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Review

Roles for NF-κB in nerve cell survival, plasticity, and disease

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Abstract

Here we review evidence of roles for NF-κB in the regulation of developmental and synaptic plasticity, and cell survival in physiological and pathological settings. Signaling pathways modulating NF-κB activity include those engaged by neurotrophic factors, neurotransmitters, electrical activity, cytokines, and oxidative stress. Emerging findings support a pivotal role for NF-κB as a mediator of transcription-dependent enduring changes in the structure and function of neuronal circuits. Distinct subunits of NF-κB may uniquely affect cognition and behavior by regulating specific target genes. NF-κB activation can prevent the death of neurons by inducing the production of antiapoptotic proteins such as Bcl-2, IAPs and manganese superoxide dismutase (Mn-SOD). Recent findings indicate that NF-κB plays important roles in disorders such as epilepsy, stroke, Alzheimer's and Parkinson's diseases, as well as oncogenesis. Molecular pathways upstream and downstream of NF-κB in neurons are being elucidated and may provide novel targets for therapeutic intervention in various neurological disorders.
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Abbreviations: IKK, IκB kinase complex; NGF, nerve growth factor; TNF, tumor necrosis factor; MAP, mitogen-activated protein; ADNF, activity-dependent neurotrophic factor; IAPs, inhibitor of apoptosis proteins

The Basics

Activation of NF-κB in neurons

Seminal studies in lymphocytes identified NF-κB as a key transcription factor involved in the regulation of cytokine production.[1] It was then shown that NF-κB resides in the cytoplasm in an inactive form consisting of three protein subunits, a transcription factor dimer and an inhibitory subunit called IκB. Several different NF-κB DNA-binding subunits have been identified including p65 (Rel-A), Rel-B, c-Rel, p50 (produced from a 105 kDa precursor), and p52 (produced from a 100 kDa precursor). Inhibitory subunits include IκBα, IκBβ, IκBγ, and Bcl-3. In neurons, the most common NF-κB complex appears to consist of p65, p50 and IκBα.[2–5] However, other complexes are present in neurons and their subunit composition may vary depending upon factors such as the developmental state of the neurons and their location within the nervous system.[6,7] The canonical mechanism of NF-κB activation involves phosphorylation of the inhibitory IκB subunit by the IκB kinase complex (IKK);[8] phosphorylation targets IκB for ubiquitination and subsequent proteasomal degradation, thereby releasing the active NF-κB factor dimer (Figure 1). NF-κB then translocates to the nucleus and binds to κB sites in promoters of target genes.

A growing list of signals that can activate NF-κB in neurons includes tumor necrosis factor-α (TNF),[9] the excitatory neurotransmitter glutamate,[3] nerve growth factor (NGF),[10,11] activity-dependent neurotrophic factor (ADNF),[12] a secreted form of amyloid precursor protein[13] and cell adhesion molecules.[14] These molecules can activate NF-κB through coupling to kinase cascades including calcium/calmodulin-dependent kinase II,[15] Akt[16,17] and protein kinase C[18] (Figure 2). One or more of the latter signaling pathways is likely to account for the high constitutive activity of NF-κB in neurons compared to nonexcitable cells.[3,15,19]

Dimer composition and transcriptional regulation

NF-κB regulates many promoters containing variations in a highly divergent consensus DNA-binding sequence (the κB site). Mice deficient in single subunits of the NF-κB family show distinct phenotypes and this translates into both qualitative and quantitative differences in target gene expression as a result of transcriptional regulation by different dimers.[20,21] Variations in the κB site appear to confer regulatory specificity for NF-κB family members by two general mechanisms. The sequence of the κB site can determine which coactivators form productive interactions with the bound NF-κB dimer.[22] This mode of specificity occurs independently of any inherent difference in DNA binding by distinct dimers.

A second mechanism conferring specificity of transcriptional regulation involves differential affinity of NF-κB dimer combinations for different κB sites. One example of the second mechanism is a variation of the κB site which preferentially binds RelB : p52 heterodimers.[23] Another example involves the c-Rel subunit of NF-κB, which appears

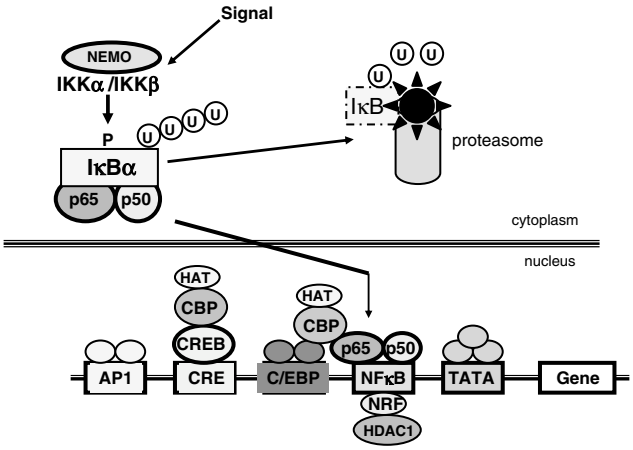

Figure 1 Protein modifications and interactions involved in the activation of NF-κB and the regulation of gene expression by this transcription factor. In the canonical pathway of NF-κB activation, incoming signals activate the IκB kinases (IKKα and IKKβ), which then phosphorylate IκBα. Phosphorylation of IκBα results in the ligation of ubiquitin (Ub), thereby targeting IκBα for proteolytic degradation in the proteasome, simultaneously releasing the NF-κB dimer (p65/p50) which can then translocate into the nucleus. NF-κB binds to specific DNA sequences in the enhancer region of genes and, together with adjacent enhancer elements (AP1 and C/EBP, for example), modulates the expression of the downstream gene. The p65 subunit can recruit CREB-binding protein (CBP/p300) to the site. CBP, which has histone acetyltransferase (HAT) activity, is a coactivator. In addition to positive modulators of NF-κB transcriptional activity, there are proteins that antagonize NF-κB activity including NRF (NF-κB repressing factor) whose activity can be modulated by acetylation. AP1, activating protein 1; CRE, CREB response element; CREB, cyclic AMP response element-binding protein; HDAC1, histone deacetylase 1

to recognize a broader range of κB sites with high affinity in comparison to dimers containing p65.[24] While the DNA-contacting residues of c-Rel and p65 appear to be identical, the broader range of high-affinity interactions by c-Rel homodimers is suggested to arise from unique residues present in the Rel homology region of c-Rel. In a physiological context, variable regulatory effects of NF-κB on different promoters offer the potential for target genes to be under the transcriptional control of distinct NF-κB subunits. How this operates within the nervous system and whether it might be a distinguishing feature of NF-κB activation by discrete stimuli and in distinct cell types remains unknown.

Plasticity and Growth

Cognitive function

A requirement for the NF-κB family of transcription factors in cognitive functions such as learning and memory has been revealed in a number of behavioral assays. This function of NF-κB appears consistent in both mammalian and invertebrate systems, and has been replicated using a variety of methods to interfere with the NF-κB pathway. For example, pharmacological and/or genetic inhibition of NF-κB results in impaired inhibitory avoidance of long-term memory and spatial navigation learning in mice. As the latter and other findings have been the subject of several recent reviews, we will not detail them here.[25,26] Whether different subunits of the NF-κB family will have primarily overlapping, or some distinct,

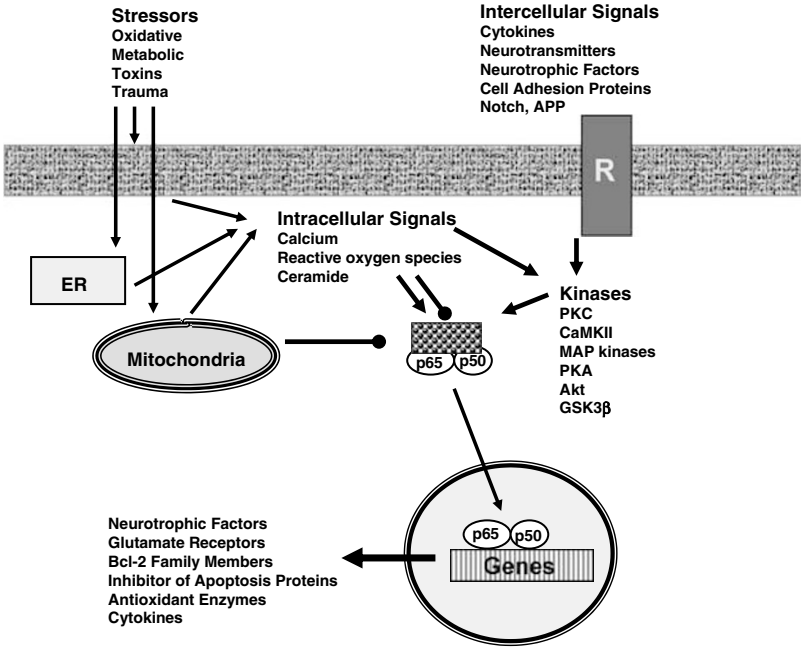

Figure 2 Examples of mechanisms of activation and inhibition of NF-κB by factors that affect neuronal survival in the contexts of developmental cell death and neurodegenerative disorders. Environmental insults such as oxidative and metabolic stress, neurotoxins and physical trauma can result in the activation or inhibition of NF-κB. For example, NF-κB is activated in neurons in response to cerebral ischemia, but is inhibited by the membrane lipid peroxidation product 4-hydroxynonenal. Typically, intracellular signals such as calcium, reactive oxygen species and ceramide mediate stress-induced modulation of NF-κB activity. Intercellular signals bind specific cell surface receptors and use a variety of pathways to activate NF-κB. Activating factors include a range of neurotransmitters, neurotrophic factors, cytokines and cell adhesion molecules. Gene targets of NF-κB that have been shown to promote the survival of neurons include those encoding BDNF, Bcl-2, Bcl-xL, *N*-methyl-D-aspartate receptor subunits, Mn-SOD and inhibitor of apoptosis proteins (IAP). Arrows indicate activation and lines with closed circles at the end indicate inhibition. See text for further information

functions within the central nervous system (CNS) remains an open and interesting question. Roles for p65, p50 and c-Rel subunits of NF-κB in cognitive function have been reported (Table 1). Deficits in contextual fear memory were found in mice lacking c-Rel[7] and impaired anxiety responses seen in p50-deficient mice,[29] while mice lacking p65 demonstrated deficits in spatial memory.[15] Mice lacking p50 are reported to have increased exploratory activity and less apparent anxiety in open field and novel object tests.[28] In contrast, c-Rel-deficient mice were reported to show decreased exploratory activity and no change in anxiety-related behavior on the open-field test.[7] While these contrasts are intriguing, it is probably too early to know whether any or all of these possible differences in subunit function are actual or only apparent due to the limited number of studies.

Characterization of the large number of genes regulated by the NF-κB family of transcription factors has been more extensive in tissues outside the CNS.[30] Broad categories of NF-κB-responsive genes include growth factors, cytokines, chemokines, inflammatory mediators and adhesion molecules, many of which have readily apparent relevance to plasticity. Several studies have revealed new transcriptional targets of NF-κB in the brain, as described in a current review.[26] Interestingly, a general role for NF-κB-mediated transcriptional regulation in long-term memory was recently revealed in a microarray study. Levenson, Sweatt, and co-workers conducted a bioinformatics analysis of transcripts with altered expression levels during NMDA-receptor-dependent contextual memory consolidation. The team searched for common regulatory elements within their identified pool of consolidation-associated genes. The cognate binding motif for NF-κB was significantly enriched in the regulatory regions of consolidation-associated genes from hippocampal area CA1 compared to randomly selected genes.[7] Which genes contained regulatory regions for NF-κB, out of their 38 plasticity-associated genes from hippocampal area CA1, as well as the functionality of the identified κB-sites, remain to be detailed.

Growth factor signaling

Neurotrophins are essential for many aspects of CNS function, from differentiation and synaptogenesis during brain development to growth and plasticity in the adult brain. Of all the growth factor pathways in the CNS, NF-κB activation by nerve growth factor (NGF) is the most well characterized to date. NGF mediates its effects by binding to both the trkA receptor and the p75 neurotrophin receptor ($p75^{NTR}$) (Figure 3). Separate activation of either the $p75^{NTR}$ or trkA is sufficient to lead to NF-κB activation.[10,31] However, interactions in the signaling pathways downstream of either trkA or $p75^{NTR}$ are likely to have potential impacts on NF-κB-dependent regulation of gene expression. In studies using chimeric receptors to isolate the signaling pathways in a neuronal cell line (PC12), Foehr *et al*. found that the $p75^{NTR}$ activated the p65, p50 and p52 subunits of NF-κB, while trkA activated only p50 and p65. Selective stimulation of either trkA or the $p75^{NTR}$ induced sets of genes with significant overlap, but certain genes were also specifically induced through one receptor or the other.[31] The $p75^{NTR}$ is a member of the TNF superfamily of receptors; all known members of this receptor family can activate the NF-κB transcription factors. Interestingly, the $p75^{NTR}$ is able to bind all neurotrophins as well as some neurotrophin precurser molecules. However, binding of different neurotrophins to the $p75^{NTR}$ does not appear equally capable of activating NF-κB.[10]

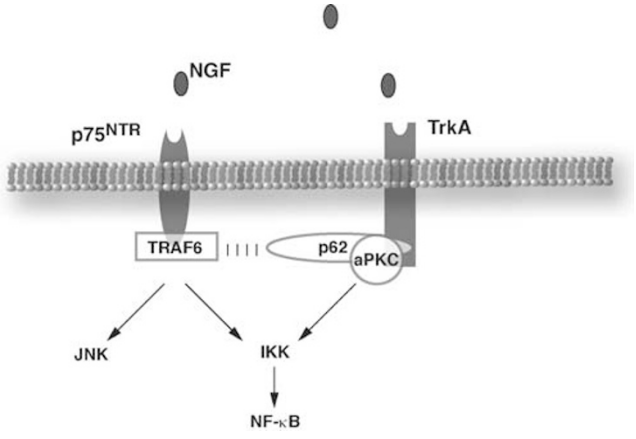

Figure 3 Nerve growth factor signaling through NF-κB. Binding of NGF to either the $p75^{NTR}$ or the TrkA receptor can lead to activation of NF-κB. TRAF6 mediates signaling downstream of the $p75^{NTR}$ leading to activation of both NF-κB and JNK. The TrkA-linked p62 scaffold binds both atypical PKC (aPKC) and TRAF6 and could serve as a platform for crosstalk between the $p75^{NTR}$ and TrkA pathways

Table 1 Behavioral phenotypes of NF-κB-deficient mice

Deficiency	Cognitive tests	Other behavior	Additional phenotype	References
p50	Impaired acquisition of active avoidance to footshock in a massed trial, normal retention	NA		27
p50	NA	Decreased anxiety[a] in open maze, and novel object test	Decreased weight	28
p65	Delayed spatial and normal cued learning in distributed radial maze trials, normal exploratory activity	Normal exploratory activity	NA	15
c-Rel	Impaired contextual and normal associative fear memory	Hypoactive in open-field test, normal anxiety[a] behavior	Normal nociception	7

[a]Anxiety is assessed by time spent in anxiogenic settings such as the center of an open-field, in an open *versus* a closed maze arm, or in close proximity to a novel object

Signaling through the p75^{NTR} has been alternatively linked to both pro-survival and pro-death functions. A possible explanation lies in the activation of divergent signaling pathways following ligand binding to the p75^{NTR}. Like other members of the TNFR superfamily, the p75^{NTR} functions through separate signaling pathways leading to both c-Jun-N-terminal kinase (JNK) and NF-κB activation. Characterization of TNFR superfamily pathways outside the nervous system has revealed that activation of JNK typically promotes cell death, while it is balanced by activation of NF-κB which most typically promotes survival.[32] Research in the past few years has revealed that the p75^{NTR} is coupled to both JNK and NF-κB activation through the tumor necrosis factor receptor-associated factor-6 (TRAF6) protein.[33] TRAF6 is one of the six TRAF family members identified to date and is expressed in most tissues, including the CNS. A dominant negative mutant of TRAF6 effectively inhibits NF-κB activation through the p75^{NTR}, while not affecting activation through trkA.[31] Deletion of TRAF6 resulted in a loss of the neurotrophin-coupled induction of apoptosis in both schwann cells and sympathetic neurons of TRAF6−/− mice.[34]

It is currently unknown how either the p75^{NTR} or trk A receptors converge to activate the IKK complex. Adaptor proteins may be involved in forming signaling complexes with TRAF6 and helping to recruit it to the p75^{NTR}. The serine/threonine kinase, IRAK, as well as RIP2, which is reported to bind directly to the p75^{NTR}, have been suggested to participate in this complex.[35,36] The scaffold protein, p62, is reported to serve as an additional adaptor protein that binds TRAF6 directly and may provide a link with the atypical protein kinases Cs (aPKCs), which can phosphorylate IKKβ.[37,38] Interestingly, p62 selectively interacts with the trkA receptor, while TRAF6 interacts with the p75^{NTR} but not trkA. In light of these findings, it has been suggested that p62 may serve as a platform for pathway interaction between NGF signals mediated by the trkA and p75^{NTR}.[39]

Elucidating the diversity of functions mediated by NGF (and pro-NGF) signaling through different neurotrophin receptors is currently an active area of research (for reviews, see Guo *et al.*[40] and Gabriel *et al.*[41]). Not surprisingly, there is evidence that NF-κB will not work alone, but may function in concert with other pathways to regulate complex neuronal processes such as plasticity, survival and dendrite development. Previous work has demonstrated that Notch activation mediates changes in gene expression responsible for the contact-dependent inhibition of dendritic growth.[42] Using primary murine hippocampal cultures, Salma-Cohen *et al.*[43] provided evidence that NF-κB activation downstream of NGF and the p75^{NTR} can regulate expression of some of the same transcripts as Notch. This pathway was suggested to function in parallel to Notch, and to allow modulation of dendrite growth by soluble factors even in the absence of cell-contact signals. A commercially available inhibitor (SN50), which blocks the nuclear localization of NF-κB, and also the nuclear induction of other transcription factors such as STAT, AP-1 and NFAT, was used in this study, and it will be important to verify the findings using alternative techniques.[44–46] Additional levels of potential interaction between Notch and NF-κB have also been suggested with Notch functioning as an IκB-like molecule.[47] NGF and other neurotrophins impact neuronal survival and differentiation as well as neurite outgrowth and activity-dependent plasticity; understanding the role of the NF-κB signaling system in these effects will be an exciting area for future research.

Cell Survival and Disease

Oncogenesis and tumor promotion

The same machinery that is involved in cell survival, growth, and proliferation can become dysregulated in human disease, leading to inappropriate growth regulation or the transformation of cells into tumors. Cancer is characteristically thought to develop with an initiating event, generally involving genetic damage, followed by a promotion phase involving proliferation of initiated precancerous cells and the possibility of incurring additional genetic mutations. In studies of cancer outside the CNS, there is strong evidence that activation of the NF-κB is often critical for the promotion phase of tumorigenesis. NF-κB functions prominently in the regulation of immune and inflammatory responses, proliferation, angiogenesis, and oncogenesis,[48–50] and typically induces antiapoptotic gene expression to promote cell survival.[8,51] Consistent with this function, mutations and translocations resulting in constitutive activation of the NF-κB pathway are found in tumors derived from many different tissues (e.g. lymphoid, epithelial, and mammary)[52] and correlate with higher grades of malignancy and a poor prognosis. In some cases, these mutations are known to directly promote tumor growth and NF-κB inhibition can inhibit growth and enhance the response to antitumor therapy.[53]

Recent evidence suggests that NF-κB will likely emerge as a prominent player in brain cancer as well. Two recent publications have highlighted oncogenic alterations in signaling pathways (trkAIII, ING4) causing dysregulated constitutive NF-κB activation which resulted in increased survival, growth, and angiogenesis of brain tumors.[54,55] A novel alternative splice variant of trkA, termed trkAIII, was identified with expression restricted to neural progenitor cells, neuroblastomas, and other neural crest-derived tumors. TrkAIII is constitutively active in a ligand-independent fashion, and was found to continuously induce activation of NF-κB in neuroblastoma cell lines. Another interesting link between NF-κB and brain cancer involves the finding that the candidate tumor suppressor protein, ING4, mediates transcriptional repression of NF-κB-responsive genes, possibly by directly binding the p65 subunit of NF-κB. In this study, low levels of ING4 correlated with higher NF-κB activity, increased expression of NF-κB-regulated genes promoting brain tumor angiogenesis, and a worse tumor grade.

Constitutive NF-κB activation has now been observed in numerous glioblastoma cell lines as well as primary glioblastoma tumors.[55,56] In most cases, however, it remains unknown how NF-κB activation influences the oncogenic potential of the tumor. NF-κB-regulated gene products associated with tumor progression and metastasis include intercellular adhesion molecule-1 (ICAM-1), matrix protein tenascin C, vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), cyclooxygenase-2 (COX-2), and matrix metalloprotease 9 (MMP9). As detailed in the next

section, NF-κB also regulates the expression of a number of antiapoptotic gene products, which could contribute to 'immortalizing' cells.

NF-κB as a regulator of cell survival

NF-κB has long been known to function as a critical regulator of apoptosis and often induces genes favoring cell survival; these gene products include cellular inhibitors of apoptosis (cIAPs), BCL2s, TRAF1/TRAF2, and superoxide dismutase (SOD). NF-κB can also modulate the expression of apoptosis-promoting cytokines such as TNFα and FAS ligand (FASL). (see www.nf-kb.org for a more complete listing). Early indications that NF-κB activation could promote survival in neurons came from studies of embryonic rat hippocampal cultures. When pretreated with TNF, the neurons were more resistant to death when exposed to metabolic and excitotoxic insults.[57–59] Inhibiting NF-κB using a decoy DNA approach provided evidence that activation of NF-κB was necessary for the neuron survival-promoting action of TNF.[57] TNF pretreatment was associated with increased production of the antiapoptotic proteins Bcl-2 and Bcl-xL, and expression of a dominant negative form of IκB inhibited the ability of TNF to protect hippocampal neurons.[59] Stimulation of neuronal cultures through either TNFR1 or TNFR2 has been reported to lead, respectively, to either transient or lasting (4 h) activation of NF-κB.[60] The TNFR2-mediated persistent NF-κB was found to be neuroprotective against excitotoxicity in cortical cultures.[60] Similar to TNF, transforming growth factor-beta1 (TGF-β1) can prevent the death of neurons by activating PI_3 kinase and extracellular signal-regulated kinases, which, in turn, activate NF-κB.[61]

A pro-survival role for NF-κB is also seen in the increased neurotoxin-induced damage to neuronal cells of mice lacking the p50 subunit of NF-κB compared to wild-type mice.[5] Additional findings suggest a role for NF-κB activation in modulating programmed death of neurons during development of the nervous system. NF-κB activity has been reported to decline in cerebellar neurons subjected to trophic factor deprivation, a model of developmental neuronal death, possibly as the result of increased levels of IκBs.[62] In addition, NGF was incapable of preventing the death of cultured sympathetic neurons when the neurons were treated with nonspecific inhibitors of NF-κB.[11]

In contrast to the findings described above, other studies suggest that NF-κB activation promotes the death of neurons under certain conditions. In models of ischemia, for example, NF-κB activation appears to contribute to brain damage and mice lacking the p50 subunit of NF-κB demonstrate decreased infarct volumes.[63,64] In some cases, however, support for proapoptotic functions of NF-κB has been based upon either associations between NF-κB activity and neuronal death without a causal relationship[65] or on experiments that employed drugs with multiple mechanisms of action such as aspirin and PDTC.[64,66,67]

Although it is well documented that NF-κB does under certain conditions actually promote the expression of pro-apoptotic genes, an alternative mechanism should be considered in the complex cellular milieu of the CNS. Activation of NF-κB in glial cells (microglia and astrocytes) might indirectly promote neuronal death. Microglia and astrocytes can, by an NF-κB-mediated mechanism, produce large amounts of proinflammatory cytokines, reactive oxygen species, and excitotoxins.[68] NF-κB can also induce nitric oxide synthase in glial cells resulting in the production of nitric oxide and related neurotoxic reactive oxygen species.[69] A recent study in which irradiated wild-type mice were transplanted with bone marrow from mice lacking inducible nitric oxide synthase provided evidence for an important role for glial nitric oxide in excitotoxin-induced neuronal death.[40] Such glia-mediated neurotoxicity may explain the decreased ischemic neuronal damage in mice in which NF-κB activity was reduced. A potential unifying hypothesis concerning the role of NF-κB in neuronal survival is that activation of NF-κB in neurons could promote their survival, whereas activation of NF-κB in glial cells may induce the production of neurotoxins.

Acute CNS trauma

The first evidence that NF-κB might play important roles in the responses of neurons to injury came from studies in which NF-κB DNA-binding activity was evaluated in brain and spinal cord tissues in animal models of acute trauma. For example, NF-κB is activated in CA1 hippocampal neurons in response to transient global forebrain ischemia in rats[65] and after focal ischemia–reperfusion in association with reactive glial cells in rats.[41] Severe epileptic seizures result in a rapid increase in the amount of activated NF-κB in the hippocampus.[70] Such activation of NF-κB under adverse conditions may represent part of a stress response mechanism designed to help neurons survive the stress. Cell culture studies have shown that activation of NF-κB in neurons can be protective against the excitotoxic and metabolic insults relevant to the pathogenesis of stroke and traumatic injury (refer to section on cell survival). When an NF-κB decoy DNA oligonucleotide was infused into the lateral ventricles of mice, seizure-induced death of hippocampal neurons was exacerbated, similar to the increased excitotoxic death of hippocampal neurons in p50-deficient mice.[5] Hippocampal granule neurons in p50 knockout mice were also more vulnerable to death induced by chemical insult with trimethyltin.[27] More recently, it was reported that selective inhibition of NF-κB in forebrain neurons with a calcium-calmodulin-dependent kinase IIα promoter-driven tetracycline transactivator resulted in increased vulnerability of the neurons to death induced by neurotoxic insults.[71]

Traumatic injury to the brain and spinal cord results in increased levels of NF-κB activity in cells within and surrounding the site of injury including neurons, astrocytes, and microglia.[72] NF-κB activity can remain elevated for long time periods (weeks to months) following a traumatic injury and likely contributes to associated inflammatory processes. Damage to cortical neurons and the blood–brain barrier were exacerbated in mice lacking TNFα receptors, which was associated with reduced NF-κB activation,[73] consistent with an adaptive neuroprotective function of NF-κB.

Chronic neurodegenerative disorders

NF-κB activity and expression of several NF-κB target genes are altered in association with the brain pathology in

Alzheimer's disease. Levels of p65 immunoreactivity are increased in neurons and astrocytes associated with amyloid plaques in the brains of Alzheimer's disease patients suggesting increased NF-κB activation in those cells.[74] Exposure of cultured neurons to amyloid β-peptide or a secreted form of amyloid precursor protein (sAPP) induced NF-κB activation,[13,75] suggesting a role for proteolytic products of APP in NF-κB activation in Alzheimer's disease brain cells. Levels of NF-κB activity are increased in cholinergic neurons in the basal forebrain of Alzheimer's patients.[76] Others have established a correlation between increased NF-κB activity and COX-2 gene transcription in brain regions affected in Alzheimer's patients.[29] Moreover, inhibition of NF-κB transcriptional activity with decoy DNA results in increased vulnerability of neurons to death induced by amyloid β-peptide.[57] Oxidative stress may impair NF-κB functions as it has been shown that membrane lipid peroxidation inhibits NF-κB activity, possibly by a direct interaction of 4-hydroxynonenal with NF-κB subunits. The proapoptotic protein prostate-apoptosis response-4 (Par-4), which is implicated in Alzheimer's disease,[77] kills neurons in part, by inhibiting NF-κB activity.[78]

As described earlier for acute trauma to the CNS, activation of neuronal NF-κB in Alzheimer's disease may be a neuroprotective defense response, and, indeed, activation of NF-κB can protect neurons against death induced by amyloid β-peptide.[9] On the other hand, activation of NF-κB in glial cells may mediate the production of proinflammatory cytokines and nitric oxide associated with the amyloid and neurofibrillary pathology in Alzheimer's disease.[79] In addition, NF-κB might also play a role in amyloidogenesis itself, since expression of APP can be induced by NF-κB.[80]

Mutations in the genes encoding APP, presenilin-1, and presenilin-2 cause inherited early-onset Alzheimer's disease. The presenilins are essential for cleavage of APP at the C-terminus of amyloid β-peptide, the final step in amyloid β-peptide production.[81] Studies of neurons expressing normal or mutant forms of presenilin-1 suggest a role for impaired ability of neurons to induce NF-κB activation under conditions of oxidative stress in the pathogenesis of Alzheimer's disease.[75] An abnormal NF-κB response occurs in neurons expressing mutant presenilin-1 such that it is activated rapidly, but then drops to very low levels for a prolonged time period. It was also reported that neurons in presenilin-1 mutant mice exhibit impaired NF-κB activation in response to exposure to trimethyltin.[82]

It was reported that there is a large increase in the percentage of dopaminergic neurons in the substantia nigra that exhibit nuclear p65 immunoreactivity in Parkinson's disease patients compared to age-matched control subjects.[83] As oxidative stress and mitochondrial dysfunction occur in neurons affected in Parkinson's disease,[84] increased NF-κB activity could be part of a neuroprotective response. Studies of animal models of Parkinson's disease further suggest a protective role for NF-κB. For example, treatment of rats with an inhibitor of NF-κB increases the vulnerability of dopaminergic cells to the neurotoxin 6-hydroxydopamine.[85]

Alterations in NF-κB signaling have also been implicated in the demise of striatal neurons in Huntington's disease. Striatal neurons in mice lacking the p50 subunit of NF-κB exhibit increased vulnerability to the mitochondrial toxin 3-nitropropionic acid.[86] Levels of Mn-SOD were increased in response to 3-nitropropionic acid in striatal cells of wild-type mice, but not in striatal cells of mice lacking p50, indicating a pivotal role for NF-κB in this neuroprotective response. Mutant Huntingtin, expressed from an inducible promoter, was found to activate NF-κB in a neuronal cell line and blockade of the NF-κB activation pathway reduced the toxicity of mutant Huntingtin.[87] In contrast, the results of some studies suggest that activation of NF-κB may promote the death of neurons under conditions such as oxidative and metabolic stress that may occur in neurodegenerative disorders.[63,88] The factors that determine whether NF-κB activation is beneficial or detrimental for neurons in the context of neurodegenerative disorders are poorly understood, but likely involve regulatory elements that determine whether NF-κB increases the expression of pro- or antiapoptotic genes.

In some cases, appropriate repair of double-strand DNA breaks can determine whether neurons live or undergo programmed cell death during development of the nervous system.[89,90] In addition, several studies have documented increased amounts of DNA damage in vulnerable neuronal populations in both patients and animal models of Alzheimer's, Parkinson's, Huntington's diseases, and stroke.[91] Activation of NF-κB by DNA damage can occur through multiple pathways, including both p53-independent and p53-dependent signaling mechanisms.[92–94] It has been reported that NF-κB is rapidly activated following DNA damage in cultured neurons in an IKK- ATM- and p53-independent manner.[95] Data in the latter study suggested that NF-κB acts upstream of p53 in acute cell death induced by DNA damage, but, on the other hand, NF-κB promotes cell survival when activated over a longer time period in the absence of severe DNA damage. However, in another study, DNA-damaging agents reduced NF-κB activity in cultured neurons and treatment with a p53 inhibitor resulted in preservation of NF-κB activity.[96] The latter study provided evidence that p53 and NF-κB compete for binding to the transcriptional cofactor CBP, suggesting a mechanism whereby p53 and NF-κB could have opposite effects on the transcription of pro- or antiapoptotic genes.

Future Directions

We now know that NF-κB is present in axons, dendrites, and synaptic terminals where it can be activated in response to a range of signals including neurotransmitters, neurotrophic factors, and cytokines. However, the range of intercellular signals and transduction mechanisms that regulate NF-κB activity in neurons is likely to be broad and complex. The identification of these pathways, and their interactions with other signaling pathways that regulate neuronal survival and plasticity will be an important topic for future investigations. The possibility of post-transcriptional regulation of either expression or activity of NF-κB subunits also remains unexplored. As NF-κB is a preformed transcription factor, its activity is not typically prominently regulated by transcriptional or translational mechanisms. However, synaptic compartments are often located at a considerable distance from the

cell body/nucleus and local mechanisms of post-transcriptional regulation are known to play special roles in aspects of synaptic function and plasticity within the CNS. Whether local translation or microRNA-mediated mRNA degradation could serve to regulate subcellular localization and function of NF-κB in the nervous system is an open question.

Knowledge of NF-κB gene targets in neurons is limited, with only a few genes having been established as NF-κB responsive. As NF-κB activation can promote cell survival, and developmental and synaptic plasticity, genes involved in these processes are undoubtedly regulated by NF-κB. It would also seem quite surprising if NF-κB functioned in isolation. A more likely scenario is that NF-κB cooperates with other transcription factors involved in neuronal plasticity including immediate-early gene products, CREB, and other mechanisms of transcriptional regulation. In some cases, the NF-κB responsive genes may serve dual functions in cell survival and plasticity. A case-in-point is BDNF which is induced by NF-κB in response to glutamate receptor activation.[97] BDNF activates a receptor tyrosine kinase (trkB) coupled to PI_3 kinase–Akt and MAP kinase signaling pathways, which promote cell survival and play a critical role in learning and memory.[98] The latter example suggests that NF-κB is a major integrator of signaling pathways that mediate adaptive responses of neurons to an ever-changing environment. Although it has generally been assumed that the only mechanism of action of NF-κB is transcriptional regulation, other mechanisms are worth considering and local actions of NF-κB in neuronal processes and at synapses are possible.

Increasing evidence suggests that NF-κB is involved in the pathogenesis of many different neurological disorders, either promoting or mitigating disease. Future research aimed at developing novel NF-κB-based preventative and therapeutic approaches to such disorders would be valuable. However, because all cell types in the nervous system express NF-κB, it is likely that ideal agents would be cell type-selective in their actions. For example, inhibitors of NF-κB that selectively target microglial cells might suppress damaging neural inflammatory processes without affecting the function of NF-κB in neurons. Unraveling the cell-type-specific functions of NF-κB in more detail is likely to aid therapeutic efforts enormously.

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