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Invited review

Dual roles of NF-κB in cell survival and implications of NF-κB inhibitors in neuroprotective therapy[1]

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Abstract

NF-κB is a well-characterized transcription factor with multiple physiological and pathological functions. NF-κB plays important roles in the development and maturation of lymphoids, regulation of immune and inflammatory response, and cell death and survival. The influence of NF-κB on cell survival could be protective or destructive, depending on types, developmental stages of cells, and pathological conditions. The complexity of NF-κB in cell death and survival derives from its multiple roles in regulating the expression of a broad array of genes involved in promoting cell death and survival. The activation of NF-κB has been found in many neurological disorders, but its actual roles in pathogenesis are still being debated. Many compounds with neuroprotective actions are strongly associated with the inhibition of NF-κB, leading to speculation that blocking the pathological activation of NF-κB could offer neuroprotective effects in certain neurodegenerative conditions. This paper reviews the recent developments in understanding the dual roles of NF-κB in cell death and survival and explores its possible usefulness in treating neurological diseases. This paper will summarize the genes regulated by NF-κB that are involved in cell death and survival to elucidate why NF-κB promotes cell survival in some conditions while facilitating cell death in other conditions. This paper will also focus on the effects of various NF-κB inhibitors on neuroprotection in certain pathological conditions to speculate if NF-κB is a potential target for neuroprotective therapy.

Introduction

NF-κB is ubiquitously expressed in peripheral and brain cells and regulates the expression of a wide variety of genes involved in cell survival, growth, stress responses, and immune and inflammatory processes[1–3]. This factor was first described by Sen and Baltimore in 1986 as a NF, that when activated by agents, such as bacterial lipopolysaccharide, bound to a 10 bp sequence in the enhancer region of the gene encoding the κ light chain (κ) of antibody molecules in B cells (B)[4]. NF-κB family members have been implicated in the development of the nervous system and plasticity of synapses[5–7]. NF-κB is persistently activated in cancer, chronic inflammation, neurodegenerative diseases, stress, stroke, trauma, heart disease, and other disease conditions[8,9]. As NF-κB is an important regulator in programmed cell death[10], it has been speculated that NF-κB may play important roles in normal brain function and neurodegenerative disorders[11,12].

NF-κB biology

c-Rel/NF-κB family NF-κB is composed of 5 members of the c-Rel (Rel) family, including NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB, and Rel. All the Rel proteins contain a conserved N-terminal region, called the Rel homology domain (RHD). The N-terminal part of the RHD contains the DNA-binding domain, whereas the dimerization domain is located from C-terminal region of the RHD[13]. Close to the C-terminal end of the RHD lies the nuclear localization signal (NLS), which is essential for the transport of active NF-κB

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complexes into the nucleus[14]. NF-κB family proteins are divided into 2 groups based on C-terminal sequences of the RHD. The members of group 1 include NF-κB proteins p105 and p100, which are precursors of p50 and p52. Limited proteolysis is required to produce p50 and p52. The second group (the Rel proteins) mainly includes c-Rel (and its retroviral homologue v-Rel), RelB, and RelA (p65)[15]. All vertebrate NF-κB proteins can form homodimers or heterodimers, except for RelB, which can only form heterodimers. These homodimers and heterodimers that exhibit differential binding specificities are p50/RelA, p50/c-Rel, p52/c-Rel, p65/c-Rel, RelA/RelA, p50/p50, p52/p52, RelB/p50 and RelB/p52[16]. The term NF-κB commonly refers specifically to a p50–RelA (p50/p65) heterodimer, which is the major Rel/NF-κB complex in most cells[14].

NF-κB dimers are sequestered in the cytoplasm by a class of inhibitor proteins, called IκB. In mammalian cells, the major regulatory IκB proteins are IκB-α, IκB-β, IκB-ε, and Bcl-3. The most common complex that is activated in mammalian cells appears to involve IκB-α, which binds to the p50/RelA heterodimer. IκB function as inhibitors through ankyrin repeats that interact with the RHD in NF-κB to mask the NLS and inhibit the nuclear translocation of NF-κB. The N-termini of these IκB proteins constitute a signal response domain, which is targeted for phosphorylation and ubiquitination by a variety of stimuli. The newly-synthesized IκB-α protein actively shuttles between the nucleus and the cytoplasm and both inhibit nuclear import and mediate the nuclear export of NF-κB/Rel proteins. In contrast, the IκB-β protein can inhibit the nuclear import of NF-κB/Rel proteins, but does not remove NF-κB/Rel proteins from the nucleus[17,18].

NF-κB activation pathway Signals that induce NF-κB activity cause the phosphorylation of IκB thereby activating the NF-κB complex. The activated NF-κB complex translocates into the nucleus and binds to DNA at the κB binding motifs and alters gene expression. Most signals that lead to the activation of NF-κB act on a high molecular weight complex containing a serine-specific IκB kinase (IKK). IKK contains at least 3 distinct subunits: IKK-α, IKK-β, and IKK-γ. IKK-α and IKK-β are catalytic kinase subunits, while IKK-γ is a regulator for sensing and integrating upstream activating signals[18]. There are 2 NF-κB activation pathways: the classical or canonical pathway and the non-canonical pathway. In the canonical pathway, the activation of the IKK complex leads to the phosphorylation of 2 specific serines (Ser32 and Ser36) in IκB-α, which targets IκB-α for ubiquitination and degradation by the 26S proteasome. In the non-canonical pathway, the p100–RelB complex is activated through phosphorylation by an IKK-α homodimer (lacking IKK-γ) to generate p52–RelB. In either pathway, the unmasked NF-κB complex can then enter the nucleus to activate target gene expression. In the classical pathway, one of the target genes activated by NF-κB can encode IκB-α, and newly-synthesized IκB-α enters the nucleus recombined with NF-κB, which can remove NF-κB from DNA, and export the complex back to the cytoplasm to restore the original latent state. Thus, the NF-κB activating pathway is a transient process, generally lasting from 30 to 60 min in most cells[20,21].

Dual roles of NF-κB in cell death and survival

NF-κB targets many genes to activate their expression. These target genes include cytokines/chemokines and their modulators, immunoreceptors, proteins involved in antigen presentation, cell adhesion molecules, acute-phase proteins, early response genes, stress response genes, cell surface receptors, transcription factors and regulators, regulators of apoptosis, growth factors, and cell death receptor ligands and their modulators. In the central nervous system (CNS), NF-κB can play an anti-apoptotic or pro-apoptotic role in cell death[22]. This is not unexpected as NF-κB regulates the genes involved in neuronal death and survival.

Anti-apoptotic activity of NF-κB A large number of studies have demonstrated that NF-κB plays a prosurvival role in proliferating cells, including tumor cells. Two actions of NF-κB make it an important cell survival transcription factor in these cells: the regulation of the cell cycle and the inhibition of apoptosis. The best example for elucidating the prosurvival action of NF-κB in cells is finding an inhibitory role of NF-κB in death receptor-induced apoptosis[23]. Binding to death receptors by TNF-α activates caspase-8 through TRAF1 and NF-κB through TRAF2. The activation of caspase-8 leads to apoptosis. Blocking NF-κB activation potentiates TNF-α-induced apoptosis, indicating NF-κB exerts anti-apoptotic action. It has been found that nerve growth factor (NGF) promotes neuronal survival through activating NF-κB[24]. Yu *et al*[25] reported that mice lacking the p50 subunit of NF-κB exhibited increased damage to hippocampal pyramidal neurons after the administration of the excitotoxin kainate. In immortalized mouse hippocampal cell line HT22 cells, glutamate-induced apoptosis was inhibited by IκB inhibitor aspirin, while the NF-κB decoy oligonucleotide potentiated it[26]. The action of NF-κB on neuronal survival is mediated through the upregulation of several prosurvival genes.

Superoxide dismutase Manganese superoxide dis-

mutase (Mn-SOD) is an important antioxidant enzyme, which is a potent scavenger of superoxide anion and is likely to serve important cytoprotective roles against cellular damage. It has been reported that NF-κB is involved in the expression of Mn-SOD[27]. The incubation of human endometrial stromal cells with TNF-α or the phorbol 12-myristate 13-acetate (TPA), a protein kinase C activator, caused marked increases in nuclear NF-κB DNA binding activity and Mn-SOD mRNA and activity. These effects of TNF-α and TPA were completely inhibited by the proteasome inhibitor MG132 and the recombinant peptide capable of blocking NF-κB nuclear translocation, SN50[28]. Activities of Mn-SOD and SOD1 increased after spinal cord injury (SCI) and exposure to neurotoxins[29,30]. The increase in SOD appeared to be NF-κB-dependent, and overexpression significantly protected against the deleterious effect of reactive oxygen species, ceramide, or *N*-methyl-*D*-aspartate (NMDA). Several other studies have shown that the overexpression of copper-Zn SOD or the activation of Mn-SOD is neuroprotective against ischemia, excitotoxicity, and Aβ toxicity[31–33].

Bcl-2 Bcl-2 and Bcl-X_L are well-defined anti-apoptotic proteins. The NF-κB binding site is identified in the promoter of murine Bcl-x[34]. Bui *et al*[35] found that NGF increased the expression of Bcl-X_L, possibly through the activation of NF-κB. Some studies indicate that TNF-α has neuroprotective effects. TNF-α increases the mRNA and protein levels of Bcl-2 and Bcl-x[36]. It has also been found that the exposure of cultured neurons to hypoxia/reoxygenation increases the levels of Bcl-2 and Bcl-X. The inhibition of NF-κB activation abolished the hypoxia-induced induction of Bcl-2 and Bcl-X, indicating that the induction of Bcl-2 and Bcl-X is mediated by NF-κB[37]. NF-κB is also reportedly involved in the activation of the Bcl-2 family member A1/Bfl-1[38].

Pro-apoptotic activity of NF-κB A large number of studies have found that NF-κB activation participates in neuronal apoptosis. The mechanism by which NF-κB translocation induces apoptosis is not completely clear, but it is assumed that this mechanism involves the regulation of 1 or more genes known to play a pro-apoptotic role in apoptosis. Among the NF-κB-responsive genes possibly involved in the control of neuronal cell death, pro-apoptotic genes p53, c-Myc, cyclin D1, Bcl-Xs, and the Fas ligand and its receptor are activated by various pathological stimuli.

p53 The p53 protein is a tumor suppressor and plays important roles in neuronal apoptosis via promoting the expression of the pro-apoptotic gene Bax and PUMA, but suppresses the expression of the cytoprotective gene Bcl-2. NF-κB may contribute to neuronal apoptosis through the induction of p53. In the study of glutamate receptor-mediated excitotoxicity, upon stimulation of glutamate receptors, a quick and robust induction in the levels of p53 mRNA and protein was observed. The induction of p53 was blocked by NF-κB inhibitors[39,40]. Qin *et al*[40] investigated the role of NF-κB in apoptosis induced by the NMDA receptor agonists in rat striatal medium spiny neurons. The administration of the excitotoxin quinolic acid and NMDA induced apoptosis in the rat striatum. The inhibition of NF-κB nuclear translocation by the SN50, a recombinant cell permeable peptide containing the p50 nuclear localization sequence, reduced apoptotic death of striatal neurons and p53 expression. Uberti *et al*[41] pretreated the neuronal cultures with aspirin, which inhibits NF-κB activation, or with a specific p53 antisense oligonucleotide, which inhibits p53 transcription, resulting in a complete prevention of glutamate-induced p53 induction and apoptosis. The NF-κB-dependent induction of p53 was also found in response to DNA damage and oxidative stress. The induced p53 was apparently involved in cell death under these conditions as the synthetic p53 inhibitor pifithrin-α blocked neuronal apoptosis[42–45]. NF-κB not only regulates the levels of p53, but also increases the stability of the DNA binding of p53, providing an additional mechanism for promoting p53-mediated pro-apoptotic signaling[46].

Cyclin D1 and c-Myc The cyclins are a family of proteins that are involved in cell cycle progression and apoptosis. The best explored link between NF-κB activation and cell cycle progression involves cyclin D1, a cyclin which is expressed relatively early in the cell cycle and is crucial to DNA synthesis[47]. The NF-κB regulation of cyclin D1 occurs at the transcriptional level and is mediated by the direct binding of NF-κB to multiple sites in the cyclin D1 promoter[48]. NF-κB promotes G_1 to S phase transition in mouse embryonic fibroblasts and in T47D mammary carcinoma cells[49]. The NF-κB-mediated induction of cyclin D1 was found in dorsal root ganglion neurons in response to ceramide-induced apoptosis. The inhibition of NF-κB blocked cyclin D1 induction and increased the viability of neurons[50]. Liang *et al*[44] reported that overstimulation NMDA receptors with quinolinic acid induced a NF-κB-dependent elevation in cyclin D1 mRNA and protein levels. The incorporation of BrdU was observed in some neurons undergoing apoptosis. NF-κB binding sites have also been identified in the c-Myc exon and upstream sites and positively regulate the expression of c-Myc[51]. In excitotoxic models, c-Myc was upregulated through NF-κB activation[39,44]. The NF-κB-dependent increase in c-Myc expression was also observed in 6-hydroxydopamine-induced Parkinson's dis-

ease[45,52].

The involvement of cell cycle regulators in neuronal apoptosis has been shown by many investigators. The expression of certain cell cycle regulators, such as cyclin D1, cyclin G, c-Myc, and cdk4 have been found during neuronal apoptosis[53–56]. To support the role of cell cycle regulators in neuronal apoptosis, some studies showed that cdk inhibitors blocked neurotrophic factor withdrawal-induced apoptosis[57]. Cyclin D1 antisense or cell cycle inhibitors and cdk inhibitors partially blocked the excitotoxin-induced apoptosis of striatal neurons[44,58], suggesting cycle regulators play an important role in neuronal apoptosis.

Bcl-Xs and BAX The *bcl-x* gene functions to regulate cell death. *Bcl-x* transcripts are alternatively spliced into a long and short form or the form lacking the transmembrane domain. The long form (*bcl-x_L*) represses cell death, while the short form (*bcl-x_s*) favors apoptosis. NF-κB binding sites have been identified in the Bcl-x promoter[59]. The NF-κB-dependent induction in Bcl-Xs has been reported. Dixon *et al*[60] showed that following ischemia and NF-κB activation, Bcl-x_s messenger RNA levels increase in the CA1 hippocampal region. In cultured endothelial cells, hypoxia decreased Bcl-2 mRNA levels, whereas the transfection of the NF-κB decoy significantly attenuated a decrease in Bcl-2 mRNA, increased Bcl-2/BAX ratio, and inhibited hypoxia-induced cell death[61]. The prolonged activation of NMDA receptors results in NF-κB nuclear translocation, release of LDH, increases in the BAX/Bcl-X_L ratio, and DNA fragmentation. SN50 blocked the NMDA-induced increase in the Bax/Bcl-X_L ratio and cell death[62]. Glutamate also reportedly increased the expression of BAX, which was inhabitable with BAY 11-7082, a selective inhibitor of IκB-α phosphorylation[63]. In cyanide-induced apoptosis, the expression levels of 2 anti-apoptotic Bcl-2 proteins, Bcl-2 and Bcl-X_L, remained unchanged after cyanide treatment, whereas the mRNA levels of Bcl-Xs and Bax began to increase within 2 h, and their protein levels increased 6 h after treatment. Both NF-κB SN50 and the NF-κB decoy blocked the upregulation of Bcl-Xs and BAX[64]. In low potassium-induced apoptosis of cortical neurons, NF-κB DNA binding increased, and this was accompanied by an elevation in Bcl-Xs transcription. The latter was abolished by the inhibition of NF-κB or the restoration of potassium levels[65].

Nitric oxide The role of nitric oxide (NO) in apoptosis is complex, as it may exert proapoptotic or antiapoptotic effects depending on experimental conditions. NF-κB plays a role in regulating the expression of NO synthase (NOS). Xie *et al*[66] defined a NF-κB binding domain in murine inducible NOS (iNOS). NF-κB stimulated the expression of iNOS. The NF-κB inhibitor pyrrolidine dithiolidin inhibited the activation of NF-κB and the production of NO in lipopolysaccharide (LPS)-treated macrophages, suggesting that the activation of NF-κB/Rel is critical in the induction of iNOS by LPS.

NOS has been demonstrated to play a proapoptotic role in several *in vitro* and *in vivo* studies. The incubation of human breast cancer cell line MCF-7 cells and differentiated neuronal PC12 cells with TNF-α increased the expression and activity of iNOS. In addition to NOS inhibitors, iNOS antisense oligonucleotides effectively prevented NO_2 generation and apoptosis, suggesting that the TNF-α-induced cell death is mediated by iNOS-derived NO[67,68]. Employing the intrastriatal injection of autologous blood in rats to model intracerebral hemorrhage, Zhao *et al*[69] demonstrated a robust and prolonged NF-κB activation and a robust induction of iNOS at both the mRNA and protein levels. In SCI models, iNOS was also found to be increased[70], and the drugs inhibiting NOS offered protective effects[71–73].

NF-κB inhibitors and neuroprotective therapy

Many human nervous system diseases have an association with NF-κB activation. These conditions, including aging[74], headache[75], pain[76], stroke[77], traumatic brain injury[78], SCI[79], Parkinson's disease[80,81], multiple sclerosis [82], Alzheimer's disease[83,84], amyotrophic lateral sclerosis [85], Huntington's disease[86], and brain tumors[87–91], have been associated with the NF-κB pathway. As NF-κB plays important roles in regulating cell survival and death in a broad array of physiological and pathological conditions, it is an attractive proposal to manipulate NF-κB functions to obtain its beneficial effects or abolish its harmful actions when it is required[92]. Multiple signaling events are involved in NF-κB activation, including the phosphorylation and degradation of IκB, NF-κB nuclear translocation, and DNA interaction, thus making it a relatively easy target for drug actions (Figure 1). There are a large number of com-pounds have been reported to inhibit NF-κB functions. These compounds mainly include antioxidants, non-steroidal anti-inflammatory drugs (NSAID), flavonoids, protease inhibitors. A few of these compounds have been used in the clinical setting.

Antioxidants Oxidative stress is one of the common pathogenic mechanisms in neurodegenerative disorders. Thus, antioxidants are frequently employed in the treatment of several neurodegenerative diseases, and are the most valuable therapeutic strategy for fighting neurodegeneration. Although it is hard to attribute a single mechanism to any antioxidants' neuroprotective effects, the inhibition of

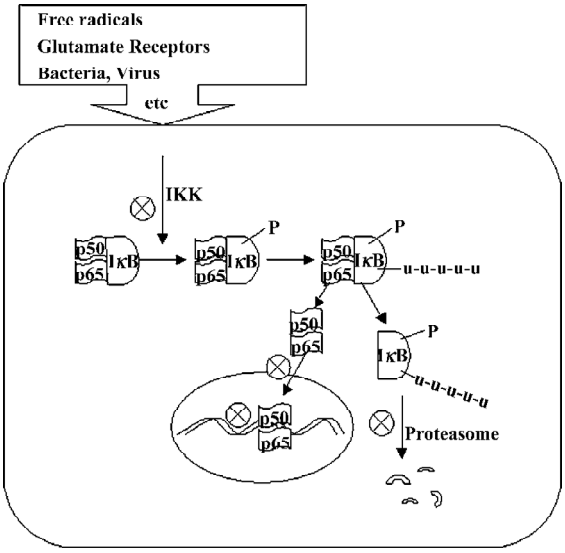

Figure 1. Schematic elustration of NF-κB activation and possible sites where drugs interfere with the NF-κB signaling pathway. NF-κB is sequestered in the cytoplasm by IκB family proteins. Upon stimulation, the IκB is phosphorylated and ubiquinated and subsequently degraded by the 26S proteasome. Degradation of IκB releases NF-κB dimers that translocate into the nucleus, where NF-κB binds to the consensus DNA sequence and regulates gene expression. ⊗: site of drug action.

NF-κB activation is a prominent feature of antioxidants. The antioxidants include *N*-acetyl-*L*-cysteine (NAC), α-lipoic acid, glutathione monoester, pyrrolidine dithiocarbamate (PDTC), tepoxalin, and flavonoids.

Free radicals are important mediators for NF-κB activation. NAC, a well-characterized antioxidant, is found to exert neuroprotective effects against free radical-related neuronal injury[93,94]. NAC influences many cellular signaling pathways, including c-Jun N-terminal kinase, p38 mitogen-activated protein kinase, and redox-sensitive activating protein-1. NAC can also prevent apoptosis and promote cell survival by activating the extracellular signal-regulated kinase pathway. NAC directly modifies the activity of several proteins by its reducing activity[95], and is demonstrated to inhibit the degradation of IκB-α and the activation of NF-κB[96–98]. In animal models of global ischemia, pretreatment with NAC (300 mg/kg) or another antioxidant PDTC (200 mg/kg) significantly reduced the infarct volume. NAC has also been reported to increase the survival of dopaminergic neurons. The local or systemic administration of NAC protected dopamine neurons against 6-hydroxydopamine-induced oxidative damage[99].

PDTC is an antioxidant that has been studied for many years. Using cell cultures, Schreck *et al*[100] found that micromolar concentrations of PDTC reversibly suppressed NF-κB activation. PDTC specifically prevented the NF-κB-dependent transactivation of reporter genes under the control of the HIV-1 long terminal repeat and simian virus 40 enhancer. In other studies, PDTC inhibited NF-κB activation while enhancing the binding activity of activator protein-1[101]. In addition, PDTC can inhibit the NF-κB-mediated production of TNF-α, hypoxia-induced dephosphorylation of Akt, and inflammatory responses[102–104]. It has been shown that treatment with PDTC significantly attenuates reperfusion-induced lung injury[105], glycerol-induced renal injury[106], cholestatic liver injury[107], and adriamycin-induced myocardial apoptosis[108]. Crack *et al*[109] observed that knockout glutathione peroxidase-1 (Gpx1) in mice increased the ischemia-induced activation of NF-κB. PDTC was able to afford partial neuropro-tection in the Gpx1-null mice. In Wistar rats, PDTC prevented NF-κB activation in the ischemic brain, as determined by the reduced DNA binding and nuclear translocation of NF-κB in neurons. PDTC treatment reduced the infarction volume by 48% when given 6 h after MCAO[110].

Flavonoids are potent antioxidants found in many natural products. They are widely used as food supplements and as anti-inflammation and antitumor drugs. Recently, many studies have demonstrated that flavonoids have neuroprotective effects in animal models[46]. Among them, *Ginkgo biloba* has received particular attention. Chen *et al*[111] found that *Ginkgo biloba* extract significantly reduced intracellular reactive oxygen species formation and NF-κB activation induced by TNF-α. Tea extracts have been previously reported to possess radical scavenger, iron chelating, and anti-inflammatory properties in a variety of tissues. Recent studies found that green tea extracts were capable of inhibiting NF-κB[112]. Studies demonstrated that green tea extracts inhibited iron-induced lipid peroxidation, NF-κB activation, and 6-hydroxydopamine (6-OHDA)-induced neuronal death. 6-OHDA-induced apoptosis of catecholaminergic PC12 cells was inhibited by green tea polyphenols and their major effective component epigallocatechin-3-gallate at a concentration of 200 mmol/L[113]. Green tea polyphenols have been shown to reduce the toxic effects of β-amyloid, ischemia/reperfusion-induced apoptosis, and the infarct volume[114,115]. Given by brain penetrating property of polyphenols, these compounds may be utilized as a class of drugs for the treatment of neurodegenerative diseases.

IκB phosphorylation and degradation inhibitors Phosphorylation and the subsequent proteasomal degradation of IκB are key steps for NF-κB activation. NSAID and cyclopentone prostaglandins are now found to be IκB inhibitors. In 1994, Kopp and Ghosh[116] reported that sodium salicylate and aspirin inhibited the activation of NF-

κB through blocking the degradation of the IκB. IKK-α and IKK-β phosphorylate IκB. Aspirin and sodium salicylate can inhibit IKK-β activity *in vitro* and *in vivo*. The mechanism by which aspirin and sodium salicylate inhibit NF-κB is the binding of these agents to IKK-β to reduce ATP binding[117]. These studies not only further explain the new mechanism of actions, but also suggest new implications of these drugs. Grilli *et al*[118] found that acetylsalicylic acid and its metabolite sodium salicylate protected neurons against neurotoxicity elicited by the excitatory amino acid glutamate in rat primary neuronal cultures and hippocampal slices. This inhibitory effect may be involved in the inhibition of NF-κB activation, protein kinase C zeta activity, superoxide anion generation, and lipid peroxidation[118–120]. Recent studies suggest that aspirin and other NSAID protected cultured mesencephalic cells against 6-OHDA, 1-methyl-4 phenylpyridinium, and glutamate-induced toxicity[121,122]. Using NSAID in Parkinson's disease (PD) has also been proposed[123]. It has been found that arthritis patients taking aspirin have a lower incident and later onset of Alzheimer's disease (AD). Emerging evidence shows that aspirin and other NSAID have multiple influences on the AD pathogenic process, including inhibiting the formation of fibrillar Aβ, destabilizing preformed fibrillar β-amyloid (Aβ), and preventing the aggregation of Aβ and attenuating its toxicity[124–126]. Recent studies also indicate that acetylsalicylic acid inhibits tau phosphorylation[127]. Other potentially interesting anti-inflammatory drugs have also been reported to exert neuroprotective effects and inhibit NF-κB, including cannabinoid dexanabinol and caffeic acid[128–130].

Recent studies have identified that cyclopentenone prostaglandins (cPG), including prostaglandin (PG)A1 and PGJ2 are ligands for peroxisome-proliferation activator receptor-γ and inhibitors of NF-κB. Rossi *et al*[131] reported that PGA1 could block NF-κB activation by inhibiting IκB phosphorylation. In a subsequent study, they further identified that PGA1 could directly inhibit IκB kinase-β[132]. PGA1 also increases the expression of IκB-α[133]. Similar inhibitory effects of PGJ2 and PGE1 on NF-κB were observed[134–136]. In addition, PGJ2 was found to interfere with DNA binding through covalently modifying the NF-κB p50 subunit[137]. Thus, cPG inhibit NF-κB by interfering in multiple sites in the NF-κB signaling pathway from IκB synthesis to DNA binding[138]. Studies have shown that cPG have neuroprotective effects under certain pathological con-ditions. Qin *et al*[139] first reported that PGA1 protected striatal neurons against NMDA receptor agonist quinolinic acid-induced apoptosis through inhibiting NF-κB activation. PGA1 also inhibited the mitochondrial toxin rotenone-induced death of dopaminergic cell line SH-SY5Y cells[140]. In recent studies, PGA1 and PGJ2 were reported to reduce ischemic brain damage through inducing heat shock proteins, inhibiting NF-κB activation, and inflammation[141–143]. These studies revealed that the administration of PGA1 and PGJ2 2–3 h post-ischemia was still effective. Other studies have also reported that PGJ2 reduced ischemic myocardial infarction[144].

Other drugs, such as estrogen, curcumin, and quercetin have been reported to inhibit IκB degradation[145–148]. All these compounds are reported to have neuroprotective effects under certain experimental conditions.

NF-κB nuclear translocation and DNA binding inhibitors NF-κB has to translocate into the nucleus in order to regulate gene expression. Drugs acting on NF-κB nuclear transport and DNA binding have received considerable attention. Lin *et al*[149] synthesized a membrane-permeable recombinant peptide NF-κB SN50. This peptide contains a signal peptide, which confers the cell membrane permeability of SN50, and a nuclear localization signal, which competes with NF-κB for nuclear entry. The peptide inhibits the nuclear translocation of NF-κB in cultured endothelial and monocytic cells stimulated with LPS or TNF-α in a concentration-dependent manner. This peptide has been widely used for dissecting cellular functions of NF-κB[150,151]. We, along with others, have successfully used SN50 for inhibiting NF-κB nuclear import *in vivo* and have found that it is very effective in blocking NF-κB nuclear entry and NF-κB-mediated target gene transcription in response to various stimuli[39,44,45,150,152–156]. An intrastriatal or nigral injection of SN50 substantially inhibited the nuclear translocation of NF-κB, inhibiting the expression of NF-κB target genes p53, c-Myc and cyclin D1, and attenuating excitotoxicity[39, 44,45,153]. One study has successfully blocked cholecystokinin-octapeptide-induced pancreatitis with an intraperitoneal injection of SN50[155]. These studies suggest that nuclear import inhibitors represent an important class of NF-κB inhibitors.

Many studies have focused on NF-κB DNA decoys. The NF-κB DNA decoys are double-stranded DNA oligonucleotides (ODN) containing the NF-κB-binding motif. When delivered to cells, it competes with NF-κB for DNA binding sites, and thus inhibits NF-κB function. Some studies have demonstrated that ODN that are delivered locally or systemically are effective in blocking NF-κB transactivation activity[157–160]. Some *in vivo* therapeutic studies with ODN have generated promising results. The systemic administration of ODN suppressed NF-κB activity, and the expression of cytokines protected liver grafts against ischemia/reperfusion-induced injury in rats[161]. The animal studies showed that NF-κB decoys reduced lung vascular perme-

ability in septic mice, improved lung function[162], and inhibited hepatic metastasis in the mice loaded with murine reticulosarcoma M5076[163]. The clinical usefulness of ODN has been tested in 2 patients with percutaneous coronary intervention. The initial results showed the suppression of restenosis with no observed adverse effect[164]. NF-κB decoys may be a potential therapeutic strategy for certain types of diseases[165,166].

Drugs that directly inhibit NF-κB DNA binding have been found, but have not been well characterized. For example, it has been reported that the metal-chelating drug aurine tricarboxylic acid inhibited NF-κB DNA interaction[167].

Neurological disorders may benefit from NF-κB inhibitors

Ischemic brain injury The distribution of NF-κB was investigated immunohistochemically in post-mortem brains of stroke patients. An enhanced immunoreactivity of NF-κB was observed in glial cells of infarcted areas, particularly in the penumbra or border zone between the ischemic and non-ischemic areas[168]. In animal studies, early activation of NF-κB has been found to precede DNA damage after ischemic attack[169,170]. It was reported that ischemia induced a TNF-like weak inducer of apoptosis (TWEAK) and its membrane receptor Fn14. TWEAK promotes neuronal cell death and activates NF-κB through the upstream kinase IKK[171]. The deletion of the neuronal IKK2 subunit or inhibition of IKK activity reduced the infarct size and neuronal cell loss. The role of NF-κB in neuronal death was further suggested, as several neuroprotective agents, such as antioxidant LY231617, PDTC, and PGA1, have been shown to inhibit NF-κB activation, reduce infarct volume, and improve behavior deficits[110,173,174]. The contribution of NF-κB activation to ischemic neuronal damage has also been assessed with either the expression of mutant IκB-α in neurons and glial, or NF-κB p50 knockout mice and transgenic mice. The results indicated that the neuronal expression of the NF-κB inhibitor reduced both the infarct size and cell death[174]. Mice lacking the p50 subunit of NF-κB develop significantly smaller infarcts after transient focal ischemia[173,175]. These studies may have established the rationale for use of NF-κB inhibitors in ischemic brain injury.

PD Recently, the role of the neuron-glia interaction and the inflammatory process in PD has been the focus of intense study by the research community. The increase in NF-κB has been found in the post-mortem brains of PD patients. In PD patients, the proportion of nigral dopaminergic neurons with immunoreactive NF-κB and interferon-γ was significantly increased in comparison with control patients[81,176]. A possible relationship between the nuclear localization of NF-κB in the mesencephalic neurons of PD patients and oxidative stress in such neurons has been shown *in vitro* with primary cultures of rat mesencephalon, where the translocation of NF-κB is preceded by a transient production of free radicals during apoptosis induced by the activation of the sphingomyelin-dependent signaling pathway with C2-ceramide. The data suggest that this oxidant-mediated apoptogenic transduction pathway may play a role in the mechanism of neuronal death in PD[176]. In animal models of PD, the inhibition of NF-κB achieves neuroprotection against the 6-OHDA- and MPTP-induced degeneration of dopaminergic neurons[44,45,112,177], suggesting that NF-κB inhibitors could be beneficial in PD.

AD The distribution of NF-κB was investigated immunohistochemically in the post-mortem cases of AD. In the AD cases, increased staining for NF-κB p65 was seen in neurons and their processes, neurofibrillary tangles, and dystrophic neurites. The neuronal staining observed in AD was strongest in the hippocampal formation and entorhinal cortex[178]. Boissière *et al*[179] studied the cellular distribution of NF-κB in the nucleus basalis of Meynert of AD and control patients. The proportion of large cholinergic neurons with elevated nuclear immunostaining of NF-κB was significantly increased in AD, suggesting an association between NF-κB functions and the process of cholinergic degeneration in AD. In another report, NF-κB immunoreactivity was found in the neutrophil of diffuse Aβ deposits. In addition, NF-κB immunoreactivity was found in the nuclei of neurons, but not in the nuclei of reactive astrocytes, in the vicinity of diffuse plaques[180]. The discovery of NF-κB activation in AD has been confirmed by other investigators[181–183]. Since inflammation is a prominent feature in AD, NF-κB may participate in the inflammatory response. A more direct connection of AD pathogenesis and NF-κB was observed as Aβ activates NF-κB[184–186]. Although an early *in vitro* study found that the activation of NF-κB by a low dose of Aβ may have neuroprotective effects[187], other studies have been observed that NF-κB inhibitors inhibit the production of Aβ[188]. In rat primary neurons and human post-mitotic neuronal cells, the Aβ peptide induced dose-dependent neuronal death, the nuclear translocation of the p65 and p50 subunits, and an apoptotic profile of gene expression. The anti-inflammatory drug aspirin and the selective IκB kinase 2 inhibitor AS602868 completely inhibited p50/p65 nuclear translocation and neuronal damage[189]. The clinical trials with some NSAID did not generate encouraging outcomes, as noted by Valerio *et al*[190], since not all NSAID can inhibit Aβ production. Better

compounds with the ability to reduce Aβ should be selected in future studies.

Excitotoxicity Excitotoxicity has been implicated in several neurodegenerative diseases. Kaltschmidt *et al*[191] reported that the ionotropic glutamate receptor agonist kainic acid (KA) activates NF-κB. Later studies defined a pro-apoptotic role of NF-κB activation and nuclear translocation mediated by AMPA/KA receptors[153,192]. Similarly, the stimulation of glutamate NMDA receptors robustly activates NF-κB through the degradation of IκB-α[139,152]. In other studies, the pharmacological upregulation of NF-κB increased glutamate-induced excitotoxicity, while the upregulation of CREB decreased excitotoxicity[193]. Grilli *et al*[118] reported a neuroprotective role of aspirin on the glutamate-induced death of hippocampal neurons, opening a new avenue for the study of excitotoxicity. Since then, several studies have reported that the inhibition of NF-κB has neuroprotective effects. In studies conducted by Casper *et al*[121], neuroprotection against glutamate-mediated excitotoxicity was also found with ibuprofen. The inhibition of NF-κB with a herbal active component glycyrrhiza acid[193], free radical scavenger OCT14117[194], and glutamate metabotropic receptor agonists (2*S*, 1'*S*,2'*S*)-(carboxy-cyclopropyl) glycine and amino-4-phosphonobutyric acid[195] was associated with a neuroprotective effect. These results suggest that NF-κB inhibitors could be suitable drugs for blocking excitotoxicity.

Summary

The signaling pathway and the role of NF-κB have been studied for more than 2 decades. However, we still have limited knowledge on the role of NF-κB in CNS neurons and the molecular mechanisms underlying its actions. Many controversial findings need to be consolidated. In particular, its dual roles in neuronal death and survival and underlying molecular mechanisms need to be carefully evaluated in relation to human neurological diseases[197–200]. The involvement of NF-κB in human diseases certainly establishes it as a potential target for therapy. Many common synthetic (eg aspirin) and traditional remedies target, at least in part, the NF-κB signaling. Our knowledge of the molecular details of the NF-κB pathway will enable us to develop more specific NF-κB inhibitors to treat neurological diseases.

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