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NF-κB in the Survival and Plasticity of Neurons

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The transcription factor nuclear factor kappa-B (NF-κB) is involved in regulating responses of neurons to activation of several different signaling pathways in a variety of physiological and pathological settings. During development of the nervous system NF-κB is activated in growing neurons by neurotrophic factors and can induce the expression of genes involved in cell differentiation and survival. In the mature nervous system NF-κB is activated in synapses in response to excitatory synaptic transmission and may play a pivotal role in processes such as learning and memory. NF-κB is activated in neurons and glial cells in acute neurodegenerative conditions such as stroke and traumatic injury, as well as in chronic neurodegenerative conditions such as Alzheimer's disease. Activation of NF-κB in neurons can promote their survival by inducing the expression of genes encoding anti-apoptotic proteins such as Bcl-2 and the antioxidant enzyme Mn-superoxide dismutase. On the other hand, by inducing the production and release of inflammatory cytokines, reactive oxygen molecules and excitotoxins, activation of NF-κB in microglia and astrocytes may contribute to neuronal degeneration. Emerging findings suggest roles for NF-κB as a mediator of effects of behavioral and dietary factors on neuronal plasticity. NF-κB provides an attractive target for the development of novel therapeutic approaches for a range of neurological disorders.

KEY WORDS: Antioxidant; apoptosis; bcl-2; calcium; learning and memory; mitochondria; transcription.

UPSTREAM AND DOWNSTREAM OF NF-κB IN NEURONS

Nuclear factor kappa-B (NF-κB) is a transcription factor consisting of NF-κB DNA-binding dimers, and the proteins that modulate the activation and function of NF-κB (1,2). The most common subunits expressed in neurons are p50 p65 (transcription factor subunits), and IκBα (inhibitory subunit) (3–6). In addition, novel and developmentally regulated NF-κB subunits may be expressed in the nervous system, including a recently described neuronal κB factor and Sp1 proteins (7,8). Ligands that activate signal transduction pathways coupled to NF-κB activation in neurons include tumor necrosis factor-α (TNF) (9), Fas ligand (10), glutamate (4), nerve growth factor (NGF; 11,12), activity-dependent neurotrophic factor (ADNF; 13), cell adhesion molecules (14) and a secreted form of amyloid precursor protein (15). In addition, electrical activity within neurons and synaptic transmission between neurons are potent stimuli for NF-κB activation and may account for the relatively high constitutive activity of NF-κB in neurons compared to non-excitable cells (4,16). In most cases the mechanism of NF-κB activation involves IκB phosphorylation by IκB kinase (IKK), a kinase that consists of two catalytic subunits (IKKα and IKKβ) and a regulatory subunit called IKKγ (17,18). Kinases upstream of IKK may include mitogen-activated protein (MAP) kinase kinase kinase-1 (19) protein kinase C (20),

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calcium/calmodulin-dependent kinase II (21) and Akt (21,22).

There are numerous genes in neurons whose expression is regulated by NF-κB. Among these are genes that encode proteins involved in: (1) Cell survival including Bcl-2, Mn-SOD and inhibitor of apoptosis proteins (IAPs) (23–25). (2) Cell death including Bcl-x(S) and Bax (26). (3) Regulation of ion homeostasis including subunits of *N*-methyl-D-aspartate receptors and voltage-dependent calcium channels, and the calcium-binding protein calbindin (27,28). Of course neurons are surrounded by glial cells including astrocytes, microglia and (in white matter) oligodendrocytes. These glial cells employ NF-κB as a mediator of transcriptional responses to a variety of stimuli including tissue injury and disease conditions (29). Examples of genes activated by NF-κB in glial cells include those encoding pro-inflammatory cytokines such as TNF and interleukin-1beta, inducible nitric oxide synthase and the cell adhesion molecule ICAM-1 (19,30). Such glia-derived NF-κB-regulated factors are likely to play important modulatory roles in neuronal plasticity and survival in physiological and pathological settings. (Fig. 1).

NF-κB IN NEURONAL PLASTICITY

Many of the signal transduction pathways that activate NF-κB, as well as the genes regulated by NF-κB are known to play important roles in plasticity of neurons during development and in the adult nervous system. Growth factors that activate receptors coupled to NF-κB activation include NGF, brain-derived neurotrophic factor (BDNF), TGFbeta and Notch ligands (11,31–33). Glutamate is a neurotransmitter and regulator of developmental and adult neuroplasticity that activates receptors that can stimulate (4,16,34), or in some cases inhibit (35) NF-κB activity. Genes involved in developmental and synaptic plasticity that are known to be regulated by NF-κB include those encoding glutamate receptor subunits, BDNF and calcium-regulating proteins (29,31). (Fig. 2).

A major role for NF-κB in development is suggested by data showing that the *Drosophila* NF-κB homolog "dorsal" is required for establishment of dorso-ventral polarity in the developing embryo (36). Studies of κB reporter mice revealed that levels of NF-κB activity change dramatically during embryonic and early postnatal development of the nervous system (37). NF-κB transcriptional activity becomes evident in neurons as axons and dendrites grow and synapses are formed, and remains high under basal conditions in neurons in most regions of the adult brain. Evidence that NF-κB plays a role in regulating neurite outgrowth comes from a study showing that NF-κB mediates stimulation of neurite outgrowth in PC12 cells in response to the Fas apoptosis inhibitory molecule (FAIM) (38). A novel guanine nucleotide exchange factor, GEFT, is expressed at high levels in neurons in the hippocampus and cerebellum. Overexpression of GEFT promotes dendrite outgrowth and dendritic spine formation, which was associated with upregulation of NF-κB (39). The latter findings suggest a role for NF-κB in the effects of signaling via GTPase-regulated pathways in the control of dendritic plasticity. NF-κB components expressed in neurons are developmentally regulated such that inducible p50 homodimers and p65/cRel dimers are present in brains of immature rats, but not adult rats (40). Neurons exhibit a constitutive level of NF-κB

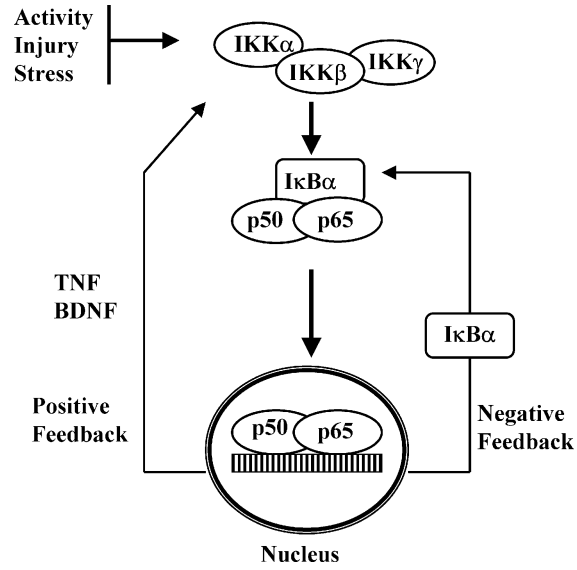

Fig. 1. The transcription factor NF-κB and its regulatory mechanisms. The inactive cytoplasmic NF-κB complex consists of the transcription factor dimer (typically p50 and p65) bound to the inhibitory subunit IκBα. NF-κB is activated when the cell is stimulated by specific signals such as activation of receptors for excitatory neurotransmitters, cytokines and cell adhesion molecules or by less specific stimuli such as oxidative stress. In most cases the stimulus results in the activation of the IKK (IkB kinase) complex which consists of IKKα and IKKβ plus the regulatory subunit IKKγ. Activated IKKβ phosphorylates IκBα resulting in degradation of IκBα by the proteasome. Degradation of IκBα results in the translocation of the p65-p50 dimer to the nucleus where it binds to the regulatory elements of certain genes thereby inducing (or in some cases repressing) their transcription. Some genes induced by NF-κB encode proteins that further activate NF-κB (TNF and BDNF, for example). Other gene targets may negatively regulate NF-κB; for example, NF-κB induces the expression of IκBα.

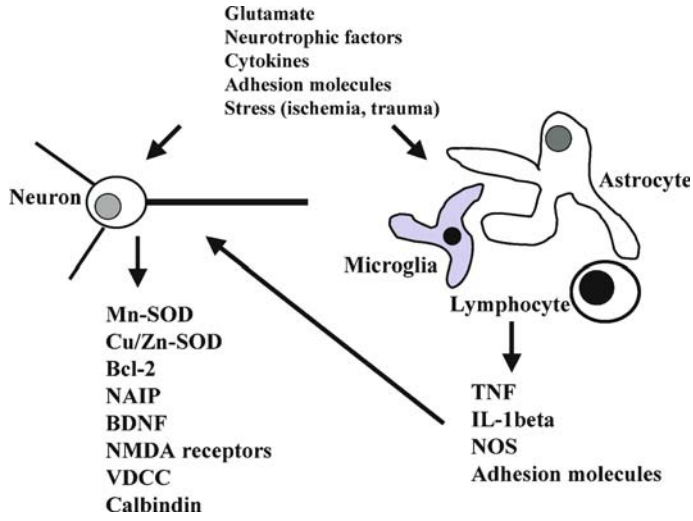

Fig. 2. Roles of NF-κB in neuronal survival and plasticity. Signals that activate NF-κB in neurons can promote cell survival and synaptic plasticity by inducing the expression of genes encoding antioxidant enzymes, anti-apoptotic proteins, neurotrophic factors, NMDA receptors and calcium-regulating proteins. On the other hand, activation of NF-κB in glial cells and lymphocytes can induce the expression of genes that encode neurotoxic agents including pro-inflammatory cytokines and reactive oxygen species. BDNF, brain derived neurotrophic factor; NAIP, neuronal apoptosis inhibitory protein; NMDA, *N*-methyl-D-aspartate; NOS, nitric oxide synthase; SOD, superoxide dismutase; TNF, tumor necrosis factor; VDCC, voltage-dependent calcium channel.

activity that far exceeds other cell types in the body. Contributing to this basal level of NF-κB activity is activation is excitatory synaptic activity, particularly ionotropic NMDA and AMPA receptors (41).

Increasing evidence suggests major roles for NF-κB in synaptic plasticity. NF-κB is present in synaptic terminals and can be activated locally at those sites in response to synaptic transmission (42,43). Calcium influx into pre-synaptic terminals and post-synaptic dendrites may be one signal that activates NF-κB during synaptic transmission (4). NF-κB may be a transcription factor pivotal for learning and memory. NF-κB is activated in association with long-term potentiation of synaptic transmission (LTP), a process believed to be a cellular mechanism of learning and memory (43). NF-κB may also be involved in more subtle forms of synaptic plasticity because, in contrast to several other transcription factors involved in LTP, NF-κB is activated in response to low frequency stimulation (44).

A pivotal role for NF-κB in synaptic plasticity is suggested by data from studies in which blockade of NF-κB activation impairs synaptic plasticity. Recordings of synaptic transmission in hippocampal slices from mice lacking TNF 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) (45). Stimulation of the axons of CA3 pyramidal neurons, which synapse on 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. When slices from wild-type mice are pretreated with κB decoy DNA, LTD cannot be induced and the amplitude of LTP is significantly decreased. More recently, it was reported that p50 knockout mice exhibit impaired learning ability (46). Moreover, in mice basal synaptic input activates NF-κB in synapses by a pathway requiring calcium influx and CaMKII and local submembranous calcium elevation, and mice lacking p65 show a selective spatial learning deficit indicating a pivotal role for NF-κB in learning and memory (47). In cultured mouse cerebellar granule cells glutamate stimulates the activation of NF-κB by a mechanism involving calcium influx and activation of the calcium-dependent protease calpain (48). The latter findings are consistent with roles for NF-κB in modulating different processes regulated by calpain including synaptic plasticity. Additional support for a role for NF-κB in synaptic plasticity associated with learning and memory comes from a study of mice in which *in vivo* stimulation of the hippocampus at high frequency resulted in increased NF-κB nuclear translocation and DNA-binding activity in hippocampal neurons (49). No such NF-κB activation was seen in the

hippocampal neurons of mice stimulated at a low frequency.

The expression of genes involved in developmental and synaptic plasticity is regulated by NF-κB, including those encoding neurotrophic factors, neurotransmitter receptors and calcium-regulating proteins. BDNF is a neurotrophic factor critical for learning and memory, and the underlying biochemical changes that occur in synapses (50). BDNF expression is induced by NF-κB, and it has been proposed that NF-κB is an important transcription factor that mediates upregulation of BDNF expression in response to synaptic activity (31). Mao et al. (8) identified novel kappa B-binding factors as Sp1-related proteins. The activity of the Sp1-related factor was reduced by stimulation of ionotropic glutamate receptors and, in turn, negatively regulate the expression of the NR1 subunit of NMDA receptors. Calcium is arguably the most important signal regulating both pre- and post-synaptic biochemical events involved in synaptic plasticity, and NF-κB can modulate neuronal calcium homeostasis (28). Finally, there is reason to believe that NF-κB plays roles in adult neurogenesis. For example NR1 is upregulated in response to NF-κB activation during neurogenesis (51).

In addition to its apparent roles in synaptic plasticity associated with learning and memory, NF-kB is involved in regulating other behaviors. Mice lacking p50−/− exhibit reduced anxiety-like behaviors when subjected to novel environments and in tests of social anxiety (52). On the other hand, p50−/− mice performed normally in tests of sensorimotor function and daily activity on a circadian rhythm. These findings suggest roles for NF-κB in emotional behaviors.

NF-κB AND NEURONAL SURVIVAL

Because NF-κB activation is critical to the cell survival-promoting effects of several different neurotrophic factors and cytokines, it follows that NF-κB activity is reduced under conditions of trophic factor deprivation. Kovacs et al. (53) have indeed found this to be true. They found that trophic factor deprivation results in a rapid and sustained increase in the level of IκB-alpha and IκB-beta in cultured cerebellar granule neurons resulting in sustained inhibition of NF-κB. A peptide inhibitor of NF-κB (SN50), blocked the ability of NGF to prevent death of cultured sympathetic neurons (12), suggesting a role for NF-κB in the control of neuronal death during development of the nervous system. Inhibition of NF-κB can induce apoptosis in cultured PC12 cells and NGF is not capable of preventing cell death so induced (54). Consistent with an anti-apoptotic role for NF-κB in developing neurons are the results of studies of the mechanism whereby the protein synthesis inhibitor cycloheximide prevents neuronal apoptosis. Low concentrations of cycloheximide that cause only a small impairment of protein synthesis can prevent apoptosis by a mechanism involving induction of Bcl-2 and the mitochondrial antioxidant enzyme Mn-SOD (55). NF-κB activity increases in response to cycloheximide, and treatment of neurons with κB decoy DNA abolishes the anti-apoptotic effect of cycloheximide, demonstrating a requirement for NF-κB activation. Cytoplasmic Cu/Zn-SOD is also upregulated in PC12 cells in response to activation of the PI3 kinase–Akt pathway; NF-κB may be the transcription factor activated by Akt that stimulates expression of Cu/Zn-SOD (22). The latter pathway may mediate the cell survival-promoting effects of NGF and other growth factors that activate receptors coupled to PI3 kinase.

Another cytokine that can prevent neuronal apoptosis via an NF-κB-mediated mechanism is transforming growth factor-beta1 (TGF-beta1). In cultured hippocampal neurons TGF-beta1 increased NF-κB transcriptional activity by a signaling pathway involving PI3 kinase and extracellular signal regulated kinases (33). The ability of TGF-beta1 to prevent neuronal apoptosis was blocked by NF-κB decoy DNA demonstrating a pivotal role for NF-κB.

The roles of NF-κB in neuronal survival are complex. Initial studies demonstrated that cultured hippocampal neurons pretreated with TNF exhibit increased cell survival when subjected to metabolic, oxidative and excitotoxic insults (27,9). Studies of TNF receptor-deficient mice provided evidence that signaling by endogenous TNF plays a role in neuronal survival *in vivo* (56). Mice lacking the p50 subunit of NF-κB exhibited increased neurotoxin induced damage to neuronal cells compared to wild-type mice (6), but decreased damage following a focal ischemic stroke (57). In addition, TNF-overexpressing mice are more resistant to glutamate-induced apoptosis than are neurons from non-transgenic control mice (58). NF-κB plays a pivotal role in the neuron survival-promoting action of TNF (59). Both the p55 (TNFR1) and p75 (TNFR2) TNF receptors are coupled to activation of NF-κB, and data suggest that either one or both types of TNF receptor can activate cell survival signaling through NF-κB. For example, studies of excitotoxic and ischemic neuronal

death in mice lacking one or both TNF receptors suggested a key role for TNFR1 in neuroprotection (60). However, other investigators provided evidence that the neuroprotective action of TNF is mediated by TNFR2 activation which is coupled to PI3 kinase, Akt and NF-κB (58). Activation of TNFR1 resulted in only transient activation of NF-κB whereas TNFR2 induced persistent NF-κB activity that was essential for neuronal survival. These findings demonstrate that the duration of NF-κB activation is a critical determinant of its ability to prevent cell death. Several studies have concluded that NF-κB activition in neurons can kill them. However, these conclusions were reached based on "guilt by association" rather than data establishing a cause-effect action of NF-κB (61). Other studies employed non-specific inhibitors of NF-κB such as aspirin, the SN50 peptide and the proteasome inhibitor PDTC (62,63,57).

Although TNF may act directly on neurons to promote their survival, activation of TNF receptors in glial cells (microglia and astrocytes) may indirectly lead to neuronal death. In response to either acute insults (ischemic event, trauma or seizures) or chronic neurodegenerative processes, microglia, macrophages and astrocytes can produce large amounts of pro-inflammatory cytokines, reactive oxygen species and excitotoxins. NF-κB is a major inducer of pro-inflammatory cytokines in glial cells, and two prominent signals for NF-κB in these cells are TNF (64) and ligands of Toll-like receptors (65). Several such glia-derived cytokines can be cytotoxic towards neurons including interleukin-1beta (66) and Fas ligand (67). In addition, NF-κB can induce nitric oxide synthase in glial cells resulting in the production of nitric oxide and related neurotoxic reactive oxygen species (68,69). Recently, a study addressed the role of nitric oxide production specifically in microglia/macrophages in excitotoxic neuronal injury *in vivo* (70). Irradiated wild-type mice were transplanted with bone marrow from mice lacking inducible nitric oxide synthase. The transplanted mice therefore contained microglia and macrophages incapable of producing nitric oxide. The vulnerability of hippocampal neurons to seizure-induced damage was significantly reduced in the transplanted mice compared to untransplanted mice and to wild-type mice transplanted with bone marrow from wild-type mice (70). Such glia-mediated neurotoxicity likely explains, at least in part, reports of decreased ischemic neuronal damage in mice in which NF-κB activity is reduced (71).

Based upon the kinds of findings just described, I have come to the conclusion that activation of NF-κB in neurons promotes their survival, whereas activation of NF-κB in glial cells may promote neuronal death by inducing neurotoxin production.

NF-κB AND NEURODEGENERATIVE CONDITIONS

NF-κB is activated in neurons and glial cells in a range of acute and chronic neurodegenerative conditions. Analyses of brain and spinal cord tissues in rodent models of stroke, epilepsy and traumatic injury suggest complex functions of NF-κB in modifying neuronal survival and recovery from injury. NF-κB influences the neurodegenerative process by directly affecting gene expression in neurons themselves and by indirectly by regulating gene expression in glial cells.

NF-κB is activated in neurons and glial cells in rodent models of stroke. For example, NF-κB is activated in CA1 hippocampal neurons following transient global forebrain ischemia in rats (61), and a delayed increase in NF-κB activation occurs a few days after focal ischemia-reperfusion in association with reactive glial cells in rats (72). Cell culture studies have shown that activation of NF-κB in neurons protects them against excitotoxic and metabolic insults relevant to the pathogenesis of stroke and traumatic injury including glucose deprivation and exposure to glutamate (27,9). The vulnerability of cortical and striatal neurons to focal ischemic injury is increased in mice lacking TNFα receptors, which is associated with decreased activation of the κB-responsive Mn-SOD gene (56,60). In addition, expression of an unresponsive mutant form of IκB in cultured hippocampal neurons increases their vulnerability to hypoxia-induced death, which was associated with decreased production of the anti-apoptotic proteins Bcl-2 and Bcl-x (24). Moreover, levels of a NF-κB-responsive IAP called NAIP increase in neurons resistant to ischemic brain injury, and overexpression of NAIP increases resistance of neurons to ischemic injury *in vivo* (73) consistent with a neuroprotective function of NF-κB.

DNA damage is increasingly implicated in the neuronal deaths that occur in several different disorders including Alzheimer's, Parkinson's and Huntington's diseases and stroke (74). Moreover, DNA damage responses may be an essential part of the apoptosis of neurons that occurs during development of the nervous system (75,76). NF-κB is activated in response to DNA damage and may contribute to the cell death process by inducing the expression of p53

(77). Exposure of cultured neurons to DNA damaging compounds resulted in a decrease in NF-κB activity and activation of p53, and pharmacological blockade of p53 resulted in a preservation of NF-κB activity and protected neurons against apoptosis (78). Similar results were observed after oxygen glucose deprivation in cultured neurons and in ischemic brain tissue. Additional findings in the latter study showed that lethal stress activates p53 and disrupts NF-κB binding to p300, thereby blocking NF-κB-mediated cell survival signaling.

The rapid increase in NF-κB activity in hippocampal neurons in response to kainate-induced seizures (within 4 h) is consistent with a neuroprotective role for this transcription factor; in contrast, NF-κB activation in glial cells is more delayed and may play a role in delayed glia-mediated neurotoxicity (79,80). The ability of intraventricular infusion of κB decoy DNA to exacerbate seizure-induced death of hippocampal neurons provides further evidence for an excitoprotective action of NF-κB, as does the increased hippocampal damage in mice lacking the p50 subunit of NF-κB (6). In addition, targeted inhibition of NF-κB in forebrain neurons, accomplished using a calcium-calmodulin-dependent kinase IIalpha promoter-driven tetracyclin transactivator, resulted in increased vulnerability of the neurons to death induced by neurotoxic insults (81). Consistent with roles for NF-κB in neuroprotection and synaptic plasticity (46) it was reported that hippocampal granule neurons in p50 knockout mice are more vulnerable to death induced by trimethyltin.

Levels of NF-κB activity were increased in cerebral cortex within 24 h of traumatic brain injury in rats and remained elevated for several days (82). Levels of p65 immunoreactivity were increased in axons within hours after traumatic brain injury, and subsequently increased in neuronal cell bodies (83). In the same brain sections levels of p65 were increased in microglia and astrocytes in the injured cortex and this increase persisted for many months, particularly in the margins of the progressively enlarging ventricle, suggesting a role for NF-κB in a prolonged inflammatory process. In a controlled cortical impact model of traumatic brain injury damage to cortical neurons, and blood–brain barrier breach, were exacerbated in mice lacking TNFα receptors (84). The latter study showed that injury-induced NF-κB activation was attenuated, and Mn-SOD production decreased in the TNFα receptor knockout mice. Neuronal damage following traumatic brain injury was decreased in transgenic mice overexpressing Mn-SOD. These findings suggest a role for injury-induced, TNFα-mediated, production of Mn-SOD in limiting the extent of neuronal death. Although less well studied than brain injury, data also suggest important roles for NF-κB in cellular responses to spinal cord injury. NF-κB activation is increased in microglia and neurons within and surrounding the injury site after traumatic spinal cord injury in the rat, which is associated with increased expression of the inducible form of nitric oxide synthase (85).

Dysregulation of cellular calcium homeostasis resulting in a prolonged elevation of intracellular calcium levels plays an important role in ischemic and traumatic neuronal death. Several gene targets of NF-κB in neurons encode proteins that can stabilize intracellular calcium levels including calcium-binding proteins and glutamate receptor subunits. Levels of the neuroprotective calcium-binding protein calbindin D28k (86,87) are increased in embryonic hippocampal neurons following treatment with TNF (27). Activation of NF-κB can also decrease glutamate-induced currents and calcium influx (28).

Neurodegenerative disorders of aging involve alterations in NF-κB activity in cells associated with the neurodegenerative process. For example, levels of p65 immunoreactivity are increased in neurons and astrocytes in the immediate vicinity of amyloid plaques in brain sections from Alzheimer's patients consistent with NF-κB activation in those cells (88). In addition, Aβ and a secreted form of APP can induce NF-κB activation in cultured neurons (15,89) suggesting a role for proteolytic products of APP in NF-κB activation in Alzheimer's disease brain cells. In addition there is a strong correlation between increased NF-κB activity and cyclooxygenase-2 gene transcription in superior temporal lobe gyrus of Alzheimer's patients (90) and levels of NF-κB activity are increased in cholinergic neurons in the basal forebrain of Alzheimer's patients (91). Activation of NF-κB in neurons in Alzheimer's disease may be a neuroprotective defense response because activation of NF-κB can protect neurons against the toxicity of Aβ(9). However, although its activation increases, oxidative stress in aging and Alzheimer's may impair the ability of NF-κB to induce gene expression (92).

Mutations in the presenilin-1 gene that cause early-onset familial Alzheimer's disease cause a perturbation in NF-κB regulation in neurons such that its activity is rapidly downregulated following exposure to oxidative insults (89). Mutant presenilin-1 causes an aberrant pattern of NF-κB activation

following exposure to apoptotic insults characterized by enhanced early activation with a subsequent prolonged depression of NF-κB activity. Consistent with the latter findings another study showed that NF-κB activation in response to exposure to trimethyltin is impaired in PS1 mutant mice (93). An additional role for NF-κB in Alzheimer's disease is suggested by studies showing that the enhancer region 5′ to the gene encoding the β-amyloid precursor protein contains NF-κB binding sites (34), suggesting a scenario in which NF-κB activation in neurons under stress leads to increased amyloid production.

Based upon the data described above suggesting that NF-κB promotes neuron survival in various *in vivo* and cell culture paradigms of neuronal injury, activation of NF-κB in neurons associated with amyloid deposits may be a cytoprotective response. In support of this, neurons with NF-κB decoy DNA increases their vulnerability to oxidative insults including exposure to Aβ (59). Other forces may impair NF-κB in Alzheimer's disease. For example, increased levels of membrane lipid peroxidation that occur in neurons in Alzheimer's disease can inhibit NF-κB activity (94). Exposure of PC12 cells to arachidonic acid (AA) results in suppression of NF-κB activity and apoptosis that cannot be prevented by NGF (95). The mechanism whereby AA inhibits NF-κB activity is not known, but could involve generation of 4-hydroxynonenal. In addition, the pro-apoptotic protein prostate-apoptosis response-4 (Par-4), which may play a role in Alzheimer's disease (96), suppresses NF-κB activity in neurons (25). On the other hand, activation of NF-κB by Aβ and other APP products might contribute to glial cell activation and inflammatory processes in Alzheimer's disease (97,68).

Parkinson's and Huntington's diseases are age-related movement disorders that involve degeneration of dopamine-producing neurons in the substantia nigra and medium spiny neurons in the striatum, respectively. It was reported that there is a 70-fold increase in the percentage of dopaminergic neurons in the substantia nigra that exhibit p65 immunoreactivity in their nuclei in Parkinson's disease patients compared to age-matched control patients (98). Increased levels of oxidative stress and mitochondrial dysfunction are implicated in the pathogenesis of both Parkinson's (99) and Huntington's (100) diseases. NF-κB activity is increased in affected cells in the substantia nigra and striatum which could represent an early protective response to ongoing oxidative stress and mitochondrial dysfunction known to occur in Parkinson's and Huntington's diseases (99,100). Consistent with this in an inhibitor of NF-κB increases the vulnerability of dopaminergic cells to the Parkinsonian neurotoxin 6-hydroxydopamine (101). In addition, mice lacking the p50 subunit of NF-κB exhibit increased damage to striatal neurons and worsened motor dysfunction after administration of the mitochondrial toxin 3-nitropropionic acid (102). NF-κB activity and levels of Mn-SOD were increased in response to 3-nitropropionic acid administration in striatal cells of wild-type mice, but not in striatal cells of mice lacking p50.

CONCLUSIONS

NF-κB is a transcription factor expressed in all cell types in the nervous system. It can be activated by many different physiological stimuli including neurotransmitters, neurotrophic factors, cell adhesion molecules and various types of cell stress. The association of NF-κB activity with processes such as synaptic plasticity and neurogenesis suggest important roles for gene targets of NF-κB in regulating these processes. Considerable evidence suggests complex roles for NF-κB in neurodegenerative conditions. On the one hand, its activation in neurons promotes their survival and plasticity. On the other hand its activation in glial cells may play a major role in inflammatory processes that can damage and kill neurons. A better understanding of the gene targets of NF-κB and their roles in health and disease may lead to novel approaches for preventing and treating various neurological disorders.

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