



Review

Role of nuclear factor κ B in the central nervous system

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Abstract:

The aim of this review was to assemble current literature data on nuclear factor kappa B (NF- κ B). Many authors believe that NF- κ B, a transcription factor, has essential influence on the regulation of numerous genes in the organism. In this review, we have focused on the role of NF- κ B and its target genes in the central nervous system functioning. Unfortunately, the contribution of NF- κ B to neuroprotection or to neurodegeneration is not clear, yet. Therefore, its exact role in these processes and potential applications in pharmacology are still to be determined.

Key words:

NF- κ B, neuroprotection, neurodegeneration

Abbreviations: A β – amyloid beta peptide, AD – Alzheimer's disease, β -APP – β -amyloid precursor protein, CNS – central nervous system, COX-2 – cyclooxygenase-2, EPO – erythropoietin, HD – Huntington's disease, IGF-1 – insulin-like growth factor-1, I κ B – inhibitory subunit of nuclear factor kappa B, IKK – I κ B kinase, iNOS – inducible nitric oxide synthase, IL – interleukin, MnSOD – manganese-superoxide dismutase, NF- κ B – nuclear factor kappa B, NGF – nerve growth factor, NMDA – N-methyl-D-aspartate, NO – nitric oxide, 6-OHDA – 6-hydroxydopamine, PD – Parkinson's disease, RHD – Rel-homology domain, ROS – reactive oxygen species, TNF – tumor necrosis factor.

The structure and activation of NF- κ B

Nuclear factor kappa B (NF- κ B) family of transcription factors is responsible for the regulation of numerous multiple target genes involved in the inflamma-

tory, immune reactions, cell proliferation, apoptosis or central nervous system (CNS) functioning. For many scientists, NF- κ B remains a central mediator of the induction of various genes in response to a great number of stress stimuli. NF- κ B family consists of several proteins including p52, p50, RelB, c-Rel, RelA(p65) (Fig. 1). The members of NF- κ B family bind forming homo- and heterodimers that are present in inactive forms in most cells. A homology of N-terminal domain called Rel-homology domain (RHD) of approximately 300 amino acids which is identical in 35–61% in all family proteins [1, 40] is the hallmark of NF- κ B family. This RHD is essential for DNA binding, dimerization and nuclear localization [25]. It is interesting that different dimeric complexes are bound to an inhibitor proteins I κ B that keeps them in the inactive state in the cytoplasm. The translocation to the nucleus is possible only when I κ B dissociates from the

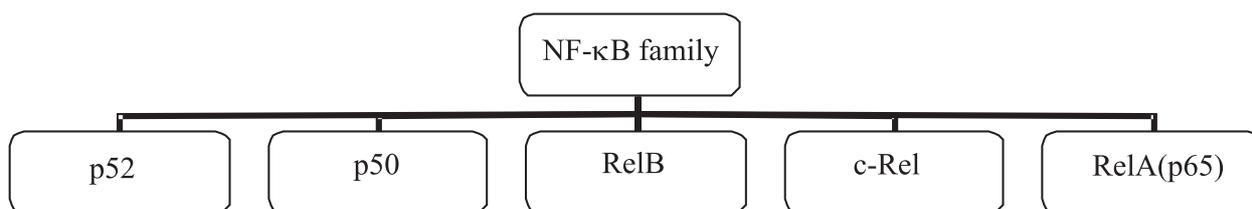


Fig. 1. The members of NF-κB family

dimer. IκB probably blocks not only this translocation but also NF-κB DNA-binding activity.

The process of NF-κB activation is not fully understood because of the complexity of interactions. The autoregulation is very likely to take part in it as tran-

fragments and then activates the expression of the target genes. The long list of factors activating NF-κB comprises neurotransmitters (e.g. glutamate), cytokines (e.g. tumor necrosis factor α (TNF- α), interleukin-1 (IL-1)), advanced glycation end products, glycated

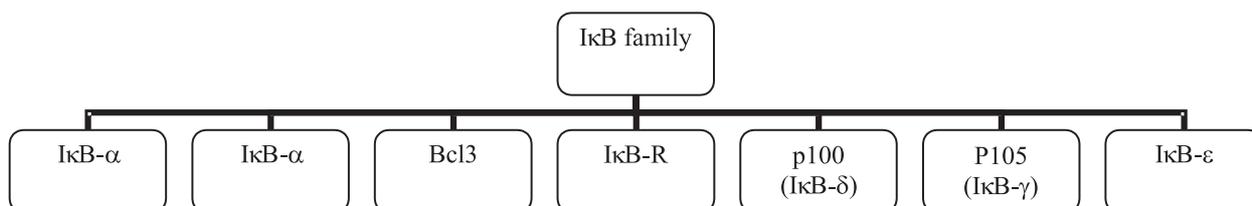


Fig. 2. The members of IκB family

scription factors belonging to this family affect their own gene expression [16]. The inactive form of NF-κB is localized in the cytoplasm associated with the inhibitory subunit, IκB. The IκB family (Fig. 2) consists of IκB- α , IκB- β , Bcl3, IκB-R, p100 (IκB- δ), p105 (IκB- γ), IκB- ϵ . All of them share ankyrin repeats – multiple copies of 30–33 amino acid sequences taking part in the interaction with NF-κB complexes [25]. The activation of NF-κB has to be preceded by the processing of IκB. Phosphorylation of IκB by IκB kinase (IKK) complex results in polyubiquitination and subsequent degradation of IκB with the involvement of the proteasome. IKK complex is composed of three proteins: two catalytic subunits IKK- α , IKK- β and the regulatory subunit IKK- γ . Their role consists in phosphorylation of two conserved serine residues in N-terminal domain of IκB proteins. The processed IκB is then ubiquitinated and finally degraded by the proteasome [44]. The released NF-κB in the form of an active heterodimer may be translocated to the nucleus, and in the presence of other transcription factors binds to the specific DNA

tau, beta amyloid, phorbol esters, UV light, oxidized lipids, stress (e.g. oxidative, physiological, physical), growth factors, drugs and chemicals, viral and bacterial infections [16, 41, 44, 50].

The expression of NF-κB target genes and its role in pathological conditions

Having entered the nucleus, NF-κB complexes interact with specific promoter and cooperatively with various transcription factors bind to DNA. The diversity of NF-κB complexes and their activators, and the variety of the target genes and cell specificities lead to numerous molecular NF-κB-dependent changes. The pathological activation, abnormal either over-expression or impairment of NF-κB may result in many diseases. As those molecular mechanisms have not been yet thoroughly studied, we can only roughly connect some facts. NF-κB regulates a vast number of genes

including those encoding cytokines (IL-1 β , IL-6, IL-8, TNF- α , MCP-1, interferon- β), death and survival proteins (Bcl-2, Bcl-xl, Bcl-xs, Bax, NIAP, p53, Myc, Fax), adhesion molecules (ICAM-1, VCAM, ELAM-1, E-Selectin), cyclooxygenase-2 (COX-2), manganese-superoxide dismutase (MnSOD), inducible nitric oxide synthase (iNOS), cyclin-D1 [9].

The disruption of normal mechanisms of NF- κ B action may lead to various abnormalities and pathologies in the organism, including inflammatory diseases, vasculopathies, atherosclerosis, toxic/septic shock, radiation damage, viral replication, cancers, neurodegenerative diseases or myocardial infarction [16]. The defects of the regulatory mechanisms of NF- κ B activation may probably contribute to those pathological conditions. For instance, dysregulation of NF- κ B is likely to play an important role in atherogenesis [6]. The increased activation of target genes connected with the production of inflammatory cytokines as well as the inhibition of cell apoptosis may be responsible for such conditions as rheumatoid arthritis or asthma [44]. It was demonstrated that activated NF- κ B was present in human atherosclerotic tissue [7] as well as in human inflamed synovial tissue from both osteoarthritis and rheumatoid arthritis patients [36]. The aberrant activation of NF- κ B may also play an important role in tumorigenesis. NF- κ B may promote both anti-apoptotic and pro-apoptotic mechanisms depending on the set of target genes or type of activator [4]. Similarly to the processes in inflammatory diseases, induction of anti-apoptotic genes may lead to cell proliferations. On the other hand, NF- κ B may induce cell death. The exact mechanism of those effects is not clear yet. Another possible mechanism contributing to the development of cancers is the regulation of cell growth and differentiation through the expression of cyclin-D1 [20]. According to Perkins [44], various types of lymphomas, leukemias and other hematopoietic tumors are associated with the amplification, overexpression or rearrangement of NF- κ B-regulated genes.

The role of NF- κ B in the CNS functions

The NF- κ B family proteins have been found in many structures of the CNS. Some authors suggested the correlation between the activation of the CNS and NF- κ B. Furthermore, NF- κ B was found to be linked

with the antioxidant defense of some neuronal structures, like the hippocampus or the cortex [16]. Interestingly, while in the most cell types NF- κ B activation is connected with pathological conditions, non-pathological endogenous signals, such as neurotransmitters, may activate this factor in the CNS [27]. The nanomolar, non toxic concentrations of glutamate were proved to activate NF- κ B in cerebellar granule neurons *in vitro* and this effect involved particularly N-methyl-D-aspartate (NMDA) receptor activation [18, 27]. It has been suggested that the role of NF- κ B involves participation in normal brain function [28]. Kaltschmidt et al. [27] have speculated that changes during cerebellar development could be controlled by glutamate-induced gene expression involving NF- κ B. Also Guerrini et al. [19] have observed glutamate-induced NF- κ B activation during mouse cerebellum development but not in adult mice.

As stimulation with glutamate, kainate, or potassium chloride resulted in a redistribution of NF- κ B from neurites to the nucleus, NF- κ B may be regarded as signal transducer, which transmits transient glutamatergic signals from distant sites to the nucleus [57]. Having taken into consideration the fact that NF- κ B inducible activity is present not only in neuronal bodies but also in synapses and postsynaptic densities, Grilli and Memo [16] have also concluded that NF- κ B may be responsible for carrying synaptic information to the nucleus. The cited authors have classified some factors triggering neuronal activation of NF- κ B and translating it into CNS-specific signals. Depolarization, neurotransmitters (e.g. glutamate), opioid agonists, nerve growth factor (NGF), glycated tau, β -amyloid are included in this group. NF- κ B is likely to influence a great number of genes important for CNS action such as those encoding neuropeptides (dynorphin, proenkephalin), β -amyloid precursor protein (β -APP), p53, iNOS, MnSOD, COX-2, MHC class I, cytokines and chemokines (TNF- α , IL-6, IL-8, GM-CSF, C-CSF) [16].

NF- κ B and neuroprotection

NF- κ B is known for its role in preventing apoptotic cell death. The study carried out by Okuda and Ogita [39] has shown that the treatment with subtoxic concentration of NMDA protected cultured cerebellar

granule neurons against glutamate-induced damage elicited by an excitotoxic glutamate concentration. The authors connected this neuroprotection with *de novo* synthesis of brain-derived neurotrophic factor, a protein whose expression is induced by NF- κ B. Another interesting study by Ravati et al. [46] linked NF- κ B activation with the inhibition of neuronal apoptosis by preconditioning with xanthine/xanthine oxidase or FeSO₄. In detail, neurons and astrocytes from neonatal rat hippocampus were incubated with the aforementioned compounds for 15 min. After 24 h of recovery, the neurons showed tolerance to staurosporine-induced apoptosis. Four hours after preconditioning, a transient activation of NF- κ B, MnSOD as well as a decrease in I κ B α were detected. As expected, the application of NF- κ B inhibitors, cycloheximide and antioxidants abolished the preconditioning-mediated neuroprotection, which only confirmed the participation of reactive oxygen species (ROS) and NF- κ B in this mechanism.

The results obtained by Digicaylioglu and Lipton [13] have suggested a connection between neuroprotection elicited by erythropoietin (EPO) and NF- κ B activation associated with its subsequent nuclear translocation. The application of EPO followed by the stimulation of its receptors was associated with protection against apoptosis evoked by NMDA or nitric oxide (NO). The authors have shown that this phenomenon entailed the activation of Janus kinase-2 (Jak2) and NF- κ B what consequently led to the transcription of NF- κ B-dependent neuroprotective genes. In addition, an intensified expression of neuroprotective genes *bcl-2* and *bcl-x1* mediated by NF- κ B was responsible at least partially for neuroprotective action of NGF against glutamate toxicity in cultured hippocampal neurons [12]. Moreover, the study performed by Heck et al. [22] provided evidence that neuroprotection against oxidative stress afforded by insulin-like growth factor-1 (IGF-1) was mediated by NF- κ B activation in immortalized hypothalamic rat GTI-7 cells. This action was dependent on the phosphoinositol (PI) 3-kinase. The neuroprotective effect of IGF-1 was abolished by NF- κ B inhibitors as well as PI 3-kinase inhibitors what confirmed the involvement of these aforesaid factors in the observed results. Barger and Mattson [3] have suggested that NF- κ B may play the role of coordinator of neuroprotective gene expression in response to various cytokines such as β -APP. The authors postulated that the influence of ROS on NF- κ B may also lead to the proper neuronal

adjustment, to an increased metabolic load and on the whole to the activation of neuroprotective program.

The study by Kassed et al. [31] has provided evidence that mice lacking NF- κ B p50 subunit were more prone to toxic degeneration of hippocampal neurons. Another study [30] has demonstrated that mice with mutations in the presenilin-1 gene, which is responsible for familial Alzheimer's disease (AD), were more susceptible to hippocampal degeneration and that it was probably due to the inhibition of NF- κ B p50 activation. Taking all these observations into account, the authors have hypothesized that the absence of NF- κ B p50 depletes neuronal pro-survival signals. These pro-survival signals probably are connected with the activation of numerous genes including *Bcl-x*, *Bcl-2*, the inhibitor-of-apoptosis proteins *c-IAP-1*, *c-IAP-2* [25]. Moreover, this suggestion may be supported by the fact that after middle cerebral artery occlusion in rats, NF- κ B binding activity decreased particularly in degenerating cells [24]. Complementary to these findings are the convincing evidences from the experiment carried out by Fridmacher et al. [15]. The forebrain-specific ablation of NF- κ B-driven gene expression in mice increased neurodegeneration after neurotoxic insults.

NF- κ B and dysfunctions of the CNS

Grilli and Memo [16] have postulated that NF- κ B proteins take part in initiation and acceleration of various neurodegenerative processes in the course of CNS diseases, such as Parkinson's disease (PD), Huntington's disease (HD) or AD. Many experimental as well as clinical studies have documented an increased activity of NF- κ B in pathological conditions of the CNS.

Amyloid beta peptide (A β) neurotoxicity is linked with the pathogenesis of neurodegeneration in AD. According to Kaltschmidt et al. [29] NF- κ B activation by low doses of A β and TNF- α leads to neuroprotection in primary neurons. Furthermore, the authors have found that over-expressed transdominant negative I κ B- α blocked NF- κ B activation and potentiated A β -mediated neuronal apoptosis. Also Barger et al. [2] have stressed the role of NF- κ B in the protective effect of TNF- α and TNF- β on hippocampal neurons against A β toxicity. This effect was likely due to suppression of ROS and Ca²⁺ accumula-

tion. On the other hand, proinflammatory pathway in AD was connected with an induction of NF- κ B-dependent macrophage-colony stimulating factor (M-CSF) [14]. Terai et al. [54] have reported that, in comparison with control postmortem cases, NF- κ B immunoreactivity was enhanced in hippocampal formation and human cerebral cortex areas affected by AD.

NF- κ B is activated in focal or global cerebral ischemia [9]. ROS are probably messengers taking part in this process. The study of Xu et al. [62] has indicated that acute inhibition of NF- κ B activation reduced brain injury in a rat model of middle cerebral artery occlusion. The authors have used a recombinant adenovirus, expressing a dominant negative form of I κ B, which was injected into the rat cortex. Consequently, the infarct size as well as neurological deficits were reduced. In human postmortem brains, the immunoreactivity of NF- κ B was enhanced in glial cells of infarcted areas but not in those unaffected by infarction [53].

Williams et al. [58] in their study have confirmed that delayed treatment (up to 6 hours after middle cerebral artery occlusion) with the proteasome inhibitor MLN519 was associated with the reduction of infarction and neurologic deficit caused by focal ischemic brain injury in rats and that this effect was due to the decreased activation of NF- κ B, reduced blood proteasome level and neutrophil infiltration. Similarly, in a rat model of transient focal cerebral ischemia, another proteasome inhibitor, PS519, reduced infarction and improved neurological function and EEG activity [45]. Interestingly, proteasome inhibitors were observed to reduce cerebellar granule cell survival under conditions of mild depolarization (25 mM KCl) and to intensify their apoptosis [42, 43]. The authors of the aforementioned studies emphasized the involvement of NF- κ B deprivation in the process of apoptosis.

Lerner-Natoli et al. [33] have observed over-expression of NF- κ B both in experimental model of epilepsy and in excitotoxicity. Another study has shown that kainate-induced seizures resulted in a rapid NF- κ B induction in adult rat limbic structures but it was not the case in juvenile rats [48]. These experimental data are consistent with the results of the study by Crespel et al. [11] who have demonstrated a significant and persistent over-expression of NF- κ B in hippocampi surgically removed from patients with hippocampal sclerosis and medial temporal lobe epilepsy. The authors have concluded that it is still to be

determined if this fact illustrates deleterious or neuro-protective properties of NF- κ B. The results obtained by Gveric et al. [21] suggest that NF- κ B activation in macrophages in multiple sclerosis lesions may amplify the inflammatory reaction through up-regulation of cytokines and adhesion molecules. As regards kainate-induced neurotoxicity, Won et al. [59] have shown the participation of NF- κ B in this process. This effect was NMDA-dependent.

In a postmortem study by Hunot et al. [23], NF- κ B immunoreactivity in the nuclei of mesencephalon dopaminergic neurons in the brains of PD patients was 70-fold higher than in control subjects. As NF- κ B activation is related to oxidative stress, the authors have suggested oxidant-mediated pathway in the PD pathology. The contribution of an aberrant regulation of NF- κ B in another pathology – ataxia telangiectasia has been postulated [26].

In an experimental model of HD, mice lacking the p50 subunit of NF- κ B occurred to be more prone to damages to striatal neurons. The administration of mitochondrial toxin 3-nitropropionic acid resulted in intensified apoptosis indicated by DNA fragmentation and increased activation of caspases [63].

Clinical application of NF- κ B inhibitors

Many pathological conditions including inflammatory diseases, neurodegenerative diseases or cancers, associated with the aberrant action of NF- κ B, would be theoretically good aim for pharmacological strategy. The therapy with NF- κ B inhibitors could be very advantageous in these cases. Perkins [44] has suggested in his review that it would be of great interest to find highly specific NF- κ B inhibitors. He has enumerated a potential list of NF- κ B inhibitors. Among the candidates for an NF- κ B inhibitor are I κ B- α super repressors, resistant to degradation. Bondeson et al. [5] have shown in their study that with adenoviral technique one can deliver NF- κ B super repressor and reduce tissue destruction as well as the inflammatory mechanisms in rheumatoid arthritis. Also Xu et al. [62] have provided evidence that the use of a recombinant adenovirus, expressing a dominant negative form of I κ B may protect the brain from ischemic injury.

Another possible therapy is connected with the use of low molecular weight inhibitors of IKK complex but as Perkins [44] has emphasized, it might unfortu-

nately lead to a generalized impairment of NF- κ B activation and dysfunctions, such as systemic lupus erythematosus or ataxia telangiectasia. Switching the activity of NF- κ B from anti-apoptotic to pro-apoptotic could be another potential strategy. Compounds modulating NF- κ B DNA binding activity or its interactions with some transcription factors might be very useful in pharmacological therapy of many disorders.

Numerous currently used anti-inflammatory drugs inhibit NF- κ B. In rat primary neuronal cultures and hippocampal slices, acetylsalicylic acid and sodium salicylate showed NF- κ B -dependent neuroprotective abilities against glutamate-induced neurotoxicity [17]. The authors have associated the presented data with the inhibition of glutamate-mediated NF- κ B activation. The findings of Kopp and Ghosh [32] are in accordance with these data. However, Vartiainen et al. [60] have not observed any influence of aspirin on NF- κ B binding activity, although it provided neuroprotection against hypoxia/reoxygenation injury.

Ibuprofen was found to act not only as a COX inhibitor but also through the stabilization of I κ B- α which resulted in the blockade of NF- κ B translocation to the nucleus [52]. Vartiainen et al. [61] have concluded from their study that although neuroprotective properties of piroxicam do not depend on COX activity, they cannot be only explained by the modulation of NF- κ B binding activity. Glucocorticoid receptor interaction with NF- κ B probably also contributes to the therapeutic properties of glucocorticoids [47]. Unlap and Jope [55] have shown that kainate-, pilocarpine- or lithium plus pilocarpine-induced NF- κ B activation was impaired in the hippocampus and cortex from adrenalectomized rats which reflects essential interactions between glucocorticoids and NF- κ B.

Antioxidants and metal chelators may also provide neuroprotection through the blockade of the persistent NF- κ B activation. Deferoxamine, an iron chelator, afforded protection against oxidative stress and decreased NF- κ B activation in lymphocytic and promonocytic cells latently infected by HIV-1 [49]. Green tea extract was demonstrated to provide neuroprotection against 6-hydroxydopamine (6-OHDA)-induced neuronal damage. As 6-OHDA was previously documented to induce NF- κ B nuclear translocation and its binding activity, green tea's polyphenols appear to inhibit NF- κ B activity mainly due to potent antioxidant and iron chelating actions [34]. Another NF- κ B inhibitor, curcumin, blocked hydrogen peroxide-, TNF-

and phorbol ester-mediated activation of NF- κ B [51]. Also herbimycin A [35] and cyclosporine A [38] prevented the activation of NF- κ B. Interestingly, it was postulated that particularly a transient NF- κ B activation caused production of survival proteins and thus neuroprotection. Clemens [9] has proposed the pathway of NF- κ B activation after cerebral ischemia which involves the active participation of ROS.

Conclusions

We are still unable to determine the exact role of NF- κ B in the organism. Therefore, its contribution to neuroprotection or neurodegeneration is unclear. According to Clemens [9], the complex role of NF- κ B is due to the fact that, depending on the interaction with other factors, it may induce genes encoding either death or survival proteins. Therefore, numerous studies have shown that under specific circumstances it may have proapoptotic or antiapoptotic action. Among antiapoptotic NF- κ B target genes, there are TNF receptor-associated factor 1 (TRAF1), TRAF2, c-IAP1 and c-IAP2, which play a role in suppressing caspase-8 activation [56]. The reports demonstrating that a transient NF- κ B activation after forebrain rat ischemia, evoked by four vessel occlusion, initiated protective factors in neurons that survived, whereas NF- κ B persistent activation induced death proteins responsible for neuronal death [10] imply that a potential usefulness of NF- κ B in the therapy should be thoroughly considered. Castagne et al. [8] have claimed that NF- κ B may evoke either death-inhibiting or death-promoting reactions. According to their theory, there are three parallel death pathways: two translation-dependent (I, II) and one translation-independent (III). NF- κ B is allegedly directly connected with translation-dependent pathway I, which could rationally explain the neuroprotective action of NF- κ B inhibitors. The pathways II and III are inhibited by the NF- κ B target genes products. The cited authors have observed that depending on the protein synthesis rate and redox status, neuroprotective or neurodegenerative effects of NF- κ B may occur. Numerous investigations that may prove clinical efficacy of pharmacological and genetic manipulations of NF- κ B signaling are in progress [37]. In summary, the aforementioned findings imply that NF- κ B may be a good target for

pharmacological strategy of numerous pathologies, including therapy of neurodegenerative diseases but this necessitates further research. Whether NF- κ B could serve in neuropharmacology as a potent coordinator of neuroprotective gene expression or not, is still an open question.

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