Interactions of Interleukin-1 With Neurotrophic Factors in the Central Nervous System

Beneficial or Detrimental?

*Wilma J. Friedman**

Department of Biological Sciences, Rutgers University, Newark, NJ

Abstract

Interleukin (IL)-1 is a multifunctional cytokine that plays a key role in mediating inflammation in the brain. Many different cell types in the brain express the IL-1 receptor and respond to this cytokine by activating cell-type-specific signaling pathways leading to distinct functional responses, which collectively comprise the inflammatory response in the brain. One key effect of IL-1 in the brain is the induction of trophic factor production by glial cells, which has traditionally been considered a neuroprotective response to injury or disease. However, recent studies have shown that nerve growth factor, which is regulated by IL-1, can induce neuronal survival or apoptosis via different receptors. This article examines the interaction of IL-1 with different trophic factors in the brain.

Index Entries: Interleukin (IL)-1; nerve growth factor (NGF); brain inflammation; neurotrophin (NT); apoptosis.

Introduction: Interleukin-1 in the Central Nervous System

Interleukin (IL)-1 is a potent and pleiotropic cytokine that influences numerous cell types in

the brain as well as in the periphery. The actions of IL-1 are generally considered to be pro-inflammatory, because it is elevated under conditions of injury, disease, and stress and elicits a cascade of events in response to these challenges. IL-1 is actually a family of proteins comprised of two pro-inflammatory molecules, IL-1α and -β, both of which activate the type 1 (signal transducing [1]) IL-1 receptor (IL-1R1). Additionally, the IL-1 family contains

an anti-inflammatory molecule, IL-1 receptor antagonist (IL-1ra), which binds to the IL-1R1 but fails to transduce a signal *(2)*. The actions of IL-1 are strictly regulated by the ability of the IL-1ra to compete for binding to the IL-1R1 *(3)* and by the presence of the IL-1R2 receptor, which binds IL-1 but does not transduce a signal, thereby functioning as a decoy receptor *(4)*.

The effects of IL-1 in the central nervous system (CNS) are complex and evoke numerous diverse functional consequences *(5)*. IL-1 acts as an endogenous pyrogen to induce fever *(6)*, influences sleep behavior *(7)*, and is a potent stimulator of the hypothalamic–pituitary–adrenal axis *(8,9)*, thereby playing a major role in stress responses. The pleiotropic nature of this cytokine is illustrated by its ability to influence all cell types in the CNS. IL-1 critically regulates inflammatory activity in the brain by inducing expression of numerous cytokines and chemokines in microglia and astrocytes *(10, 11)*. This cytokine influences oligodendrocyte progenitors, causing growth arrest and promoting differentiation and maturation *(12)*; additionally, it directly influences neuronal function, modulating synaptic activity of hippocampal neurons *(13,14)*. Many review articles have been written about different aspects of IL-1 function in the brain *(5,10,15,16)*. This article examines cell-type-specific actions of this cytokine and focuses on the interaction of IL-1 with neurotrophic factors, giving particular attention to nerve growth factor (NGF).

Inflammatory Effects of IL-1

Glia

In the CNS, most of the studies on IL-1 expression and function have focused on its role under inflammatory conditions resulting from injury or disease *(17,18)*. Under these conditions, IL-1 is produced initially by microglia and subsequently by astrocytes and invading macrophages *(19,20)*. IL-1 promotes inflammation by inducing glial production of additional

cytokines *(21–24)*, such as IL-6 *(25)*, tumor necrosis factor (TNF)-α *(26)*, colony-stimulating factors *(27)*, and chemokines *(11)*, as well as other pro-inflammatory molecules, such as adhesion molecules, matrix metalloproteinases (MMPs; ref. *11*) cyclooxygenase-2, and inducible nitric oxide synthase *(10)*. The induction by IL-1 of all these pro-inflammatory molecules serves to activate glial cells within the CNS as well as to recruit macrophages and lymphocytes from the periphery to sites of damage in the brain. IL-1 also elicits the expression of a variety of growth factors in the brain, such as ciliary neurotrophic factor (CNTF), fibroblast growth factor (FGF), and NGF. The interaction of IL-1 with these factors is the main subject of this article and is addressed in more detail later.

Neurons

The hippocampus is the region of the brain with the highest level of IL-1R1 expression *(28–31)*. Effects of IL-1 on these neurons include regulation of synaptic activity resulting in modulation of long-term potentiation (LTP) *(13,14,32,33)*. Although exogenously applied IL-1 inhibits hippocampal LTP, endogenous IL-1 expression is increased and appears to be required during LTP *(34,35)*, suggesting a dose-dependent effect of IL-1 on LTP. Additionally, IL-1β can regulate synaptophysin expression in cortical neurons, can increase Tau phosphorylation, and may be an important mediator of β-amyloid-induced neurotoxicity *(36)*. Therefore, IL-1β has direct and distinct cell-type-specific effects on neurons and glia in the brain.

Signaling Mechanisms

The mechanisms governing the diverse actions of IL-1β in different cell types are not well-understood, although several different signaling pathways have been implicated. Inflammatory effects of IL-1 in macrophages, microglia, lymphocytes, and astrocytes involves binding of the cytokine to the IL-1R1; recruitment of the IL-1 receptor accessory protein and the adapter proteins MyD88, IRAK, and TRAF6;

and activation of a kinase cascade leading to nuclear translocation of the nuclear factor (NF)-κB transcription factor (reviewed in refs. *5* and *37*). In the brain, NF-κB activation in glia mediates the regulation of cytokines and growth factors by IL-1 *(25,38,39)*. However, other signal transducing pathways can also be activated by IL-1β, including the p38 and Jun-N-terminal kinase (JNK)-mitogen-activated protein kinase (MAPK) pathways *(40,41)*. Activation of p38 has been suggested to regulate the effects of IL-1β on LTP in hippocampal neurons *(42)* and on Tau phosphorylation in cortical neurons *(36)*. The specific pathway activated may differ in distinct cell types and may mediate the distinct biological consequences of IL-1β actions. We recently directly compared activation of IL-1 signaling in hippocampal neurons vs astrocytes and demonstrated that this cytokine activated the NF-κB pathway in astrocytes—but not neurons—and conversely activated the p38 MAPK pathway, with consequent activation of the CAMP response element binding protein (CREB) transcription factor in hippcampal neurons—but not astrocytes *(43)*. Therefore, the pleiotropic effects of IL-1 are mediated through activation of different signaling pathways in distinct cell types, leading to cell-specific actions, which collectively constitute the neural response to inflammation.

IL-1 Regulation of Trophic Factors

One of the consequences of IL-1 action in the brain is the induction of trophic factors, which generally have been believed to have a neuroprotective role. Several different families of neurotrophic factors have been identified that influence neuronal survival and function. The family of such factors that was first identified is the neurotrophin (NT) family, which consists of NGF, brain-derived neurotrophic factor (BDNF), and NT-3 and NT-4 *(44,45)*. Additionally, there is the glial cell-line-derived neurotrophic factor (GDNF) family, which consists of GDNF, neurturin, persephin, and artemin *(46)*; the FGF family; and the family of neu-

ropoietic cytokines, which includes CNTF, leukemia inhibitory factor, oncostatin M, and several others that signal through a common receptor complex *(47–49)*. Specific members of all these trophic factor families are induced in the brain following injury and, when provided exogenously, can rescue different populations of CNS neurons from death. These studies have led to the general conclusion that inflammation-associated induction of trophic factors always serves a protective role; however, a close examination of the role of NGF after injury demonstrates this is not always the case. Several examples of neuronal rescue by trophic factors are highlighted here, followed by a discussion of NGF actions in brain inflammation.

Ciliary Neurotrophic Factor

Of the neuropoietic cytokines, production of CNTF is strongly induced after injury *(50)* and depends on the actions of IL-1 *(51)*. The elevated levels of CNTF that result from CNS injury contribute to astrogliosis *(52,53)* but can also play a role in rescuing specific neuronal populations (such as motoneurons) from degeneration *(54–57)*. CNTF, along with other factors such as GDNF and NTs, may also play a role in supporting striatal neurons that are compromised in animal models of Huntington's disease *(58)*. This growth factor also regulates the survival of oligodendrocytes during development *(59)* and disease *(60)*.

Fibroblast Growth Factor

Basic FGF (bFGF) is expressed in normal brain in a variety of neuronal and glial populations, and its expression is increased following injury in endothelial and glial cells *(61,62)*. bFGF can afford neuroprotection to various neuronal populations and also participates in regulating survival and proliferation of neural progenitor cells *(63,64)*. bFGF production by astrocytes is stimulated by CNTF *(65,66)*, and both factors contribute to astrogliosis *(52,53,67)*. FGF receptors are expressed on all cell types in the brain, but injury can increase expression of

certain FGF receptors on astrocytes *(68)*, which is consistent with the role of FGF in regulating gliosis.

GDNF Family

The GDNF family of factors interacts with a family of glycosylphosphatidylinositol-linked receptors known as the GDNF receptors α *(69)* and signals through the ret receptor tyrosine kinase *(70,71)*. Knockout studies of different members of the GDNF family and their receptors have demonstrated the importance of these factors in the development of specific neuronal populations *(46,72)*. Moreover, exogenously provided GDNF can rescue specific populations such as substantia nigra neurons *(73,74)*, locus coeruleus neurons *(75)*, striatal neurons *(76)*, and motoneurons *(77–79)* from lesion-induced death. Little is known about the regulation of endogenous production of these factors in the brain under inflammatory conditions, although GDNF messenger RNA (mRNA) expression is upregulated in hippocampal neurons by seizures *(80)*.

Neurotrophins

Different members of the NT family act on specific neuronal populations to influence survival, differentiation (including neurite outgrowth and neurotransmitter expression), and synaptic function. Neurotrophins bind to two different types of receptors: (a) a member of the tyrosine kinase receptor family, which consists of TrkA, -B, and -C and (b) a common receptor called the p75 NT receptor (p75^{NTR}) *(81–83)*. The effects of NTs—especially NGF—on survival and differentiation have been very well-established over the last 50 yr (primarily from studies on peripheral sympathetic or sensory neurons or PC12 cells *[84–87]*) and require activation of the TrkA receptor *(88,89)*. Both in the brain and the periphery, NTs play an important role in neuronal survival. In particular, BDNF influences survival of developing CNS neurons *(90)* via the TrkB receptor *(91–93)* and can rescue many different neuronal popu-

lations from death following injury *(94–98)*. Moreover, in addition to effects on neuronal survival, normal synaptic function of hippocampal neurons requires BDNF signaling via TrkB *(99–101)*. In contrast to the widespread expression of TrkB and TrkC in the brain, TrkA is expressed in only a few populations of neurons, including striatal interneurons and the basal forebrain (BF) cholinergic neurons that project to the hippocampus and cortex *(102–104)*. Consistent with its role in neuronal survival, exogenously provided NGF can rescue BF neurons after axotomy in vivo *(105–107)*.

NGF in Brain Inflammation

Under normal physiological conditions, expression of NGF in the adult brain is quite low relative to other neurotrophic factors and is restricted to specific neurons in the hippocampus and cortex *(108–111)*. NGF, but not the other NTs, is specifically upregulated in glia by inflammatory cytokines, such as IL-1 in vitro *(38,39,112–114)* and after different types of insults in vivo *(115–117)*.

Most of the studies investigating the role of trophic factors in brain inflammation have demonstrated a survival or rescue response of injured neurons, as discussed earlier. These observations have led to the assumption that the widespread increase in NGF production in the brain following injury indicates a general role in the rescue of damaged neurons; however, this assumption is not consistent with the limited expression of the TrkA receptor in the brain. Notably, in contrast to the restricted expression of TrkA, p75^{NTR} is induced in many CNS regions after injury *(118–120)*. p75^{NTR} is a member of the Fas/TNF-receptor family of death receptors *(121–123)* and has been shown to mediate apoptosis in various cell types *(124–127)*. A specific role for p75^{NTR} in mediating cell death following CNS injury has been demonstrated for hippocampal neurons *(128,129)* and spinal cord oligodendrocytes *(130)*. These studies led to the emerging concept that NGF could be a survival or a death factor, depending on which receptor
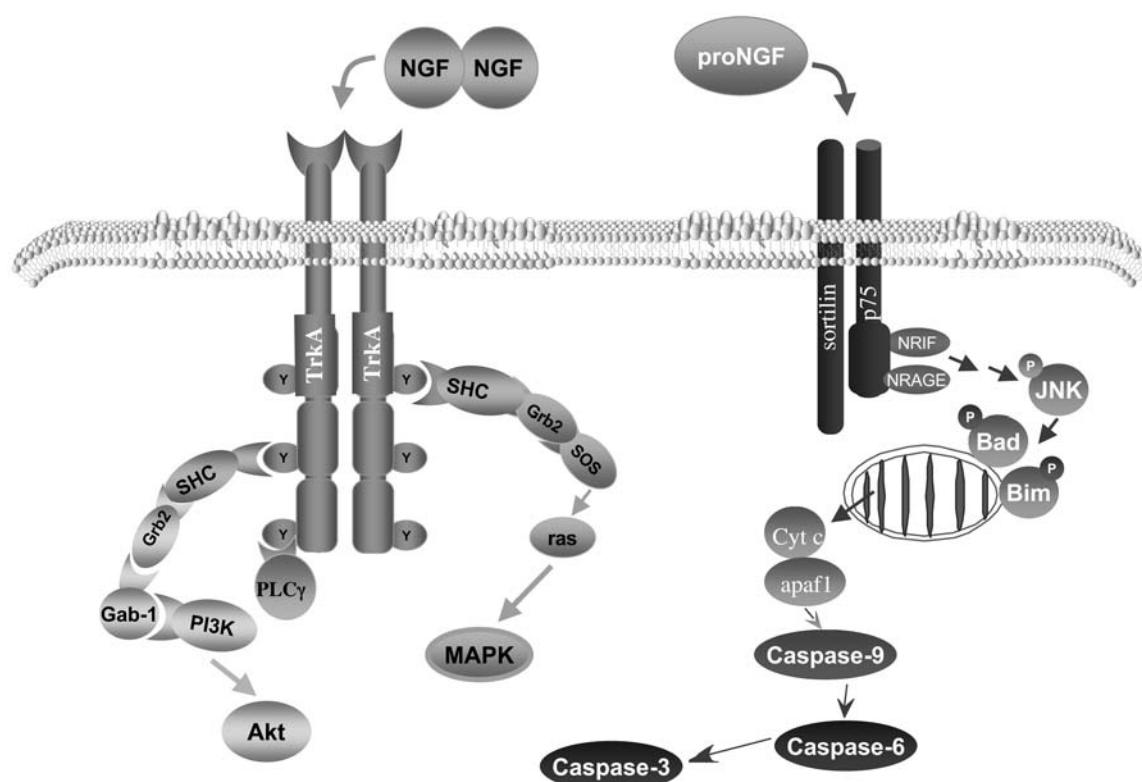
Fig. 1. Schematic diagram of signaling pathways activated by TrkA or p75 neurotrophin receptor (p75^{NTR}). TrkA signaling via Akt and mitogen-activated protein kinase influences neuronal survival and differentiation, and p75^{NTR} activation of the intrinsic caspase pathway leads to apoptosis.

was activated (Fig. 1; refs. *122, 131,* and *132)*; however, many questions remained concerning how these differential effects of NGF might be regulated.

Pro- vs Mature Neurotrophins

The recent demonstration that proNGF can bind selectively and with high affinity to p75^{NTR} *(133)* suggests that survival vs death effects of NTs might be determined by which form of the protein is secreted under specific conditions *(134–136)*. It has been known for many years that NGF is synthesized as a precursor that is cleaved intracellularly by furin and other proconvertases *(137)*. However, proNGF and proBDNF can also be secreted and cleaved extracellularly by plasmin and

MMP-7 *(133,134)*. Abundant levels of proNGF and proBDNF have been detected in the brain *(138,139)*. In normal brain, secreted proBDNF is cleaved by extracellular plasmin to regulate hippocampal LTP *(139)*. An absence of apoptosis under these conditions may result from the lack of p75^{NTR} expression in the normal adult hippocampus. However, the upregulation of p75^{NTR} occurring after injury may put these neurons at risk. Prior studies demonstrating the increased expression of NGF mRNA under inflammatory conditions could not distinguish whether the cleaved or uncleaved form of the protein was secreted.

Clearly, regulation of proNT cleavage will play an important role in determining the apoptotic activity of these factors, and little is known regarding how these events are regulated. The

same enzymes regulating extracellular proNT cleavage, plasmin and MMP-7, have many functions that impact neuronal survival—especially after injury; therefore, the balance of these enzymes and their inhibitors are critically important. In recent studies examining several different injury models, proNGF was shown to play a key role in mediating death of cortical neurons after lesion *(128)* and oligodendrocytes and spinal cord injury *(130,140)*. Therefore, increased production of proNGF under inflammatory conditions may lead to interaction with upregulated p75^{NTR} and its recently identified coreceptor sortilin *(141)*, leading to cell death (Fig. 1).

Clearly, binding of NGF or proNGF to p75^{NTR} does not always lead to cell death, because other cell types in the brain, such as astrocytes, express p75^{NTR} but do not die in response to NGF or proNGF treatment in vitro or under inflammatory conditions in vivo. The p75 receptor has emerged as a very complex signaling molecule with the ability to interact as a coreceptor with Trk receptors, sortilin, and the Nogo receptor to mediate survival signaling *(142)*, apoptosis *(141)*, and axonal growth inhibition *(143,144)*, respectively. This receptor signals by recruiting different proteins to interact with its cytoplasmic domain to mediate different functional responses. Many proteins have been identified that can interact with the 75^{NTR} cytoplasmic domain *(145,146)*. However, researchers have not yet determined which of these proteins mediates specific functional responses, although two of these proteins, NGF receptor-interacting factor (NRIF) and NT receptor-interacting MAGE homolog (NRAGE) have been implicated in apoptotic signaling *(147–149)*. Therefore, additional studies are needed to understand the mechanisms governing cell-type-specific signaling of p75^{NTR} and functional consequences in different cell types.

Conclusions

One of the key early events in CNS inflammation is the production of inflammatory cytokines—particularly IL-1—by glia and invading macrophages. IL-1 binds to its receptor complex on different cell types within the brain and activates cell-type-specific signaling pathways leading to distinct functional responses. One of the major consequences of IL-1 actions on glial cells is the induction of a panoply of cytokines and growth factors. This induction of growth factors generally has been regarded as a means of providing trophic support to rescue injured neurons. However, recent studies have demonstrated that the p75^{NTR} is also induced under inflammatory conditions in the brain and can mediate death, rather than rescue, of injured neurons. One possibility is that expression of p75^{NTR} may be part of an injury response to eliminate neurons that are damaged and can no longer function properly. This action appears to require the production of proNGF, rather than mature NGF; therefore, it will be important to understand the regulation of proNGF cleavage under normal versus inflammatory conditions.

The studies discussed in this article demonstrate that although inflammation-associated induction of trophic factors may rescue some populations of injured neurons, our increasing knowledge of NGF, or proNGF, actions via the p75^{NTR} show that trophic factors can also elicit neuronal cell death. Therefore, the increased expression of NGF after brain injury cannot be assumed to mediate a rescue response. The consequences of cytokine and trophic factor induction after injury depend on which receptors and signaling pathways are activated in distinct cell types under different physiological or pathological conditions.

Acknowledgments

References

1. Sims J. E., Gayle M. A., Slack J. L., et al. (1993) Interleukin 1 signaling occurs exclusively via the type 1 receptor. *Proc. Natl. Acad. Sci. USA* **90**, 6155–6159.
2. O'Neill L. A. and Dinarello C. A. (2000) The IL-1 receptor/toll-like receptor superfamily: crucial receptors for inflammation and host defense. *Immunol. Today* **21**, 206–209.
3. Hannum C. H., Wilcox C. J., Arend W. P., et al. (1990) Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. *Nature* **343**, 336–340.
4. Colotta F., Re F., Muzio M., et al. (1993) Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science* **261**, 472–475.
5. Rothwell N. J. and Luheshi G. N. (2000) Interleukin 1 in the brain: biology, pathology and therapeutic target. *Trends Neurosci.* **23**, 618–625.
6. Dascombe M. J. (1985) The pharmacology of fever. *Progress Neurobiol.* **25**, 327–373.
7. Fang J. D., Wang Y., and Krueger J. M. (1998) Effects of interleukin-1β[???] on sleep are mediated by the type 1 receptor. *Am. J. Physiol.* **43**, R655–R660.
8. Berkenbosch F., Van Oers J., Del Rey A., Tilders F., and Besedovsky H. (1987) Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. *Science* **238**, 524–526.
9. Sapolsky R., Rivier C., Yamamoto G., Plotsky P., and Vale W. (1987) Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science* **238**, 522–524.
10. Basu A., Krady J. K., and Levison S. W. (2004) Interleukin-1: a master regulator of neuroinflammation. *J. Neurosci. Res.* **78**, 151–156.
11. John G. R., Lee S. C., Song X., Rivieccio M., and Brosnan C. F. (2005) IL-1-regulated resonses in astrocytes: relevance to injury and recovery. *Glia* **49**, 161–176.
12. Vela J. M., Molina-Holgado E., Arevalo-Martin A., Almazan G., and Guaza C. (2002) Interleukin-1 regulates proliferation and differentiation of oligodendrocyte progenitor cells. *Mol. Cell Neurosci.* **20**, 489–502.
13. Bellinger F. P., Madamba S., and Siggins G. R. (1993) Interleukin 1β inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. *Brain Res.* **628**, 227–234.
14. Murray C. A. and Lynch M. A. (1998) Evidence that increased hippocampal expression of the cytokine interleukin-1B is a common trigger for age- and stress-induced impairments in long-term potentiation. *J. Neurosci.* **18**, 2974–2981.
15. O'Connor J. J. and Coogan A. N. (1999) Actions of the pro-inflammatory cytokine IL-1 beta on central synaptic transmission. *Exp. Physiol.* **84**, 601–614.
16. Vitkovic L., Bockaert J., and Jacque C. (2000) "Inflammatory" cytokines: neuromodulators in normal brain? *J. Neurochem.* **74**, 457–471.
17. Nieto-Sampedro M. and Berman M. A. (1987) Interleukin-1-like activity in rat brain: sources, targets, and effect of injury. *J. Neurosci. Res.* **17**, 214–219.
18. Giulian D. (1987) Ameloid microglia as effectors of inflammation in the central nervous system. *J. Neurosci. Res.* **18**, 155–171.
19. Davies C. A., Loddick S. A., Toulmond S., Stroemer R. P., Hunt J., and Rothwell N. J. (1999) The progression and topographic distribution of interleukin-1beta expression after permanent middle cerebral artery occlusion in the rat. *J. Cereb. Blood Flow Metab.* **19**, 87–98.
20. Pearson V. L., Rothwell N. J., and Toulmond S. (1999) Excitotoxic brain damage in the rat induces interleukin-1beta protein in microglia and astrocytes: correlation with the progression of cell death. *Glia* **25**, 311–323.
21. Benveniste E. N. (1992) Cytokines: influence on glial cell gene expression and function. In: Neuroimmunoendocrinology, 52, Blalock J. E., ed. Karger, Basel, pp. 106–153.
22. Merrill J. E. and Benveniste E. N. (1996) Cytokines in inflammatory brain lesions: helpful and harmful. *Trends Neurosci.* **19**, 331–338.
23. Basu A., Krady J. K., O'Malley M., Styren S. D., DeKosky S. T. and Levison S. W. (2002) The type 1 interleukin-1 receptor is essential for the efficient activation of microglia and the induction of multiple proinflammatory mediators in response to brain injury. *J. Neurosci.* **22**, 6071–6082.
24. Lee S. C., Liu W., Dickson D. W., Brosnan C. F. and Berman J. W. (1993) Cytokine production by human fetal microglia and astrocytes. Differential induction by lipopolysaccharide and IL-1 beta. *J. Immunol.* **150**, 2659–2667.
25. Sparacio S. M., Zhang Y., Vilcek J., and Benveniste E. N. (1992) Cytokine regulation of interleukin-6 gene expression in astrocytes involves activation of an NF-κB-like nuclear protein. *J. Neuroimmunol.* **39**, 231–242.

26. Chung I. Y. and Benveniste E. N. (1990) Tumor necrosis factor-a production by astrocytes: induction by lipopolysaccharide, IFN-g, and IL-1B. *J. Immunol.* **144**, 2999–3007.
27. Aloisi F., Care A., Borsellino G., et al. (1992) Production of hemolymphopoietic cytokines (IL-6, IL-8, colony-stimulating factors) by normal human astrocytes in response to IL-1 beta and tumor necrosis factor-alpha. *J. Immunol.* **149**, 2358–2366.
28. Cunningham E. T. Jr., Wada E., Carter D. B., Tracey D. E., Battey J. F., and De Souza E. B. (1992) *In situ* histochemical localization of type I interleukin-1 receptor messenger RNA in the central nervous system pituitary, and adrenal gland of the mouse. *J. Neurosci.* **12**, 1101–1114.
29. Yabuuchi K., Minami M., Katsumata S., and Satoh M. (1994) Localization of type 1 interleukin-1 receptor mRNA in rat brain. *Mol. Brain Res.* **27**, 27–36.
30. Ericsson A., Liu C., Hart R. P. and Sawchenko P. E. (1995) Type 1 interleukin-1 receptor in the rat brain: distribution, regulation, and relationship to sites of IL-1 cellular activation. *J. Comp. Neurol.* **361**, 681–698.
31. Friedman W. J. (2001) Cytokines regulate expression of the type 1 interleukin-1 receptor in rat hippocampal neurons and glia. *Exp. Neurol.* **168**, 23–31.
32. Katsuki H., Nakai S., Hirai Y., Akaji K., Kiso Y., and Satoh M. (1990) Interleukin-1B inhibits long-term potentiation in the CA3 region of mouse hippocampal slices. *Eur. J. Pharmacol.* **181**, 323–326.
33. Kelly A., Lynch A., Vereker E., et al. (2001) The anti-inflammatory cytokine, interleukin (IL)-10, blocks the inhibitory effect of IL-1 beta on long term potentiation. A role for JNK. *J. Biol. Chem.* **276**, 45,564–45,572.
34. Schneider H., Pitossi F., Balschun D., Wagner A., del Rey A., and Besedovsky H. O. (1998) A neuromodulatory role of interleukin-1beta in the hippocampus. *Proc. Natl. Acad. Sci. USA* **95**, 7778–7783.
35. Ross F. M., Allan S. M., Rothwell N. J., and Verkhratsky A. (2003) A dual role for interleukin-1 in LTP in mouse hippocampal slices. *J. Neuroimmunol.* **144**, 61–67.
36. Li Y., Liu L., Barger S. W., and Griffin W. S. T. (2003) Interleukin-1 mediates pathological effects of microglia on tau phosphorylation and on synaptophysin synthesis in cortical neurons through a p38-MAPK pathway. *J. Neurosci.* **23**, 1605–1611.
37. O'Neill L. A. and Greene C. (1998) Signal transduction pathways activated by the IL-1 receptor family: ancient signaling machinery in mammals, insects, and plants. *J. Leukoc. Biol.* **63**, 650–657.
38. Friedman W. J., Thakur S., Seidman L., and Rabson A. B. (1996) Regulation of nerve growth factor mRNA by interleukin-1 in rat hippocampal astrocytes is mediated by NFκB. *J. Biol. Chem.* **271**, 31,115–31,120.
39. Heese K., Hock C., and Otten U. (1998) Inflammatory signals induce neurotrophin expression in human microglial cells. *J. Neurochem.* **70**, 699–707.
40. Dunne A. and O'Neill L. (2003) The interleukin-1 receptor/Toll-like receptor superfamily: signal transduction during inflammation and host defense. *Science STKE* **171**, re3.
41. O'Neill L. (2002) Signal transduction pathways activated by the IL-1 receptor/toll-like receptor superfamily. *Curr. Top. Microbiol. Immunol.* **270**, 47–61.
42. Coogan A. N., O'Neill L. A. J., and O'Connor J. J. (1999) The p38 mitogen-activated protein kinase inhibitor SB203580 antagonizes the inhibitory effects of interleukin-1 on long-term potentiation in the rat dentate gyrus in vitro. *Neuroscience* **93**, 57–69.
43. Srinivasan D., Yen J. -H., Joseph D. J., and Friedman W. J. (2004) Cell type specific interleukin-1β signaling in the central nervous system. *J. Neurosci.* **24**, 6482–6488.
44. Barde Y. A. (1990) The nerve growth factor family. *Prog. Growth Factor Res.* **2**, 237–248.
45. Huang E. J. and Reichardt L. F. (2001) Neurotrophins: roles in neuronal development and function. *Annu. Rev. Neurosci.* **24**, 677–736.
46. Baloh R. H., Enomoto H., Johnson E. M. Jr., and Milbrandt J. (2000) The GDNF family ligands and receptors—implications for neural development. *Curr. Opin. Neurobiol.* **10**, 103–110.
47. Patterson P. H. (1992) The emerging neuropoietic cytokine family: first CDF/LIF, CNTF, and IL-6; next ONC, MGF, GCSF? *Curr. Opin. Neurobiol.* **2**, 94–97.
48. Murphy M., Dutton R., Koblar S., Cheema S., and Bartlett P. (1997) Cytokines which signal through the LIF receptor and their actions in the nervous system. *Prog. Neurobiol.* **52**, 355–378.
49. Muller-Newen G. (2003) The cytokine receptor gp130: faithfully promiscuous. *Science STKE* **2003**, PE40.

50. Ip N. Y., Wiegand S. J., Morse J., and Rudge J. S. (1993) Injury-induced regulation of ciliary neurotrophic factor mRNA in the adult brain. *Eur. J. Neurosci.* **5**, 25–33.

51. Herx L. M., Rivest S., and Yong V. W. (2000) Central nervous system-initiated inflammation and neurotrophism in trauma: IL-1 beta is required for the production of ciliary neurotrophic factor. *J. Immunol.* **165**, 2232–2239.

52. Winter C. G., Saotome Y., Levison S. W., and Hirsch D. (1995) A role for ciliary neurotrophic factor as an inducer of reactive gliosis, the glial response to central nervous system injury. *Proc. Natl. Acad. Sci. USA* **92**, 5865–5869.

53. Levison S. W., Ducceschi M. H., Young G. M., and Wood T. L. (1996) Acute exposure to CNTF in vivo induces multiple components of reactive gliosis. *Exp. Neurol.* **141**, 256–268.

54. Sendtner M., Kreutzberg G. W., and Thoenen H. (1990) Ciliary neurotrophic factor prevents the degeneration of motor neurons after axotomy. *Nature* **345**, 440,441.

55. Oppenheim R. W., Prevette D., Yin Q. W., Collins F., and MacDonald J. (1991) Control of embryonic motoneuron survival in vivo by ciliary neurotrophic factor. *Science* **251**, 1616–1618.

56. Masu Y., Wolf E., Holtmann B., Sendtner M., Brem G., and Thoenen H. (1993) Disruption of the CNTF gene results in motor neuron degeneration. *Nature* **365**, 27–32.

57. Richardson P. M. (1994) Ciliary neurotrophic factor: a review. *Pharmacol. Ther*. **63**, 187–198.

58. Alberch J., Perez-Navarro E., and Canals J. M. (2004) Neurotrophic factors in Huntington's disease. *Prog. Brain Res.* **146**, 195–229.

59. Louis J. C., Magal E., Takayama S., and Varon S. (1993) CNTF protection of oligodendrocytes against natural and tumor necrosis factor-induced death. *Science* **259**, 689–692.

60. Linker R. A., Maurer M., Gaupp S., et al. (2002) CNTF is a major protective factor in demyelinating CNS disease: a neurotrophic cytokine as modulator in neuroinflammation. *Nat. Med.* **8**, 620–624.

61. Frautschy S. A., Walicke P. A., and Baird A. (1991) Localization of basic fibroblast growth factor and its mRNA after CNS injury. *Brain Res.* **553**, 291–299.

62. Gomez-Pinilla F., Lee J. W., and Cotman C. W. (1992) Basic FGF in adult rat brain: cellular distribution and response to entorhinal lesion and fimbria-fornix transection. *J. Neurosci.* **12**, 345–355.

63. Alzheimer C. and Werner S. (2002) Fibroblast growth factors and neuroprotection. *Adv. Exp. Med. Biol.* **513**, 335–351.

64. Yoshimura S., Takagi Y., Harada J., et al. (2001) FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. *Proc. Natl. Acad. Sci. USA* **98**, 5874–5879.

65. Jiang F., Levison S. W., and Wood T. L. (1999) Ciliary neurotrophic factor induces expression of the IGF type I receptor and FGF receptor 1 mRNAs in adult rat brain oligodendrocytes. *J. Neurosci. Res.* **57**, 447–457.

66. Albrecht P. J., Dahl J. P., Stoltzfus O. K., Levenson R., and Levison S. W. (2002) Ciliary neurotrophic factor activates spinal cord astrocytes, stimulating their production and release of fibroblast growth factor-2, to increase motor neuron survival. *Exp. Neurol.* **173**, 46–62.

67. Gomez-Pinilla F., Vu L., and Cotman C. W. (1995) Regulation of astrocyte proliferation by FGF-2 and heparan sulfate in vivo. *J. Neurosci.* **15**, 2021–2029.

68. Belluardo N., Wu G., Mudo G., Hansson A. C., Pettersson R., and Fuxe K. (1997) Comparative localization of fibroblast growth factor receptor-1, -2, and -3 mRNAs in the rat brain: in situ hybridization analysis. *J. Comp. Neurol.* **379**, 226–246.

69. Jing S., Wen D., Yu Y., et al. (1996) GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-a, a novel receptor for GDNF. *Cell* **85**, 1113–1124.

70. Trupp M., Arenas E., Fainzilber M., et al. (1996) Functional receptor for GDNF encoded by the c-ret proto-oncogene. *Nature* **381**, 785–789.

71. Durbec P., Marcos-Gutierrez C. V., Kilkenny C., et al. (1996) GDNF signalling through the ret receptor tyrosine kinase. *Nature* **381**, 789–793.

72. Oppenheim R. W., Houenou L. J., Johnson J. E., et al. (1995) Developing motor neurons rescued from programmed and axotomy-induced cell death by GDNF. *Nature* **373**, 344–346.

73. Lin L. -F. H., Doherty D. H., Lile J. D., Bektesh S., and Collins F. (1993) GDNF: a gial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* **260**, 1130–1132.

74. Beck K. D., Valverde J., Alexi T., et al. (1995) Mesencephalic dopaminergic neurons protected by GDNF from axotomy-induced degeneration in the adult brain. *Nature* **373**, 339–341.

75. Arenas E., Trupp M., Åkerud P., and Ibáñez C. F. (1995) GDNF prevents degeneration and promotes the phenotype of brain noradrenergic neurons in vivo. *Neuron* **15**, 1465–1473.

76. Perez-Navarro E., Arenas E., Reiriz J., Calvo N., and Alberch J. (1996) Glial cell line-derived neurotrophic factor protects striatal calbindin-immunoreactive neurons from excitotoxic damage. *Neuroscience* **75**, 345–352.

77. Henderson C. E., Phillips H. S., Pollock R. A., et al. (1994) GDNF: a potent survival factor for motoneurons present in peripheral nerve and nuscle. *Science* **266**, 1062–1064.

78. Yan Q., Matheson C., and Lopez O. T. (1995) In vivo neurotrophic effects of GDNF on neonatal and adult facial motor neurons. *Nature* **373**, 341–344.

79. Tomac A., Lindqvist E., Lin L. -F. H., et al. (1995) Protection and repair of the nigrostriatal dopaminergic system by GDNF in vivo. *Nature* **373**, 335–339.

80. Humpel C., Hoffer B., Strömberg I., Bektesh S., Collins F., and Olson L. (1994) Neurons of the hippocampal formation express glial cell line-derived neurotrophic factor messenger RNA in response to kainate-induced excitation. *Neuroscience* **59**, 791–795.

81. Barbacid M. (1994) The trk family of neurotrophin receptors. *J. Neurobiol.* **25**, 1386–1403.

82. Friedman W. J. and Greene L. A. (1999) Neurotrophin signaling via Trks and p75. *Exp. Cell Res.* **253**, 131–142.

83. Patapoutian A. and Reichardt L. F. (2001) Trk receptors: mediators of neurotrophin action. *Curr. Opin. Neurobiol.* **11**, 272–280.

84. Levi-Montalcini R. and Angeletti P. U. (1968) The nerve growth factor. *Physiol. Rev.* **48**, 534–569.

85. Levi-Montalcini R. (1987) The nerve growth factor 35 years later. *Science* **237**, 1154–1162.

86. Thoenen H. and Barde Y. A. (1980) Physiology of nerve growth factor. *Physiol. Rev.* **60**, 1284–1335.

87. Barde Y. A. (1994) Neurotrophins: a family of proteins supporting the survival of neurons. *Prog. Clin. Biol. Res.* **390**, 45–56.

88. Kaplan D. R., Hempstead B., Martin-Zanca D., Chao M. V., and Parada L. F. (1991) The trk proto-oncogene product is a receptor for nerve growth factor. *Science* **252**, 554–558.

89. Klein R., Jing S., Nanduri V., O'Rourke E., and Barbacid M. (1991) The trk proto-oncogene encodes a receptor for nerve growth factor. *Cell* **65**, 189–197.

90. Hofer M. M. and Barde Y. -A. (1988) Brain-derived neurotrophic factor prevents neuronal death in vivo. *Nature* **331**, 261,262.

91. Oppenheim R. W., Yin Q. W., Prevette D., and Yan Q. (1992) Brain-derived neurotrophic factor rescues developing avian motoneurons from cell death. *Nature* **360**, 755–757.

92. Klein R., Smeyne R. J., Wurst W., et al. (1993) Targeted disruption of the trkB neurotrophin receptor gene rsults in nervous system lesions and neonatal death. *Cell* **75**, 113–122.

93. Minichiello L. and Klein R. (1996) TrkB and TrkC neurotrophin receptors cooperate in promoting survival of hippocampal and cerebellar granule neurons. *Genes Dev.* **10**, 2849–2858.

94. Sendtner M., Holtman B., Kolbeck R., Thoenen H., and Barde Y. -A. (1992) Brain-derived neurotrophic factor prevents the death of motoneurons in newborn rats after nerve section. *Nature* **360**, 757–759.

95. Spina M. B., Squinto S. P., Miller J., Lindsay R. M., and Hyman C. (1992) Brain-derived neurotrophic factor protects dopamine neurons against 6-hydroxydopamine and N-methyl-4-phenylpyridinium ion toxicity: involvement of the glutathione system. *J. Neurochem.* **59**, 99–106.

96. Yan Q., Elliott J., and Snider W. D. (1992) Brain-derived neurotrophic factor rescues spinal motor neurons from axotomy-induced cell death. *Nature* **360**, 753–755.

97. Giehl K. M. and Tetzlaff W. (1996) BDNF and NT-3, but not NGF, prevent axotomy-induced death of rat corticospinal neurons in vivo. *Eur. J. Neurosci.* **8**, 1167–1175.

98. Alcantara S., Frisen J., del Rio J. A., Soriano E., Barbacid M., and Silos-Santiago I. (1997) TrkB signaling is required for postnatal survival of CNS neurons and protects hippocampal and motor neurons from axotomy-induced cell death. *J. Neurosci.* **17**, 3623–3633.

99. Patterson S. L., Abel T., Deuel T. A. S., Martin K. C., Rose J. C., and Kandel E. R. (1996) Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron* **16**, 1137–1145.

100. Korte M., Griesbeck O., Gravel C., et al. (1996) Virus-mediated gene transfer into hippocampal CA1 region restores long-term potentiation in brain-derived neurotrophic factor mutant mice. *Proc. Natl. Acad. Sci. USA* **93**, 12,547–12,552.

101. Martinez A., Alcantara S., Borrell V., et al. (1998) TrkB and TrkC signaling are required for maturation and synaptogenesis of hippocampal connections. *J. Neurosci.* **18**, 7336–7350.

102. Holtzman D. M., Li Y., Parada L. F., et al. (1992) p140trk mRNA marks NGF-responsive

forebrain neurons: evidence that trk gene expression is induced by NGF. *Neuron* **9**, 465–478.

103. Fagan A. M., Garber M., Barbacid M., Silos-Santiago I., and Holtzman D. M. (1997) A role for trkA during maturation of striatal and basal forebrain cholinergic neurons in vivo. *J. Neurosci.* **17**, 7644–7654.

104. Ringstedt T., Lagercrantz H., and Persson H. (1993) Expression of members of the trk family in the developing postnatal rat brain. *Dev. Brain Res.* **72**, 119–131.

105. Williams L. R., Varon S., Peterson G. M., Wictorin K., Björklund A., and Gage F.H. (1986) Continuous infusion of nerve growth factor prevents basal forebrain neuronal death after fimbria fornix transection. *Proc. Natl. Acad. Sci. USA* **83**, 9231–9235.

106. Fischer W., Wictorin K., Björklund A., Williams L. R., Varon S., and Gage F. H. (1987) Amelioration of cholinergic neuron atrophy and spatial memory impairment in aged rats by nerve growth factor. *Nature* **329**, 65–68.

107. Kromer L. F. (1987) Nerve growth factor treatment after brain injury prevents neuronal death. *Science* **235**, 214–216.

108. Ayer LeLievre C., Olson L., Ebendal T., Seiger A., and Persson H. (1988) Expression of the beta-nerve growth factor gene in hippocampal neurons. *Science* **240**, 1339–1341.

109. Phillips H. D., Hains J. M., Laramee G. R., Rosenthal A., and Winslow J. W. (1990) Widespread expression of BDNF but not NT-3 by target areas of basal forebrain cholinergic neurons. *Science* **250**, 290–294.

110. Maisonpierre P. C., Belluscio L., Friedman B., et al. (1990) NT-3, BDNF, and NGF in the developing rat nervous system: Parallel as well as reciprocal patterns of expression. *Neuron* **5**, 501–509.

111. Ernfors P., Merlio J. -P., and Persson H. (1992) Cells expressing mRNA for neurotrophins and their receptors during embryonic rat development. *Eur. J. Neurosci.* **4**, 1140–1158.

112. Spranger M., Lindholm D., Bandtlow C., et al. (1990) Regulation of nerve growth factor (NGF) synthesis in the rat central nervous system: comparison between the effects of interleukin-1 and various growth factors in astrocyte cultures and in vivo. *Eur. J. Neurosci.* **2**, 69–76.

113. Gadient R. A., Cron K. C., and Otten U. (1990) Interleukin-1 beta and tumor necrosis factor-

alpha synergistically stimulate nerve growth factor (NGF) release from cultured rat astrocytes. *Neurosci. Lett.* **117**, 335–340.

114. Carman-Krzan M., Vigé X., and Wise B. C. (1991) Regulation by interleukin-1 of nerve growth factor secretion and nerve growth factor mRNA expression in rat primary astroglial cultures. *J. Neurochem.* **56**, 636–643.

115. Oderfeld-Nowak B. and Bacia A. (1994) Expression of astroglial nerve growth factor in damaged brain. *Acta. Neurobiol. Exp.* **54**, 73–80.

116. Goss J. R., O'Malley M. E., Zou L., Styren S. D., Kochanek P. M., and DeKoskey S. T. (1998) Astrocytes are the major source of nerve growth factor upregulation following traumatic brain injury in the rat. *Exp. Neurol.* **149**, 301–309.

117. Micera A., Vigneti E., and Aloe L. (1998) Changes of NGF presence in nonneuronal cells in response to experimental allergic encephalomyelitis in Lewis rats. *Exp. Neurol.* **154**, 41–46.

118. Gage F. H., Batchelor P., Chen K. S., et al. (1989) NGF receptor reexpression and NGF-mediated cholinergic neuronal hypertrophy in the damaged adult neostriatum. *Neuron* **2**, 1177–1184.

119. Ernfors P., Henschen A., Olson L., and Persson H. (1989) Expression of nerve growth factor receptor mRNA is developmentally regulated and increased after axotomy in rat spinal cord motoneurons. *Neuron* **2**, 1605–1613.

120. Peterson S. and Bogenmann E. (2003) Osmotic swelling induces p75 neurotrophin receptor (p75NTR) expression via nitric oxide. *J. Biol. Chem.* **278**, 33,943–33,950.

121. Casaccia-Bonnefil P., Kong H., and Chao M. V. (1998) Neurotrophins: the biological paradox of survival factors eliciting apoptosis [see comments]. *Cell Death Differ.* **5**, 357–364.

122. Barker P. A. (1998) p75NTR: a study in contrasts [see comments]. *Cell Death Differ.* **5**, 346–356.

123. Miller F. D. and Kaplan D. R. (1998) Life and death decisions: a biological role for the p75 neurotrophin receptor [editorial; comment]. *Cell Death Differ.* **5**, 343–345.

124. Rabizadeh S., Oh J., Zhong L., et al. (1993) Induction of apoptosis by the low-affinity NGF receptor. *Science* **261**, 345–358.

125. Casaccia-Bonnefil P., Carter B. D., Dobrowsky R. T., and Chao M. V. (1996) Death of oligodendrocytes mediated by the interaction of nerve

growth factor with its receptor p75. *Nature* **383**, 716–719.

126. Frade J. M., Rodriguez-Tebar A., and Barde Y. A. (1996) Induction of cell death by endogenous nerve growth factor through its p75 receptor. *Nature* **383**, 166–168.

127. Friedman W. J. (2000) Neurotrophins induce death of hippocampal neurons via the p75 receptor. *J. Neurosci.* **20**, 6340–6346.

128. Roux P. P., Colicos M. A., Barker P. A., and Kennedy T. E. (1999) p75 neurotrophin receptor expression is induced in apoptotic neurons after seizure. *J. Neurosci.* **19**, 6887–6896.

129. Troy C. M., Friedman J. E., and Friedman W. J. (2002) Mechanisms of p75-mediated death of hippocampal neurons: role of caspases. *J. Biol. Chem.* **277**, 34,295–34,302.

130. Beattie M. S., Harrington A. W., Lee R., et al. (2002) ProNGF induces p75-mediated death of oligodendrocytes following spinal cord injury. *Neuron* **36**, 375–386.

131. Carter B. D. and Lewin G. R. (1997) Neurotrophins live or let die: does p75 decide? *Neuron* **18**, 187–190.

132. Casaccia-Bonnefil P., Gu C., Khursigara G., and Chao M. V. (1999) p75 neurotrophin receptor as a modulator of survival and death decisions. *Microsc. Res. Tech.* **45**, 217–224.

133. Lee R., Kermani P., Teng K. K., and Hempstead B. L. (2001) Regulation of cell survival by secreted proneurotrophins. *Science* **294**, 1945–1948.

134. Chao M. V. and Bothwell M. (2002) Neurotrophins: to cleave or not to cleave. *Neuron* **33**, 9–12.

135. Ibanez C. (2002) Jekyll-Hyde neurotrophins: the story of proNGF. *Trends Neurosci.* **25**, 284–286.

136. Hempstead B. L. (2002) The many faces of p75NTR. *Curr. Opin. Neurobiol.* **12**, 260–267.

137. Seidah N. G., Benjannet S., Pareek S., et al. (1996) Cellular processing of the nerve growth factor precursor by the mammalian pro-protein convertases. *Biochem. J.* **314 (Pt 3)**, 951–960.

138. Fahnestock M., Michalski B., Xu B., and Coughlin M. D. (2001) The precursor pro-nerve growth factor is the predominant form of nerve growth factor in brain and is increased in Alzheimer's disease. *Mol. Cell Neurosci.* **18**, 210–220.

139. Pang P. T., Teng H. K., Zaitsev E., et al. (2004) Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science* **306**, 487–491.

140. Harrington A., Leiner B., Blechschmitt C., et al. (2004) Secreted proNGF is a pathophysiological death-inducing ligand after adult CNS injury. *Proc. Natl. Acad. Sci. USA* **101**, 6226–6230.

141. Nykjaer A., Lee R., Teng K., et al. (2004) Sortilin is essential for proNGF-induced neuronal cell death. *Nature* **427**, 843–848.

142. Hempstead B. L., Martin-Zanca D., Kaplan D. R., and Chao M. V. (1991) High affinity NGF binding requires co-expression of the trk proto-oncogene and the low affinity NGF receptor. *Nature* **350**, 678–683.

143. Wang K. C., Kim J. A., Sivasankaran R., Segal R., and He Z. (2002) p75 interacts with the Nogo receptor as a co-receptor for Nogo, MAG and OMgp. *Nature* **420**, 74–78.

144. Wong S. T., Henley J. R., Kanning K. C., Huang K. H., Bothwell M., and Poo M. M. (2002) A p75(NTR) and Nogo receptor complex mediates repulsive signaling by myelin-associated glycoprotein. *Nat. Neurosci.* **11**, 11.

145. Chao M. V. (2003) Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat. Rev. Neurosci.* **4**, 299–309.

146. Barker P. A. (2004) p75NTR is positively promiscuous: novel partners and new insights. *Neuron* **42**, 529–533.

147. Salehi A. H., Roux P. P., Kubu C. J., et al. (2000) NRAGE, a novel MAGE protein, interacts with the p75 neurotrophin receptor and facilitates nerve growth factor-dependent apoptosis. *Neuron* **27**, 279–288.

148. Salehi A. H., Xanthoudakis S., and Barker P. A. (2002) NRAGE, a p75 neurotrophin receptor-interacting protein, induces caspase activation and cell death through a JNK-dependent mitochondrial pathway. *J. Biol. Chem.* **277**, 48,043–48,050.

149. Linggi M. S., Burke T. L., Williams B. B., et al. (2005) NRIF is an essential mediator of apoptotic signaling by the p75 neurotrophin receptor. *J. Biol. Chem.* **8,** 155–167.