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NF-κB functions in the nervous system: From development to disease

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ABSTRACT

The transcription factor nuclear factor-κB (NF-κB) is an ubiquitously expressed dimeric molecule with post-translationally regulated activity. Its role in the immune system and host defense has been well characterized over the last two decades. In contrast, our understanding of the function of this transcription factor in the nervous system (NS) is only emerging. Given their cytoplasmic retention and nuclear translocation upon stimulus, NF-κB members are likely to exert an important role in transduction of signals from synaptic terminals to nucleus, to initiate transcriptional responses. This report describes recent findings deciphering the diverse functions of NF-κB in NS development and activity, which range from the control of cell growth, survival and inflammatory response to synaptic plasticity, behavior and cognition. Particular attention is given to the specific roles of NF-κB in the various cells of the NS, e.g. neurons and glia. Current knowledge of the contribution of NF-κB to several neurodegenerative disorders, such as Alzheimer's, Parkinson's and Huntington's diseases is also summarized.

1. The NF-κB signaling pathway in the nervous system

1.1. *The NF-κB/IκB families*

The transcription factor nuclear factor-κB (NF-κB) was discovered 20 years ago by the laboratory of D. Baltimore because of its ability to bind to the enhancer of the immunoglobulin (Ig) κ light chain gene in B cells [1]. It is in fact an ubiquitously expressed transcription factor with post-translationally regulated activity. In mammals, the NF-κB/Rel family of transcription factors comprises five members, p50, p52, p65 (Rel-A), c-Rel and Rel-B, which share a N-terminal 300 amino acid Rel homology domain allowing DNA binding, dimerization and nuclear localization [2]. These proteins form homo- or hetero-dimers [3] that are retained inactive in the cytoplasm by interaction with inhibitory molecules, called IκBs, which mask the NF-κB nuclear localization and DNA binding domains [4,5]. IκBs constitute another evolutionary conserved multigenic family, composed of IκBα, IκBβ, IκBε, IκBγ, IκBζ, Bcl-3, and the precursors of p50 and p52, p105 and p100, respectively [4,6,7]. Nuclear translocation of NF-κB can be induced by multiple stimuli including inflammation, infection, injury and stress [8]. The canonical pathway of NF-κB activation passes through the activation of an IκB kinase (IKK) complex, composed of two catalytic subunits, IKK1/α and IKK2/β, and a regulatory subunit NF-κB essential modulator (NEMO)/IKKγ. Upon stimulation, this complex triggers phosphorylation of two N-terminal serines within the IκBs, leading to their ubiquitination and degradation through the proteasome pathway [3,9]. Freed NF-κB dimers then migrate to the nucleus, bind to κB sites with consensus sequence GGGRNNYYCC (N = anybase, R = purine, and Y = pyrimidine) in the promoter or enhancer regions of target genes, and

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activate their transcription. Among the numerous genes regulated by NF-κB [8], are those encoding IκBα and IκBε, therefore providing a feedback mechanism whereby resynthesized IκBα and IκBε binds to DNA-bound dimers and export them out to the cytosol [10,11]. Another pathway of activation, or alternative pathway, has been described that involves phosphorylation of IKKα by NF-κB-inducing kinase (NIK), which then triggers inducible processing of the p100, causing the release of p52-containing dimers. This alternative pathway is currently thought to operate only in the immune system, upon stimulation by lymphotoxin (LT) β, B-cell-activating-factor (BAFF) or CD40 [12]. Even though degradation/resynthesis of the IκBs constitutes a seminal step in the control of NF-κB activation, many other regulatory mechanisms, including phosphorylation, ubiquitination, acetylation or sumoylation of upstream or downstream effectors, IKK subunits or NF-κB proteins themselves, provide a fine tuning of NF-κB signaling [13–20].

1.2. *Composition of NF-κB dimers*

Within the NS, the overall features of the canonical NF-κB transactivation cascade are conserved. The transcriptionally active form of NF-κB in the NS is primarily the p50/p65 heterodimer [21–30], although other dimers are emerging as important alternate effectors. c-Rel-containing dimers have been described during development [22] and in response to hypoxia in the hippocampus [31], to nerve growth factor (NGF) in sympathetic neurons [32], to interleukin (IL)-1β in primary cerebellar granular neurons [33] and to amyloid β (Aβ) peptide in primary cortical neurons [34]. The higher affinity of c-Rel homo-dimers for κB sites in comparison to p65 homo-dimers is likely one of the elements accounting for the specificity of the NF-κB transcriptional response in a given cell [33,35]. An additional factor may rely on the κB site sequence itself, which determines the selectivity of the interaction with coactivators [36]. Interactions between NF-κB and cAMP response element binding protein (CBP) [37–39] have indeed been described in neurons, and might explain the reports of κB-binding complexes distinct from bona fide NF-κB family members in grey matter extracts [40], developing cortex [41], cerebellum or primary cell cultures from microglia and neurons [42]. A possible interference between the NF-κB and Sp1 transcription factors nevertheless remains, as regards the binding to subsets of κB sites in neurons [43–45].

1.3. *Activating stimuli*

A wide array of stimuli which activate NF-κB in the immune system, do so in the NS, including cytokines (tumor necrosis factor κ (TNFα) and IL-1), chemokines, lipopolysaccharide (LPS), virus (HIV [24]), injury or oxidative stress (caused by superoxide and nitric oxide). Some of these activators may exert additional functions in the NS. For instance, TNFα or nitric oxide have been reported to regulate synaptic plasticity [46–49]. NF-κB is also activated by stimuli characteristic of the NS, such as neurotrophins (NGF and S100ββ) [50–52], neurotransmitters (glutamate [25,26,53,54], metabotropic glutamate receptor type 5 (mGlutR5) agonists [55], membrane depolarization [56], synaptic activity [28,57–59], amyloid β (Aβ) peptide [60], neural cell adhesion molecule (N-CAM) [30] or sleep deprivation [61,62]). Cell type and stimulus specificities are observed. For example, IL-1β induces NF-κB activity in astrocytes, but not in neurons [63]. On the other hand, glutamate activates NF-κB p50/65 solely in neurons [26]. Only NGF, and neither neurotrophin (NT)-3 nor brain-derived neurotrophic factor (BDNF), activates NF-κB in Schwann cells [50]. This activation is mediated through the p75/neurotrophin receptor (NTR) in Schwann cells [50] and in oligodendrocytes [64], but requires also tyrosine protein kinase receptor A (TrkA) in neurons [65,66]. However, all neurotrophins signal to NF-κB in microglial cells [67]. Activation of NF-κB in neurons is triggered by several signaling cascades, including p21(ras)/phosphatidylinositol-3-kinase (PI3K)/AKT, protein kinase C and calcium–calmodulin-dependent kinase II [56,57,68]. TNF treatment of primary astrocytes or neuronal cells induces a biphasic nuclear translocation of NF-κB controlled in its late phase by IκBα [69]. In contrast, IL-1β stimulation leads to sustained IκBβ-dependent NF-κB activation in a glial cell line [70]. These observations indicate that the feedback mechanism described above and the specific features of IκB members are operating in the NS. More interestingly, a novel mode of NF-κB activation by transglutaminase 2, independent of the classical IKK pathway and which involves polymerization of IκBα by this enzyme, has been recently described in microglia that could account for a cell type specific signaling [71,72]. Tyrosine phosphorylation of IκBα in primary hippocampal neurons or PC12 cells treated with NGF [73] and Ca^{++}-dependent protease calpain-degradation of IκBα upon glutamate treatment of cerebellar granule cells [54] have also been reported.

1.4. *Inhibiting stimuli*

NF-κB activity in the NS can be negatively regulated by a number of molecules, including transforming growth factor β (TGFβ), glycogen synthase kinase-3 (GSK-3β), IL-4, IL-10, glucocorticoids (reviewed in [74]). For instance, TGFβ2 inhibits NF-κB activity in cerebellar granule neurons [75]. In cortical neurons, the lipid peroxidation product 4-hydroxy-2-3-nonenal alters an upstream component of the NF-κB signaling pathway [76]. In astrocytes, NF-κB activation is negatively regulated by GSK-3β [77]. In activated glial cells under central nervous system (CNS) neuroinflammatory disease conditions, IL-4 inhibits NF-κB via a peroxisome proliferator activated receptor (PPAR)-γ-mediated mechanism, and thereby allows survival of differentiating oligodendrocyte precursors [78].

1.5. *Target genes*

Our current knowledge of the genes regulated by NF-κB in NS is scanty and relies mainly on extrapolation of genes identified in the immune system (see [8] for an extensive compilation). The past 3 years have seen the completion of the first microarray studies with neural tissue. As such, several new TNF-responsive genes were identified in a human glioblastoma cell line in comparison with 3T3 or Hela cells [79], as well as 17 genes specifically regulated by p50 in mouse hippocampus upon treatment with trimethyltin (TMT), a neurotoxic chemical [80]. In the CA1 region of hippocampus, 12 genes, out

of 38 genes selectively modulated by contextual long-term memory consolidation, contain c-Rel binding sites [81]. More recently, transcriptome analysis of hippocampus and cortex of mice, in which NF-κB activity is selectively ablated in forebrain neurons, spotted the protein kinase A catalytic α subunit as a new κB-responsive gene [82]. Other NF-κB target genes identified in the NS, which may be relevant for a specific function in this organ, include N-CAM [83], inducible nitric oxide synthase (NOS-II) [84], amyloid β precursor protein (APP) [53], β-secretase (BACE, the first and rate-limiting enzyme for APP cleavage) [85], μ-opioid receptors [86], BDNF [87], inducible cyclooxygenase-2 (COX-2) [88], calcium/calmodulin-dependent protein kinase II δ [80].

2. NF-κB and nervous system development

2.1. *Developmental changes in NF-κB activity*

Changes in NF-κB-binding activities and in the composition of the DNA binding complexes have been reported during NS development, therefore suggesting specific functions for the various NF-κB members. For instance, p50/p65 and p65/c-Rel dimers, and possibly p50/c-Rel, are detected in brain at embryonic day 17 (E17), whereas only p50/p65 dimers are seen in adult telencephalon [22]. Immunoreactivity against the various NF-κB members revealed a selective expression of these proteins during post-natal development (days 4–7 post-natal (PN)) in neuroblasts of the subventricular zone (SVZ) and rostral migratory stream in the telencephalon, which persists into adulthood in the SVZ, the predominant neurogenic region in the adult brain. These observations raise the possibility, yet to be demonstrated, of a nuclear NF-κB activity in these cells underlying migration processes and/or generation/survival of new neurons [89]. The current hypotheses regarding a potential role of NF-κB in neural stem cells are summarized in a recent review and will not be discussed here [90]. Restriction of NF-κB activity during development may rely in part on brain-expressed X-linked 1 (Bex1), a small adaptor-like protein of unknown function that interacts with p75/NGF, inhibits NF-κB activity and NGF-induced PC12 differentiation, as well as neuronal differentiation of brain SVZ neural precursors [91]. After birth, a strong and transient κB-binding activity (days 7–9 PN) and κB-dependent expression of a β-globin-reporter transgene (days 5–10 PN) is observed in the developing cerebellum that may be attributable to endogenous glutamate stimulation, since it is abolished upon intraperitoneal injection of glutamate receptor antagonists [92]. In the caudal brainstem, a structure enclosing many nuclei involved in cardiorespiratory control, NF-κB-binding activity increases during normoxia from day 2 PN to reach high levels at day 15 PN and peaks at day 60 PN [93].

Analysis of transgenic mice in which NF-κB activity was monitored through the expression of a reporter protein put under the control of NF-κB sites (Table 1), have identified the stages and sites where NF-κB is activated during development and in the adult. However, depending on the κB-responsive element chosen, the number of site repeats and the mouse model, a number of differences were observed from study to study. As regards the HIV κB site used for one mouse model [94,95], it was shown that this site binds complexes in EMSA that do not contain NF-κB in developing rat brain [41]. Therefore, only observations confirmed with different κB cis-acting elements and/or from crosses of the κB-sensor mice with other transgenics known to specifically inhibit NF-κB activity, can ascertain the relevance of the data. Indeed, during embryogenesis NF-κB activity was detected in the CNS as early as E12.5 in the spinal cord and certain nuclei of the rhombencephalon (olivary and cerebellar nuclei) of transgenic mice expressing the reporter gene lacZ under the control of κB sites from the p105 gene or Igκ enhancer [27]. The β-galactosidase staining spreads to pontine nuclei at E14.5 and to epithalamus at E18.5 in these animals. At E13, roof and floor plate lacZ staining of HIV κB-lacZ mice is lost in a tumor necrosis factor receptor-associated factor 6 $(TRAF6)^{-/-}$ background, an adaptor molecule for NGF receptor (NGFR), TNF receptor (TNFR) and IL receptor (ILR) signaling, suggesting a putative role of NF-κB in patterning of the neural tube [95].

Table 1 – Transgenic mouse models to monitor NF-κB activity in the nervous system

Mice	Phenotype
κB-β-globin	Global transcriptional NF-κB-reporter activity in normal brain and induction upon ischemia [119,123]; NF-κB activity in developing cerebellum [92]; induced NF-κB activity associated with loss of nociception in sciatic nerves of diabetic mice [186]
κB-lacZ	Identification of constitutive sites of NF-κB activity in the nervous system (from E12.5 to various regions in adult brain) [27,94,95] and inducible activity after infection [216]; chemical exposure [80]; sleep deprivation [62]; sciatic nerve injury [178]; ischemic injury [121]
κB-luciferase	Detection of inducible NF-κB activity in brain upon reoxygenation of hypoxic animals [217]

2.2. *Developmental functions*

The variety of structures harboring NF-κB activation during development likely reflects diverse functions according to stages and/or cell types. The neuroprotective function of NF-κB during neural development is now well established and has been shown to be cell- and/or time-restricted. Suppression of NF-κB activity by the super-repressor or κB decoy DNA has no effects on the survival of pyramidal neurons in somatosensory cortex slice cultures of P3 neonatal mice [96]. However, at earlier steps it results in apoptotic death of embryonic E16 cortical neurons or E18 sensory neurons from the trigeminal and nodose dorsal root ganglia (DRG) [94,97,98]. Conversely, overexpression of p65 in embryonic nodose neurons promotes cell survival. Complete abrogation of NF-κB activity in $IKK1^{-/-}IKK2^{-/-}$ mice leads to demise at E12.5 of embryos, which 70% present a defect in neural tube closure due to enhanced apoptosis in the neuroepithelium [99]. Increased apoptosis in spinal cord and DRG is also described in these mutant embryos

[99] as well as in p65$^{-/-}$ E12 and E14 embryonic sensory neurons from the trigeminal and nodose ganglia [97,98]. Signaling via the ciliary neurotrophic factor (CNTF) cytokine, and to a lesser extent via the NGF p75/NTR-mediated pathway, is responsible for the NF-κB-dependent survival of developing embryonic neurons, whereas BDNF survival properties are NF-κB-independent [97,98].

NF-κB activity has been shown to be also critical for regulating growth of neural processing in developing NS. Indeed, neurite outgrowth during NGF-induced differentiation of PC12 cells requires IKK2, is blocked by the SN50 peptide and involves c-Rel-containing dimers [100]. Use of the super-repressor or κB decoy DNA indicates that length and complexity of arborization are affected not only in vitro in somatosensory cortex slice cultures of P3 neonatal mice but also during development of the peripheral nervous system (PNS) at intermediate stages between E16 and P3, with a maximum at P0 in sensory neurons of the nodose ganglia [96]. NF-κB activity thus appears essential in a limited window of development for sensory neuron growth. Further investigations will tell whether this time-dependent effect also holds true for the growth of neurons in the CNS. What drives NF-κB activity during neurite outgrowth in vivo is still unclear, but involves phosphorylation of IκBα and proteasome function [96]. Neurite growth and neuronal survival are supported by different thresholds of NF-κB activity. Binding of c-Rel-containing dimers to high affinity κB sites likely discriminates target genes involved in these two processes, as well as specific signaling. For instance, Fas apoptosis inhibitory molecule (FAIM) antagonizes Fas-induced cell death, but regulates neurite growth of PC12 cells upon NGF treatment, of day 1 PN superior cervical ganglion neurons, and of E15 cortical neurons in a p65-dependent fashion via interaction with TrkA and p75/NTR [101].

3. NF-κB and central nervous system

3.1. NF-κB and neurons

3.1.1. NF-κB activation in neurons

High levels of NF-κB activity are detected in neurons in vitro and in vivo in various regions of the CNS, in particular in hippocampus, cortex, granular layer of cerebellum and pontine nuclei [23,26,27,57,94]. Brain cells that express a β-galactosidase transgene under the control of κB sites in vivo are exclusively neurons [27,94]. These findings revealed a constitutive stimulation of NF-κB in certain neurons of the brain and suggested that endogenous synaptic transmission could account for such activation. NF-κB and in particular p65-containing complexes are present in synaptic terminals [21,28,57]. Moreover, NF-κB-binding activity is induced in a number of learning and memory assays. Examples include its activation in mouse hippocampus by long-term potentiation (LTP) [102] or after inhibitory avoidance [103], in rat amygdala by fear-potentiated startle [58], and in crab brain after retrieval [59]. MGltuRs also activate NF-κB in the CA1 region of the hippocampus through PI3K and not the serine/threonine protein kinase AKT [55]. Therefore, NF-κB has been proposed to serve a dual function in neurons: it acts as a signal transducer transmitting information from active synapse to the nucleus via retrograde transport [21,28,57,104] and as a transcription regulator when it reaches the nucleus. The calcium-responsive signaling cascade is important for synaptic-dependent and basal NF-κB activity in neurons [56,57,105].

3.1.2. Synaptic activity and plasticity

Evidence has accumulated over the years for a role of NF-κB in synaptic signaling and transcriptional regulation mechanisms required for long-term plasticity. Since comprehensive reviews about NF-κB and synaptic activity have been recently published [74,106], only highlights and recent data will be elaborated here. κB decoy DNA blocks LTP induction in the hippocampus [46] and amygdala [58] as does ablation of the TNF signaling pathway in TNFR$^{-/-}$ mice [46]. More recently, loss of neuronal NF-κB in neuron-targeted NF-κB-deficient animals, which conditionally overexpress the super-repressor in forebrain neurons, was shown to slightly impair hippocampal basal synaptic transmission and inhibit the late phase of LTP [82]. Interestingly, deficit in c-Rel also slightly reduces basal synaptic transmission [55]. As for neuronal NF-κB-deficient mice, paired-pulse facilitation is not affected, suggesting that in both cases, there is no decrease in neurotransmitter release. Additional tests indicate that pre- and post-synaptic functions are normal in c-Rel$^{-/-}$ mice and that diminution in synaptic transmission is ascribable to a reduction in the number and not efficacy of synaptic inputs in the CA1 [55]. Moreover, neuronal-deficient NF-κB mice and c-Rel$^{-/-}$ mutants share a deficit in a form of long-term depression (LTD) dependent on mGlutR [82]. However, absence of neuronal NF-κB precludes induction of LTD, whereas c-Rel is required only for its late phase. These findings suggest that c-Rel is important for basal synaptic transmission in hippocampus and maintenance of LTD, whereas other members of the NF-κB family, in particular p65 might be responsible for induction of LTD and the late phase of LTP. The individual role of each NF-κB member in synaptic plasticity remains an important issue that should be explored in the near future with the analysis of new NF-κB member tissue-deficient mice.

3.1.3. Cognition and behavior

It is now obvious from several studies using pharmacological inhibitors of the NF-κB signaling pathway or different genetic mouse models (Table 2) that NF-κB plays a role in memory formation, cognition and behavior. A link between NF-κB and long-term memory was first proposed in crabs [107] and confirmed by treatment of crabs with sulfasalazine, an inhibitor of IKKs, which impaired memory reconsolidation [59]. Use of κB decoy DNA then indicated the involvement of NF-κB in long-term retention of fear memory in rats [39,58], inhibitory avoidance long-term memory [103] and spatial long-term memory in the Morris water maze task [108] in mice. P65-deficient mice rescued from embryonic death on a TNFR1$^{-/-}$ background displayed spatial memory defects when challenged in a radial arm maze [57]. c-Rel$^{-/-}$ mice are deficient in several hippocampal-dependent functions, such as contextual long-term memory consolidation [81] and long-term passive avoidance memory, and are also significantly hypoactive in the open-field task [55]. However, they harbor normal response in associative fear memory that involves

Table 2 – Mouse models to study the functions of NF-κB in the nervous system

Mice	Phenotype	Cell type
Transgenic overexpression of IκB-DN		
Tet-inducible-IκB-DN × CAMKIIα-tTA	Loss of neuroprotection upon excitotoxic damage [127]; reduced hippocampal synaptic transmission, impaired late LTP and LTD, impaired formation of spatial memory in Morris water maze but normal object recognition [82]	Forebrain neurons
GFAP-IκB-DN	Reduced inflammation and lesion after spinal cord injury [158]; no effect on ischemic brain damage [124]	Astrocytes
NSE-IκB-DN	Reduced ischemic brain damage [124]	Neurons
Transgenic overexpression of IKK-modulators		
Tet-inducible-IKK2-DN × CAMKIIα-tTA	Reduced ischemic damage [126]	Forebrain neurons
Tet-inducible-IKK2-DP × CAMKIIα-tTA	Enhanced ischemic damage [126]	Forebrain neurons
Knock-outs of NF-κB family members		
$p50^{-/-}$	Increased neural damage after excitotoxic injury [218]; increased striatal neuronal apoptosis in an experimental model of HD [213]; increased hippocampal neuronal apoptosis after chemical exposure [109]; increased susceptibility to noise- and age-induced hearing loss and neural degeneration [133]	[a]
$p65^{-/-}$	Impaired survival of E12 and E14 trigeminaland nodose sensory neurons to NGF and increased apoptosis in vivo [97,98]; myelin deficiency of DRG-derived Schwann cells in vitro [159]; loss of FAIM-induced increase in neurite outgrowth of E15 cortical neurons [101]	[a]
$p65^{-/-}TNFR^{-/-}$	Impaired formation of spatial memory in radial arm maze but normal excitatory behavior [57]	[a]
$p65^{-/-}TNF^{-/-}$	Increased Schwann cell apoptosis after axotomy [175]	[a]
$c\text{-}Rel^{-/-}$	Loss of Il-1β neuroprotective function against NMDA-mediated neurotoxicity [33]; reduced hippocampal synaptic transmission, impaired late LTD, impaired formation of long-term passive avoidance memory [55] and contextual fear memory [81]; hypoactive in open-field task, but normal nociception and anxiety behavior [81]	[a]
Knock-outs of IKKs		
$IKK1^{-/-}IKK2^{-/-}$	Increased apoptosis in neural tissue (including neural tube, spinal cord, DRG) leading to defect in neural tube closure [99]	[a]
$IKK2^{flox/flox}$ × CAMKIIα-CRE ($IKK2^{nKO}$)	Reduced ischemic damage [126]	Forebrain neurons
$IKK2^{flox/flox}$ × Nestin-CRE ($IKK2^{CNSKO}$)	Reduced ischemic damage; lesion comparable to $IKK2^{nKO}$ [126]	Neurons and glia

DN: dominant negative; DP: dominant positive.
[a] All cell type expressing the gene(s).

amygdala, in nociception and anxiety tests [81]. $p50^{-/-}$ mice, that lack both p50 and its precursor p100, present impaired learning in an active avoidance assay [109]. They also display reduced anxiety-like behavior in exploratory drive and anxiety tests [110]. In these knock-out mice, deletion of the individual NF-κB gene occurs in every cell type, and thereby prevents the discrimination between the function of NF-κB in neurons versus glia. Recent data with cell-restricted ablation of NF-κB demonstrates the prominent role of neuronal NF-κB in memory and cognition. Indeed, loss of neuronal NF-κB impairs spatial long-term memory formation in the Morris water maze task whereas non-spatial working/episodic memory is unaltered [82]. Altogether, these various studies indicate that NF-κB activation is essential for the mechanisms of long-term memory formation, especially those requiring the hippocampus. Very few data are currently available concerning the pathway by which NF-κB is activated and the transcriptional cascade accounting for its function in learning and memory. Classical IKK activation and degradation of IκBα mediate NF-κB nuclear translocation by fear conditioning [58]. In the rat amygdala, p65 acetylation occurs after fear conditioning, which increases p65 DNA binding activity and favors interaction with CBP [39]. Histone deacetylase (HDAC)-mediated deacetylation then behaves as an intranuclear molecular switch, which terminates the NF-κB transcriptional response involved in the formation of fear memory [39]. A novel transcriptional signaling cascade has been recently identified in neurons, in which NF-κB regulates the expression of the α

catalytic subunit of PKA in the hippocampus and consequently the CREB pathway [82]. The phosphorylation of CREB at Ser 133 by PKA is an essential molecular switch that converts short- to long-term memory [111,112]. Moreover, PKA has been shown to regulate long-lasting forms of synaptic plasticity [113,114]. The PKA/CREB pathway could therefore underlie the regulation of the late phase of LTP and spatial memory formation by NF-κB.

3.1.4. *Neuronal survival*

Besides its role in synaptic activity, NF-κB exhibits major and opposed functions in neurons as it can both promote and protect against cell death. These conflicting neuroprotective and neurodegenerative roles of NF-κB have been discussed in several reviews [115–117]. Only a few examples illustrating how the analysis of mouse genetic models contribute to our understanding of the function of NF-κB in neuronal survival in the CNS (Table 2) will be discussed here. Global ischemia activates p50/p65 dimers in neurons of rats [29,118], mice [119] and humans in penumbra-like areas [120], and promotes cell death [119,121]. Activation of NF-κB in glial cells also occurs during cerebral ischemia in humans [122] and rats [118]. Use of $p50^{-/-}$ mice, which presented reduced ischemic damage, first demonstrated the involvement of NF-κB in cerebral ischemia [119,123]. However, the significance of this data was difficult to evaluate, considering the fact that in these mice both activation and repression of NF-κB are affected. A recent study with transgenic mice that express the super-repressor under the control of a neuron-specific (NSE) or glial-specific (GFAP) promoter clearly demonstrates that only NF-κB loss in neurons, and not in astrocytes, reduces the infarct size [124]. In this type of injury, NF-κB activation in neurons, resulting at least in part from the binding of tumor necrosis factor-like WEAK inducer of apoptosis (TWEAK) to its receptor fibroblast growth factor-inducible 14 (Fn14) [125], contributes directly to cell death. IKK2 is activated in neurons by cerebral ischemia [126]. Loss of IKK2 by neuron-targeted deletion or expression of a trans-dominant negative mutant of IKK2 in forebrain neurons reduces ischemic brain damage in a similar way to that seen in neuron plus glia-deficient IKK2 knock-out mice. Conversely, activation of IKK2 by a constitutively active trans-dominant mutant of IKK2 in neurons increases infarct size [126]. These findings suggest that neuronal IKK2 has a major role in NF-κB-induced neuronal toxicity upon ischemia. In contrast, another NF-κB mouse model, with the super-repressor selectively expressed in basal forebrain neurons, is more sensitive to excitotoxic stress in vitro, revealing a neuroprotective function for NF-κB [127]. Another example of the neuroprotective role of NF-κB in neurons of the CNS is brought about by recent data disclosing a so far unknown role of NF-κB in the protection of primary auditory neurons and sensory cells from damage- and age-related degeneration. Spiral ganglion neurons (SGNs) are the primary carrier of auditory information from the sensory cells (hair cells) of the cochlea to the CNS. Degeneration of SGNs and/or hair cells occurs with age and cochlea injuries, resulting from noise, ototoxins, diseases or genetic mutations, and underlies most cases of hearing impairment. Several studies reported NF-κB translocation in hair cells in response to hypoxia [128], kanamycin treatment [129], acoustic trauma [130], as well as in SGN nuclei [131]. The few SGNs that do not undergo apoptosis after exposure of the round-window membrane of the gerbil cochlea to ouabain, a Na(+)K(+)ATPase inhibitor, are all selectively labeled by NF-κB, thus suggesting a protective role of NF-κB in enhancing the survival of type II neurons [132]. Moreover, $p50^{-/-}$ mice present an accelerated hearing loss and neural degeneration with age. This hearing impairment is not due to defects in hair-cell survival nor lateral wall function, but is rather associated with an exacerbated excitotoxic-like damage of afferent nerve fibers and loss of SGNs, concomitant with a rise of several calcium-buffering proteins. $p50^{-/-}$ mice also present an increased susceptibility to noise-induced hearing loss [133]. Besides this neuroprotective function upon injury, NF-κB might also regulate normal hair cell survival since massive apoptosis of hair cells has been observed in vitro when NF-κB activity is blocked by a cell-permeable inhibitory peptide [134] and NF-κB activity, independent of TRAF6, has been detected in the cochlear canal of κB-reporter transgenic mice with a HIV-derived NF-κB cis-acting element [95]. Collectively, these findings suggest that promotion or protection against neuronal death is likely to depend on the cell stimulus and type, the nature of activated NF-κB dimers and the duration of the stimulus [33,135].

3.2. *NF-κB and glia*

3.2.1. *Astrocytes and microglia*

Astrocytes and microglia, the two immune-regulatory cells of the CNS [136,137], are activated coordinately in response to injury, infection, and a variety of neurodegenerative and neuroinflammatory conditions [138–141]. Evidence has accumulated over the years indicating that the NF-κB signaling pathway plays an essential role in glial cell activation [74,116,142,143], which is not surprising given the seminal function of this transcription factor in the immune system. Many stimuli trigger NF-κB activation both in astrocytes and microglia (reviewed in [74]), resulting in the production of proinflammatory mediators including chemokines, cytokines such as TNFα, IL-1, IL-6, cytokine-induced neutrophil chemoattractant (KC), matrix metalloproteinase-9 or NOS-II [136,137,144–148]. In microglia, NF-κB, associated in a complex with poly(ADP-ribose) polymerase-1 (PARP-1) and high-mobility group protein 1(Y) (HMG-1(Y)), upregulates β-integrin CD11a expression, and thereby controls migration of the cells to the site of injury [149]. Activation of NF-κB in glia can be neuroprotective or promote neuronal death depending on the context, i.e. cell type, stimulus, duration and threshold levels of effectors. There is evidence that a critical NF-κB dosage is required for cell survival, and that either too little or too much is detrimental [150]. For instance, glia-derived reactive oxygen species (ROS) have been shown to protect neurons [151–153], whereas these molecules can also exert neurotoxic effects [154–156]. NF-κB regulates erythropoietin-differentiation of neuronal stem cells into astrocytes in vitro [157]. Recent analyses of transgenic mice overexpressing a trans-dominant negative mutant of NF-κB in astrocytes led to a considerable breakthrough in our understanding of the role of NF-κB in these cells. Inhibition of astrocytic NF-κB in transgenic mice expressing the super-repressor under the control of the GFAP promoter has no effect on ischemic brain damage, in contrast

to neuronal NF-κB inhibition [124]. These experiments may suggest a low contribution of astrocytic NF-κB in cerebral ischemia. Alternatively, it is possible that in these mice NF-κB inhibition is too low to see any phenotype. Indeed, the same approach undertaken by the group of Bethea, led to transgenic mice in which NF-κB activation by TNF or spinal cord injury (SCI) is completely prevented [158]. The fact that under physiological conditions, these astroglial NF-κB-deficient mice display normal locomotor behavior and retain complete integrity of spinal cord architecture without any increase in apoptosis, demonstrate that NF-κB in astrocytes is not a critical regulator of spinal cord development and function. However, loss of astrocytic NF-κB activity results in functional recovery after SCI [158]. Locomotor performance is improved, white matter sparing is increased, whereas expression of TGFβ2 and essential constituents of the glial scar, such as chondroitin sulfate proteoglycans, are decreased. Downregulation of chemokines involved in blood cell chemotaxis, CXCL10/IP-10 and CCL2/MCP-1, could explain the reduced infiltration of leukocytes in the vicinity of the lesion, which may restrain the inflammatory response after injury. Collectively, these findings establish the essential contribution of the astrocytic NF-κB signaling pathway to the pathophysiology of SCI.

3.2.2. *Oligodendrocytes*

Little is known about the role of NF-κB in oligodendrocytes. These glial cells are responsible for the myelination of nerve cells of the CNS, a function performed by Schwann cells in the PNS. As NF-κB has been shown to orchestrate the myelination process in Schwann cells [159], it is likely but remains to be established that NF-κB exerts the same function in oligodendrocytes, even though they produce a slightly different kind of myelin. NF-κB could also regulate the remyelination process by oligodendrocytes, as TNFα was shown to be required for both remyelination and proliferation of oligodendrocyte progenitors cells (OPCs) [160]. Again as for other cells of the NS, NF-κB exhibits antagonistic properties in oligodendrocytes: it has a prosurvival role and promotes maturation of OPCs, through a platelet-derived growth factor-α (PDGF-α) receptor signaling pathway triggered by binding of a soluble factor produced by non-activated microglia [161], as well as survival of oligodendrocytes after TNF exposure [162]. NF-κB translocation of p50, p65, and c-Rel-containing dimers mediates, in contrast, ROS-induced apoptotic cell death of oligodendrocytes [163]. NF-κB activation in oligodendrocytes is important in response to stress and injury. Immunoreactivity for p65 NF-κB in oligodendrocytes located at the edge of active lesions and on microglia/macrophages throughout plaques has indeed been reported in multiple sclerosis, a disease which often sees destruction of oligodendrocytes, therefore compromising the repair process [164].

Recent data indicate that glia, in particular astrocytes and OPCs, are active participants in synaptic transmission [165,166]. Moreover, constitutive TNFα release by glial cells promotes, in hippocampal neurons, upregulation of AMPA receptors [47], internalization of inhibitory $GABA_A$ receptors [48], and thereby increases synaptic strength. Transgenic mouse models in which NF-κB activity is abrogated in one of these cell types should undoubtedly resolve the question as to whether and how such activity in astrocytes or OPCs contributes to synaptic signaling.

4. NF-κB and peripheral nervous system

4.1. *Schwann cells*

4.1.1. *Myelination*

In the PNS, Schwann cells are the supplier of myelin, which forms a multilayered insulating membrane along axons that enhances impulse conduction [167]. In developing PNS, neurons signal to the pre-myelinating p75/NTR-expressive Schwann cells to activate a differentiation program resulting in the generation of the myelin sheath by mature Schwann cells. NF-κB, in particular p65, has been shown to play a cardinal role in the differentiation of Schwann cells into those exhibiting the myelinating phenotype. In vivo, nuclear NF-κB activity, detected both by immunostaining of activated p65 and p65 DNA binding activity, follows the sequences of Schwann cell differentiation and myelinating program: it is present in immature Schwann cells of the rat sciatic nerve at birth, and then declines after day 8 PN to undetectable levels in adult [159]. NF-κB is also found activated in Schwann cells during myelination in vitro. Its inhibition by the super-repressor prevents myelination and activation of Oct-6, a POU domain transcription factor essential for progression to the myelinating lineage. Consistently, DRG-Schwann cell cocultures from $p65^{-/-}$ mice display a myelin deficiency, due to a defect of Schwann cells to ensheath neurons [159]. Altogether, these findings demonstrate that NF-κB stimulation is an essential step in Oct-6 activation and commitment to myelination. Identifying the signaling pathways that trigger such NF-κB activity in immature p75/NTR-expressive Schwann cells as well as the genes, besides Oct-6, that are selectively induced by NF-κB are the next issues to be solved. Myelination in Schwann cells is enhanced by BDNF working through p75/NTR [168], and NGF binding to p75/NTR activates NF-κB [169]. The specific intracellular cascade leading to NF-κB activation during myelination may therefore involve p75/NTR, phosphatidyinositol-3-kinase and AKT signaling [170].

4.1.2. *Survival*

P75/NTR-mediated NF-κB activation by NGF in Schwann cells occurs through the recruitment of adaptor molecules, such as TRAF6 and receptor-interacting protein 2 (RIP2), thereby eliciting a prosurvival signal, whereas activation of the Jun-N-terminal kinase (JNK)-mediated p75/NTR pathway is required for a pro-apoptotic response [171]. RIP2 has been shown to trigger NGF-induced NF-κB activity in a TRAF6-independent manner and to be required for rescuing survival of Schwann cells upon NGF treatment [172]. TRAF6 is also an essential player of p75-mediated NF-κB signaling, since $TRAF6^{-/-}$ Schwann cells present a strong decrease in NGF-induced NF-κB transactivation [171]. Schwann cells, transduced with an adenovirus expressing the super-repressor or from DRG $p65^{-/-}$ animals, behave as wild-type controls [159]. This indicates that proliferation or survival of Schwann cells, in the absence of stimulus, does not require NF-κB activity.

4.1.3. *Response to nerve injury*

Due to the essential role of NF-κB in myelination during development of the PNS, it is tempting to speculate the existence of an analogous capacity in remyelination after nerve injury. In support of this possibility, it was shown that angiotensin II, which enhances rat sciatic nerve regeneration after crush injury in vivo, induces NF-κB translocation in Schwann cells in vitro [173]. However, the role of NF-κB in response to nerve damage is probably complex, since NF-κB activation mediates both cell differentiation and ceramide-induced apoptosis induced by NGF through the p75/NTR in Schwann cells [50,174]. Outcome of Schwann cells depends on intracellular ceramide concentration, which is linked to p75/NTR expression levels [174]. Besides the NGF/p75NTR signaling, the TNFα/TNFR1 pathway is the other transduction mechanism known to trigger Schwann cell death. In axotomised mouse neonates, TNFα increases Schwann cell death apoptosis in the distal nerve segment, when cell density is low, together with p65 translocation, and upregulation of p75/NTR [175]. Increased cell density protects Schwann cells from both TNF- or NGF-induced apoptosis in vitro [175]. However, absence of p65 in $p65^{-/-}TNF\alpha^{-/-}$ mutant mice potentiates TNF-independent Schwann cell apoptosis in the distal nerve fragment following axotomy [175], suggesting a prosurvival role for NF-κB. More studies are definitely required to understand how NF-κB regulates Schwann cell fate upon injury and determine how it participates to the regeneration process.

4.2. *Sensory neurons*

DRG contain the cell bodies of sensory neurons, from which emanates bifurcated axons which forms a synapse within the spinal cord at the central end, while the peripheral sensory ending resides in a sensitive tissue. Adult rat sensory neurons in intact DRG in vivo have very low κB-binding activity [176], in contrast to hippocampal or cortical neurons. This indicates that NF-κB activity is not required for survival of these cells under physiological conditions, in contrast to developing embryonic sensory neurons. However, upon peripheral nerve injury, NF-κB activation is a major player of the survival response of adult DRG neurons. Partial or complete sciatic nerve transection, chronic constriction injury or sciatic nerve crush [176–178] result in rapid NF-κB activation that persists for several days in the ipsilateral lumbar DRG neurons. In dissociated adult rat DRG neurons, which mimic to some extend nerve axotomy, suppression of NF-κB activity by an inhibitory peptide, SN50, or κB decoy DNA leads to neuronal death, increasing with cell size. Cell death occurs through a caspase-independent mechanism that involves mitochondrial oxidative stress [176]. Interestingly, TNFα, which increases NF-κB-binding activity in vivo in rat DRG after intraplantar injection [51], is locally released by adult sensory neurons in vitro [176] or in vivo upon injury [179]. Survival of medium to large sensory neurons therefore requires NF-κB activity that is stimulated by a unique local paracrine TNFα release [176], consistent with other studies with isolated cultured neurons where TNFα-dependent NF-κB activation is neuroprotective [180,181].

4.3. *Nociception*

Recent studies indicate that NF-κB is involved in nociception and may regulate the pathogenesis of neuropathic pain through the expression of inflammatory mediators. In rat neuropathic pain models, local injections of κB decoy DNA, at the site of nerve injury downregulate NF-κB p65 nuclear activity, suppress expression of proinflammatory cytokines, NOS-II or COX-2, and significantly alleviate thermal hyperalgesia [182,183]. NF-κB activation in these peripheral neuropathy models has been proposed to be negatively regulated by ZA-3, a zinc-binding protein [184,185]. In contrast, a receptor for advanced glycation end products (RAGE)-dependent NF-κB activation has been discovered in diabetic patients and in a streptozotocin-induced experimental mouse model of diabetic neuropathy that controls IL-6 expression, is reversed by insulin treatment, and induces a loss of pain perception [186].

5. NF-κB and neurodegenerative disorders

The NF-κB signaling pathway is altered in many chronic neurodegenerative diseases. As discussed above, NF-κB may exert a dual role: it may promote survival of neurons by inducing the expression of neuronal anti-apoptotic genes and contributes to neurodegeneration by inducing the synthesis of inflammatory mediators in glial cells.

5.1. *Alzheimer's disease*

Alzheimer's disease (AD) is the most common form of neurodegenerative disorder with dementia in the elderly. The neuropathological hallmarks of AD include deposits of Aβ peptides, accumulation of abnormal tau protein filaments in neurofibrillary tangles, extensive neurodegeneration and loss, but also signs of chronic inflammation. First reports indicated an increased p65 immunoreactivity both in neurons and glial cells at the vicinity of early plaques in post-mortem brain examinations of AD patients [151] as well as in cholinergic neurons of the basal forebrain [187] and in hippocampus and entorhinal cortex of AD patients [122]. However, a detailed analysis of plaque stages in AD patients revealed a strong decrease in nuclear p65 immunoreactivity in the cells surrounding plaques from early to late stages of the disease in comparison to healthy controls [188]. Aβ peptides, the 39–43 amino acid toxic derivatives of APP, activate NF-κB in neuroblastoma [60,189] and in primary cultures of cerebellar granule cells [151] through binding to neuronal RAGE [189,190]. In turn, neurons can trigger and promote microglial activation by expressing macrophage colony-stimulating factor (M-CSF), thus participating in the pathogenic process [189]. In rat cortical astrocytes, Aβ stimulates NOS-II expression and NO production via a NF-κB-dependent mechanism, therefore supporting the importance of oxidative damage and astrocyte NF-κB signaling in AD neuropathogenicity [191]. Accordingly, gene expression profiling of post-mortem human cortical microglia treated for 24 h with low dose of Aβ revealed upregulation of many NF-κB target genes, including IL-8 [192]. SAPPβ, an alternative secreted proteolytic cleavage product of APP, also activates NF-κB and stimulates inflammatory

mediator production (IL-6, NOS-II) in microglial cells [193], as well as in neuroblastoma and primary hippocampal neurons [194]. Increased microglial κB-dependent gene activation has been reported in LPS-treated transgenic mice expressing apolipoprotein E4 (apoE4), the main genetic risk factor of AD [195]. Moreover, Aβ stimulation of microglia or monocytes leads to neuronal TNFα-dependent expression of NOS-II and apoptosis [155]. Inhibition of NF-κB activity in microglia by expression of the super-repressor blocks Aβ neurotoxicity [196]. These observations establish a pivotal role for microglial NF-κB signaling in mediating Aβ toxicity, whereas NF-κB activation in neurons has been shown to be a survival determinant in AD [188]. Indeed, pretreatment of neurons with TNFs [181] or low doses of Aβ peptides [188] protects them against a high cytotoxic dose of Aβ. Conversely, high doses of Aβ peptides induce in a dose-dependent fashion neuronal apoptosis, which is mediated by the nuclear translocation of p50 and p65, and Bcl-XL reduced and Bax-induced levels [197]. Neuroprotection against Aβ is also elicited by sAPP in primary neurons and PC12 cells by a mechanism requiring NF-κB activation [198,199]. Neurons in transgenic mice expressing the human mutPS-1 gene (M146L), causally linked to many cases of early-onset inherited AD, exhibit increased neurodegeneration and impaired NF-κB p50 activation following exposure to the TMT neurotoxin [200]. In neurons, mGlu5 activation promotes a c-Rel-dependent anti-apoptotic pathway, responsible for survival in response to Aβ, and which includes upregulation of Bcl-XL and manganese superoxide dismutase (MnSOD) [34]. Beside neurotoxicity, Aβ peptides are also responsible for NF-κB activation and apoptosis in oligodendrocytes [154]. The identification of several κB-binding sites upstream of APP [53] and BACE genes [85] raises the possibility, yet to be demonstrated, of a role of NF-κB in amyloidogenesis itself.

5.2. *Parkinson's disease*

Parkinson's disease (PD) is characterized by a preferential degeneration of dopaminergic neurons in the substantia nigra and the appearance of intracytoplasmic inclusions coined Lewy bodies. A 70-fold increase in the proportion of dopaminergic neurons exhibiting nuclear p65 immunoreactivity was observed post-mortem in the brains of PD patients compared to age-matched control subjects [201]. It has been proposed that production of free radicals, which is necessary for NF-κB activation and subsequent neuronal death in cultures of rat mesencephalon [201] or PC12 cells [202], might be the mechanism underlying neuronal death in PD. Whereas a nuclear translocation of NF-κB in various cell types, including PC12 cells, SH-SY5Y neuroblastoma cells or primary cultures of dopaminergic neurons following treatment with 1-methyl-4-phenyl-4-phenylpyridinium ion (MPP+), 6-hydroxydopamine, dopamine or ceramide is well established [203–206], the role of NF-κB in dopaminergic neurons is still largely controversial. NF-κB has been described as promoting [204] or delaying [205] dopamine-induced apoptosis in PC12 cells. Recent data with dopaminergic neuronal MN9D cells [72] argue in favor of a drug-specific activation of NF-κB as a survival factor for dopaminergic neurons. In addition, use of $p50^{-/-}$-deficient mice suggests that NF-κB plays a minor role in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, although hydroxyradical production is enhanced [207].

5.3. *Hungtington's disease*

In Hungtington's disease (HD), expansion of polyglutamine tract in exon 1 of huntingtin (Htt) results in protein aggregation that induces selective degeneration of striatal projection neurons and cortical pyramidal neurons. Several lines of evidence indicate that NF-κB regulates this polyglutamine-induced neurodegeneration. Injection of the mitochondrial toxin 3-nitropropionic acid (3PN), which mimics the neurodegeneration induced by mutant Htt, leads to NF-κB activation and expression of the pro-apoptotic genes, myc and p53 in medium-size striatal neurons [208]. Activated NF-κB is also detected in cortical and striatal neurons of HD transgenic mice, and mutant Htt has been shown to activate the IKK complex through direct association with NEMO in PC12 cells [209]. Inhibition of the NF-κB pathway decreased significantly mutant Htt-induced toxicity in cell cultures and in brain slices [209], maybe in part because of the possible downregulation of transglutaminase 2, an enzyme transcriptionally regulated by NF-κB proposed to cross-link mutant Htt [210–212]. These various studies suggest an inducing role of NF-κB in the neurodegenerative process occurring in HD. In contrast, $p50^{-/-}$-deficient mice, which are deprived of both p50 and the inhibitory p105 precursor, when exposed to intrastriatal infusion of 3PN display increased damage to striatal neurons [213]. Since, mutant Htt has been recently reported to accumulate in glial nuclei of HD brains and glial cells expressing mutant Htt increased neuronal vulnerability [214], NF-κB might also participate in the neurodegeneration induced by mutant Htt via its potential activation in glial cells.

6. Concluding remarks

In spite of the major advances accomplished recently towards unraveling the role of NF-κB in the NS, many questions regarding how this multifunctional transcription factor finely tunes normal and pathological NS processes remain to be answered. In particular, deciphering how NF-κB activity is differentially regulated in the various functional cells in the NS, to provide specific responses to developmental, synaptic, trophic or injury stimuli will be a major issue. Important future topic of investigations will deal with the evaluation of the functional significance of individual NF-κB family members in these processes as well as the identification of their specific target genes and the signal transduction cascades involved. Since functional interplay between NF-κB and other signaling cascades, in particular AP1 or CREB, is likely to contribute to the function of NF-κB [63,215], another challenging issue will be to precisely define the complex relationships between NF-κB and these pathways in the NS. Understanding how and when the NF-κB signaling pathway is helpful or harmful in the NS during progression of NS diseases will also be essential for the development of future therapeutic strategies.

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