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COMMENTARY

Nuclear Factor-κB/Rel Proteins

A POINT OF CONVERGENCE OF SIGNALLING PATHWAYS RELEVANT IN NEURONAL FUNCTION AND DYSFUNCTION

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ABSTRACT. Nuclear factor-κB (NF-κB)/Rel designates a family of transcription factors participating in the activation of a wide range of genes crucially involved in immune and inflammatory function. NF-κB/Rel proteins have been demonstrated recently in primary neurons and in several brain areas. Functional significance of these proteins is still not understood completely, but since certain subsets of neurons appear to contain constitutively active DNA-binding activity, it seems likely that they may participate in normal brain function. A growing body of evidence is accumulating for a specific activation of NF-κB/Rel proteins in the CNS, and in particular in neuronal cells, during neurodegenerative processes associated to etiologically unrelated conditions. Whether NF-κB activation is part of the neurodegenerative process or of protective mechanisms is a matter of debate. This issue will be reviewed here with particular attention to the available reports on the activity of NF-κB/Rel proteins in both experimental paradigms of neurodegeneration and post-mortem brain tissue of patients affected by various neurological diseases. We hypothesize that NF-κB/Rel proteins may represent the point of convergence of several signalling pathways relevant for initiating or accelerating the process of neuronal dysfunction and degeneration in many neurological diseases, including Parkinson's disease, Alzheimer's disease, CNS viral infections, and possibly others. If NF-κB/Rel proteins represent an integrating point of several pathways potentially contributing to neuronal degeneration, molecules that finely modulate their activity could represent a novel pharmacological approach to several neurological diseases. BIOCHEM PHARMACOL **57**;1:1–7, 1999. © 1998 Elsevier Science Inc.

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NF-κB§/Rel is a transcription factor that was first discovered in the nuclei of mature B lymphocytes, where it bound specifically to a decameric sequence (5′-GGGACTTTCC-3′) in the kappa light chain enhancer region [1]. Over the years, the NF-κB/Rel system has become recognized as a central mediator of rapid and coordinated induction of genes in response to external, primarily pathogenic stimuli. Most of the genes known to be activated by NF-κB/Rel are indeed involved in the immune and inflammatory responses or, more generally speaking, in response to stress. An inappropriate regulation of NF-κB/Rel-mediated transcription has also been associated with pathological conditions including acute inflammatory reactions, toxic/septic shock, acute phase reactions, atherosclerosis, radiation damage, viral replication, myocardial infarction, and cancer and in several neuropathologies (for review, see Refs. 2–4).

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§ *Abbreviations:* AD, Alzheimer's disease; APP, amyloid precursor protein; AT, ataxia telangiectasia; COX-2, cyclooxygenase-2; GM-CSF, granulocyte, monocyte-colony stimulating factor; IL, interleukin; IRF, interferon regulatory factor; LOX, lipoxygenase; MHC, major histocompatibility complex; NF-κB, nuclear factor-kappa B; PD, Parkinson's disease; ROS, reactive oxygen species; and TNF, tumour necrosis factor.

THE NF-κB/REL SYSTEM

Understanding the activation of NF-κB/Rel has become increasingly complicated with the discovery of an entire family of transcription factors that autoregulate themselves through dimeric interaction and influence their own gene expression. The major proteins belonging to the family of NF-κB/Rel regulators include NF-κB1 (p50), NF-κB2 (p52), RelA (p65), relB, and c-rel. They all share the presence of a Rel homology domain of about 300 amino acids displaying a 35–61% identity between various family members [2–4]. Unlike other transcription factors, NF-κB proteins mainly reside in the cytoplasm in an inactive form bound to an inhibitory protein referred to as IκB. Upon appropriate stimulation, active NF-κB is released rapidly from the cytoplasmic complex by phosphorylation and ubiquination-dependent degradation of IκB. The IκB-released NF-κB dimer translocates to the nucleus, where it binds cognate DNA sequences and activates transcription of specific target genes. Members of the family can form

homo- and heterodimers between different subunits that bind with different affinities to variants of the κB motif in target genes. A further level of complexity in the system is accomplished by different affinities of dimeric complexes with different subunit composition for different members of the IκB family. A great variety of signals has been reported to activate NF-κB in several cell phenotypes. They include inflammatory cytokines, phorbol esters, oxidative stress, UV light, bacterial and viral products, and growth factors [2–5]. How such diverse stimuli can ultimately result in activation of NF-κB is not fully understood. Two second messengers have gained consensus as final intracellular mediators of NF-κB-activating stimuli: ROS (for review, see Ref. 3) and ceramide [5].

NF-κB PROTEINS IN THE BRAIN

The finding that proteins belonging to the NF-κB family are present in the CNS is relatively recent. The first report of a κB-like activity in neurons came in 1993 from Rattner and colleagues [6], who demonstrated that this activity mediated neuronal HIV-1 promoter activation.

The presence of these transcriptional modulators in neurons was then widely documented *in vitro* and *in vivo*, by both immunolocalization studies and electrophoretic mobility shift assays [7–11]. Of particular interest with regard to the CNS location and function of NF-κB/Rel proteins was the demonstration that unlike most of the cells in the periphery, except for B lymphocytes, a high constitutive NF-κB activity could be present in neurons. In particular, nuclear NF-κB specific immunostaining appeared to be present only in specific cellular subsets in rat cortex and hippocampus [8]. In light of this observation, it was hypothesized that the activation state of NF-κB might correlate with neuronal activity and that the modulator might be involved in regulation of the cellular antioxidant program in metabolically very active neurons, such as those of the cortex and hippocampus [5, 8]. A possible culprit under those conditions could be identified in glutamate that at nanomolar, non-toxic concentrations has been shown to activate NF-κB in cerebellar granule cells [10, 11]. Neuronal NF-κB inducible activity was demonstrated in neuronal bodies and, intriguingly, also in synapses [7, 12] and in postsynaptic densities [13], suggesting its role as a messenger carrying synaptic information to the nucleus. It would be no surprise, considering the role of NF-κB proteins in immune function, if these proteins were also found in an inactive cytoplasmic form in glial cells, including primary astrocytes, astrocytoma cell line microglia, and Schwann cells [14–16]. As far as the nature of the signals that trigger NF-κB activation within the CNS, they could be classified in two major groups. The first includes signals that are active also in the periphery, such as inflammatory cytokines (TNFα, IL-1), phorbol esters, oxidative stress, UV light, and bacterial and viral products [2–5]. The second represents CNS-specific signals, including depolarization, neurotransmitters like glutamate [9, 10] and opioids [17], nerve growth factor [18], and several diverse neurotoxic stimuli like glutamate at micromolar concentrations [19, 20], glycated tau [21], and β-amyloid [21–23]. A schematic representation of the NF-κB/Rel system operative in the CNS is shown in Fig. 1. The number of genes relevant for CNS function that might be regulated by members of the NF-κB family is still limited [3, 4, 24, 25]. The list includes genes encoding inflammatory cytokines (IL-6, TNFα, GM-CSF, C-CSF), chemokines (MCP-1, IL-8), MHC class I, inducible nitric oxide synthase, COX-2, manganese-superoxide dismutase, APP, p53, and neuropeptides (dynorphin, proenkephalin).

NF-κB AND NEUROPATHOLOGIES

A growing body of evidence is accumulating for a specific activation of NF-κB/Rel proteins in both neuronal and non-neuronal cells in neurodegeneration associated with etiologically unrelated conditions.

NF-κB is activated *in vivo* in a number of model systems of brain injury. Increased NF-κB DNA binding activity was demonstrated in the ipsilateral cortex after traumatic brain injury [26] and transient focal cerebral ischemia [27, 28], as well as after seizures induced by kainate or pilocarpine [29, 30]. Activation of NF-κB was demonstrated in experimental allergic encephalitis, a well-characterized model of CNS autoimmune injury, which is regarded as an animal model of multiple sclerosis. The increase in transcription factor activity strictly correlated with the course of clinical disease and was localized to microglia, macrophages/monocytes, and T lymphocytes [15].

NF-κB has also been shown to be activated in human brains of patients affected by several neurological diseases. The first report of NF-κB activation in brains of patients affected by AD came from Yan *et al.* [21]. In particular, in AD brains a specific activation of NF-κB p50 and p65 was documented in neuronal subsets showing signs of degeneration like glycated tau accumulation. Immunohistochemical analysis of brain sections from AD patients revealed that NF-κB p65 subunit was activated only in areas affected by the disease [31] and in both neurons and astrocytes surrounding early stage plaques [23]. This activation was correlated to β-amyloid deposition since the peptide is a potent NF-κB activator *in vitro* [23], possibly via interaction with the receptor for advanced glycation end products (RAGE) [22]. More recently, nuclear translocation of NF-κB in cholinergic neurons of the nucleus basalis of Meynert appeared to be increased significantly in AD brains compared with age-matched controls [32]. The first example of an NF-κB target gene with potential relevance in AD was the APP gene, whose proteolytic product is β-amyloid. Two stimuli potentially involved in neurodegeneration associated with AD, the inflammatory cytokine IL-1β and the excitotoxin glutamate, were shown to modulate NF-κB activity, interacting with the APP gene promoter region [9, 19].

Immunohistochemical techniques were used to study the

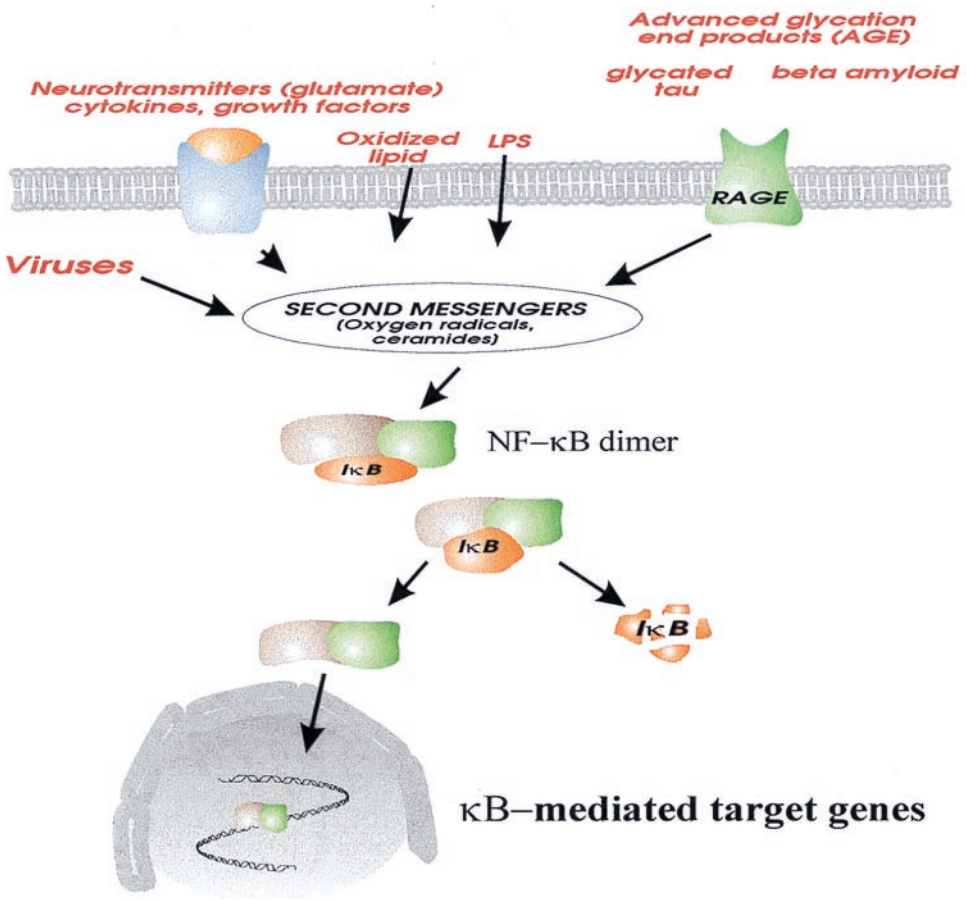

FIG. 1. Schematic representation of the extra- and intracellular signals that may activate the NF-κB/Rel system in neuronal cells. Abbreviations: LPS, lipopolysaccaride; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; and IκB, inhibitor of κB proteins.

expression and cellular localization of NF-κB in mesencephalic dopaminergic neurons in PD patients and age-matched controls. In PD patients, the number of neurons with positive nuclei was 70-fold more than in control subjects, suggesting that NF-κB translocation, which is essential to its activation, was related to the pathophysiology of PD [33].

Since the discovery of the role of NF-κB as a well-studied regulator of viruses, its potential involvement in CNS viral infections has been investigated. In particular, NF-κB has an established role in the replication of HIV-1, which is known to have profound effects in the brain, including neurodegeneration (AIDS–dementia complex). NF-κB activation in HIV-mediated CNS disease has been hypothesized to contribute to the induction of cytokines such as IL-6, TNFα, and GM-CSF, which could, in turn, be active participants in the histopathological lesions and clinical outcome of the disease [34]. A more direct role for NF-κB in the neurodegeneration associated with HIV-1 infection may also be hypothesized based on reports of a correlation between its activation and neuronal dysfunction [20]. The role of NF-κB family members in CNS viral infections is likely to be much wider. Evidence for such a role has been collected for at least another virus, the polyoma virus JC [35]. AT is a human disease characterized by neurological, immunological, and radiobiological problems, caused by a mutation in the *Atm* protein kinase gene. Aberrant NF-κB regulation, specifically a high constitutive activation, has been found in fibroblasts from AT patients and demonstrated to be implicated in their high sensitivity to ionizing radiation [36, 37]. Recently, electron microscopic evidence of neuronal degeneration in the cerebellar cortex of *Atm* knockout mice was reported [38]. In light of these observations, a possible correlation between neurological deficiencies and NF-κB activation would certainly deserve more extensive investigation.

In recent years, several clinical and experimental findings have suggested that inflammation may be a common component of several neurodegenerative conditions. Inflammatory cells (activated microglia) and mediators (cytokines, complement factors, acute phase reactants) are indeed commonly found to be closely associated to degenerating neurons [39]. In such a respect, the role of NF-κB/Rel proteins in neurodegenerative disorders may be greater than expected. NF-κB proteins are, in fact, ideal mediators of genetic programs underlying inflammation in CNS, since they are activated by inflammatory signals and, in turn, activate genes involved in inflammation [40]. On these

bases, it could be proposed that NF-κB/Rel may represent the point of convergence of multiple signalling pathways relevant for initiating or accelerating the process of neuronal dysfunction and degeneration in several neurodegenerative disorders.

NF-κB AND NEURONAL DEATH

The contribution of NF-κB family members to cell death and cell survival pathways is an intriguing and debated issue. We recently found that, at concentrations compatible with plasma levels reached during the treatment of chronic inflammatory states, salicylates may prevent glutamate-induced cell death in primary cultures of cerebellar granule cells and in hippocampal slices. The mechanism of action of salicylates in preventing glutamate-induced neuronal death appeared to correlate with the ability of these drugs to inhibit the glutamate-induced activation of NF-κB DNA-binding activity [20]. On the other hand, an anti-apoptotic role of NF-κB has been documented in other neuronal paradigms. NF-κB has been suggested to have a role in the neuroprotection of hippocampal neurons, since IκB antisense treatment resulted in an enhanced survival after β-amyloid exposure [41]. Furthermore, soluble APP, a neuroprotective product of APP metabolism, is an NF-κB activator [42]. Apparently opposing roles of NF-κB/Rel proteins in cell survival and death also have been reported in the periphery and are efficaciously referred to as "Janus faces" of NF-κB [43]. As suggested recently by Baichwal and Baeuerle [44], NF-κB is probably important in determining the fine balance between cell rescue and cell death that is fundamental for the normal life of each organism, in several cellular phenotypes. It is not clear, however, how cells translate NF-κB activation in a program promoting death or survival. At present, we can only speculate on factors that may affect choice between death and survival effectors in neuronal as well as in non-neuronal cells.

As previously underlined, NF-κB is not homogeneously expressed in the brain, and it shows diversity in subunit expression and subcellular compartmentation. In different cells, the relative expression of the different members of the NF-κB family may influence the composition of the dimers and, as a consequence, the affinity of the activated complex to specific DNA sequence motifs located in the regulatory regions of different genes. Moreover, activation of distinct patterns of genes by the simultaneous activation of other regulatory transcription factors may certainly contribute to opposite cell fates in different cell types but also within the same cell type perhaps depending on activation and metabolic state. Other actors may play a role on the same stage. HMG-like proteins have been shown to determine whether NF-κB may function as an activator or a repressor of transcription [45]. One exciting prospect originating from studies on CRE (cyclic AMP regulatory element)-mediated transcription [46] is that spatially distinct intracellular signalling may influence gene expression in a unique way. This issue basically stands on the observation that synaptic inputs that influence cytoplasmic and/or nuclear calcium levels differentially regulate distinct programs of gene expression and, therefore, distinct long-term neuronal changes. Detailed studies on the correlation between spatiotemporal dynamics in the activation of second messengers, including ROS and ceramide subcellular generation, and NF-κB function might disclose unexpected information. Finally, another concept to be applied to this debated issue is the concept of "threshold." Activation of NF-κB-mediated nuclear response may consist of a gradual recruitment of genes as a function of the intensity and temporal course of the triggering stimulus. This would imply a hierarchy in the NF-κB dimeric complexes to be activated, as well as in the genes whose transcription is initiated. For example, the physiological activation of glutamate receptors, which generates a short-lasting increase of intracellular calcium concentrations, may result in the activation of a restricted number of transactivators, among which are certain NF-κB complexes. Increasing glutamate concentrations at the synaptic level and/or abnormally stimulating glutamate receptors, as is likely to occur in some neuropathologies, may result in the activation of a larger number of transcription factors. These additional nuclear modulators, coordinately with NF-κB, might extend the number and/or amplify the level of transcription of NF-κB target genes to finally alter the cellular response. The checkpoint that discriminates between NF-κB-mediated physiological and pathological responses may be cell-specific, influenced by the nature and the intensity of the extracellular stimulus, and able to be modified continuously by the constitutive metabolic and functional context of the transcriptional machinery.

PHARMACOLOGY OF THE NF-κB/REL SYSTEM

Since the discovery of the involvement of NF-κB in different pathologies, as described above, molecules endowed with the ability of interfering with NF-κB activation and/or transcriptional activity have attracted great interest. Although for the majority of these molecules the precise mechanism and site of action are not completely clarified, the inhibitory effects on the NF-κB system appear to contribute to the large pharmacological spectrum of some of them, such as immunosuppressants and anti-inflammatory drugs.

Glucocorticoids are potent NF-κB inhibitors. Several mechanisms potentially underlie this property. Activation of glucocorticoid receptor was shown to induce transcription of the IκBα gene [47, 48]. In addition, activated glucocorticoid receptors directly interact with and inhibit activated NF-κB subunits [49].

Among non-steroidal anti-inflammatory drugs, several molecules have been shown to block activation of NF-κB complexes. The mechanism of action of salicylates in preventing NF-κB activation in T cells was suggested to be inhibition of IκB phosphorylation and degradation [50]. In primary neurons, the mechanism responsible for the inhi-

TABLE 1. Modulators of the NF-κB system

Drug	Pharmacological class	Proposed mechanism of action
Cyclosporin A	Immunosuppressant	Non-competitive inhibition of the proteasome, inhibition of IκB degradation
Herbimycin A	Tyrosine kinase inhibitor	Covalent modification of p50
IRF-1/2	Transcription factor	Physical interaction with NF-κB
Epigallocatechin	Anti-neoplastic	Physical interaction with NF-κB
Glucocorticoids	Anti-inflammatory	Up-regulation of IκBα, binding to NF-κB
Salycilates	Anti-inflammatory	Inhibition of IκBα degradation
Tepoxaline	Anti-inflammatory	Iron chelation
Deferoxamine	Anti-inflammatory	Iron chelation
Curcumin	Anti-inflammatory	Inhibition of IκBα degradation
IL-10	Cytokine	Unknown
Na^+ nitroprussiate	Nitric oxide donors	*S*-nitrosylation of p50

bition of glutamate-induced NF-κB activation and neuroprotection has not been investigated in detail. In light of the different composition of the activated NF-κB complexes in the two experimental paradigms, i.e. the p50–p65 heterodimer in HIV-long terminal repeat transfected T cells and a p50 homodimer in cerebellar neurons [20], one cannot exclude the possibility that diverse mechanisms of action of salicylate in inhibiting NF-κB activation may take place.

Tepoxaline, a dual COX/LOX inhibitor, appeared to prevent cytokine-mediated NF-κB induction by reducing the amount of available iron [51]. Iron chelation has also been claimed for inhibition of NF-κB by deferoxamine [52]. Curcumin, an antitumour agent with anti-inflammatory and anti-oxidant properties, inhibits TNF-mediated NF-κB activation by preventing phosphorylation and degradation of IκBα [53]. A direct physical interaction with NF-κB subunits has been suggested for IRF-1 and -2 [54, 55] and for epigallocatechin-3-gallate, potent antitumour agents with anti-inflammatory and anti-oxidant properties [56].

The immunosuppressant cyclosporin A has been shown to be capable of inhibiting lipopolysaccaride-induced NF-κB activation. Apparently, cyclosporin A acts as a noncompetitive inhibitor of the chymotrypsin-like activity of the 20S proteasome, thereby inhibiting IκB degradation [56]. Intriguingly, like salicylates, cyclosporin A has also been shown to be neuroprotective [57].

IL-10 is a potent anti-inflammatory cytokine. It has been shown to interfere with the activation of NF-κB, and this activity has been correlated with its ability to block the synthesis of other proinflammatory cytokines [58].

The tyrosine kinase inhibitor herbimycin A has been shown to inhibit IL-1-induced NF-κB by covalently modifying the p50 subunit so as to interfere with its DNA binding activity [59].

NO donors such as sodium nitroprussiate and *S*-nitroso-*N*-acetylpenicillamine were shown to directly inhibit the DNA-binding activity of NF-κB family proteins. A suggested mechanism was *S*-nitrosylation of the C62 residue of the p50 subunit [60]. Table 1 summarizes the proposed site and mechanism of action of a number of NF-κB inhibitors.

CONCLUSIONS

The pharmacology of the NF-κB system is opening up interesting perspectives in the development of novel strategies for therapeutic intervention in different diseases associated with an inflammatory response, including neurodegenerative diseases. In fact, there is the possibility to interfere at the nuclear level with the point of convergence of different signalling pathways that are triggered by distinct pathogenetic stimuli and that are relevant in neuronal dysfunction. Although the impact of the transcriptional pharmacology approach in clinical use and, in particular, in acute and chronic neurodegenerative disorders has still to be evaluated, it certainly deserves great attention. At the very least, we hope this speculative commentary may provoke thought and discussion on the possible rationale for developing inhibitors of NF-κB in the treatment of neurodegenerative disorders.

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