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

Beneficial or Detrimental?

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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

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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 neuropoietic 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

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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 populations 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

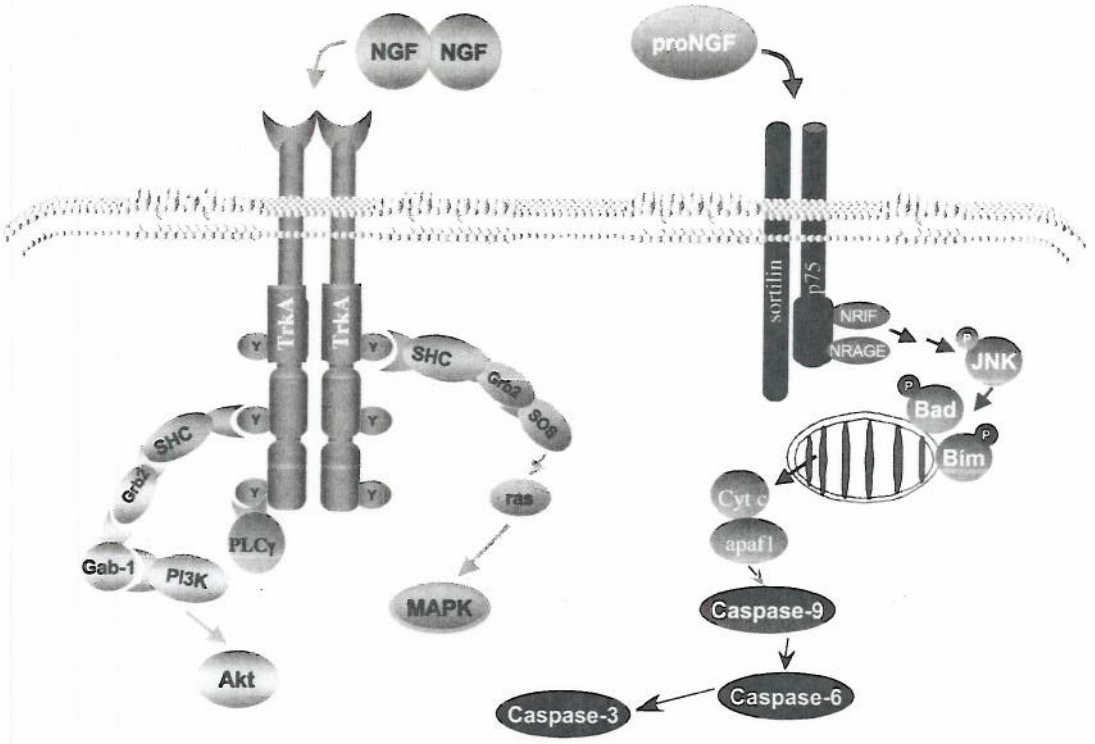

Fig. 1. Schematic diagram of signaling pathways activated by TrkA or p75 neurotrophin receptor ($p75^{NTR}$). TrkA signaling via Akt and mitogen-activated protein kinase influences neuronal survival and differentiation, and $p75^{NTR}$ activation of the intrinsic caspase pathway leads to apoptosis.

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.

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