Down-regulation of the Neurotrophin Receptor TrkB following Ligand Binding

EVIDENCE FOR AN INVOLVEMENT OF THE PROTEASOME AND DIFFERENTIAL REGULATION OF TrkA AND TrkB*

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This study examines the mechanisms by which the tyrosine kinase receptor TrkB is down-regulated following binding of brain-derived neurotrophic factor (BDNF). In primary cultures of cerebellar granule neurons, BDNF-induced reduction of TrkB receptors was largely prevented by the addition of specific proteasome inhibitors. HN10 cells, a neuronal cell line that can be readily transfected, also showed a marked down-regulation of cell surface TrkB following BDNF exposure. In addition, we observed that prolonged exposure to nerve growth factor of TrkA-transfected cells did not lead to the down-regulation seen with BDNF and TrkB. TrkA and TrkB chimeric molecules were therefore expressed in HN10 cells and tested for ligand-induced regulation. These experiments led to the conclusion that the motives responsible for down-regulation are contained in the cytoplasmic domain of TrkB, and a short sequence in the juxtamembrane domain of TrkB was identified that confers nerve growth factor-induced down-regulation when inserted into TrkA.

The members of the nerve-growth factor (NGF)† family, also designated neurotrophins, are factors that play a critical role in the development of the vertebrate nervous system (for reviews, see Refs. 1–3). In mammals, they comprise NGF, BDNF (brain-derived neurotrophic factor), NT3 (neurotrophin 3), and NT4/5 (neurotrophin 4/5). Their trophic actions are mainly mediated by tyrosine kinase receptors belonging to the Trk family. Whereas NGF is the ligand for the TrkA receptor, BDNF and NT4/5 are the ligands for TrkB, and NT3 is a promiscuous ligand with some selectivity for TrkC. Binding of a neurotrophin to the appropriate Trk receptor leads to dimerization and transphosphorylation of tyrosine residues in the intracellular domain of the Trk receptor and subsequent activation of cytoplasmic signaling pathways, such as the Ras/Raf/MAP kinase pathway (for review, see Ref. 4).

Neurotrophins and their receptors are also involved in the function of the mature central nervous system, where some of them, in particular BDNF (5) and TrkB (6), are widely expressed. For example, neurotrophins play a role in the modulation of synaptic transmission, including neurotransmitter release, postsynaptic responses to neurotransmitters, and facilitation of long term potentiation (for reviews, see Refs. 7 and 8). These functions are reminiscent of the actions of neurotransmitters, and it is conceivable that the duration of the signal elicited by the neurotrophins, like that of neurotransmitters, may be regulated. Yet comparatively little is known on the regulation of neurotrophin receptors following ligand binding, although a few previous studies have indicated unexpected differences in the duration of signaling elicited by BDNF and NGF. Whereas both stimulate GTP binding to Ras in chick sensory neurons (9, 10), prolonged exposure to BDNF leads to a complete loss of Ras activation, in contrast to NGF (10). In cerebellar granule cells, desensitization of Ras signaling by BDNF is accompanied by a disappearance of TrkB-binding sites (10). Down-regulation of TrkB signaling upon BDNF exposure has also been reported in cultures of cortical (11, 12) and hippocampal neurons (12, 13), reflected in either an impairment of phosphatidylinositol hydrolysis (12) or decreased phosphorylation of PLC-γ (11). Furthermore, treatment of both striatal and hippocampal cultures for 24 h with BDNF decreased c-Fos induction upon acute BDNF stimulation (13). Marked decrease of binding to radiolabeled BDNF (10, 13) and/or of Trk tyrosine phosphorylation (11, 13) was also observed upon BDNF treatment for 2 or more days.

As the mechanisms underlying the loss of response to BDNF with time are largely unknown, we investigated the regulation of the TrkB receptors by their ligands, using both cultured cerebellar granule cells and the neuronal cell line HN10 (14). These cells, unlike A293 cells transfected with TrkB (10), do show a marked down-regulation of TrkB following prolonged stimulation with BDNF, and as they can be readily transfected with cDNA constructs, we could investigate the TrkB domains accounting for its down-regulation by comparison to TrkA.

EXPERIMENTAL PROCEDURES

Neurotrophins—Recombinant human NGF, BDNF, NT3, and NT4/5 produced in Chinese hamster ovary cells or Escherichia coli were obtained from Genentech Inc. or Regeneron/Amygen Partners. BDNF produced using the vaccinia virus system (15) was also used, with identical results.

Cell Culture—HN10 cells (14) were kept in culture in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum, in...
an atmosphere of 5% CO\textsubscript{2}. Cerebellar granule cells were prepared from P6 rats as described (16). Briefly, cerebella were dissected and incubated for 20 min at 37 °C in phosphate-buffered saline containing 10 mM glucose, 1 mg/ml albumin, 10 mg/ml DNase, and 0.5 mg/ml papain. The cells were dissociated by trituration through a plastic pipette, pelleted at 900 g for 5 min, and resuspended by using an Eagle's medium containing 10% fetal calf serum. The cells were plated at a density of 20 × 10\textsuperscript{3} on 10-cm polystyrene-coated dishes, and the medium was changed after 12 h to a serum-free complete medium (17) with or without 20 ng/ml BDNF.

**Plasmids—** Rat TrkA, TrkB, and TrkA/TrkB chimeras cDNAs, without signal peptide sequences, were cloned, using NheI and NotI into pRc CMV AC7 (pAC7), a vector that provides the signal sequence peptide of basal membrane protein 40 (18). Chimeric molecules between TrkA and TrkB were constructed by polymerase chain reaction, using an overlap extension procedure. All constructs were sequenced by the protein sequence pep...
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Loss of TrkB Binding in HN10 Cells following BDNF Treatment—We used the neuronal cell line HN10 (14) to get more information on the structural elements of TrkB required for activation of the degradation machinery. HN10 cells were chosen for these experiments because, in contrast to cerebellar granule cells, they can be efficiently transfected. Following transfection with a wild-type TrkB cDNA, radiolabeled BDNF was cross-linked to HN10 cell surface receptors (Fig. 3). After immunoprecipitation of cell lysates with a Trk-specific antibody, a radioactive band at ~150 kDa was detected (Fig. 3, lane 6), corresponding to a cross-linked complex between TrkB and radiolabeled BDNF. This band was absent in the cells transfected with an empty vector (Fig. 3, lane 5) or when binding of the radiolabeled neurotrophin was competed for by a 100-fold excess unlabeled BDNF (Fig. 3, lane 7). Immunoprecipitates from TrkB-expressing cells treated for 24 h with 100 ng/ml BDNF revealed a dramatic decrease in receptor cross-linking, suggesting a loss of cell surface-binding sites caused by BDNF treatment (Fig. 3, lane 8). Since previous experiments with primary neuronal cultures had pointed to a differential regulation of signaling by NGF and BDNF (10), we hypothesized that TrkA and TrkB could be differentially regulated by their ligands. We thus transiently transfected HN10 cells with TrkA and cross-linked cell surface receptors with radiolabeled NGF (Fig. 3). In contrast to TrkB-expressing cells treated with BDNF (Fig. 3, lane 8), TrkA-expressing cells retained their ability to bind NGF upon treatment for 24 h with 100 ng/ml NGF (Fig. 3, lane 4). It thus appears that cell surface TrkB is down-regulated by BDNF, unlike TrkA following exposure to NGF. These experiments suggest then that TrkB contains structural motives leading to down-regulation that may be absent in TrkA.

The Cytoplasmic Domain of TrkB Is Responsible for Down-regulation of the Receptor—To get insight into structural elements accounting for the down-regulation of TrkB, we generated chimeric receptors between TrkA and TrkB (Fig. 4) that were tested for ligand-dependent regulation in HN10 cells.

We first tested chimeric receptors consisting of the extracellular domain of one receptor fused to the intracellular domain of the other. When the intracellular domain of TrkB was replaced by the corresponding domain of TrkA, the resulting chimeric receptor (named TrkB/TM/NGF, see Fig. 4) could bind BDNF (Fig. 5A, lane 5) but was no longer down-regulated by BDNF (Fig. 5A, lane 6). Conversely, chimeric receptors composed of the extracellular domain of TrkA and the intracellular domain of TrkB (TrkA/B, Fig. 4) bound NGF and were down-regulated following NGF treatment (Fig. 5A, compare lanes 3 and 4). Replacing the intracellular domain of TrkB by that of TrkA was therefore sufficient to cause down-regulation upon NGF stimulation. The transmembrane domain had no role in this effect, since receptors containing the extracellular domain of TrkA and the intracellular domain of TrkB with the transmembrane domain of either TrkA (TrkATM/B, Fig. 4) or TrkB (TrkB/TrkA/B, Fig. 4) down-regulated equally in response to NGF (Fig. 5A, compare lanes 3 and 4 with lanes 1 and 2 in right panel). These results show that the intracellular part of TrkB contains a
motif conferring ligand-dependent down-regulation to TrkA. Furthermore, this experiment indicates that the differential regulation for TrkA and TrkB is not due to properties related to the extracellular domain of the receptors or to the neurotrophins, such as binding affinity, kinetics, or stability of the ligand.

An Intracellular Sequence of TrkB Can Induce Down-regulation of TrkA—The cytoplasmic sequences of TrkB causing down-regulation were further investigated by swapping smaller domains of the intracellular part of TrkB into the TrkA backbone. The following TrkA chimeric receptors were constructed (Fig. 4): TrkA/JMB, in which the juxtamembrane domain of TrkA (a sequence of ~80 amino acids between the transmembrane and the tyrosine kinase domains) was replaced by the corresponding domain of TrkB; TrkA/TKB, containing the tyrosine kinase domain of TrkB (~230 amino acids) fused to the juxtamembrane and the carboxyl-terminal domains of TrkA and TrkA/CTB, in which the carboxyl terminus of TrkA (a sequence of ~15 amino acids downstream of the tyrosine kinase domain) was replaced by that of TrkB. The cDNAs encoding for these molecules were transfected into HN10 cells, and the resulting receptors were tested for NGF-induced down-regulation (Fig. 6A, left panel). Replacement of the juxtamembrane domain of TrkA with the corresponding domain of TrkB resulted in a receptor (TrkA/JMB) that could be down-regulated by NGF (Fig. 6A, left panel, lanes 1 and 2). In contrast, replacement of the tyrosine kinase domain of TrkA by that of TrkB (TrkA/TKB) could not transfer the potential for down-regulation to TrkA (Fig. 6A, left panel, lanes 3 and 4). Whereas in some experiments, the carboxyl-terminal domain of TrkB seemed to confer a modest down-regulation to TrkA (TrkA/CTB, see Fig. 6A, lanes 3 and 7), the result was not consistent as indicated by the quantification of the results of several experiments (Fig. 6B). If the juxtamembrane domain of TrkB would be the only significant motif accounting for the differential behavior of TrkA and TrkB, it would be expected that replacement of this domain in TrkB by that of TrkB (TrkB/JMA) would result in a TrkB molecule (TrkB/JMA) that does not down-regulate. However, TrkB/JMA still showed ligand-induced down-regulation (Fig. 6B, right panel, lanes 3 and 4). This suggests that the juxtamembrane domain of TrkB is sufficient, although not necessary, for receptor down-regulation.

Binding of Shc or of PLC-γ to the TrkB Receptor Is Not Required for TrkB Down-regulation—Since the juxtamembrane and the carboxyl-terminal domains of TrkB contain the binding sites for Shc and PLC-γ, respectively, we next tested whether the activation of the signaling pathways elicited by the phosphorylation of these substrates could be involved in TrkB
down-regulation. By using the TrkA<sup>TM/B</sup> backbone (Fig. 4), a molecule that binds NGF and is down-regulated by its ligand just like TrkB (see Fig. 5 A), we introduced point mutations to inactivate the binding sites for Shc, PLC-γ, or both simultaneously, by replacing tyrosines 499 and 794, respectively, by phenylalanine residues (Fig. 4). As Fig. 7A shows, abolishment of binding of the Trk receptor to either Shc, PLC-γ, or to both did not interfere with the capability of the receptor to down-regulate. Regulatory domains acting independently of the Shc and of the PLC-γ signaling pathways seem therefore to be responsible for TrkB down-regulation.

The results obtained with the chimeric and mutant receptors constructed are summarized in Fig. 8. They indicate that whereas the cytoplasmic domain of TrkB accounts for down-regulation following ligand exposure, it is not the tyrosine kinase domain, but rather small flanking domains, that are responsible for the down-regulation of TrkB, compared with TrkA. Activation of the Shc or of the PLC-γ signaling pathways or of both does not seem to be required for BDNF-induced down-regulation of TrkB.

**DISCUSSION**

This study was prompted by previous observations reporting on a marked decrease of binding of radiolabeled BDNF to primary cultures of cerebellar granule neurons following prolonged exposure of these cells to BDNF (10). In previous studies on TrkB signaling using primary cultures of central nervous system neurons (11, 12, 13), decreases were observed following prolonged BDNF exposure in phosphatidylinositol hydrolysis (12), in the phosphorylation of substrates such as PLC-γ1 (11) and the mitogen-activated protein kinases Erk1 and Erk2 (13), or in the induction of c-Fos (13). Some of these reports also showed ligand-induced down-regulation of the TrkB protein (11, 13). In contrast to our study, however, the protein down-regulation was reported to occur after several days of treatment with high concentrations of neurotrophin and was in some cases attributed to transcriptional control. In the system we used, the down-regulation of TrkB was rapid, pointing to a regulation at the post-transcriptional level. It is possible that longer exposures to the neurotrophin would also induce regulation at the transcriptional level. Following TrkB degradation, a compensatory TrkB mRNA up-regulation may also ensue, and this may explain why in a previous study (10) protein down-regulation was not observed. In line with this, we observed in our system a reappearance of the TrkB protein after longer BDNF exposures (data not shown).

As such, ligand-mediated receptor down-regulation is common among receptor tyrosine kinases (RTKs), the activated
ligand-receptor complexes being internalized and either degraded or recycled to the cell surface (for review, see Ref. 30). A prerequisite is receptor activation, and indeed we could show in granule cells that only BDNF concentrations that were enough to induce phosphorylation of the receptor were also able to down-regulate it and that the Trk tyrosine kinase inhibitor K252a was able to block down-regulation (data not shown). This probably explains why the truncated, kinase inactive form of TrkB is not down-regulated by BDNF (Fig. 1A). Typically, the internalized receptors that are not recycled to the cell surface are targeted to the lysosomal degradation system. However, in the present study, lysosomal inhibitors could not significantly prevent degradation of TrkB, whereas blockers of the ubiquitin-proteasome pathway were very efficient in stabilizing the receptor. The ubiquitin-proteasome pathway is commonly involved in the degradation of short-lived intracellular proteins, such as I-kB (31), c-Jun (32), and the cyclins (33), and it is somewhat surprising that a transmembrane protein may be degraded by the proteasome. However, there are a few previous reports also implicating the proteasome system in the regulation of transmembrane proteins, including several RTKs, such as the receptors for c-Kit (34, 35), platelet-derived growth factor (36), Her2/neu, also called c-Erb-B2 (37, 38), and the Met receptor (39). This proteolytic pathway usually requires ubiquitination of the protein to be degraded (for review, see Refs. 28 and 29), and receptor ubiquitination in transformed cells has indeed been described for a few RTKs (36, 40, 41). We were not able to demonstrate direct ubiquitination of TrkB in the cerebellar granule cells. This may relate to the difficulty of looking for endogenous TrkB receptors in primary cell cultures, as all other studies used cell lines with high overexpression to demonstrate ligand-induced ubiquitination. The fact that protein-ubiquitin complexes are short-lived intermediates of degradation and substrates for isopeptidases that can rapidly remove the poly-ubiquitin chain further complicates the detection of ubiquitinated proteins. Examples also exist of completely ubiquitination-independent proteasome degradation, as illustrated by the case of the enzyme ornithine decarboxylase (42). Furthermore, the receptor may not be itself ubiquitinated but instead interacts with a ubiquitinated protein that directs the complex to the proteasome. An example for this is the degradation of c-Fos upon ubiquitination of the associated protein c-Jun (43). In the neuronal cell line HN10 (14), which also showed a pronounced regulation of cell surface TrkB, TrkB receptors were co-precipitated with ubiquitin complexes (data not shown) using a hexahistidine-tagged ubiquitin cDNA construct (a kind gift of Drs. Mathias Treier and Dirk Bohmann, EMBL). However, in the majority of our experiments, ubiquitination of TrkB was independent of BDNF, suggesting that TrkB may be constitutively ubiquitinated. Thus, although the pharmacological data suggest the involvement of the proteasome in TrkB degradation, it remains unclear whether TrkB is directly ubiquitinated.

In order to identify domains within the TrkB sequence that are involved in the degradation, we tested various constructs for the down-regulation in HN10 cells. Their rapid growth, the lack of endogenous Trk receptors, and especially their excellent transfectability are properties that make these cells particu-
FIG. 6. Identification of an intracellular sequence of TrkB responsible for down-regulation of the receptor. 
A, HN10 cells were transfected with either TrkA/JMB (lanes 1 and 2, left panel), TrkA/TKB (lanes 3 and 4, left panel), TrkA/CTB (lanes 5 and 6, right panel), or TrkB/JMA (lanes 3 and 4, right panel). Treatment with NGF (lanes 1 and 2) or BDNF (lanes 3 and 4) was for 24 h (lanes 2, 4, and 6); lanes 1, 3, and 5 were untreated. Cross-linking was performed with the appropriate radiolabeled neurotrophin, and the lysates were immunoprecipitated with anti-Trk antiserum. B, densitometric analysis of the results. Shown are the means of three independent experiments.

FIG. 7. Binding of Shc and/or of PLC-γ is not required for TrkB down-regulation. A, HN10 cells were transfected with either TrkA (lanes 1 and 2), TrkA/TMB (lanes 3 and 4), TrkA/TMB.delShc (lanes 5 and 6), TrkA/TMB.delPLC (lanes 7 and 8), or TrkA/TMB.delShc.delPLC (lanes 9 and 10). Treatment with NGF was performed for 24 h (lanes 2, 4, 6, 8, and 10) or not at all (lanes 1, 3, 5, 7, and 9). Cross-linking was with radiolabeled NGF, and lysates were immunoprecipitated with anti-Trk antiserum. B, densitometric analysis of the results. Shown are the means of three independent experiments.
larly useful in the context of our studies. In particular, direct comparisons can be made between different Trk receptors in the same cell system. Treatment of TrkB-expressing HN10 cells with BDNF led to down-regulation of the surface TrkB receptor. TrkA, in contrast, remained unchanged after NGF treatment of TrkA-expressing HN10 cells. These two highly related receptors seem therefore to be regulated differently. Instead of creating deletions of the Trk receptors, we opted for a domain swapping approach between TrkA and TrkB. The high degree of relatedness between these two receptors makes correct folding of the mutant Trk molecules much more likely than with deletion constructs. The results obtained with these chimeras revealed that motives responsible for the down-regulation of TrkB are located within the intracellular domain. Further mapping suggested that an independent regulatory domain exists in the juxtamembrane domain, a sequence of ~80 amino acids, which can induce down-regulation of the otherwise stable receptor when swapped into the TrkA backbone. Surprisingly, however, replacement of this domain in otherwise stable receptor when swapped into the TrkA backbone might help develop strategies selectively interfering with the down-regulation of Trk receptors. This could be especially relevant when long term administration of TrkB ligands may be required (45), such as in situations aimed at preventing the degeneration of TrkB-expressing neurons.

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FIG. 8. Summary of the results obtained with the Trk chimeric molecules. The different subdomains are represented to scale, according to the number of amino acids (A.A.). Abbreviations: see Figs. 6 and 7.
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