BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) IS A KEY MEDIATOR OF LEARNING PLASTICITY

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ABSTRACT

The neurotrophins (NTs) are growth factors that play a critical role in the development, maintenance, survival, and death of the nervous system. BDNF is one of the neurotrophin family and plays a pivotal function in synaptic and learning plasticity. BDNF activates two different receptors, the Trk family of receptor tyrosine kinases and p75NTR, a member of the TNF receptor superfamily. These two receptors have a very unique function, Trk has a survival-dependent signaling through Ras-ERK, PI-3 kinases and PLC-γ, and p75NTR has a dual function: as a survival via activation of NF-κB and promoting apoptosis through activation of JNK, ceremide and some death adaptor proteins. BDNF can modulate hippocampal LTP through TrkB, LTP is a neurophysiologic model for learning process. BDNF can enhance acquisition of information, storage, consolidation and also recall memories. TrkB receptor can also regulate synaptic strength and plasticity. Several of apoptotic pathways from p75NTR can be suppressed by TrkB receptor-mediating signaling and p75NTR can modify ligand-binding specificity and affinity to TrkR with important development consequences.

Keywords: *neurotrophin, growth factors, nervous system, synaptic function, learning plasticity, Trk receptors*

WHAT ARE NEUROTROPHINS?

Neurotrophins are proteins that control neuronal differentiation and survival, and consequently play important roles in the developing and adult stages of the nervous system. They now include Nerve Growth Factor (NGF) discovered by Rita Levi-Montalcini in 1952 (Levi-Montalcini., 1987), Brain-Derived Neurotrophic Factor (BDNF) (Barde et al., 1982), Neurotrophin-3 (NT-3), Neurotrophin 4/5(NT-4/5), and Neurotrophin-6 and 7. The cellular actions of NTs are mediated by two types of receptors: a high-affinity tyrosine receptor kinase (Trk) and a low-affinity pan-neurotrophin recetor (p75NTR) (Bibel et al., 2000). Each Trk is preferentially activated by one or more NTs ¾ TrkA by NGF, TrkB by BDNF and NT-4/5 and TrkC by NT-3¾ and is responsible for mediating cellular responses (Huang et al., 2003), whereas p75 is a member of the tumor necrosis factor receptor family and can interact with all of NTs. (Lee et al., 2001).

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The trophic effects of NTs depend on gene regulation: recent studies have revealed some actions in mediating axonal guidance (Tucker., 2002), synaptic plasticity (Schinder et al., 2000), injury protection (Blesch et al., 1998). BDNF has emerged as an important player in learning plasticity (Gooney et al., 2001, Lu., 2003), and memory acquisition (Tyler et al., 2002), consolidation and reconsolidation (Lee et al., 2004), retention memory and recall (Mizuno et al 2000).

THE NTS RECEPTOR

NT-mediated activation of Trk receptor leads to a variety of biological responses which include proliferation and survival, axonal and dendritic growth also for remodeling, assembly and remodeling cytoskeleton, membrane trafficking and modifications of synaptic functions (Kaplan et al ., 2000, Patapoutian et al ., 2001, Huang et al ., 2001) (Figure 1)

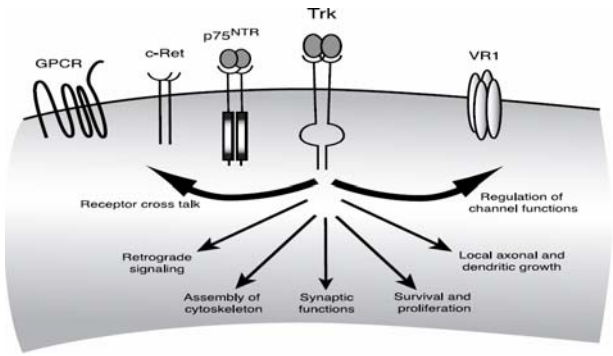

Figure 1. Major functions of Trk receptors (copied from Huang et al., 2003)

The pan-neurotrophin receptor, p75NTR, also regulates the responsiveness of Trk receptors to neurotrophins. In the presence of p75NTR, NT3 is much less effective at activating TrkA, and NT3 and NT4 are much less effective at activating TrkB. In other words, the presence of p75NTR enhances the specificity of TrkA and TrkB for their primary ligand (Bibel et al., 1999, Lee et al., 2001). Thus, the specificity of neuronal responses to neurotrophins can be modulated by the type of receptor, differential splicing, and the absence or presence of p75NTR (Mischel et al., 2001) (Figure 2).

There are 2 types of Trk receptors: full length Trk and truncated Trk. The functions of these truncated isoforms of TrkB is poorly understood. Despite some evidence suggesting that truncated receptors alone can affect intracellular signaling directly (Hapner et al., 1998), a recent study also indicate, that truncated isoforms help regulate the surface expression of full-length TrkB (Haapsalo et al., 2002).

For a neuron to be responsive to a neurotrophin, it requires that a Trk receptor is expressed on the surface of the cell. In some cultured CNS neurons, Trk receptors are localized to intracellular vesicles in the absence of signals. Electrical activity, cAMP, and Ca^{2+} stimulate Trk insertion into the cell surface by exocytosis of cytoplasmic membrane vesicles containing Trk (Du et al., 2003)

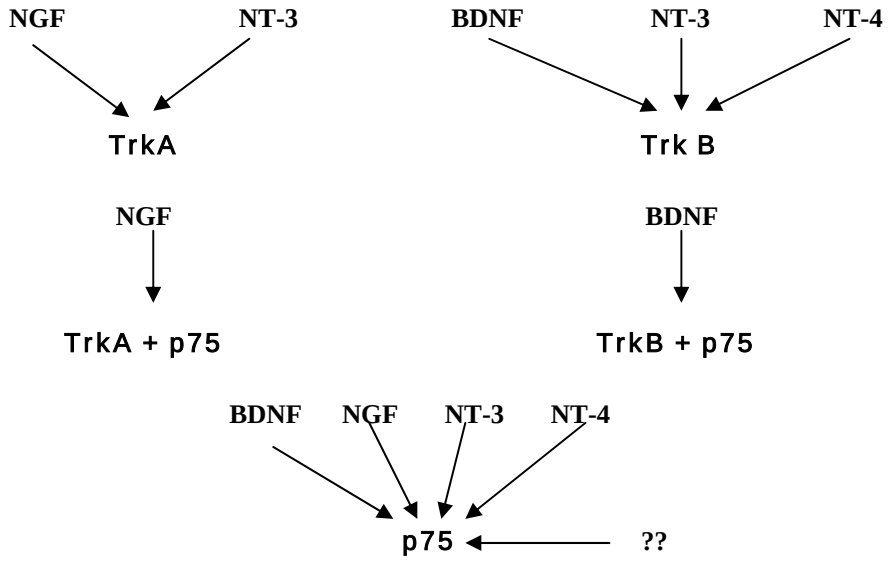

Figure 2. p75NTR gives specificity to Trk receptor (Modified from Lee et al., 2001)

SIGNALLING BDNF VIA TrkB RECEPTOR

BDNF induces activation of TrkB in neurons and is accompanied by a cascade of well-defined cellular events. Activation of the small GTPases Ras and Rap1 has been linked to the Raf-1/B-Raf → MAPK/ERK kinase (MEK) → an extracellular signal-related kinase (ERK) pathway for transcriptional regulation and differentiative signaling (York et al., 1998), while the PI-3kinase → PDK → Akt cassette targets and inactivates proapoptotic substrates such as Forkhead, p53, Bad (Brunnet et al., 1999). The lipid enzyme phospholipase C-γ (PLC-γ) can bind directly to activated Trk on Tyr^{785} residue → IP3 and diacylglicerol (DAG), also indirectly with autophosphorylated receptor on Tyr^{490} (Teng et al., 2004).

Activation of Trk receptors regulates the expression and activities of ion channels, neurotransmitter receptors, and other receptor tyrosine kinases. Regulation of activity through lipid metabolism and protein phosphorylation, localization of proteins and organelles, and local regulation of protein translation, in addition to control of gene expression. Each of these mechanisms affects function of the synapse, and these mechanisms are attractive candidates to mediate the important roles that neurotrophins have in regulating synaptic plasticity in the hippocampus and elsewhere (Alonso et al., 2004). BDNF activation of TrkB promotes the phosphorylation and dephosphorylation of the NMDA receptor subunit NR2B with phosphorylation increasing the open probability of the NMDA receptor ion channel and

thereby rapidly enhancing synaptic transmission (Lin et al., 1999)

SIGNALING BDNF VIA p75NTR

Neurotrophin binding to p75NTR promote survival of some cells and apoptosis of others as well as affects axon outgrowth both in vivo and in vitro. Pro survival pathways activated by p75NTR include NFkB (found only in Schwan cell culture) and Akt (Wooten et al., 2001, Roux et al., 2001). Ligand binding to p75NTR also stimulate several proapoptotic pathways, which include the Jun kinase signaling cascade, sphingolipid turnover, and association with several adaptors (e.g., NRAGE and NADE) that directly promote cell cycle arrest and apoptosis (Mukai et al., 2000, Salehi et al., 2000, Whitfield et al., 2001). p75NTR also activates the small G proteins Rac and Rho that directly affect growth cone motility (Harrington et al., 2002). An important consequence is, that in the absence of Trk receptor activation, neurotrophins are much more effective at inducing apoptosis through p75NTR (Teng et al., 2004).

Like several peptide neurotransmitters, NTs are synthesized as precursors or pro-proteins; proteolytic cleavage was thought to be necessary for the generation of biologically active proteins. Recent evidence shows that uncleaved pro-NGF binds to p75NTR with high affinity and causes cell death (Dechant et al., 2002), in contrast, the binding pro-NGF to TrkA which promote cell survival is not as strong as that for mature NGF (Lee et al., 2001a), the same result with BDNF. This suggests that the proteolytic processing of NTs may be crucially involved in determining their receptor interactions and consequently the outcome of their biological activity (Hempstead., 2002). Signaling through p75NTR does not appear to be important to give affect on Long-Term Potentiation (LTP), and also has little expression in the hippocampus (Xu et al., 2000)

MEMORY IN MAMMALS SAME WITH LONG-TERM POTENTIATION IN THE HIPPOCAMPUS?

What mechanism is used to store explicit memory-information about people, places and objects? An important component of the medial temporal system of higher vertebrates, involved in the storage of explicit memory, is the hippocampus. Hippocampus has 3 major pathways: the perforant pathway, the mossy fiber pathway and the Schaffer collateral pathway (Kandell et al., 2000). Terje Lomo (1973) discovered Long-Term Potentiation, a brief high-frequency train of stimuli (a tetanus) to any of the three major synaptic pathways, which increases the amplitude of the excitatory postsynaptic potentials in the target hippocampal neurons (Lomo., 2003), although the mechanism underlying LTP are not the same in all three pathways.

LTP is a neurophysiologic model to understand the plasticity in the hippocampus and has 2 phases: a short-term phase of LTP (called early LTP) lasting 1-3 hours; this early phase produces no change in the number of synapses and does not require new protein synthesis. A late phase of LTP lasts for at least 24 hours and requires new protein and RNA synthesis; this phase recruits the cAMP-PKA-MAPK-CREB signaling pathway (Weisskopf et al., 1994). The cellular-physiological studies suggest, that the late phase of LTP involves activation of growth and neurotrophic factor and also neurotransmitter release. The properties of this late phase of LTP are equivalent with the long-term memory storage (Kandell., 2000). Some data suggest that BDNF is capable of modulating synaptic function in the hippocampus as an initiation and maintenance of LTP, while as tetanic stimulation enhances the expression of BDNF mRNA in the hippocampus. During modulation of high frequency transmission of LTP, BDNF requires the activation of MAPK and PI3K signaling (Gottschalk et al., 1999).

THE ROLE OF BDNF IN LEARNING PLASTICITY

Long-term Potentiation (LTP) in the hippocampus is an activity-dependent modification of synaptic strength and is considered a potential cellular mechanism underlying learning and memory (Bliss et al., 1993). BDNF is implicated in synaptic plasticity such as LTP which played a role in learning and memory (Yamada et al., 2002, Malenka et al., 2004).

Based on the finding that BDNF can rapidly potentiate synaptic transmission at the neuromuscular synapses, in primary cultures of hippocampal neurons, application of BDNF has been found to rapidly enhance synaptic transmission (Li et al., 1998, Lu et al., 1999) and neurotransmitter release (Tyler et al., 2002a). BDNF-mediated synaptic potentiation requires intracellular Ca^{2+} (West et al., 2001) and activation of calsium/calmodulin-dependent protein kinases (CaMKs) (Xia et al., 2005). Activation of NMDA receptor of glutamate generates LTP, whereas inhibition and deletion of NMDA receptor impair LTP and spatial learning and memory (Tsien et al., 1996). BDNF/TrkB signaling enhances hippocampal synaptic transmission and efficacy by increasing NMDA receptor activity,

which is very crucial for spatial memory in hippocampus (Mizuno et al., 2003).

Mizuno et al (2000) used an antisense BDNF oligonucleotide treatment to the mice led to impairment of not only acquisition, but also maintenance and/or recall of spatial memory in water maze training (Mizuno et al., 2000). TrkB plays also a role in the initiation and maintenance of LTP; a study with mice with loss of TrkB from excitatory pyramidal neurons in the hippocampus and forebrain, showed interference with memory acquisition and consolidation in many learning paradigms (Minichiello et al., 1999).

CONCLUSION

The discovery of neurotrophins show, that they open the chance for adult neurons to survive, change the fate of cells, axon growth, dendrite pruning, synaptic function and also learning plasticity. Not only these proteins but also the Trk receptors play a role in synaptic transmission and learning processes. This field of neuroscience is still wide open and needs to be explored.

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