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TRPC Channels as Novel Effectors of BDNF Signaling: *Potential Implications for Rett Syndrome*

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Abstract

In addition to their prominent role as survival signals for neurons in the developing nervous system, neurotrophins have established their significance in the adult brain as well, where their modulation of synaptic transmission and plasticity may participate in associative learning and memory. These crucial activities are primarily the result of neurotrophin regulation of intracellular Ca^{2+} homeostasis and, ultimately, changes in gene expression. Outlined in the following review is a synopsis of neurotrophin signaling with a particular focus upon BDNF and its role in hippocampal synaptic plasticity and neuronal Ca^{2+} homeostasis. Neurotrophin signaling through Trk and p75^{NTR} receptors are also discussed, reviewing recent results that indicate signaling through these two receptor modalities leads to opposing cellular outcomes. We also provide an intriguing look into the TRPC family of ion channels as distinctive targets of BDNF signaling; these channels are critical for capacitative Ca^{2+} entry, which, in due course, mediates changes in neuronal structure including dendritic spine density. Finally, we expand these topics into an exploration of mental retardation, in particular Rett Syndrome, where dendritic spine abnormalities may underlie cognitive impairments. We propose that understanding the role of neurotrophins in synapse formation, plasticity and maintenance will make fundamental contributions to the development of therapeutic strategies to improve cognitive functions in developmental disorders associated with mental retardation.

Keywords

BDNF; TrkB receptor; p75^{NTR} receptor; capacitative Ca^{2+} entry; TRPC channels; dendritic spines; Rett Syndrome; MeCP2

1. Introduction

The neurotrophins are a family of secretory proteins involved in neuronal survival and differentiation during early brain development (Barde, 1989). These proteins are released from target tissue and serve as chemoattractants for growing undifferentiated nerve cell processes, i.e. neurites, with the consequence being the formation of functional synapses. Furthermore, the neurotrophins play a crucial role as survival signals, given that there is only a limited amount available for release, as postulated in the *neurotrophin hypothesis* (Levi-Montalcini, 1987). The growing neurites compete for neurotrophins, hence, those that receive the proteins will continue to grow and mature; however, those that do not will be pruned and die. In this way,

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the overabundance of neurons produced early in development is reduced to that which is necessary to innervate all target tissue (Oppenheim, 1991). Recently, however, the family of neurotrophic factors in general, and brain-derived neurotrophic factor (BDNF) in particular, has emerged as potent modulators of activity-dependent synaptic plasticity in the mature central nervous system (CNS). It is essential, then, to elucidate the signaling mechanisms and downstream targets utilized by neurotrophins so that these newly recognized functions might be better understood.

Neurotrophins exert their varied actions through the activation of intracellular signaling cascades via two distinctive transmembrane receptors, the Trk family of receptor protein kinases and the p75^{NTR} receptor (Barbacid, 1993). A significant amount of research has uncovered many facets of neurotrophin signaling, however, there is still plenty to be learned. This is clearly demonstrated by the recent, unexpected finding that TRPC channel activation is a downstream consequence of BDNF signaling in particular. The TRP family of ion channels was originally described in *Drosophila* photoreceptors, and their mammalian homologues are currently implicated in a variety of cellular functions, ranging from sensory transduction (e.g. temperature, touch, pain, osmolarity, pheromone, taste) to modulation of the cell cycle (Montell et al., 2002; Clapham, 2003). Members of the TRP ion channel family also play a critical role in capacitative Ca²⁺ entry (Birnbaumer et al., 1996), a relatively unexplored form of sustained Ca²⁺ signaling neurons (Putney, 2003). Intriguingly, TRPC-mediated Ca²⁺ elevations may underlie the morphological sculpting of neuronal dendrites by BDNF, i.e. an increase in the density of dendritic spines, the site of ~90% of excitatory synapses in the brain (Peters et al., 1991).

By focusing upon any one aspect of these signaling cascades, the ability to reveal a role for neurotrophins in disease states begins to materialize. Mutations and chromosomal aberrations causing mental retardation (MR) have consistently been associated with dendritic anomalies, including the morphology and density of dendritic spines (Fiala et al., 2002). Of these, Rett syndrome (RTT) is an X-linked neurodevelopmental disorder and the leading cause of severe mental retardation in females, affecting 1:10,000–15,000 births worldwide (Neul and Zoghbi, 2004). Loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2) have been recently identified in RTT patients (Amir et al., 1999). MeCP2 binds specifically to CpG-methylated DNA and is thought to inhibit gene transcription by recruiting co-repressor and histone deacetylase complexes and altering the structure of genomic DNA (Nan et al., 1998). One of the recently described targets of MeCP2 is the *BDNF* gene, suggesting that a deregulation of BDNF expression may be the cause of the structural anomalies observed in RTT patients, especially the reduced dendritic branching and loss of dendritic spines.

2. Mechanisms of Neurotrophin Signaling

2.1 Neurotrophin signaling through Trk receptors

Four neurotrophins have been identified in mammals, and all are widely expressed in the CNS: nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and NT-4/5 (Lewin and Barde, 1996). They exert their effects by binding to pan-neurotrophin p75^{NTR} receptors, members of the tumor necrosis factor receptor superfamily, and to specific tyrosine kinase receptors, members of the *trk* family of protooncogenes related to insulin and epidermal growth factor receptors (Barbacid, 1993; Reichardt, 2006). NGF binds selectively to TrkA, BDNF and NT4/5 to TrkB, and NT3 to TrkC, and with a lower affinity to TrkB as well (Chao, 1992). Binding of a neurotrophin to a specific Trk receptor stimulates its kinase activity, leading to the activation of phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK, also known as extracellular-signal regulated kinase, ERK), and phospholipase C- γ (PLC- γ) signaling pathways (Segal and Greenberg, 1996; Huang and Reichardt, 2003).

Activation of Trk receptors by autophosphorylation following neurotrophin-induced dimerization initiates several intracellular signaling cascades (Fig. 1). Of these, the one mediated by Ras-MAPK/ERK has been involved in hippocampal function because (1) MAPK is abundantly expressed in hippocampal pyramidal dendrites; (2) is activated by Ca^{2+} influx via NMDA receptors or voltage-gated L-type Ca^{2+} channels; and (3) because it is necessary for the induction of long-term potentiation (LTP), for hippocampal-dependent associative learning and for BDNF-induced spine formation (Bading et al., 1993; Rosen et al., 1994; English and Sweatt, 1997; Atkins et al., 1998; Alonso et al., 2004). Within hippocampal presynaptic terminals, MAPK/ERK-dependent phosphorylation of synapsin-I resulted in higher density of docked neurotransmitter vesicles in glutamatergic terminals, increased frequency of miniature excitatory postsynaptic currents (mEPSCs), increased paired-pulse facilitation, facilitated neurotransmitter release during high-frequency activity with consequent increases in LTP and enhancements in hippocampus-dependent learning (Kushner et al., 2005). Second, the PI3-K cascade is responsible for dendritic targeting of BDNF and TrkB mRNA (Righi et al., 2000) and has been implicated in hippocampal-dependent spatial learning (Mizuno et al., 2003). Lastly, the PLC- γ cascade also plays a critical role in hippocampal synaptic plasticity, as demonstrated by the lack of long-term potentiation (LTP) in conditional knockout mice carrying a deletion of the PLC- γ adaptor site in Trk receptors (Minichiello et al., 2002).

2.2 Neurotrophin signaling through p75^{NTR} receptors

The activation of membrane-bound p75^{NTR} and Trk receptors by neurotrophin binding – in addition to physical interactions between them – organizes precise signaling cascades that control their varied actions throughout development, such as cell survival, differentiation, neurite outgrowth and synaptic function (Chao, 2003; Patapoutian and Reichardt, 2001; Huang and Reichardt, 2003; Hempstead, 2002; Nykjaer et al., 2005; Roux and Barker, 2002; Dechant and Barde, 2002). Interaction of neurotrophins with p75^{NTR} results in the activation of different signaling cascades mostly involved in the regulation of cell fate, such as NF- κ B or c-jun N-terminal kinase (Kaplan and Miller, 2000; Roux and Barker, 2002; Gentry et al., 2004).

Recent observations regarding the differential role of the two types of membrane receptors have uncovered an intriguing level of complexity in neurotrophin signaling, namely opposing functional actions of p75^{NTR} and Trk receptors (Lu et al., 2005). For example, while Trk receptors are essential for neuronal survival, p75^{NTR} have been implicated in neuronal apoptosis (Rabizadeh et al., 1993; Frade et al., 1996; Bamji et al., 1998; Miller and Kaplan, 2001). Second, p75^{NTR} signaling has been linked to the inhibition of axonal growth, an opposing effect to that of Trk receptors (Yeo et al., 1997; Kohn et al., 1999; Walsh et al., 1999; Yamashita et al., 1999). Third, while TrkB receptors have been shown to be critical for the role of BDNF in hippocampal long-term potentiation (LTP) (Minichiello et al., 1999; Minichiello et al., 2002; Xu et al., 2000), recent reports indicate that p75^{NTR} is necessary for the induction and/or expression of hippocampal long-term depression (LTD) (Rosch et al., 2005; Woo et al., 2005). With regard to dendritic differentiation, p75^{NTR} and Trk receptors also seem to have functional antagonisms. TrkB activity has been shown to modulate dendritic growth (Yacoubian and Lo, 2000), while a recent report using p75^{NTR} knockout and p75^{NTR} overexpressing mice indicates that these receptors negatively modulate dendritic morphology in hippocampal pyramidal neurons (Zagrebelsky et al., 2005). Specific receptor activation at different developmental stages may underlie these effects, whereby p75^{NTR} activity modulates dendritic arborization of subventricular zone-derived neurons within a few days *in vitro*, while TrkB plays a role in dendritic differentiation after longer times in culture (Gascon et al., 2005). Lastly, dendritic spine density in hippocampal pyramidal neurons was higher in p75^{NTR} knockout mice, which also showed a reduction in the proportion of stubby (Type-I) spines (Zagrebelsky et al., 2005). On the other hand, mice with a conditional deletion of the TrkB receptor have reduced spine density and a higher proportion of long spines (Luikart et

al., 2005; von Bohlen und Halbach et al., 2006). In addition, the proportion of stubby (Type-I) spines was reduced in CA1 pyramidal neurons of adult transgenic mice expressing a dominant-negative TrkB (Chakravarthy et al., 2006). On the other hand, BDNF increased spine density and the proportion of stubby (Type-I) spines through the activation of Trk receptors (Tyler and Pozzo-Miller, 2001; Tyler and Pozzo-Miller, 2003). Intriguingly, brief exposures to k-252a, an inhibitor of receptor tyrosine kinases such as Trks, caused a significant increase in spine density in CA1 pyramidal neurons expressing enhanced yellow fluorescent protein (eYFP) (Chapleau & Pozzo-Miller, in preparation). However, most of these spines are of the long and thin Type-III, known to be highly motile and unstable structures (Dailey and Smith, 1996; Dunaevsky et al., 1999) and characteristic of immature synapses (Sorra and Harris, 2000). The fact that longer exposures to k-252a by itself caused spine loss (Tyler and Pozzo-Miller, 2001), suggests that an initial increase in long and thin spines may precede spine regression leading to spine pruning (Segal et al., 2000). Alternatively, these observations may reflect the functional antagonism between p75^{NTR} and Trk receptor signaling for dendritic spine formation and maintenance. In this interpretation, preferential activation of p75^{NTR} by spontaneously released BDNF under conditions of Trk receptor inhibition (i.e. in the presence of k-252a) leads to an initial and transient increase in thin and unstable spines, followed by a persistent spine loss. Further complexity was uncovered by the outgrowth of dendritic filopodia through the interaction of the truncated TrkB receptor (TrkB.T1) with p75^{NTR}, intriguingly enough, in the absence of neurotrophin binding (Hartmann et al., 2004). Altogether, these observations support the “yin and yang” model of functional antagonism between Trk and p75^{NTR} signaling (Lu et al., 2005).

2.3 Biological actions of pro-neurotrophins and mature neurotrophins

The model of functional antagonism between p75^{NTR} and Trk receptor signaling has been extended to explain the intriguing observations that the pro-neurotrophins (30–35kDa), the neurotrophin precursors, often have opposite biological effects than the proteolytically cleaved mature neurotrophins (12–13kDa). In this interpretation, mature neurotrophins bind preferentially to Trk receptors, while secreted pro-neurotrophins do so with the p75^{NTR} (Lu et al., 2005). Out of the functional antagonistic actions mentioned above, this view is so far supported by the opposing effects of mature and pro-neurotrophins on neuronal survival and synaptic plasticity. For example, interaction of mature NGF with TrkA receptors leads to cell survival, while binding of secreted proNGF to p75^{NTR} causes apoptosis (Lee et al., 2001; Harrington et al., 2004). In addition, the induction of LTP requires extracellular cleavage of proBDNF by tissue plasminogen activator (tPA)/plasmin to form mature BDNF, which then binds to TrkB receptors (Pang et al., 2004). On the other hand, binding of secreted proBDNF to p75^{NTR} promotes the induction of LTD (Woo et al., 2005). These intriguing observations warrant further study of the role of extracellular proteases in the range of cellular processes mediated by neurotrophins (Chao and Bothwell, 2002; Lu, 2003b).

3. Does BDNF Cause Calcium Mobilization from Intracellular Stores?

One of the prominent signaling cascades activated by Trk neurotrophin receptors, the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP₂) by activated PLC- γ leading to the formation of inositol-tris-phosphate (IP₃) and subsequent Ca²⁺ mobilization from smooth endoplasmic reticulum (ER) through IP₃ receptors (IP₃Rs) (Berridge, 1998), is expected to cause Ca²⁺ elevations in neurons (Segal and Greenberg, 1996; Huang and Reichardt, 2003). This pathway converges on the same IP₃R-containing Ca²⁺ stores targeted by other metabotropic receptors in hippocampal pyramidal neurons, such as group-I metabotropic glutamate receptors (mGluR) (Conn and Pin, 1997). The amplification of Ca²⁺ signals by mobilization from intracellular stores may allow the enhancement of such processes as transmitter release and gene expression, both of which are fundamental for LTP induction.

Although NMDA receptors are well-known Ca^{2+} entry routes necessary for LTP induction, thapsigargin, an inhibitor of the smooth endoplasmic reticulum Ca^{2+} -ATPase (SERCA) pump, also prevents LTP induction (Harvey and Collingridge, 1992), suggesting a role for Ca^{2+} mobilization from intracellular stores in synaptic plasticity.

NGF was initially reported to increase Ca^{2+} levels in PC12 cells (Pandiella-Alonso et al., 1986), most likely by PLC- γ stimulation (Vetter et al., 1991), leading to IP_3 formation and subsequent release from smooth ER cisterns endowed with IP_3 Rs. BDNF induces rapid phosphorylation of PLC- γ 1 increasing phosphatidylinositol (PI) turnover and IP_3 levels in embryonic cortical neurons in culture (Widmer et al., 1992; Widmer et al., 1993) causing Ca^{2+} elevations (Behar et al., 1997; Matsumoto et al., 2001; Zirrgiebel et al., 1995). BDNF also induces elevations of intracellular Ca^{2+} in embryonic hippocampal neurons in culture (Berninger et al., 1993; Canossa et al., 1997; Finkbeiner et al., 1997; Marsh and Palfrey, 1996; Li et al., 1998), but not in cultured cerebellar granule cells (Gaiddon et al., 1996); but see ref. (Numakawa et al., 2001)}, and cultured neurons and acute slices from visual cortex (Pizzorusso et al., 2000); but see refs. (Mizoguchi et al., 2002; Mizoguchi and Nabekura, 2003). Lastly, intracellular Ca^{2+} stores are important for BDNF-induced synaptic potentiation in acute hippocampal slices (Kang and Schuman, 2000). Unfortunately, most published Ca^{2+} imaging studies regarding the actions of neurotrophins on neuronal Ca^{2+} homeostasis were done without simultaneous membrane voltage control, making it difficult to isolate the contribution of cell depolarization to the observed Ca^{2+} changes. Therefore, experimental evidence of neurotrophin-initiated Ca^{2+} signaling is sparse, controversial and limited to cell lines or embryonic neurons maintained in primary culture. It should be noted that the rapid and short-lived Ca^{2+} elevations induced by focal and brief BDNF applications to dendrites and spines of dentate granule cells in acute slices were sensitive to voltage-gated Ca^{2+} channel blockers (Kovalchuk et al., 2002) and always associated with the fast membrane depolarization proposed to mediated by TTX-insensitive $\text{Na}_v1.9$ channels (Kafitz et al., 1999; Blum et al., 2002). As such, these BDNF-induced Ca^{2+} signals reflect voltage-gated Ca^{2+} influx secondary to membrane depolarization, and not the predicted PLC γ / IP_3 R-mediated Ca^{2+} mobilization from intracellular stores.

4. Does BDNF Induce Capacitative Calcium Entry?

In addition to well-established voltage- and ligand-gated mechanisms of Ca^{2+} influx in neurons (Berridge, 1998), Ca^{2+} entry associated with depletion of intracellular Ca^{2+} stores is beginning to emerge as a fundamental component of neuronal Ca^{2+} signaling. In non-excitabile cells, the depletion of these stores activates plasma membrane channels often called store-operated channels (SOCs), allowing Ca^{2+} entry for their replenishment. In both excitable (i.e. neurons and cardiac and skeletal muscle cells) and non-excitabile cells, this process has been named capacitative (or store-operated) Ca^{2+} entry (Putney, 1986; Berridge, 1995; Parekh and Putney, 2005). Cultured hippocampal neurons seem to exhibit capacitative Ca^{2+} entry (Baba et al., 2003; Bouron, 2000; Emptage et al., 2001), and impairments in this Ca^{2+} influx mechanism have been observed in neurons from transgenic mice carrying Alzheimer's disease-associated mutations in presenilin (Yoo et al., 2000).

Members of the transient receptor potential (TRP) ion channel family have been proposed to play a critical role in capacitative Ca^{2+} entry (Birnbaumer et al., 1996). TRP channels were originally described in *Drosophila* photoreceptors, where *trp* mutants exhibit a transient response to continuous light (Montell et al., 1985). Their mammalian homologues are currently implicated not only in capacitative Ca^{2+} entry but also in a variety of cellular functions, ranging from sensory transduction (e.g. temperature, touch, pain, osmolarity, pheromone, taste) to modulation of the cell cycle (Clapham, 2003; Montell et al., 2002). Mammalian TRP homologues are classified into TRPC (canonical, or short form), TRPV (vanilloid), TRPM

(melastatin), TRPP (polycystin), and TRPML (mucolipin) subfamilies (Clapham, 2003). All mammalian TRPC proteins (TRPC1 through TRPC7) appear to be homologues of the TRP channels involved in *Drosophila* phototransduction, in that they function as receptor-operated channels. Of relevance for this review, TRPC proteins are widely expressed in brain (Mizuno et al., 1999), including the hippocampus (Philipp et al., 1998; Li et al., 1999; Strubing et al., 2001).

TRPC channels can be activated in neurons by stimulation of G_q/G_{11} -type G protein-coupled receptors (i.e. group-I mGluRs) and receptor tyrosine kinases (i.e. Trk receptors) leading to PLC-dependent hydrolysis of PIP_2 into IP_3 and diacylglycerol (DAG). The activation mechanism of mammalian TRPC channels is still highly controversial, mostly because it has been studied exclusively in cell lines expressing specific subunits forming homomeric channels. Some TRPC channels have been proposed to be gated by a direct interaction with IP_3 Rs (Kiselyov et al., 1998), others by DAG itself (Hofmann et al., 1999), or even by a soluble Ca^{2+} influx factor produced in response to Ca^{2+} store depletion (Clapham et al., 2001). The fact that most TRPC channels are able to form functional heteromeric channels with activation properties distinct from those of the homomers contributes to the current disparity in the proposed models for the activation and modulation of native TRPC channels in central neurons. It is worth mentioning that whether TRPC channels are indeed SOCs, or if a causal relationship exists between non-selective cationic currents mediated by TRPC channel subunits and the processes of store-operated or capacitative Ca^{2+} entry are highly debated issues to date (Clapham, 1996; Birnbaumer et al., 1996; Boulay et al., 1997; Zhu et al., 1998; Clapham, 2003; Montell et al., 2002; Putney, 2004). The recent identification of a Ca^{2+} sensor for store depletion has provided a major advance in our molecular understanding of store-operated Ca^{2+} entry. Stromal interacting molecule 1 (STIM1) has an EF-hand domain predicted to face the ER lumen, and mutated residues expected to reduce its Ca^{2+} binding affinity activate store-operated Ca^{2+} entry in non-excitable cells with full intracellular stores (Liou et al., 2005; Roos et al., 2005; Zhang et al., 2005). The properties of STIM1 and its re-distribution to ER regions near the plasma membrane upon store depletion leading to the activation of Ca^{2+} -release activated channels (CRAC) strongly support a physical interaction model (Luik et al., 2006; Wu et al., 2006), reminiscent of the dyad and triad junctions that underlie excitation-contraction coupling in skeletal and cardiac muscle (Cheng et al., 1993; Franzini-Armstrong et al., 1999). Indeed, a functionally relevant physical interaction between TRPC1-containing channels and IP_3 Rs is mediated by the cellular immediate early gene Homer (Yuan et al., 2003).

Intriguingly, when BDNF was applied in the absence of extracellular Ca^{2+} , transient elevations in the intracellular Ca^{2+} concentration were significantly reduced, but not completely blocked, suggesting that both Ca^{2+} influx and its mobilization from intracellular stores contribute to the effects of BDNF (Canossa et al., 1997; Finkbeiner et al., 1997; Marsh and Palfrey, 1996; Li et al., 1998). It has been assumed that Trk receptor activation does not modulate plasma membrane ion channels, other than by direct or indirect protein phosphorylation (Segal and Greenberg, 1996; Huang and Reichardt, 2003). However, TrkB receptor-initiated formation of IP_3 and subsequent Ca^{2+} mobilization from IP_3 R-containing intracellular Ca^{2+} stores is one of the best-established mechanisms for activation of non-selective cationic currents mediated by plasma membrane TRPC channels (Montell et al., 2002; Clapham, 2003). In fact, it is this precise intracellular signaling pathway that is believed to underlie the activation of I_{BDNF} , a non-selective cationic current described in dissociated pontine neurons (Li et al., 1999) and CA1 pyramidal neurons of the hippocampus (Amaral and Pozzo-Miller, 2005) (Amaral & Pozzo-Miller, submitted). Furthermore, I_{BDNF} was always associated with slow and sustained Ca^{2+} elevations in CA1 pyramidal neurons under voltage-clamp in the presence of the Na^+ channel blocker tetrodotoxin. Figure 2 illustrates our working hypothesis for TRPC activation by BDNF-initiated TrkB signaling. Consistent with this view, TRPC3/6 channels mediate BDNF-evoked Ca^{2+} signals in growth cones of cultured cerebellar granule cells (Li et al.,

2005), whereas xTRPC1, a *Xenopus* homolog of TRPC1, plays a similar role in BDNF-induced growth cone turning *in vitro* (Wang and Poo, 2005).

Non-selective cationic currents resembling TRPC currents have been described in cortical and hippocampal neurons (Alzheimer, 1994; Haj-Dahmane and Andrade, 1996; Congar et al., 1997). Recent evidence indicates that TRPC1-containing channels mediate cation currents activated by the selective group-I mGluR agonist DHPG in Purkinje neurons (Kim et al., 2003). Similar DHPG-evoked currents sensitive to TRPC inhibitors were also recorded in hippocampal pyramidal neurons (Gee et al., 2003; Rae and Irving, 2004), and midbrain dopamine neurons (Tozzi et al., 2003). In addition, membrane currents mediated by TRPC channels activated by group-I mGluRs in response to endogenously released glutamate have been observed in Purkinje cells (Kim et al., 2003), dopamine neurons of the *substantia nigra compacta* (Bengtson et al., 2004), and neurons in the lateral amygdala (Faber et al., 2006). It is worth noting that I_{BDNF} in pontine (Li et al., 1999) and CA1 neurons (Amaral and Pozzo-Miller, 2005) (Amaral & Pozzo-Miller, submitted) is markedly different from the much faster and transient TTX-insensitive Na^+ current activated by TrkB ligands in several regions of the brain (Kafitz et al., 1999). BDNF, like classical neuropeptides, is synthesized and packaged in dense-core vesicles for their delivery to dendrites and axons, where it is slowly released by large Ca^{2+} elevations evoked by high frequency spike trains (Lessmann et al., 2003; Brigadski et al., 2005). Indeed, BDNF is most effectively released from hippocampal neurons by theta burst-like stimulation (Balkowiec and Katz, 2002). In summary, the intracellular cascades that converge on Ca^{2+} mobilization and IP_3 formation represent intriguing signaling links between TrkB receptor activation, group-I mGluR activation, and those prominent Ca^{2+} -dependent processes that are responsible for synaptic plasticity (Berridge, 1998; Zucker, 1999).

5. Physiological and Morphological Consequences of BDNF Signaling

5.1 Presynaptic effects: neurotransmitter release

Several of the multiple actions of BDNF in neuronal function are mediated by intracellular signaling cascades that are either dependent or highly sensitive to intracellular Ca^{2+} elevations, such as neurotransmitter release or short- and long-term synaptic plasticity. BDNF can contribute to neuronal Ca^{2+} homeostasis through direct or indirect actions on membrane depolarization at both presynaptic and postsynaptic sites. At the presynaptic level, BDNF enhances excitatory synaptic transmission by direct presynaptic mechanisms. BDNF rapidly potentiates evoked and spontaneous cholinergic synaptic transmission at *Xenopus* neuromuscular junction in culture (Lohof et al., 1993), an effect mediated by increased presynaptic Ca^{2+} levels and dependent upon both extracellular Ca^{2+} levels and presynaptic depolarization (Stoop and Poo, 1996; Boulanger and Poo, 1999). Acute application of BDNF also enhances spontaneous and evoked glutamatergic excitatory postsynaptic currents in cultured hippocampal neurons (Lessmann et al., 1994; Levine et al., 1995a; Li et al., 1998; Schinder et al., 2000; Berninger et al., 1999). Long-term treatment of postnatal hippocampal slice cultures with BDNF increases the frequency of mEPSCs recorded from CA1 pyramidal neurons, without affecting their amplitude or kinetics (Tyler and Pozzo-Miller, 2001). The latter effect of BDNF was specific on a rapidly recyclable pool of vesicles. Indeed, BDNF selectively increased the density of synaptic vesicles docked at the active zone of asymmetric spine synapses, without affecting those in the main vesicle cluster (the reserve pool?) (Tyler and Pozzo-Miller, 2001). Furthermore, BDNF selectively enhanced evoked FM1-43 destaining in acute hippocampal slices, but only when presynaptic terminals were dye-loaded with a hyperosmotic shock with sucrose (Tyler et al., 2006), a manipulation that only engages the readily releasable pool of vesicles (Stevens and Tsujimoto, 1995; Rosenmund and Stevens, 1996). Enhancement of GABA-mediated inhibitory synaptic transmission by BDNF in cultured hippocampal neurons also seems to be mediated by presynaptic Ca^{2+} signaling, as chronic BDNF treatment increases the expression and channel density of presynaptic P/Q and

N-type channels, without affecting postsynaptic L-type channels (Baldelli et al., 2000; Baldelli et al., 2002). In contrast to the mechanism of action in glutamatergic terminals, these effects of BDNF on inhibitory terminals in culture seem to be selective on Ca^{2+} channel clustering, without affecting the readily releasable pool (Baldelli et al., 2005).

A potential downstream effector of this action of BDNF is the Ras-MAPK/ERK signaling cascade. First, BDNF enhances glutamate release from synaptosomes *in vitro* by MAPK-dependent phosphorylation of synapsin-I, an effect absent in preparations from synapsin-I and/or -II knockout mice (Jovanovic et al., 2000). Second, Ras overexpressing mice show enhanced features of presynaptic function that are the counterpart of the ones observed in BDNF knockout mice (Pozzo-Miller et al., 1999; Kushner et al., 2005). Because one of the major functions of synapsins is to regulate the trafficking of synaptic vesicles between distinct pools within presynaptic terminals (McGuinness et al., 1989; Llinas et al., 1991; Greengard et al., 1993), it seems likely that BDNF facilitates synaptic vesicle docking via the modulation of presynaptic vesicle proteins (Pozzo-Miller et al., 1999; Tartaglia et al., 2001; Tyler et al., 2002b). Indeed, myosin VI, a minus end-directed actin-based motor, is critical for BDNF modulation of transmitter release and LTP induction at hippocampal synapses (Yano et al., 2006).

It should be noted that despite consistent observations on transmitter release probability, as well as short- and long-term synaptic plasticity (Poo, 2001; Lu, 2003a), the effects of bath-applied exogenous BDNF on basal evoked synaptic transmission in acute slices has remained controversial. Over the years, different laboratories have reported almost every possible outcome, including an enhancement of excitatory transmission (Kang and Schuman, 1995), a depression of inhibitory transmission (Tanaka et al., 1997), no effect on excitatory transmission (Gottschalk et al., 1998), or no effect on excitatory and minimal depression of inhibitory transmission (Frerking et al., 1998). It has been speculated that the poor penetration of BDNF (a highly charged basic molecule) into relatively thick acute hippocampal slices is responsible for the contradictory results (Kang et al., 1996), although no BDNF effects were observed when recording from neurons at different depths in acute slices (Frerking et al., 1998). Alternatively, changes induced by the slicing procedure may have inadvertently affected synaptic physiology at different extents in different laboratories, such as changes in dendritic spine density (Kirov and Harris, 1999), expression of c-fos and zif268 and glutamate receptor content (Taubenfeld et al., 2002), and more important in the context of this review, levels of BDNF mRNA (Taubenfeld et al., 2002) and protein levels (Danzer et al., 2004).

5.2 Postsynaptic effects: Ca^{2+} homeostasis and NMDA receptors

The modulation of Ca^{2+} -dependent signaling pathways within postsynaptic compartments is another potential mechanism of action of BDNF on synaptic function. BDNF was shown early on to rapidly and transiently increase intracellular Ca^{2+} levels in cultured hippocampal neurons (Berninger et al., 1993). In addition, BDNF potentiates spontaneous Ca^{2+} oscillations in cultured hippocampal neurons (Sakai et al., 1997). However, these effects on Ca^{2+} levels can be accounted for only by enhanced network activity leading to spike-driven voltage-dependent Ca^{2+} influx, most likely through its enhancement of glutamate release (Berninger and Poo, 1996; Tyler et al., 2002b). In fact, tetrodotoxin (TTX), the AMPA/kainate receptor antagonist CNQX, and the NMDA receptor antagonist APV, all completely blocked spontaneous Ca^{2+} oscillations, as well as the potentiation of their frequency by BDNF (Sakai et al., 1997). Intriguingly, when BDNF was applied in the absence of extracellular Ca^{2+} , these elevations were significantly reduced, but not completely blocked (Canossa et al., 1997; Finkbeiner et al., 1997; Marsh and Palfrey, 1996; Li et al., 1998), suggesting that both Ca^{2+} influx and its mobilization from intracellular stores contribute to the effects of BDNF (Amaral and Pozzo-Miller, 2005). In contrast, BDNF failed to increase Ca^{2+} levels in cultured cerebellar granule cells (Gaiddon et al., 1996); but see ref. (Numakawa et al., 2001)}, and in cultured neurons

and acute slices from visual cortex (Pizzorusso et al., 2000); but see refs. (Mizoguchi et al., 2002; Mizoguchi and Nabekura, 2003). Similarly, extracellular Ca^{2+} was required for BDNF to increase the frequency of miniature excitatory postsynaptic currents (mEPSC) on cultured hippocampal neurons (Li et al., 1998).

The posttranslational modification of ion channels or neurotransmitter receptors by neurotrophins via protein phosphorylation may provide the molecular mechanism of their action at hippocampal synapses. For example, covalent modifications of the NMDA class of glutamate receptors may have profound effects on hippocampal synaptic plasticity. BDNF rapidly and selectively enhanced the phosphorylation of NMDA receptor subunits 1 and 2B in isolated postsynaptic densities (Lin et al., 1998; Suen et al., 1997), and it increased the open channel probability of NMDA receptors (Jarvis et al., 1997; Levine et al., 1998). Neurotrophins have also been shown to enhance voltage-gated ionic currents (Lesser et al., 1997), including Ca^{2+} currents (Levine et al., 1995b). As mentioned above, chronic BDNF treatment of embryonic hippocampal neurons in culture increases the expression and channel density of presynaptic P/Q and N-type channels, without affecting postsynaptic L-type channels (Baldelli et al., 1999; Baldelli et al., 2000; Baldelli et al., 2002). Consistently, BDNF did not affect dendritic Ca^{2+} signals evoked by back-propagating action potentials (bAPs) in CA1 pyramidal neurons in slice cultures, nor the fraction of their block by the L-type channel blocker nimodipine (McCutchen et al., 2002). Thus, the modulation of other postsynaptic Ca^{2+} channels by BDNF could be related to synaptic plasticity, while L-type Ca^{2+} channel modulation by other neurotrophins may contribute to more classic neurotrophic effects, such as neuronal survival and differentiation through modulation of gene transcription. Considering that specific Ca^{2+} entry pathways, such as voltage-gated Ca^{2+} channels or NMDA receptors, lead to differential activation of particular effector genes, differential BDNF modulation of dendritic Ca^{2+} signals originating from various sources of Ca^{2+} may ultimately be expressed by differential activation of signaling pathways that control the expression of particular genes (Ghosh and Greenberg, 1995). In this manner, enduring changes in synaptic function and structure thought to underlie memory consolidation are ultimately translated into long-term changes in gene expression (Kandel, 2001).

5.3 Structural effects: dendritic spines

Neurotrophins were first shown to increase the length and complexity of dendrites of cortical pyramidal neurons when applied to slice cultures of ferret visual cortex (McAllister et al., 1995). Cortical pyramidal neurons in slice cultures treated with Trk “receptor-bodies” to scavenge endogenous neurotrophins showed limited dendritic growth and even dendritic retraction (McAllister et al., 1997), confirming that endogenous neurotrophins play a critical role in dendritic development. In addition, cortical pyramidal neurons that overexpress BDNF exhibit increased dendritic arborization, as well as enhanced rates of spine retraction and formation (Horch and Katz, 2002; Horch et al., 1999). BDNF was later shown to increase spine density in CA1 pyramidal neurons, an effect blocked by the scavenger TrkB-IgG, the receptor tyrosine kinase inhibitor k-252a, and inhibitors of the MAPK/ERK signaling cascade (Tyler and Pozzo-Miller, 2001; Alonso et al., 2004). In addition to increasing spine density *per se*, BDNF also increased the proportion of stubby spines (Type-I) under conditions of *both* action potential-dependent *and* independent synaptic transmission (Tyler and Pozzo-Miller, 2003). Even when SNARE-dependent vesicular synaptic transmission was abolished with *Botulinum* neurotoxin C, BDNF was still capable of inducing spine formation. Under these conditions, however, BDNF selectively increased the proportion of thin spines (Type-III), while decreasing the proportion of stubby spines (Type-I). Consistent with an activity-dependent process of morphological differentiation of synapses, the effects of BDNF on hippocampal spines suggest that it cooperates with spontaneous miniature synaptic activity to sculpt the fine structure of CA1 pyramidal neurons in the postnatal hippocampus. Since BDNF

increases quantal transmitter release from presynaptic terminals (Tyler and Pozzo-Miller, 2001; Tyler et al., 2002b; Tyler et al., 2006) and plays a role in *de novo* spine formation and the morphological sculpting of existing spines (Tyler and Pozzo-Miller, 2001; Tyler and Pozzo-Miller, 2003; Alonso et al., 2004), its actions widely span the synaptic cleft.

Changes in the structure of dendritic spines, such as their formation, elimination or variations in morphology are believed to be dependent upon the dynamics of the actin cytoskeleton, while proteins affecting actin cytoskeleton dynamics are, in turn, sensitive to changes in Ca^{2+} concentrations (Yuste and Bonhoeffer, 2001). Considering the sustained increase in cytoplasmic Ca^{2+} concentration upon activation of I_{BDNF} in CA1 neurons (Amaral and Pozzo-Miller, 2005) and that MAPK/ERK1/2 activation is Ca^{2+} -sensitive (Agell et al., 2002), it is likely that the TRPC channels mediating I_{BDNF} are a vital source of the essential Ca^{2+} required for the BDNF-induced increase in dendritic spine density. Indeed, inhibition or siRNA-mediated knockdown of TRPC channels prevented not only the BDNF-induced sustained depolarization and dendritic Ca^{2+} elevation, but also the increase in spine density (Amaral & Pozzo-Miller, submitted). These observations support a significant physiological role for the BDNF-induced postsynaptic current mediated by TRPC3 channels, namely the formation of dendritic spines. Moreover, the BDNF-induced structural remodeling of spiny dendrites of CA1 pyramidal neurons has consequences for Ca^{2+} signals evoked by coincident pre and postsynaptic activity. Dendritic Ca^{2+} signals evoked by coincident excitatory postsynaptic potentials (EPSPs) and backpropagating action potentials (bAPs) were always larger than those triggered by bAPs in CA1 neurons exposed to BDNF (Pozzo-Miller, 2006), representing a potential consequence of neurotrophin-mediated dendritic remodeling of hippocampal neurons. Lastly, BDNF promoted spine formation also in granule cells of the dentate gyrus (Danzer et al., 2002) and in cultured hippocampal neurons, where the effect was “gated” by cAMP (Ji et al., 2005).

6. BDNF, MeCP2 and Dendritic Spine Pathologies in Rett Syndrome

Neurological disorders associated with mental retardation (MR) are characterized by a prevalent deficit in cognitive function and adaptive behavior that range in phenotype severity and are often accompanied by specific symptoms. MR-associated disorders that have environmental, neurodegenerative or genetic origins have long been associated with structural anomalies of dendritic spines (Fiala et al., 2002). The pioneering studies by Huttenlocher (Huttenlocher, 1970; Huttenlocher, 1974), Marin-Padilla (Marin-Padilla, 1972; Marin-Padilla, 1976), and Purpura (Purpura, 1974; Purpura, 1975) described strikingly similar abnormalities in the dendritic organization of cortical neurons from human patients with unclassified MR-associated disorders. These pyramidal neurons showed a reduction in the number and length of dendritic branches, a significant loss of dendritic spines, and a predominance of long “tortuous” spines. Interestingly, no other neuropathologies were found in these patients. Since then, similar features of dendritic branching, as well as spine density and morphology have been described in other MR-associated genetic developmental disorders, ranging from autosomal genetic forms of MR (e.g. Down’s syndrome, Angelman syndrome) to X chromosome linked forms of MR (e.g. Rett Syndrome, Fragile-X syndrome) (Kaufmann and Moser, 2000; Fiala et al., 2002; Newey et al., 2005). Thus, it seems that dendritic and spine anomalies are the major brain pathologies underlying the cognitive impairments observed in humans with MR, because such dendritic and spine changes will reduce postsynaptic surface area and the density of mature excitatory synapses.

One MR-associated disorder with an intriguing link to BDNF signaling is Rett Syndrome (RTT). Rett syndrome (RTT) is an X-linked neurodevelopmental disorder and the leading cause of severe mental retardation in females, affecting 1:10,000–20,000 births worldwide without a predisposition to any particular racial or ethnic group (Percy, 2002; Neul and Zoghbi,

2004). Patients with RTT are born healthy and achieve standard developmental milestones until 6–18 months of age, when they begin a regression period associated with loss of acquired cognitive, social, and motor skills (Armstrong, 1997). Later symptoms and deficits include irregularities in motor activity, characterized by a stereotypic hand movement or useless hand movements, altered breathing patterns, gait and motor imbalance and continued cognitive decline. As the period of regression concludes, the individuals are often left in a severely impaired condition with a majority of children developing seizure activity, although seizure frequency diminishes with age. As the children get older, a period of stabilization occurs where they develop greater communication abilities with their eyes, yet motor function continues to regress gradually (Percy and Lane, 2005). It has recently been shown that RTT patients have loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2) (Amir et al., 1999). MeCP2 binds specifically to CpG-methylated DNA and is thought to inhibit gene transcription by recruiting co-repressor and histone deacetylase complexes and altering the structure of genomic DNA (Nan et al., 1998). Because other neurodevelopmental disorders with autistic features have also been associated with MeCP2 dysfunction, the role of MeCP2 in neuronal function may extend beyond Rett Syndrome (Percy, 2002). Intriguingly, one of the targets of MeCP2-mediated transcriptional repression is the gene encoding brain-derived neurotrophic factor, BDNF, whereby MeCP2 binds to the promoter region of the *BDNF* gene and represses its transcription (Chen et al., 2003; Martinowich et al., 2003) (see below).

The neuropathology of RTT reveals several areas of abnormal brain development (Armstrong et al., 1995; Bauman et al., 1995b; Bauman et al., 1995a). Several studies reported abnormal dendritic structure in the frontal cortex (Jellinger et al., 1988). In addition, the area and length of pyramidal neuron dendrites are significantly decreased in the frontal and motor cortices as well as in the *subiculum*, while dendritic length was not affected in the hippocampus (Armstrong et al., 1995). Another group reported a thickening and shortening of dendrites in the frontal cerebral and cerebellar cortices (Cornford et al., 1994). Finally, a reduction in the levels of microtubule-associated protein-2 (MAP-2), a dendritic protein involved in microtubule stabilization, was found throughout the neocortex of RTT brains (Kaufmann et al., 1995; Kaufmann et al., 2000). Relevant to the role of neurotrophins in dendritic spine formation and maturation, RTT brains have reduced spine density in dendrites of the frontal cortex (Belichenko et al., 1994). In addition, the levels of cyclooxygenase-2, a protein enriched in dendritic spines, are reduced in the frontal cortex in RTT (Kaufmann et al., 1997). With regards to synapse density, reduced levels of the synaptic vesicle protein synaptophysin were detected in the motor, frontal and temporal cortices by immunofluorescence (Belichenko et al., 1997), although another study reported unaltered synaptophysin levels in frontal cortex and cerebellum (Cornford et al., 1994).

To further the understanding of RTT, a number of different mouse models have been generated, either carrying a null deletion of *MECP2* (Chen et al., 2001; Guy et al., 2001) or expressing a truncated, non-functional form of the wildtype MeCP2 protein (*MECP2*³⁰⁸) (Shahbazian et al., 2002). These mice have common phenotypes, including delayed onset of symptoms (approximately at 5 weeks of age), motor impairment and abnormal gait; the null *MECP2* mice have hindlimb irregularities, while the *MECP2*³⁰⁸ mice have forelimb impairment (Shahbazian and Zoghbi, 2002; Armstrong, 2005). In addition, null *MECP2* mice have altered synaptic transmission and plasticity, including impaired hippocampal LTP (Asaka et al., 2006), and reduced excitatory transmission in the hippocampus (Nelson et al., 2006) and neocortex (Dani et al., 2005). Deficits in hippocampal LTP and hippocampal-dependent learning and memory were also observed in the *MECP2*³⁰⁸ mice expressing the truncated protein (Moretti et al., 2006). On the other hand, transgenic mice that mildly overexpress wildtype MeCP2 (~2X wildtype levels) display a higher rate of hippocampal-dependent learning and enhanced LTP, though they developed a neurological phenotype that included seizures after 20 weeks of age (Collins et al., 2004).

Intriguingly, observations regarding neuronal and synaptic morphology in these mouse models of RTT have produced varying results, sometimes inconsistent with the neuropathology found in RTT patients (Armstrong et al., 1995; Bauman et al., 1995b; Bauman et al., 1995a). Pyramidal neurons of layer II/III of the neocortex of null *MECP2* hemizygous mice (*MECP2*^{-y}) are smaller and have reduced dendritic branching as observed in RTT brains, although no differences were found in dendritic spine density (Kishi and Macklis, 2004), a distinctive feature observed in one study of the cortex of RTT patients (Belichenko et al., 1994). Another study of the somatosensory cortex of null *MECP2* hemizygous mice (*MECP2*^{-y}) reported that dendrites of layer II/III neurons were thinner and have fewer spines than those of wildtype littermates (Fukuda et al., 2005). On the other hand, transient overexpression of wildtype MeCP2 in cultured cortical neurons lead to a significant increase in dendritic and axonal length and arborization, while neurons overexpressing a non-functional, truncated form of MeCP2 (*MECP2*²⁹³) only showed increases in dendritic and axonal branching (Jugloff et al., 2005). Quantitative analyses of dendritic morphology in neurons from layers III and V of the frontal cortex of *MECP2*³⁰⁸ mice, which express a truncated *MECP2* allele, reported no major abnormalities in dendritic branching (Moretti et al., 2006). Further analyses at the EM level in area CA1 of the hippocampus yielded no differences in the density of asymmetric synapses and in the number of synaptic vesicles, either docked at the active zone or in the main vesicle cluster within the terminals. However, the mean length of the postsynaptic density (PSD) was smaller in *MECP2*³⁰⁸ mice, driven by a concomitant increase in the smaller PSDs and a decrease in the larger ones (>150nm) (Moretti et al., 2006). Since the size of the active zone is tightly correlated with the size of the PSD across the synaptic cleft (Harris and Sultan, 1995; Boyer et al., 1998; Schikorski and Stevens, 1999), the observation of smaller PSDs and similar numbers of docked vesicles in the *MECP2*³⁰⁸ mice suggests that the density of docked vesicles is increased in the mutant active zone. Intriguingly, *BDNF* null mice have fewer docked vesicles at asymmetric spine synapses in area CA1 (Pozzo-Miller et al., 1999), while exogenous BDNF increases docked vesicles at the same synapses (Tyler and Pozzo-Miller, 2001). These apparent discrepancies clearly warrant further investigations of the role of wildtype and mutant MeCP2 on dendritic and synaptic morphology in specific brain regions as a potential underlying mechanism for the functional impairments observed in animal models and RTT patients.

The molecular pathways contributing to the pathogenesis of Rett Syndrome remain unclear. Considering that the best characterized function of MeCP2 is as a transcriptional repressor, numerous gene expression profiles have been conducted on RTT patients and in the available mouse models of RTT (Colantuoni et al., 2001; Tudor et al., 2002; Ballestar et al., 2005; Delgado et al., 2006; Nuber et al., 2005). However, these studies identified several genes that are either upregulated or downregulated, but their contribution to the disease remains unknown. A more targeted approach, such as chromatin immunoprecipitation, has identified the promoter region of the *BDNF* gene as a target of MeCP2 transcriptional control (Chen et al., 2003; Martinowich et al., 2003). These studies demonstrated that MeCP2 binds to and represses the transcription of mouse *BDNF* promoter IV, equivalent to the rat *BDNF* III promoter, which is well known to be activated by neuronal activity and the ensuing voltage-gated Ca²⁺ influx (Tao et al., 1998). As expected, the levels of *BDNF* exon IV transcript were low in cultured cortical neurons from wildtype mice in the absence of neuronal activity (i.e. in the presence of TTX). On the other hand, neurons from *MECP2* null mice showed a 2-fold increase in their basal levels of *BDNF* exon IV transcript, as predicted from its transcriptional repressor function. Furthermore, *BDNF* exon IV transcript levels induced by a strong depolarizing stimulus (i.e. KCl) were similar between control and mutant cells, due to the large increase observed in wildtype neurons and the already elevated levels in *MECP2* null neurons, which were unresponsive to KCl depolarization (Chen et al., 2003). Considering that BDNF is a positive modulator of excitatory synaptic function (Thoenen, 2000; Poo, 2001; Tyler et al., 2002a; Tyler et al., 2002b; Lu, 2003a; Bramham and Messaoudi, 2005), the observation of

elevated BDNF levels (at least in terms of its activity-dependent mRNA transcripts) was unexpected and somewhat puzzling. However, BDNF protein levels measured by ELISA were found to be lower in brain samples of *MECP2* null mice at 6–8 weeks of age compared to wildtype controls, a difference not observed at 2 weeks (Chang et al., 2006). In addition, conditional deletion of the *BDNF* gene in *MECP2* null mice exacerbated the onset of the RTT-associated phenotypes of the *MECP2* null animals, which included hypoactivity in the running wheel and reduced action potential frequency in pyramidal neurons of acute cortical slices *in vitro*. Surprisingly, overexpression of *BDNF* slowed down the disease progression in *MECP2* null mice, with increased wheel running behavior and augmented action potential firing in cortical neurons (Chang et al., 2006). Since BDNF mRNA and protein levels are tightly regulated by neuronal activity, the reduced firing frequency of neurons from *MECP2* null mice (Dani et al., 2005) may cause the reduced BDNF protein levels measured by ELISA (Chang et al., 2006). The discrepancy between the elevated basal levels of *BDNF* exon IV transcripts in cultured *MECP2* neurons (Chen et al., 2003) and the reduced BDNF protein levels in *MECP2* brain tissue (Chang et al., 2006) likely originate from different basal conditions (TTX in culture *vs.* naïve fresh brain samples), developmental age (embryonic *vs.* postnatal), or the modulation of mRNA translation into protein. Whether direct or indirect, the relationship between *MeCP2* function and BDNF-mediated signaling seems potentially relevant to the speculated impairments in Rett Syndrome, especially with regards to synaptic function (Dani et al., 2005; Asaka et al., 2006; Moretti et al., 2006; Nelson et al., 2006).

Unfortunately, the few available studies of neurotrophin levels in RTT patients have not yielded results consistent with the “BDNF hypothesis of Rett”, at least at a first approximation. First, reduced NGF levels were observed in cerebral spinal fluid (CSF) of RTT patients, a difference not found in blood serum levels, while BDNF was unaffected in CSF or blood serum RTT samples (Lappalainen et al., 1996; Vanhala et al., 1998; Riikonen and Vanhala, 1999; Riikonen, 2003). Second, the expression levels of NGF and its receptor TrkA were reduced in postmortem RTT brains, as assessed by immunohistochemistry (Lipani et al., 2000), while the number of basal forebrain neurons expressing p75^{NTR} was unaffected in RTT brains (Wenk and Hauss-Wegrzyniak, 1999). Third, NGF serum levels tend to decrease with age in RTT patients, opposite to the characteristic developmental increase in healthy individuals (Calamandrei et al., 2001). Taken together, these few reports reveal our incomplete understanding of the potential and intriguing role of neurotrophin signaling in the pathogenesis of Rett syndrome. Furthermore, they underscore the need for further cellular and molecular studies, perhaps at the single cell level, that explore the consequences of mutant *MeCP2* expression on neurotrophin expression, targeting and/or release, as well as signaling through its p75^{NTR} and Trk receptors.

7. Conclusions

The intracellular signaling cascades activated by BDNF binding to TrkB receptors include several well-characterized protein kinases that target most of the routes of Ca²⁺ entry into hippocampal neurons, while the role of p75^{NTR} signaling is only beginning to emerge. In addition to its strong presynaptic actions on quantal neurotransmitter release, the activation of a slowly developing depolarizing TRPC current associated with Ca²⁺ signals by BDNF is a likely mechanism for its modulation of synaptic transmission and plasticity. The information gained from future experiments in this rapidly evolving field will integrate the actions of BDNF at synapses with the requirement of Ca²⁺ signals necessary for the induction of synaptic plasticity and the structural remodeling of dendrites and spines thought to underlie memory consolidation. Whether a deregulation of BDNF signaling is responsible for the functional and structural consequences of *MeCP2* mutations in the pathogenesis of Rett syndrome is yet to be proven, but it is certainly an exciting possibility that deserves further exploration. Ultimately, the challenge ahead is to consolidate the varied functional and structural

consequences of BDNF signaling through p75^{NTR} and TrkB receptors at both sides of the synaptic cleft at excitatory synapses in the hippocampus with its intriguing role in the consolidation of hippocampal-dependent learning. Indeed, BDNF represents the prototypical example of a consolidation factor necessary for trans-synaptic plasticity at hippocampal synapses.

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Abbreviations

BDNF

brain derived neurotrophic factor

Trk

	tropomyosin-related kinase
<i>p75^{NTR}</i>	pan-neurotrophin receptor 75KD
<i>TRPC</i>	canonical transient receptor potential channel
<i>CNS</i>	central nervous system
<i>NMDA</i>	N-methyl-D-aspartate
<i>AMPA</i>	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
<i>VGCC</i>	voltage-gated Ca ²⁺ channel
<i>MR</i>	mental retardation
<i>RTT</i>	Rett Syndrome
<i>MeCP2</i>	methyl-CpG-binding protein 2

Figure 1.

Intracellular signaling cascades activated by BDNF-stimulated autophosphorylation of TrkB receptors may affect prominent pathways responsible for elevations of intracellular Ca²⁺ levels in neurons. Activation of the PLC-γ/IP₃ signaling pathway leads to Ca²⁺ mobilization from IP₃-sensitive intracellular stores. In addition, NMDA receptors and voltage-gated Ca²⁺ channels could be directly phosphorylated by activated TrkB receptors or indirectly through the Ras-MAPK/ERK or PI3-K pathways. Combined, these covalent modifications potentially enhance Ca²⁺ signals within spines and dendrites.

Figure 2.

TrkB-initiated stimulation of PLC γ causes PIP₂ hydrolysis and formation of DAG and IP₃. Activation of IP₃R leads to Ca²⁺ mobilization from intracellular stores. Native TRPC channels expressed in hippocampal neurons, most likely heteromultimeric, may be gated by a diffusible factor, Ca²⁺ ions released from IP₃-sensitive Ca²⁺ stores, a physical interaction with activated IP₃R or by DAG itself. TRPC channels are known to mediate a non-selective cationic current that requires intact IP₃R signaling, full intracellular Ca²⁺ stores and extracellular Ca²⁺ ions.