Chapter 20

The role of brain-derived neurotrophic factor in neural circuit development and function

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Chapter outline

20.1 Introduction to neurotrophins

The discovery of nerve growth factor (NGF) nearly 70 years ago revolutionized the field of embryology and development. Groundbreaking work by Rita Levi-Montalcini and Stanley Cohen in the 1950s demonstrated the rapid neurite outgrowth of tumor cells transplanted into an embryo, and they subsequently isolated and characterized NGF as the responsible factor; this seminal work led to the Nobel Prize in Physiology or Medicine in 1986. Further work identified a family of homologous secreted proteins, known as neurotrophins, that are essential for survival, development, and plasticity in the nervous system (Lessmann et al., 2003). Neurotrophins include NGF (Levi-Montalcini, 1964), brain-derived neurotrophic factor (BDNF) (Barde et al., 1982), neurotrophin-3 (NT-3) (Hohn et al., 1990), and neurotrophin-4 (NT-4) (Hohn et al., 1990). BDNF, discovered in the 1980s by Yves-Alain Barde and Hans Thoenen, is the most abundantly and broadly expressed growth factor in the central nervous system (CNS) and has been studied most thoroughly among the neurotrophins for its role in synaptic plasticity in neural circuits. In this chapter, we will discuss the signaling mechanisms of

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BDNF; how it functions in developing and mature neurons; and finally its role in normal behavior, disease states, and potential therapeutic applications.

20.2 BDNF transcription, translation, processing, and signaling

20.2.1 Gene structure and transcriptional regulation

The structure of the BDNF gene is quite complex and produces dozens of transcripts that will ultimately result in a single protein product, with evidence suggesting functional regulation of its transcription by multiple cellular processes (Cunha et al., 2010). The BDNF gene in rodents and humans consists of at least eight 5′ untranslated exons (I–VIII), each with its own promoter. The human BDNF gene contains two novel exons: Vh, which has its own promoter, and VIIIh, which is not linked to an independent promoter (Pruunsild et al., 2007). These transcripts are each spliced to the common 3′ translated exon IX containing the protein coding domain (Aid et al., 2007; Liu et al., 2005, 2006; Pruunsild et al., 2007). Due to alternative splicing of exon II into IIA, IIB, and IIC products, and the existence of two distinct polyadenlylation signals within the coding sequence resulting in transcripts containing either long (~2.85 kb) or short (~0.35 kb) 3′ untranslated regions (UTRs), there are at least 24 potential transcription products of the rodent BDNF gene (see Fig. 20.1) (Aid et al., 2007; Liu et al., 2005, 2006; Timmusk et al., 1993; An et al., 2008). Research has indicated that the short 3′ UTR leads to localization to the cell body while the long form is found in dendrites, suggesting that the UTR may functionally regulate transport and local dendritic synthesis of BDNF (An et al., 2008).

Studies suggest that specific exons control tissue- and temporal specificity of BDNF expression: for example, exon IV transcripts are present throughout the brain from early embryonic timepoints, whereas exon V is expressed postnatally and predominately in cortical brain regions.

Furthermore, exons are differentially regulated by DNA methylation, histone acetylation, and neuronal activity. DNA methylation normally suppresses expression of exons I, IV, V, VIII, and IX, while histone acetylation typically regulates expression of exons III, VII, and IX (Aid et al., 2007). Neuronal depolarization too leads to induction of exons I, IV, V, VII, and IX. Exon IV, also referred to as the "activity-dependent" exon, shows long-lasting upregulation after neural activity, and its promoter has been characterized to contain binding sites for cAMP-response element binding (CREB) proteins, calcium-responsive transcription factor, and methyl-CpG binding protein 2 (MeCP2) (Shieh et al., 1998; Tao et al., 1998; Tabuchi et al., 2002; Chen et al., 2003a, 2003b; Martinowich et al., 2003). Indeed, knock-in mice harboring a mutation of the CREB binding site upstream of exon IV leads to disrupted sensory-driven transcription of exon IV in the cortex (Hong et al., 2008).

Intracellular calcium influx through L-type calcium channels (Zafra et al., 1992) and n-methyl-D-aspartate (NMDA)-type glutamate receptors (Zafra et al., 1990, 1991, 1992) have also been directly linked to increased transcription of

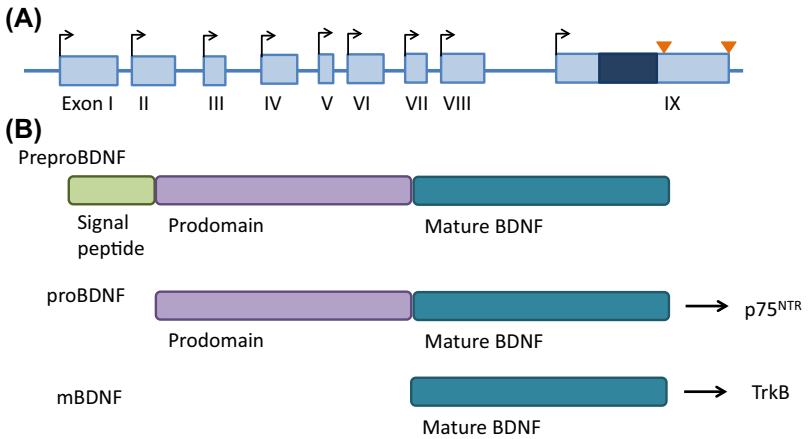

FIGURE 20.1 Structure of the brain-derived neurotrophic factor (BDNF) gene and protein from mouse and rat. (A) The BDNF gene consists of nine exons (I–IX). The coding region (dark blue box) is within exon IX and followed by either a short or long (indicated by orange triangles) polyadenylation sequence. (B) The BDNF protein starts as preproBDNF containing the signal peptide (green), prodomain (purple) and mature protein (blue). After the signal peptide is cleaved off, proBDNF remains and binds preferentially to the $p75^{NTR}$ receptor. The prodomain may also be cleaved off to leave mature BDNF which preferentially binds to the TrkB receptor.

BDNF. Other stimuli that regulate exon-specific transcription of BDNF include seizures, learning paradigms, stress, exercise, and antidepressant treatment, some of which will be covered in detail in subsequent sections of this chapter (Cunha et al., 2010).

20.2.2 Epigenetic regulation of BDNF

As alluded to in the previous section, transcription of BDNF can be controlled by histone acetylation and DNA methylation, two important epigenetic regulatory mechanisms. In this section, we will discuss factors influencing the epigenetic regulation of BDNF expression. DNA methylation, the addition of methyl groups to poly-cytosine-guanine sites (CpG islands), is typically associated with transcriptional silencing. Maintenance of methylation on DNA is mediated by DNA methyltransferase 1 (DNMT1), while de novo methylation is established by DNA methyltransferases 3a and b (DNMT3a/b). Neural activity, a major activator of BDNF transcription as described in the previous section, is associated with alterations in the DNA methylation status of specific regions within the BDNF gene. For example, the CREB binding site within the promoter region of BDNF becomes demethylated allowing increased binding of phospho-CREB in the hypothalamus during heat conditioning in early postnatal development in chicks, while two other CpG sites in the BDNF promoter regions show increased methylation coincident with increased DNMT3a binding (Yossifoff et al., 2008). Furthermore, fear conditioning in rats leads to upregulation of BDNF exon IV transcription associated with significant demethylation of this region in the CA1 of hippocampus (Lubin et al., 2008). Demethylation of BDNF exon IV by fear conditioning could be reversed by pharmacological inhibition of DNA methyltransferases or by blocking NMDA receptors (Lubin et al., 2008). Pharmacological inhibition of DNMTs also led to enhanced BDNF transcription that was occluded by NMDA receptor blockade in mouse hippocampus (Autry et al., 2015).

Adverse stimuli have been associated with decreases in BDNF transcription and hypermethylation of regions of the BDNF gene. In a model of posttraumatic stress disorder in rats, the promoter region of BDNF exon IV is hypermethylated contributing to reduced BDNF mRNA expression in the CA1 of hippocampus (Roth et al., 2011). Similar increases in methylation in the promoter of BDNF exon IV are correlated with depression-related behavior in adult mice treated with methylmercury perinatally (Onishchenko et al., 2008). Poor parental care in early postnatal life also leads to decreases in BDNF mRNA expression linked with increased methylation of exon IX in early life and both exon IV and IX in adults in the rat prefrontal cortex (Roth et al., 2009). BDNF transcription was also suppressed in the cortex and hippocampus of adult rats deprived of light exposure, and this suppression was correlated with hypermethylation of BDNF promoter IV (Karpova et al., 2010). Together, these studies illustrate the key role of methylation and activity of DNA methyltransferase enzymes on activity-dependent expression of BDNF, particularly transcription driven by exon IV expression.

One way by which methylation leads to dynamic changes in gene expression is illustrated by methyl CPG binding protein 2's (MeCP2) regulation of BDNF transcription. MeCP2 has been shown to regulate BDNF exon IV silencing during periods of low neuronal activity through the recruitment of a corepressor Sin3a (Chen et al., 2003a; Martinowich et al., 2003). Upon neuronal stimulation, MeCP2 is released from the promoter through its phosphorylation at Ser-421 leading to an increase in pCREB activity at the promoter, and thus unsilencing BDNF transcription (Chen et al., 2003a). However, the nature of the regulation of *BDNF* by MeCP2 remains contentious. MeCP2 has subsequently been shown to bind ubiquitously in the genome and also been shown to increase transcription under certain circumstances and in specific brain regions (Chahrour et al., 2008; Cohen et al., 2011). Recent studies have revealed an even more complex landscape of MeCP2 functions, showing that it can bind to non-CpG methylated sequences as well as to unmethylated and hydroxymethyl CpG (hMCG) sequences (Kinde et al., 2015). All these processes have been predominantly studied in in vitro systems, and it is possible that each of these mechanisms may act in specific neuronal states, contexts, and developmental stages.

In addition to direct modification of DNA, epigenetic regulation can occur through modifications of histones, the octamer of proteins around which DNA is coiled and compacted within the nucleus. The n-terminal "tail" region of histone proteins can be modified enzymatically in a number of ways that produces a so-called "histone code" that is either permissive or repressive to transcription at specific genetic sites (Kouzarides, 2007). Histone acetylation is associated with increased transcription, and this modification is added by histone acetyl-transferases (HATs) and removed by histone deacetylases (HDACs); histone methylation is associated with transcriptional activation at lysine 4 of H3 (H3K4), while trimethylation at lysine 27 of H3 (H3K27) is associated with transcriptional repression. These modifications are added by histone methyltransferases (HMTs) and removed by histone demethylases (HDMTs). Acetylation of histone protein H4 in promoter IV of BDNF is associated with increased transcription at this locus during extinction of fear conditioning (Bredy

et al., 2007), and treatment with HDAC inhibitor valproic acid enhances fear memory acquisition, extinction, and reconsolidation in mice (Bredy et al., 2007; Bredy and Barad, 2008). Histone acetylation of H3 and H4 is decreased in aged rats contributing to reduced expression of BDNF and decreased long-term potentiation (LTP) in hippocampal slices, and these molecular and physiological changes could be reversed by acute treatment with HDAC inhibitors (Zeng et al., 2011). Furthermore, methylation of H3K4 at BDNF promoters in exons III and IV was associated with long-term exposure to an enriched environment in mice (Kuzumaki et al., 2011). H3K4 methylation is also enhanced during fear conditioning at BDNF exon I promoter in rats (Gupta et al., 2010). Together, these studies illuminate the importance of epigenetic regulation at the DNA and histone level in expression of BDNF.

20.2.3 Translation and processing

The translation of BDNF and its folding and vesicle packaging are heavily influenced by the 3′ UTR, the prodomain region, as well as posttranslational modifications. Under basal neuronal conditions, the short 3′ UTR BDNF mRNA is primarily translated while the long form acts in cis as a repressor (Lau et al., 2010). However, under high levels of neuronal activity, the long 3′ UTR BDNF mRNA is rapidly and robustly expressed. As previously mentioned, studies show that the long 3′ UTR BDNF mRNA may be localized to dendrites, thus ensuring local and rapid effects of BDNF upon neural stimulation (An et al., 2008; Vicario et al., 2015). Such rapid upregulation of BDNF in the hippocampus and cortex have been demonstrated to underlie important processes in learning and memory as well as antidepressant behavior, which we will discuss in detail in Section IV.

The protein product of BDNF coding exon IX is preproBDNF (Lessmann et al., 2003). This product contains a signal peptide and the proBDNF sequence. The signal peptide is responsible for sequestering the protein to the endoplasmic reticulum. This sequence is cleaved to produce the 32 kilodalton (kDa) proBDNF, allowing transport to the Golgi apparatus (Lessmann et al., 2003). Within the Golgi bodies, proBDNF may undergo several posttranslational modifications such as N-acetylation (Bradshaw et al., 1998) and C-amidation (Eipper et al., 1992), though how these modifications affect packaging and other downstream effects is not currently well understood.

20.2.4 Constitutive and activity-dependent secretion

BDNF, in contrast to other neurotrophins, such as NT-3 and NGF that are largely constitutively secreted, is preferentially sorted into the activity-dependent, or regulated, pathway for release (Goodman et al., 1996; Farhadi et al., 2000; Adachi et al., 2005). The prodomain of proBDNF allows proper protein folding (Heymach et al., 1996) and sorting to either the constitutive or activity-dependent secretory pathway (Lee et al., 2001). ProBDNF (32 kDa) itself may be packaged into vesicles with the enzyme tissue plasminogen activator (tPA/plasmin) which will cleave proBDNF to the 14-kDa mature BDNF (mBDNF) extracellularly (Waterhouse and Xu, 2009); or alternatively proBDNF may be cleaved intracellularly by furin or proconvertases into mBDNF for secretion (Lessmann and Brigadski, 2009). Both proBDNF and mBDNF can be secreted in an activity-dependent manner or via the constitutive secretory pathway, and evidence suggests that proBDNF predominates extracellularly (Mowla et al., 2001; Yang et al., 2009), though this view is not undisputed (Matsumoto et al., 2008).

Importantly, the targeting of BDNF to the activity-dependent pathway is controlled by the val66met mutation; this single nucleotide polymorphism (SNP) found in the prodomain at nucleotide 196, which causes a valine to methionine substitution, leads to inefficient activity-dependent release of BDNF and has been associated with multiple psychiatric disorders that we will discuss in detail in subsequent sections (Egan et al., 2003). This mutation may affect binding of the prodomain to sorting receptors including carboxypeptidase E (CPE) or sortilin (Lou et al., 2005; Chen et al., 2005). BDNF vesicular localization is reduced in cultured cells lacking the binding domain of sortilin (Chen et al., 2005), which demonstrates the essential role for this receptor in sorting BDNF into the regulated pathway. Another intriguing protein of interest in the transport of BDNF is huntingtin protein encoded by the huntingtin gene (htt): mutant forms of huntingtin that cause Huntington's disease lead to reduced microtubule-dependent trafficking of BDNF-containing vesicles compared to wild-type htt (Gauthier et al., 2004).

Biologically active forms of BDNF are thought to be composed of noncovalently associated homodimers, though recombinant proteins do appear to form heterodimers (for example, BDNF/NT-3) in cell lines (Jungbluth et al., 1994). In addition to secretion of de novo translated proteins, BDNF may also be endocytosed and recycled for re-release within the same neuron (Santi et al., 2006; von Bartheld et al., 2001). Further study is required to tease apart the function of BDNF in homodimeric form as opposed to its action in heterodimers.

20.2.5 Pre- and postsynaptic release

Historically, BDNF has been thought to act at presynaptic sites to enhance neurotransmission via its tropomysin-related kinase B (TrkB) receptors as revealed by studies of the canonical neuromuscular junction synapse (NMJ) (Lohof et al., 1993). It is now appreciated that BDNF (Dieni et al., 2012; Matsuda et al., 2009) and TrkB signaling (Alder et al., 2005; Chen et al., 1999) are involved in plasticity processes both pre- and postsynaptically. Specifically, visualization of BDNF trafficking using green fluorescent protein (GFP)-tagged BDNF in cultured cortical or hippocampal neurons reveals localization of BDNF at axons as well as dendrites (Adachi et al., 2005; Matsuda et al., 2009; Jakawich et al., 2010). However, use of a myc-tagged BDNF only reveals localization in dendrites at presynaptic release sites in hippocampal neurons (Dieni et al., 2012).

More recently, studies have used the trisynaptic circuit of the hippocampus to study pre- and postsynaptic effects of BDNF. In this canonical circuit, neurons of the dentate gyrus (which receive input from the perforant path originating in the entorhinal cortex) project to the CA3 which in turn sends axons to CA1. Early experiments showed that deficits in CA3-CA1 LTP in global BDNF knockouts could be recapitulated by presynaptic deletion of BDNF in CA3 alone (Zakharenko et al., 2003). In dentate gyrus granule cells, application of BDNF stimulated depolarization and calcium influx when applied at the postsynaptic dendrites but not at the presynaptic axons. These effects are blocked by voltage clamping of the dentate granule cells during perforant path stimulation, revealing a postsynaptic effect of BDNF signaling (Kovalchuk et al., 2002).

Previous studies were unable to localize the effects of BDNF signaling because they did not examine the effects of BDNF in concert with the TrkB receptor, and largely relied on application of exogenous BDNF rather than examining release of endogenous BDNF. Recently, experiments have used selective knockout of BDNF and TrkB from pre- or postsynaptic sites in slices and in behaving mice to examine both components of BDNF signaling in parallel. Selective deletion of BDNF or TrkB from presynaptic CA1 neurons or postsynaptic CA3 neurons in the hippocampus has revealed distinct roles for each type of signaling in both basal neurotransmission, synaptic plasticity, and behavior: presynaptic BDNF and postsynaptic TrkB are required for induction of LTP while postsynaptic BDNF and presynaptic TrkB are essential for LTP maintenance (Lin et al., 2018). In addition, loss of presynaptic TrkB expression leads to impaired release probability, while both pre- and postsynaptic loss of TrkB lead to deficits in memory tasks illustrating a critical role for both retrograde and anterograde BDNF signaling in hippocampal functions (Lin et al., 2018). Together, these studies reveal that BDNF signaling via TrkB receptors have localized and temporally specific effects on synaptic plasticity.

20.2.6 Receptors and intracellular cascades

Neurotrophins are able to bind to two classes of receptors, the pan-neurotrophin 75 receptor (p75NTR) and tropomyosin-related kinase receptors (TrkRs). The p75NTR receptor belongs to the tumor necrosis factor (TNF) family of receptors and is associated with apoptosis pathways (Chao, 2003). p75NTR binds to BDNF, NT-3, and NT-4/5 with similar affinity (Chao, 2003). There are three subtypes of Trk tyrosine kinase receptors: TrkA which binds NGF, TrkB which binds BDNF and NT-4/5, and TrkC which binds to NT-3 (Reichardt, 2006). p75NTR is predominately expressed in the peripheral nervous system (PNS) in adults and is transiently expressed in the central nervous system during early development, or in adults in response to cellular insults including injury and inflammation (Lee et al., 2001). In contrast, TrkB is widely expressed across the CNS and in some subsets of PNS neurons of the sensory system (Lee et al., 2001).

Additionally, both proBDNF and mBDNF appear to be secreted and have been demonstrated to activate distinct receptors and intracellular cascades (Woo et al., 2005; Yang et al., 2009). ProBDNF binds to the low-affinity p75NTR receptor that plays a role in apoptosis via activation of the jun kinase pathway (Lessmann et al., 2003; Roux and Barker, 2002). mBDNF binds preferentially to its high-affinity receptor, tropomysin-related kinase B (TrkB) (Lee et al., 2001). Binding of mBDNF leads to the autophosphorylation of TrkB, which activates various intracellular cascades (Levine et al., 1998). TrkB receptor activation can lead to signaling in at least three distinct intracellular cascades that impact cellular function on multiple timescales: (1) the phospholipase C gamma (PLC γ) pathway which leads to activation of protein kinase C, (2) the phosphatidylinositol 3-kinase (PI3K) which activates serine/threonine kinase AKT, and (3) mitogen-activated protein kinase (MAPK, or extracellular signal related kinase ERK) and several downstream effectors (Reichardt, 2006). In the section detailing BDNF's function in neurons, we will discuss in detail the cellular functions and physiological contexts under which each of these signaling pathways become activated (Fig. 20.2).

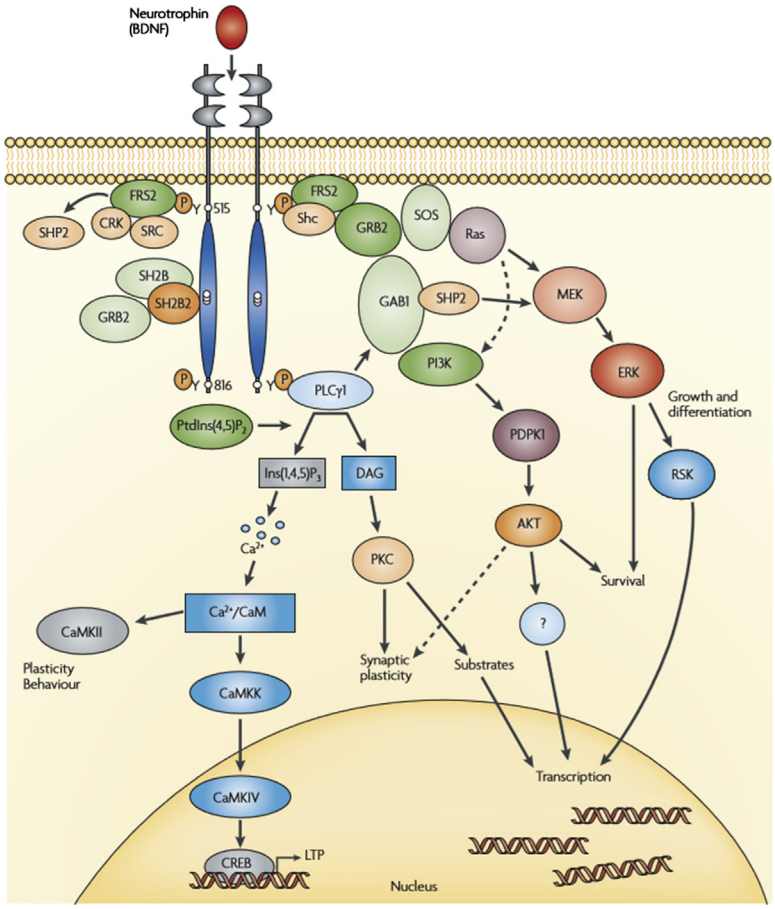

FIGURE 20.2 Brain-derived neurotrophic factor (BDNF) receptor—mediated signaling pathways. Three main signaling pathways are engaged by binding of BDNF to the TrkB receptor. TrkB receptor activation can lead to signaling in at least three distinct intracellular cascades that impact cellular function on multiple timescales: (1) the phospholipase C gamma (PLC γ) pathway which leads to activation of protein kinase C, (2) the phosphatidylinositol 3-kinase (PI3K) which activates serine/threonine kinase AKT, and (3) mitogen-activated protein kinase (MAPK, or extracellular signal—related kinase ERK) and several downstream effectors. *Figure reproduced with permission of Springer Nature.*

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20.2.7 Effector and target of local protein synthesis

BDNF signaling can enhance translation of several mRNAs and itself can be locally translated at dendrites in response to specific types of stimuli. BDNF has been associated with increases in both the initiation and elongation steps of translation through several mechanisms leading to enhanced synthesis of a subset of neuronal mRNAs. BDNF application to hippocampal or cortical neurons in slice or dissociated cultures leads to the translocation of initiation factor eukaryotic initiation factor 4e (eIF4e) to mRNA granules localized at synapses (Smart et al., 2003). In addition, BDNF-TrkB signaling is associated with enhanced phosphorylation of both eIF4e and eIF4e-binding protein (eIF4eBP) which both lead to upregulation of translation initiation via mammalian target of rapamycin (mTOR), extracellular-related kinase (ERK), and mitogen-activated protein kinase (MAPK) intracellular cascades (Kanhema et al., 2006; Takei et al., 2001, 2004; Schratt et al., 2004). BDNF signaling is also associated with rapid, transient phosphorylation of eukaryotic elongation factor 2 (eEF2) which can lead to arrest of elongation; however, this effect was observed specifically at nonsynaptic sites, suggesting that this process may work in concert with enhanced initiation at synapses to coordinate compartment-specific protein translation (Kanhema et al., 2006). Indeed, further research showed loss of eEF2 phosphorylation with enhanced protein synthesis after BDNF application in cortical neurons (Inamura et al., 2005).

Multiple lines of evidence suggest that BDNF treatment leads to the selective enhancement of a subset of mRNAs comprising around 4% of transcripts expressed within a specific cell type (Schratt et al., 2004; Yin et al., 2002), with a concomitant decrease in translation of certain transcripts (Rivera et al., 2002; Raab-Graham et al., 2006; Castren et al., 2002). Many of these transcripts are associated with synaptic plasticity, including calcium-modulated kinase II alpha

(CamKIIα), Staufen (Stau1), activity-regulated cytoskeletal protein (Arc), NR1, and GluA1 (Aakalu et al., 2001; Yin et al., 2002; Ying et al., 2002; Kelleher et al., 2004; Kanhema et al., 2006; Takei et al., 2004; Jourdi et al., 2009).

BDNF is also known to be rapidly translated under certain physiological conditions. In cultured hippocampal neurons, loss of spontaneous neurotransmission through blockade of NMDA receptors led to a rapid increase in synaptic strength accompanied by increased translation of plasticity-related transcripts via dephosphorylation of eEF2 (Sutton et al., 2006). In vivo studies showed that NMDA receptor blockade led to rapid enhancement of BDNF protein levels dependent on protein translation mechanisms including mTOR signaling (Li et al., 2010) and eEF2 dephosphorylation (Autry et al., 2011), suggesting a similar molecular mechanism as illustrated in hippocampal cultures. Further research revealed that mice lacking the kinase responsible for phosphorylation of eEF2 did not show enhanced BDNF synthesis in response to treatment with an NMDA receptor antagonist (Nosyreva et al., 2013). Finally, as will be further discussed in the following section, BDNF signaling via TrkB may directly feed into mTOR-dependent rapid protein synthesis during memory consolidation. These mechanisms associated with rapid translation of BDNF at synapses play an essential role in certain behaviors, which we will discuss in subsequent sections.

20.3 BDNF functions in the nervous system

20.3.1 Dendritic and axonal development

BDNF is critical during development for neuronal survival and axon guidance (Yoshii and Constantine-Paton, 2010). BDNF knockouts have severe developmental impairments and die soon after birth (Ernfors et al., 1994). BDNF generally acts as a target-derived messenger during development, meaning that it is synthesized and secreted from postsynaptic neurons, and upon binding to TrkB, the receptors internalize to stimulate intracellular signaling cascades that lead to neurite outgrowth (Yoshii and Constantine-Paton, 2010). Signaling in this manner, BDNF has been shown to be essential for the development of several neuron types including dopaminergic, GABAergic, cholinergic, and serotonergic neurons (Pillai, 2008).

BDNF, acting via TrkB binding, exerts several cellular effects related to growth cone turning, neurite outgrowth, and circuit tuning during early development, particularly in hippocampal and cortical neurons (Ahmed et al., 1995). Neurotrophins have been shown in cultured cells to guide axon growth cones through a cyclic AMP-mediated mechanism (Song et al., 1997) and help sensory neurons turn toward beads conjugated to BDNF in vivo in mouse limb buds (Tucker et al., 2001). In the visual cortex of ferrets, application of BDNF increases length and complexity of dendrites in layer IV pyramidal neurons (McAllister et al., 1995) and subsequent studies revealed that this effect is activity dependent (McAllister et al., 1996) and, through use of TrkB antibodies, that endogenous BDNF regulates dendritic growth (McAllister et al., 1997). In *Xenopus laevis*, application of exogenous BDNF increases axonal branching in retinal ganglion, while reducing BDNF signaling through application of antibodies leads to decreased axonal complexity (Cohen-Cory and Fraser, 1995). BDNF binding to TrkB at the distal axon of cortical neurons leads to axon outgrowth via activation of Erk1/2 signaling that stimulates expression of map kinase phosphatase 1 (MKP-1) which targets c-Jun n-terminal kinase (JNK). This in turn increases microtubule dynamics necessary for cytoskeletal remodeling, allowing axon collateral branching (Jeanneteau et al., 2010). Overexpression of BDNF during development leads to dendritic sprouting and structural instability in cortical neurons (Horch et al., 1999) and their neighboring neurons (Horch and Katz, 2002) suggesting that BDNF acts in a spatially restricted manner to induce structural effects. However, reduction in BDNF or TrkB expression was not sufficient enough to produce deficits in axonal phenotypes, though this effect may be due to developmental compensation by other neurotrophins and receptors (Martinez et al., 1998; Lyckman et al., 2005).

By contrast, BDNF acting through $p75^{NTR}$, when TrkB expression is low during early development, may lead to axon retraction. Studies show that the genetic deletion of $p75^{NTR}$ disrupts developmental axon pruning (Singh et al., 2008; Park et al., 2010). Together, these studies illustrate the central role for BDNF signaling either through TrkB or $p75^{NTR}$ in sculpting axons and dendrites during development in an activity dependent manner.

20.3.2 Cell health and survival

Cell health and survival were some of the earliest appreciated effects of neurotrophin signaling and in particular BDNF. BDNF knockout mice show massive reductions in cell numbers of specific neural populations including vestibular ganglia, trigeminal ganglia, and dorsal root ganglia (Ernfors et al., 1994). In the adult, increased BDNF signaling through either viral expression (Benraiss et al., 2001) or recombinant protein infusion (Scharfman et al., 2005) can enhance adult neurogenesis in rats while reduced BDNF signaling in BDNF- (Sairanen et al., 2005) and TrkB- (Bergami et al., 2008)

deficient mouse lines leads to reduced adult neurogenesis. In addition, the val66met mutation disrupting activity-dependent secretion of BDNF is also associated with reductions in adult neurogenesis (Bath et al., 2008). Alternatively, action of proBDNF via the $p75^{NTR}$ can lead to programmed cell death. These opposing effects of BDNF on cell survival dependent on signaling mechanism may be significant for shaping the brain during development or dynamic plasticity mechanisms.

20.3.3 Neuronal differentiation, synapse formation, and maturation

BDNF plays an essential role in the differentiation of cells to a neuronal fate. Neuronal differentiation of embryonic stem cells from cortex and hippocampus is enhanced by treatment with exogenous BDNF (Ahmed et al., 1995; Shetty and Turner, 1998). Alternatively, BDNF knockout leads to reduced differentiation of interneurons in the mouse cortex, hippocampus, and striatum (Jones et al., 1994).

BDNF can also rapidly increase synaptic activity in neurons (Lohof et al., 1993), suggesting that BDNF may specifically enhance synaptogenesis in addition to the previously detailed effects on dendritic and axonal morphology. Infusion of exogenous BDNF increases the number of synaptic puncta visualized by immunostaining in the optic tectum of *X. laevis* tadpoles (Alsina et al., 2001). Indeed, multiple studies have also demonstrated the enhancement of dendritic spine formation by application of exogenous BDNF in dissociated hippocampal cultures and hippocampal slices (Alonso et al., 2004; Amaral et al., 2007; Ji et al., 2010; Tyler and Pozzo-Miller, 2001, 2003). Spine formation mediated by BDNF signaling depends on ERK signaling (Alonso et al., 2004), TRPC3 signaling (Amaral and Pozzo-Miller, 2007), and increased actin polymerization via cofilin (Rex et al., 2007) and m-calpain (Zadran et al., 2010). In addition to such structural synaptogenesis, further research revealed functional maturation of developing neuromuscular junction synapses by examining excitatory postsynaptic currents (EPSCs) (Wang et al., 1995).

At central synapses, BDNF can enhance the formation and maturation of both excitatory and inhibitory synapses, as demonstrated in cultured hippocampal neurons (Vicario-Abejon et al., 1998). In the hippocampus, the predominant effect of BDNF application on developing synapses is the enhancement of glutamate release by increasing presynaptic vesicle release probability via the ERK signaling cascade (Sallert et al., 2009; Tyler et al., 2006; Mohajerani et al., 2007). At inhibitory gamma-aminobutyric acid (GABAergic) synapses, BDNF overexpression accelerates maturation of inhibition in the cortex leading to premature closure of the visual critical period (Hanover et al., 1999; Huang et al., 1999). The effects of BDNF at GABAergic synapses in the visual cortex appear to be activity-dependent because dark-rearing conditions slowed maturation of inhibitory circuits (Mandolesi et al., 2005), and this effect was lost in mice overexpressing BDNF (Gianfranceschi et al., 2003). Altogether, these results illustrate how BDNF signaling affects differentiation of neurons and the formation and maturation of excitatory and inhibitory synaptic connections (Fig. 20.3).

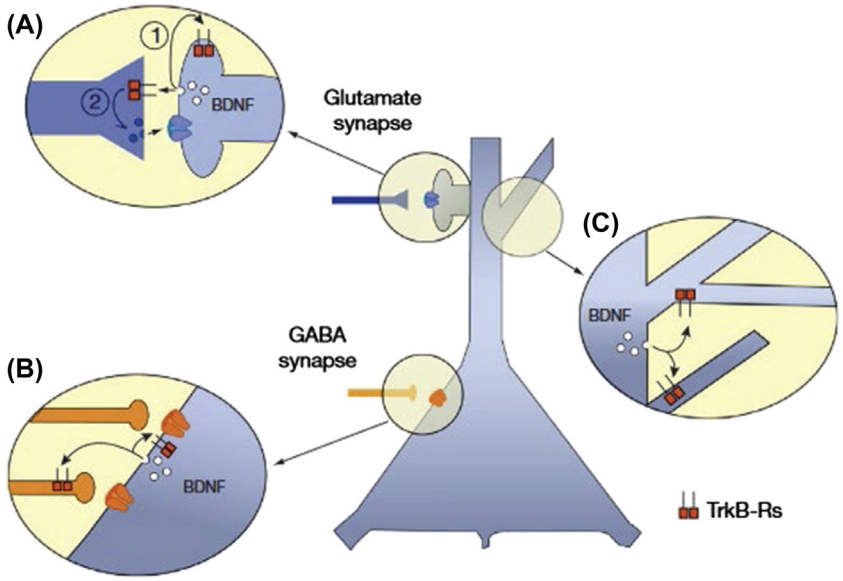

FIGURE 20.3 Effect of brain-derived neurotrophic factor (BDNF) at synapses. BDNF has multiple actions on glutamatergic and GABAergic synapses both pre- and postsynaptically. (A) At glutamatergic synapses, postsynaptic TrkB receptor activation increases the size of dendritic spines while activation of presynaptic TrkB receptors increases miniature glutamatergic activity. (B) At GABAergic synapses, postsynaptically secreted BDNF increases the number of GABAergic synapses and increases the frequency of GABAergic miniature activity. (C) BDNF signaling additionally contributes to length and branching of dendrites. *Figure reproduced with permission of Elsevier Inc.*

20.3.4 Cellular plasticity

BDNF is essential for synaptic plasticity in mature brain circuits (Poo, 2001) and thus is critical for learning and memory processes (Lu et al., 2008). As mentioned, BDNF and TrkB are localized both pre- and postsynaptically, and BDNF can be released in an activity-dependent manner (Waterhouse and Xu, 2009). Both excitatory and inhibitory synapse formation and maturation are modulated by BDNF (Kovalchuk et al., 2004), and experimental data reveal that both spontaneous and evoked neurotransmission is impacted by BDNF signaling (Schuman, 1999; Tyler et al., 2006; Lin et al., 2018). These effects of BDNF are all fundamental to establishing the cellular underpinnings for long-term potentiation (LTP), the long-lasting activity-dependent facilitation of synaptic transmission, and presumed physiological substrate for learning and memory.

Studies of the mechanisms of LTP have revealed direct effects of BDNF on this process primarily in hippocampal synapses. Low concentrations of BDNF are sufficient to produce postsynaptic depolarizations in cortical, hippocampal, and cerebellar neurons (Kafitz et al., 1999), similar to the synaptic effects classically attributed to fast-acting neurotransmitters. Further studies revealed that reduced BDNF-TrkB signaling via genetic deletions or pharmacological inhibition leads to impaired LTP in the hippocampus (Korte et al., 1995, 1996, 1998; Minichiello et al., 1999; Monteggia et al., 2004). These effects can be rescued by application of exogenous BDNF or viral expression of BDNF (Korte et al., 1995; Patterson et al., 1996). Furthermore, LTP is diminished in mice carrying the val66met mutation, indicating the importance of activity-dependent secretion of BDNF for plasticity (Ninan et al., 2010). Application of exogenous BDNF can facilitate the conversion of weak synaptic activity, which would not typically lead to plasticity, into LTP (Kovalchuk et al., 2002). Loss of TrkB signaling in either pre- or postsynaptic neurons of CA1−CA3 synapses led to reduced LTP formation (Gartner et al., 2006; Lin et al., 2018).

BDNF acts within seconds of neural activity or application of the factor on synaptic function (Kovalchuk et al., 2004) but may also have sustained effects that support LTP via dendritic protein translation or feedforward transcription of BDNF (Kang and Schuman, 1996). This feedforward transcription occurs through TrkB-mediated CREB activation, as discussed in the previous section on BDNF transcription (Lu et al., 2008). Long-lasting effects of BDNF may also be attributed to structural plasticity, as demonstrated by the dependence of spine enlargement at hippocampal CA1−CA3 synapses on BDNF (Tanaka et al., 2008). Indeed, actin polymerization associated with dendritic spine formation is essential for LTP maintenance in rat hippocampus (Fukazawa et al., 2003). Together, these data emphasize the critical role for BDNF in neuronal plasticity.

20.4 BDNF's role in behavior and disease

20.4.1 Learning and memory

While *BDNF* was first identified within the context of developmental processes and cell survival in the nervous system, work over the last two decades has implicated it as a critical mediator of memory formation. Newly learned information gets stored as long-term memory through a protein synthesis−dependent process known as consolidation. The well-established role of BDNF in LTP, considered a cellular correlate of memory consolidation, first implicated BDNF in this process. Indeed, as mentioned in the previous section, the ability of BDNF signaling to induce protein synthesis led researchers to propose that BDNF release might be a crucial trigger for memory consolidation. Blocking BDNF synthesis or TrkB function, both genetically and pharmacologically, has been shown to impair memory consolidation. Heterozygous BDNF-mutant mice are impaired in Morris water maze acquisition (Linnarsson et al., 1997) and contextual fear conditioning (Liu et al., 2004), while forebrain-specific TrkB knockouts display deficits in a spatial water maze task and moderate deficits in a radial arm maze task (Minichiello et al., 1999). Here we discuss the role of BDNF signaling in the consolidation of different types of memories within distinct and overlapping neural circuits and behavioral paradigms.

20.4.1.1 Hippocampal memory consolidation and persistence

The dorsal hippocampus is essential for the consolidation of contextual memories, such as autobiographical memories of places, things, and people. De novo gene expression in the hippocampus has been shown to be essential for contextual memory consolidation, and early in vitro studies implicated BDNF as a key signaling molecule mediating this process. BDNF has been shown to increase in the hippocampus following training in a variety of paradigms, such as the Morris water maze and the radial maze (Kesslak et al., 1998; Mizuno et al., 2000), inhibitory avoidance (Alonso et al., 2002; Ma et al., 1998), contextual fear conditioning (Hall et al., 2000); and olfactory recognition (Broad et al., 2002). Additionally, BDNF Exon IV expression is induced in the hippocampus following contextual fear memory formation (Lubin et al.,

2008). Thus, BDNF is both synthesized during consolidation and plays an important role in the synthesis of other proteins essential for consolidation.

Memory consolidation is a dynamic process usually taking several hours to days to complete. But when is BDNF signaling/synthesis required during consolidation? To examine this question, Alonso et al., employed two techniques to gain temporal control of BDNF synthesis and signaling. BDNF antisense oligodeoxynucleotides that knocked down BDNF synthesis for a short period, or anti-BDNF antibodies, which prevented BDNF signaling before training, blocked the consolidation of a contextual inhibitory avoidance memory (Alonso et al., 2002). Notably, while blocking BDNF's actions impaired consolidation, increasing its levels facilitated memory formation. Infusion of BDNF into the hippocampus 1 h or 4 h after training facilitated memory, while blocking BDNF signaling with an anti-BDNF antibody at the same timepoints impaired consolidation when tested the next day (Alonso et al., 2002). Anti-BDNF antibodies injected 6 h posttraining no longer affected memory consolidation, but an injection 12 h after training blocked memory consolidation when tested 7 days later (Bekinschtein et al., 2007). Surprisingly, recombinant BDNF injections into dorsal hippocampi were able to rescue the amnesia induced by anisomycin (a protein synthesis inhibitor). One hypothesis to account for this effect is that BDNF activates PKMζ independently of protein synthesis, and this mechanism overrides the requirement of protein synthesis (Mei et al., 2011). Another possibility is that a very small subset of proteins is active at this timepoint and that BDNF may be downstream of these proteins. Indeed, BDNF signaling is required for a rapid wave of protein synthesis within the first few minutes of consolidation, likely via activation of the mTOR pathway (Bambah-Mukku et al., 2014; Chen et al., 2012). In addition, this early wave of BDNF signaling leads to the phosphorylation of CaMKIIα and the transcription factor CREB, resulting in the expression of the transcription factor CCAAT enhancer binding protein β (C/EBPβ), which in turn leads to BDNF Exon IV expression at later stages of consolidation. This autoregulatory feedback loop activated by BDNF terminates around 48 h after training, a timepoint at which protein synthesis inhibitors no longer affect consolidation (Bambah-Mukku et al., 2014).

20.4.1.2 BDNF roles in cortical memory formation

As mentioned above, several studies have examined the role of BDNF synthesis and release within the dorsal hippocampus during contextual memory consolidation. While the hippocampus is essential for memory consolidation, it is just one part of an extended circuit that encompasses several other brain regions, including the cortex and amygdala. These connections are bidirectional and likely involve reciprocal changes in strength that might be mediated by molecules such as BDNF. Indeed, the medial prefrontal cortex (mPFC) is connected to several brain regions, including the hippocampus, and has been shown to be essential for memory consolidation, extinction, and retrieval. Several lines of evidence implicate BDNF in these distinct cortex-dependent memory functions. The prefrontal cortex consists of two main subdivisions, the prelimbic and the infralimbic. BDNF action in these subdivisions controls distinct aspects of memory formation. Sustained BDNF signaling through its receptor TrkB is required for contextual memory consolidation in the prelimbic cortex (Choi et al., 2012; Ye et al., 2017). In fact, BDNF release from hippocampal synapses onto prelimbic neurons leads to memory strengthening, partly through the suppression of memory extinction. While the molecular mechanisms underlying this effect remain largely unexplored, evidence indicates the recruitment of neuroligin signaling and the strengthening of hippocampal-prefrontal synapses (Ye et al., 2017). Several studies have examined the role of the mPFC in memory extinction. Extinction is a process of new learning that leads to the updating of an associative memory. In the case of fear learning, this manifests as a reduced fear response resulting from repeated exposures to the fear inducing stimulus, but in the absence of the aversive outcome. The infralimbic cortex is critical for this process. In a striking result, BDNF infusion into the infralimbic cortex was shown to cause fear extinction even in the absence of repeated contextual exposures, suggesting that BDNF might be the main signal driving neuronal firing in this region (Peters et al., 2010). Subsequent work has implicated the ventral hippocampus as a source of infralimbic BDNF release supporting extinction (Rosas-Vidal et al., 2014). Together, these data illustrate the circuit-specific function of BDNF at multiple steps of learning, memory formation, memory consolidation, and extinction processes.

20.4.2 Stress, depression-like behavior, and antidepressant efficacy

Major depressive disorder (MDD) is a neuropsychiatric disease characterized by feelings of anxiety and guilt, loss of pleasure, increased or decreased appetite, and changes in sleep patterns (Shelton, 2007). Because MDD is a leading cause of disability worldwide, there is intense research interest in studying the causes and potential treatments for this disorder. The rate of MDD in women is double that in men, though the reasons for this difference are currently unknown (Becker et al., 2007). Risk factors for MDD include early life trauma, a history of stressful life events, as well as acute stress

(Charney and Manji, 2004). Research has shown that BDNF is reduced by stress (Martinowich et al., 2007) and is increased by antidepressant treatment (Castren and Rantamaki, 2010), making it an attractive candidate for study into the mechanisms of susceptibility to stress and depression, as well as a potential target for therapeutics.

A major anatomical hallmark of MDD and other stress-related disorders is a marked reduction in hippocampal and prefrontal cortex volume (Bremner et al., 2000). Postmortem hippocampal and prefrontal cortex tissue from suicide victims and patients with MDD reveals decreased levels of BDNF and TrkB, as well as reduced serum BDNF (Castren et al., 2007; Castren and Rantamaki, 2010; Thompson Ray et al., 2011; Castren, 2004; Pandey et al., 2008; Dwivedi et al., 2003). On the other hand, antidepressant treatment showed normalization of BDNF levels in both postmortem tissue and blood serum. Intriguingly, the val66met polymorphism that leads to reduced activity-dependent secretion of BDNF has been associated with increased incidence of MDD in certain human populations, such as males with homozygous mutations and patients with a history of early life stress (Frielingsdorf et al., 2010; Gatt et al., 2009). Together, these findings suggest that reduced neurotrophin signaling in cortex and hippocampus may underlie either susceptibility for or reactivity to stress and depression (Yu and Chen, 2011), and these alterations may be reversed with antidepressant treatment.

Conversely, BDNF signaling is enhanced by stress and MDD in the nucleus accumbens and amygdala. For example, human patients with MDD show increased BDNF expression in the nucleus accumbens (Krishnan et al., 2007). In addition, volumetric studies reveal an increased volume of the amygdala in human patients with MDD (Tebartz van Elst et al., 2000; Frodl et al., 2002), and studies in rodents demonstrate increased BDNF expression in the amygdala (Yu and Chen, 2011). These results, together with findings in corticolimbic regions, illuminate a circuit-specific role for BDNF in reactivity to or susceptibility to stress and MDD.

Chronic stress leads to several well-characterized cellular and behavioral effects: decreased hippocampal spine density, reduced hippocampal plasticity, and deficits in learning and memory, as well as increased depression-like behavior (Willner, 2005; McEwen and Magarinos, 1997; Yan et al., 2010). Because these effects are also strongly linked to actions of BDNF, researchers have extensively studied how BDNF signaling impacts susceptibility to stress and stress-related mood disorders. Indeed, in mice and rats, it has been shown that chronic stress leads to reductions in BDNF and TrkB levels in hippocampus and cortex (Duman and Monteggia, 2006). However, studies have been unable to define the precise role of BDNF signaling in stress susceptibility (Advani et al., 2009; Autry et al., 2009). Discrepancies in experimental results can likely be attributed to the choice of stressor and duration of stress; variation in endpoint criteria, such as physiological or behavioral assays; strain of mice or rats; and brain areas studied. BDNF heterozygous mice, for example, show increased depression-related behavior after short-term stress (Advani et al., 2009). By contrast, conditional or inducible male BDNF mutants show depression-related behavior that is indistinguishable from controls after chronic stress (Ibarguen-Vargas et al., 2009), though further experiments detected more pronounced depression-related behavior specifically in females (Autry et al., 2009). Moreover, selective deletion of BDNF from the ventral tegmental area leads to decreased depression-related behaviors (Berton et al., 2006), and recent data suggest that this effect is directly mediated through BDNF-TrkB signaling (Wook Koo et al., 2016). These differences in experimental results highlight the importance of brain circuitry and associated behaviors, and sex in the study of stress-induced physiological and behavioral alterations. Together, these studies reveal a circuit-specific and sex-dependent role of BDNF in the susceptibility to stress.

It is important to note here that moderate levels of stress can also enhance contextual memory consolidation (McGaugh, 2003). The adrenal glucocorticoid stress hormones, acting through their receptors glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), play a critical role in memory consolidation and retrieval (Chen et al., 2012; Morimoto et al., 1996; Roozendaal, 2000). Surprisingly, pharmacological blockade of GR leads to an impairment in memory formation, primarily through molecular mechanisms shared with the BDNF signaling pathway, including the activation of the CamKIIα-CREB pathway (Chen et al., 2012). In fact, the memory impairment caused by hippocampal GR inhibition can be rescued by the coadministration of BDNF, substantiating the direct interaction between these pathways within hippocampal neurons (Chen et al., 2012). Whether this molecular intersection is disrupted during chronic stress and whether the BDNF pathway can hold therapeutic promise in rescuing memory impairments during chronic stress remains to be investigated.

In line with findings described in humans, BDNF mRNA and protein levels are enhanced in cortex and hippocampus with antidepressant treatments, including electroconvulsive therapy (ECT) as well as several classes of pharmacological antidepressants (Balu et al., 2008; Nibuya et al., 1995; Altar et al., 2003). Furthermore, BDNF infusion leads to antidepressant-like effects (Hu and Russek, 2008; Shirayama et al., 2002; Hoshaw et al., 2005).

Depression-related behavior is normal in most models of BDNF deficiency (heterozygous mice, region-specific deletions in forebrain, regions of hippocampus and dorsal raphe nucleus) (Chourbaji et al., 2004; Monteggia et al., 2004, 2007), though none of these models of BDNF deficiency are able to respond to antidepressant treatment (Malberg and Blendy, 2005; Tardito et al., 2006; Hu and Russek, 2008; Monteggia et al., 2004, 2007; Adachi et al., 2008, 2017). One

exception is that deletion of BDNF from the ventrotegmental area (VTA) leads to an antidepressant-like behavioral response (Berton et al., 2006; Krishnan et al., 2007). Additionally, loss of TrkB receptor activity is also associated with reduced behavioral responses to antidepressants in mice overexpressing a dominant negative TrkB subunit (TrkB.T1) (Saarelainen et al., 2003). In summary, these data reveal the critical role of BDNF and TrkB signaling in mood-related behavior and antidepressant efficacy.

20.4.3 Neurodevelopmental disorders

20.4.3.1 Rett Syndrome

Rett syndrome, a neurodevelopmental disorder caused by loss of function mutations in the MeCP2 gene, affects 1 in 10,000 females (Amir et al., 1999) (Amaral et al., 2007). This disease is associated with symptoms including seizures and respiration issues; stereotyped hand-wringing; and impaired cognitive, language, and social skills. As previously discussed in the section covering BDNF transcription, MeCP2 acts primarily as a transcriptional repressor via binding to CpG sites and recruiting a repressor complex (Lewis et al., 1992; Nan et al., 1998; Adachi et al., 2009), though some genes are upregulated with loss of MeCP2 (Chahrour et al., 2008; Yasui et al., 2007). BDNF, as mentioned, contains binding sites for MeCP2 (Klose et al., 2005) and is affected by manipulations of MeCP2 expression (Chen et al., 2003a).

At present, there is little clinical data to support a connection between BDNF and RTT (Amaral et al., 2007). In patients with RTT, structural abnormalities have been observed including shortened dendrites (Chapleau et al., 2009), as well as reduced levels of BDNF expression (Abuhatzira et al., 2007; Deng et al., 2007). Levels of BDNF in serum or cerebrospinal fluid of RTT patients are unchanged in comparison to healthy individuals (Vanhala et al., 1998; Riikonen, 2003), though the relationship of neuronal expression to central and peripheral circulating levels of BDNF is unclear. Intriguingly, human studies reveal conflicting data on how the val66met polymorphism impacts symptoms of RTT syndrome (Nectoux et al., 2008; Zeev et al., 2009). Together, these data illustrate the need for further clinical study on the role of BDNF in RTT.

Despite a lack of clear-cut clinical evidence, there are several preclinical links strongly implicating an essential role for BDNF in molecular, cellular, and behavioral alterations associated with RTT and MeCP2 loss of function. Mouse models of MeCP2 deletion show a delayed onset of molecular and behavioral changes associated with RTT syndrome, and this timeline corresponds to the observed decrease in BDNF after MeCP2 deletion (Chang et al., 2006; Wang et al., 2006). Furthermore, deletion of BDNF exacerbates RTT-like symptoms in MeCP2 null mice, while BDNF overexpression delays symptom onset in this animal model (Chang et al., 2006). Intriguingly, loss of BDNF expression in excitatory neuron phenocopies aspects of MeCP2 deletion including hind-limb clasping, reduced neuronal size, and smaller brain size (Chang et al., 2006; Chen et al., 2001; Guy et al., 2001). Indeed, MeCP2 knockout neurons display deficits in axonal transport of BDNF (Roux et al., 2012). This transport deficit may in part be responsible for impaired activity-dependent presynaptic BDNF release in hippocampus of MeCP2 knockout mice (Li et al., 2012). These studies reveal a potential role for BDNF signaling in symptom onset and disease progression of RTT, highlighting the need for future research in this area.

20.4.3.2 Fragile X syndrome

Another neurodevelopmental disorder associated with disruption of the function of a single gene is Fragile X syndrome (FXS). FXS is responsible for the majority of inherited intellectual disabilities, affecting 1 in 4000 males and 1 in 8000 females (Santoro et al., 2012). Symptoms of FXS include cognitive impairments, communication deficits, repetitive behavior, and autism-like features (Chonchaiya et al., 2009). FXS is caused by mutations leading to loss of expression of the fragile X mental retardation 1 (Fmr1) gene from the X chromosome (Verkerk et al., 1991). Fmr1 knockout models closely resemble the behavioral, molecular, and cellular aspects of FXS (Bakker et al., 1994; Spencer et al., 2011). Anatomical features of FXS include disruptions in differentiation and migration of neural progenitor cells during development (Castren et al., 2005; Tervonen et al., 2009; Callan and Zarnescu, 2011; Saffary and Xie, 2011; Sheridan et al., 2011), alterations in dendritic spine formation (Comery et al., 1997; Irwin et al., 2001), as well as abnormalities in synapse development and circuit activity (Gibson et al., 2008; Bassell and Warren, 2008). The FMR1 gene specifically codes for the protein fragile mental X retardation protein (FMRP). FMRP, highly expressed in neurons, is an RNA-binding protein that controls the proper localization and translation of a variety of transcripts, including mRNAs for neuronal and synapse function (Devys et al., 1993; Zalfa et al., 2003, 2007; Darnell et al., 2011; Ascano et al., 2012; Khandjian et al., 1996; Feng et al., 1997; Stefani et al., 2004; Tatavarty et al., 2012; Dictenberg et al., 2008).

Clinical data implicating a role for BDNF in the manifestation of FXS is promising, but limited at present. Several human studies have implicated BDNF-TrkB signaling in the pathology of characteristic FXS symptoms, such as epilepsy,

attention deficits, autism-like features, and cognitive impairments (Nelson et al., 2001; Perry et al., 2001; Miyazaki et al., 2004; Correia et al., 2010; Scharfman, 2005; Shim et al., 2008). One Finnish population study demonstrates that the incidence of epilepsy in men with FXS is linked to two mutations in the BDNF gene (Louhivuori et al., 2009). However, there is no observable association of the val66met polymorphism, one of the SNPs uncovered in the previous study, with FXS in a Spanish patient population (Tondo et al., 2011). Further study will be necessary to illuminate a direct clinical relationship between BDNF and FXS.

On the other hand, basic research on genetic models of Fmr1 knockout has identified a significant effect of BDNF on synaptic and behavioral deficits associated with FXS. Application of BDNF is able to rescue deficits observed in hippocampal LTP in FMR1 knockout mice (Lauterborn et al., 2007). Research shows that TrkB receptor and sortilin, responsible for appropriate vesicular packaging of BDNF, may be targets of FMRP (Darnell et al., 2011). Several behavioral abnormalities in FMR1 knockout mice, including hyperactivity and altered sensory responses (Chen and Toth, 2001; Frankland et al., 2004; Spencer et al., 2011), are rescued by genetic reduction of BDNF levels (Uutela et al., 2012). However, learning deficits in FMR1 knockouts (Guo et al., 2011) were exacerbated by reduction in BDNF levels (Uutela et al., 2012), suggesting a circuit-specific function of FMRP regulation of BDNF levels in symptoms associated with FXS. These data illustrate that the interplay of FMRP and BDNF in specific brain areas contributes to symptoms of FXS, and further mechanistic insight into the circuit-level function of this molecular dynamic is critical for understanding the pathology of FXS.

20.4.4 Neurodegenerative diseases

20.4.4.1 Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia and is distinguished by age-related progressive loss of cognition and memory formation and by characteristic amyloid beta plaques and neurofibrillary tangles in brain tissue. These deficits are accompanied by loss of neural function in the cortex and hippocampus (Selkoe, 2002; Braak and Braak, 1991; Masliah et al., 1994). Studies in patients with AD show that BDNF mRNA and protein levels are decreased in these brain regions (Phillips et al., 1991; Connor et al., 1997; Holsinger et al., 2000; Hock et al., 2000; Narisawa-Saito et al., 1996) and in blood serum (Laske et al., 2007). Injection of a virus expressing BDNF into the entorhinal cortex was sufficient to reverse synaptic and cognitive deficits in a mouse model of AD generated by expression of a mutated form of human amyloid precursor protein (APP) (Nagahara et al., 2009). Similar mouse models of AD expressing mutant forms of APP show reductions in BDNF expression in the cortex and hippocampus (Peng et al., 2009; Devi and Ohno, 2012). Intriguingly, pharmacological enhancement of TrkB activation reverses memory deficits in a mouse model of AD (Devi and Ohno, 2012), and further research showed that BDNF secretion by transplanted neural stem cells was also able to enhance cognitive function in a mouse model of AD (Blurton-Jones et al., 2009). These studies reveal the beneficial effects of BDNF on symptoms of AD, emphasizing the need for further research into the role of BDNF in AD pathology and potential therapies.

20.4.4.2 Huntington's disease

Huntington's disease (HD), caused by mutations in the huntingtin (htt) gene, is an autosomal dominant neurodegenerative disease. HD leads to progressive cognitive and motor dysfunction mediated by loss of striatal projection neurons (Reiner et al., 1988). HD is caused by mutations characterized by expansions of CAG repeats leading to poly-glutamine (polyQ) residues in the huntingtin protein. In the case of HD, the link to BDNF may be fairly straightforward given that huntingtin is responsible for axonal transport of BDNF as previously described (Gauthier et al., 2004). Indeed, studies of postmortem human tissue from patients with HD reveal decreased BDNF mRNA and protein levels in multiple brain areas including the cortex, striatum, substantia nigra, and cerebellum (Zuccato et al., 2008; Seo et al., 2004; Ferrer et al., 2000), as well as in blood serum (Ciammola et al., 2007). Research has revealed no association of the critical val66met BDNF mutation to disease progression or severity in patients with HD (Kishikawa et al., 2006; Mai et al., 2006; Metzger et al., 2006; Alberch et al., 2005); however, this lack of association may be due to the fact that htt mutations appear to only affect transport of val-containing BDNF and not met-BDNF (del Toro et al., 2006).

Several mouse models of HD-containing knock-ins of disease-causing HD mutations show deficits characteristic of the human disease including cognitive decrements, motor dysfunction, and early death, as well as decreased levels of BDNF in cortex and striatum (Zuccato et al., 2005; Giralt et al., 2011; Xie et al., 2010; Spires et al., 2004). Overexpression of BDNF in these brain areas (Giralt et al., 2011; Xie et al., 2010), antidepressant treatment (known to enhance BDNF mRNA and protein expression as described previously) (Peng et al., 2008), as well as pharmacological agonism of TrkB receptor

(Jiang et al., 2013), all lead to improved HD-related phenotypes. These studies reveal a crucial role for BDNF in the symptoms of HD and suggest that BDNF therapeutics may relieve symptoms and improve lifespan in patients with HD.

20.5 Conclusions

In the 35 years since its discovery, intense research has revealed the multifaceted role of BDNF in the function of neurons from development and survival to plasticity and behavior. Given that BDNF is expressed highly from development to adulthood and extensively throughout the brain and even in the peripheral nervous system, it is no surprise that BDNF is critical in behavior and disease. Many open questions regarding how the complex regulation of BDNF may relate to neural function and disease still remain. For example, given the complexity of BDNF's transcription and translation, how is the expression of BDNF controlled within specific neural circuits or cell types? Is the function of proBDNF and mBDNF coordinated across development and in the adult? Are there distinct molecular processes controlling the localization and rapid translation of BDNF at synaptic versus extrasynaptic sites? Given the various functions of BDNF across circuit and timepoints, can it be a viable target for therapeutic development? With the advent of new technologies for gene modification, cell type−specific expression profiles, and advanced imaging techniques, future research into these questions will no doubt reveal more insights into the important function of BDNF in neurons in the coming decades.

List of acronyms and abbreviations

AD	Alzheimer's disease
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Arc	Activity-regulated cytoskeletal protein
BDNF	Brain-derived neurotrophic factor
CA1/2/3	Cornu ammonis 1/2/3
CamKII alpha	Calcium/calmodulin dependent kinase II alpha
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CpG	Poly-cytosine-guanine sequences
cre	Calcium response element
CREB	cAMP response element binding protein
DNA	Deoxyribonucleic acid
DNMT	DNA methyltransferase
EPSC	Excitatory postsynaptic current
Fmr1	Fragile X mental retardation 1
FMRP	Fragile X mental retardation protein
FXS	Fragile X syndrome
GABA	Gamma aminobutyric acid
GR	Glucocorticoid receptor
HDAC	Histone deacetylase
HMT	Histone methyltransferase
htt	Huntingtin
LTD	Long-term depression
LTP	Long-term potentiation
MDD	Major depressive disorder
MeCP2	Methyl-CpG binding protein 2
mTOR	Mammalian target of rapamycin
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NT-3/4/5	Neurotrophin 3/4/5
PKM	Protein kinase m
PNS	Peripheral nervous system
RNA	Ribonucleic acid
RTT	Rett syndrome
UTR	Untranslated region
VTA	Ventral tegmental area

Glossary

A single-nucleotide polymorphism is a single-nucleotide variation in the genome between members of the same species or between paired chromosomes in an individual.

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