Neurotrophin-Mediated Rapid Signaling in the Central Nervous System: Mechanisms and Functions
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Neurotrophins comprise a family of secreted proteins that promote growth, survival, and differentiation of neurons in the central and peripheral nervous systems. They act by binding to two kinds of plasma membrane receptors, the Trk receptor tyrosine kinases (Trk receptors) and the p75 pan-neurotrophin receptor (p75NTR). There are several subtypes of Trk receptor kinases that are characterized by specific affinity for the different neurotrophins. Nerve growth factor (NGF) binds preferentially to TrkA, whereas brain-derived neurotrophic factor (BDNF) and neurotrophin (NT)-4/5 show a high affinity for TrkB. NT-3, on the other hand, predominantly activates TrkC but can also bind to TrkA and TrkB, albeit with lower affinity (4). Binding of neurotrophins to Trk receptors triggers ligand-induced receptor dimerization and autophosphorylation of tyrosine residues in the intracellular kinase domain. Within seconds to minutes, the tyrosine phosphorylation is followed by the activation of diverse signaling cascades, such as the phosphatidylinositol 3-kinase (PI3K)/Akt, MAPK, and PLC-γ pathways (FIGURE 1) (4, 27, 32, 64). These intracellular signaling pathways modulate gene expression in a cell type-specific manner and are responsible for most of the long-term effects of neurotrophins related to neuronal growth, survival, and differentiation (27, 58, 64) (FIGURE 1). The molecular mechanisms underlying these "classical," slow effects of neurotrophins have been reviewed in excellent earlier articles (17, 27, 32). In the present review, we focus on BDNF and summarize the evidence for its rapid neuronal actions, including changes in neuronal excitability, synaptic transmission, and neural plasticity.

**Pro Forms of Neurotrophins are Biologically Active**

Neurotrophins are synthesized as pre/neurotrophin precursors of ~27 kDa, which are further processed within the intracellular protein transport pathway (for review see Ref. 41). The prepeptides serve as the signal for the translocation of the neurotrophin precursors into the lumen of the endoplasmic reticulum and are then cleaved off. The resulting proneurotrophins are further processed, and the propeptide is finally cleaved off to generate mature neurotrophins of ~13 kDa. These form stable homodimers that are secreted in both constitutive and regulated pathways (41) and that represent high-affinity ligands for the Trk receptor kinases (4). The functional importance of the pro region of BDNF was demonstrated in a recent study that investigated the consequences of a single nucleotide polymorphism in this region. This polymorphism is defined by replacement of valine66 with methionine (20) and is associated with memory deficits and abnormal hippocampal function in humans (20). At the cellular level, the Val/Met substitution affects the intracellular trafficking of BDNF to synapses and attenuates the regulated activity-dependent release of BDNF without affecting its constitutive secretion (14, 20).

Although the pro region of neurotrophins was thought originally to act merely as an intracellular targeting domain, recent studies have provided evidence that the pro forms of NGF and BDNF are secreted and cleaved extracellularly by specific proteases of the extracellular matrix, such as plasmin (40, 55), a protease that is known to contribute to synaptic plasticity (3). The molecular mechanisms underlying these "classical," slow effects of neurotrophins have been reviewed in excellent earlier articles (17, 27, 32). In the present review, we focus on BDNF and summarize the evidence for its rapid neuronal actions, including changes in neuronal excitability, synaptic transmission, and neural plasticity.
low-affinity receptor for mature neurotrophins (40, 48). Subsequently, several other studies have established a role for proNGF in p75NTR-dependent neuronal apoptosis (40, 55). Proneurotrophins may thus play roles as important as those of the established “mature” neurotrophin forms. In the future, it will be interesting to determine whether proneurotrophins contribute directly to synaptic signaling and neuronal plasticity.

Release of Neurotrophins

The molecular mechanisms of activity-dependent neurotrophin release are under intensive study (2, 12, 24, 26, 41), and several, in part contradictory models have been proposed (FIGURE 2). Hartmann et al. (26) have expressed recombinant BDNF-green fluorescent fusion protein (GFP) in hippocampal microcultures and found it to be located predominantly at postsynaptic sites.
Activity-dependent release of the BDNF-GFP from these postsynaptic sites was visualized by time-lapse fluorescence microscopy with a temporal resolution of seconds to minutes. This approach enabled visualization of postsynaptic BDNF-GFP release that required postsynaptic Ca\(^{2+}\) influx through ionotropic glutamate receptors or voltage-gated Ca\(^{2+}\) channels (26) (FIGURE 2A). The authors suggested that BDNF acts as a "synaptic messenger" of activity-dependent synaptic plasticity, which is released from postsynaptic neurons. By contrast, evidence for a presynaptic release of BDNF-GFP from axons, in cortical cultures, was presented by Kohara et al. (34). These authors visualized the transfer of BDNF-GFP from presynaptic axon terminals to postsynaptic neurons. The transynaptic BDNF-GFP transfer was activity dependent and was blocked by an extracellular BDNF scavenger (34). The contrasting findings of Hartmann et al. (26) compared with Kohara et al. (34) may be the result of the use of different methodological approaches and less likely the result of the use of different preparations (hippocampal vs. cortical neurons).

The mechanisms of regulated release of native BDNF from hippocampal neurons have been investigated by Balkowiec and Katz (2). They found that the electrical stimulation patterns used widely for induction of hippocampal long-term potentiation (LTP), such as 100-Hz tetanic or theta-burst stimulation, are significantly more effective in releasing native BDNF than lower-frequency stimulations (2). BDNF release is dependent on the activation of voltage-gated Na\(^{+}\) channels and the subsequent Ca\(^{2+}\) influx through voltage-gated N-type Ca\(^{2+}\) channels. In addition, the inhibition of caffeine/ryanodine-sensitive Ca\(^{2+}\) release from intracellular stores inhibits BDNF release, indicating a role for Ca\(^{2+}\)-induced Ca\(^{2+}\) release in activity-dependent secretion of BDNF (2) (FIGURE 2B).

In addition to neurotrophin release following Ca\(^{2+}\) influx, Ca\(^{2+}\)-influx-independent forms of neurotrophin release have been described (9, 12, 25). One of these release mechanisms (FIGURE 2C) involves the activation of PLC and the subsequent mobilization of Ca\(^{2+}\) from intracellular stores (9). Canossa et al. (12) have expressed recombinant Trk-receptor mutants in which only the TrkBFL kinase domain (FIGURE 1) and the Y\(^{816}\)–PLC-g site (FIGURE 1) remained intact in a variant of PC-12 cells (nnr5 cells) as well as in cultured hippocampal neurons. These two sites were found to be sufficient and necessary for mobilization of intracellular Ca\(^{2+}\) and triggering of neurotrophin release following activation of the mutant receptors. Neurotrophin release is also triggered following activation of inositol 1,4,5-trisphosphate (IP\(_{3}\))-induced Ca\(^{2+}\) release by the G protein-coupled

### FIGURE 2: Neuronal release of neurotrophins

A: postsynaptic release of BDNF-green fluorescent fusion protein (GFP) requires postsynaptic Ca\(^{2+}\) influx through ionotropic glutamate receptors (N-methyl-D-aspartate receptor (NMDAR); \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)) or voltage-operated Ca\(^{2+}\) channels (VOCC) (26). B: dual requirement of extracellular and intracellular Ca\(^{2+}\) for activity-dependent secretion of native BDNF. Ca\(^{2+}\) influx through N-type VOCC drives Ca\(^{2+}\)-dependent Ca\(^{2+}\) release from intracellular stores by ryanodine receptors (RyR) (2). C: Ca\(^{2+}\)-influx-independent neurotrophin release involves PLC activation and IP\(_{3}\)-mediated Ca\(^{2+}\) release from intracellular stores (12). Glutamate-induced neurotrophin release is mediated by metabotropic glutamate receptor type I (mGluRI) and subsequent activation of PLC. VOCC, voltage-operated Na\(^{+}\) channel.
metabotropic glutamate receptor I and activation of \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (12).

\[ \text{Ca}^{2+} \] release from intracellular stores was also found to be instrumental for BDNF secretion in another study using hippocampal neurons (24). In that study, BDNF was overexpressed by 10- or 20-fold by the use of adenoviral vectors. Its release was induced by electrical field stimulation, resulting in bursts of action potentials at frequencies that are able to induce LTP, and was dependent on IP_{3}-mediated \( \text{Ca}^{2+} \) release. In contrast to the results of Balkowiec and Katz (2), Gärtner and Staiger (24) found that BDNF secretion was independent of extracellular \( \text{Ca}^{2+} \).

Neurotrophins Enhance Neurotransmitter Release

The neurotrophins NT-3 and BDNF, but not NGF, modulate the efficacy of synaptic transmission (47, 58). This effect appears to be presynaptic in origin and to be mediated by the Trk family of receptor tyrosine kinases (47). Boulanger and Poo (11) have reported that presynaptic depolarization is a critical factor in determining the synaptic action of BDNF at Xenopus neuromuscular synapses, the potentiation of synaptic efficacy by BDNF is facilitated when the presynaptic site is depolarized. Importantly, the effect of depolarization does not require \( \text{Ca}^{2+} \) influx and the increase in synaptic strength occurs through the enhancement of presynaptic transmitter release. Thus this study indicated that presynaptic depolarization interacts directly with BDNF-induced signaling, possibly through the synaptic release of endogenous neurotrophins that act in an autocrine or paracrine fashion to potentiate synaptic transmission (11).

Studies on preparations of mammalian nerve terminals (synaptosomes) have indicated that neurotrophins induce the presynaptic release of the neurotransmitters ACh (33), glutamate (28), and GABA (28). In the study by Jovanovic et al. (28), the release of the excitatory neurotransmitter glutamate and the inhibitory transmitter GABA was shown to be independent of \( \text{Ca}^{2+} \) influx but linked to BDNF-induced MAPK activity and synapsin phosphorylation (28) (FIGURE 3). Overall, their results suggested a direct interaction of BDNF/TrkBFL signaling with synapsin, a protein required for synaptic vesicle release (65). The reported \( \text{Ca}^{2+} \)-independent induction of transmitter release following activation of presynaptic Trk receptors is unexpected, because most neurotransmitters require \( \text{Ca}^{2+} \) influx for their activity-dependent release. In conclusion, there is accumulating evidence that neurotrophin-evoked actions may self-amplify. In this positive feedback loop, neurotrophin release at active synapses increases the amount of presynaptic neurotransmitter release, and thus postsynaptic responses, which in turn increases the amount of released neurotrophins. Such a positive feedback mechanism has been shown by Knipper et al. (33). In the rat hippocampus, activation of muscarinic ACh receptors increases NGF and BDNF transcript levels and NGF proteins, whereas conversely NGF and BDNF enhance the release of ACh from hippocampal synaptosome preparations.

Neurotrophin-Mediated Activation of Ion Channels

**Neurotrophin-dependent phosphorylation of N-methyl-D-aspartate receptors**

BDNF can exert modulatory effects on both excitatory and inhibitory synaptic transmission, mostly through an interaction with the respective ionotropic channels. Levine et al. (43) have shown that addition of exogenous BDNF to the bath increases the firing rate of cultured hippocampal neurons within 2–3 min. Moreover, the mean amplitude of evoked excitatory postsynaptic currents increases in the presence of BDNF (43). The increase in synaptic strength is due to an increased open probability of N-methyl-D-aspartate (NMDA) receptors (42) following BDNF/TrkBFL-mediated phosphorylation of the NMDA receptor subunits NR1 (66) and NR2B (45, 62).

Evidence for a direct interaction between TrkBFL and NMDA receptor phosphorylation has been provided recently (54). In that study, Fyn, a nonreceptor Src-family tyrosine kinase, was coimmunoprecipitated with TrkBFL and the NR2B subunit. The extent of TrkB-Fyn-NR2B protein interaction increased in behavioral tests for spatial learning, whereas the phosphorylation of other nonreceptor tyrosine kinases was not affected (54). These data identified a postsynaptic neurotrophin-mediated signaling...
munoprecipitation using anti Trk antibodies identified TrpC3 as a putative candidate protein responsible for the ion influx. TrpC3 is a member of the transient receptor potential channel family. Ion influx through Trp channels is generally activated through signal transduction pathways (16) and not by voltage activation. Intriguingly, coexpression of TrpC3 and TrkB in HEK-293T cells enabled the reconstitution of a BDNF-mediated cation influx that was similar to the BDNF-induced cation influx in neurons (44). These results suggest that activation of TrkB and PLC-\(\gamma\)/H9253 leads to an IP\(_{3}\)-dependent, store-operated influx of Ca\(^{2+}\) and Na\(^{+}\) through TrpC3 (FIGURE 4B). The authors concluded that the interplay between neuro-

Neurotrophin-induced cation influx through TrpC3 channels

Li et al. (44) have found that brief application of BDNF to pontine neurons induces a PLC-\(\gamma\)/IP\(_{3}\)-dependent, nonselective cation current. Coin-

cascade (FIGURE 4A) that may contribute to neuronal plasticity and memory formation. The mechanisms mediating rapid modulation of synaptic properties by neurotrophins have been studied primarily at excitatory synapses. There is increasing evidence, however, that neurotrophins also modulate GABAergic transmission (15, 53, 67, 70). These findings have been reviewed in detail elsewhere (60) and will, therefore, not be addressed here.

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FIGURE 4. Distinct mechanisms of BDNF-mediated rapid actions

A: TrkB\(^{FL}\)-dependent phosphorylation activates the nonreceptor protein tyrosine kinase Fyn that in turn increases the open probability of postsynaptic NMDA receptors. B: TrkB/PLC-\(\gamma\)-mediated, IP\(_{3}\)-dependent Ca\(^{2+}\) store depletion activates ion influx through transient receptor potential C3 (TrpC3) channels. C: BDNF/TrkB activates the Na\(^{+}\) channel Nav1.9. The resulting depolarization activates VOCC and thus produces Ca\(^{2+}\) influx. D: truncated TrkB receptor 1 (TrkB-T1) mediates G protein-dependent PLC activation, IP\(_{3}\)-dependent Ca\(^{2+}\) release from Ca\(^{2+}\) stores, and subsequent activation of store-operated ion channels (SOCC).
trophins and Trp channels might be involved in synaptic transmission by altering membrane potentials, which in turn might facilitate synaptic Ca$^{2+}$ entry through voltage-gated channels or NMDA glutamate receptors (44).

**Rapid gating of the Na$^+$ channel Nav1.9 by BDNF/TrkB**

Besides the induction of acute neurotrophin effects through intracellular signaling cascades within seconds to minutes (11, 43, 44, 47), a much faster and distinctly different excitatory action of neurotrophins has been reported. BDNF and NT-4/5 are effective at much lower concentrations than glutamate (29). The study cited also revealed that the rapid neurotrophin-evoked depolarization results from the immediate activation of a Na$^+$ conductance. The Na$^+$ conductance (BDNF-evoked $I_{Na}$) is insensitive to tetrodotoxin, a highly potent blocker of those voltage-gated Na$^+$ channels that are involved in action potential firing (13).

Molecular reconstitution enabled the identification of the molecular mechanisms of the rapid excitatory action of BDNF and NT-4/5 (10). By screening candidate transcripts with an antisense mRNA expression approach, Blum et al. (10) have identified the Na$^+$ channel Nav1.9 and the receptor tyrosine kinase TrkB as the key components for the BDNF-evoked $I_{Na}$ in HEK-293 cells, stimulation of recombinant TrkB receptors by BDNF induces Na$^+$ influx through the coexpressed Na$^+$ channel Nav1.9, whereas expression of only Nav1.9 or TrkB fails to reconstitute the BDNF-evoked $I_{Na}$. Both the reconstituted and neuronal current are insensitive to TTX but highly sensitive to the Na$^+$ channel blocker saxitoxin. This interaction between TrkB and Nav1.9 also mediates BDNF-evoked excitation in cultured hippocampal neurons, because the targeted elimination of Nav1.9 by antisense mRNA expression blocks BDNF-evoked depolarization needed in neurons (10). TrkB and Nav1.9 also mediate BDNF-evoked excitation in cultured hippocampal neurons, because the targeted elimination of Nav1.9 by antisense mRNA expression blocks the BDNF-evoked $I_{Na}$ in this preparation (10).

The gating mechanism of Nav1.9 by activated TrkB receptors is still unknown. On the basis of its molecular structure, Nav1.9 belongs to the family of voltage-gated Na$^+$ channels. Members of this family are thought to be gated exclusively by changes in the membrane potential (13). Nevertheless, both the study cited (10) and a further study (46) have reported that recombinant Nav1.9 channels cannot be opened by common voltage-step protocols. Opening of Nav1.9 can be achieved only by activation of the TrkB receptor with BDNF indicating that Nav1.9 is gated by ligand binding rather than by voltage steps (10). In dorsal root ganglia and in duodenum myenteric neurons, Nav1.9 was reported to contribute to a TTX-insensitive, voltage-dependent Na$^+$ current (18, 63). Nav1.9 may, therefore, exist in different functional states: in a voltage-dependent state and, in addition, in a ligand-dependent state, dependent perhaps on different molecular contexts.

The protein domains involved in the interaction between TrkB and Nav1.9 have not yet been identified. Surprisingly, K-252a, an inhibitor of Trk receptor kinase activity, blocks the TrkB-mediated activation of Nav1.9 (29). This has been attributed to steric hindrance, inhibiting the interaction between the TrkB receptor and the Na$^+$ channel, rather than blocking "slow" phosphorylation-dependent steps (6, 29). Alternatively, K-252a could act as a competitive inhibitor of the binding of ATP to the TrkB receptor (1), an early step in the autophosphorylation and activation of all Trk receptors. In this case, prephosphorylated TrkB receptors would be a structural prerequisite for the rapid activation of Nav1.9 by BDNF BDNF binding and the subsequent dimerization of the "primed" receptors might then be sufficient for the gating of Nav1.9 (FIGURE 4C). It needs to be pointed out that the phenomenon of rapid BDNF-elicted depolarization has been, thus far, reported only in a series of studies from the same group (10, 29, 39, 61) and has only been indirectly confirmed by other studies (15, 23). In future studies, it will be important to have the effect of BDNF-evoked depolarization confirmed by other laboratories and, especially, to determine whether physiologically released BDNF is capable of depolarizing neurons in intact neuronal networks.

Fujisawa et al. (23) provided evidence for a role for the BDNF-TrkB-Nav1.9 pathway in the long-term regulation of neuronal network activity. The authors reported that when hippocampal neurons are treated briefly with BDNF, chaotic fluctuations of the membrane potential are stabilized. In neurons with irregular, unpredictable oscillations of the membrane potential, BDNF stabilizes the membrane potential fluctuations and enhances the accuracy of action potentials in terms of spike reliability and temporal precision. Interestingly, in an artificial model neuron based on the Hodgkin-Huxley theory, the incorporation of a voltage-insensitive, Nav1.9-like conductance is sufficient to...
mimic the BDNF effect (23).

**Neurotrophin-induced Ca\(^2+\) signaling in glial cells by truncated TrkB receptors**

In addition to TrkB\(^{FL}\), truncated versions of the TrkB receptor are expressed in the central nervous system (4). These truncated TrkB receptors, TrkB-T1 and TrkB-T2, are alternative splicing products (4). They possess the receptor domain of TrkB\(^{FL}\) but lack the intracellular kinase domain. Recently, Rose et al. (61) have revealed that truncated TrkB receptors can induce intracellular signaling and mediate rapid neurotrophin-evoked Ca\(^2+\) transients in glial cells. These BDNF-induced Ca\(^2+\) signals reflect PLC/IP\(_3\)-dependent release of Ca\(^2+\) from intracellular stores, which is followed by Ca\(^2+\) entry through store-operated Ca\(^2+\) channels (61). Since truncated TrkB receptors lack the binding site for PLC-\(\gamma\) and the activation of the BDNF-induced Ca\(^2+\) signals is G protein dependent (61), it is not PLC-\(\gamma\) but most likely another PLC isofrom that mediates this Ca\(^2+\) signaling. Due to its predominant expression in glial cells, TrkB-T1, but not TrkB-T2, is believed to be the most likely candidate for this acute neurotrophin effect (FIGURE 4D). Because Ca\(^2+\) signals in glial cells are known to modulate neuronal activity (7), BDNF may act as a mediator between neurons and glial cells (59).

### Regulation of Synaptic Plasticity Through Neurotrophins

It is well established that neurotrophins participate in activity-dependent neuronal plasticity (30, 47). BDNF is implicated directly in hippocampal LTP, a synaptic model for learning and memory (5, 8). The facilitating action of BDNF on LTP induction has been attributed to both presynaptic and postsynaptic mechanisms (11, 19, 21, 30, 47, 72, 74). The crucial role of BDNF and TrkB receptors in the induction of LTP has been studied intensively in engineered mouse models (35–38, 51, 52, 57, 72, 74). In bdnf knockout mice, hippocampal LTP is impaired (35), an effect that can be rescued by virus-mediated reexpression of the BDNF gene in the CA1 region (36, 57).

The generation of conditional TrkB mutants and mice with a targeted mutation in the TrkB\(^{FL}\) receptor has been instrumental in the analysis of the molecular mechanism underlying the coupling of neurotrophin signaling to LTP (38, 51, 52). After binding of BDNF, the TrkB receptor dimerizes and activates its internal kinase domain, which then autophosphorylates several specific tyrosine residues, most importantly the so-called shc site (Y515) and the PLC-\(\gamma\) site (Y816) (FIGURE 1). Whereas the shc site of TrkB\(^{FL}\) couples the activated receptor to the Ras/MAPK pathway and the PI3K pathway, the PLC-\(\gamma\) interaction of TrkB is responsible for the formation of the second messengers IP\(_3\) and diacylglycerol and, consequently, Ca\(^2+\) release from intracellular Ca\(^2+\) stores (FIGURE 1).

Minichiello et al. (51) have found that hippocampal LTP is impaired in mice with a mutation in the PLC-\(\gamma\) adaptor site of TrkB\(^{FL}\) but not in mice with a mutated shc site. Furthermore, the trkB\(^{PLC-PLC}\) mutants, but not the trkB\(^{PLC}\) mice, show substantial impairment of their Ca\(^2+\)-dependent signaling pathway from the Ca\(^2+\)-calmodulin-dependent kinase IV to the Ca\(^2+\)-regulated transcription factor cAMP response element binding protein (CREB) (38, 51) (compare with FIGURE 1). This was surprising, because previous studies indicated that both the Ras/MAPK pathway and the PLC-\(\gamma\) pathway couple neuronal neurotrophin signaling to CREB-dependent gene expression (22). Previous results have also suggested a major role for the TrkB-MAPK pathway when LTP is triggered by hippocampal microinjection of BDNF in vivo (73). In these experiments, MAPK signaling was necessary for BDNF-induced LTP, the activation of CREB, and the upregulation of the immediate early gene called activity-regulated cytoskeleton-associated protein (Arc).

Recently, Kovalchuk et al. (39) have shown that locally applied BDNF evokes Ca\(^2+\) transients in dendrites and spines of hippocampal neurons but not at presynaptic sites. This rise in intracellular Ca\(^2+\) is dependent purely on depolarization-induced Ca\(^2+\) influx via voltage-operated Ca\(^2+\) channels. When dendritic (postsynaptic) BDNF application is combined with a weak burst of synaptic stimulation, an immediate and robust induction of LTP is observed. Since BDNF mediates rapid membrane depolarization, it was suggested that the coupling of BDNF-TrkB to the Na\(^+\) channel Na\(_1\) is of importance (FIGURE 4C) provides the molecular basis for the proposed instructive role of BDNF in LTP induction (10, 39, 49). It remains to be seen whether the instructive role of BDNF in LTP induction includes both molecular mechanisms, the TrkB-Nav1.9 interaction (10, 39) and TrkB-PLC-\(\gamma\) signaling (51), or whether BDNF has distinct roles in LTP induction, e.g., at different synaptic locations or at different time scales.

Rapid BDNF-evoked excitation of neurons by TrkB/Nav1.9 mediates the opening of voltage-gated Ca\(^2+\) channels (39). This Ca\(^2+\) entry through the plasma membrane might activate Ca\(^2+\)-dependent signaling pathways that regulate activity-dependent gene expression (71). In particular, Ca\(^2+\)-dependent transcription factors such as CREB (22) and the calcium-responsive transcription factor CaRF (69) are possible targets of rapid BDNF-induced Ca\(^2+\) influx. Both factors are known to be responsible for the activity-dependent regulation...
of BDNF expression (68, 69). Rapid neurotrophin signaling might thus contribute to activity-dependent expression of neurotrophins themselves and to the establishment of long-lasting LTP and long-term memory, which are known to depend on de novo transcription (31, 50).

Concluding Remarks

Neurotrophins are responsible for intriguingly complex neuronal signaling processes. Interplay between fast and slow signaling events regulates not only basic cellular phenomena such as neuronal growth, survival, and differentiation but also specifically neuronal phenomena such as synaptic transmission and neuronal plasticity, which underlie memory formation and cognitive attributes. One of the most challenging questions of neurotrophin function will be how spatial and temporal availability of acutely secreted neurotrophins contribute to the multiple signaling pathways that regulate neuronal functions in the central nervous system.

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