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Actions of Neurotrophic Factors and Their Signaling Pathways in Neuronal Survival and Axonal Regeneration

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Abstract

Adult axons in the mammalian central nervous system do not elicit spontaneous regeneration after injury, although many affected neurons have survived the neurotrauma. However, axonal regeneration does occur under certain conditions. These conditions include: (a) modification of regrowth environment, such as supply of peripheral nerve bridges and transplantation of Schwann cells or olfactory ensheathing glia to the injury site; (b) application of neurotrophic factors at the cell soma and axon tips; (c) blockade of growth-inhibitory molecules such as Nogo-A, myelin-associated glycoprotein, and oligodendrocyte-myelin glycoprotein; (d) prevention of chondroitin-sulfate-proteoglycans-related scar tissue formation at the injury site using chondroitinase ABC; and (e) elevation of intrinsic growth potential of injured neurons via increasing intracellular cyclic adenosine monophosphate level. A large body of evidence suggests that these conditions achieve enhanced neuronal survival and axonal regeneration through sometimes overlapping and sometimes distinct signal transduction mechanisms, depending on the targeted neuronal populations and intervention circumstances. This article reviews the available information on signal transduction pathways underlying neurotrophic-factor-mediated neuronal survival and neurite outgrowth/axonal regeneration. Better understanding of signaling transduction is important in helping us develop practical therapeutic approaches for encouraging neuronal survival and axonal regeneration after traumatic injury in clinical context.

Index Entries: Neurotrophic factor; neuronal survival; axonal regeneration; signal transduction pathway; central nervous system.

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Introduction

Because of lack of spontaneous axonal regeneration in the adult mammalian central nervous system (CNS), damage to axon tracts in the human CNS (such as brain and spinal cord) often results in devastating and persistent functional deficits, although many of the affected neurons survive the traumatic injury. The main reasons behind this failure of spontaneous axonal regeneration following CNS injury include (a) restricted supply of appropriate trophic factors and their cognate receptors *(1,2);* (b) presence of myelin-associated axon-growth inhibitory molecules, including Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin glycoprotein (OMgp), along the projection pathway of growing axons *(3);* (c) presence of chondroitin-sulphate-proteoglycans-related scar tissue at injury site as a physical barrier for regrowing axons to pass *(4);* and (d) low intrinsic capability or potential of injured adult neurons to regrow axons *(3).*

In recent decades, several trophic factors, such as neurotrophic growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3 and NT-4/5, ciliary neurotrophic factor (CNTF), leukemia inhibitory factor and some interleukins (ILs), glial-cell-line-derived neurotrophic factor (GDNF), and fibroblast growth factor (FGF), have been identified as potent factors in promoting neuronal viability and neurite outgrowth/axonal regeneration of adult CNS neurons *(5–9).* Although some of these trophic factors share common signaling transduction pathways in eliciting their biological actions under certain conditions, distinct mechanism(s) may underlie their actions under other conditions.

On the other hand, neuronal populations respond differently to different neurotrophic factors. Although survival is a prerequisite for axonal regeneration and possible functional recovery after injury, neuronal protection and promotion of axonal regeneration can be completely different properties of trophic factors. This means that increased neuronal survival may not necessarily result in enhanced axonal regeneration. For example, BDNF and NT-4/5 are known to be potent factors in promoting adult retinal ganglion cell (RGC) survival but fail to promote RGC axonal regeneration *(10).* Regarding axonal regeneration, axonal regrowth can occur in three forms in adult CNS after injury: (a) collateral sprouting from intact neurons into denervated areas; (b) regenerative growth of injured axons originating close to the injury site and passing beyond the lesion to re-establish connections with target areas; and (c) regenerative sprouting proximal to, and not far beyond, the injury site.

Certain neurotrophic factors may have vastly different effects on these three forms of axonal growth. For example, BDNF and NT-4/5 promote neurite growth of RGCs within the retina *(5,11)* but not long-distance regeneration into a peripheral nerve bridge *(10).* Furthermore, neurotrophic factors also appear to interact with a number of other effectors, such as cyclic adenosine monophosphate (cAMP) of second messenger system, and overcome inhibitory action induced by growth-inhibitory molecules such as MAG. This article focuses predominantly on the signaling transductions elicited by certain neurotrophic factors in promoting neuronal survival and axonal regenerative growth. The interactions of these neurotrophic factors with other major effectors on neuronal survival and axonal regeneration are also discussed.

Neurotrophins

NTs are a family of growth factors consisting of NGF, BDNF, NT-3, and NT-4/5 in mammals and NT-6 and -7 in fish. They are critical for neural survival, development, function maintenance, and plasticity of the CNS *(12,13).* It is well-known that the major action of neurotrophins is to promote neuronal survival *(1,14).* In fact, NTs were originally identified as important mediators of neuronal survival during development. However, during recent decades, their functions have been extended beyond survival, and now they include the

regulation of axonal and dendritic outgrowth, synapse formation and function, cell migration, cell proliferation, and survival of adult neurons *(15–18).*

Many studies have shown that NTs elicit their biological functions through binding with their specific high-affinity cognate tyrosine kinase (Trk) receptor. Dimerization of these receptors results in activation of the Trks present in the cytoplasmic domains. The specific high-affinity receptor for NGF is TrkA *(19–21);* the specific high-affinity receptor for both BDNF and NT-4/5 is TrkB *(22,23);* and the specific high-affinity receptor for NT-3 is TrkC *(24).* However, crosstalk also occurs. For example, apart from TrkC, NT-3 also binds to TrkA and TrkB, although with a much lower affinity *(17).* Furthermore, all NTs bind to the low-affinity NT receptor $p75^{NTR}$ *(25).* Because both full-length and truncated forms of Trk receptors and different forms of NTs exist, their biological actions vary significantly. For example, full-length TrkB increases proximal dendritic branching, whereas truncated TrkB promotes net elongation of distal dendrites *(26).* On the other hand, unprocessed precursors of NGF and BDNF are death-inducing—rather than protecting—ligands for neurons via $p75^{NTR}$ *(27,28).* Therefore, it is important for us to understand the double faces of the endogenous neurotrophic factors in the maintenance and function of the CNS.

As the expression levels of NT and their receptors vary greatly among different neuronal populations, cellular responses to NTs also differ significantly among CNS neurons. Although one NT has a major impact on one neuronal population, it may have no effect on another. On the other hand, a neuronal population may respond differently to specific NTs. RGCs respond to BDNF and NT-4/5 but not NGF and NT-3 *(10,29);* however, in spinal cord, NT-3 and BDNF promote axonal regeneration and functional recovery after injury *(15,16,18,30).*

NTs can be transported both retrogradely and anterogradely *(31–34).* Upon binding with their cognate Trk receptors, NTs are known to activate protein kinase A (PKA), Ras/phosphotidyl inositol 3′-phosphate-kinase (PI-3K)/Akt, and Ras/Raf/mitogen-activated protein kinase (MAPK) and MAPK/extracellular signal-regulated kinase (ERK) signal transduction pathways, leading to their biological actions (refs. *2, 35–42;* Fig. 1). Activation of PKA, Ras/PI-3K/Akt (referred to as PI-3K/Akt below), or Ras/Raf/ MAPK/ERK (referred to as MAPK/ERK below) signaling pathway in the absence of NT has been shown to be sufficient to both protect certain neuronal populations *(43–46)* and enhance neurite growth *(47,48).* During the past few years, other neurotrophic factors, such as CNTF and GDNF, have also been shown to activate these Trks. The signaling pathways elicited by these neurotrophic factors are discussed in CNTF and Related Cytokines and GDNF and Related Ligands sections. Elucidation of this shared mechanism of neurotrophic action has been a major conceptual advance of the past decade *(13).*

Nerve Growth Factor

The core concept of the neurotrophic factor theory is that targets of innervation secrete limited amounts of survival factors (neurotrophic factors) that function to ensure a balance between the size of a target organ and the number of innervating neurons *(13,49).* Neurons that obtain sufficient amounts of these neurotrophic factors survive, and those that do not are eliminated. NGF, the first NT to be characterized, was discovered as a factor able to support survival of sympathetic and sensory spinal neurons in culture *(50).* Later studies have shown that NGF is synthesized and secreted by sympathetic and sensory target organs. From these sources, it is captured in nerve terminals by receptor-mediated endocytosis and is retrogradely transported through axons to neuronal cell bodies, where it acts to promote neuronal survival and differentiation *(13).* However, subsequent evidence has demonstrated that apart from NGF, other sources of neurotrophic factors also exist, and some of the important neurotrophic factors are discussed in Brain-Derived Neurotrophic

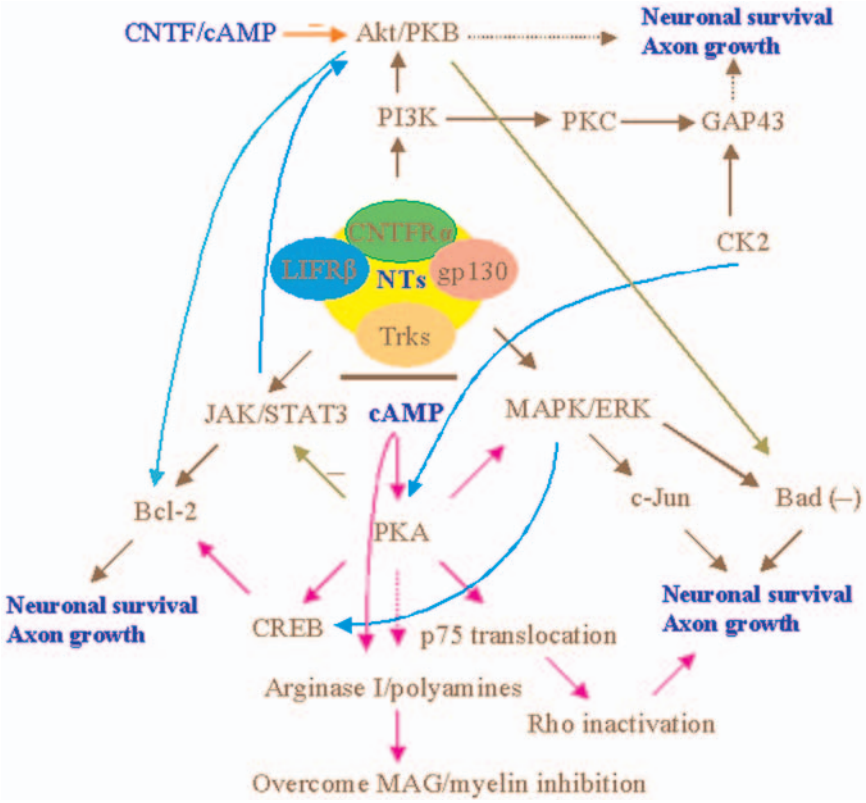

Fig. 1. Signaling transduction pathways and possible biological functions of neurotrophins/CNTF and elevation of cAMP in neuronal survival and axonal regeneration. Neurotrophic factors, including neurotrophin family members and CNTF, all act on the MAPK/ERK, PI-3K/Akt, and JAK/STAT3 pathways. On the other hand, cAMP interacts, directly or indirectly, with neurotrophic factors on these three pathways via PKA. cAMP appears to acts on various sites after activating PKA to render its biological actions.

Factor and NT-4/5 and Neurotrophin-3 sections. It is now known that neurotrophic factors can derive from infiltrating macrophages, surrounding glial cells or even neighboring neurons to act in an autocrine or paracrine fashion to support neuronal survival *(51–53)*.

Binding of NGF with its cognate receptor TrkA results in phosphorylation of cytoplasmic tyrosine residues on the cytoplasmic domains of these receptors, and phosphorylation of these residues further activates the receptor. Consequently, intracellular signaling cascades, which include MAPK/ERK, PI-3K/Akt, and phospholipase C (PLC)–γ1 pathways, are activated to play an important role in transducing biological signals and actions of NGF *(54–57)*. Notably, although activation of Ras is a very complex process, it has been shown to lead to activation of either PI-3K or MAPK pathway to promote neuronal survival *(58,59)*.

Activated PI-3K/Akt and MAPK/ERK pathways also promote survival by phosphorylating and activating transcription factors such as cAMP-response element-binding protein (CREB) *(60,61)*. MAPK activation of CREB in neurons also leads to the expression of Bcl-2 protein *(62)*, which is well-known to be a very important anti-apoptotic factor *(63,64)*. Recent evidence suggests that sustained MAPK activation depends on continual regeneration of TrkA receptors *(65)*. The microtubule-associated protein 1 B (MAP1B) is a major phosphorylation substrate in neurons for the serine/threonine kinase glycogen synthase kinase (GSK)-3β, a

downstream product of the PI-3K/Akt pathway *(66)*. NGF engagement with the TrkA receptor activates GSK-3β, enabling it to phosphorylate MAP1B; GSK-3β phosphorylation of MAP1B acts as a molecular switch to regulate microtubule dynamics in growing axons *(57,66)*. Importantly, available information suggests that both MAPK and Akt, each on a different serine residue, phosphorylate the pro-apoptotic protein Bad that is sequestered by protein 14-3-3, thereby preventing apoptosis in an alternative process *(60,67,68)*.

Long-distance axonal regeneration induced by NGF has been observed in cerulospinal axons and primary sensory axons but not corticospinal, raphaespinal, and local motor axons in spinal cord *(69–71)* or cholinergic axons in hippocampus and dentate gyrus *(72,73)*. Currently, it is not clear which mechanisms NGF acts through to achieve axonal regeneration. However, regarding neurite growth, different mechanisms appear to be involved in different types of neuron. Although engagement of NGF with TrkA was shown to involve the MAPK/ERK pathway, but not the PI-3K pathway, to enhance neurite growth in PC12 cells *(57,74)*, opposite pathway mechanism (PI-3K but not MAPK) occurred in dorsal root ganglion sensory neurons *(75)*. Interestingly, evidence shows that although Ras is both necessary and sufficient for NGF-stimulated axon growth, the Ras effectors Raf and Akt induce distinct morphologies: Activated Raf-dependent signaling in the MAPK/ERK pathway is primarily responsible for axonal elongation, whereas active Akt of the PI-3K/Akt pathway is critical for branching and for increasing axonal caliber *(76)*. Therefore, it is likely that the morphology of axonal outgrowth depends on the relative strengths of Akt and Raf pathway activations *(17)*.

Brain-Derived Neurotrophic Factor and NT-4/5

Neuronal protection and enhancement of neurite outgrowth/axonal regeneration mediated by BDNF and NT-4/5 have been well-documented *(10,11,30,77–82)*. In fact, all NTs appear to share PI-3K/Akt and MAPK/ERK signaling pathways in their signaling transduction. For BDNF and NT-4/5, several studies have shown that the PI-3K pathway, the MAPK pathway, or both participate(s) in signaling transduction on certain neuronal populations *(40,83–85)*. For example, activation of the PI-3K pathway was necessary to mediate BDNF-induced motoneuron survival *(84)*, whereas both PI-3K and MAPK pathways were involved in BDNF-dependent survival of RGCs *(40)*. Additionally, both PI-3K/Akt and MAPK/ERK pathways were involved in the rescue of cerebellar granule neurons *(83)*. As mentioned earlier, PI-3K/Akt and MAPK/ERK pathways lead to phosphorylation of the transcription factor CREB as well as downregulation of pro-apoptotic factor Bad, which promotes neuronal survival by regulating gene expression *(60,61, 67)*. Apart from these pathways in achieving neuronal protection, BDNF has also been shown to suppress cleavage and enzymatic activity of the neuronal cell death effector caspase-3 *(37)*; therefore, it is likely that BDNF also achieves neuronal protection via this pathway.

Although both BDNF and NT-4/5 are ligands for TrkB and have similar actions on certain neuronal populations, they also appear to have distinct biological actions under certain conditions. For example, BDNF promoted RGC survival, whereas NT-4/5 failed to do so in vitro *(86)*. BDNF was shown to support predominantly polarized neurite outgrowth from cultured RGCs, whereas NT-4/5 induced intensely branched symmetrical arbors *(11,87)*. Recently, we found that BDNF, but not NT-4/5, promoted RGC survival over an extended period of time *(88)*. The different activities of BDNF and NT-4/5 are further confirmed by a study in which the *NT-4/5* gene was knocked into BDNF locus, and conversely to BDNF-null mutants that died shortly after birth, the NT-4/5-replaced BDNF-deficient mice survived *(89)*.

Although many studies have demonstrated that BDNF and NT-4/5 exert their biological

actions via the PI-3K/Akt and MAPK/ERK pathways after binding with the cognate receptor TrkB, much of the evidence is directed toward the effect on neuronal survival. Alhough involvement of the PKA and PI-3K/Akt pathways in BDNF-induced neurite outgrowth in vitro has been documented *(90),* direct information on the exact mechanisms underlying BDNF- and NT-4/5-induced axonal regeneration in vivo is lacking. However, possible participation of the PI-3K/Akt and MAPK/ERK pathways in BDNF- and NT-4/5-induced axonal regeneration can be postulated indirectly. It has been shown that CREB activation leads to axonal regeneration *(91),* and both BDNF and NT-4/5 activate CREB via the PI-3K/Akt and MAPK/ERK pathways. Therefore, it is likely that the PI-3K/Akt and MAPK/ERK pathways are involved in action of BDNF and NT-4/5 in promoting axonal regeneration. It would be important to verify whether this is true through in vivo experiments. BDNF and NT-4/5 were also demonstrated to increase the expression of growth-associated protein (GAP)-43 *(80,92),* a protein known to be closely associated with neurite outgrowth or axonal regeneration *(93–95).* Enhanced axonal regeneration by BDNF may also be achieved via upregulation of BDNF.

Neurotrophin-3

Similarly to other NT family members (NGF, BDNF, and NT-4/5), NT-3 has also been widely shown to promote neuronal survival and enhance neurite growth/axonal regeneration of certain neuronal populations *(85).* After binding with the cognate receptor TrkC, NT-3 causes rapid tyrosine phosphorylation in the MAPK/ERK *(85)* and PI-3K/Akt *(76,96)* pathways to render their neuronal protection. Although all NTs share some common signaling transduction pathways, such as PI-3K/Akt and MAPK/ERK, and often protect the same neuronal populations *(97–99),* responsive neuronal populations to a particular NT often are different from those that are responsive to the other NTs *(10,29,100).* Surprisingly, NT-3 and BDNF sometimes appear to elicit opposite actions in neuronal protection: BDNF abolishes the survival effect of NT-3 in axotomized Clarke neurons of adult rats *(100),* whereas endogenous BDNF and NT-3 antagonistically regulate survival of axotomized corticospinal neurons *(101).* In terms of promoting axonal regeneration, NT-3 has been often shown to be effective in enhancing axonal regeneration and functional recovery after spinal cord injury (16), indicating a potential for possible therapeutic application in the future. Regarding the mechanisms underlying NT-3-induced neurite outgrowth/axonal regeneration, information is not only limited but also controversial. Although the MAPK/ERK pathway was demonstrated to be actively involved in NT-3-induced neurite extension of spiral ganglion neurons *(102),* neurite outgrowth of adult dorsal root ganglia was promoted following inhibition of the MAPK/ERK pathway *(103).* The exact mechanisms underlying NT-3-dependent neurite outgrowth and, particularly, axonal regeneration in vivo remain to be elucidated.

CNTF and Related Cytokines

Numerous studies have confirmed the protective effect of CNTF and certain cytokines on CNS neurons *(9,104–106).* We and others showed that CNTF promoted neurite outgrowth and axonal regeneration of adult RGCs *(10,107),* an effect that could be significantly potentiated by cAMP elevation *(81,108).* Furthermore, we also found that enhanced production of CNTF in the distal end of injured optic nerves promoted both RGC survival and axonal regeneration *(109).* Most recently, we found that sustained supply of CNTF via adeno-associated viral vector-mediated transfer of *CNTF* gene was more potent than BDNF in protecting the viability of injured adult RGCs (Leaver S, Cui Q, Roger J, Verhaagen J, and Harvey AR, submitted).

The CNTF receptor is composed of an extracellular CNTF-binding subunit, CNTF receptor-α (CNTFR)α, and two transmembrane proteins,

gp130 and leukemia inhibitory factor receptor-β (refs. *110–112;* Fig. 1). Through this receptor complex, CNTF elicits its biological actions primarily via the Janus kinase (JAK)/signal transducer and activators of transcription-3 (STAT3) signaling pathway, but involvement of other signaling pathways such as PI-3K/Akt and MAPK/ERK has also been observed (refs. *106,108,113–118;* Fig. 1). Although CNTF-dependent activation of the PI-3K/Akt and MAPK/ERK pathways induces phosphorylation (and thus inactivation) of pro-apoptotic Bad as well as activation of anti-apoptotic Bcl-2 proteins that lead to neuronal protection *(38,67,116,119,120),* CNTF and other cytokines such as IL-1, IL-10, epidermal growth factor, and platelet-derived growth factor mainly activate JAK/STAT3 for various biological actions, including neuronal protection *(106,113,115, 121–127).* Recently, we systematically characterized signaling transduction in CNTF/ cAMP-induced adult rat RGC survival and axonal regeneration. We showed that although CNTF did not exert any effect on the PKA pathway, it activated the other three pathways (PI-3K/Akt, MAPK/ERK, and JAK/STAT3) to promote both RGC survival and axonal regeneration in adult rats *(108).* Support for the positive effect of CNTF in the eye comes from studies showing the location of various CNTFRα neuronal populations, including RGCs, in the retina *(128)* and is further strengthened by cAMP via upregulation of CNTFRα *(108).*

As discussed earlier, both the PI-3K/Akt and MAPK/ERK pathways play an important role in mediating neuronal survival. Involvement of the PI-3K/Akt and MAPK/ERK pathways in neurite outgrowth in vitro and axonal regeneration in vivo has also been reported *(129–132).* However, the protective effects of the PI-3K/Akt and MAPK/ERK pathways are not always consistent among the neuronal populations examined. For certain neuronal populations, activation of the PI-3K/Akt pathway plays a critical role in protecting the neuronal viability *(59,131),* whereas activation of the MAPK/ERK pathway does not have any effect *(59,116,131)* or has a merely minor influence *(36,133)* on the viability. Additionally, conflicting results on the effect of the MAPK pathway activation in neural protection have also been documented; apart from beneficial or protective effects of activation of the MAPK/ERK pathway, inhibition of the MAPK/ERK pathway also protects against damage resulting from focal cerebral ischemia *(134).* In our studies, pathway inhibition of MAPK/ERK, PI-3K/Akt or JAK/STAT3 in the absence of CNTF and cAMP elevation also promoted RGC survival *(108).* Whether the latter observations are achieved by pathway inhibition directly or indirectly via activation of other mechanism(s) is currently under investigation. Preliminary results indicate that activation of macrophages occurs under some of the aforementioned conditions; therefore, it is possible that macrophage activation induced by pathway inhibition is responsible for the observed enhancement of RGC survival in our studies.

GDNF and Related Ligands

GDNF and its three relatives, neurturin, artemin, and persephin, constitute a novel family of neurotrophic factors: the GDNF family ligands (Fig. 2). GDNF was originally identified as a survival factor for the embryonic dopaminergic neurons of the midbrain *(135,136).* Later, GDNF was widely shown to protect neuronal survival and promote axonal regeneration of various neurons *(8,30,104,137–143)*—particularly motoneurons *(30,144,145).* GDNF and related ligands signal through a multicomponent receptor complex that comprises a glycosylphosphatidylinositol-anchored cell-surface molecule (GDNF family receptor [GFR]-α) and rearranged during transfection (*RET*) Trk, thereby triggering the activation of multiple signaling pathways in responsive cells. GDNF, neurturin, artemin, and persephin bind to GFR-α1, GFR-α2, GFR-α3, and GFR-α4, respectively (Fig. 2). The GDNF family ligands and the GFR-α complex bring two molecules of

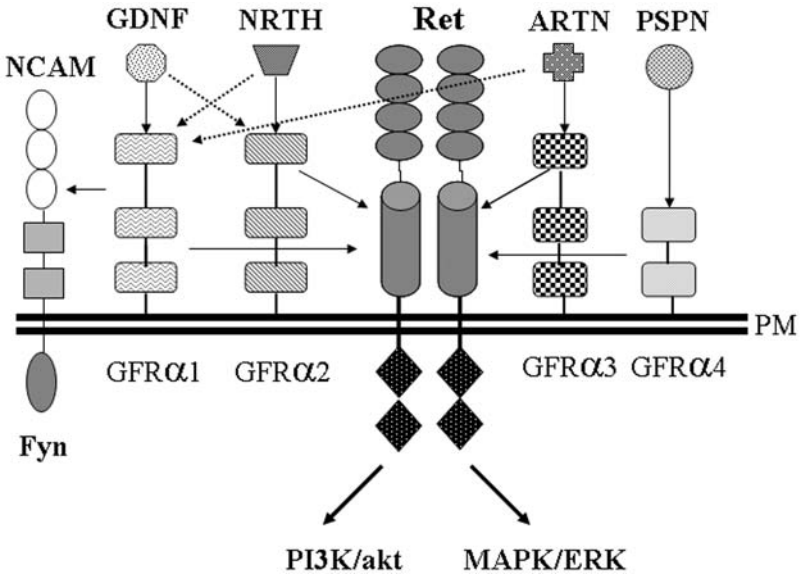

Fig. 2. Signaling transduction pathways elicited by GDNF family members (GDNF, neurturin, artemin, and persephin). GDNF and related ligands signal through a multicomponent receptor complex comprising a GFR-α and RET Trk, triggering the activation of multiple signaling pathways, including PI-3K/Akt and MAPK/ERK.

RET together, triggering transphosphorylation of specific tyrosine residues in their Trk domains as well as intracellular signaling transduction *(136,146)*. However, recent evidence has also demonstrated that GDNF family ligands signal independently of RET—particularly through the neural cell adhesion molecule (NCAM; Fig. 2) *(146,147)*.

RET activates several intracellular pathways to regulate survival, neurite outgrowth, and synaptic plasticity. After binding with GFR-α1 and RET, GDNF also stimulates the PI-3K/Akt and MAPK/ERK pathways to exert its biological actions *(148–151)*. By binding to NCAM, GDNF stimulated axonal growth in hippocampal and cortical neurons in a RET-independent fashion *(146)*. Additionally, association of upregulation of βII-tubulin and GAP-43 with GDNF was also reported; administration of GDNF at injury site in spinal cord increased βII-tubulin and GAP-43 messenger RNA (mRNA) expression in rubrospinal tract neurons *(152)*. Therefore, upregulation of βII-tubulin and GAP-43 may play a role in GDNF-induced axonal regeneration.

Fibroblast Growth Factor

Several members of the FGF family—particularly FGF2—are closely involved in neuronal protection *(153,154)*. In addition to neuronal protection, FGFs have also been shown to enhance neurite outgrowth and axonal regeneration *(155–163)*. It is known that FGFs exert their neuroprotection by interacting with numerous signaling pathways, including activation of the MAPK/ERK pathway, expression and gating of *N*-methyl-D-aspartate receptors, maintenance of calcium homeostasis, and regulation of enzymes that detoxify reactive oxygen species *(164–166)*. FGFs also prevent apoptosis via anti-apoptotic pathways by increasing neuronal *Bcl-xL* and *Bcl-2* expression *(166)* or by inhibiting the activation of caspase-3-like proteases *(167)*. Additionally, FGFs activate PI-3K/Akt and stimulate the phosphorylation of Bad *(167)*, a process also known to protect neuronal viability. However, under certain conditions, FGF-induced neuronal protection could be MAPK/ERK- or PI-3K/Akt-pathway-independent *(46,168)*; it is still not

clear how FGFs achieve their neuronal protection under these conditions.

To elicit their biological effects, FGFs interact with their high-affinity receptors, which are transmembrane proteins with a cytoplasmic portion containing a Trk activity, and enhance protein tyrosine phosphorylation and MAPK activity *(165).* Interestingly, neurite outgrowth stimulated by three cell adhesion molecules (L1, NCAM, and N-cadherin) is also FGF-receptor-dependent, and PLCγ is a key downstream effector for this response *(157,169,170).* It was recently shown that the FGF receptor uses the endocannabinoid signaling system to couple to an axonal growth response: CB1 cannabinoid receptor antagonists inhibit axonal growth responses stimulated by N-cadherin and FGF2; three CB1 cannabinoid receptor agonists mimic the N-cadherin/FGF2 response at a step that is downstream from FGF receptor activation but upstream from calcium influx into cells *(171).*

Role of cAMP in Neuronal Survival and Axonal Regeneration

cAMP of second messenger system has diverse effects on neuronal functions. It is involved in survival, process expression, modulation of growth cone responses to a range of diffusible and nondiffusible factors, and enhancement of neurite outgrowth *(45,107, 172–176).* For example, in culture, cAMP elevation promotes survival of spinal motoneurons *(45),* alters the response of these neurons to a combination of growth factors (including BDNF, CNTF, GDNF, and FGF *[45]*), modulates growth cone turning direction *(177),* and overcomes the inhibitory effects of myelin-associated inhibitory factors such as MAG *(41,178, 179).* In vitro, responsiveness of purified embryonic or neonatal RGCs to a range of trophic factors requires cAMP elevation *(180)* or membrane depolarization *(181);* greater RGC viability or improved survival is obtained if cAMP is elevated in the presence of a mixture of factors, including BDNF, CNTF, and insulin growth factor-1. The survival of immature RGCs in young rats in vivo is also enhanced if retinal cAMP levels are increased in the presence of both BDNF and CNTF *(182).* The mechanisms underlying cAMP-dependent actions appear to be very diverse and complex (Fig. 1). Evidence shows that an increase in cAMP level can influence the expression of the NT genes via calcium-mediated mechanisms *(183–185).* Elevation of cAMP also allows the translocation of MAPK to the nucleus in response to appropriate trophic stimulation *(181)* and increases surface levels of relevant receptors (e.g., TrkB) by recruiting them from intracellular stores *(181).* Because neurotrophic factors and cAMP activate the MAPK/ERK and PI-3K/Akt pathways to exert their biological actions *(38,108,115),* the observed cAMP-induced neuronal protection may result from coordinated action of the MAPK and PI-3K/Akt pathways (Fig. 1). However, it has recently been demonstrated that TrkB expression can be regulated by the cAMP/CREB pathway *(186);* therefore, it is also possible that TrkB and cAMP act together to elicit their biological actions. On the other hand, under a different condition (serum withdrawal), cAMP has been shown to inhibit, rather than enhance, BDNF-induced protection of cultured cortical neurons via the PI-3K pathway *(187),* indicating double faces of cAMP elevation on neuronal survival under different conditions. Therefore, a higher level of cAMP confers multiple biological actions and neuronal responsiveness by acting in concert with various factors *(68,180),* including pathway activation *(108),* autocrine neurotrophic mechanism *(188),* and membrane depolarization *(181).*

On the other hand, it has been documented that pharmacological elevation of cAMP alone does not promote neuronal survival *(180,182)* or axonal regeneration *(189).* We also failed to observe positive effects of cAMP elevation alone on neuronal survival and axonal regeneration, but a synergistic effect was seen when CNTF was co-applied *(81).* A similar synergistic effect of cAMP elevation and neurotrophic factors was observed in the survival of embryonic

rat motoneuron *(45)* and adult cat β-RGCs *(190)*. Interestingly, although RGC survival was not affected by cAMP elevation in our studies, cAMP elevation was found to activate the MAPK/ERK, PI-3K/Akt, and JAK/STAT3 pathways *(81,108)*, an effect that might participate in neuronal protection under certain conditions.

Numerous recent studies have shown that cAMP elevation promotes neurite outgrowth or axonal regeneration. A raised level of cAMP has also been reported to reduce the effect of growth-inhibitory molecules in adult neurons. In young neurons, which contain a relatively high level of cAMP, axonal growth is promoted by MAG, an effect that is blocked by inhibiting PKA *(178,191)*. However, MAG inhibits axonal growth in older neurons and blocks NT-elicited increases in cAMP level *(178)*; these changes occur at a time when there is maturational loss of regenerative capacity. Elevation of cAMP or activation of PKA has been shown to be sufficient to reverse inhibition of neurite outgrowth by MAG-expressing cells in vitro *(178,191)*.

Enhanced axonal growth in vivo has also been observed after cAMP elevation *(48, 192–195)*. Of these in vivo studies, axonal regeneration and functional recovery induced by cAMP elevation after spinal cord injury *(48, 192–194)* are particularly important because they provide new insight into the mechanisms of axonal regeneration and may help develop possible clinical strategies in treatment of spinal cord injury. Additionally, despite the fact that the level of cAMP in neurons may drop following axotomy *(81,182)*, elevated cAMP can be easily achieved via direct application of cAMP analogs *(108,192,193,195,196)* or application of rolipram, an inhibitor of the enzyme phosphodiesterase that degrades cAMP *(48,194)*.

cAMP acts primarily on the PKA pathway, leading to activation of various signaling pathways and phosphorylation of GSK-3β to exert its biological functions *(108,197)*. This has been confirmed by numerous experiments in which the cAMP-elicited biological actions were blocked by the PKA inhibitor KT5720 *(193)*. Filbin and colleagues *(41,178)* previously demonstrated that NGF and BDNF elevated cAMP to overcome MAG-dependent inhibition of axonal regeneration through TrkA and TrkB receptors. They identified arginase I and polyamines as downstream products of cAMP-activated pathway in the blockade of the MAG–RhoA inhibitory pathway *(179)*. Arginase I has also been identified as an anti-apoptotic factor *(198)*, whereas polyamines has been identified as cytoskeleton, glutamate receptors, and potassium channel modulators *(199–202)*. In the process of axonal regrow inhibition, guanosine triphosphate (GTP)ase RhoA appears to play a critical role in mediating the action of axon-growth inhibition. Activation of the RhoA pathway was shown to lead to sequential Rho-associated kinase/LIM kinase/cofillin-mediated actin filament depolymerization and collapse of growth cone *(203–206)*; RhoA inactivation increased neurite growth in vitro *(207–209)* and axonal regeneration in vivo *(210)*. Current information suggests a blockade of the RhoA pathway as the main action for cAMP-induced activation of PKA phosphorylation and its downstream products (arginase I and polyamines) in promoting axonal regeneration (refs. *179* and *210*; Fig. 1). This may also be one of the mechanisms in which an increased level of cAMP regulates growth cone responsiveness to MAG and overcomes other growth inhibitory molecules, resulting in facilitation of axonal regrowth.

It remains unclear how elevation of cAMP achieves the blockade of the MAG–RhoA pathway. As mentioned earlier, we recently systematically characterized the signaling transduction pathways underlying the CNTF/cAMP-induced neuronal survival and axonal regeneration and documented that elevation of cAMP led to activation of the MAPK/ERK, PI-3K/Akt, and JAK/STAT3 pathways, an effect that significantly potentiated CNTF-induced RGC axonal regeneration *(81,108)*. A similar synergistic effect in promoting axonal regeneration has also been observed in spinal cord *(196)*.

On the other hand, in growth cones, molecules such as GAP-43 and βIII-tubulin are phosphorylated to render biological actions. Both GAP-43 and βIII-tubulin are known to be involved in cytoskeletal dynamics and to amplify growth cone responsiveness to ligands and extracellular cues *(94,211,212).* cAMP and PKA may also play an important role in these respects, because the response of a neurite to a given guidance molecule can be modulated by changing cAMP levels and/or by blocking PKA *(173,174).* In addition to upregulation of TrkB *(181),* elevation of cAMP also increases CNTFRα mRNA expression in the retina *(108).* A similar observation was obtained in vitro: Forskolin, which enhances intracellular cAMP levels, increased CNTFRα mRNA expression in cultured neonatal olfactory ensheathing cells *(213).* In the presence of exogenous neurotrophic factors such as BDNF and CNTF, the increased level of their receptors by cAMP elevation may also facilitate the action of CNTF on neuronal survival and axonal regeneration. Therefore, the cAMP-mediated RhoA inactivation leading to enhancement of axonal regeneration likely is achieved through interactions among multiple mechanisms involving at least the PKA, MAPK/ERK, PI-3K/Akt, and JAK/STAT3 pathways.

Effect of Trophic Factors on Inhibitory Molecules

The presence of various axonal regeneration inhibitory molecules (Nogo, MAG, and OMgp) in the myelin and oligodendrocytes of the CNS has been well-documented over the last 15 yr *(214–217).* IN-1 antibodies, which are raised in hybridoma cells and are able to block the action of Nogo molecules, have been used in several studies and have demonstrated some success in promoting axonal regeneration in the CNS—particularly in the adult spinal cord *(218,219).* Because Nogo was later shown to be expressed in the optic nerve and ganglion cell layer of the retina *(220),* it was not surprising that RGC axonal outgrowth was enhanced by IN-1 treatment in vitro *(221).* In vivo, we observed a synergistic effect of IN-1 antibodies and CNTF in promoting RGC axonal regeneration *(81).* This is consistent with a previous report in developing rats in which IN-1 acted synergistically with BDNF to further enhance the regrowth of intracranially crushed RGC axons into the distal side of the optic nerve *(222).* A similar synergistic effect of IN-1 and NT-3 in promoting axonal regeneration was also reported in spinal cord *(223).*

Three different isoforms of Nogo were cloned (Nogo-A, -B, and -C), with identification of two inhibitory domains (Nogo-66 and Amino-Nogo) in Nogo A *(224–226).* All isoforms share a common C-terminal domain of 188 amino acids *(224,225,227).* A 66-amino acid subdomain within the common C-terminal domain is expressed on the surface and binds to a glycosylphosphatidylinositol (GPI)-linked Nogo-66 receptor expressed by neurons *(226).* Nogo-A, MAG, and OMgp are all known to bind to NgR to elicit their inhibitory effects (Fig. 3). However, NgR is a (GPI)-anchored protein, and it requires a transmembrane-interacting partner to transduce the inhibitory signal within the cell. Over the last 3 yr, rapid progress has been made in our understanding of signaling transduction of these inhibitory molecules; Nogo-A, MAG, and OMgp all act through the same Nogo-66 receptor, which forms a receptor complex with $p75^{NTR}$ and LINGO-1 for transduction of intracellular inhibitory signals, leading to activation of the RhoA pathway (refs. *103–205* and *228–233;* Fig. 3). However, $p75^{NTR}$ has no affinity for NgR ligands—it is the ectodomain of NgR that binds to the three ligands, and the signal transduction is mediated by the intercellular domain of $p75^{NTR}$ through Rho GTPases *(234).* The potential contribution of this NgR/$p75^{NTR}$/LINGO-1 to the RhoA signaling pathway in CNS regenerative failure is clearly shown by the ability of RhoA blockade to promote injured axons to regrow even in their native hostile CNS environment, where large amounts of inhibitory molecules are present *(233,235).*

NTs can act to overcome inhibition of RhoA elicited by MAG *(236).* The exact mechanisms

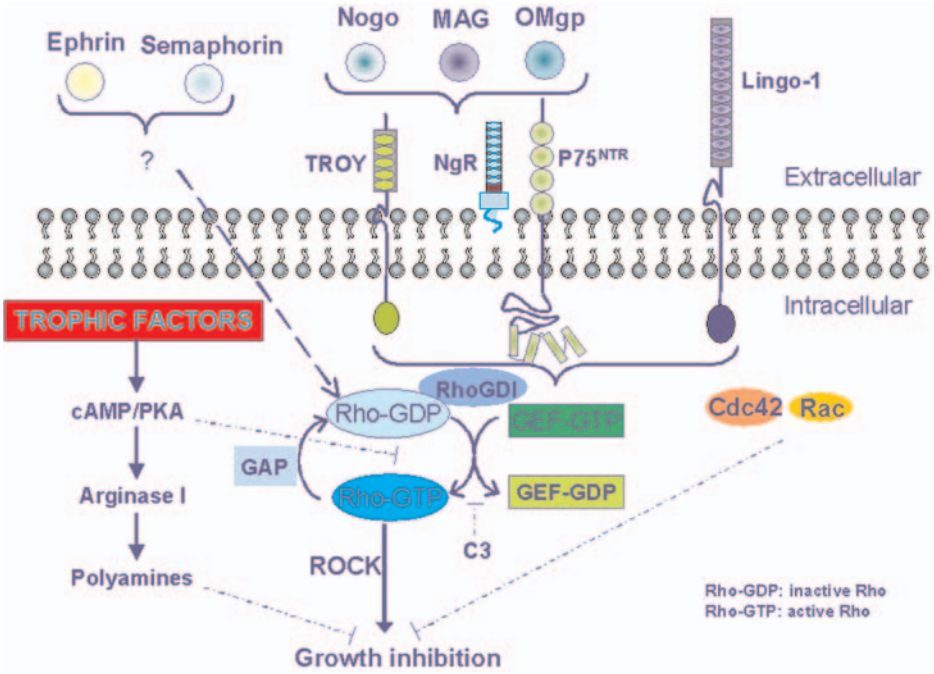

Fig. 3. Signaling transduction pathways elicited by growth-inhibitory molecules such as Nogo, MAG, and OMgp and growth-repulsive molecules such as ephrin and semaphorin, leading to axon-growth inhibition. All inhibitory molecules appear to converge on RhoA to inhibit axonal regrowth.

underlying this NT-induced blockade of MAG inhibition are not known. It likely involves cAMP elevation and signaling transduction of multiple pathways. On the other hand, IN-1 antibody treatment upregulates the expression of BDNF, GAP-43, and transcription factor STAT *(237)*, whose signal pathways contribute to the enhanced axonal regeneration. Although IN-1 promotes axonal regeneration and improves functional recovery at least in some parts of the CNS *(219,238,239)*, blockade of Nogo alone only renders a small number of axons to regrow. This is not surprising, because blocking Nogo alone still leaves other inhibitory molecules such as MAG and OMgp to exert inhibitory effects, and other factors still exist to hinder axonal regrowth. For example, the scar tissue is still present to form a physical barrier for axons to pass through, and the injured neurons are still of low growth potential or lack trophic support. With the identification of differential Nogo receptor distributions in different neurons or at different developmental ages *(226)*, this also may help explain the lack of action of IN-1 antibodies in certain parts of the CNS *(240)*. Surprisingly, studies in Nogo-deficient mice after spinal cord injury have yielded stark divergence in regeneration phenotype in three laboratories *(241–243)*. A study by Schwab et al. *(242)* showed improved regenerative and plastic responses in mice lacking Nogo-A, but the real numbers of axons that grew were few. A study by Strittmatter et al. *(241)* found only enhanced regeneration in young—not adult—mice lacking Nogo-A/B. On the other hand, Tessier-Lavigne et al. *(243)* failed to detect any evidence of enhanced axonal growth in mice lacking Nogo-A/B/C or Nogo-A/B. Notably, in our study, the number of regenerating adult RGC axons was not affected by IN-1 treatment alone *(81)*.

Although Nogo-A, MAG, and OMgp all act through NgR to exert their inhibitory effects, a peptide that disrupts interactions of Nogo

receptor with its ligands has been shown to promote robust sprouting of uninjured, but limited, regeneration of damaged spinal cord tract fibers *(244).* Extensive axon regeneration was also observed in both normal and degenerating white matter tracts in the presence of inhibitory molecules; however, regenerating axons were stopped at the glial scar formation site *(245,246).* These results further confirm that apart from Nogo-A, MAG, and OMgp, other factors such as chondroitin-sulfate-proteoglycans-related scar tissue play an important part in impeding axon regrowth *(247,248).* The important role of chondroitin sulfate-proteoglycans as the main inhibitory molecules in scar tissue *(246)* and subsequent degradation of these molecules leading to enhanced axon regeneration in spinal cord *(249)* has been documented.

p75^{NTR}

p75^{NTR} is a member of the extensive tumour necrosis factor family. Earlier studies have shown that p75^{NTR} exhibits predominantly low-affinity binding for all NTs and helps enhance the survival of neurons and glial cells under certain conditions *(250–252).* An important feature of p75^{NTR} is its alteration of the affinity of Trk binding and the ligand specificity of Trk receptors. BDNF, NT-3, and NT-4/5 all bind to TrkB in the absence of p75^{NTR}, , whereas only BDNF renders a functional response upon co-expression of TrkB; similarly, p75^{NTR} restricts TrkA signaling to NGF, although both NGF and NT-3 bind TrkA *(253,254).* Although p75^{NTR} was initially shown to act together with NTs to promote the survival of certain neuronal populations, it later emerged as a death-related receptor and often acted in a cell-type-, developmental-stage-, or pathological-state-specific fashion. It was demonstrated that NT-induced apoptosis by binding p75^{NTR} *(28)*—especially when Trk was not expressed *(255).* The importance of p75^{NTR} during development is evident because deletion of p75^{NTR} causes severe nervous system defects *(256).*

Surprisingly, p75^{NTR} was recently shown to be a coreceptor for axon-regrowth inhibitors such as Nogo-66, MAG, and OMgp *(203,204).* As mentioned earlier, interaction of myelin-associated inhibitors with the NgR/p75^{NTR}/LINGO-1 complex activates the small GTPase RhoA, which causes growth cone collapse or inhibition of neurite growth *(257,258).* Enhanced sympathetic fiber growth into the cerebellar white matter has been observed in mice lacking the p75^{NTR} *(259).* In the absence of the NGF/p75^{NTR} binding, collateral sprouting of sensory axons mediated by NGF is enhanced *(260),* and BDNF/p75^{NTR} binding compromises neurite outgrowth of cerebellar neurons in vitro *(90).* Nevertheless, the rate of axonal elongation in the crushed facial nerve and neuronal survival are not affected in p75^{NTR}-deficient mice *(261).* p75^{NTR} often confers diverse and often opposing biological actions in the nervous system. The many faces of p75^{NTR} were recently reviewed *(25,262).*

Although NgR and LINGO-1 are widely expressed in the CNS, p75^{NTR} is downregulated in most parts of the CNS during development, and many CNS neurons that are sensitive to myelin-associated inhibitors do not express p75^{NTR}. Therefore, it has been suggested that there are p75^{NTR} homolog(s) more widely expressed in the adult CNS that could substitute for p75^{NTR} in the process of regenerative inhibition. An exciting advance was recently made in helping to solve this perplexing mystery: TROY, a member of tumor necrosis factor family, was independently identified by two laboratories to be a p75^{NTR} homolog that binds to NgR, with an affinity eightfold stronger than the interaction between p75^{NTR} and NgR, to form an NgR/TROY/LINGO-1 complex and to mediate the inhibitory activity of myelin inhibitors *(263,264).* However, even in the absence of both p75^{NTR} and TROY functions, neurite lengths are still shorter than control, suggesting the possibility of additional signaling pathways underlying myelin-mediated neurite growth inhibition. Because some neurons, such as RGCs, are known to express TROY but not p75^{NTR} *(263),* it is important to know

whether enhanced axonal regeneration can be obtained when the NgR/TROY/LINGO-1 signaling transduction pathway is disrupted.The effect of adeno-associated viral vector-mediated gene transfer of TROY-silencing RNA on regeneration of injured adult RGC axons is currently under investigation in our laboratory.

Conclusion

Available information suggests that multiple mechanisms are involved in the failure of axonal regeneration in the mammalian CNS. Neurotrophic factors interact with various factors to achieve neuronal protection and enhancement of axonal regeneration. Therefore, any single-aspect attempt to tackle the poor axonal regeneration after traumatic CNS injury in the adult seems to fail. Combined experimental approaches, including neutralization of inhibitory molecules (IN-1 antibody, inhibitory-molecule-receptor-mediated signaling interruption via peptide receptor blockers, negative dominant forms of the receptors or relevant silencing RNAs), blockade of inhibitory signaling pathways (RhoA pathway inhibitors), supply of appropriate neurotrophic factors (e.g., BDNF, NT-3, NT-4/5, CNTF, GDNF, FGF), modification of axonal regeneration environment (e.g., peripheral nerve graft or Schwann cell/olfactory ensheathing glia transplantation), prevention of scar tissue formation (Chondroitinase ABC), and elevation of intrinsic regrowth capability (cAMP elevation) will be necessary to circumvent this devastating condition and to achieve possible functional recovery following CNS injury in the human *(81,192,193,210,244,249,265).*

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