NF-κB in neuronal plasticity and neurodegenerative disorders

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NF-κB is widely known for its ubiquitous roles in inflammation and immune responses, as well as in control of cell division and apoptosis. These roles are apparent in the nervous system, but neurons and their neighboring cells employ the NF-κB pathway for distinctive functions as well, ranging from development to the coordination of cellular responses to injury of the nervous system and to brain-specific processes such as the synaptic signaling that underlies learning and memory. Here we discuss the regulation of NF-κB activity by neurotransmitters and neurotrophic factors and the physiological and pathological effects of NF-κB activation in neurons and glial cells. Based on work in animal models, it appears that manipulation of NF-κB signaling may prove valuable in treating such conditions as ischemic stroke, physical trauma to the brain or spinal cord, and neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.

NF-κB in the nervous system: what, when, and where

The molecular composition of NF-κB DNA-binding dimers, and the proteins that modulate the activation and function of NF-κB, have been reviewed previously (1). As in other organ systems, functional NF-κB complexes are present in essentially all cell types in the nervous system, including neurons, astrocytes, microglia, and oligodendrocytes (2). The most common subunits expressed are p50, p65, and IκBα. In addition, novel and developmentally regulated NF-κB subunits may be expressed in the nervous system, including a recently described neuronal κB factor (3). Receptor-linked signal transduction pathways that ultimately result in NF-κB activation, such as those activated by TNF-α and Fas ligand, have also been documented in neurons and glial cells (4). Additional neuron-specific signals that activate NF-κB include nerve growth factor (NGF) (5) and the secreted form of β-amyloid precursor protein (βAPP) (Figure 1) (6). A major pathway leading to NF-κB activation involves IκB phosphorylation by IκB kinase (IKK), which consists of two catalytic subunits (IKK-α and IKK-β) and a regulatory subunit called IKK-γ. Neural cells express mitogen-activated protein kinase/extracellular signal–regulated kinase kinase 1 (MEKK1), which may be an important mediator of IKK phosphorylation in response to cell surface receptor activation. Interestingly, electrical activity within neurons and synaptic transmission between neurons are potent stimuli for NF-κB activation, and such neuronal activity may account for the relatively high constitutive activity of NF-κB in brain tissue compared with other tissues (2).

As in other organs, NF-κB influences the expression of a complex array of genes in the nervous system and, in general, the genes serve important functions in cellular responses to injury and in neuronal plasticity (Table 1). Genes encoding several different injury-responsive cytokines are induced by NF-κB in glia and neurons. These include TNF-α and IL-6, which are produced in particularly high amounts by microglia and astrocytes; βAPP, an injury-responsive cytokine/neurotrophic factor; the calcium-binding protein calbindin-D28k, which may play roles in modulating calcium-mediated neuronal signaling and cell death; inhibitor-of-apoptosis proteins (IAPs), which can protect neurons against apoptosis in experimental models of stroke and seizures; manganese superoxide dismutase (Mn-SOD), a mitochondrial antioxidant enzyme that has been shown to be neuroprotective; and Bcl-2, the prototypical member of the Bcl-2 family of antiapoptotic proteins. Additional genes induced by NF-κB in glial cells include the cell adhesion molecule intercellular adhesion molecule-1, the inducible form of nitric oxide synthase, and glial fibrillary acidic protein.

NF-κB in development and plasticity of the nervous system

Many of the same signal transduction pathways that regulate neuronal survival and growth during development of the nervous system appear to be centrally involved in various neurodegenerative conditions. Knowledge gained from studies of the function of NF-κB in developing neurons is therefore likely to be relevant to the pathogenesis of neurological disorders. An evolutionarily conserved role for NF-κB in development is suggested by data showing that the

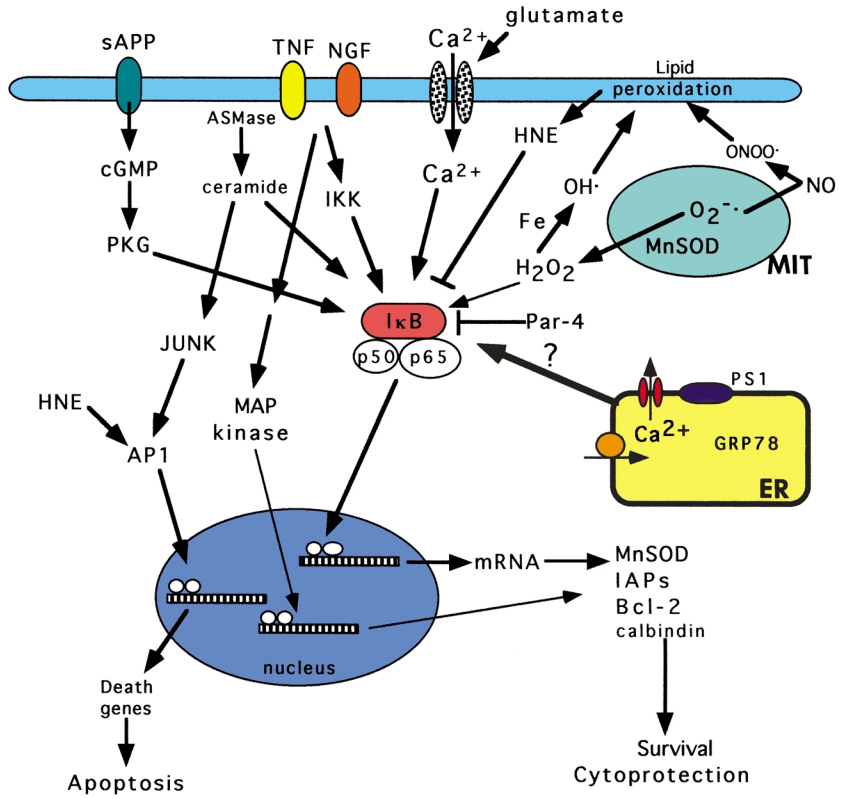

Figure 1
Signaling pathways that regulate NF-κB activity in neurons, and their possible involvement in the pathogenesis of neurodegenerative disorders. NF-κB in its inactive form is present in the cytosol as a three-subunit complex, with the prototypical components being p65 and p50 (transcription factor dimer) and IκBα (inhibitory subunit). NF-κB is activated by signals that activate IκB kinase (IKK), resulting in phosphorylation of IκBα; this targets IκBα for degradation in the proteosome and frees the p65-p50 dimer, which then translocates to the nucleus and binds to consensus κB sequences in the enhancer region of κB-responsive genes. Diverse signals can induce NF-κB activation, including TNF-α, sAPPα, NGF, and glutamate; increases in levels of intracellular Ca^{2+} and reactive oxygen species such as H_2O_2 can be potent activators of NF-κB. NF-κB induces the expression of several different genes that promote neuron survival, including those encoding manganese superoxide dismutase (Mn-SOD), inhibitor-of-apoptosis proteins (IAPs), Bcl-2, and calbindin. Several signals that inhibit NF-κB activity are generated in neurons undergoing apoptosis; examples include prostate apoptosis response-4 (Par-4) and the lipid peroxidation product 4-hydroxynonenal (HNE). NF-κB is modulated by signals emanating from the endoplasmic reticulum (ER) and mitochondria (MIT). AP1, activator protein-1; GRP78, glucose-regulated protein-78; JUNK, Jun NH_2-terminal kinase; PKG, cGMP-dependent protein kinase.

Drosophila NF-κB homologue "dorsal" is required for establishment of dorso-ventral polarity in the developing embryo (7). In the developing rat nervous system, levels of NF-κB activity change, with levels peaking in the cerebellum during the early postnatal period at a time when synaptogenesis is occurring (8). The particular NF-κB subunits expressed in neurons are also developmentally regulated; for example, inducible p50 homodimers and p65/cRel dimers are present in brains of young rats, but not in adults (9). A peptide inhibitor of NF-κB (SN50) blocks the ability of NGF to prevent death of cultured sympathetic neurons (10), suggesting a role for NF-κB in the control of neuronal death during development of the nervous system. The antiapoptotic role of NF-κB in developing neurons is seen in the mechanism whereby the protein synthesis inhibitor cycloheximide prevents neuronal apoptosis. Levels of cycloheximide that cause only a small impairment of protein synthesis can prevent apoptosis by inducing Bcl-2 and the antioxidant enzyme Mn-SOD (11), a process that depends on NF-κB activation; treatment of neurons with κB decoy DNA abolishes the antiapoptotic effect of cycloheximide.

The presence of NF-κB in synaptic terminals located at considerable distances from the neuronal cell body, and its ability to be activated locally at those sites, strongly suggest that this transcription factor modulates synaptic function (2). Stimulation of glutamate receptors and membrane depolarization stimulate NF-κB activation in neurons, probably via a calcium-mediated mechanism. NF-κB is also activated in association with long-term potentiation (LTP) of synaptic trans-

mission, a process believed to be a cellular mechanism of learning and memory (12). Moreover, NF-κB is activated in response to low-frequency stimulation, in contrast to other transcription factors (e.g., c-fos and NGFI-A) that are induced only by high-frequency stimulation parameters that induce LTP (13).

More direct evidence that NF-κB regulates synaptic function comes from studies showing that blockade of NF-κB activation alters synaptic plasticity. Electrophysiological measurements of synaptic plasticity in hippocampal slices from mice lacking TNF-α receptors, and in slices incubated in the presence of κB decoy DNA, suggest an important role for NF-κB in the process of long-term depression (LTD) of synaptic transmission (14). Stimulation of Schaffer collateral axons (axons of CA3 pyramidal neurons that form synapses with dendrites of CA1 pyramidal neurons) at a frequency of 1 Hz induces LTD in slices from wild-type mice, but not in slices from TNF receptor knockout mice (Figure 2). When slices from wild-type mice are pretreated with κB decoy DNA, LTD cannot be induced and the amplitude of LTP is significantly decreased (14); these results provide direct evidence for a requirement for NF-κB activation in synaptic plasticity. The gene targets that mediate the effects of NF-κB on synaptic function are not clear. However, whole-cell perforated patch clamp recordings in cultured rat hippocampal neurons have provided evidence that activation of NF-κB can modulate sensitivity of neurons to glutamate (a neurotransmitter of central importance in the processes of LTD and LTP), possibly by affecting the expression or regulation of specific *N*-methyl-D-aspartate and/or 2-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subunits (15).

Finally, NF-κB may play an important role in the apoptotic death of neurons that occurs during normal development of the nervous system. Such natural neuronal death is thought to be regulated by electrical activity in neurons and by competition of neurons for a limited supply of neurotrophic factors produced by target cells upon which synapses form. Depolarization of neurons (2) and stimulation of neurotrophic factor receptors (5) can each activate NF-κB. In particular, the activity-dependent neurotrophic factor (ADNF), a trophic factor that appears to play a widespread role in mammalian development, appears to act through this pathway (16). As has been established in non-neural cells, NF-κB regulates the expression of genes encoding proteins that modify the apoptotic process at premitochondrial steps. For example, NF-κB induces expression of Bcl-2, A1/Bfl-1, and Mn-SOD, which stabilize mitochondrial function and thereby prevent apoptosis (Table 1).

NF-κB–mediated glial cell activation

The extensive literature on the involvement of NF-κB in regulating cytokine cascades suggests that, although NF-κB activation can prevent apoptosis of the cell in which it is activated, it may indirectly lead to apoptosis of other cells by promoting production of cytotoxic agents such as nitric oxide (Figure 3). Microglial cells, in particular, can produce neurotoxic reactive oxygen species and excitotoxins when activated. Cytokine-mediated activation of microglia may explain the ability of inhibitors of NF-κB to protect against cell damage in certain experimental paradigms that involve an inflammatory response (17). Systemic administration of LPS and TNF-α to rats induces a rapid and transient increase in the NF-κB–mediated transcriptional activation of IκB in microvascular cells and microglia throughout the brain (18). Microglial activation is associated with a marked increase in expression of cyclooxygenase-2, an oxyradical-generating enzyme, and agents that inhibit NF-κB can suppress LPS-induced cyclooxygenase-2 expression, suggesting an important role for NF-κB in microglial activation and oxyradical production.

The role of microglial NF-κB in neuronal injury is complicated by the fact that activated microglia produce neurotrophic factors. For example, activated microglia produce NGF, bFGF, and TNF, each of which has been shown to prevent neuronal death in various experimental models of neurodegenerative disorders. Activation of NF-κB in astrocytes results in increased expression of nitric oxide synthase and increased nitric oxide production. A potent inducer of NF-κB activation in astrocytes is bradykinin, an inflammatory mediator produced in the brain in response to ischemia and trauma (19). Acting through an NF-κB–mediated pathway, bradykinin induces production in astrocytes of IL-6, which stimulates production of several inflammation-related cytokines.

Production of proinflammatory cytokines by microglia and astrocytes is counterbalanced by anti-

Table 1
Examples of stimuli that activate NF-κB in the central nervous system

Stimulus	Cell type	Effect	Genes modulated
TNF	Neurons	Prevention of apoptosis	Mn-SOD, calbindin, Bcl-2, glutamate recep.
	Astrocytes	Prevention of apoptosis	Mn-SOD, calbindin
	Microglia	Cytokine production	TNF, IL-6, TGF-β
Glutamate	Neurons	Synaptic plasticity, prevention of apoptosis	glutamate receptors? Mn-SOD, calbindin
NGF	Neurons	prevention of apoptosis	Bcl-2
Oxyradicals	Many cells	Prevention of apoptosis	Mn-SOD, calbindin
Amyloid β-peptide	Neurons	Stress response, protective activation, neurotoxicity	Mn-SOD
	Microglia		NOS, cytokines
sAPPα	Neurons	Neuroprotection	Mn-SOD

See ref. 21 and the supplementary reference list (www.jci.org/cgi/content/full/107/3/247/DC1).

inflammatory cytokines that include TGF-β and IL-10. For example, exposure of cultured human fetal brain microglia to LPS and TNF-α results in a marked increase in production of RANTES that is mediated by NF-κB, and the production of RANTES is markedly suppressed in cells treated with either IL-10 or TGF-β. In addition to regulation by cytokines, NF-κB is subject to modulation by neurotransmitters and neuromodulators. Because glutamate is the major excitatory neurotransmitter in the brain, and ATP is an important activity-dependent signal, modulation of NF-κB by these signals may play important roles in neuronal plasticity and in cellular responses to brain injury. Finally, as in neurons, NF-κB in astrocytes can induce production of cytoprotective proteins involved in maintenance of cellular calcium homeostasis and suppression of oxyradical production.

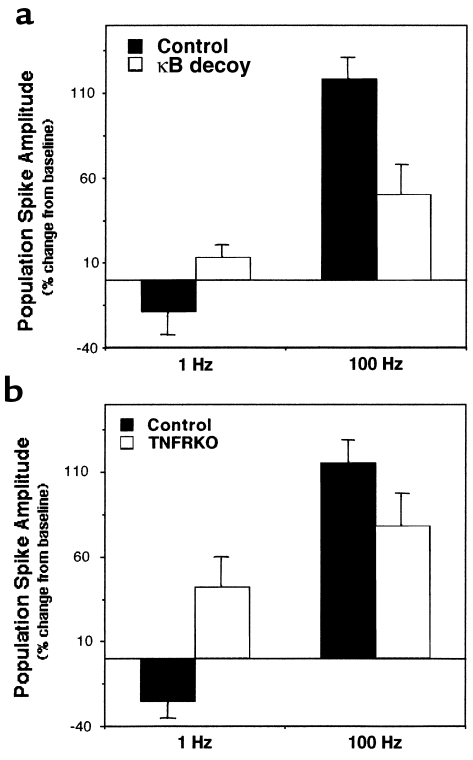

Figure 2
NF-κB in synaptic plasticity. (**a**) Population spike amplitudes recorded from hippocampal slices from adult mice, pretreated with either scrambled control DNA or κB decoy DNA and stimulated at either 1 or 100 Hz. Note that κB decoy DNA prevents LTD of synaptic transmission induced by stimulation at 1 Hz and attenuated long-term enhancement of synaptic transmission induced by stimulation at 100 Hz. (**b**) Population spike responses recorded from hippocampal slices from wild-type mice (Control) and mice lacking TNF-α receptors (TNFRKO) after stimulation at either 1 or 100 Hz. Note that LTD of synaptic transmission is not induced by stimulation at 1 Hz in slices from TNFRKO mice, and that long-term enhancement of synaptic transmission is attenuated in slices from TNFRKO mice. Modified from ref. 23.

NF-κB in acute neurodegenerative conditions

Stroke, severe epileptic seizures, and traumatic brain and spinal cord injuries are major causes of disability and death worldwide. Injury to the brain or spinal cord induces a cascade of signaling events that stimulate NF-κB activation in injured neurons and in injury-responsive glial cells. Cellular and molecular analyses of brain and spinal cord tissues in experimental rodent models of stroke, epileptic seizures, and traumatic injury have begun to reveal the complex functions of NF-κB in modifying neuronal degeneration and recovery. It has become clear that NF-κB influences the neurodegenerative process by directly affecting gene expression in neurons themselves and by indirectly regulating gene expression in glial cells.

Ischemic brain injury. NF-κB activation is greatly increased in brain tissues in rodent models of stroke or cardiac arrest. For example, NF-κB is activated in CA1 hippocampal neurons of rats following transient global forebrain ischemia, and a delayed increase in NF-κB activation occurs several days after focal ischemia/reperfusion in association with reactive glial cells. Data from studies of mice lacking the p50 subunit of NF-κB suggest that, overall, NF-κB activation enhances ischemic neuronal death (20), but its effects differ between cell types such that, whereas activation of NF-κB in microglia promotes ischemic neuronal degeneration, activation of NF-κB in neurons may increase their survival after a stroke. Cell culture studies have clearly shown that activation of NF-κB in neurons protects them against excitotoxic and metabolic insults relevant to the pathogenesis of stroke, including glucose deprivation and exposure to glutamate (21, 22). In addition, the cortical and striatal neurons of mice lacking TNF-α receptors fail to induce the κB-responsive Mn-SOD gene and are more vulnerable to focal ischemic injury (8). The neuroprotective effect of endogenous TNF-α is likely mediated by NF-κB activation in neurons, because mice lacking p50 and mice treated with κB decoy DNA exhibit increased vulnerability of hippocampal neurons to excitotoxicity (22). Further evidence that NF-κB serves a protective function in neurons comes from studies showing that levels of a κB-responsive IAP called neuronal apoptosis inhibitory protein-1 (NAIP) increase in neurons resistant to ischemic brain injury, and that overexpression of NAIP increases resistance of neurons to ischemic injury in vivo (23).

Seizures. NF-κB activity is rapidly increased in hippocampal neurons within 4–16 hours following kainate-induced seizures, and is followed by a delayed and sustained increase in NF-κB activity in glial cells. An excitoprotective role for seizure-induced neuronal NF-κB activation is suggested by studies showing that intraventricular infusion of κB decoy DNA prior to administration of kainate results in a significant increase in the extent of neuronal death in regions

CA1 and CA3 of hippocampus (22). Moreover, seizure-induced neuronal degeneration is increased in mice lacking the p50 subunit of NF-κB; p50 is required for the vast majority of κB DNA-binding activity in the hippocampus (22). Cultured hippocampal neurons from p50-deficient mice exhibit enhanced elevations of intracellular calcium levels following exposure to glutamate, and are more vulnerable to excitotoxicity compared with neurons from wild-type mice. These data suggest that the p50 subunit of NF-κB plays a major role in protecting neurons against excitotoxicity. However, it should be noted that lack of the p50 subunit could have different outcomes depending upon the complement of other NF-κB subunits expressed, since p50 can form homodimers that may repress transcription or p65/p50 heterodimers that stimulate transcription.

Excitotoxic and ischemic injury to neurons is mediated, in part, by dysregulation of cellular calcium homeostasis resulting in a prolonged elevation of intracellular calcium levels. Activation of NF-κB in neurons can stabilize intracellular calcium levels under ischemia-like conditions (6). This may result from induction of several different genes, including those encoding calcium-binding proteins and glutamate receptor subunits. For example, levels of the cytoprotective calcium-binding protein calbindin-D28k are increased in embryonic hippocampal neurons following treatment with TNF-α (21). Calbindin expression is increased in hippocampal neurons in response to kainate-induced seizures and may contribute to the relatively greater resistance of CA1 neurons to seizures as compared with CA3 neurons that do not express calbindin (24). Treatment of the cultured neurons with TNF-α for 24–48 hours results in decreased glutamate-induced currents, and this effect of TNF-α is abolished by treatment with κB decoy DNA (15). The latter studies demonstrate that NF-κB can reduce neuronal sensitivity to glutamate, perhaps by suppressing expression of specific glutamate receptor subunits.

Traumatic injury. Levels of NF-κB activity are increased in cerebral cortex within hours of traumatic brain injury in rats, after which they remain elevated for at least 24 hours. Within neurons in the injured cortex, levels of p65 immunoreactivity increase first in the axons and subsequently in neuronal cell bodies (25). Neighboring microglia and astrocytes also show increased levels of p65. This increase in immunoreactivity persists for many months, particularly in the margins of the progressively enlarging ventricle, suggesting a role for NF-κB in a prolonged inflammatory process. Sullivan et al. (26) showed, using a controlled cortical impact model of traumatic brain injury, that damage to cortical neurons and blood-brain barrier breach are exacerbated in mice lacking TNF-α receptors. In this study, injury-induced NF-κB activation was attenuated and Mn-SOD production decreased in the TNF-α receptor knockout mice. Conversely, neuronal damage following traumatic brain injury was decreased in transgenic mice overexpressing Mn-SOD, suggesting that production of Mn-SOD following trauma is TNF-α–dependent and limits the extent of neuronal death. Although less well studied than brain injury, spinal cord injury also appears to be restricted by this cellular response. In traumatic spinal cord injury in the rat, both NF-κB and the inducible form of nitric oxide synthase are activated in microglia and neurons within and surrounding the injury site (27).

NF-κB in chronic neurodegenerative disorders

Alzheimer's disease. Studies of postmortem brain tissue from patients with Alzheimer's disease (AD) have revealed increased NF-κB activity in cells involved in the neurodegenerative process. p65 immunoreactivity increases in neurons and astrocytes in the immediate vicinity of amyloid plaques in brain sections from AD patients, consistent with NF-κB activation in those cells (2). Other studies have shown that amyloid β-peptide (Aβ) can activate NF-κB in cultured neurons (28), suggesting a molecular mechanism by which amyloid may act during AD pathogenesis. This activation of NF-κB may be neuroprotective, since TNF-α can protect neurons against Aβ-induced death via an NF-κB–mediated mechanism. More recent studies have demonstrated a strong correlation between increased NF-κB activity and cyclooxygenase-2 transcription in superior temporal lobe gyrus of AD patients (29). In addition, immunohistochemical studies suggest that levels of NF-κB activity are increased in cholinergic neurons in the basal forebrains of AD patients (30); dysfunction and degeneration of cholinergic neurons is believed to contribute greatly to cognitive impairment in AD.

Further insight into the pathogenesis of AD comes from study of the α-secretase–derived form of secreted amyloid precursor protein (sAPPα), which is potently excitoprotective and antiapoptotic in central nervous system neurons. As the result of aberrant proteolytic processing of βAPP, levels of sAPPα may be decreased. NF-κB activation following exposure to sAPPα is correlated with increased resistance to metabolic and excitotoxic insults (6). By activating NF-κB, sAPPα can counteract the proapoptotic actions of mutations in the *Presenilin-1* gene, mutations that are causally linked to early-onset inherited forms of AD (31). Interestingly, cells expressing mutant presenilin-1 exhibit an aberrant pattern of NF-κB activation following exposure to oxidative insults. In these cells, early activation of this pathway is enhanced, followed by a prolonged depression of NF-κB activity (31). Pretreatment of cells expressing mutant presenilin-1 with sAPPα restores the normal pattern of activation of NF-κB and prevents cell death following exposure to apoptotic insults.

Interestingly, the enhancer region 5′ to the gene encoding βAPP contains κB-binding sites, raising the possibility that NF-κB activation in neurons under stress leads to increased βAPP production.

Based upon these in vivo and cell culture data, it seems likely that activation of NF-κB in neurons associated with amyloid deposits is a cytoprotective response. Indeed, treatment of neurons with κB decoy DNA increases their vulnerability to oxidative insults including exposure to Aβ. On the other hand, the increased levels of membrane lipid peroxidation that occur in neurons degenerating in AD may endanger neurons by suppressing NF-κB activation. For instance, the lipid peroxidation product 4-hydroxynonenal, which may mediate oxidative stress–induced neuronal apoptosis in AD and related disorders, strongly inhibits NF-κB activation (32). Moreover, prostate apoptosis response-4 (Par-4), a proapoptotic protein implicated in the pathogenesis of neuronal degeneration in AD, strongly suppresses NF-κB activation in cultured neural cells. Modulation of NF-κB by Aβ might also contribute to glial cell activation in AD, as suggested by studies showing that Aβ induces NF-κB activation and nitric oxide production in astrocytes.

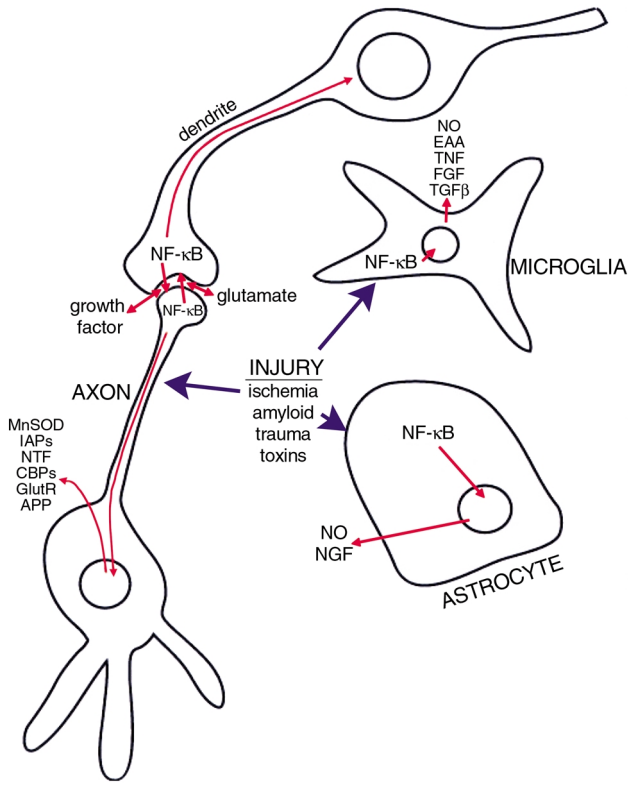

Figure 3
Complex roles for NF-κB in integrating signaling between and within neurons and glial cells. Following brain injury, NF-κB is activated in neurons and glial cells (astrocytes and microglia). Activation of NF-κB in neurons induces production of antiapoptotic gene products and proteins involved in modulating synaptic plasticity. Activation of NF-κB in glial cells results in production of proinflammatory cytokines, and potentially neurotoxic reactive oxygen species and excitotoxins. APP, amyloid precursor protein; CBPs, calcium-binding proteins; EAA, excitatory amino acid; GlutR, glutamate receptors; IAP, inhibitor-of-apoptosis proteins; NO, nitric oxide; NTF, neurotrophic factor.

Other chronic neurodegenerative disorders. Three prominent neurodegenerative disorders that affect brain and/or spinal cord regions that control body movements are Parkinson's and Huntington's diseases and amyotrophic lateral sclerosis (ALS). In Parkinson's disease, dopamine-producing neurons in the substantia nigra are selectively destroyed; in Huntington's disease, neurons in the striatum (caudate and putamen) degenerate; and in ALS, spinal cord motor neurons (and to a lesser extent upper motor neurons in the cerebral cortex) degenerate. Patients with each disorder manifest severe motor dysfunction characterized by inability to initiate or control body movements. Immunohistochemical analyses of brain sections from Parkinson's patients revealed a 70-fold increase, relative to age-matched controls, in the proportion of dopaminergic neurons in the substantia nigra exhibiting nuclear p65 immunoreactivity (33). Spinal cords of patients with ALS show increased NF-κB activation in astrocytes associated with degenerating motor neurons (34). Increased levels of oxidative stress and mitochondrial dysfunction are implicated in the pathogenesis of Parkinson's disease and ALS. The increased NF-κB activity in the affected neurons may therefore represent an early protective response to ongoing oxidative stress and mitochondrial dysfunction. Indeed, mice lacking the p50 subunit of NF-κB suffer increased damage to striatal neurons and enhanced motor dysfunction after administration of the mitochondrial toxin 3-nitropropionic acid (35). In response to this treatment, NF-κB activity and Mn-SOD levels increase in striatal cells of wild-type, but not p50-defecient, mice. Thus, NF-κB activation serves a neuroprotective function in this animal model of Huntington's disease.

A final example of evidence supporting a role for NF-κB in chronic neurological disorders comes from studies of multiple sclerosis. Analyses of neural tissue from patients with multiple sclerosis indicate that NF-κB is activated at high levels in microglia of active plaques; Bonetti and colleagues (36) have hypothesized that this increased NF-κB activity accounts for the paucity of oligodendrocyte apoptosis in multiple sclerosis. In support of this hypothesis, exposure of cultured oligodendrocytes to hydrogen peroxide results in NF-κB activation, and treatment of oligodendrocytes with pharmacological agents that enhance NF-κB activation can prevent cell death.

Implications for therapeutic intervention

The emerging data described above suggest that NF-κB plays important roles in cellular responses to injury of

the nervous system in both acute and chronic neurodegenerative conditions. Proteins involved in NF-κB signaling are therefore potentially important targets for therapeutic intervention in an array of neurological disorders. In general it appears that activation of NF-κB in neurons protects them against degeneration, whereas activation of NF-κB in microglia promotes neuronal degeneration.

One approach to activating NF-κB in neurons therapeutically is to administer neurotrophic factors or cytokines that act primarily on these cells, and work in models of neurodegenerative disorders suggests several candidate molecules, including sAPPα and ADNF. Another interesting approach to neuroprotection that may involve NF-κB activity is neuronal preconditioning. Maintenance of rats and mice on a dietary restriction regimen results in increased resistance of neurons to various oxidative, metabolic, and excitotoxic insults in experimental models relevant to Alzheimer's, Parkinson's, and Huntington's diseases and stroke (see supplementary references at www.jci.org/cgi/content/full/107/3/247/DC1). The latter studies have shown that the neuroprotective effect of dietary restriction involves induction of a mild stress response that results in increased production of heat-shock proteins. The beneficial effects of dietary restriction can be mimicked by administration of 2-deoxy-D-glucose, a nonmetabolizable glucose analog that induces a metabolic stress (see supplementary references). NF-κB is responsive to both dietary restriction and 2-deoxy-D-glucose administration, consistent with a role in the neuroprotective response.

Drugs that inhibit NF-κB are being developed for treating cancers and are beginning to be tested for efficacy in animal models of neurodegenerative conditions, such as stroke, where glial activation and inflammation may play a major role in the disease process. These agents include proteosome inhibitors, which inhibit NF-κB activation by preventing degradation of IκB, and peptide and oligonucleotide inhibitors that block DNA-binding activity. Use of such agents in neurodegenerative disorders is complicated by the possibility that inhibition of NF-κB in neurons may exacerbate the neurodegenerative process, and by the considerable data suggesting that NF-κB plays critical roles in processes such as learning and memory that may be compromised by inhibitors of NF-κB.

Note. Due to space constraints, a number of important references could not be included below. Interested readers can find a supplementary reading list at www.jci.org/cgi/content/full/107/3/247/DC1.

1. Baeuerle, P., and Baltimore, D. 1996. NF-κB: ten years after. *Cell.* **87**:13–20.
2. O'Neill, L.A., and Kaltschmidt, C. 1997. NF-kappa B: a crucial transcription factor for glial and neuronal cell function. *Trends Neurosci.* **20**:252–258.
3. Moerman, A.M., Mao, X., Lucas, M.M., and Barger, S.W. 1999. Characterization of a neuronal κB-binding factor distinct from NF-κB. *Brain Res. Mol. Brain Res.* **67**:303–315.
4. Bruce, A.J., et al. 1996. Altered neuronal and microglial responses to brain injury in mice lacking TNF receptors. *Nat. Med.* **2**:788–794.
5. Carter, B.D., et al. 1996. Selective activation of NF-κB by nerve growth factor through the neurotrophin receptor p75. *Science.* **272**:542–545.
6. Barger, S.W., and Mattson, M.P. 1996. Induction of neuroprotective κB-dependent transcription by secreted forms of the Alzheimer's β-amyloid precursor. *Brain Res. Mol. Brain Res.* **40**:116–126.
7. Hoch, M., and Jackle, H. 1993. Transcriptional regulation and spatial patterning in Drosophila. *Curr. Opin. Genet. Dev.* **3**:566–573.
8. Schmidt-Ullrich, R., et al. 1996. NF-κB activity in transgenic mice: developmental regulation and tissue specificity. *Development.* **122**:2117–2128.
9. Bakalkin, G.Y., Yakovleva, T., and Terenius, L. 1993. NF-κB-like factors in the murine brain. Developmentally-regulated and tissue-specific expression. *Brain Res. Mol. Brain Res.* **20**:137–146.
10. Maggirwar, S.B., Sarmiere, P.D., Dewhurst, S., and Freeman, R.S. 1998. Nerve growth factor-dependent activation of NF-κB contributes to survival of sympathetic neurons. *J. Neurosci.* **18**:10356–10365.
11. Furukawa, K., Estus, S., Fu, W., and Mattson, M.P. 1997. Neuroprotective action of cycloheximide involves induction of Bcl-2 and antioxidant pathways. *J. Cell Biol.* **136**:1137–1150.
12. Meberg, P.J., Kinney, W.R., Valcourt, E.G., and Routtenberg, A. 1996. Gene expression of the transcription factor NF-κB in hippocampus: regulation by synaptic activity. *Brain Res. Mol. Brain Res.* **38**:179–190.
13. Worley, P.F., et al. 1993. Thresholds for synaptic activation of transcription factors in hippocampus: correlation with long-term enhancement. *J. Neurosci.* **13**:4776–4786.
14. Albensi, B.C., and Mattson, M.P. 2000. Evidence for the involvement TNF and NF-κB in hippocampal synaptic plasticity. *Synapse.* **35**:151–159.
15. Furukawa, K., and Mattson, M.P. 1998. The transcription factor NF-κB mediates increases in calcium currents and decreases in NMDA and AMPA/kainate-induced currents in response to TNFα in hippocampal neurons. *J. Neurochem.* **70**:1876–1886.
16. Glazner, G.W., Camandola, S., and Mattson, M.P. 2000. NF-κB mediates the cell survival-promoting action of an activity-dependent neurotrophic factor peptide. *J. Neurochem.* **75**:101–108.
17. Qin, Z.H., Wang, Y., Nakai, M., and Chase, T.N. 1998. Nuclear factor-κB contributes to excitotoxin-induced apoptosis in rat striatum. *Mol. Pharmacol.* **53**:33–42.
18. Laflamme, N., and Rivest, S. 1999. Effects of systemic immunogenic insults and circulating proinflammatory cytokines on the transcription of the inhibitory factor kappaB alpha within specific cellular populations of the rat brain. *J. Neurochem.* **73**:309–321.
19. Schwaninger, M., et al. 1999. Bradykinin induces interleukin-6 expression in astrocytes through activation of nuclear factor-κB. *J. Neurochem.* **73**:1461–1466.
20. Schneider, A., et al. 1999. NF-κB is activated and promotes cell death in focal cerebral ischemia. *Nat. Med.* **5**:554–559.
21. Cheng, B., Christakos, S., and Mattson, M.P. 1994. Tumor necrosis factors protect neurons against metabolic-excitotoxic insults and promote maintenance of calcium homeostasis. *Neuron.* **12**:139–153.
22. Yu, Z.F., Zhou, D., Bruce-Keller, A.J., Kindy, M.S., and Mattson, M.P. 1999. Lack of the p50 subunit of NF-κB increases the vulnerability of hippocampal neurons to excitotoxic injury. *J. Neurosci.* **19**:8856–8865.
23. Xu, D.G., et al. 1997. Elevation of neuronal expression of NAIP reduces ischemic damage in the rat hippocampus. *Nat. Med.* **3**:997–1004.
24. Gary, D.S., Christakos, S., and Mattson, M.P. 1999. Concentration- and cell type-specific effects of calbindin on vulnerability of hippocampal neurons to seizure-induced injury. *Brain Res. Mol. Brain Res.* **75**:89–95.
25. Nonaka, M., et al. 1999. Prolonged activation of NF-κB following traumatic brain injury in rats. *J. Neurotrauma.* **16**:1023–1034.
26. Sullivan, P.G., et al. 1999. Exacerbation of damage and altered NF-κB activation in mice lacking tumor necrosis factor receptors after traumatic brain injury. *J. Neurosci.* **19**:6248–6256.
27. Bethea, J.R., et al. 1998. Traumatic spinal cord injury induces nuclear factor-kappaB activation. *J. Neurosci.* **18**:3251–3260.
28. Barger, S.W., et al. 1995. Tumor necrosis factors α and β protect neu-

rons against amyloid β-peptide toxicity: evidence for involvement of a κB-binding factor and attenuation of peroxide and Ca^{2+} accumulation. *Proc. Natl. Acad. Sci. USA.* **92**:9328–9332.
29. Lukiw, W.J., and Bazan, N.G. 1998. Strong nuclear factor-κB-DNA binding parallels cyclooxygenase-2 gene transcription in aging and in sporadic Alzheimer's disease superior temporal lobe neocortex. *J. Neurosci. Res.* **53**:583–592.
30. Boissiere, F., et al. 1997. Nuclear translocation of NF-κB in cholinergic neurons of patients with Alzheimer's disease. *Neuroreport.* **8**:2849–2852.
31. Guo, Q., Robinson, N., and Mattson, M.P. 1998. Secreted APPα counteracts the pro-apoptotic action of mutant presenilin-1 by activation of NF-κB and stabilization of calcium homeostasis *J. Biol. Chem.* **273**:12341–12351.
32. Camandola, S., and Mattson, M.P. 2000. The lipid peroxidation product 4-hydroxy-2,3-nonenal inhibits constitutive and inducible activity of NF-κB in neurons. *Brain Res. Mol. Brain Res.* **85**:53–60.
33. Hunot, S., et al. 1997. Nuclear translocation of NF-κB is increased in dopaminergic neurons of patients with Parkinson disease. *Proc. Natl. Acad. Sci. USA.* **94**:7531–7536.
34. Migheli, A., Piva, R., Atzori, C., Troost, D., and Schiffer, D. 1997. c-Jun, JNK/SAPK kinases and transcription factor NF-κB are selectively activated in astrocytes, but not motor neurons, in amyotrophic lateral sclerosis. *J. Neuropathol. Exp. Neurol.* **56**:1314–1322.
35. Yu, Z.F., Zhou, D., Cheng, G., and Mattson, M.P. 2000. Neuroprotective role for the p50 subunit of NF-κB in a mouse model of Huntington's disease. *J. Mol. Neurosci.* **15**:31–44.
36. Bonetti, B., et al. 1999. Activation of NF-κB and c-jun transcription factors in multiple sclerosis lesions. Implications for oligodendrocyte pathology. *Am. J. Pathol.* **155**:1433–1438.