

## Appendix A14.16

### Neurotrophic Signaling Cascades: a Focus on Brain-Derived Neurotrophic Factor

Neurotrophins are a family of regulatory factors that mediate the differentiation and survival of neurons, as well as the modulation of synaptic transmission and synaptic plasticity (Patapoutian and Reichardt, 2001; Poo, 2001). The neurotrophin family now include—among others—nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), NT4/5 and NT6 (Patapoutian and Reichardt, 2001). These various proteins are closely related in terms of sequence homology and receptor specificity. They bind to and activate specific receptor tyrosine kinases belonging to the Trk family of receptors, including TrkA, TrkB, TrkC and a pan-neurotrophin receptor P75 (Patapoutian and Reichardt, 2001; Poo, 2001). Additionally, there are two isoforms of TrkB receptors: the full length TrkB and the truncated form of TrkB, which does not contain the intracellular tyrosine kinase domain (Fryer, 1996). The truncated form of TrkB can thus function as a dominant-negative inhibitor for the TrkB receptor tyrosine kinase, thereby providing another mechanism to regulate BDNF signaling in the CNS (Gonzalez, 1999; Eide, 1996). Indeed, under certain pathological conditions, such as Alzheimer's disease, the immunoreactivity of full length TrkB receptor isoform is selectively lost in both temporal lobe and frontal cortex (Allen, 1999).

Neurotrophins can be secreted constitutively or transiently, and often in an activity-dependent manner. Recent observations support a model wherein neurotrophins are secreted from the dendrite and act retrogradely at presynaptic terminals where they act to induce long-lasting modifications (Poo, 2001). Within the neurotrophin family, BDNF is a potent physiological survival factor which has also been implicated in a variety of pathophysiological conditions, such as Parkinson's disease, Alzheimer's disease, and diabetic peripheral neuropathy (Nagatsu et al., 2000; Pierce and Bari, 2001; Salehi et al., 1998). The cellular actions of BDNF are mediated through two types of receptors: a high affinity tyrosine receptor kinase (Trk B) and a low affinity pan-neurotrophin receptor (p75). TrkB is preferentially activated by BDNF and NT4/5, and appears to mediate most of the cellular responses to these neurotrophins. The functions of the p75 receptor are more diverse and complex than those of the Trks. In vitro studies have shown that p75 enhances the sensitivity of TrkA expressing neurons to the survival promoting effect of NGF, whilst decreasing their sensitivity to neurotrophin NT3 (Bibel et al., 1999; Kaplan and Miller, 2000). Direct interaction between p75 and Trk receptors, together with changes in ligand affinity and Trk signaling, account (at least in part) for these effects of p75 (Bibel et al., 1999; Kaplan and Miller, 2000). Recent studies has shown that p75-mediated activation of NFκB plays a role in enhancing the survival response of developing sensory neurons to NGF (Hamanoue et al., 1999). Binding of BDNF initiates TrkB dimerization, and

transphosphorylation of tyrosine residues in its cytoplasmic domain (Patapoutian and Reichardt, 2001). The phosphotyrosine residues of Trk B receptor function as binding sites for recruiting specific cytoplasmic signaling and scaffolding proteins. Binding of cytoplasmic src-homology 2 (SH2)-domain-containing scaffolding proteins, including shc and Grb2, which recognize specific phosphotyrosine residues on the receptor, can thus result in the recruitment of a variety of effector molecules. This recruitment of effector molecules generally occurs via interaction of proteins with modular binding domains SH2, SH3 (named after homology to the src oncogenes—src homology domains); SH2 domains are a stretch of ~100aa's that allows high affinity interactions with certain phospho-tyrosine motifs. The ability of multiple effectors to interact with phosphotyrosines is undoubtedly one of the keys to the pleiotropic effects that neurotrophins can exert. These pleiotropic and yet distinct effects of growth factors are mediated by varying degrees of activation of three major signaling pathways--the Ras/MAP kinase pathway, the PI-3 kinase pathway, and the phospholipase C- $\gamma$ 1 pathways. Among these pathways, the effects of the PI3 kinase pathway and the MAP kinase pathway have been most directly linked to the cell survival effects of neurotrophins (Patapoutian and Reichardt, 2001).

### **Signaling Through the MAP Kinase Cascade**

Shc recruitment and phosphorylation results in recruitment to the membrane of a complex of the adaptor Grb-2 and the Ras exchange factor son of sevenless (SOS), thereby stimulating transient activation of Ras. Ras, in turn, activates PI3K, the p38 MAPK/MAPK-activating protein kinase 2 pathway and the c-Raf/ERK pathway. Among the targets of ERK are the ribosomal S6 kinases (RSKs). Both RSK and MAPK-activating protein kinase 2 phosphorylate CRE-binding protein (CREB) and other transcription factors. Recent studies have demonstrated that the activation of the MAP kinase pathway can inhibit apoptosis by inducing the phosphorylation of BAD (Bcl-x1/Bcl-2 Associated Death promoter), and increasing the expression of the anti-apoptotic protein Bcl-2, the latter effect likely involves the cAMP response element binding protein (CREB) (Bonni et al., 1999, Riccio et al., 1997). Phosphorylation of BAD occurs via activation of Rsk. Rsk phosphorylates BAD and thereby promotes its inactivation. Activation of Rsk also mediates the actions of the MAP kinase cascade and neurotrophic factors on the expression of Bcl-2. Rsk can phosphorylate the cAMP response element binding protein (CREB), leading to induction of Bcl-2 gene expression.

MAP kinases are abundantly present in the brain, and in recent years have been postulated to play a major role in a variety of long term CNS functions, both in the developing and mature CNS (Suzuki et al., 1995; Fukunaga and Miyamoto, 1998; Kornhauser and Greenberg, 1997; Matsubara et al., 1996; Robinson et al., 1998). With respect to their actions in the mature CNS, MAP kinases have been implicated in mediating neurochemical processes associated with long term facilitation (Martin et al., 1997), long term potentiation (English and

Sweatt, 1996; English and Sweatt, 1997), associative learning (Atkins et al., 1998), one-trial and multi-trial classical conditioning (Crow et al., 1998), long term spatial memory (Blum et al., 1999), and have also been postulated to integrate information from multiple, infrequent bursts of synaptic activity (Murphy et al., 1994). Importantly for the present discussion, MAP kinase pathways have recently been demonstrated to regulate the responses to environmental stimuli and stressors in rodents (Xu et al., 1997), and to couple PKA and PKC to cAMP response element binding protein phosphorylation in area CA1 of hippocampus (Roberson et al., 1999, Roberson et al., 1996). These recent studies suggest the possibility of a broad role for the MAPK cascade in regulating gene expression in long-term forms of synaptic plasticity (Roberson et al., 1999). Thus, overall, the data suggests that MAP kinases play important physiological roles in the mature CNS, and furthermore, may represent important targets for the actions of CNS-active agents (Nestler, 1998; Yuan et al., 1998).

### **The PI3K-Akt Pathway: A Major Pathway Mediating Neuronal Survival**

The PI3K-Akt pathway is also particularly important for mediating neuronal survival under a wide variety of circumstances. Trk receptors can activate PI3K through at least two distinct pathways, the relative importance of which differs between neuronal subpopulations. In many neurons, Ras-dependent activation of PI3K is the most important pathway through which neurotrophins promote cell survival. In some cells, however, PI3K can also be activated through three adaptor proteins, Shc, Grb-2 and Gab-1. Binding to phosphorylated tyrosine 490 of Shc results in recruitment of Grb-2. Phosphorylated Grb-2 provides a docking site for Gab-1, which in turn is bound by PI3K (Brunet et al., 2001).

PI3 kinase directly regulates certain cytoplasmic apoptotic pathways. Akt has been proposed to act both prior to the release of cytochrome c by pro-apoptotic Bcl-2 family members, and subsequent to the release of cytochrome c, by regulating components of the apoptosome. Akt phosphorylates the pro-apoptotic Bcl-2 family member BAD, thereby inhibiting BAD's pro-apoptotic functions (Datta et al., 1997).

Akt may also promote survival in an indirect fashion by regulating another major signaling enzyme—glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) (Woodgett, 2001). Thus, elevated GSK-3 $\beta$  has been shown to promote apoptosis in cultured neurons (Bijur et al. 2000). Furthermore, neurotrophin withdrawal increases, whereas phosphorylation by Akt decreases GSK-3 $\beta$  activity (Hetman et al., 2000). Moreover, a series of studies indicates that Akt controls a major class of transcriptional factors—the Forkhead box transcription factor, class O (FOXO) subfamily of Forkhead transcriptional regulators (FKHR, FKHL1 and AFX). Several groups have independently shown that Akt directly phosphorylates FOXOs and inhibits their ability to induce the death genes (Brunet et al., 1999) (Dijkers et al., 2000). Finally, activation of Akt also results in phosphorylation of NF- $\kappa$ B. Transcription activated by NF- $\kappa$ B has been shown recently

to promote neuronal survival (Maggirwar et al., 1998). Thus, PI3K acting through Akt may promote survival by variety of mechanisms; precisely which of these mechanisms is operative in the actions of neurotrophins, and under what circumstances is the focus of extensive current research.

### **Signaling Through PLC- $\gamma$**

Phosphorylated Trk receptors also recruit PLC- $\gamma$ 1. The Trk kinase then phosphorylates and activates PLC- $\gamma$ 1, which acts to hydrolyze phosphatidylinositides to generate diacylglycerol (DAG) and inositol 1,4,5 triphosphate (IP<sub>3</sub>). IP<sub>3</sub> induces the release of Ca<sup>2+</sup> stores, increasing levels of cytoplasmic Ca<sup>2+</sup> and thereby activating many pathways controlled by Ca<sup>2+</sup>. In recent work, it has been shown that neurotrophins activate protein kinase C (PKC)  $\delta$ , which is required for activation of the ERK cascade and for neurite outgrowth (Patapoutian and Reichardt, 2001).

### **Neurotrophins Also Function as Synaptic Modulators**

It is now clear that neurotrophins not only support cell survival, but also play important roles as “synaptic modulators” by regulating synapse development, synaptic transmission, and indirectly the formation of long-term potentiation (LTP) (Poo, 2001). Neurotrophic factors secreted by either pre-or postsynaptic cells are important in synapse development and normal maintenance; furthermore, overexpression of BDNF in transgenic mice increases the number of synapses in sympathetic ganglia and accelerates the maturation of inhibitory pathways in the developing visual cortex (Huang et al., 1999). In addition to more long-term effects, neurotrophic factors also acutely regulate synaptic transmission. In this context, BDNF specifically induces potentiation of glutamatergic synapses, with the potentiation only being observed when the postsynaptic neuron uses glutamate as a transmitter (and is not seen with GABA) (Lessmann and Heumann, 1998).

In addition to regulating synaptic efficacy, BDNF appears to function as a modulator that is required for the induction, expression, and/or maintenance of LTP. Genetic deletion of BDNF in mice disrupts normal induction of LTP, which can be rescued by reintroducing BDNF either by transfecting hippocampal slices with BDNF-expressing adenovirus or the exogenous administration of BDNF (Korte et al., 1996) (Patterson et al., 1996). By contrast, exogenous application of BDNF does not potentiate basal synaptic transmission. BDNF does, however, reduce the tetanus-induced depression of transmitter release at CA3-CA1 synapse of young rats, allowing sufficient postsynaptic activation for the induction of LTP (Pozzo-Miller et al., 1999). These data suggested that BDNF is a permissive factor required for formation of LTP rather than mediating LTP directly.

What is sometimes less well appreciated is the fact that BDNF also has a number of much more acute effects on synaptic plasticity and neurotransmitter release, and facilitates the release of glutamate, GABA, dopamine and serotonin (Goggi et al., 2002; Matsumoto et al., 2001; Schinder et al., 2000). In this context, BDNF has been shown to potentiate both excitatory and inhibitory transmission, albeit via different mechanisms; BDNF strengthens excitation primarily by augmenting the amplitude of AMPA receptor-mediated miniature EPSCs (mEPSCs) but enhances inhibition by increasing the frequency of mIPSC and increasing the size of GABAergic synaptic terminals. Furthermore, full-length trkB receptor immunoreactivity (trkB-IR) has not only been found in glutamatergic pyramidal and granule cells, but also in some interneuron axon initial segments, axon terminals forming inhibitory-type synapses onto somata and dendritic shafts, and excitatory-type terminals likely to originate extrahippocampally. Together, these results suggest that trkB is contained in some GABAergic interneurons, neuromodulatory (e.g., cholinergic, dopaminergic, and noradrenergic) afferents, and/or glutamatergic afferents (Drake et al., 1999).

### **Retrograde Transportation of the Neurotrophin Receptors as a Signal to the Cell Body**

Unlike most other internalized receptors, which are usually degraded after internalization, neurotrophin–Trk complexes in endocytic vesicles function as signal transducers and provide a mechanism for long-range signaling in the neuronal cytoplasm. Several studies have provided support for the retrograde transportation model of neurotrophin–Trk complexes. For sympathetic ganglionic neurons, internalization of NGF–TrkA complexes at axon terminals and retrograde transport of these complexes to the cell body is responsible for the NGF-dependent effects on neuronal survival (Riccio et al., 1997). The tyrosine kinase activity of TrkA is required to maintain the complex in an autophosphorylated state on its arrival in the cell body and for propagation of the signal to the transcription factor CREB within the nucleus (Riccio et al., 1997). Similarly, in the isthmo-optic nucleus (ION) of chick embryos, transport of BDNF alone does not promote the survival of ION neurons when axonal TrkB is inactivated (von Bartheld et al., 1996). These results indicate that endocytotic vesicles containing neurotrophin–Trk complexes may be functionally active and should be viewed as activated signaling complexes that spread the cytosolic signaling of neurotrophin–Trk complexes to distant parts of the neuron via active transport mechanisms. Intriguingly, as has recently been shown with another tyrosine kinase (ErbB-4 receptor tyrosine kinase), other hitherto unappreciated methods, such as cleavage of receptor fragments, may also be operative in trafficking signals from extracellular receptors to intracellular and nuclear targets (Ni et al., 2001). Whether such novel signaling mechanisms are also utilized by neurotrophin receptors will undoubtedly be the focus of considerable future research.

## **BDNF Signaling is Regulated by Neuronal Activity**

The neurotrophic functions of neurotrophins depend in large part on a cytoplasmic signal-transduction cascade, whose efficacy may be influenced by the presence of electrical activity in the neuron. Seizure activity, as well as non-seizure activity of a frequency/intensity capable of inducing long-term potentiation (LTP), have been shown to elevate BDNF mRNA levels, and facilitate the release of BDNF from hippocampal and cortical neurons (Poo, 2001). Although BDNF was originally considered to only be transported retrogradely, recent evidence indicates that BDNF can also act anterogradely to modulate synaptic plasticity (Poo, 2001). High-frequency neuronal activity and synaptic transmission have also been shown to elevate the number of TrkB receptors on the surface of cultured hippocampal neurons through activation of the CAM Kinase II pathway, and may therefore facilitate the synaptic action of BDNF (Du et al., 2000). Thus, electrically active nerve terminals may be more susceptible to synaptic potentiation by secreted neurotrophins compared to inactive terminals. Neuronal or synaptic activity is also known to promote the effects of neurotrophins on the survival of cultured retinal ganglion cells; here, neuronal or synaptic activity elevates cAMP levels to enhance the responsiveness of the neuron to neurotrophins, apparently by recruiting extra TrkB receptors to the plasma membrane (Meyer-Franke et al., 1998). Moreover, the internalization of BDNF receptor TrkB is also upregulated by activity as a retrograde signal to the cell body in cultured hippocampal neurons (Du et al., **in preparation**, Du 2004). The activity-dependent regulation of BDNF signaling on BDNF synthesis and release, TrkB insertion onto neuronal surfaces and activated TrkB tyrosine kinase internalization are crucial for its influence on synaptic plasticity and neuronal survival.

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