

**Significance of NF- $\kappa$ B as a pivotal therapeutic target in the neurodegenerative pathologies of Alzheimer's disease and multiple sclerosis.**

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## **Significance of NF- $\kappa$ B as a pivotal therapeutic target in the neurodegenerative pathologies of Alzheimer's disease and multiple sclerosis.**

### **Abstract:**

**INTRODUCTION:** Advances in molecular pathogenesis suggest that the chronic inflammation is a shared mechanism in the initiation and progression of multiple neurodegenerative diseases with diverse clinical manifestations such as Alzheimer's disease (AD) and multiple sclerosis (MS). Restricted cell renewal and regenerative capacity makes the neural tissues extremely vulnerable to the uncontrolled inflammatory process leading to irreversible tissue damage.

**AREAS COVERED:** A predominant consequence of increased inflammatory signaling is the upregulation of the transcription factor, nuclear factor- kappa B (NF- $\kappa$ B) with subsequent neuroprotective or deleterious effects depending on the strength of the signal and the type of NF- $\kappa$ B dimers activated. We discuss the interplay between neuroinflammation and neurodegeneration keeping in focus NF- $\kappa$ B signaling as the point of convergence of multiple pathways associated with the development of the neurodegenerative pathologies, AD and MS.

**EXPERT OPINION:** Considerable interest exists in developing efficient NF- $\kappa$ B inhibitors for neurodegenerative diseases. The review includes an overview of natural compounds and rationally designed agents that inhibit NF- $\kappa$ B and mediate neuroprotection in AD and MS. The key chemical moieties of the natural and the synthetic compounds provide efficient leads for the development of effective small molecule inhibitors that selectively target NF- $\kappa$ B activation; this would result in the desired benefit to risk therapeutic effects.

**Key words:** (In alphabetical order)

Amyloid;

Disease modifying agents;

Drug target

Natural compounds;

Neurodegeneration;

Neuroinflammation;

Polyphenols

Promoter

Terpenoids

Therapeutic target/mechanism;

### **List of abbreviations:**

AMPA:  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionate; APP: amyloid precursor protein; APOE: apolipoprotein e; ATP: adenosine 5'-triphosphate; BACE 1: beta-site amyloid precursor protein cleaving enzyme 1; BBB: blood brain barrier; BDNF: brain derived neurotrophic factor; CaMK: calcium-calmodium dependent kinase II; CNS: central nervous system; CSF: cerebrospinal fluid; DMD: disease modifying drugs; EAE: experimental autoimmune encephalomyelitis; ERK: extracellular signal-regulated kinase; FPR2: formyl peptide receptor-2; IL: interleukin; IKK:  $\kappa$ B kinase; iNOS: induced nitric oxide synthase; IRAK-2: interleukin-1 receptor-associated kinase-2; JNK: Jun-N-terminal kinase; Mn-SOD: manganese superoxide dismutase; metabotropic glutamate (mGlu) receptor; MAPK: Mitogen activated phosphorylation kinases; NO: nitric oxide; NP: neuritic plaque; NFT: neurofibrillary tangle; NMDA: N-methyl-D-Aspartate; NEMO: NF- $\kappa$ B essential modulating domain ; NSAID: non-steroidal anti-inflammatory drugs; PPAR- $\gamma$ :peroxisome proliferator-activated receptor- $\gamma$ ; PKC: protein kinase C; PPMS: primary progressive multiple sclerosis; RAGE: Receptor associated advanced glycation end products; ROS: reactive oxygen species; RRMS: relapsing and remitting multiple sclerosis; SOD: superoxide dismutase; SPMS: secondary progressive multiple sclerosis; STAT 3: Signal transducer and activator of transcription 3; TGF: transforming growth factor; TNF: tumor necrosis factor; USFDA: United States Food and Drug Administration.

## **Introduction**

Neurodegenerative diseases refer to those conditions in which neurons in the brain and spinal cord undergo progressive degeneration and eventual death. The glial cells of the central nervous system (CNS) contribute significantly to the initiation and progression of the degenerative process. Since one CNS cell type can impact another cell type, the cumulative intracellular and intercellular responses determine the distinct pathological and clinical features of the specific neurodegenerative disease. Examples of neurodegenerative diseases include Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington disease (HD) [1]. Although the genetic and environmental factors that initiate degeneration differ among these diseases, a shared biochemical cascade of inflammatory events plays a central role in mediating the neuronal cell loss. Neuroinflammation may be triggered by enhanced endogenous neuronal/synaptic activity or autoimmune responses as well as by exogenous injury, infection or other external factors [2, 3].

The transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a critical regulator of immune and inflammatory responses [4]. In mammals, the NF- $\kappa$ B/Rel family comprises five members; p50, p52, p65 (Rel-A), c-Rel and Rel-B proteins, that form homo or hetero-dimers and remain in an inactive form in complex with the inhibitory molecules called the I $\kappa$ B proteins in resting cells. The typical I $\kappa$ B family members include I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$ , I $\kappa$ B $\epsilon$ , p100 and p105 proteins [5]. Activation of NF- $\kappa$ B can be induced by canonical and non-canonical pathways. Canonical NF- $\kappa$ B pathway is activated by numerous signals mediated by innate and adaptive immune receptors. Non-canonical NF- $\kappa$ B pathway is triggered by signaling from a subset of tumor necrosis factor family of receptors (TNFR). Activation of NF- $\kappa$ B by either pathway involves a proteasome-dependent step that allows for the generation of DNA-binding dimers. Signaling via the canonical pathway

involves stimulation of the IKK complex composed of  $IKK\alpha$ ,  $IKK\beta$  and  $IKK\gamma$ /NEMO (NF- $\kappa$ B essential modulator). Activation of IKK leads to  $IKK\beta$  mediated phosphorylation of I $\kappa$ B proteins followed by ubiquitination and degradation by proteasomes releasing the NF- $\kappa$ B dimers from the inhibitory complex. Activation of non-canonical pathway occurs at slower kinetics, is mediated by  $IKK\alpha$  and facilitates nuclear translocation primarily of RelB containing dimers. Activated NF- $\kappa$ B dimers then translocate to the nucleus, bind specific DNA fragments and induce expression of target genes (Fig 1) [1, 6].

### **1.1. NF- $\kappa$ B in the CNS health:**

First reported in the CNS in 1986, multiple studies subsequently have confirmed the ubiquitous expression and activity of NF- $\kappa$ B in brain cells including the neurons, astrocytes, microglia and oligodendrocytes. NF- $\kappa$ B exists as both constitutive and inducible complex in the neurons [7]. The constitutive form is transcriptionally active as evidenced by the nuclear localization of the p50 and p65 subunits in the neurons of the cortex and hippocampus [8]. Physiologically the constitutive NF- $\kappa$ B has been associated with growth and development of dendrites, neuronal survival, formation of synaptic plasticity and long-term memory. In conditional neuronal NF- $\kappa$ B-deficient mice, loss of NF- $\kappa$ B signaling impaired synaptic transmission, spatial memory formation, and plasticity [9].

A number of physiological stimuli including membrane depolarization or glutamergic signal transduction lead to rapid activation of the inducible NF- $\kappa$ B localized in the synapses, cytoplasm and dendrites of the neurons. Functionally, the inducible NF- $\kappa$ B has been reported as critical for the neuroprotective adaptive responses following exposure to sub-threshold noxious stimuli. [6,

10]. Complete abrogation of the DNA binding ability of NF- $\kappa$ B factors induces apoptosis of the neuronal cells. Cell death is preceded by reduction in the NF- $\kappa$ B regulated transcription of anti-apoptotic genes suggesting that a minimal threshold of NF- $\kappa$ B activity is needed for neuronal survival [6] (Fig1B). Several kinase pathways including the calcium-calmodium dependent kinase-II (CaMK), the protein kinases-C (PKC) and the ras/phosphatidylinositol 3-kinase (PI3K) pathways have been implicated in activating neuronal NF- $\kappa$ B signaling [1, 10]. However, recently using a diverse array of detection methods Listwak et al., have shown that not only the constitutive but also the induced NF- $\kappa$ B activity is many fold lower in neuronal cells as compared to non-neuronal cells in the CNS [11]. The microglia, astrocytes and oligodendrocytes constitute the non-neuronal glial cells actively involved in maintaining the structural and functional homeostasis in the CNS [12]. Unlike neurons, NF- $\kappa$ B is present in the cytoplasm as an inactive complex with the I $\kappa$ B proteins in glial cells under physiological conditions [13, 14].

## **1.2. NF- $\kappa$ B and neurodegenerative diseases:**

Considerable evidence suggests that the activation of NF- $\kappa$ B in the CNS triggers multicellular responses and gene transactivation intricately associated with the initiation and progression of neurodegenerative diseases. Various endogenous and exogenous stimuli activate NF- $\kappa$ B enhancing transactivation of inflammatory molecules and production of free radicals in glial cells [1]. The contribution of neuronal NF- $\kappa$ B to the pathogenesis of neurodegenerative diseases depends largely on two non-mutually exclusive mechanisms: upregulation due to direct effects on neurons or increase due to indirect effects via modulation by glial cells [15]. Interestingly, it has been suggested that the activation of distinct NF- $\kappa$ B subunits could have opposite effects on neuronal viability [6]. Glutamate induced stimulation of cerebellar granule cells via the N-methyl-D-aspartate (NMDA) receptor activate p65:p50 dimers and enhance transactivation of

pro-apoptotic factors [16]. In contrast, IL-1 $\beta$  stimulation of neurons mediates neuroprotection by activating c-rel containing dimers and transactivation of anti-apoptotic factors [15, 16]. Thus the effect of NF- $\kappa$ B stimulation on neuronal survival and death potentially depend on the strength of signal and the nature of NF- $\kappa$ B dimers stimulated [17] (Fig 1). The following sections discuss the critical role of NF- $\kappa$ B in neurodegenerative pathology using Alzheimer's disease (AD) and multiple sclerosis (MS) as specific examples.

## **2. Role of NF- $\kappa$ B in the pathogenesis of AD:**

**2.1. *NF- $\kappa$ B mediated neuroprotective responses in early AD:*** AD, the leading cause of dementia, is clinically characterized by loss of memory, progressive impairment of cognition and various neuropsychiatric disturbances. Pathologically AD affected brain exhibits deposits of amyloid-beta (A $\beta$ ) as neuritic plaques (NPs) and hyperphosphorylated aggregated tau protein as neurofibrillary tangles (NFTs). A consequence of intracellular and parenchymal accumulation of NPs and NFTs is activation of NF- $\kappa$ B in the neural and glial cells with subsequent protective or detrimental effects [15, 17].

A $\beta$  is produced by proteolytic cleavage of amyloid precursor protein (APP) by  $\beta$  and  $\gamma$ -secretase [18]. The genes encoding APP and beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) exhibit  $\kappa$ B binding sites in the promoter region. In neuronal cells A $\beta_{1-42}$  peptide has been shown to regulate APP and BACE1 proteins in NF- $\kappa$ B dependent manner [19]. Under physiological conditions activation of NF- $\kappa$ B by endogenous A $\beta$  reduces  $\beta$ APP, BACE1 and the  $\gamma$ -secretase activity, thereby lowering A $\beta$  processing and facilitating A $\beta$  homeostasis. However in AD, exposure to high A $\beta$  concentrations upregulates NF- $\kappa$ B activation increasing  $\beta$ APP and A $\beta$  processing, precipitating a feed-back loop that favor exacerbated A $\beta$  production [20].

Considerable evidence suggests a critical role for apolipoprotein e (APOE) in the formation of fibrillary A $\beta$  and neuritic plaque [21]. Both rodent and human *APOE* gene promoter contain functional NF- $\kappa$ B site. A $\beta$  has been shown to upregulate *APOE* in astroglial cells. This upregulation was inhibited by decoy- $\kappa$ B nucleotides supporting a critical role for NF- $\kappa$ B in *APOE* function [14]. Activated microglia are invariant histological features in AD brains, where they exhibit waxing and waning of numbers, and activation state during plaque progression [12]. Initially, the microglial cells bind and phagocytose A $\beta$  peptides via a group of cell surface receptor complex consisting of scavenger receptor CD36,  $\alpha$ 6- $\beta$ 1 integrin, and CD47 [22]. The response of microglia has been shown to vary with the length of the A $\beta$ -peptide and the signaling pathway [22]. Stimulation with the A $\beta$ <sub>25-35</sub> fragments induces secretion of cytokines such as TNF- $\alpha$  and of neurotrophic factors such as nerve growth factor (NGF) and brain derived nerve factor (BDNF) in NF- $\kappa$ B-dependent manner [23, 24]. Stimulation of neuronal cells by TNF- $\alpha$  has been shown to upregulate transactivation of anti-apoptotic gene products and neurotrophins such as Bcl-2 and NGF respectively. Decoy  $\kappa$ B nucleotides mediate cell death by blocking neurotrophins and anti-apoptotic factors supporting an essential role for NF- $\kappa$ B in the neuroprotective process [17]. In primary neuronal cells, exposure to A $\beta$ <sub>25-35</sub> peptide increase NF- $\kappa$ B mediated transactivation of manganese superoxide dismutase (Mn-SOD), suppress peroxynitrite production and inhibit membrane depolarization, thereby preventing apoptosis induced by oxidative stress [25]. In metabotropic glutamate receptor-5 (mGlu5) agonist pre-treated primary cortical neurons or neuroblastoma cells, A $\beta$  induced toxicity was suppressed by selective activation of c-rel containing NF- $\kappa$ B dimers and transactivation of anti-apoptotic genes, Mn-SOD and Bcl-XI [26] (Figs 1B, 2A). These NF- $\kappa$ B mediated neuroprotective effects have been largely observed in early stages of neuronal regeneration in AD [23].



2.2. Neuronal NF- $\kappa$ B and neurodegeneration in advanced AD: Exposure of primary neuronal cells or post-mitotic neurons to A $\beta$ <sub>1-42</sub> peptide has been shown to strongly activate the p50:p65 dimers and mediate neuronal cell death (Fig 1) [24, 27]. Consistent with the cellular studies, increased immunostaining for NF- $\kappa$ B-p65 has been observed in neurons and their processes in the hippocampal formation and entorhinal cortex in AD [8]. Comparison of the cellular distribution of NF- $\kappa$ B in the nucleus basalis of Meynert of AD and control patients showed that the proportion of large cholinergic neurons with elevated nuclear p65 was significantly increased in AD, suggesting an association between NF- $\kappa$ B functions and the process of cholinergic degeneration [28]. Mechanistically, the A $\beta$  induced neuronal apoptosis has been attributed to the increase in the ratio of pro-apoptotic gene (*BAX*) transcription to that of the anti-apoptotic gene *Bcl-Xl*, and/or to the reduction in constitutively activated NF- $\kappa$ B with consequent increase in the cytoplasmic I $\kappa$ B proteins [17]. These observations substantiate a direct role of neuronal NF- $\kappa$ B activation in the pathogenesis of AD (Fig 1B, 2B).

Chronic imbalance in the production and clearance of A $\beta$  leads a persistent increase in its steady-state levels in the CNS parenchyma [24]. Excessive accumulation of A $\beta$ <sub>1-42</sub> stimulates microglial cells by signaling via receptor associated advanced glycation end products (RAGE) and peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), phosphorylates IKK proteins, and enhances NF- $\kappa$ B mediated transactivation of inflammatory cytokines and neurotoxic molecules such as glutamate and reactive oxygen species (ROS)/induced nitric oxide synthase (iNOS) [12] (Fig 2B). Increased presence of activated glial cells presenting elevated NF- $\kappa$ B and HLA-DR expression are commonly observed around the A $\beta$  plaques in postmortem AD tissue. Increased presence of NF- $\kappa$ B mediated IL-1 $\beta$ , IL-6, and TNF- $\alpha$  cytokines have been reported in the affected tissues, serum and CSF of AD patients [1, 8, 29]. The localized increase in free radical

generation promotes increased APP processing, A $\beta$  deposition and tau phosphorylation. Animal models that over express the mutant human APP protein have shown a direct relationship between the amount of A $\beta$  aggregates and elevated levels of inflammatory cytokines TNF- $\alpha$ , IL-6, IL-12, IL-1 $\beta$ , and IL-1 $\alpha$  [29, 30].

Crosstalk between microglia and astrocytes could further amplify the inflammatory and neurotoxic responses. Astrocytes exposed to the APP fragments release large amounts of glutamate through upregulation of glutaminase expression and mediate increased excitotoxicity. This is supported by the observation that co-cultures of microglia and astrocytes stimulated with lipopolysaccharide produced significantly more neurotoxic factors than either cell type alone [31]. Extracellular accumulation of glutamate, stimulates adjacent neurons via the NMDA/ $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/Kainate (KA) receptors causing massive calcium influx that initiates a cascade of events involving intracellular signaling kinases and activation of calcium-dependent enzymes in arachidonic acid metabolism [25]. Accumulation of oxygenated arachidonic acid metabolites lead to neuronal cell death. Furthermore chronic activation of extrasynaptic NMDA receptors leads to sustained neuronal A $\beta$  release via amyloidogenic APP expression [32]. Factors released from injured neurons stimulate microglia and adjacent astrocytes initiating a paracrine loop that exacerbate neurotoxicity. This is supported by the observation that in mixed neuronal-glia cell cultures, A $\beta$  induces increasing degree of neurotoxicity in an NF- $\kappa$ B dependent manner in the presence of higher proportion of glial cells [33]. Furthermore NF- $\kappa$ B specific inhibitor prevents iNOS and ROS upregulation in A $\beta$  stimulated cultures of astrocytes or mixed cortical cells [34]. Recently microRNAs, non-coding highly conserved regulatory small RNAs, have been suggested as strong players in mediating inflammatory neurodegeneration. The miRNAs act as repressors of specific mRNA by binding complementary RNA sequences. Upregulation of several NF- $\kappa$ B

regulated miRNAs such as miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a, miRNA-155 and miRNA-339 5p have been observed in stressed primary human neuronal-glia cells and in post-mortem AD brain tissues[35]. In AD brains, miRNA-125b is observed as the most abundant exhibiting strong positive correlation with glial fibrillary acidic protein and vimentin and negative correlation with reduced cyclin dependent kinase 2A [35, 36]. Collectively, NF- $\kappa$ B signaling induced by multiple mechanisms in neurons, microglia and astrocytes represents a point of convergence of many pathways that accelerate the progression of neuroinflammation to neurodegeneration in AD (Fig 2B).

### **3. Multiple sclerosis (MS):**

Affecting over 2.5 million people worldwide, MS is a complex heterogeneous disorder of the CNS that begins as a relapsing remitting (RRMS) disease and often advances to a secondary progressive (SPMS) stage. Few MS patients exhibit primary progressive (PPMS) course from onset. The disease mechanism is extensively investigated in experimental autoimmune encephalomyelitis (EAE), an animal model that shares many clinical and histological features with human MS [37]. A feed-back loop between the CNS infiltration of circulating mononuclear cells, activation of microglial cells, secretion of toxic molecules that induce oligodendrocyte apoptosis and demyelination mediates MS pathology. The extent of demyelination and axonal injury determines the clinical disease.

#### **3.1. NF- $\kappa$ B and MS pathogenesis:**

Multiple NF- $\kappa$ B polymorphisms have been associated with increased susceptibility to MS. Structural polymorphism with an amino acid change from cysteine to arginine in position 738 in exon-4 of *I $\kappa$ B $\beta$* , is associated with predisposition to MS. Another polymorphism implicated in PPMS is an 8 base insertion in the promoter region of *NF $\kappa$ B1A*, the gene encoding I $\kappa$ B $\alpha$  [38]. NF- $\kappa$ B signaling plays a central role in the activation of both peripheral inflammatory cells and

the CNS resident glial cells that ultimately mediate inflammatory demyelination (Fig 3). Activated p65 has been reported in macrophages, microglia, astrocytes and oligodendrocytes in spinal cord lesions in EAE [37]. Macrophages in active demyelinating lesions of MS have been shown to overexpress p65, c-Rel, and p50 subunits of NF- $\kappa$ B [39]. Nuclear localization of p65 has also been observed in hyperactive astrocytes and oligodendrocyte surrounding the plaques in MS brains [39, 40]. Few studies have addressed the selective significance of the role of NF- $\kappa$ B signaling in the CNS in EAE/MS. Genetic deletion of the inhibitor of IKK $\beta$  specifically in CNS neurons has been shown to enhance the expression of immune mediators, reduce the levels of neuroprotective molecules and increase axonal damage resulting in severe, non-resolving EAE. This suggests that the NF- $\kappa$ B in neurons is critical in modulating the severity of autoimmune demyelination by enhancing neuroprotection and suppressing immune responses. Suppression of NF- $\kappa$ B by CNS restricted ablation of NEMO or IKK $\beta$  has been shown to ameliorate EAE [41]. In contrast, in a conditional ablation model in which the expression of a human transdominant negative I $\kappa$ B- $\alpha$ 1 was regulated in the basal forebrain and in selected neuronal subpopulations in the cerebellum and spinal cord, the clinical course and axonal densities in EAE was not affected [42].

A large number of studies have investigated the role of NF- $\kappa$ B in T cells in MS pathology. Mice lacking p105/p50 subunit of NF- $\kappa$ B are resistant to myelin oligodendrocyte glycoprotein (MOG) induced EAE due to failure of T cells to differentiate into encephalitogenic effector cells [43]. Absence of the c-rel subunit of NF- $\kappa$ B is associated with near complete resistance to MOG induced EAE due to impaired function of Th17 cells and interruption of the positive feedback loop for NF- $\kappa$ B targets including IL-6 and other chemokines that increase the permeability of the blood brain barrier (BBB) [44]. DNA microanalysis of peripheral blood lymphocytes at the peak of acute relapse and at the point of complete remission showed differential expression of 43

genes, many of which are regulated by NF- $\kappa$ B and/or regulate NF- $\kappa$ B activation, thereby substantiating the central role of NF- $\kappa$ B transcriptional regulation in T cells during MS relapse. For example, BTRC,  $\beta$ -transducin repeat containing protein, a RING E3 protein that mediates ubiquitination of I $\kappa$ B $\alpha$  is one of the genes upregulated in T cells in MS relapse [45]. It has been suggested that persistent oscillation between activation and inactivation of NF- $\kappa$ B in autoreactive T cells mediated by subclinical infections or stress potentially contribute to the fluctuation of disease activity from relapse to remission in RRMS [45]. More recently modulation of the immuno-inflammatory transcriptome by the NF- $\kappa$ B regulated miRNAs has been implicated in the pathogenesis of RRMS. Thirty-three miRNAs have been shown to exhibit significant differences in expressions in MS patients as compared to healthy controls. An increase of miR223 and miR-23a in the peripheral blood cells and a reduction in the serum of some patients has been reported [46]. The different trend between extracellular and intracellular miRNA levels has been suggested to reflect a possible regulatory role of circulating miRNAs in intercellular communications.[46].

#### **4. NF- $\kappa$ B as a therapeutic target for neurodegenerative diseases:**

As discussed above A $\beta$  aggregates, myelin debris and other CNS endogenous molecules as well as exogenous factors activate NF- $\kappa$ B in neural and glial cells mediating neuroinflammation and neurodegeneration [24]. Inhibition of neurodegeneration and promotion of neuroprotection following suppression of neuroinflammation has been demonstrated in animal models of AD and MS [47, 48]. Indeed the potential of non-steroidal anti-inflammatory drugs (NSAIDs) in reducing the risk of AD and the efficacy of glucocorticoids in the management of acute episodes of MS are largely attributed to the inhibition of NF- $\kappa$ B signaling [49, 50]. In A $\beta$  induced astroglial cells, sodium salicylate has been shown to block NF- $\kappa$ B activation, suppress upregulation of APOE

and potentially inhibit further A $\beta$  processing [23]. Mechanistically corticosteroids activated glucocorticoid receptor which in turn binds NF- $\kappa$ B-p65 in the nucleus interfering with its DNA binding activity and consequent suppressing transactivation of target genes [50]. Despite its significant anti-inflammatory potential studies in models of AD suggest a negative influence of glucocorticoids in disease pathology. In transgenic mice that develop both A $\beta$  and tau pathologies glucocorticoids upregulate BACE1 and increased A $\beta$  deposition accelerating AD development [51]. Furthermore, corticosteroids also increase excitotoxicity by suppressing glutamate transporter in microglia [49]. It has been suggested that a combination of corticosteroids, NMDA receptor blocking agents and cholinesterase inhibitors may exhibit better efficacy suppressing neuroinflammation and neurodegeneration in AD [49]. The following is a summary of recent progress in the natural products, their synthetic derivatives and disease modifying agents for the treatment of AD and/or MS with a focus on NF- $\kappa$ B as a mechanistic target.

4.1.: Polyphenols: Several natural polyphenolic flavanoids and non-flavanoids have been assessed for beneficial effects in neurodegenerative diseases [52]. In addition to the potent anti-oxidant capacity many polyphenols target different molecules, affect multiple signaling pathways and exert pleiotropic cellular effects.

4.1.1. Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a type of phenol rich in grapes and red wine with potent anti-oxidant ability, has received considerable attention recently for its neuroprotective effects (Table 1). Resveratrol mediated neuroprotection has been attributed to three potential mechanisms including 1) scavenging ROS; 2) modulation of multiple kinase signal transduction pathways and 3) activation of specific sirtuins (SIRT1) pathway [52, 53]. Both inhibition of mitogen activated protein kinase (MAPK) and/or activation of SIRT1 pathway suppress NF- $\kappa$ B signaling [54, 55]. Inhibition of MAPK prevents phosphorylation of I $\kappa$ B kinases

thereby preventing activation of NF- $\kappa$ B complex [55]. The DNA binding ability and transcriptional activity of NF- $\kappa$ B-p65 is modulated by the acetylation status of specific lysine residues in its transactivation domain. SIRT1, a member of the NAD(+)-dependent deacetylases, deacetylates Lys301 of p65 and compromise its DNA binding ability, consequently inhibiting transcription of target genes [54]. In primary microglia and astrocyte cultures, resveratrol suppressed A $\beta$  induced cell proliferation and cytokine production. In mixed neuronal/glial cell cultures it suppresses A $\beta$  induced NF- $\kappa$ B activation and prevented microglia dependent neuronal apoptosis [54]. In pheochromocytoma cells resveratrol prevented A $\beta$  induced apoptosis by inhibiting ROS, suppressing pro-apoptotic BAX and upregulating anti-apoptotic Bcl-2 gene transcription [56]. Treatment with resveratrol prevented A $\beta$  induced neurotoxicity in animal models of AD by suppressing transactivation of iNOS and other cytotoxic factors [47]. LD55, a synthetic analog of resveratrol (Table 1) without the hydroxyl group, also reduced A $\beta$  plaque formation and neuroinflammation in a model of AD suggesting that the neuroprotective effects of resveratrol can occur even in the absence of its anti-oxidant potential [57]. However a non hydroxylated trimethoxy analog of resveratrol did not protect neuronal cells from glutamate mediated toxicity [58]. In EAE, resveratrol ameliorated disease by inducing apoptosis of activated T cells in the periphery and by suppressing pro-inflammatory responses [48]. Resveratrol and SIRT1 activators such as SRT1720 or SRT501 (Table 1) have been shown to reduce retinal ganglion cell loss, protect against optic neuritis and exert neuroprotective effects without suppressing inflammation in EAE [59, 60]. However, in alternate models of autoimmune demyelination daily oral administration of resveratrol exacerbated the disease suggesting that caution should be exercised in extrapolating its efficacy in EAE for MS patients [61]. Thus resveratrol, its small molecule functional analogs and SRT1 activators offer considerable promise as inhibitors of neuroinflammation and neurodegeneration for AD and MS.

4.1.2. Polyphenolic curcuminoids are mixtures of curcumin (Table 1), bisdemethoxycurcumin, and demethoxycurcumin (Table 1) derived from the traditional herb turmeric or *Curcuma longa* [30]. Pretreatment with curcumin prevented neurotoxicity in 6-hydroxydopamine (6-OHDA) induced neuronal cells by preventing ROS production and intracellular oxidative stress [62]. Curcumin has also been shown to improve spatial memory loss in a rat model of AD [63]. Furthermore curcuminoids have been shown to inhibit toxic amyloid aggregate, suppress A $\beta$  oligomer formation and accelerate disaggregation of amyloid plaque supporting a therapeutic potential [64]. It has been suggested that the curcuminoid mixtures and its individual components could exhibit distinct effects on the inflammatory and apoptosis gene expression profiles. In an A $\beta$  peptide infused model of AD, while demethoxycurcumin was more effective in reducing IL-1 $\beta$  secretion, the curcuminoid mixture suppressed COX-2, FasL and Fas receptor expression in the hippocampus [30]. Treatment with curcumin has been shown to ameliorate EAE by inhibiting pro-inflammatory cytokine responses in microglial cells and preventing differentiation of neural antigen specific T cells [65, 66]. The divergent effects of curcumin depend on its pleiotropic molecular effects including regulation of signal transduction pathways that lead to activation of transcription factors. Demethoxycurcumin has been shown to inhibit I $\kappa$ B $\alpha$  phosphorylation, prevent NF- $\kappa$ B activation and suppress proinflammatory gene expression in lipopolysaccharide stimulated microglial cells [67]. Treatment with tetrahydrocurcumin inhibit interleukin-1 receptor-associated kinase (IRAK-1) activity by suppressing upregulation of NF- $\kappa$ B dependent miRNA146 in A $\beta$  stimulated human astroglial cells. In addition, curcumin also has been shown to suppress NF- $\kappa$ B mediated IRAK-2 activity and mediate neuroprotection [68]. Despite the promising therapeutic potential, poor water solubility, fast degradation profile and poor bioavailability are significant hurdles for the clinical use of curcumin. Nanocurcumin is a stable form of curcumin that has been shown to cross the BBB into the CNS [69, 70]. A highly stable nanoformulation of curcumin has been shown to mediate significant improvements in



working and cue memory in a mouse model of AD despite being poorer than the native curcumin in reducing the A $\beta$  plaque density [69].

4.1.3: Epigallocatechin-3-gallate (EGCG) (Table 1), a major polyphenolic extract of green tea, has been shown to exhibit significant neuroprotective effects against a variety of toxic insults and neuronal injuries [52]. In  $\beta$ -amyloid-induced pheochromocytoma12 cells EGCG treatment prevent apoptosis by inhibiting activation of ERK/p38 MAPK and NF- $\kappa$ B signaling pathways [71]. EGCG inhibits the fibrillization of A $\beta$  in vitro by interfering with IKK $\beta$  activation and consequently suppressing NF- $\kappa$ B mediated transactivation of  $\beta$ -secretase and release of soluble APP [72]. In animal models of AD EGCG improve memory function by reducing NF- $\kappa$ B mediated  $\beta$ - and  $\gamma$ -secretase activities and consequently the extracellular A $\beta$  levels [73]. In EAE, while treatment with EGCG alone suppress disease by inhibiting NF- $\kappa$ B mediated transactivation of inflammatory mediators, combination of EGCG and glatiramer acetate has been shown to reduce neuronal cell death and promote axonal outgrowth of primary neurons [74].

## **4.2: Terpenoids:**

Terpenoids are widespread class of secondary metabolites, alternatively referred to as terpenes or isoprenoids. Chemically all terpenoids may be considered to be derived from a basic branched C5 unit isoprene (2-methyl-1, 3-butadiene) and are classified based on the number of C5 units present in the molecule as hemi, mono, di or tri terpenoids [75]. Plant-derived triterpenoids, such as oleanolic acid are known to exhibit potent anti-inflammatory properties. A synthetic methyl ester analog of oleanolic acid (Table 1), has been shown to suppress A $\beta$  peptide induced proliferation and cytokine production in microglial cells and inhibit intracellular

oxidative stress in primary neuronal cells or mixed neuron-glia cultures [76]. Treatment with oleanolic acid has been shown to prevent EAE by suppressing peripheral inflammation and preventing CNS infiltration of inflammatory cells [77]. The suppressive potential of triterpenoids has been attributed to blocking the canonical NF- $\kappa$ B pathway by direct inhibition of I $\kappa$ B kinases [75]. Glycyrrhizic acid (GA), a triterpenoid saponin glycoside from the roots and rhizomes of licorice has been suggested to possess significant anti-inflammatory potential. Diammonium glycyrrhizinate (DG) (Table 1), the salt form of glycyrrhizin acid (GA), has been shown to inhibit A $\beta$ <sub>1-42</sub> induced activation of p65 and MAPK signaling pathways in microglial cells and attenuate memory deficits in A $\beta$ <sub>1-42</sub> induced AD in mice [78]. Xanthoceraside (Table 1), a triterpenoid saponin extracted from the husks of *Xanthoceras sorbifolia* Bunge has been shown to suppress MAPK and NF- $\kappa$ B signaling and inhibit the release of nitric oxide (NO) and pro-inflammatory cytokines in A $\beta$  peptide induced microglial cells [79]. Adenanthin (Table1), a diterpenoid isolated from the leaves of *Isodon adenanthus*, has been shown to exhibit preventive and therapeutic effects in EAE. Adenanthin reduce the stimulatory capacity of macrophages, suppress Th1 and Th17 cells and proinflammatory cytokines as well as upregulate regulatory T cell populations [80]. Mechanistically adenanthin has been shown to suppress the DNA binding activity of recombinant p65 protein in a dose dependent manner [75, 80]. Tripchlorolide (table1) a small molecule analog of triptolide derived from the Chinese herb *Tripterygium Wilfordii* Hook F (TWHF) is a diterpenoid. Treatment with triptolide inhibits A $\beta$  peptide induced pro-inflammatory cytokines in microglial cells by inhibiting p38 MAPK and NF- $\kappa$ B signaling pathways [81]. In addition, triptolide has been shown to protect neuronal cell lines and primary cortical neurons against microglia mediated A $\beta$  induced toxicity by inhibiting NF- $\kappa$ B and JNK pathways and consequently attenuate cyclooxygenase -2 (COX-2), iNOS and cytokine production [82]. Triptolide has been shown to ameliorate EAE by inhibiting I $\kappa$ B $\alpha$  phosphorylation, preventing NF-

$\kappa$ B nuclear translocation and upregulating heat shock protein 70 (Hsp70). It has been suggested that the Hsp70 binds the p65 subunit, stabilizes and sequesters the NF- $\kappa$ B: $\kappa$ B- $\alpha$  complex in the cytoplasm thereby preventing immuno-inflammatory responses [83].

#### **4.3: NF- $\kappa$ B targeting disease modifying drugs (DMD):**

Considerable experimental data suggest that many of the DMDs suppress the neuroinflammation-neurodegeneration process act by inhibiting NF- $\kappa$ B activation either directly or indirectly [1, 4]. The efficacy of previously developed anti-cytokine therapies is attributed to the shifting of the proinflammatory cytokine responses to an anti-inflammatory cytokine profile, a process which integrally involves NF- $\kappa$ B mediated transactivation of inflammatory and inhibitory genes [84]. Compelling evidence also suggest that in addition to the protection against loss of cholinergic neurons, the effects of anti-cholinesterase's in suppressing A $\beta$  mediated pathology can also be attributed to the inhibition of NF- $\kappa$ B mediated inflammatory signaling [85].

**4.3.1:** Sphingosine-based phospholipids are abundant structural components of cell membranes. Phosphorylation of sphingosine by sphingosine kinase forms sphingosine-1-phosphate (S1P) that acts binding S1P specific receptors predominantly expressed in lymphoid tissues, resting T cells and B cells. Lymphocyte egress from secondary lymphoid organs is facilitated by a S1P gradient mediated by S1P receptor subtype 1. Derived from the natural product myriocin, a metabolite of the fungus *Isaria sinclairii*, fingolimod is a structural analog of S1P (Table1). It acts by binding the S1P receptor on lymphocytes and prevent egression of effector T cell from lymph nodes thereby suppressing immuno-inflammatory responses [86]. Considerable evidence suggests that the fingolimod also binds S1P receptors on astrocytes and microglia and reduce gliosis and neurodegeneration [87]. In AD models fingolimod has been shown to ameliorate oligomeric A $\beta$ -induced neuronal damage by upregulating BDNF synthesis.

Mechanistically fingolimod has been shown to prevent increase in intracellular calcium, suppress NF- $\kappa$ B activation and eliminate the NF- $\kappa$ B/IL-6/STAT3 amplification cascade in antigen activated cells [88]. Quinolone 3 carboxamide derivatives such as laquinimod have been shown to suppress NF- $\kappa$ B activation in astrocytes and ameliorate disease in a model of cuprizone-induced demyelination [89].

4.3.2: Vasoactive intestinal peptide (VIP) (Table1) and pituitary adenylate cyclase activating polypeptide (PACAP) (Table1) are bioactive peptides widely expressed in central and peripheral nervous system that exhibit potent anti-inflammatory and neurotrophic properties [90, 91]. In EAE, VIP and PACAP ameliorate disease by suppressing CNS infiltration of autoreactive T cells and by skewing the effector T cell response from pro-inflammatory to anti-inflammatory phenotype [91]. In mixed neuronal/glial cell cultures treatment with VIP inhibit A $\beta$  mediated NF- $\kappa$ B activation in glial cells and suppress degeneration of neuronal cells. VIP suppresses NF- $\kappa$ B activation by blocking IKK, thereby inhibiting phosphorylation and degradation of I $\kappa$ B $\alpha$  [90].

4.3.3: Signal transduction inhibitors: Several strategies have been attempted to inhibit signaling molecules that enhance inflammatory and/or apoptotic cellular responses. A large number of kinase inhibitors have been evaluated in models of cancer and inflammation with suggested potential for neuroinflammatory neurodegenerative diseases [4, 92]. High similarity between the kinase sub-family members, presence of ubiquitous ATP binding sites in all kinases, presence of numerous other non-kinase proteins that utilize ATP and the need to block more than one kinase are significant challenges in developing selective kinase inhibitors without off-target effects [92]. It has been suggested that inhibition of p38 MAPK, in particular p38 $\alpha$  could represent an attractive neuroprotective strategy in both MS and AD [93]. In rats injected A $\beta$ <sub>1-42</sub> peptides, an inhibitor of p38 MAPK (Table1) suppress nuclear NF- $\kappa$ B in hippocampal neurons

[93]. A eukaryotic translation initiation factor 2 phosphatase inhibitor (Table1) attenuate  $A\beta$  induced microglial activation and neuronal cell death by suppressing IKK activation, I $\kappa$ B degradation and the subsequent nuclear translocation of p65 [94].

4.3.4. Decoy nucleotides that inhibit NF- $\kappa$ B mediated transcriptional activity have been shown to inhibit  $A\beta$ -triggered release of cytochrome c, rescue expression of BCL-XL, and interfere with intracellular accumulation and extracellular deposition of  $A\beta$  [95]. Direct targeting of NF- $\kappa$ B with NBD (NEMO binding domain peptide) (Table 1) that disrupts the integrity of the IKK complex or administration of IKK inhibitory compound PS-1145 has been shown to ameliorate EAE [96]. Peptides derived from the transactivation domain of p65 (Table1) selectively inhibit NF- $\kappa$ B activation induced by various inflammatory stimuli, suppress NF- $\kappa$ B-mediated gene expression and increase apoptosis in monocytic macrophage like cells [97]. A peptide derived from the glucocorticoid induced leucine zipper (GILZ) (Table1), a protein that binds and sequesters the p65 subunit of NF- $\kappa$ B in the cytoplasm has been shown to ameliorate EAE by inhibiting activation of inflammatory cells and cytokine secretion [98]. In addition the GILZ-peptide has been shown to suppress glutamate synthesis by lipopolysaccharide activated macrophages suggesting neuroprotective potential and applications in AD [99].

## **5. Conclusions and future perspectives:**

Disorders of the brain and nervous system have been recognized as major health challenges by the global burden of disease study [100]. Despite considerable advances in the elucidation of the underlying molecular mechanisms, few treatments exist that can reverse or slow the course of chronic neurological diseases. Considerable evidence support common inflammatory mechanism in the progression of various chronic neurodegenerative diseases with diverse clinical manifestations. A predominant consequence of increased inflammatory signaling is the

upregulation of the inducible transcription factor NF- $\kappa$ B with ensuing self-sustaining and self-propagating vicious cycle of uncontrolled, prolonged inflammation that drives the neurodegenerative process [2]. Hence interruption of this vicious cycle by targeting the NF- $\kappa$ B signaling pathway constitutes an attractive disease-modifying therapeutic strategy for neurodegenerative pathologies [2]. However, caution should be exercised in the development and evaluation of potential NF- $\kappa$ B inhibitors for CNS diseases since constitutively active NF- $\kappa$ B in neurons is critical for neuronal growth and survival [2, 4]. Furthermore the wide spectrum of inducible NF- $\kappa$ B responses from neuroprotection to neurodegeneration depending on the strength of the triggering event(s) and the type of NF- $\kappa$ B dimers activated adds to the complexity of the therapeutic regimen [15]. The beneficial effects of anti-NF- $\kappa$ B therapeutic strategies are likely to be effective in pathological conditions that exhibit highly stimulated NF- $\kappa$ B that disrupts homeostatic function such as the sporadic or rapidly progressing advanced AD. A better understanding of the molecular events that determine the point of conversion(s) of NF- $\kappa$ B responses from being protective to damaging effects is needed for therapeutic modulation of neuroinflammation and neurodegeneration.

## **6. Expert opinion:**

Numerous studies support the critical role of chronic inflammation as a common denominator of multiple neurodegenerative diseases with varied clinical features. Sustained or unregulated activation of NF- $\kappa$ B is integral to the persistence of inflammation making NF- $\kappa$ B pathway an important therapeutic target. Indeed several USFDA approved drugs including dexamethasone and donepezil inhibit NF- $\kappa$ B signaling as part of their therapeutic effects. Considerable efforts by pharmaceutical industry and academic drug discovery units are directed towards developing targeted inhibitors of NF- $\kappa$ B. Strategies that block molecules upstream of NF- $\kappa$ B pathway or the

associated signaling adapters or those that target the I $\kappa$ B inhibitory proteins have been shown to exhibit significant propensity for systemic and off-target toxicities. An additional level of complexity to be taken into consideration in targeting NF- $\kappa$ B in the CNS is the dual and opposite roles of activated NF- $\kappa$ B in neuronal survival and apoptosis. Recent elucidation of mechanisms of NF- $\kappa$ B suggest that while the activation of c-rel containing dimers mediate neuroprotective effects by upregulating neurotrophic and anti-apoptotic genes, increased activation of p65/p50 dimers predominantly precipitate neurodegeneration by increasing transactivation of pro-apoptotic and neurotoxic mediators in the CNS. Under physiological conditions a homeostatic balance exists between the proportions of activated c-rel containing dimers and p65/p50 dimers that maintain neuroprotection while preventing neurotoxicity. Superimposition of secondary stressors such as aging, increased oxidative stress or injury in susceptible hosts, increases activated p65/p50 dimers and shifts the balance towards inflammation and neurodegeneration (Fig 1B). Strategies that directly target p65/p50 dimers are likely to regain the homeostasis. Since elevated p65 is highly expressed only in pathologically activated cells, selective targeting of this NF- $\kappa$ B subunit may yield therapeutic drugs with better safety profile. In recent years chemical derivatives of natural compounds that inhibit NF- $\kappa$ B have been evaluated for therapeutic potential in neurodegenerative diseases. Mechanistically the active chemical moiety of many natural compounds such as the diterpenes have been shown to form adducts with select residues of p65, compromising its DNA binding and transactivation ability.

Importantly the expanding network of NF- $\kappa$ B interactors has increased the potential for identifying newer targets for specific inhibition. The challenge lies in targeting large interfaces of protein-protein and protein-DNA interactions. Nevertheless, advances in high throughput screening platforms, structural biology, computational biology and rational drug design

strategies augment the identification and development of select NF- $\kappa$ B inhibitors with potential therapeutic value. Characterization of the synthetic derivatives of natural compounds and the rationally designed agents will promote the development of small-molecule inhibitors of RelA with better benefit to risk ratio for human therapeutics.

#### 7. Article highlights box:

1. In the CNS, the ability of NF- $\kappa$ B to mediate either neuroprotective effects or to promote neuroinflammation progressing to neurodegeneration has been attributed to the composition of the NF- $\kappa$ B dimers. While activation of c-rel containing dimers promotes neuroprotection, upregulation of the p65 subunit of NF- $\kappa$ B via the canonical pathway mediate neuroinflammation and apoptosis of CNS cells.
2. Many naturally occurring compounds or their functional derivatives exert neuroprotective efficacy by inhibiting the canonical NF- $\kappa$ B pathway. For example, diterpenoids like adenanthin or the functional analogs of resveratrol such as the sirtuin activators have been shown to interact with the p65 subunit interfering with its DNA binding and transcriptional ability.
3. The active moiety of the natural compounds and peptide mimics of the NF- $\kappa$ B interacting proteins can provide efficient lead agent(s) for developing specific small molecule inhibitors of p65/NF- $\kappa$ B. Based on the ubiquitous expression and diverse functions of NF- $\kappa$ B in multiple cellular events, such specific inhibitors are likely to be most effective in conditions with highly elevated activated p65 such as the spontaneous AD or MS relapses.



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**Figure Legend:**

Fig 1: Schematic representation of NF- $\kappa$ B activation pathways in neurodegeneration and neuroprotection. Stimulation of neural or glial cells with stimuli such as IL-1 $\beta$  or NGF (nerve growth factor), BDNF (brain derived nerve factor) or membrane glutamate receptor-5 (mGlu5) leads to phosphorylation of IKK proteins, ubiquitination of I $\kappa$ B $\alpha$  and activation of c-rel containing NF- $\kappa$ B heterodimers, which upon translocation to the nucleus mediate transactivation of anti-inflammatory genes (such as IL-10 and glucocorticoid induced leucine zipper (GILZ), anti-apoptotic factors (such as Bcl-2) and neuroprotective factors such as NGF, manganese-superoxide dismutase (Mn-SOD). Stimulation with noxious stimuli such as myelin fragments or A $\beta$  peptides increases intracellular Ca<sup>++</sup> and oxidative stress, leads to phosphorylation of IKK proteins, ubiquitination of I $\kappa$ B $\alpha$  and activation of p50:p65 NF- $\kappa$ B heterodimer which upon translocation to the nucleus induces transactivation of pro-inflammatory genes (such as IL-12, IL-17), pro-apoptotic genes (such as caspases, Bax) and neurotoxic factors [glutamate, induced nitric oxide synthase (iNOS)]. (B) In health a homeostatic balance between activated c-rel containing dimers and the p65:p50 dimers plays a role in maintaining synaptic activity, neuronal plasticity and health. Increase in activated p65:p50 dimers leads to enhanced transactivation of pro-apoptotic and excitotoxic factors leading to neuroinflammation and neurodegeneration. NF- $\kappa$ B targeting agents edge the disrupted balance towards the homeostatic level.

Fig 2: Role of NF- $\kappa$ B in AD neurodegeneration: (A) In susceptible hosts, factors associated with normal cognitive decline such as aging, oxidative/metabolic stressors/toxins/ trauma leads to intracellular accumulation of A $\beta$  peptides in neural and glial cells. Initially the affected neurons exhibit increased intracellular Ca<sup>++</sup> that stimulate NF- $\kappa$ B signaling with subsequent release of



reactive oxygen species (ROS) as well as transactivation of neurotrophins such as nerve growth factor (NGF) and anti-apoptotic genes such as Bcl-2. In pre-plaque stages A $\beta$  peptides derived from damaged neurons stimulate resting microglial cells to secrete TNF- $\alpha$  which in turn inhibits the neurotoxicity induced by ROS. Activated glial cells also exhibit increased NF- $\kappa$ B signaling and transactivation of neurotrophic factors such as NGF and brain derived nerve factor (BDNF). Thus the cumulative effect in early AD shifts in favor of neuroprotection. (B): Continued excessive extracellular accumulation of A $\beta$  peptides and tau aggregates induces increased intracellular Ca<sup>++</sup>, activation of NF- $\kappa$ B, release of ROS, induced nitric oxide synthase (iNOS), nitric oxide (NO) by neuronal cells with concomitant activation of microglial cells. Both glial and neural cells upregulate NF- $\kappa$ B mediated synthesis of excitotoxic glutamate, inflammatory cytokines and oxidative stress promoting neuronal damage. The adjacent astrocytes stimulated by A $\beta$  deposits also upregulate NF- $\kappa$ B mediated release of free radicals and cytokines. Continued aggregation of deposits initiates a positive feed-back loop between activated glia and astrocytes and neuronal cells leading to synaptic dysfunction, cell death and persistent AD.

Fig 3: Model of the role of NF- $\kappa$ B in mediating neurodegeneration in multiple sclerosis. NF- $\kappa$ B is upregulated in a variety of cell types in MS. Elevated NF- $\kappa$ B in peripheral mononuclear cells induces inflammatory cytokines and activate endothelial cells which in turn upregulate NF- $\kappa$ B activation and increase expression of adhesion molecules facilitating infiltration of mononuclear cells into the CNS parenchyma. Activated microglia release reactive oxygen species (ROS) increase oxidative stress mediating tissue damage. Resolving glia phagocytose tissue debris. Activated glial cells also exhibit increase NF- $\kappa$ B activation and secretion of anti-inflammatory cytokines (IL-10) and neurotrophins (NGF). During relapse reactivated glial cells exhibit elevated

NF- $\kappa$ B mediated transactivation of pro-inflammatory cytokines, ROS, induced nitric oxygen synthase (iNOS) initiating demyelination and axonal injury leading to neurodegeneration.

Table 1: Potential NF- $\kappa$ B inhibitors.

AD; Alzheimer's disease, MS; multiple sclerosis; Mn-SOD; manganese superoxide dismutase; VIP; vasoactive intestinal peptide, PACAP; pituitary adenylate cyclase-activating peptide, NEMO; NF- $\kappa$ B essential modulator, GILZ; glucocorticoid leucine zipper, EAE; experimental autoimmune encephalomyelitis.

Table 1: Potential NF- $\kappa$ B inhibitors

			Mechanism/s of NF- $\kappa$ B inhibition	References
Polyphenols	Resveratrol and functional analogs	Resveratrol	Suppress neuroinflammation by sirt1 dependent deacetylation of p65 and prevent apoptosis of by p53deacetylation.	50, 51, 54-55, 57.
			Exacerbate EAE-increased CNS infiltration.	58-59,62
		LD-55	Suppress microglial activation and plaque density in AD model	56
	Curcuminoids	Curcumin	Suppression of I $\kappa$ B $\alpha$ kinase activation. Inhibit miRNA.	63,64,69-71
		Desmethoxy curcumin		
		Epigallocatechin gallate (EGCG)	Inhibiting activation of p38 MAPK and NF- $\kappa$ B signaling. Reduce NF- $\kappa$ B mediated $\beta$ - and $\gamma$ -secretase activities.	72-74
Imidazole derivatives	Sirtuin activators	SRT 1720	Induces NF- $\kappa$ B mediated transactivation of FOXO3, increases MnSOD activity. Prevented neuronal loss without suppressing inflammation in EAE.	58,60
Terpenoids	Triterpene/ triterpenoids	Oleanolic acid	Inhibit phosphorylation of I $\kappa$ B $\alpha$	76,78
		Xanthoceraside	Prevent mitochondrial dysfunction, Inhibit nuclear translocation of NF- $\kappa$ B	80
		Diammonium glycyrrhizinate	Prevent MAPK signaling and nuclear translocation of p65	76, 79
	Diterpenoids	Adenanthin	Interfere with the DNA-binding activity of NF- $\kappa$ B to its response DNA sequence	76,81
		Tripchlorolide	Inhibit I $\kappa$ B $\alpha$ phosphorylation Inhibit DNA binding activity of NF- $\kappa$ B	76,82-83
Disease modifying agents/ drugs		Fingolimod hydrochloride	Prevent S1P mediated activation of NF- $\kappa$ B and gene transcription.	88,89
		VIP	Inhibit phosphorylation and ubiquitination of I $\kappa$ B $\alpha$	90,91
		PACAP	Inhibit phosphorylation and ubiquitination of I $\kappa$ B $\alpha$	91
		p38 $\alpha$ inhibitors	Inhibit phosphorylation of I $\kappa$ B $\alpha$	93

	Signal transduction inhibitors	Salubrinal	IKK activation, IκB degradation and nuclear translocation of NF-κB	94
		NEMO binding domain peptide	IKK activation	96
		p65 peptide	Inhibit phosphorylation and nuclear translocation of p65	97
		GILZ peptide	Inhibit nuclear translocation of p65	98,99

Figure 1a.

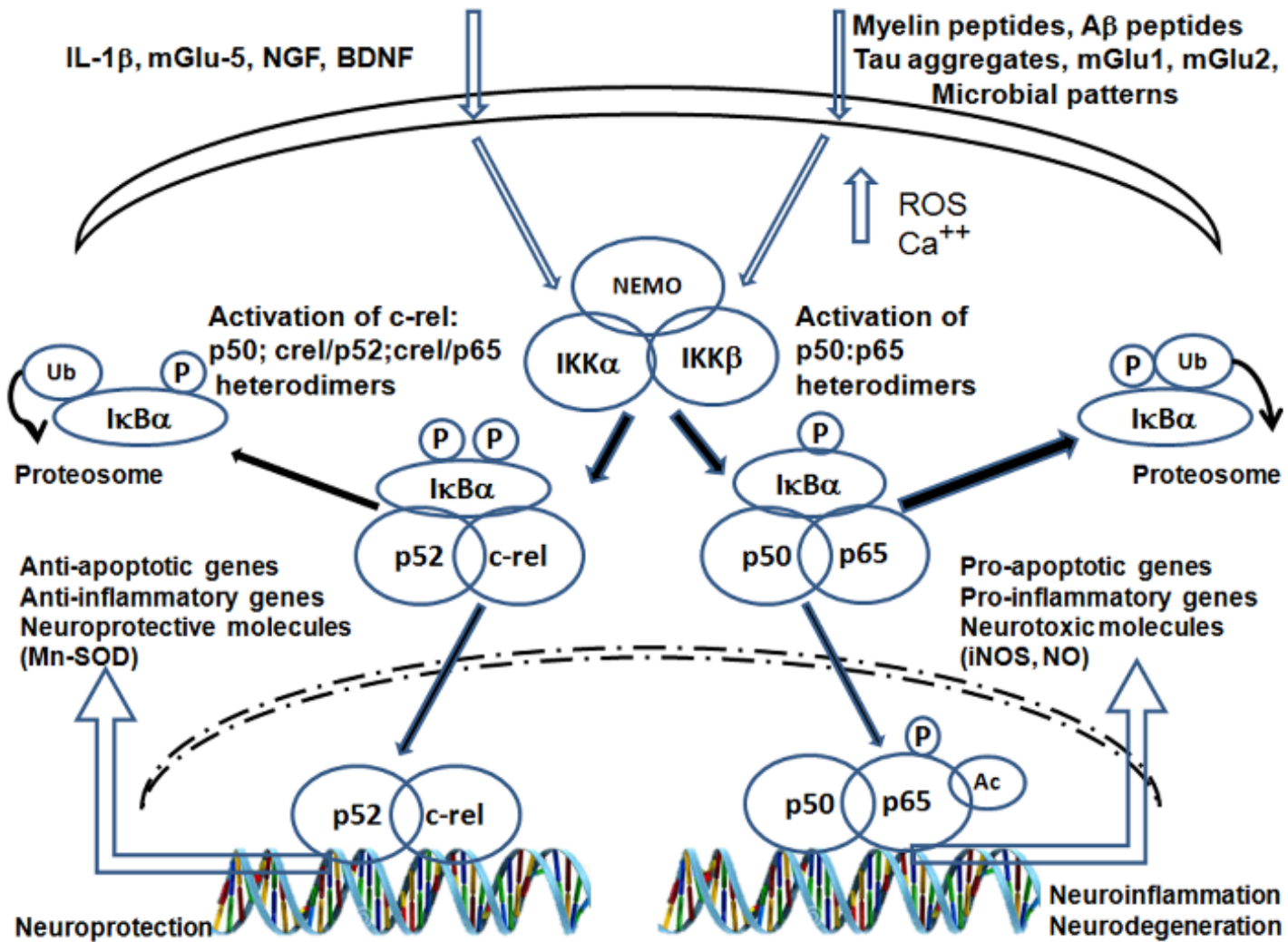


Figure 1b.

Non-canonical activation

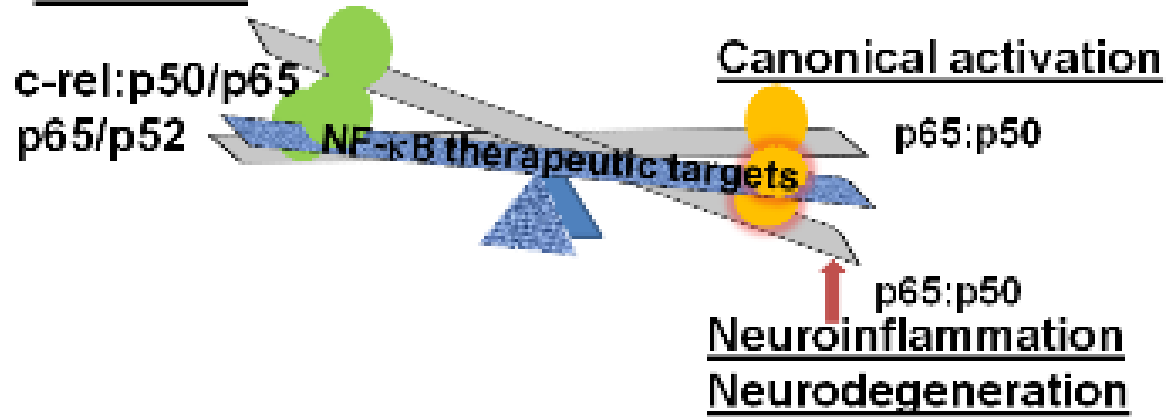


Figure 2a.

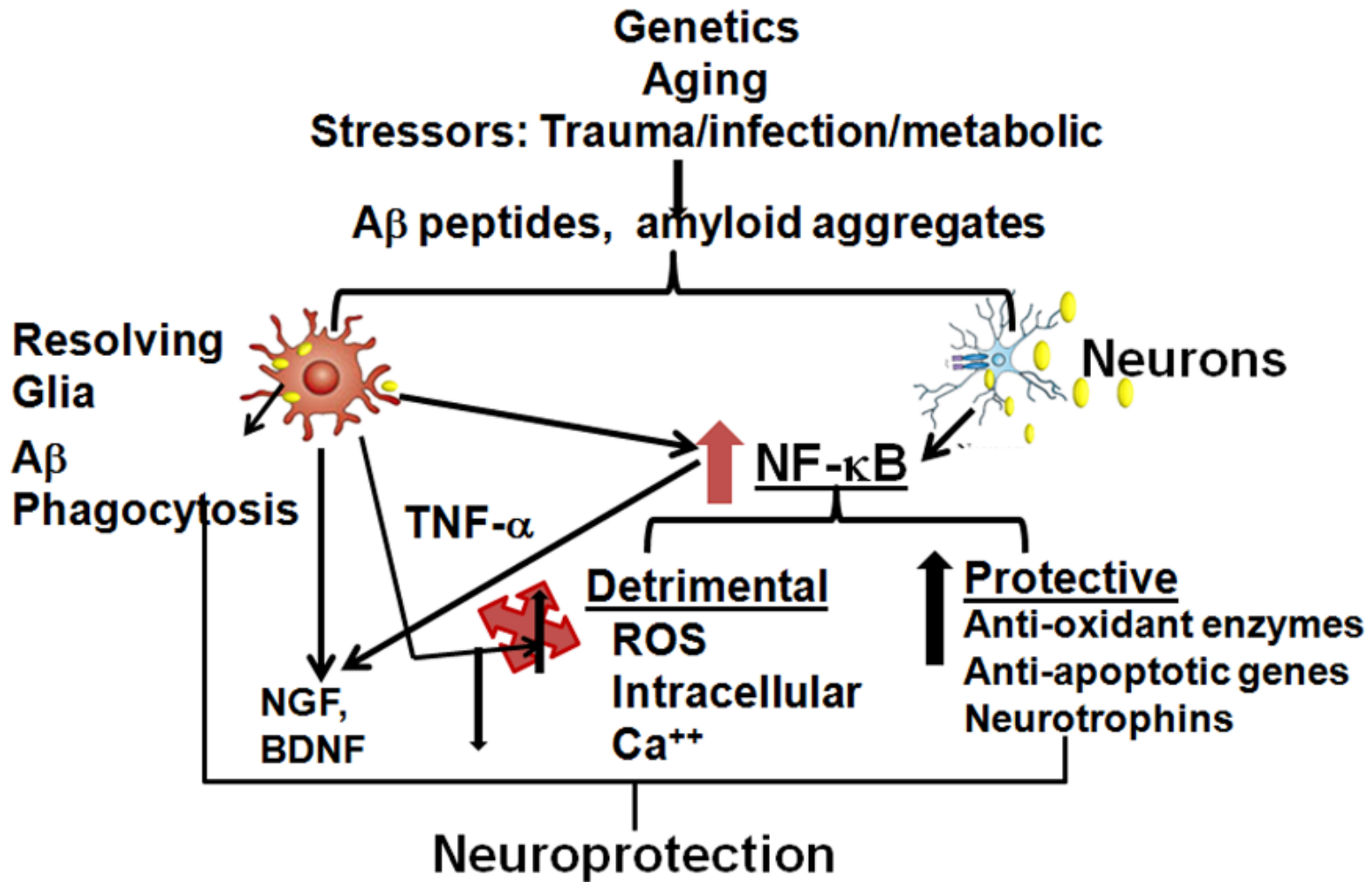


Figure 2b.

