Cooperation between BDNF and glutamate in the regulation of synaptic transmission and neuronal development

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Abbreviations: BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; CRTC, CREB-regulated transcription coactivator; mEPSCs, miniature excitatory postsynaptic currents; TORC, transducers of regulated CREB activity

BDNF belongs to a family of closely related neurotrophic factors termed neurotrophins and is widely expressed in the developing and mature central nervous system. During postnatal development, BDNF levels are dynamically regulated, in part by activity-dependent mechanisms. In this context, glutamate, the major excitatory neurotransmitter in the mammalian brain, increases the transcription and release of BDNF. The biological functions of BDNF are mediated by binding to TrkB receptor tyrosine kinase, that leads to the activation of three major intracellular signaling pathways, including MAPK, PI3K and PLCγ1. TrkB-mediated signaling can propagate to the nucleus to regulate gene transcription through the activation of several transcription factors including CREB. Compelling evidence supports an important role of BDNF in the survival and differentiation of selective populations of neurons in the peripheral and central nervous systems.

BDNF and Synaptic Transmission

In addition to its trophic effects during brain development, BDNF has been shown to exert acute effects on synaptic transmission and plasticity. In particular, BDNF enhances excitatory synaptic transmission through pre- and postsynaptic mechanisms. In this regard, BDNF enhances glutamate release, the frequency of miniature excitatory postsynaptic currents (mEPSCs), NMDA receptor activity and the phosphorylation of NMDA receptor subunits. Our recent studies revealed a novel cooperative interaction between BDNF and glutamate in the regulation of dendritic development. Indeed, we found that the effects of BDNF on dendritic growth of cortical neurons require both the stimulation of cAMP response element-binding protein (CREB) phosphorylation by BDNF and the activation of the CREB-regulated transcription coactivator 1 (CRTC1) by glutamate. Together, these studies highlight the importance of the cooperation between BDNF and glutamate in the regulation of synaptic transmission and neuronal development.

BDNF and Dendritic Development

In addition to its effects on the regulation of synaptic transmission, considerable evidence indicates that BDNF regulates dendritic growth during brain development. In particular, BDNF plays an important role in controlling the dendritic growth of pyramidal neurons in the developing visual cortex. Other studies have revealed that overexpression of BDNF in pyramidal neurons induces sprouting of basal dendrites, and release of BDNF from single cells elicits local dendritic growth in nearby neurons. Because dendritic morphology determines the number, pattern and types of synapses received by a neuron, regulation of cortical dendritic growth by BDNF is likely to play a major role for the proper functioning of the brain. Despite these observations, the cellular and molecular mechanisms underlying the effects of BDNF on dendritic development remain largely unknown. In a recent study aimed at identifying the signaling mechanisms through which BDNF regulates dendritic growth, our group identified a novel cooperative interaction between BDNF and glutamate in the regulation of excitatory synaptic transmission.

Key words: BDNF, CREB, CRTC, dendrite, glutamate, neuronal development, NMDA receptors, TORC, synaptic transmission

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in the brain and is involved in activity-dependent transcription of BDNF and in late-phase long-term potentiation.\textsuperscript{36,37} By using a mutant form of CREB unable to bind CRTC1, we demonstrated that BDNF-induced dendritic development also requires a functional interaction between CREB and CRTC1. Consistent with this observation, inhibition of CRTC1 by RNA interference suppressed BDNF-induced dendritic growth. In addition, we found that the translocation of CRTC1 from the cytoplasm to the nucleus of cortical neurons, which is a necessary step for the interaction between CREB and CRTC1, resulted from the activation of NMDA receptors by glutamate. Finally, nuclear translocation of CRTC1 by glutamate, via stimulation of NMDA receptors and calcineurin, was shown to be essential for the effects of BDNF on dendritic development.\textsuperscript{31}

Together, these results indicate that regulation of dendritic growth by BDNF requires both the stimulation of CREB phosphorylation by BDNF and the induction of CRTC1 nuclear translocation by glutamate through NMDA receptor activation (Fig. 1). These data provide evidence for a novel cooperative interaction between BDNF- and glutamate-mediated signaling that converges on CREB to regulate the expression of target genes involved in dendritic development.

**Conclusions**

An increasing number of studies support the existence of functional and cooperative interactions between BDNF and glutamate. In particular, glutamate and BDNF co-regulate one another such that glutamate increases the transcription and secretion of BDNF and, conversely, BDNF enhances glutamate release. Other studies provide evidence that BDNF regulates the phosphorylation and expression of NMDA receptor subunits. These cooperative actions of BDNF and glutamate have important implications for the regulation of synaptic transmission and plasticity in the central nervous system. Our studies extend these observations by revealing a novel cooperative interaction between BDNF and glutamate that converges on CREB to increase the transcription of target genes involved in dendritic development.\textsuperscript{31}

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