci *13*, 2610-2616.
Dechant, G., Tsoulfas, P., Parada, L.F., and Barde, Y.A. (1997). The neurotrophin receptor p75 binds neurotrophin-3 on sympathetic neurons with high affinity and specificity. J Neurosci *17*, 5281-5287.
Deinhardt, K., and Chao, M.V. (2014). Trk receptors. Handb Exp Pharmacol *220*, 103-119.
Deinhardt, K., Kim, T., Spellman, D.S., Mains, R.E., Eipper, B.A., Neubert, T.A., Chao, M.V., and Hempstead, B.L. (2011). Neuronal growth cone retraction relies on proneurotrophin receptor signaling through Rac. Sci Signal *4*, ra82.
Dieni, S., Matsumoto, T., Dekkers, M., Rauskolb, S., Ionescu, M.S., Deogracias, R., Gundelfinger, E.D., Kojima, M., Nestel, S., Frotscher, M.*, et al.* (2012). BDNF and its pro-peptide are stored in presynaptic dense core vesicles in brain neurons. J Cell Biol *196*, 775-788.

Dincheva, I., Glatt, C.E., and Lee, F.S. (2012). Impact of the BDNF Val66Met polymorphism on cognition: implications for behavioral genetics. Neuroscientist *18*, 439-451.
Du, J., Feng, L., Yang, F., and Lu, B. (2000). Activity- and Ca(2+)-dependent modulation of surface expression of brain-derived neurotrophic factor receptors in hippocampal neurons. J Cell Biol *150*, 1423-1434.
Du, J.L., and Poo, M.M. (2004). Rapid BDNF-induced retrograde synaptic modification in a developing retinotectal system. Nature *429*, 878-883.
Du, J.L., Wei, H.P., Wang, Z.R., Wong, S.T., and Poo, M.M. (2009). Long-range retrograde spread of LTP and LTD from optic tectum to retina. Proc Natl Acad Sci U S A *106*, 18890-18896.
Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M.*, et al.* (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell *112*, 257-269.
Elmariah, S.B., Crumling, M.A., Parsons, T.D., and Balice-Gordon, R.J. (2004). Postsynaptic TrkB-mediated signaling modulates excitatory and inhibitory neurotransmitter receptor clustering at hippocampal synapses. J Neurosci *24*, 2380-2393.
Esteban, P.F., Yoon, H.Y., Becker, J., Dorsey, S.G., Caprari, P., Palko, M.E., Coppola, V., Saragovi, H.U., Randazzo, P.A., and Tessarollo, L. (2006). A kinase-deficient TrkC receptor isoform activates Arf6-Rac1 signaling through the scaffold protein tamalin. J Cell Biol *173*, 291-299.
Evans, S.F., Irmady, K., Ostrow, K., Kim, T., Nykjaer, A., Saftig, P., Blobel, C., and Hempstead, B.L. (2011). Neuronal brain-derived neurotrophic factor is synthesized in excess, with levels regulated by sortilin-mediated trafficking and lysosomal degradation. The Journal of biological chemistry *286*, 29556-29567.
Fan, G., Egles, C., Sun, Y., Minichiello, L., Renger, J.J., Klein, R., Liu, G., and Jaenisch, R. (2000). Knocking the NT4 gene into the BDNF locus rescues BDNF deficient mice and reveals distinct NT4 and BDNF activities. Nat Neurosci *3*, 350-357.
Figurov, A., Pozzo-Miller, L.D., Olafsson, P., Wang, T., and Lu, B. (1996). Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature *381*, 706-709.
Fu, A.K., and Ip, N.Y. (2007). Cyclin-dependent kinase 5 links extracellular cues to actin cytoskeleton during dendritic spine development. Cell Adh Migr *1*, 110-112.
Gallo, G., and Letourneau, P.C. (2004). Regulation of growth cone actin filaments by guidance cues. J Neurobiol *58*, 92-102.
Gartner, A., Polnau, D.G., Staiger, V., Sciarretta, C., Minichiello, L., Thoenen, H., Bonhoeffer, T., and Korte, M. (2006). Hippocampal long-term potentiation is supported by presynaptic and postsynaptic tyrosine receptor kinase B-mediated phospholipase Cgamma signaling. J Neurosci *26*, 3496-3504.
Gauthier, L.R., Charrin, B.C., Borrell-Pages, M., Dompierre, J.P., Rangone, H., Cordelieres, F.P., De Mey, J., MacDonald, M.E., Lessmann, V., Humbert, S.*, et al.* (2004). Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell *118*, 127-138.

Genoud, C., Knott, G.W., Sakata, K., Lu, B., and Welker, E. (2004). Altered synapse formation in the adult somatosensory cortex of brain-derived neurotrophic factor heterozygote mice. J Neurosci *24*, 2394-2400.
Giza, J.I., Kim, J., Meyer, H.C., Anastasia, A., Dincheva, I., Zheng, C.I., Lopez, K., Bains, H., Yang, J., Bracken, C.*, et al.* (2018). The BDNF Val66Met Prodomain Disassembles Dendritic Spines Altering Fear Extinction Circuitry and Behavior. Neuron *99*, 163-178 e166.
Glerup, S., Olsen, D., Vaegter, C.B., Gustafsen, C., Sjoegaard, S.S., Hermey, G., Kjolby, M., Molgaard, S., Ulrichsen, M., Boggild, S.*, et al.* (2014). SorCS2 regulates dopaminergic wiring and is processed into an apoptotic two-chain receptor in peripheral glia. Neuron *82*, 1074-1087.
Glorioso, C., Sabatini, M., Unger, T., Hashimoto, T., Monteggia, L.M., Lewis, D.A., and Mirnics, K. (2006). Specificity and timing of neocortical transcriptome changes in response to BDNF gene ablation during embryogenesis or adulthood. Mol Psychiatry *11*, 633-648.
Gomes, C., Ferreira, R., George, J., Sanches, R., Rodrigues, D.I., Goncalves, N., and Cunha, R.A. (2013). Activation of microglial cells triggers a release of brain-derived neurotrophic factor (BDNF) inducing their proliferation in an adenosine A2A receptor-dependent manner: A2A receptor blockade prevents BDNF release and proliferation of microglia. J Neuroinflammation *10*, 16.
Gonzalez, A., Moya-Alvarado, G., Gonzalez-Billaut, C., and Bronfman, F.C. (2016). Cellular and molecular mechanisms regulating neuronal growth by brain-derived neurotrophic factor. Cytoskeleton (Hoboken) *73*, 612-628.
Gorba, T., and Wahle, P. (1999). Expression of TrkB and TrkC but not BDNF mRNA in neurochemically identified interneurons in rat visual cortex in vivo and in organotypic cultures. Eur J Neurosci *11*, 1179-1190.
Gottmann, K., Mittmann, T., and Lessmann, V. (2009). BDNF signaling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses. Exp Brain Res *199*, 203-234.
Grabert, J., and Wahle, P. (2008). Neuronal activity and TrkB ligands influence Kv3.1b and Kv3.2 expression in developing cortical interneurons. Neuroscience *156*, 618-629.
Gray, K., and Ellis, V. (2008). Activation of pro-BDNF by the pericellular serine protease plasmin. FEBS Lett *582*, 907-910.
Guo, J., Ji, Y., Ding, Y., Jiang, W., Sun, Y., Lu, B., and Nagappan, G. (2016). BDNF pro-peptide regulates dendritic spines via caspase-3. Cell Death Dis *7*, e2264.
Guo, W., Ji, Y., Wang, S., Sun, Y., and Lu, B. (2014). Neuronal activity alters BDNF-TrkB signaling kinetics and downstream functions. J Cell Sci *127*, 2249-2260.
Guo, W., Nagappan, G., and Lu, B. (2018). Differential effects of transient and sustained activation of BDNF-TrkB signaling. Dev Neurobiol *78*, 647-659.
Haapasalo, A., Sipola, I., Larsson, K., Akerman, K.E., Stoilov, P., Stamm, S., Wong, G., and Castren, E. (2002). Regulation of TRKB surface expression by brain-derived neurotrophic factor and truncated TRKB isoforms. J Biol Chem *277*, 43160-43167.
Hao, L., Yang, Z., and Lei, J. (2018). Underlying Mechanisms of Cooperativity, Input Specificity, and Associativity of Long-Term Potentiation Through a Positive Feedback of Local Protein Synthesis. Front Comput Neurosci *12*, 25.

Harris, K.D. (2008). Stability of the fittest: organizing learning through retroaxonal signals. Trends Neurosci *31*, 130-136.
Hartmann, M., Brigadski, T., Erdmann, K.S., Holtmann, B., Sendtner, M., Narz, F., and Lessmann, V. (2004). Truncated TrkB receptor-induced outgrowth of dendritic filopodia involves the p75 neurotrophin receptor. J Cell Sci *117*, 5803-5814.
Harward, S.C., Hedrick, N.G., Hall, C.E., Parra-Bueno, P., Milner, T.A., Pan, E., Laviv, T., Hempstead, B.L., Yasuda, R., and McNamara, J.O. (2016). Autocrine BDNF-TrkB signalling within a single dendritic spine. Nature *538*, 99-103.
Hedrick, N.G., Harward, S.C., Hall, C.E., Murakoshi, H., McNamara, J.O., and Yasuda, R. (2016). Rho GTPase complementation underlies BDNF-dependent homo- and heterosynaptic plasticity. Nature *538*, 104-108.
Hempstead, B.L. (2006). Dissecting the diverse actions of pro- and mature neurotrophins. Curr Alzheimer Res *3*, 19-24.
Hempstead, B.L. (2015). Brain-Derived Neurotrophic Factor: Three Ligands, Many Actions. Trans Am Clin Climatol Assoc *126*, 9-19.
Hempstead, B.L., Martin-Zanca, D., Kaplan, D.R., Parada, L.F., and Chao, M.V. (1991). High-affinity NGF binding requires coexpression of the trk proto-oncogene and the low-affinity NGF receptor. Nature *350*, 678-683.
Hering, H., and Sheng, M. (2001). Dendritic spines: structure, dynamics and regulation. Nat Rev Neurosci *2*, 880-888.
Hermey, G., Plath, N., Hubner, C.A., Kuhl, D., Schaller, H.C., and Hermans-Borgmeyer, I. (2004). The three sorCS genes are differentially expressed and regulated by synaptic activity. J Neurochem *88*, 1470-1476.
Hill, J.L., and Martinowich, K. (2016). Activity-dependent signaling: influence on plasticity in circuits controlling fear-related behavior. Curr Opin Neurobiol *36*, 59-65.
Hong, E.J., McCord, A.E., and Greenberg, M.E. (2008). A biological function for the neuronal activity-dependent component of Bdnf transcription in the development of cortical inhibition. Neuron *60*, 610-624.
Hu, B., Nikolakopoulou, A.M., and Cohen-Cory, S. (2005). BDNF stabilizes synapses and maintains the structural complexity of optic axons in vivo. Development *132*, 4285-4298.
Huang, J.K., Dorey, K., Ishibashi, S., and Amaya, E. (2007). BDNF promotes target innervation of Xenopus mandibular trigeminal axons in vivo. BMC Dev Biol *7*, 59.
Huang, Z.J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M.F., Maffei, L., and Tonegawa, S. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. Cell *98*, 739-755.
Humbert, S., and Saudou, F. (2005). [Huntington's disease: intracellular signaling pathways and neuronal death]. J Soc Biol *199*, 247-251.
Ibata, K., Sun, Q., and Turrigiano, G.G. (2008). Rapid synaptic scaling induced by changes in postsynaptic firing. Neuron *57*, 819-826.
Itami, C., Kimura, F., Kohno, T., Matsuoka, M., Ichikawa, M., Tsumoto, T., and Nakamura, S. (2003). Brain-derived neurotrophic factor-dependent unmasking of "silent" synapses in the developing mouse barrel cortex. Proc Natl Acad Sci U S A *100*, 13069-13074.
Jakawich, S.K., Nasser, H.B., Strong, M.J., McCartney, A.J., Perez, A.S., Rakesh, N., Carruthers, C.J., and Sutton, M.A. (2010). Local presynaptic activity gates homeostatic

changes in presynaptic function driven by dendritic BDNF synthesis. Neuron *68*, 1143-1158.
Jansen, P., Giehl, K., Nyengaard, J.R., Teng, K., Lioubinski, O., Sjoegaard, S.S., Breiderhoff, T., Gotthardt, M., Lin, F., Eilers, A.*, et al.* (2007). Roles for the pro-neurotrophin receptor sortilin in neuronal development, aging and brain injury. Nature neuroscience *10*, 1449-1457.
Jeanneteau, F., and Chao, M.V. (2013). Are BDNF and glucocorticoid activities calibrated? Neuroscience *239*, 173-195.
Jeanneteau, F., Garabedian, M.J., and Chao, M.V. (2008). Activation of Trk neurotrophin receptors by glucocorticoids provides a neuroprotective effect. Proc Natl Acad Sci U S A *105*, 4862-4867.
Ji, Y., Lu, Y., Yang, F., Shen, W., Tang, T.T., Feng, L., Duan, S., and Lu, B. (2010). Acute and gradual increases in BDNF concentration elicit distinct signaling and functions in neurons. Nat Neurosci *13*, 302-309.
Ji, Y., Pang, P.T., Feng, L., and Lu, B. (2005). Cyclic AMP controls BDNF-induced TrkB phosphorylation and dendritic spine formation in mature hippocampal neurons. Nat Neurosci *8*, 164-172.
Jovanovic, J.N., Benfenati, F., Siow, Y.L., Sihra, T.S., Sanghera, J.S., Pelech, S.L., Greengard, P., and Czernik, A.J. (1996). Neurotrophins stimulate phosphorylation of synapsin I by MAP kinase and regulate synapsin I-actin interactions. Proc Natl Acad Sci U S A *93*, 3679-3683.
Jovanovic, J.N., Thomas, P., Kittler, J.T., Smart, T.G., and Moss, S.J. (2004). Brain-derived neurotrophic factor modulates fast synaptic inhibition by regulating GABA(A) receptor phosphorylation, activity, and cell-surface stability. J Neurosci *24*, 522-530.
Jung, H., Yoon, B.C., and Holt, C.E. (2012). Axonal mRNA localization and local protein synthesis in nervous system assembly, maintenance and repair. Nat Rev Neurosci *13*, 308-324.
Kaplan, D.R., and Miller, F.D. (2000). Neurotrophin signal transduction in the nervous system. Curr Opin Neurobiol *10*, 381-391.
Kim, T., and Hempstead, B.L. (2009). NRH2 is a trafficking switch to regulate sortilin localization and permit proneurotrophin-induced cell death. The EMBO journal *28*, 1612-1623.
Kim, Y., Sung, J.Y., Ceglia, I., Lee, K.W., Ahn, J.H., Halford, J.M., Kim, A.M., Kwak, S.P., Park, J.B., Ho Ryu, S.*, et al.* (2006). Phosphorylation of WAVE1 regulates actin polymerization and dendritic spine morphology. Nature *442*, 814-817.
Kohara, K., Kitamura, A., Adachi, N., Nishida, M., Itami, C., Nakamura, S., and Tsumoto, T. (2003). Inhibitory but not excitatory cortical neurons require presynaptic brain-derived neurotrophic factor for dendritic development, as revealed by chimera cell culture. J Neurosci *23*, 6123-6131.
Kohara, K., Yasuda, H., Huang, Y., Adachi, N., Sohya, K., and Tsumoto, T. (2007). A local reduction in cortical GABAergic synapses after a loss of endogenous brain-derived neurotrophic factor, as revealed by single-cell gene knock-out method. J Neurosci *27*, 7234-7244.
Kolarow, R., Brigadski, T., and Lessmann, V. (2007). Postsynaptic secretion of BDNF and NT-3 from hippocampal neurons depends on calcium calmodulin kinase II signaling and proceeds via delayed fusion pore opening. J Neurosci *27*, 10350-10364.

Korte, M., Carroll, P., Wolf, E., Brem, G., Thoenen, H., and Bonhoeffer, T. (1995). Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci U S A *92*, 8856-8860.
Koshimizu, H., Kiyosue, K., Hara, T., Hazama, S., Suzuki, S., Uegaki, K., Nagappan, G., Zaitsev, E., Hirokawa, T., Tatsu, Y.*, et al.* (2009). Multiple functions of precursor BDNF to CNS neurons: negative regulation of neurite growth, spine formation and cell survival. Molecular brain *2*, 27.
Kossel, A.H., Cambridge, S.B., Wagner, U., and Bonhoeffer, T. (2001). A caged Ab reveals an immediate/instructive effect of BDNF during hippocampal synaptic potentiation. Proc Natl Acad Sci U S A *98*, 14702-14707.
Kovalchuk, Y., Hanse, E., Kafitz, K.W., and Konnerth, A. (2002). Postsynaptic Induction of BDNF-Mediated Long-Term Potentiation. Science *295*, 1729-1734.
Koyama, R., and Ikegaya, Y. (2005). To BDNF or not to BDNF: that is the epileptic hippocampus. Neuroscientist *11*, 282-287.
Kramar, E.A., Lin, B., Lin, C.Y., Arai, A.C., Gall, C.M., and Lynch, G. (2004). A novel mechanism for the facilitation of theta-induced long-term potentiation by brain-derived neurotrophic factor. J Neurosci *24*, 5151-5161.
Kuczewski, N., Porcher, C., Ferrand, N., Fiorentino, H., Pellegrino, C., Kolarow, R., Lessmann, V., Medina, I., and Gaiarsa, J.L. (2008). Backpropagating action potentials trigger dendritic release of BDNF during spontaneous network activity. J Neurosci *28*, 7013-7023.
Kundakovic, M., Gudsnuk, K., Herbstman, J.B., Tang, D., Perera, F.P., and Champagne, F.A. (2015). DNA methylation of BDNF as a biomarker of early-life adversity. Proc Natl Acad Sci U S A *112*, 6807-6813.
Lai, K.O., Wong, A.S., Cheung, M.C., Xu, P., Liang, Z., Lok, K.C., Xie, H., Palko, M.E., Yung, W.H., Tessarollo, L.*, et al.* (2012). TrkB phosphorylation by Cdk5 is required for activity-dependent structural plasticity and spatial memory. Nat Neurosci *15*, 1506-1515.
Lambert, W.M., Xu, C.F., Neubert, T.A., Chao, M.V., Garabedian, M.J., and Jeanneteau, F.D. (2013). Brain-derived neurotrophic factor signaling rewrites the glucocorticoid transcriptome via glucocorticoid receptor phosphorylation. Mol Cell Biol *33*, 3700-3714.
Lang, S.B., Stein, V., Bonhoeffer, T., and Lohmann, C. (2007). Endogenous brain-derived neurotrophic factor triggers fast calcium transients at synapses in developing dendrites. J Neurosci *27*, 1097-1105.
Lauri, S.E., Vesikansa, A., Segerstrale, M., Collingridge, G.L., Isaac, J.T., and Taira, T. (2006). Functional maturation of CA1 synapses involves activity-dependent loss of tonic kainate receptor-mediated inhibition of glutamate release. Neuron *50*, 415-429.
Lee, F.S., and Chao, M.V. (2001). Activation of Trk neurotrophin receptors in the absence of neurotrophins. Proc Natl Acad Sci U S A *98*, 3555-3560.
Lee, R., Kermani, P., Teng, K.K., and Hempstead, B.L. (2001). Regulation of cell survival by secreted proneurotrophins. Science *294*, 1945-1948.
Lessmann, V. (1998). Neurotrophin-dependent modulation of glutamatergic synaptic transmission in the mammalian CNS. Gen Pharmacol *31*, 667-674.
Lessmann, V., and Brigadski, T. (2009). Mechanisms, locations, and kinetics of synaptic BDNF secretion: an update. Neurosci Res *65*, 11-22.

Levine, E.S., Crozier, R.A., Black, I.B., and Plummer, M.R. (1998). Brain-derived neurotrophic factor modulates hippocampal synaptic transmission by increasing N-methyl-D-aspartic acid receptor activity. Proc Natl Acad Sci U S A *95*, 10235-10239.
Levine, E.S., and Kolb, J.E. (2000). Brain-derived neurotrophic factor increases activity of NR2B-containing N-methyl-D-aspartate receptors in excised patches from hippocampal neurons. J Neurosci Res *62*, 357-362.
Li, Y., Jia, Y.C., Cui, K., Li, N., Zheng, Z.Y., Wang, Y.Z., and Yuan, X.B. (2005). Essential role of TRPC channels in the guidance of nerve growth cones by brain-derived neurotrophic factor. Nature *434*, 894-898.
Li, Y.X., Xu, Y., Ju, D., Lester, H.A., Davidson, N., and Schuman, E.M. (1998). Expression of a dominant negative TrkB receptor, T1, reveals a requirement for presynaptic signaling in BDNF-induced synaptic potentiation in cultured hippocampal neurons. Proc Natl Acad Sci U S A *95*, 10884-10889.
Liao, L., Pilotte, J., Xu, T., Wong, C.C., Edelman, G.M., Vanderklish, P., and Yates, J.R., 3rd (2007). BDNF induces widespread changes in synaptic protein content and up-regulates components of the translation machinery: an analysis using high-throughput proteomics. J Proteome Res *6*, 1059-1071.
Lim, Y.S., McLaughlin, T., Sung, T.C., Santiago, A., Lee, K.F., and O'Leary, D.D. (2008). p75(NTR) mediates ephrin-A reverse signaling required for axon repulsion and mapping. Neuron *59*, 746-758.
Lin, Y., Bloodgood, B.L., Hauser, J.L., Lapan, A.D., Koon, A.C., Kim, T.K., Hu, L.S., Malik, A.N., and Greenberg, M.E. (2008). Activity-dependent regulation of inhibitory synapse development by Npas4. Nature *455*, 1198-1204.
Liu, Y., Zhang, L.I., and Tao, H.W. (2007). Heterosynaptic scaling of developing GABAergic synapses: dependence on glutamatergic input and developmental stage. J Neurosci *27*, 5301-5312.
Lu, B. (2003). BDNF and activity-dependent synaptic modulation. Learn Mem *10*, 86-98.
Lu, B., and Chow, A. (1999). Neurotrophins and hippocampal synaptic transmission and plasticity. J Neurosci Res *58*, 76-87.
Lu, Y., Christian, K., and Lu, B. (2008). BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? Neurobiol Learn Mem *89*, 312-323.
Lu, Y., Ji, Y., Ganesan, S., Schloesser, R., Martinowich, K., Sun, M., Mei, F., Chao, M.V., and Lu, B. (2011). TrkB as a potential synaptic and behavioral tag. J Neurosci *31*, 11762-11771.
Luikart, B.W., Nef, S., Virmani, T., Lush, M.E., Liu, Y., Kavalali, E.T., and Parada, L.F. (2005). TrkB has a cell-autonomous role in the establishment of hippocampal Schaffer collateral synapses. J Neurosci *25*, 3774-3786.
Luikart, B.W., Zhang, W., Wayman, G.A., Kwon, C.H., Westbrook, G.L., and Parada, L.F. (2008). Neurotrophin-dependent dendritic filopodial motility: a convergence on PI3K signaling. J Neurosci *28*, 7006-7012.
Maffei, L. (2002). Plasticity in the visual system: role of neurotrophins and electrical activity. Arch Ital Biol *140*, 341-346.
Magby, J.P., Bi, C., Chen, Z.Y., Lee, F.S., and Plummer, M.R. (2006). Single-cell characterization of retrograde signaling by brain-derived neurotrophic factor. J Neurosci *26*, 13531-13536.

Mahadeo, D., Kaplan, L., Chao, M.V., and Hempstead, B.L. (1994). High affinity nerve growth factor binding displays a faster rate of association than p140trk binding. Implications for multi-subunit polypeptide receptors. J Biol Chem *269*, 6884-6891.
Mai, J., Fok, L., Gao, H., Zhang, X., and Poo, M.M. (2009). Axon initiation and growth cone turning on bound protein gradients. J Neurosci *29*, 7450-7458.
Marcinkiewicz, M., Savaria, D., and Marcinkiewicz, J. (1998). The pro-protein convertase PC1 is induced in the transected sciatic nerve and is present in cultured Schwann cells: comparison with PC5, furin and PC7, implication in pro-BDNF processing. Brain research Molecular brain research *59*, 229-246.
Martinez, A., Alcantara, S., Borrell, V., Del Rio, J.A., Blasi, J., Otal, R., Campos, N., Boronat, A., Barbacid, M., Silos-Santiago, I.*, et al.* (1998). TrkB and TrkC signaling are required for maturation and synaptogenesis of hippocampal connections. J Neurosci *18*, 7336-7350.
Matsumoto, T., Rauskolb, S., Polack, M., Klose, J., Kolbeck, R., Korte, M., and Barde, Y.A. (2008). Biosynthesis and processing of endogenous BDNF: CNS neurons store and secrete BDNF, not pro-BDNF. Nature neuroscience *11*, 131-133.
McAllister, A.K., Katz, L.C., and Lo, D.C. (1997). Opposing roles for endogenous BDNF and NT-3 in regulating cortical dendritic growth. Neuron *18*, 767-778.
McAllister, A.K., Katz, L.C., and Lo, D.C. (1999). Neurotrophins and synaptic plasticity. Annu Rev Neurosci *22*, 295-318.
McAllister, A.K., Lo, D.C., and Katz, L.C. (1995). Neurotrophins regulate dendritic growth in developing visual cortex. Neuron *15*, 791-803.
Menna, E., Disanza, A., Cagnoli, C., Schenk, U., Gelsomino, G., Frittoli, E., Hertzog, M., Offenhauser, N., Sawallisch, C., Kreienkamp, H.J.*, et al.* (2009). Eps8 regulates axonal filopodia in hippocampal neurons in response to brain-derived neurotrophic factor (BDNF). PLoS Biol *7*, e1000138.
Minichiello, L. (2009). TrkB signalling pathways in LTP and learning. Nat Rev Neurosci *10*, 850-860.
Minichiello, L., Calella, A.M., Medina, D.L., Bonhoeffer, T., Klein, R., and Korte, M. (2002). Mechanism of TrkB-mediated hippocampal long-term potentiation. Neuron *36*, 121-137.
Miyamoto, Y., Yamauchi, J., Tanoue, A., Wu, C., and Mobley, W.C. (2006). TrkB binds and tyrosine-phosphorylates Tiam1, leading to activation of Rac1 and induction of changes in cellular morphology. Proc Natl Acad Sci U S A *103*, 10444-10449.
Mizoguchi, H., Nakade, J., Tachibana, M., Ibi, D., Someya, E., Koike, H., Kamei, H., Nabeshima, T., Itohara, S., Takuma, K.*, et al.* (2011). Matrix metalloproteinase-9 contributes to kindled seizure development in pentylenetetrazole-treated mice by converting pro-BDNF to mature BDNF in the hippocampus. The Journal of neuroscience : the official journal of the Society for Neuroscience *31*, 12963-12971.
Mizui, T., Ishikawa, Y., Kumanogoh, H., Lume, M., Matsumoto, T., Hara, T., Yamawaki, S., Takahashi, M., Shiosaka, S., Itami, C.*, et al.* (2015). BDNF pro-peptide actions facilitate hippocampal LTD and are altered by the common BDNF polymorphism Val66Met. Proc Natl Acad Sci U S A *112*, E3067-3074.
Mizui, T., Ohira, K., and Kojima, M. (2017). BDNF pro-peptide: a novel synaptic modulator generated as an N-terminal fragment from the BDNF precursor by proteolytic processing. Neural Regen Res *12*, 1024-1027.

Mou, X., Peterson, C.B., and Prosser, R.A. (2009). Tissue-type plasminogen activator-plasmin-BDNF modulate glutamate-induced phase-shifts of the mouse suprachiasmatic circadian clock in vitro. Eur J Neurosci *30*, 1451-1460.
Mowla, S.J., Farhadi, H.F., Pareek, S., Atwal, J.K., Morris, S.J., Seidah, N.G., and Murphy, R.A. (2001). Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. The Journal of biological chemistry *276*, 12660-12666.
Mowla, S.J., Pareek, S., Farhadi, H.F., Petrecca, K., Fawcett, J.P., Seidah, N.G., Morris, S.J., Sossin, W.S., and Murphy, R.A. (1999). Differential sorting of nerve growth factor and brain-derived neurotrophic factor in hippocampal neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience *19*, 2069-2080.
Nagappan, G., and Lu, B. (2005). Activity-dependent modulation of the BDNF receptor TrkB: mechanisms and implications. Trends Neurosci *28*, 464-471.
Nagappan, G., Zaitsev, E., Senatorov, V.V., Jr., Yang, J., Hempstead, B.L., and Lu, B. (2009). Control of extracellular cleavage of ProBDNF by high frequency neuronal activity. Proceedings of the National Academy of Sciences of the United States of America *106*, 1267-1272.
Nagerl, U.V., Eberhorn, N., Cambridge, S.B., and Bonhoeffer, T. (2004). Bidirectional activity-dependent morphological plasticity in hippocampal neurons. Neuron *44*, 759-767.
Nelson, S.B., and Valakh, V. (2015). Excitatory/Inhibitory Balance and Circuit Homeostasis in Autism Spectrum Disorders. Neuron *87*, 684-698.
Nielsen, M.S., Madsen, P., Christensen, E.I., Nykjaer, A., Gliemann, J., Kasper, D., Pohlmann, R., and Petersen, C.M. (2001). The sortilin cytoplasmic tail conveys Golgi-endosome transport and binds the VHS domain of the GGA2 sorting protein. The EMBO journal *20*, 2180-2190.
Ninan, I., Bath, K.G., Dagar, K., Perez-Castro, R., Plummer, M.R., Lee, F.S., and Chao, M.V. (2010). The BDNF Val66Met polymorphism impairs NMDA receptor-dependent synaptic plasticity in the hippocampus. J Neurosci *30*, 8866-8870.
Nykjaer, A., Lee, R., Teng, K.K., Jansen, P., Madsen, P., Nielsen, M.S., Jacobsen, C., Kliemannel, M., Schwarz, E., Willnow, T.E.*, et al.* (2004). Sortilin is essential for proNGF-induced neuronal cell death. Nature *427*, 843-848.
Nykjaer, A., and Willnow, T.E. (2012). Sortilin: a receptor to regulate neuronal viability and function. Trends Neurosci *35*, 261-270.
Oh, H., Lewis, D.A., and Sibille, E. (2016). The Role of BDNF in Age-Dependent Changes of Excitatory and Inhibitory Synaptic Markers in the Human Prefrontal Cortex. Neuropsychopharmacology *41*, 3080-3091.
Ohba, S., Ikeda, T., Ikegaya, Y., Nishiyama, N., Matsuki, N., and Yamada, M.K. (2005). BDNF locally potentiates GABAergic presynaptic machineries: target-selective circuit inhibition. Cereb Cortex *15*, 291-298.
Ohira, K., Homma, K.J., Hirai, H., Nakamura, S., and Hayashi, M. (2006). TrkB-T1 regulates the RhoA signaling and actin cytoskeleton in glioma cells. Biochem Biophys Res Commun *342*, 867-874.
Okada, D., Ozawa, F., and Inokuchi, K. (2009). Input-specific spine entry of soma-derived Vesl-1S protein conforms to synaptic tagging. Science *324*, 904-909.
Oppenheim, R.W. (1989). The neurotrophic theory and naturally occurring motoneuron death. Trends Neurosci *12*, 252-255.

Pang, P.T., Teng, H.K., Zaitsev, E., Woo, N.T., Sakata, K., Zhen, S., Teng, K.K., Yung, W.H., Hempstead, B.L., and Lu, B. (2004). Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science *306*, 487-491.
Panja, D., and Bramham, C.R. (2014). BDNF mechanisms in late LTP formation: A synthesis and breakdown. Neuropharmacology *76 Pt C*, 664-676.
Panja, D., Kenney, J.W., D'Andrea, L., Zalfa, F., Vedeler, A., Wibrand, K., Fukunaga, R., Bagni, C., Proud, C.G., and Bramham, C.R. (2014). Two-stage translational control of dentate gyrus LTP consolidation is mediated by sustained BDNF-TrkB signaling to MNK. Cell Rep *9*, 1430-1445.
Park, H., and Poo, M.M. (2013). Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci *14*, 7-23.
Parkhurst, C.N., Yang, G., Ninan, I., Savas, J.N., Yates, J.R., 3rd, Lafaille, J.J., Hempstead, B.L., Littman, D.R., and Gan, W.B. (2013). Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell *155*, 1596-1609.
Patterson, S.L., Abel, T., Deuel, T.A., Martin, K.C., Rose, J.C., and Kandel, E.R. (1996). Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron *16*, 1137-1145.
Peng, Y.R., Zeng, S.Y., Song, H.L., Li, M.Y., Yamada, M.K., and Yu, X. (2010). Postsynaptic spiking homeostatically induces cell-autonomous regulation of inhibitory inputs via retrograde signaling. J Neurosci *30*, 16220-16231.
Pereira, D.B., and Chao, M.V. (2007). The tyrosine kinase Fyn determines the localization of TrkB receptors in lipid rafts. J Neurosci *27*, 4859-4869.
Petersen, C.M., Nielsen, M.S., Nykjaer, A., Jacobsen, L., Tommerup, N., Rasmussen, H.H., Roigaard, H., Gliemann, J., Madsen, P., and Moestrup, S.K. (1997). Molecular identification of a novel candidate sorting receptor purified from human brain by receptor-associated protein affinity chromatography. The Journal of biological chemistry *272*, 3599-3605.
Poo, M.M. (2001). Neurotrophins as synaptic modulators. Nat Rev Neurosci *2*, 24-32.
Rattiner, L.M., Davis, M., and Ressler, K.J. (2004). Differential regulation of brain-derived neurotrophic factor transcripts during the consolidation of fear learning. Learn Mem *11*, 727-731.
Rauskolb, S., Zagrebelsky, M., Dreznjak, A., Deogracias, R., Matsumoto, T., Wiese, S., Erne, B., Sendtner, M., Schaeren-Wiemers, N., Korte, M.*, et al.* (2010). Global deprivation of brain-derived neurotrophic factor in the CNS reveals an area-specific requirement for dendritic growth. J Neurosci *30*, 1739-1749.
Reichardt, L.F. (2006). Neurotrophin-regulated signalling pathways. Philos Trans R Soc Lond B Biol Sci *361*, 1545-1564.
Rivera, C., Li, H., Thomas-Crusells, J., Lahtinen, H., Viitanen, T., Nanobashvili, A., Kokaia, Z., Airaksinen, M.S., Voipio, J., Kaila, K.*, et al.* (2002). BDNF-induced TrkB activation down-regulates the K+-Cl- cotransporter KCC2 and impairs neuronal Cl- extrusion. J Cell Biol *159*, 747-752.
Rodriguez-Tebar, A., and Barde, Y.A. (1988). Binding characteristics of brain-derived neurotrophic factor to its receptors on neurons from the chick embryo. J Neurosci *8*, 3337-3342.

Rose, C.R., Blum, R., Pichler, B., Lepier, A., Kafitz, K.W., and Konnerth, A. (2003). Truncated TrkB-T1 mediates neurotrophin-evoked calcium signalling in glia cells. Nature *426*, 74-78.
Roth, T.L., Lubin, F.D., Funk, A.J., and Sweatt, J.D. (2009). Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry *65*, 760-769.
Roth, T.L., and Sweatt, J.D. (2011). Epigenetic marking of the BDNF gene by early-life adverse experiences. Horm Behav *59*, 315-320.
Rutherford, L.C., DeWan, A., Lauer, H.M., and Turrigiano, G.G. (1997). Brain-derived neurotrophic factor mediates the activity-dependent regulation of inhibition in neocortical cultures. J Neurosci *17*, 4527-4535.
Rutherford, L.C., Nelson, S.B., and Turrigiano, G.G. (1998). BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. Neuron *21*, 521-530.
Sadakata, T., Kakegawa, W., Mizoguchi, A., Washida, M., Katoh-Semba, R., Shutoh, F., Okamoto, T., Nakashima, H., Kimura, K., Tanaka, M.*, et al.* (2007). Impaired cerebellar development and function in mice lacking CAPS2, a protein involved in neurotrophin release. J Neurosci *27*, 2472-2482.
Sajikumar, S., and Korte, M. (2011). Metaplasticity governs compartmentalization of synaptic tagging and capture through brain-derived neurotrophic factor (BDNF) and protein kinase Mzeta (PKMzeta). Proc Natl Acad Sci U S A *108*, 2551-2556.
Salio, C., Averill, S., Priestley, J.V., and Merighi, A. (2007). Costorage of BDNF and neuropeptides within individual dense-core vesicles in central and peripheral neurons. Dev Neurobiol *67*, 326-338.
Sallert, M., Rantamaki, T., Vesikansa, A., Anthoni, H., Harju, K., Yli-Kauhaluoma, J., Taira, T., Castren, E., and Lauri, S.E. (2009). Brain-derived neurotrophic factor controls activity-dependent maturation of CA1 synapses by downregulating tonic activation of presynaptic kainate receptors. J Neurosci *29*, 11294-11303.
Samadi, P., Boutet, A., Rymar, V.V., Rawal, K., Maheux, J., Kvann, J.C., Tomaszewski, M., Beaubien, F., Cloutier, J.F., Levesque, D.*, et al.* (2013). Relationship between BDNF expression in major striatal afferents, striatum morphology and motor behavior in the R6/2 mouse model of Huntington's disease. Genes Brain Behav *12*, 108-124.
Sanchez, A.L., Matthews, B.J., Meynard, M.M., Hu, B., Javed, S., and Cohen Cory, S. (2006). BDNF increases synapse density in dendrites of developing tectal neurons in vivo. Development *133*, 2477-2486.
Santi, S., Cappello, S., Riccio, M., Bergami, M., Aicardi, G., Schenk, U., Matteoli, M., and Canossa, M. (2006). Hippocampal neurons recycle BDNF for activity-dependent secretion and LTP maintenance. EMBO J *25*, 4372-4380.
Sasi, M., Vignoli, B., Canossa, M., and Blum, R. (2017). Neurobiology of local and intercellular BDNF signaling. Pflugers Arch *469*, 593-610.
Savas, J.N., Ribeiro, L.F., Wierda, K.D., Wright, R., DeNardo-Wilke, L.A., Rice, H.C., Chamma, I., Wang, Y.Z., Zemla, R., Lavallee-Adam, M.*, et al.* (2015). The Sorting Receptor SorCS1 Regulates Trafficking of Neurexin and AMPA Receptors. Neuron *87*, 764-780.
Schratt, G.M., Nigh, E.A., Chen, W.G., Hu, L., and Greenberg, M.E. (2004). BDNF regulates the translation of a select group of mRNAs by a mammalian target of

rapamycin-phosphatidylinositol 3-kinase-dependent pathway during neuronal development. J Neurosci *24*, 7366-7377.
Schratt, G.M., Tuebing, F., Nigh, E.A., Kane, C.G., Sabatini, M.E., Kiebler, M., and Greenberg, M.E. (2006). A brain-specific microRNA regulates dendritic spine development. Nature *439*, 283-289.
Schropel, A., von Schack, D., Dechant, G., and Barde, Y.A. (1995). Early expression of the nerve growth factor receptor ctrkA in chick sympathetic and sensory ganglia. Mol Cell Neurosci *6*, 544-566.
Seidah, N.G., Benjannet, S., Pareek, S., Chretien, M., and Murphy, R.A. (1996). Cellular processing of the neurotrophin precursors of NT3 and BDNF by the mammalian proprotein convertases. FEBS Lett *379*, 247-250.
Seil, F.J. (2003). TrkB receptor signaling and activity-dependent inhibitory synaptogenesis. Histol Histopathol *18*, 635-646.
Seil, F.J., and Drake-Baumann, R. (2000). TrkB receptor ligands promote activity-dependent inhibitory synaptogenesis. J Neurosci *20*, 5367-5373.
Sharma, N., Deppmann, C.D., Harrington, A.W., St Hillaire, C., Chen, Z.Y., Lee, F.S., and Ginty, D.D. (2010). Long-Distance Control of Synapse Assembly by Target-Derived NGF. Neuron *67*, 422-434.
Shen, W., Wu, B., Zhang, Z., Dou, Y., Rao, Z.R., Chen, Y.R., and Duan, S. (2006). Activity-induced rapid synaptic maturation mediated by presynaptic cdc42 signaling. Neuron *50*, 401-414.
Shimojo, M., Courchet, J., Pieraut, S., Torabi-Rander, N., Sando, R., 3rd, Polleux, F., and Maximov, A. (2015). SNAREs Controlling Vesicular Release of BDNF and Development of Callosal Axons. Cell Rep *11*, 1054-1066.
Shin, C.Y., Kundel, M., and Wells, D.G. (2004). Rapid, activity-induced increase in tissue plasminogen activator is mediated by metabotropic glutamate receptor-dependent mRNA translation. The Journal of neuroscience : the official journal of the Society for Neuroscience *24*, 9425-9433.
Shivarama Shetty, M., and Sajikumar, S. (2017). 'Tagging' along memories in aging: Synaptic tagging and capture mechanisms in the aged hippocampus. Ageing Res Rev *35*, 22-35.
Singh, B., Henneberger, C., Betances, D., Arevalo, M.A., Rodriguez-Tebar, A., Meier, J.C., and Grantyn, R. (2006). Altered balance of glutamatergic/GABAergic synaptic input and associated changes in dendrite morphology after BDNF expression in BDNF-deficient hippocampal neurons. J Neurosci *26*, 7189-7200.
Singh, K.K., Park, K.J., Hong, E.J., Kramer, B.M., Greenberg, M.E., Kaplan, D.R., and Miller, F.D. (2008). Developmental axon pruning mediated by BDNF-p75NTR-dependent axon degeneration. Nat Neurosci *11*, 649-658.
Skeldal, S., Sykes, A.M., Glerup, S., Matusica, D., Palstra, N., Autio, H., Boskovic, Z., Madsen, P., Castren, E., Nykjaer, A*., et al.* (2012). Mapping of the interaction site between sortilin and the p75 neurotrophin receptor reveals a regulatory role for the sortilin intracellular domain in p75 neurotrophin receptor shedding and apoptosis. J Biol Chem *287*, 43798-43809.
Slipczuk, L., Bekinschtein, P., Katche, C., Cammarota, M., Izquierdo, I., and Medina, J.H. (2009). BDNF activates mTOR to regulate GluR1 expression required for memory formation. PLoS One *4*, e6007.

Snider, W.D., and Lichtman, J.W. (1996). Are neurotrophins synaptotrophins? Mol Cell Neurosci *7*, 433-442.
Song, M., Martinowich, K., and Lee, F.S. (2017). BDNF at the synapse: why location matters. Mol Psychiatry *22*, 1370-1375.
Stahlberg, M.A., Kügler, S., and Dean, C. Visualizing BDNF cell-to-cell transfer reveals astrocytes are the primary recipient of neuronal BDNF. bioRxiv preprint
Suen, P.C., Wu, K., Levine, E.S., Mount, H.T., Xu, J.L., Lin, S.Y., and Black, I.B. (1997). Brain-derived neurotrophic factor rapidly enhances phosphorylation of the postsynaptic N-methyl-D-aspartate receptor subunit 1. Proc Natl Acad Sci U S A *94*, 8191-8195.
Sutter, A., Riopelle, R.J., Harris-Warrick, R.M., and Shooter, E.M. (1979). Nerve growth factor receptors. Characterization of two distinct classes of binding sites on chick embryo sensory ganglia cells. J Biol Chem *254*, 5972-5982.
Swanwick, C.C., Harrison, M.B., and Kapur, J. (2004). Synaptic and extrasynaptic localization of brain-derived neurotrophic factor and the tyrosine kinase B receptor in cultured hippocampal neurons. J Comp Neurol *478*, 405-417.
Szumlinski, K.K., Kalivas, P.W., and Worley, P.F. (2006). Homer proteins: implications for neuropsychiatric disorders. Curr Opin Neurobiol *16*, 251-257.
Tanaka, J., Horiike, Y., Matsuzaki, M., Miyazaki, T., Ellis-Davies, G.C., and Kasai, H. (2008). Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. Science *319*, 1683-1687.
Tao, X., West, A.E., Chen, W.G., Corfas, G., and Greenberg, M.E. (2002). A calcium-responsive transcription factor, CaRF, that regulates neuronal activity-dependent expression of BDNF. Neuron *33*, 383-395.
Teng, H.K., Teng, K.K., Lee, R., Wright, S., Tevar, S., Almeida, R.D., Kermani, P., Torkin, R., Chen, Z.Y., Lee, F.S*., et al.* (2005). ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. The Journal of neuroscience : the official journal of the Society for Neuroscience *25*, 5455-5463.
Teng, K.K., Felice, S., Kim, T., and Hempstead, B.L. (2010). Understanding proneurotrophin actions: Recent advances and challenges. Developmental neurobiology *70*, 350-359.
Tongiorgi, E., Domenici, L., and Simonato, M. (2006). What is the biological significance of BDNF mRNA targeting in the dendrites? Clues from epilepsy and cortical development. Mol Neurobiol *33*, 17-32.
Trang, T., Beggs, S., Wan, X., and Salter, M.W. (2009). P2X4-receptor-mediated synthesis and release of brain-derived neurotrophic factor in microglia is dependent on calcium and p38-mitogen-activated protein kinase activation. J Neurosci *29*, 3518-3528.
Turrigiano, G. (2007). Homeostatic signaling: the positive side of negative feedback. Curr Opin Neurobiol *17*, 318-324.
Tyler, W.J., Alonso, M., Bramham, C.R., and Pozzo-Miller, L.D. (2002). From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem *9*, 224-237.
Tyler, W.J., and Pozzo-Miller, L.D. (2001). BDNF enhances quantal neurotransmitter release and increases the number of docked vesicles at the active zones of hippocampal excitatory synapses. J Neurosci *21*, 4249-4258.

Tyler, W.J., Zhang, X.L., Hartman, K., Winterer, J., Muller, W., Stanton, P.K., and Pozzo-Miller, L. (2006). BDNF increases release probability and the size of a rapidly recycling vesicle pool within rat hippocampal excitatory synapses. J Physiol *574*, 787-803.
Vicario-Abejon, C., Collin, C., McKay, R.D., and Segal, M. (1998). Neurotrophins induce formation of functional excitatory and inhibitory synapses between cultured hippocampal neurons. J Neurosci *18*, 7256-7271.
Vignoli, B., Battistini, G., Melani, R., Blum, R., Santi, S., Berardi, N., and Canossa, M. (2016). Peri-Synaptic Glia Recycles Brain-Derived Neurotrophic Factor for LTP Stabilization and Memory Retention. Neuron *92*, 873-887.
Wang, D.O., Martin, K.C., and Zukin, R.S. (2010). Spatially restricting gene expression by local translation at synapses. Trends Neurosci *33*, 173-182.
Wang, J., Bains, H., Anastasia, A., and Bracken, C. (2018). NMR backbone resonance assignments of the prodomain variants of BDNF in the urea denatured state. Biomol NMR Assign *12*, 43-45.
Wang, X., Berninger, B., and Poo, M. (1998). Localized synaptic actions of neurotrophin-4. J Neurosci *18*, 4985-4992.
Wetsel, W.C., Rodriguiz, R.M., Guillemot, J., Rousselet, E., Essalmani, R., Kim, I.H., Bryant, J.C., Marcinkiewicz, J., Desjardins, R., Day, R.*, et al.* (2013). Disruption of the expression of the proprotein convertase PC7 reduces BDNF production and affects learning and memory in mice. Proceedings of the National Academy of Sciences of the United States of America *110*, 17362-17367.
Wierenga, C.J., Ibata, K., and Turrigiano, G.G. (2005). Postsynaptic expression of homeostatic plasticity at neocortical synapses. J Neurosci *25*, 2895-2905.
Will, T.J., Tushev, G., Kochen, L., Nassim-Assir, B., Cajigas, I.J., Tom Dieck, S., and Schuman, E.M. (2013). Deep sequencing and high-resolution imaging reveal compartment-specific localization of Bdnf mRNA in hippocampal neurons. Sci Signal *6*, rs16.
Wong, Y.H., Lee, C.M., Xie, W., Cui, B., and Poo, M.M. (2015). Activity-dependent BDNF release via endocytic pathways is regulated by synaptotagmin-6 and complexin. Proc Natl Acad Sci U S A *112*, E4475-4484.
Woo, N.H., Teng, H.K., Siao, C.J., Chiaruttini, C., Pang, P.T., Milner, T.A., Hempstead, B.L., and Lu, B. (2005). Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nature neuroscience *8*, 1069-1077.
Yamada, M.K., Nakanishi, K., Ohba, S., Nakamura, T., Ikegaya, Y., Nishiyama, N., and Matsuki, N. (2002). Brain-derived neurotrophic factor promotes the maturation of GABAergic mechanisms in cultured hippocampal neurons. J Neurosci *22*, 7580-7585.
Yang, J., Harte-Hargrove, L.C., Siao, C.J., Marinic, T., Clarke, R., Ma, Q., Jing, D., Lafrancois, J.J., Bath, K.G., Mark, W.*, et al.* (2014). proBDNF negatively regulates neuronal remodeling, synaptic transmission, and synaptic plasticity in hippocampus. Cell reports *7*, 796-806.
Yang, J., Siao, C.J., Nagappan, G., Marinic, T., Jing, D., McGrath, K., Chen, Z.Y., Mark, W., Tessarollo, L., Lee, F.S.*, et al.* (2009). Neuronal release of proBDNF. Nature neuroscience *12*, 113-115.
Yang, M., Lim, Y., Li, X., Zhong, J.H., and Zhou, X.F. (2011). Precursor of brain-derived neurotrophic factor (proBDNF) forms a complex with Huntingtin-associated

protein-1 (HAP1) and sortilin that modulates proBDNF trafficking, degradation, and processing. The Journal of biological chemistry *286*, 16272-16284.
Yano, H., Ninan, I., Zhang, H., Milner, T.A., Arancio, O., and Chao, M.V. (2006). BDNF-mediated neurotransmission relies upon a myosin VI motor complex. Nat Neurosci *9*, 1009-1018.
Zagrebelsky, M., Holz, A., Dechant, G., Barde, Y.A., Bonhoeffer, T., and Korte, M. (2005). The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons. J Neurosci *25*, 9989-9999.
Zakharenko, S.S., Patterson, S.L., Dragatsis, I., Zeitlin, S.O., Siegelbaum, S.A., Kandel, E.R., and Morozov, A. (2003). Presynaptic BDNF required for a presynaptic but not postsynaptic component of LTP at hippocampal CA1-CA3 synapses. Neuron *39*, 975-990.
Zanin, J.P., Unsain, N., and Anastasia, A. (2017). Growth factors and hormones pro-peptides: the unexpected adventures of the BDNF prodomain. J Neurochem *141*, 330-340.
Zeisel, A., Hochgerner, H., Lönnerberg, P., Johnsson, A., Memic, F., van der Zwan, J., Häring, M., Braun, E., Borm, L., La Manno, G*., et al.* (2018). Molecular architecture of the mouse nervous system. bioRxiv preprint.