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Stefka Mincheva-Tasheva[1] and Rosa M. Soler[1]

Abstract

Intracellular pathways related to cell survival regulate neuronal physiology during development and neurodegenerative disorders. One of the pathways that have recently emerged with an important role in these processes is nuclear factor-κB (NF-κB). The activity of this pathway leads to the nuclear translocation of the NF-κB transcription factors and the regulation of anti-apoptotic gene expression. Different stimuli can activate the pathway through different intracellular cascades (canonical, non-canonical, and atypical), contributing to the translocation of specific dimers of the NF-κB transcription factors, and each of these dimers can regulate the transcription of different genes. Recent studies have shown that the activation of this pathway regulates opposite responses such as cell survival or neuronal degeneration. These apparent contradictory effects depend on conditions such as the pathway stimuli, the origin of the cells, or the cellular context. In the present review, the authors summarize these findings and discuss their significance with respect to survival or death in the nervous system.

Keywords

NF-κB, neuronal survival, neurotrophic factors, RelA/p65, neurodegenerative disorders, motoneuron

Introduction

Neurons and non-neuronal cells of the nervous system require for their survival and function extracellular and intracellular signaling molecules such as neurotrophic factors or calcium. These molecules activate intracellular signaling pathways, which in turn regulate the activation or inhibition of gene expression. Intracellular pathways are the mechanisms that regulate cellular events during nervous system development, adulthood, and disease (Airaksinen and Saarma 2002; Chao 2003). New evidences that emerged during the past 10 years have shown the complex regulation of these pathways and expanded the list of those regulating neuronal survival and function. One of these pathways is the nuclear factor-κB (NF-κB). The NF-κB pathway was discovered in 1986 as a transcription modulator of the light chain of B lymphocyte immunoglobulins (Sen and Baltimore 1986). Subsequent studies showed that NF-κB is a ubiquitously expressed dimeric transcription factor involved in cellular processes such as inflammation, adhesion, proliferation, differentiation, apoptosis, and oncogenesis. This family of transcription factors also has an important role during nervous system development and pathology. The effects caused by NF-κB activity in the nervous system are usually based on the control of neuronal apoptosis, neurite outgrowth, and synaptic plasticity. Genes regulated by NF-κB dimers are mainly responsible for these functions, and the long list of these genes creates an intricate intracellular network that contributes to the complexity of the pathway. The list of NF-κB functions in the central and peripheral nervous system is apparently not finished, and some of these functions are in fact contradictory. The present review of the NF-κB pathway places special emphasis on its function in the developing nervous system and in neurological disorders.

NF-κB Family Members

NF-κB is a dimer composed of members of the Rel family of transcription factors: RelA (p65), RelB, c-Rel, p50, and p52. All these proteins have in common a highly conserved 300-amino acid domain called Rel homology

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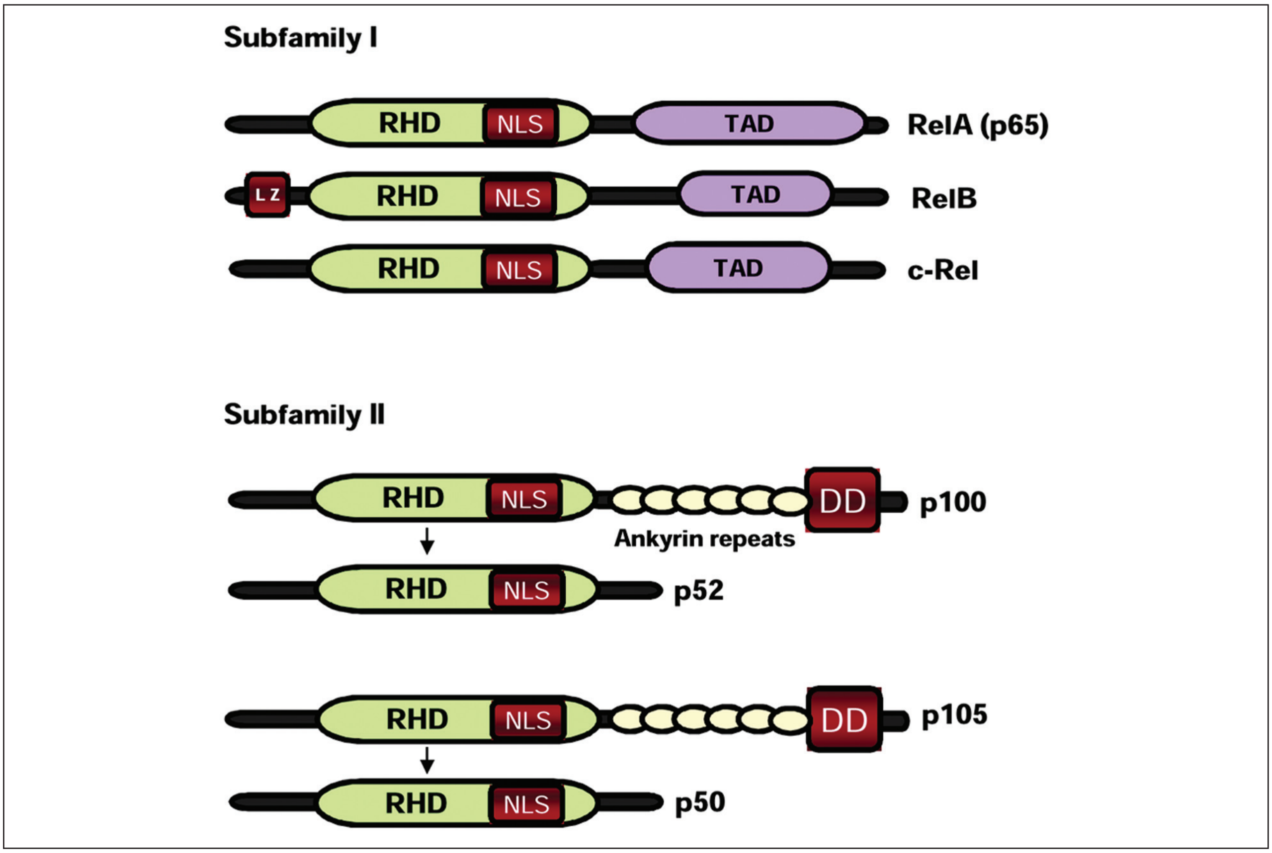

Figure 1. NF-κB family members. RelA, RelB, and c-Rel constitute the NF-κB subfamily I characterized by the presence of Rel homology domain (RHD), responsible for NF-κB dimerization, IkB interaction, and association to the DNA. This domain contains the nuclear localization sequence (NLS), responsible for NF-κB nuclear translocation. The members of NF-κB subfamily I also contain the transactivation domain (TAD), responsible for their transcriptional activity. RelB has a leucine zipper motif (LZ). p100 and p105 and their mature forms p52 and p50, respectively, constitute the NF-κB subfamily II. They also contain the RHD with NLS; however, in their c-terminal end p100 and p105 contain several ankyrin repeats and a death domain (DD). After proteasome degradation, ankyrin repeats and the DD are released and the mature products of these proteins, p52 and p50, are composed only by RHD with NLS.

domain (RHD). The RHD is responsible for NF-κB dimerization, NF-κB and IκB interaction, and NF-κB dimer association with DNA (Huxford and others 1999) and contains the nuclear localization sequence (NLS) necessary for NF-κB translocation to the nucleus (Ghosh and others 1998).

The NF-κB proteins can be classified into two subfamilies depending on their structure (Fig. 1). Subfamily I includes RelA, c-Rel, and RelB; the members of this subfamily contain a transcription activation domain (TAD). Subfamily II includes the proteins p52 and p50, generated from their precursors, p100 and p105, respectively; these do not contain the TAD and are unable to activate gene transcription after NF-κB activation. The p100 and p105 precursors contain several ankyrin domains that are processed by the proteasome when the pathway is activated. Thus, these immature forms of p52 and p50 may be considered as inhibitors of the NF-κB signaling pathway (Ghosh and others 1998). Even though it is possible to find different homo- or heterodimers of NF-κB members in the cells, in mammalians the most abundant form is the RelA/p50 heterodimer.

The NF-κB Inhibitors: IκB

In the absence of stimuli NF-κB homo- and/or heterodimers are present in the cytoplasm and form inactive complexes with their inhibitors, which are members of the IκB (Inhibitor κB) protein family (IκBα, IκBβ, IκBε, IκBγ, IκBδ, and Bcl-3) (Fig. 2A). When the pathway is activated, NF-κB dimers are released from the inhibitor and translocated to the nucleus where they bind to the κB sequences of the DNA. The IκB inhibitors have in common their three-dimensional structure and a variable number of ankyrin-repeat motifs located in their amino-terminal segment. These ankyrin motifs are responsible

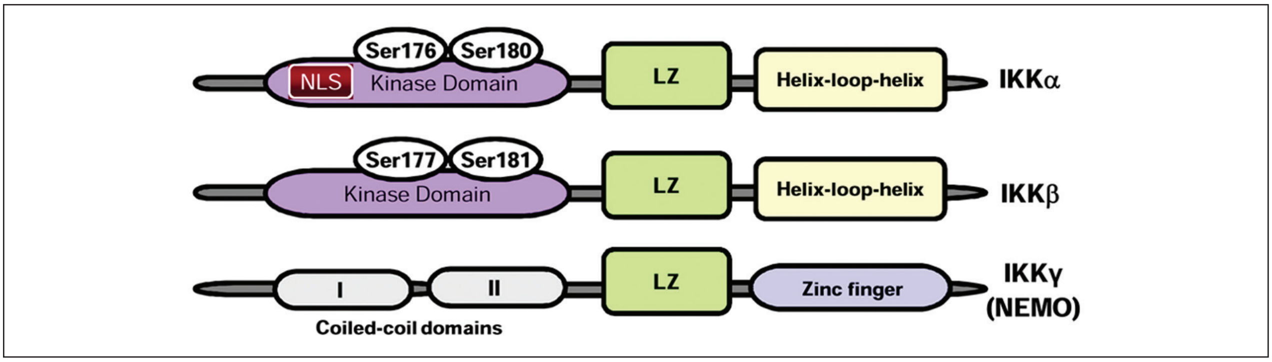

Figure 2. Members of the NF-kB inhibitors (IκB) and IκB kinase complex (IKKα, IKKβ, and IKKγ). A) The inhibitory κB (IκB) family consists in seven members: IκBα, IκBβ, IκBγ, IκBε, Bcl-3 and IκBς. They have in common the conserved ankyrin repeat motifs that are essential for the IκB/NF-κB interaction. IκBα and IκBβ have in their carboxyl-terminal end a domain rich in proline, glutamic acid/aspartic acid, serin and threonine residues (PEST domain) The PEST domain may interact directly with the DNA-binding region of one of the NF-κB subunits. Bcl-3 also contains a transactivation domain (TAD). B) IKKα and IKKβ members of IκB kinase family contain a kinase domain, a leucine zipper domain, and a helix-loop-helix domain, responsible for their kinase activity and dimerization. Phosphorylation of Ser176 and Ser180 or Ser177 and Ser181 located in the kinase domain induces IKKα and IKKβ kinase activity, respectively. IKKα kinase domain contains the NLS responsible for its nuclear localization. The regulatory subunit IKKγ, also called NEMO, contains four domains—two coiled-coil, a leuzine zipper, and a zinc finger—required for IKK complex formation and function.

for the IκB/NF-κB interaction (Baeuerle 1998). IκBα and IκBβ have in their carboxyl-terminal end a domain rich in proline, glutamic acid/aspartic acid, serine, and threonine residues (PEST domain). The PEST domain may interact directly with the DNA-binding region of one of the NF-κB subunits and is required for inhibition of DNA binding (Ernst and others 1995).

IκBα is the most frequent expressed form of NF-κB inhibitors in the nervous system. It has been well established that NF-κB activation induces IκBα phosphorylation at Ser32 and Ser 36 residues of the ankyrin repeats. This phosphorylation leads to the IκB release of the complex, its polyubiquitinization at Lys21 and Lys22 residues, and its degradation by the 26S proteasome (Chen and others 1995). However, the reduction of IκBα protein level into the cytoplasm is temporary because IκBα is one of the earliest genes transcribed after NF-κB activation (Ito and others 1994). Thus IκBα protein is reduced after the activation of the pathway, and 1 hour later the levels of the protein increase in response to the newly synthesized IκBα (Place and others 2001). IκBα contains NLS, which permits the localization of newly synthesized IκBα into the nucleus where IκBα binds with RelA/p50 dimers, removing them from the κB DNA sequences. Then IκBα NES (nuclear export sequence) promotes the translocation of this inactive complex from the nucleus to the cytoplasm (Tam and others 2000).

In some cell types, IκBα can also be removed from NF-κB by phosphorylation at Tyr42, located in the ankyrin motifs (Takada and others 2003). This phosphorylation induces IκBα detachment from the complex, but not its degradation by the proteasome. Thus, IκBα protein level does not decrease early after Tyr42 phosphorylation (Imbert and others 1996).

The Kinases of the Inhibitors: IκB Kinases

IκB phosphorylation require the catalytic activation of a serine-threonine kinase complex called IκB kinases (IKKs). The IKK complex is composed of three elements: two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, NEMO (also called IKKγ) (Fig. 2B). IKKα and IKKβ contain a helix-loop-helix domain and a leucine-zipper domain (Häcker and Karin 2006; Woronicz and others 1997; Zandi and others 1997). The leucine-zipper domain is involved in the modulation of the kinase activity, and the helix-loop-helix domain is responsible for IKK homo- or heterodimerization (Zandi and others 1997). Some studies indicate that the IKKα/IKKβ heterodimers activate the NF-κB pathway more efficiently than the IKK homodimers (Huynh and others 2000). The IKKα and IKKβ catalytic domains show 65% homology and their kinase activation is induced by the phosphorylation at two serine residues (Ser177/Ser181 of IKKβ and Ser176/Ser180 of IKKα) (Kwak and others 2000). IKKα and IKKβ contribute differentially to IKK complex activation. Studies using IKKβ mutants demonstrated that this kinase is responsible for NF-κB activation after tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), or lipopolysaccharide (LPS) stimulation (Delhase and others 1999). IKKα and IKKβ also have different cellular distribution. IKKβ is distributed predominantly in the cytoplasm, whereas IKKα has both nuclear and cytoplasmic localization. The cytoplasmic localization of IKKs is related to their ability to phosphorylate IκBα and the consequent RelA/p50 translocation to the nucleus. The presence of IKKα in the nucleus is related to the expression of NF-κB responsive genes through the phosphorylation and acetylation of histone 3 (Yamamoto and others 2003). These findings demonstrated that IKKα and IKKβ kinases have different functions based on their cellular distribution.

NF-κB Signaling Pathways: Canonical, Non-Canonical, and Atypical

In the nervous system, the NF-κB pathway can be activated in a variety of ways. The classical IKK-dependent mechanisms include the canonical and non-canonical pathways, but a new IKK-independent mechanism, the atypical pathway, has been described (Bender and others 1998; Kato and others 2003). Canonical and non-canonical pathways are usually distinguished by two main characteristics: the NF-κB dimer translocated to the nucleus (RelA/p50 and RelB/p52, respectively) and the IκB contribution to their activation (IκB dependent and IκB independent, respectively) (Heissmeyer and others 1999). However, both of them require the presence of the IKK complex for their activation. In contrast, the atypical pathway is IKK-independent but IκB dependent and induces RelA/p50 nuclear translocation (Perkins 2007).

The proteins and NF-κB dimers involved in the activation of the three different pathways are summarized in Figure 3 and the principal differences that characterize these pathways in Figure 4. The "canonical pathway" (also called classical pathway) is the most common form of NF-κB activation in all cell types. This form is characterized by the activation of dimers composed of p50 and RelA or c-Rel. In mammalian cells, the most abundant partner of p50 is RelA. The canonical pathway is generally activated in response to stimuli such as cytokines (TNF-α, TNF-β, IL-1, CNTF, or CT-1) (Barger and others 1995; Middleton and others 2001; Sparacio and others 1992), neurotrophins (Burke and Bothwell 2003), or oxygen-glucose deprivation (Sarnico and others 2009). The activation of this pathway depends on Ser181 and Ser180 phosphorylation of IKKα and IKKβ, respectively. Activated IKK-complex phosphorylates IκBα (Ser32 and/or Ser36), promoting its degradation by the proteasome 26S, and also induces p105 phosphorylation, which in turn promotes the generation of the mature form, p50 (Heissmeyer and others 1999). RelA/p50 heterodimers are released from the inhibitor and translocated to the nucleus, where they bind to the DNA κB sites and induce the activation or repression of specific genes.

TNF-α is the most powerful activator of the canonical pathway. TNF associate factor-2 (TRAF-2) is the adaptor protein recruited to the TNFR1 receptor and becomes responsible for the canonical pathway activation. Together with the cellular inhibitor of apoptosis-1/2 (c-IAP1/2), TRAF2 contributes to the polyubiquitination of RIP1, which in turn activates RelA/p50 through the IKK complex. Activation of NF-κB by TNF-α usually induces protection from cell death, which promotes the transcription of anti-apoptotic target genes such as c-IAP1 and TRAF2 (Chu and others 1997; Wang and others 1998).

IKKα and IKKβ have different effects on the canonical NF-κB pathway activation. IKKβ is the predominant kinase responsible for IκBα and p105 phosphorylation (Li and others 1999c). Studies using IKKβ knockout mice show a clear reduction of IκBα degradation and RelA activation (Li and others 2003). In addition, these mice have a phenotype similar to RelA knockout, reinforcing the central role of IKKβ in the canonical pathway activation (Beg and Baltimore 1996; Li and others 1999a; Li and others 1999b). Even though IKKα phosphorylation also stimulates the canonical NF-κB pathway, this activation occurs in response to certain stimuli such as IL-1 or TNF-α when IKKβ is inhibited (Lam and others 2008; Solt and others 2007).

The "atypical pathway" is IKK independent but IκBα dependent and promotes RelA/p50 nuclear translocation (Fig. 4). In the nervous system, the activation of this pathway has been related to stimuli such as hydrogen peroxide, erythropoietin, or neurotrophic factors (Bui and others 2001; Gallagher and others 2007; Takada and others 2003). The atypical NF-κB pathway is initiated by tyrosine (Tyr42) phosphorylation at the N-terminus of the IκBα inhibitor or by serine phosphorylation at its PEST domain (Bender and others 1998; Kato and others 2003; Schwarz and others 1996). IκBα phosphorylation at Tyr42 is mediated by Syk (spleen tyrosine kinase) in response to CNTF or NGF (Bui and others 2001; Gallagher and others 2007) or by members of the Src family of tyrosine kinases in response to BDNF stimulation (Gavaldà and others 2004). This phosphorylation leads to the release of IκBα from the RelA/p50 dimer. Liberated IκBα is not degraded by the proteasome as it occurs during canonical pathway activation (Bui and others 2001; Takada and others 2003). IκBα can also be serine-phosphorylated by CKII (casein kinase II) at Ser293 located in the PEST domain (Schwarz and others 1996). In contrast to the tyrosine phosphorylation of IκBα, serine phosphorylation promotes calpain-mediated IκBα degradation (Wei 2009).

The "non-canonical pathway," also known as the IκB-independent pathway, is characterized by the translocation

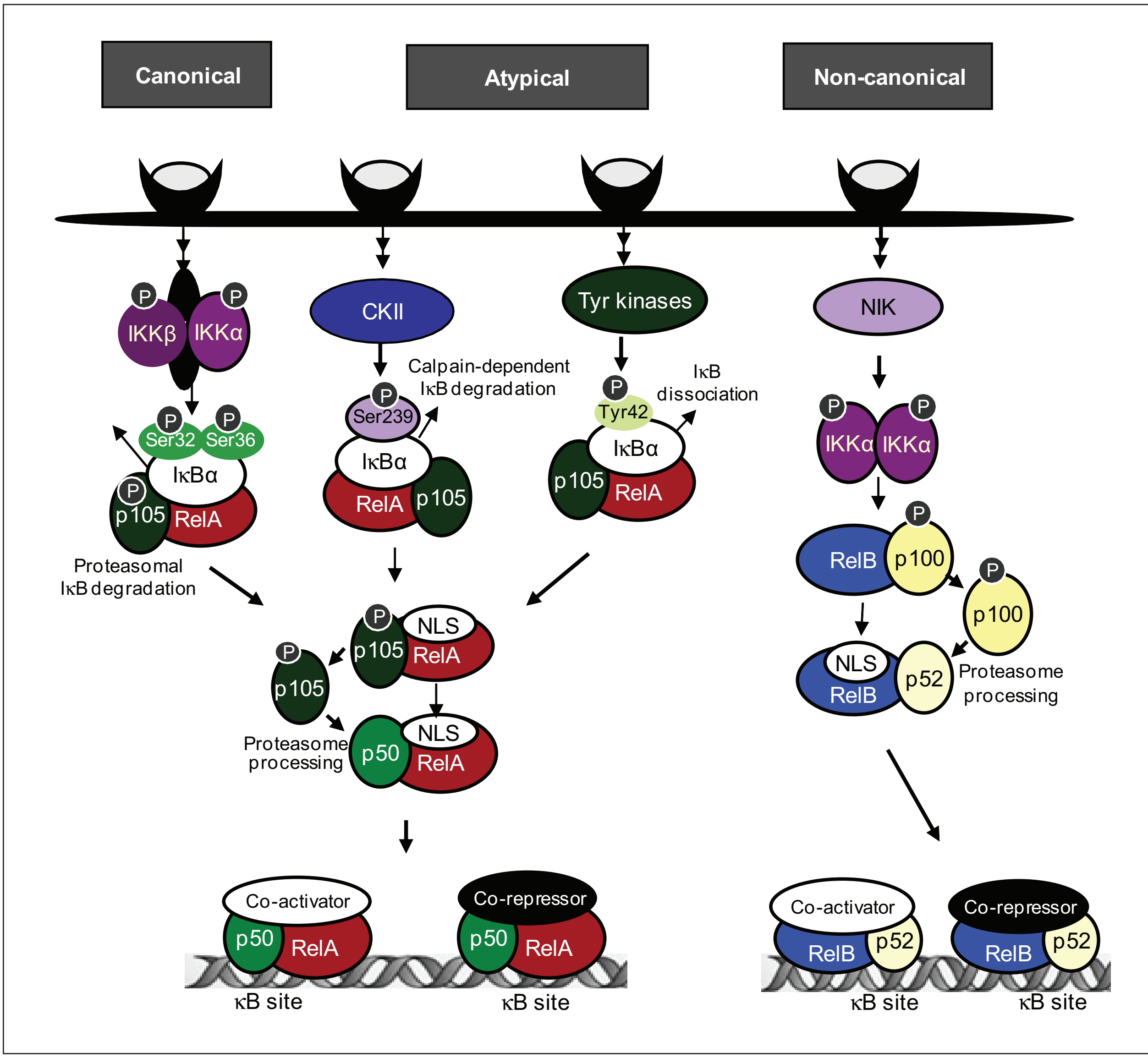

Figure 3. NF-κB activation pathways. Schematic representation of the three different pathways to activate NF-κB: canonical, non-canonical, and atypical. The canonical and non-canonical are IKK dependent and the atypical depends on casein kinase II (CKII) or tyrosine kinases. Canonical and atypical activation are mediated by IκB phosphorylation in serine or tyrosine residues, inducing IκB release of the complex (Ser293 or Tyr42). IκB phosphorylated at Ser293 is degraded by the proteasome or by the protease calpain, and Tyr42 phosphorylation induces IκB dissociation of the complex without protein degradation. The non-canonical pathway is IκB independent. Its activation is due to p100 phosphorylation induced by NF-κB-inducing kinase (NIK) and IKKα activity. IκBα release or the proteasome processing of p100 unmasks RelA or RelB nuclear localization sequence (NLS), respectively, promoting their translocation to the nucleus. Canonical and atypical activation induce gene expression or repression by the nuclear translocation of the RelA/p50 heterodimer, whereas the non-canonical activation exerts its nuclear function through RelB/p52 translocation.

of the RelB/p52 heterodimer (Fig. 4). The activation of this pathway is mainly mediated by IKKα activity induced by the NF-κB-inducing kinase (NIK) (Bonizzi and others 2004). IKKα phosphorylation leads to a polyubiquitination-dependent degradation of the p100 precursor to the active form p52. The newly formed heterodimers RelB/p52 translocate to the nucleus, where they target κB elements activating genes related to cellular functions, including Cox-2, Cycline D, Mn-SOD, and Bcl-x_L (Holley and others 2010; Jacque and others 2005; Maehara and others 2000; Zhang and others 2007). This pathway is activated by a limited number of stimuli,

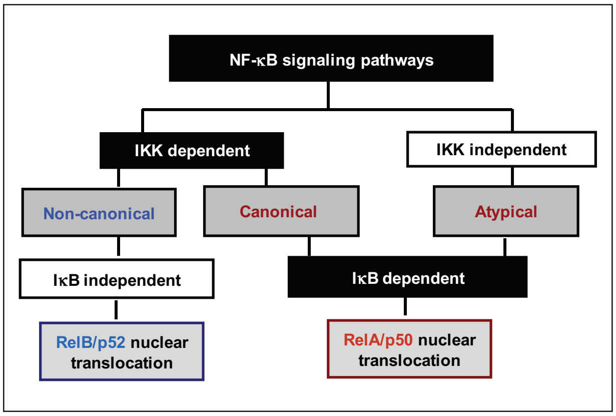

Figure 4. Schematic description of the principal differences of NF-κB pathways activation. The convergence and divergence points of the different mechanisms to activate NF-κB pathways are summarized: non-canonical and canonical are IKK dependent, atypical is IKK independent; canonical and atypical are IκB dependent, non-canonical is IκB independent; canonical and atypical induce RelA/p50 nuclear translocation, non-canonical induces RelB/p52 nuclear translocation.

including lymphotoxin B, CD40 ligand, LPS, and neurotrophic factors (Müller and Siebenlist 2003; Bhattacharyya and others 2010).

Regulation of the Transcriptional Activity of NF-κB by Posttranslational Modifications of RelA

In addition to IκBα inhibitor degradation, other steps are involved in the control of NF-κB-mediated gene expression. Several studies have described posttranslational modifications of the NF-κB members containing TAD domain—RelA, RelB, and c-Rel—that affect both RHD and TAD domains (Fig. 5). When RelA is liberated from the inhibitor IκBα, it can be phosphorylated at several serine residues by different kinases, promoting conformational changes and favoring RelA binding to co-activators. For example, phosphorylation at Ser276 of the RHD domain by PKA, MSK1, and MSK2 (mitogen- and stress-activated protein kinase 1 and 2) promotes RelA interaction with the transcriptional co-activators CBP (CREB binding protein) and p300 (Olson and others 2007; Zhong and others 1998). PKA and MSK kinases are in turn regulated by the ERK/MAPK signaling pathway in response to different stimuli, including TNF-α (Vermeulen and others 2003). Otherwise, Ser311 phosphorylation of the RHD by PKCξ regulates CBP and RelA interaction (Duran and others 2003). Within the TAD domain there are several serine residues susceptible to phosphorylation by kinases: Ser468 phosphorylation occurs predominantly within the nucleus and is induced by the GSK-3b kinase (Buss and others 2004; Schwabe and Brenner 2002); Ser529 is phosphorylated by the CKII kinase when RelA is liberated from the IκBα inhibitor in response to IL-1 or TNF-α (Wang and others 2000); Ser535 can be phosphorylated by CAMKIV (Bae and others 2003) and Ser536 by IKKs in response to cytokines and mediated by the PI 3-kinase/Akt pathway (Gutierrez and others 2008; Sizemore and others 2002).

RelA also can be modified by reversible acetylation at different lysine residues. This site-specific acetylation regulates distinct biological activities of the NF-κB complex. For example, acetylation at Lys310, Lys314, and Lys315 is required for full transcriptional RelA activity (Chen and others 2005b; Rothgiesser and others 2010a; Rothgiesser and others 2010b). However, acetylation at Lys122 and Lys123 exerts negative effects on NF-κB-mediated transcription (Kiernan and others 2003).

Crosstalk between NF-κB and Other Transcription Factors

It has been reported that some transcription factors can regulate or be regulated by IKK and/or NF-κB. Tumor suppressor p53 can promote NF-κB activation, but this does not occur through the classical activation of the IKKs. The expression of p53 stimulates the ribosomal serine/threonine kinase RSK1, which in turn phosphorylates the RelA subunit of NF-κB at Ser536. RSK1-phosphorylated RelA is retained into the nucleus and contributes to the pro-apoptotic function of p53 (Bohuslav and others 2004). Thus, p53 and NF-κB cooperatively induce apoptotic cell death in damaged cells including neurons (Aleyasin and others 2004). On the other hand, RelA activates p53 promoter in response to stress and suppresses cell growth (Wu and Lozano 1994). In microglial cells, a recent study demonstrates the interaction between NF-κB and FOXO3a during oxygen-glucose deprivation (OGD) (Shang and others 2010). Using knockdown strategies, these studies pointed out that FoxO3a reduction facilitates p65 translocation to the nucleus in microglia during oxidative stress and promotes microglial cell survival. Finally, a novel transcriptional mechanism involving NF-κB, PKA, and CREB has been described. NF-κB controls PKA expression and consequently CREB activation; this mechanism is essential to regulate memory formation (Kaltschmidt and others 2006).

The NF-κB Knockout Mice

Studies using knockout mice for different gene components of the NF-κB pathway have improved our understanding of the role of these proteins in the physiological

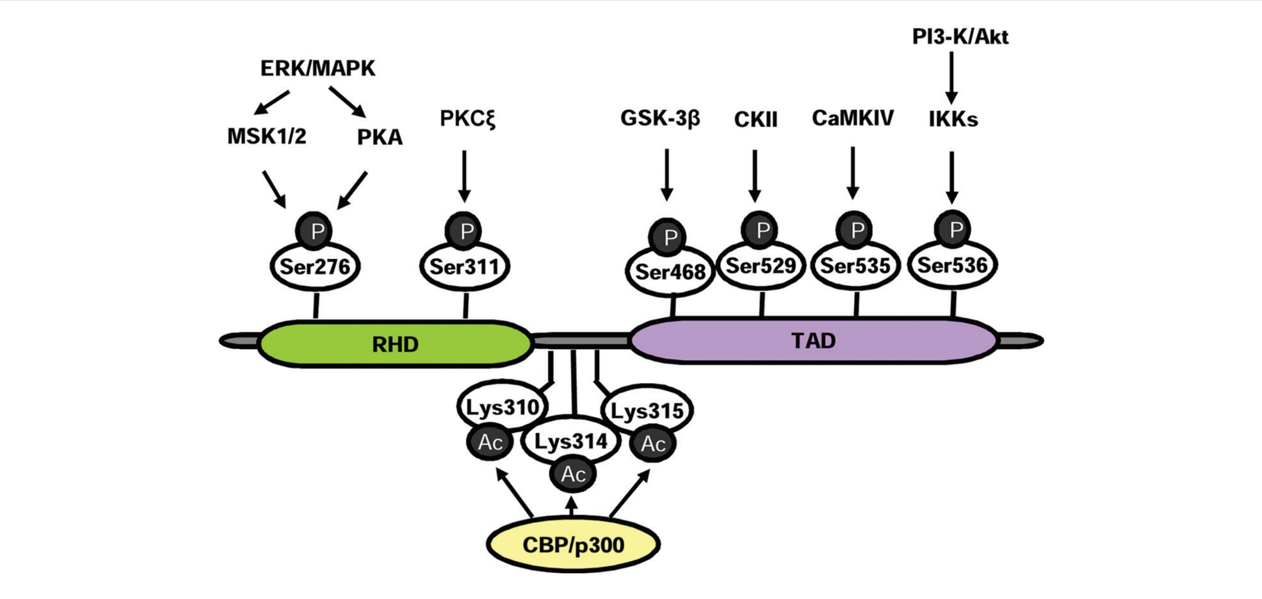

Figure 5. Posttranslational modifications of RelA. Several posttranslational modifications induce increased RelA transcriptional activity. Phosphorylation at different serine residues located in Rel homology domain (RHD) or in transcriptional activation domain (TAD) is mediated by protein kinases from different families. Ser276 phosphorylation at RHD is mainly mediated by ERK/MAPK through the mitogen- and stress-activated kinase-1 (MSK1/2) and protein kinase A (PKA), and Ser311 phosphorylation is mediated by protein kinase C-β (PKCζ). Phosphorylation at TAD is mediated by the following kinases: glycogensynthase kinase-3β (GSK3β) at Ser468, casein kinase II (CKII) at Ser529, Ca^{2+}/Calmodulin-Dependent Protein Kinase IV (CaMKIV) at Ser535, and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway induce activation of IκB kinases (IKKs), which mediate Ser536 phosphorylation of RelA. Acetylation of lysines located outside of RHD or TAD are mediated by CREB binding protein (CBP) or p300 co-activators.

Table 1. Phenotype Characteristics of Knockout Mice of NF-κB Pathway Members

Knockout mice	Phenotype/Alterations	References
RelA	Embryonic death at E15-16; sensitivity to TNF-α; apoptotic death of hepatocytes, defects in the nervous system	(Beg and others 1995; Middleton and others 2000; Niscols and others 2003)
RelB	Multiple pathological lesions; defects in the development of T cell death	(Weih and others 1995; Yilmaz and others 2003)
c-Rel	Defects in lymphocyte proliferation, humoral immunity, neuronal survival, synaptic plasticity	(Ahn and others 2008; Deenick and others 2010; Grumont and others 1998; Köntgen and others 1995; Pizzi and others 2002)
p50	Defects in the immune response; neuronal degeneration	(Lu and others 2006; Sha and others 1995; Yu and others 2000)
p52	Lymphatic nodes abnormality and defects in T cell response	(Beinke and Ley 2004; Franzoso and others 1998)
IKKα	Death 1 day after birth; block the differentiation of keratinocytes and skeletal and epidermal defects	(Li and others 1999)
IKKβ	Embryonic death at E12.5-13.5; sensitivity to TNF-α and hepatic apoptosis; conditional survival of B cells, effects in the nervous system	(Bockhart and others 2009; Li and others 1999; Li and others 2003)
IKKγ (NEMO)	Embryonic death at E10-13; hepatic and B cell apoptosis and developmental defects of lymphocytes T and B cells	(Kim and others 2003; Rudolph and others 2000)

TNF-α = tumor necrosis factor-α.

processes related to development. In Table 1, we summarize the main features of these mice. RelA knockout die during embryonic development (E15-16) due to a massive liver apoptosis (Beg and others 1995). These mice also show defects in the nervous system, such as reduced survival of nodose neurons in response to CNTF and CT-1 cytokines (Middleton and others 2000). The lack of RelA also compromises peripheral myelin formation by Schwann cells (Nickols and others 2003). These findings point out the role of RelA in peripheral nervous system development affecting both neuronal and non-neuronal cells. To further determine the function of RelA during nervous system development, different knockdown strategies have been generated using embryonic neuronal models. These studies have demonstrated that RelA is also involved in neuronal survival of sensorial neurons and spinal cord motoneurons in response to neurotrophic factors (Hamanoue and others 1999; Mincheva and others 2011). RelB knockout mice have shown no defects during embryonic development (Weih and others 1995). These mice show defects in the secondary structure of lymphoid organs and abnormal hematopoiesis throughout life (Yilmaz and others 2003). There are no evidences indicating that RelB is involved in nervous system development. c-Rel knockout mice show defects in neuronal survival (Pizzi and others 2002) and synaptic plasticity related to memory formation (Ahn and others 2008). In the immune system, c-Rel knockout show impaired lymphocyte physiology (Köntgen and others 1995).

p50 knockout mice have a normal development and show changes in both specific and non-specific immune function (Grumont and others 1998; Sha and others 1995). They also show age-related degeneration of neuronal and non-neuronal cells, including caspase-3 activation and apoptotic cell death (Lu and others 2006), increased cell damage in response to the excitotoxic stimuli (Yu and others 1999), and increased apoptosis of striatal neurons in a Huntington disease model (Yu and others 2000). p52 knockout mice show a normal development and no changes in the nervous system have been described, but they have defects in the architecture of the lymphatic ganglia (Beinke and Ley 2004; Franzoso and others 1998).

IKKα knockout mice die shortly after birth because of skin and skeletal abnormalities caused by the blockade of keratinocyte differentiation (Li and others 1999b). No defects during nervous system development have been described in these mice. IKKβ knockout embryos die because of a massive liver apoptosis between 12.5 and 13.5 embryonic days due to the reduction of RelA activation in the liver cells (Li and others 1999a). In the nervous system, the specific deletion of IKKβ in sensory neurons of the dorsal root ganglia demonstrated that IKKβ is a negative modulator of sensory neuron excitability (Bockhart and others 2009). IKKγ knockout mice die during embryogenesis. Their phenotype is characterized by a massive hepatic apoptosis induced by TNF stimulation (Rudolph and others 2000) and impaired B cells development (Kim and others 2003), but no defects in nervous system development have been reported.

Summarizing the information provided by these knockout mice, we can conclude that RelA, c-Rel, and IKKβ have an important role in nervous system development. However, we cannot completely discard the involvement of the rest of the members of the pathway in more specific functions that have not been tested yet. In this context, studies using double knockout strategies are providing new information. For example, IKKα and IKKβ double knockout presents an excessive apoptosis in the neural tube, spinal cord, and dorsal root ganglia, leading to the abnormality of neural tube closure (Li and others 2000). Some other double knockout strategies have been generated, such as RelA/p50, but no evidences of neuronal abnormalities have been described in their phenotypes (Franzoso and others 1997; Franzoso and others 1998; Grossmann and others 2000; Horwitz and others 1997; Lo and others 2006; Weih and others 1997).

NF-κB and the Nervous System

In the early 1990s, several studies showed the presence of RelA/p50 heterodimers in astrocytes (Sparacio and others 1992), Schwann cells (Carter and others 1996), microglia (Nakajima and Kohsaka 1998), and neurons (Kaltschmidt and others 1993; Meffert and others 2003; Schmidt-Ullrich and others 1996) in several regions of the developing and adult nervous system. These observations and subsequent reports suggest the involvement of NF-κB in physiological processes of the nervous system during development and during adult life. This was the beginning of many studies dedicated to analyzing the functions of NF-κB in the nervous system. In the following paragraphs, we review previous and recent results that contribute to this hypothesis, but we also reexamine the role of NF-κB in nervous system pathologies. First of all, we will cite the specific activators of NF-κB and the specific genes and proteins regulated by NF-κB in the nervous system.

Activators of the NF-κB Pathway in the Nervous System

There are many reports showing the specific activators of NF-κB pathway in the nervous system (reviewed in Kaltschmidt and others 2005). NF-κB is activated in both neuronal and non-neuronal cells, and the physiological response of these cells depends on the stimulus and the cellular origin. These responses include cell

Table 2. Neuroprotective Effects Induced by NF-κB Pathway Activation in the Nervous System

NF-κB activators	Cell type	Effects	Reference
CNTF	Sensory neurons	Survival and neurite growth	(Gallagher and others 2007)
CT-1	Sensory neurons	Survival	(Middleton and others 2000)
GDNF	Astrocytes	Neuroprotection in cerebral ischemia	(Chu and others 2008)
BDNF	Neurons	Survival and neurite growth	(Gutierrez and others 2005)
	PC12	Neurite outgrowth	(Sole and others 2004)
NGF	Neurons	Survival	(Maggirwar et al, 1998; Carter and others 1996)
	Schwann cells	Myelin formation	
IGF-1	Neurons	Survival	(Heck and others 1999)
Neurotrophic factors cocktail	Neurons	Survival	(Mincheva and others 2011)
TNF-α	Neurons	Synaptic plasticity	(Albensi and Mattson 2000)
cAMP	Schwann cell	Myelin formation	(Yoon and others 2008)

TNF-α = tumor necrosis factor-α.

Table 3. Neuronal degeneration NF-κB Pathway Activation in the Nervous System

NF-κB activators	Cell type	Effects	Reference
TNF-α	Neurons; glia	Neuronal degeneration and death	(Mir and others 2008)
Focal cerebral ischemia	Neurons	Neuronal death	(Stephenson and others 2000)
Amyloid	Astrocytes; oligodendrocytes	NO production increased; apoptosis	(Akama and others 1998; Xu and others 2001)
NMDA	Neurons	Apoptotic death	(Kitaoka and others 2004)
LPS	Microglia	Cox-2 expression	(Bauer and others 1997)
Kainic acid	Neurons	Apoptotic death	(Nakai and others 2000)
Oxidative stress	Neurons	Neuronal death	(Shou and others 2002)
Glutamate	Neurons	Apoptotic death	(Grilli and Memo 1999a)
IL-1β	Neurons	Depressive-like behaviors	(Koo and others 2010)
H_2O_2	Oligodendrocytes	Cell death	(Vollgraf and others 1999)

TNF-α = tumor necrosis factor-α; IL-1β = interleukin-1β.

survival, apoptotic cell death, neurite outgrowth, neuronal differentiation and plasticity, or cell proliferation. Table 2 lists the stimuli that cause "positive effects" on neuronal and non-neuronal cells. These include survival, neurite outgrowth, differentiation, proliferation, and plasticity. For example, activation of NF-κB mediated by neurotrophic factors promotes neuronal survival, neurite outgrowth, myelin formation, and axonal regeneration in various experimental models *in vivo* and *in vitro*, both in mature and developing cells (Mincheva and others 2011). However, NF-κB activation can also induce "negative effects" such as cell death and toxicity (Akama and others 1998; Bauer and others 1997; Grilli and Memo 1999; Kitaoka and others 2004; Koo and others 2010; Mir and others 2008; Nakai and others 2000; Shou and others 2002; Stephenson and others 2000; Vollgraf and others 1999; Xu and others 2001). Table 3 lists some of the known stimuli that cause neuronal negative effects. For example, in Alzheimer disease (AD), β-amyloid protein induces NF-κB activation in neurons, which produces cell toxicity because of nitric oxide production and release from astrocytes (Akama and others 1998). In fact, these different stimuli cause different events in the different types of cells present in the nervous system. This could explain the "apparently contradictory" effects caused by NF-κB activity that were mentioned at the beginning of this review.

Genes and Proteins Regulated after NF-κB Activation in the Nervous System

Independent studies over the past 10 years have proposed NF-κB as one of the main pathways controlling neuronal survival. This regulation is based on the ability of NF-κB to exert transcriptional control (activation or inhibition) over several pro- or anti-apoptotic genes (Table 4). For example, Bcl-2 and Bcl-x_L promoters have binding sites for NF-κB dimers (Tamatani and others 1999) or NF-κB positively regulates cIAP gene expression (Baud and Karin 2001). Moreover, TNFR1/2 adaptor proteins TRAF1 and TRAF2 increase when NF-κB is activated, and TRAF1 and TRAF2 themselves are able to induce IKK phosphorylation, which in turn activates the NF-κB pathway (Häcker and Karin 2006; Wang and others 1998). Along the same line, we have recently demonstrated that the NF-κB pathway also regulates the level of one protein essential for motoneuron physiology, Survival Motor Neuron (SMN) (Mincheva and others 2011).

On the other hand, NF-κB activation can promote apoptosis and cell death in the nervous system (Kaltschmidt and others 2000; Kaltschmidt and others 2002; Pizzi and others 2002). For example, in response to oxidative stress, NMDA receptor activation or apoptotic stimuli of the NF-κB pathway increases the expression of the pro-apoptotic genes Bax and Bcl-xs in cortical neurons (Shou and others 2002). In some diseases, such as cerebral ischemia, RelA increases the expression of Bim and Noxa pro-apoptotic genes (Inta and others 2006). Even though NO participation in neuronal apoptosis is still under debate, the transcriptional control of the inducible nitric oxide synthase (iNOS) is also regulated by NF-κB (Xie and others 1994). The cell cycle regulator Cyclin D is also controlled by NF-κB and has been related to neuronal apoptosis in striate and cortical neurons (Liang and others 2007).

Finally, under NF-κB transcriptional control other factors related to neuronal homeostasis are also regulated, such as antioxidant enzymes (Maehara and others 2000; Rojo and others 2004), adhesion molecules (Simpson and Morris 2000), transcription factors (Khorooshi and others 2008; Qin and others 1999; Wu and Lozano 1994), and neurotrophic factors (Saha and others 2006).

Role of NF-κB in the Nervous System during Development and in the Adult

Control of Apoptosis

As mentioned above, there are defects in neural tube closure in IKKα and IKKβ double knockout caused by the apoptosis of the neuroepithelium (Li Q and others 2000). During embryogenesis NF-κB transcriptional activity is detected in the central nervous system, particularly in the spinal cord and brain nuclei (Schmidt-Ullrich and others 1996). One of the first observations of NF-κB activity in the spinal cord coincides with the beginning of motoneuron neurotrophic factor dependence and the programmed cell death period (Schmidt-Ullrich and others 1996; Yeo and Gautier 2004). Our recent results demonstrated that reduction of some NF-κB pathway members causes apoptotic cell death of embryonic spinal cord motoneurons, even in the presence of neurotrophic factors (Mincheva and others 2011). NF-κB activation can also be required for peripheral nervous system neuronal survival. Studies using embryonic sympathetic and sensory neurons indicated that NF-κB activation is necessary for NGF-induced cell survival (Maggirwar et al., 1998 and Mincheva-Tasheva unpublished results). All these observations highlight the important role of NF-κB signaling pathway in the regulation of apoptotic cell death during neuronal development (Fig. 6).

Involvement in Neurite Outgrowth

NF-κB signaling has been implicated in control of axon initiation, branching and elongation, and dendrite density in the adult. Studies using different neuronal models including PC12 cells (Azoitei and others 2005; Sole and others 2004), sensory neurons (Gallagher and others 2007; Gutierrez and others 2005; Gutierrez and others 2008), and hippocampal neurons (Sanchez-Ponce and others 2011) have demonstrated that NF-κB blockade reduces neurite length and branching. A recent review extensively discusses the role of NF-κB pathway in modulating the growth and morphology of neuronal processes, including axon and dendrites (Gutierrez and Davies 2011).

Involvement of NF-κB in Synaptic Plasticity, Memory, and Learning

NF-κB plays an important role in synaptic signaling and learning in the mature nervous system (Kaltschmidt and Kaltschmidt 2009). Independent genetic studies have demonstrated that RelA, c-Rel, and p50 are involved in memory formation. RelA/TNFR1 double knockout mice have defects in spatial learning memory (Meffert and others 2003), c-RelA knockouts have impaired hippocampus-dependent memory formation (Ahn and others 2008), and p50 knockout present deficit in short-term memory (Denis-Donini and others 2008). The importance of NF-κB in these processes may be related to the presence and function of NF-κB family members in the pre- and postsynaptic space, which contributes to transduction of synaptic signals to transcriptional changes (Meffert and others 2003). In these processes of learning and memory, NF-κB also cooperates with other transcription factors and signaling pathways. For example, NF-κB controls synaptic plasticity

Table 4. Target Genes Regulated by NF-κB Pathways and their Cellular Effects in the Nervous System

Target genes	Pathway	Cellular function	References
Bcl-2, Bcl-x	C	Anti-apoptotic	(Tamatani and others 1999)
Bcl-xL	A, C, non-C	Anti-apoptotic	(Bui and others 2001)
c-FLIP	X	Anti-apoptotic	(Chu and others 1997)
TRAF1, 2	X	Anti-apoptotic	(Wang and others 1998)
IAPs	C	Anti-apoptotic	(Chu and others 1997)
Bax, Bcl-xs	X	Pro-apoptotic	(Shou and others 2002)
Bim, Nova	C	Pro-apoptotic	(Inta and others 2006)
Smn	C	Survival Motor Neuron	(Mincheva and others 2011)
CREB	C	Transcription factor	(Mincheva and others 2011)
p53	C	Transcription factor	(Wu and Lozano 1994)
STAT2	X	Transcription factor	(Khorooshi and others 2008)
c-Myc	C	Transcription factor	(Qin and others 1999)
Mn-SOD	C	Antioxidant enzyme	(Maehara and others 2000)
Cu/Zn-SOD	C	Antioxidant enzyme	(Rojo and others 2004)
Cox-2	Non-C	Enzyme responsible for inflammation	(Kaltschmidt and others 2002)
iNOS	C	Nitric oxide synthesis	(Xie and others 1994)
IkBa	C	NF-κB inhibitor	(Bui and others 2001)
BDNF	C	Neurotrophic factor	(Saha and others 2006)
NCAM	C	Neural adhesion molecule	(Simpson and Morris 2000)
Cyclin D1	Non-C	Cell cycle regulator	(Liang and others 2007)

C = canonical NF-κB pathway; non-C = non-canonical NF-κB pathway; A = atypical NF-κB pathway; X = no information.

by regulating the expression of the catalytic subunit of PKA, an essential memory regulator, and phosphorylation of CREB (Kaltschmidt and others 2006).

NF-κB and Neurodegenerative Disorders

To better understand the molecular mechanisms of the pathology of neurodegenerative disorders, it is important to understand the signal transduction processes that regulate neuronal survival and differentiation during development. These mechanisms could be involved in the pathology of these diseases, and there are evidences suggesting this hypothesis. Several studies associate the alteration of NF-κB activity with neurodegenerative diseases such as Alzheimer, Parkinson, Huntington, or amyotrophic lateral sclerosis (ALS), and in processes related to injury or ischemia. In general terms, authors propose that NF-κB activation in neurons exerts a neuroprotective role in the degenerative process of these diseases (Cardoso and Oliveira 2003; Fridmacher and others 2003; Smith and others 2009). However, there are also evidences indicating that it causes neuronal death. Analysis of brain samples showed an increase of activated NF-κB in AD patients compared with healthy individuals (Kaltschmidt and others 1997; Kaltschmidt and others 1999). This NF-κB activation can contribute to the pathological changes observed in AD-inducing proinflammatory and cytotoxic genes, or can be a part of the cellular protection mechanism depending on the genetic program and the time of exposure to the stimulus. In mice models of AD (Tg2576), the increase of NF-κB activity has been related to neuronal apoptosis and the onset and development of the disease (Niu and others 2010). Two independent studies have demonstrated the involvement of NF-κB in Aβ42 oligomer production (Buggia-Prevot and others 2008; Valerio and others 2006). Taking into consideration these reports, NF-κB can be considered as a pharmacological target for AD treatment by directly inhibiting the production of Aβ peptides (Paris and others 2007). More detailed studies have shown that the specific inhibition of NF-κB activity in microglia, but not in neurons, blocks Aβ-induced neurotoxicity (Chen and others 2005a). Along the same line and based on the ability of NF-κB to block caspase activation in neurons, it has been proposed that the pharmacological induction of NF-κB activity can be a beneficial therapeutic target in AD therapy (Cardoso and Oliveira 2003).

There are also evidences that NF-κB may participate in Parkinson disease (PD) although its role in dopaminergic neurons survival is still controversial. Some authors have shown that the activation of NF-κB pathway is essential for the apoptotic death induced by dopamine in PC12 cells (Panet and others 2001); and NF-κB activation contributes to 6-hydroxydopamine-induced apoptosis of dopaminergic neurons (Li and others 2008). However, other authors suggest the neuroprotective role of NF-κB

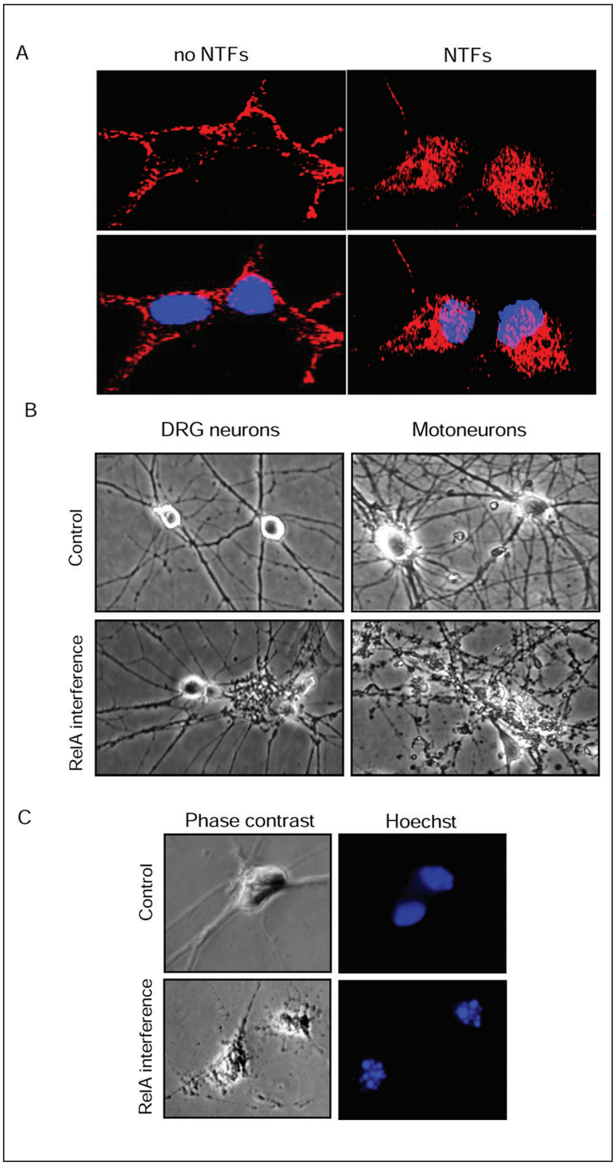

Figure 6. Effects of NF-κB activation in neurons. (A) Confocal images of RelA subcellular localization in cultured motoneurons (MNs) in the absence (no NTFs) or the presence (NTFs) of neurotrophic factors. NTFs treatment induces RelA translocation to the nucleus indicating the activation of the pathway (RelA, red; Hoechst nuclear dye, blue). (B) and (C) show the effect of inactivating NF-κB pathway using an RNA interference approach. (B) Phase contrast images of cultured dorsal root ganglion (DRG) neurons (left) and MNs (right) in the presence of NTFs under control (top) or RelA interference (bottom) conditions. (C) Nuclear apoptotic morphology of MNs cultured in RelA interference conditions (bottom).

activation based on its ability to block the apoptotic cell death caused by auto-oxidized dopamine (Lee and others 2001). In the same line of evidences, it has been described that the exogenous administration of the neurotrophic factor GDNF induces RelA/p52 nuclear translocation and protects dopaminergic neurons in an early rat model of PD (Cao and others 2008).

Although not widely studied, NF-κB pathway may also participate in Huntington disease. p50-deficient mice show an increased loss of striatal neurons and consequent motor dysfunction (Yu and others 2000), and in mammalian cells human hungtingtin (Htt) co-immunoprecipitates with p50 (Takano and Gusella 2002). Other members of NF-κB signaling can also contribute to neurodegeneration induced by mutated Htt. It has been reported that inhibition of IKKγ or IKKβ activity, or IκBα degradation, can reduce Htt-induced toxicity and promote striatal neuronal survival (Khoshnan and others 2004). In later studies, the same authors demonstrated an antagonistic effect for the different IKKs. IKKα overexpression or IKKβ inhibition protects neurons from death induced by mutant Htt (Khoshnan and others 2009).

Indirect effects of NF-κB pathway have also been related to neurodegenerative disorders of the spinal cord motoneurons. In spinal cords of ALS patients, NF-κB is activated in glial cells but not in motoneurons (Migheli and others 1997; Pyo and others 2010). Studies using SOD transgenic mice demonstrated that pharmacological induction of NF-κB pathway in motoneurons prolongs survival by blocking apoptosis (Del Signore and others 2009; Ryu and others 2005). However, some authors suggest a beneficial effect of NF-κB pathway pharmacological inhibitors in the spinal cord of ALS mutant mice (Xu and others 2006). From all these results, it is feasible to conclude that although NF-κB activity might have a role in the pathology and therapy of these degenerative disorders, additional data are required to establish the clinical relevance, as we discuss below.

NF-κB and Neuronal Injury

NF-κB activation has been observed in response to brain and spinal cord ischemia and trauma (Xu and others 2005). The analysis of experimental models of stroke and injury reveals that the NF-κB pathway may modulate neuronal degeneration or protection. There are several examples of these opposite effects. Mice lacking the p50 subunit develop significantly smaller infarct size (Nurmi and others 2004), and there are evidences that IKK/NF-κB signaling contributes to ischemic brain damage (Schwaninger and others 2006). On the other hand, some data in hippocampus and striatum provide evidences that NF-κB participates in survival signaling following temporary focal ischemia (Duckworth and others 2006). A recent study demonstrates that transgenic inhibition of glial NF-κB attenuates pain and the inflammatory response following chronic constriction of the sciatic nerve (Fu and others 2010).

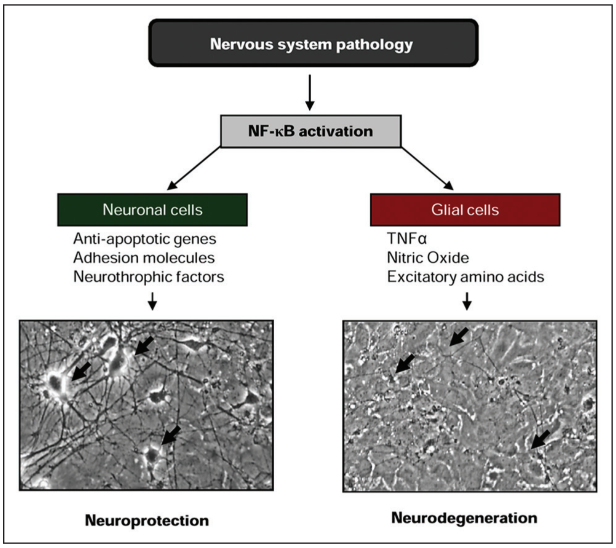

Figure 7. Hypothesis for NF-kB function in nervous system physiology and pathology. A) Model for NF-κB homeostasis suggested by Kaltschmidt. This model proposes that under physiological conditions RelA binds to nuclear co-activators which promote cell survival by activating the transcription of anti-apoptotic genes. RelA-induced IB protein expression controls NF-B homeostasis inactivating the pathway. Under pathologic conditions deregulation of NF-B activity leads RelA binding to nuclear co-repressors blocking the anti-apoptotic gene expression and promotes neuronal cell death. B) Opposite effects of NF-kB activation on neuronal and on glial cells under pathologic conditions. As suggested by Mattson and Camandola's hypothesis, the same NF-κB activating stimulus can induce opposite effects on neurons. NF-κB activation in neurons under some pathologic conditions such as injury or stroke promotes the expression of anti-apoptotic genes, neurotrophic factors, or adhesion molecules, which in turn have a neuroprotection role. The same pathological stimuli in astrocytes or microglia induce the expression of nitric oxide, TNF-α, and/or excitatory amino acids, leading to neuronal degeneration. Representative images of the NF-κB activation effect on motoneurons (MNs) (left) and glial cells (right) when both types of cells are cocultured: NF-κB activation in MNs induces cell survival (arrows) whereas NF-κB activation in glial cells induces cell death.

All together these results illustrate the controversial role of NF-κB pathway in neuronal damage and disorders. To find an answer to these apparently contradictory results, two hypotheses have been generated. The most recent, proposed by Kaltschmidt in 2005, is the model for NF-κB homeostasis (Kaltschmidt and others 2005) (Fig. 7A). This model defends the premise that low levels or high levels of NF-κB activation maintained over a long time period (weeks to months) cause neuronal death. Under physiological conditions, nuclear RelA promotes survival by activating the transcription of anti-apoptotic genes through its binding to co-activators. The maintenance of "physiological" NF-κB activation depends on IκB protein expression that is responsible for bringing RelA back to the cytoplasm and deactivating the pathway. However, pathologic conditions can lead to low or hyper-activation of NF-κB, which can switch RelA from a selective promoter to a dominant repressor of anti-apoptotic genes by recruiting corepressors and inducing neuronal cell death. The more supported hypothesis was proposed by Mattson and Camandola in 2001 (Mattson and Camandola 2001). These authors suggest that NF-κB activation in neurons induces anti-apoptotic genes that mediate cell survival, whereas NF-κB activation in glial cells results in the production of proinflammatory cytokines that mediate neuronal death (Fig. 7B). Thus, the same stimulus produces opposite responses by activating NF-κB in different cell types. One of the cytokines that can be produced by glial cells is TNF-α. Binding of TNF-α to TNFR1 and TNFR2 receptor activates the NF-κB pathway. TNFR1 activation in glial cells induces the production of NO, which may lead to neuronal death, whereas TNFR2 activation in neurons increases the expression of anti-apoptotic genes. This hypothesis has been supported by several studies demonstrating that TNF-α toxicity in neurons is only observed in the presence of glial cells (Mir and others 2008; Taylor and others 2005; Tolosa and others 2011). These studies showed that microglia, macrophages, and astrocytes produce proinflammatory cytokines, free radicals, and excitotoxins in response to TNF-α-induced NF-κB activation and thereby promote neuronal death. Furthermore, in neuronal injury models the inhibition of the pathway only in astrocytes demonstrated that neurons are protected from cell death when NF-κ is silenced in astrocytes (Meunier and others 2007). Similar results were obtained in hippocampal neurons in response to kainic acid excitotoxicity, when the *IKKβ* gene was specifically deleted in microglia (Cho and others 2008). Based on these observations, the use of glial-specific NF-κB pathway inhibitors has been proposed as a potential therapy in neurodegenerative disorders such as AD (Chen and others 2005a) or ALS (Crosio and others 2011).

Concluding Remarks

This review describes a number of important functions of the NF-κB pathway in the nervous system. The pathway's function in the regulation of apoptosis, neurite outgrowth, and synaptic plasticity during development and memory formation and learning in adult life has been well studied; however, new evidences are emerging about its role in neurodegenerative disorders and neuronal injury. Although some of the results could lead to confusion about the function of the pathway during these processes, these recent studies confirm Mattson and Camandola's hypothesis concerning the importance of the stimuli, context, and cellular origin of NF-κB activation, but among the context and the stimuli, cell type appears to be the decisive factor determining NF-κB function during development and neurodegeneration. It remains to be determined whether NF-κB up- or down-regulation in a neuron under pathologic conditions is the origin of cell degeneration or is a neuroprotective reaction. When these issues have been clarified, NF-κB activity regulation can be proposed as a therapeutic target in some neurodegenerative disorders.

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