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Original Publication:

Upinder Kaur, Priyanjalee Banerjee, Aritri Bir, Maitrayee Sardar Sinha, Atanu Biswas and Sasanka Chakrabarti, Reactive Oxygen Species, Redox Signaling and Neuroinflammation in Alzheimers Disease: The NF-kappa B Connection, 2015, Current Topics in Medicinal Chemistry, (15), 5, 446-457.
http://dx.doi.org/10.2174/1568026615666150114160543

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Reactive Oxygen Species, Redox Signaling and Neuroinflammation in Alzheimer's Disease: The NF-κB Connection

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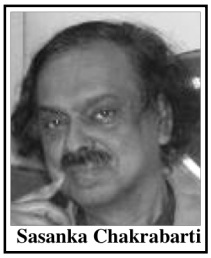
Sasanka Chakrabarti

Abstract: Oxidative stress and inflammatory response are important elements of Alzheimer's disease (AD) pathogenesis, but the role of redox signaling cascade and its cross-talk with inflammatory mediators have not been elucidated in details in this disorder. The review summarizes the facts about redox-signaling cascade in the cells operating through an array of kinases, phosphatases and transcription factors and their downstream components. The biology of NF-κB and its activation by reactive oxygen species (ROS) and proinflammatory cytokines in the pathogenesis of AD have been specially highlighted citing evidence both from post-mortem studies in AD brain and experimental research in animal or cell-based models of AD. The possibility of identifying new disease-modifying drugs for AD targeting NF-κBsignaling cascade has been discussed in the end.

Keywords: Alzheimer's disease, amyloid beta, cytokines, NF-κB, oxidative stress, redox signaling.

INTRODUCTION

Oxidative stress as a major driving force in the pathogenesis of Alzheimer's disease (AD) has been generally accepted because of compelling evidence of accumulation of oxidative damage markers of protein, DNA and phospholipids in post-mortem AD brain as well as in the brains of AD transgenic animals [1-3]. The redox proteomic data obtained from MCI (mild cognitive impairment) and AD post-mortem brains have been very convincing in identifying oxidative damage to key enzymes and proteins that may play a major role in AD pathogenesis [4,5]. The depletion of reduced glutathione, accumulation of redox-active transition metals and decrease in the activities of antioxidant enzymes are also indicative of a pro-oxidant milieu in AD brain [1-3,6,7]. In addition, there is a growing body of information in different experimental models indicating the pro-oxidative nature of amyloid beta peptide, which amply rationalizes the oxidative damage theory of AD pathogenesis [3,8,9]. However, a major caveat exists in our understanding of the relationship between oxidative stress and AD. The role of altered redox signaling pathways in AD pathogenesis especially in the early phase of the disease has not been explored in details so far, but this is an area which not only can reveal the initial molecular events of AD pathology, but also may provide clues for identifying new drug targets.

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In the present review, we will provide a brief outline of AD highlighting the clinical manifestations, neuropathology, pathogenesis, risk factors and available therapy or rather the lack of it, and then proceed to describe the importance of altered redox signaling in AD pathogenesis focusing on the NF-κB pathway and linking it with neuroinflammation. The review will also describe some novel approaches for AD therapy by interfering with NF-κB signaling.

ALZHEIMER'S DISEASE: OVERVIEW

Dementia of the Alzheimer's type predominantly affects the memory and gradually involves the visuospatial and language domains; progressing from a preclinical phase to mild cognitive impairment and finally to dementia [10-12]. In the course of its progression, various neuropsychiatric and behavioral abnormalities develop and the disease incapacitates the patients with regards to executive functioning [12]. The mean duration of the disease process is around 8 years from the onset of clinical features to death [13].

Recent estimates have revealed that there are more than 35.6 million people living with dementia worldwide, and this is expected to rise to 65.7 million by 2030 with age specific prevalence doubling every 5 years after 65 years of age, and AD accounts for the majority of such dementia patients [14]. By far the commonest type of AD is sporadic AD, and autosomal dominance is seen in only about 5% cases of AD (familial AD). Familial AD usually has an earlier age of onset caused by a mutation of any of the 3 genes e.g. Amyloid Precursor Protein (*APP*), Presenilin 1 (*PS 1*) and Presenilin 2 (*PS 2*) [15]. On the other hand, the sporadic form of the dis-

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ease has a complex multi-factorial etiology with aging being the most dominant risk factor. Epidemiological studies have identified multiple risk factors for sporadic AD that include hypertension, head injury, mid-life obesity, hypercholesterolemia, hyperhomocysteinemia, type 2 diabetes and Al toxicity [14,16].

Parts of the brain predominantly affected by AD include the hippocampus, enterorhinal cortex, amygdala and different areas of neocortex which show severe loss of cholinergic neurons. The typical neuropathological features of AD brain include extracellular neuritic plaques or some other varieties of amyloid plaques and intraneuronal neurofibrillary tangles [17,18]. The neuritic plaque consists of a central core of deposition of oligomerized amyloid beta peptide (primarily Aβ42 and Aβ40) surrounded by degenerating neuronal processes (dystrophic neurites), while the intraneuronal neurofibrillary tangles are composed of paired helical filaments of hyperphosphorylated tau proteins [17,18]. This typical neuropathology is associated with diffuse loss of neurons, degeneration of axons, dendrites and synapses, gliosis and the presence of inclusion bodies [17,18]. Several neuropathological staging methods are available including the recent recommendations of National Institute on Aging / Alzheimer's Association [17,18].

The pathogenesis of AD includes interdependent damage pathways of oxidative stress, mitochondrial dysfunction, calcium dysregulation, ER stress, synaptic dysfunction, microglial activation and inflammatory response and abnormal accumulation and aggregation of amyloid beta peptides (Aβ42, Aβ40 etc) or hyperphosphorylated tau [3,19-22]. For long it has been held that many of these damage pathways operating in the AD brain are the outcome of excessive formation, accumulation and aggregation of Aβ42, and the soluble oligomers of Aβ42 primarily trigger these toxic events (amyloid cascade hypothesis) [20,21]. Although the cause for the excessive production or accumulation of Aβ42 in AD, especially for the sporadic variety, is not apparent, the detailed pathways of formation of these peptides from amyloid precursor protein (APP) by sequential proteolysis by β-secretase (BACE 1) and γ-secretase have been elucidated [20]. The trafficking of the amyloid beta peptide from endoplasmic reticulum through trans-golgi network, secretory vesicles, plasma membrane and endosomes and also the degradation of the peptide by neprilysin, insulin degrading enzyme (IDE), endothelin converting enzyme - 1 etc. have also been worked out in considerable details [20, 23].

At present, the drugs approved for AD aim to correct the symptoms of cholinergic deficiency or to antagonize glutamate mediated excitotoxicity, but various supporting drugs are also used to provide symptomatic relief or to treat the comorbidities and the risk factors. The cholinesterase inhibitors like donepezil, gallantamine and rivastigmine tend to restore the synaptic levels of acetylcholine and are useful in mild to moderate cases of AD. Memantine, an NMDA-receptor associated channel blocker, though effective in moderate to severe cases of AD does not have substantial impact on disease progression. Apart from these four drugs approved by FDA, there are many potential disease-modifying agents under various phases of clinical trials, but quite a few of them, most notably the drugs targeting amyloid beta peptide metabolism and clearance, have been rejected in the course of the trials [24,25]. The scenario at present is not only disappointing, but also it has raised fundamental questions about AD disease models. Nevertheless the novel drug development for AD should emphasize on primary mediators involved in neurotoxicity.

ROS AND INFLAMMATION IN AD BRAIN

The two interdependent mechanisms of AD pathogenesis that are relevant in the present review are oxidative stress and inflammatory reactions which work in concert in AD brain and both impinge on NF-κB pathway. The involvement of oxidative damage in AD pathogenesis has been highlighted already [1-5]. It will be logical to present a brief outline of inflammatory response in AD brain, before returning to ROS and redox signaling. Although there are many unanswered questions, an enormous body of evidence has linked inflammation with AD pathogenesis from studies of postmortem AD brains and experimental models of this disease [26,27]. Microglial activation by fibrillar or soluble oligomeric amyloid beta and possibly other inducers lead to the release of inflammatory cytokines, complement components and chemokines such as IL-1β, TNF-α, IL-6, IFN-γ, monocyte chemotactic protein - 1 (MCP-1), macrophage inflammatory protein (MIP-1α, MIP-1β) etc., and reactive astrocytes also contribute to the process [26-28]. The oligomeric and fibrilar forms of amyloid beta also activate the complement pathway by binding to C1q and C3b in the absence of any antibody [26,28]. Various complement fragments and the end product of complement activation, membrane attack complex (MAC), have been found to accumulate near the plaques and over the dystrophic neurites in AD brain [26,28]. The activated microglia which express pro-inflammatory surface markers like CD45, CD40, CD35, MHC class II etc. also accumulate in large numbers around the neuritic plaques, and elevated levels of various cytokines and chemokines are found in AD brain [26-28]. The soluble oligomeric or fibrillar forms of amyloid beta bind to microglia via numerous receptors such as the immunoglobulin Fc receptor, complement receptor, receptor for advanced glycation end products (RAGE), serpin receptor complex, scavenger receptor class B type 1, formyl peptide chemotactic receptor, a complex receptor of CD36/CD47/α6β1integrin etc., and can trigger the secretion of cytokines through activation of NF-κB [26,29]. The cytokines released by microglial activation unleash a self-perpetuating cycle of inflammatory response and also interact with amyloid β peptide oligomers and distressed neurons triggering apoptosis, oxidative damage and excitotoxicity [26-28,30]. Some cytokines also upregulate APP expression and facilitate amyloidogenic processsing of the protein [26-28,30]. The final outcome of this inflammatory response is neuronal and synaptic degeneration. However, neuroinflammation in AD may not be purely injurious, and alternative activation of microglia in AD brain has been evidenced which assists in regeneration and repair through cytokines like IL-4, IL-10 and TGFβ [26,30]. There are studies which imply that common molecular pathways stimulated by Aβ42 and inflammatory mediators in AD brain cause increased activity of NF-κB. It is not certain whether the activation of NF-κB associated with inflammatory response in AD aggravates the brain damage or

provides neuroprotection and neuroregeneration because of the varied nature of the genes upregulated by NF-kB. In general, the activation of glial (inducible) NF-κB causes neuronal death and degeneration while that of neuronal (consitutive) NF-κB provides neuroprotection and plasticity [31,32]. The activation of NF-κB in astrocytes also aggravates the proinflammatory response and tissue injry [26]. The duration of NF-κB activation, transient or sustained, also determines the nature of cellular response in the brain [32].

ROS and Redox Signaling

The multiple sources and complex chemistry of intracellular ROS, the interdependent radical chain reactions damaging proteins, phospholipids and DNA and the attenuation of these toxic radical reactions by enzymic and non-enzymic antioxidants have been elaborately reviewed by many authors and will not be discussed in details here. In short, there are mitochondrial and extra-mitochondrial sources of ROS consisting of superoxide radicals ($O_2^{\cdot -}$), hydrogen peroxide, hydroxyl radicals ($OH^{\cdot}$), nitric oxide (NO) and peroxynitrite radical ($ONOO^{-}$). Some of these radicals react among themselves either spontaneously or by metal-catalyzed and enzyme-catalyzed reactions [3]. The mitochondrial source of ROS consists of primarily the respiratory chain complex I and complex III and several other enzymes like pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, aconitase, α-glycerophosphate dehydrogenase and dihydroorotate dehydrogenase [33]. The extra-mitochondrial sources include the membrane -bound NADPH oxidases, nitric oxide synthase, cycloxygenase, lipoxygenase, xanthine oxidase and cytochrome P450 dependent enzymes which generate ROS as part of normal metabolism or following activation of receptors by growth factors and cytokines [3].

For long the role of ROS in many degenerative diseases including AD has been attributed to the direct damaging effects of these radicals on different biomolecules causing structural and functional derangement of cells and organelles. However, there is a paradigm shift in our understanding of ROS involvement in disease mechanisms recently. There is accumulating evidence of the involvement of ROS in cell signaling pathways or transcriptional activation of genes, and more emphasis is, therefore, given on altered redox-signaling in disease mechanisms instead of direct radical mediated damage to cell organelles. The modulation of insulin or growth factor or cytokine signaling pathways or the activation of the trascription factor NF-κB by H_2O_2 or other oxidants are some of the early but convincing studies in redox signaling mechanisms [34,35,36,37]. In redox signaling, ROS (most commonly H_2O_2 because of its relative stability and diffusibility) oxidize reactive thiol groups of key redox-responsive proteins altering their properties in a fashion somewhat similar to activity modulation of enzymes by reversible phosphorylation – dephosphorylation (Fig. **1**). The thiol groups of free cysteines are not reactive having pKa values of 8 - 9, but within the special microenvironments of some proteins the pKa values of some thiol groups may be lowered to 4 - 5 converting these groups to nucleophilic thiolate anions [38,39]. On reaction with H_2O_2, thiolates form sulfenic acid (SOH) residues, which may be further oxidized to sulfinic acid or sulfonic acid groups [38,39]. The SOH residues of the proteins may react with other thiol groups of the same or different proteins forming intramolecular or intermolecular disulfide linkages or amide groups of proteins to form sulphenyl amides, or alternatively, these may react with thiol residues of glutathione causing S-glutathionylation of proteins [38,39,40]. Apart from the modification of protein thiols by direct oxidation by H_2O_2, a change in the cellular redox state e.g. altered ratio of GSSG:GSH (oxidized glutathione:reduced glutathione) may lead to increased S-glutathionylation of proteins [40]. The protein disulfide linkages may be reduced by glutaredoxin-reduced glutathione-glutathione reductase or thioredoxin-thioredoxin reductase [38,40,41]. Apart from cysteine oxidation, the redox signaling may entail other kinds of protein modifications such as thiol alkylation, histidine oxidation to 2-oxo-histidine, protein nitrosylation and carbonylation [38,40,41]. Apparently, plenty of such redox-sensitive target proteins like phosphatases, kinases and other components of cell signaling pathways or transcription factors may act as substrates for such reversible covalent modifications [38-41]. These protein modifications especially protein sulfenylation may change the activity status of the proteins [38-41]. Thus, the reversible protein modificatios of cell signaling components and transcription facors by ROS may lead to a wide range of cellular responses in various physiological and pathological conditions [38-41]. For example, several protein phosphatases like tyrosine protein phosphatase 1B (PTP1B), serine-threonine protein phosphatase 2A (PP2A), dual-specificity protein phosphatase (MAP kinase phosphatase1), lipid phosphatase (PTEN) act as negative modulators of insulin signaling by dephosphorylating specific down-stream components [42]. These phosphatases require specific cysteine residues in the reduced form for their activity and are good targets for redox regulation [42]. Thus ROS can oxidize the essential cysteine residues, inactivate the phosphatases and thereby enhance insulin signaling [42]. Similarly, H_2O_2 generated following PDGF binding to receptors (PDGF-R) may inactivate the low-molecular weight protein tyrosine phosphatase (LMW-PTP) by inducing disulfide bond formation between cys 12 and cys 17, and this phenomenon prevents the dephosphorylation of PDGF-R and sustains the activated state [34,43]. Likewise, in case of EGF signaling, H_2O_2 generated by NOX activation causes inactivation of several phosphatases like PTP1B, PTEN and SHP-2 by oxidation of specific cysteine residues preventing the dephosphorylation of EGF receptor (EGF-R) [43]. Additionally, EGF-R may undergo protein sulfenylation at cys 797 by a direct action of H_2O_2 leading to an enhanced receptor tyrosine kinase activity [43]. Apart from the modulation of insulin and growth factor signaling cascades, redox reactions through cysteine oxidation regulate the activities of many non-receptor protein kinases like Akt, PKC, cytosolic Src, p21 ras, ataxia telangiectasia mutated (ATM) protein kinase and a set of serine-threonine kinases comprising of ERK 1/2, JNK and p38 [39,43,44].

The redox-sensitive transcription factors like AP-1, SP1, HIF-1, NRF-2, NF-κB, Nrf-2, CREB, p53 etc. constitute a large family of proteins which can be activated in a number of ways by ROS causing expression changes in a wide variety of genes regulating growth, survival, differentiation, cy-

toprotection and apoptosis [38,45,46]. The ROS may either cause an increased synthesis of a transcription factor or may activate an existing transcription factor. The increased synthesis of the transcription factors by ROS may be brought about by increased mRNA stability, activation of MAP kinases or increased efficiency of translation [38]. On the other hand, ROS may activate an existing transcription factor by thwarting its proteasomal degradation or releasing it from an inhibitory binding partner or causing post-translational modifications leading to nuclear translocation or increasing its DNA binding propensity [38,45-50]. For example, Nrf-2 is localized in cytosol in association with Kelch-like ECH associating protein 1(Keap1) which prompts its degradation by the proteasome pathway. The ROS oxidize specific cysteine residues of Keap1 leading to its dissociation from Nrf-2 [46]. The release of Nrf-2 from Nrf-2-Keap1 complex is facilitated by phosphorylation of Nrf-2 by several ROS activated kinases like PKC and PERK [46]. The released Nrf-2 translocates to nucleus and heteromerizes with one of the small Maf proteins, and the heterodimer binds to an antioxidant responsive element (ARE) present at the regulatory sites of different genes [46]. The binding of Nrf-2 heterodimer causes transcriptional activation of phase II detoxification enzymes, enzymes for glutathione synthesis, heat-shock proteins etc. [46]. In case of hypoxia-inducible factor (HIF), the activation occurs in a different way. HIF in the transcriptionally active form is a dimer of HIF-α and HIF-β. In normoxic condition HIF-α is hydroxylated at two proline residues by prolyl hydroxylase domain (PHD) enzyme and then rapidly degraded by the proteasomal pathway. Under hypoxic condition or in the presence of ROS or some NO donors, PHD is inactivated leading to diminished hydroxylation and consequent stabilization of HIF-α [46]. HIF-α then dimerizes with HIF-β, translocates to nucleus, binds to the hypoxia-response element in different genes and activates or suppresses the process of transcription [46].

There are several tricky issues with ROS signaling especially with specificity of the signaling process for a highly diffusible compound like H_2O_2. Moreover, the members of the signaling cascade are usually present in low quantity and have lower rate constants for reaction with H_2O_2 compared to a large number of competing antioxidant molecules. These issues have been adequately discussed in several reviews, but we would not delve further in this problem in the present discussion [38,39]. On the contrary, in the context of the current discussion we will present, an elaborate description of the transcription factor NF-κB highlighting its role in coupling ROS signaling and inflammatory mediators in the backdrop of Alzheimer's disease and its potential in drug development.

Biology of NF-κB

Although originally identified in connection with the regulation of immunoglobulin synthesis, it is now established that NF-κB is present in all kinds of cells controlling the transcription of a wide variety of genes under diverse physiological and pathological conditions [51,52]. These genes include pro-apoptotic and pro-survival genes, pro-inflammatory cytokines, antioxidant enzymes, pro-oxidant enzymes and many others [51,52]. The NF-κB family members RelA/p65, RelB, cRel, p52 (derived from the precursor p100) and p50 (derived from the precursor p105) are characterized by a Rel homology domain (RHD) of 300 amino acids, which mediates dimerization as well as DNA binding [51,52]. The DNA binding site is a 10-bp stretch of DNA with the consensus sequence GGGPuNNPyPyCC [51,53]. Apart from the RHD, each of RelA/p65, RelB and cRel also contains a carboxy-terminal transactivation domain to upregulate gene transcription following DNA binding, and in addition RelB also contains a leucine-zipper domain [51,53]. The other members of NF-κB family like p50 and p52 do not contain any transactivation domain, while their precursors p105 and p100 also contain ankyrin repeats and glycine-rich regions [51,53]. The proteolytic cleavage of p105 and p100 occurs at the glycine-rich region in the proteasomal complex by a process known as regulated ubiquitin proteasome dependent pathway [53-55]. The members of NF-κB family can form homodimers and heterodimers among themselves, but RelB forms heterodimers only with p50 or p52 [51,52]. Although different combinations of homodimers and heterodimers are present in different cells and in different conditions, the most predominant form of NF-κB normally is RelA-p50 [51]. All combinations of NF-κB dimers, however, cannot upregulate transcription because p50 and p52 do not have transactivation domains, but instead homo or heterodimers of p50 and p52 can bind to kB DNA binding site and prevent the binding of a transcriptionally active dimer like RelA-p50 [51,53,56]. However, the availability of different types of dimers probably indicates that the dimers may bind to different kB DNA binding sites of a wide variety of genes with different affinities regulating their functions.

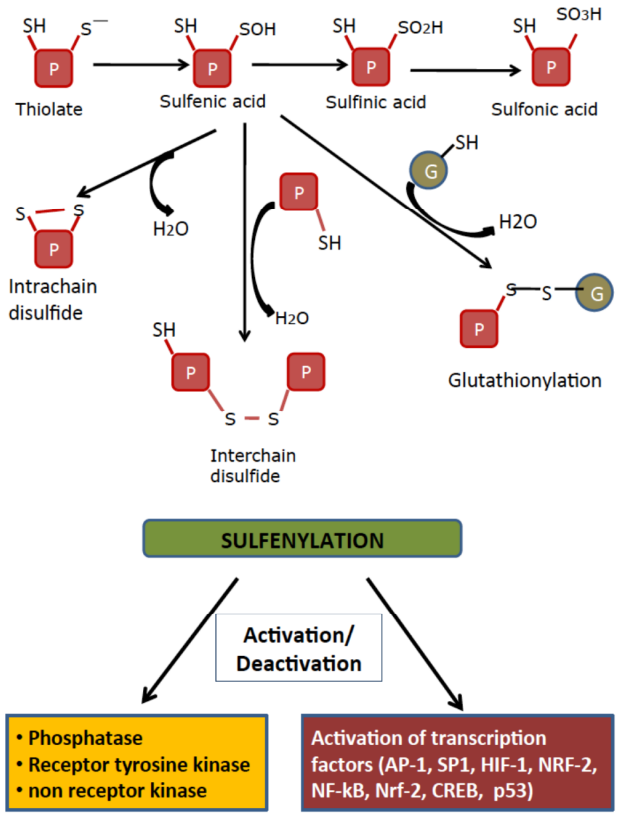

Fig. (1). Redox dependent sulfenylation of proteins lead to activation /deactivation of kinases, phosphatases and transcription factors.

Normally NF-κβ dimers remain cytosolic and in inactive state in resting cells by interaction with IkB, but is induced to active form by a bewildering set of stimuli. Bacteria or bacterial products (lipopolysaccharide or LPS), viruses or viral products (double-stranded RNA, TAT, gp160 etc.), cytokines and chemokines, growth factors, UV radiation, oxidative stress, receptor ligands (CD 4 ligand, CD 40 ligand, CD 35 ligand etc.), modified proteins (advanced glycation end products, amyloid beta, oxidized LDL etc.) and many others can activate NF-κB [57]. The constitutively active form of NF-κB, however, is also demonstrated in several cell types including neurons [51]. The IkB family of proteins comprises of three typical IkBs e.g. IkBα, IkBβ, IkBε and atypical members like IkBζ and Bcl3 [51,52]. The precursor proteins p100 and p105 of NF-κB family which contain ankyrin repeats may also be included in IkB family [51]. In general, the formation of a complex of NF-κB dimer with a typical member of IkB family prevents the nuclear translocation and gene activation function of NF-κB [51,52]. The IkB proteins interact through their ankyrin repeat domains, mask the nuclear localization signals in RHDs of NF-κB dimers and keep the latter in cytosol in inactive form, but the complete molecular details of this interaction are far more complex and still not clearly understood [51,58]. The activation process of NF-κB has been best elucidated in the context of IkBα and RelA-p50 dimer. The phosphorylation of serine 32 and 36 of IkBα leads to ubiquitnation and proteasomal degradation of IkBα which allows the nuclear translocation of NF-κB and upregulation of a large set of genes [51,52,58,59]. With other members of IkB family such as IkBβ and IkBε similar phosphorylation (serine 19 and 23 for IkBβ or serine 157 and 161 for IkBε) and degradation cycles probably occur but with a much delayed kinetics [36,51,62]. The precursor proteins p105 and p100 can behave like IkB because of the presence of ankyrin repeats and can hold the Rel proteins in inactive form in cytosol e.g.RelB-p100 dimer [51,52,62,63]. The phosphorylation of p100 at serine residues leads to ubiquitination and regulated proteasomal degradation to generate p52 and consequent activation and nuclear translocation of RelB-p52 dimer of NF-κB [51,52,62,63]. Similarly p105 can bind to NF-κB dimers preventing their nuclear translocation, but after phosphorylation at serine residues near C-terminal region undergoes complete degradation like IkB proteins [62]. Alternatively, p105 can be constitutively processed to generate p50 at a low level [51,62]. The phosphorylation of is mediated by the IkB kinase complex (IKK) which comprises of two kinases IKKα and IKKβ, a regulatory subunit called NF-κB essential modulator (NEMO) and other additional units like ELKS [51,54,62,63]. IKKα and IKKβ have 50% identity in amino acid sequence, and each contains a N-terminal kinase domain and leucine-zipper domain assisting in dimerization and a C-terminal helix-loop-helix domain regulating kinase activity [51,53].

CANONICAL AND NON-CANONICAL ACTIVATION OF NF-κB

Although NF-κB is activated by a wide array of stimuli, the two alternative pathways of activation can be distinguished in terms of the nature of stimulus, the IKK subunits involved and IkB substrates used. In the canonical pathway, Toll like receptor ligands (pathogen associated molecules like LPS, dsRNA), proinflammatory cytokines, genotoxic agents etc. activate IKKβ subunit which then phosphorylates IkBα or IkBβ without the involvement of NEMO leading to NF-κB activation [51,52]. The activation of IKKβ subunit in the canonical pathway requires the recruitment of several upstream factors like TNF receptor associated factors (TRAF) family of proteins and RIP kinase [51,52,62]. In the non-canonical pathway, several members of TNF family like lymphotoxin β, BAFF, ligands of CD40, CD27 and CD30 etc. activate IKKα through involvement of TRAF2 and TRAF3 and the upstream kinase known as NF-κB inducing kinase or NIK [51,52,63,64]. NIK causes phosphorylation and activation of IKKα which in turn specifically phosphorylate p100 subunit of RelB-p100 inactive complex [51,52]. The subsequent proteasomal degradation of p100 generates p52 causing activation of RelB-p52 dimer of NF-κB as described earlier [51,52].

ROS and NF-κB

There is now compelling evidence to suggest that NF-κB is a redox-sensitive transcription factor and direct activation of NF-κB by H_2O_2 and other ROS have been demonstrated in a number of cell lines in different experimental conditions [65-69]. Further, the modulation by H_2O_2 or superoxide radicals has also been observed when NF-κB activation has been induced by cytokines in different cell lines [70,71]. Likewise, when cells are exposed to conditions of oxidative stress such as hypoxia or reperfusion injury, the activation of NF-κB by endogenous ROS has been clearly demonstrated [66,72,73]. The toxic intermediates of lipid peroxidation, in particular 4-hydroxynonenal, also have been shown to be involved in NF-κB activation in various experimental conditions [74-76] In conformity with these findings, antioxidants of various types and most notably N-acetylcysteine and pyrrolidine thiocarbamate have been shown to prevent NF-κB activation by different inducers like cytokines, viruses, dsRNA, endotoxins, phorbol ester, lipopolysaccharide etc. in a large number of cell lines [67,69,75]. The overexpression of antioxidant enzymes in cell lines also prevents NF-κB activation induced by cytokines or other proinflammatory agents [77,78]. However, methodological problems have often led to inconsistent results in experiments studying the direct actions of ROS on NF-κB signaling in different cell lines, and new approaches such as steady-state titration with H_2O_2 have been suggested for rectification of the problem [37,79-81]. It is suggested that ROS may be the generic modulator of NF-κB signaling system induced by different stimuli, but at the same time the action of ROS may be specific at the level of a single gene [79,81]. Nevertheless, it is also to be appreciated that methodology alone is not responsible for varied reports of ROS actions on NF-κB signaling pathway. Indeed, ROS can affect NF-κB signaling cascade in multiple and often opposing ways that may be cell or tissue specific [52,82]. The ROS can affect the NF-κB subunits or IkB or IKK directly or indirectly through other upstream kinases or phosphatases [52,82]. Thus, oxidation of cys 62 of p50 by ROS prevents the DNA binding of NF-kB, whereas dimerization of NEMO following disulfide bond formation between cys 54 and cys 347 may activate IKK leading to

NF-κB activation [52,82]. In contrast, the oxidation of cys 179 of IKKβ by ROS may inhibit the kinase activity with concomitant inactivation of NF-κB [82]. Conversely, ROS may cause tyrosine phosphorylation of IkB through SyK and CKII activation leading to the release of IkBα from its association with NF-κB dimer of RelA-p50 [52,83]. On the other hand, ROS may inhibit ubiquitination of IkBα for subsequent proteasomal degradation and thus may suppress or delay the NF-κB activation induced by TNF-α as seen in HEK293 cell line [70]. These few examples illustrate the multitude of mechanisms by which ROS may impact the complex regulation of NF-κB signaling in different conditions [52,82]. Although the ROS mediated activation of NF-κB has been explored extensively in cell lines and primary culture of mammalian cells, the evidence of NF-κB activation is seen in many animal models of disease. In several studies ROS dependent NF-κB activation has been documented in animal models of lung inflammation, cerebral reperfusion injury, endothelial damage and atherogenesis [84-87]. Likewise NF-κB activation has also been reported in animal models of diseases like AD, Parkinson's disease, type 2 diabetes and athersclerosis, and interestingly these conditions are all associated with increased oxidative stress [53]. Further, age-related activation or increased DNA binding of NF-κB has been reported in various tissues during aging and dietary antioxidants have been shown to inhibit nuclear translocation of activated NF-κB [53,88].

As indicated earlier that NF-κB alters the transcription of a large array of genes which interestingly also include several antioxidant and pro-oxidant genes [52]. The important antioxidant enzymes and proteins whose transcriptions are regulated by NF-κB include SOD1 and SOD2, glutathione peroxidase, glutathione S-transferase, heme oxygenase, ferritin heavy chain, metallothionein-3 and NAD(P)H-quinone oxidoreductase [52]. The pro-oxidant genes under NF-κB control include cycloxygenase-2 (COX 2), inducible nitric oxide synthase (iNOS), NADPH oxidase (NOX) and several lipoxygenases [52].

NF-κB AND ALZHEIMER'S DISEASE

The above account clearly indicates that NF-κB is a central regulator of ROS signaling as well as the inflammatory and immune response of the cells and tissues, and it also coordinates the cross-talk between inflammatory mediators and ROS in patho-physiological conditions. Seen in this light NF-κB signaling is likely to play a crucial role in AD pathogenesis because both oxidative stress and inflammation are key elements of this disorder. Further, transcriptional activation by NF-κB is also linked to cell survival, differentiation and apoptosis which have clear implications in neurodegeneration. It will be interesting, therefore, to accumulate the evidence that connects NF-κB signaling with AD either in post-mortem human brain or in different animal and cell-based models.

In post-mortem AD brain, high immunoreactivity for p65 subunit of NF-κB has been observed in amyloid plaques as well as within plaque-adjacent neurons and astroglia indicating NF-κB activation in this condition [89]. In temporal cortex of post-mortem AD brain, an increased immunoreactivity for p65 subunit of NF-κBdimer has been observed compared to control [90]. Similarly, immunohistochemistry with polyclonal antibody against p65 subunit has revealed an enhanced NF-κB content in neurons, dystrophic neurites and neurofibrillary tangles in hippocampus and entorhinal cortex in post-mortem AD brain compared to control [91]. In another post-mortem study in AD brain, increased immunoreactivity for p65 subunit of NF-κB has been observed in the nuclei of neurons, in the vicinity of amyloid plaques, in diffuse β amyloid deposits and in the cytosol of some neurons with neurofibrillary tangles [92]. Systematic studies by Lukiw and colleagues have shown abundant presence of severa NF-κB regulated microRNAs, miRNA 155, miRNA 146a, miRNA 125b and miRNA 9 in the disease affected areas compared to unaffected areas in AD brain or similar anatomical regions of age-matched controls [93,94]. These miRNAs are known to interfere with mRNAs coding for proteins involved in synaptogenesis, inflammatory response, neurotrophic functions and amyloidogenesis [94]. In this respect it is interesting to point out that certain environmental factors like HSV-1 and aluminium exposure which have been implicated in sporadic AD pathogenesis are known inducers of NF-κB and proinflammatory miRNA expression [93].

The evidence of increased NF-κB activity in post-mortem AD brain is probably related to increased oxidative stress, inflammatory reactions and toxicity of accumulated amyloid beta peptides, and experimental studies provide strong support to this. Thus, a single microinjection of oligomeric Aβ42 in rat brain cortex results in an increased expression of COX2, IL-1 and TNF-α through activation of NF-κB in reactive astrocytes in the vicinity of the injection site [95]. In another study the toxicity of amyloid beta peptide on cell lines or primary culture of neurons is mediated by H_2O_2 and lipid peroxides with an increased activation of NF-κB signaling [96]. In neural cell line NG108-15, amyloid beta 42 causes a loss of cell viability with release of inflammatory cytokines TNF-α, MCP-1 and IL-10 through activation of JNK and NF-κB [97]. In co-culture of cortical neurons and microglia, amyloid beta peptide causes neuronal toxicity and death through activation of glial NF-κB which involves acetylation of lys 310 of p65 subunit [98]. In hippocampal neuronal culture, amyloid beta peptide (Aβ40 or Aβ25 - 35) can induce cell death with increase in intracellular Ca^{2+} and ROS, and the process is protected by TNF-α or TNF-β through activation of NF-κB [99]. In an interesting study it has been shown that pretreatment of primary culture of cerebellar granule cells to low-dose of Aβ40 or TNF-α prevents cell death on a subsequent challenge by a neurotoxic dose of Aβ40 [100]. The protective effect of this pre-treatment with low-dose of Aβ40 or TNF-α is mediated by NF-κB activation and involves ROS, since the phenomenon is prevented by the antioxidant PDTC [100]. The authors suggest that activation of NF-κB by TNF-α or Aβ40 follows an inverted U shaped curve, where a low dose activates NF-κB optimally through low amount of ROS, but a higher dose produces more ROS inactivating p65 subunit of NF-κB [100]. In a related study the activation of NF-κB by a low dose of Aβ40 or Aβ25-35 involving ROS has been demonstrated in primary culture of neurons [89]. Consistent with the neuroprotective action of NF-κB activation, one study has reported that TNF-α treatment of SHSY5Y cells upregulates Mn-SOD

gene through NF-κB activation which subsequently protects the cells from a challenge by amyloid beta peptide or iron-mediated oxidative stress [101]. Another study identifies a resistant clone of PC12 cells against oxidative stress with constitutively high NF-κB activity [102]. On the contrary, Aβ25-35 induced cell death in SHSY5Y cells is said to be mediated by ROS, (poly-ADP) ribose polymerase (PARP-1) activation and NF-κB activation [103]. Aluminium toxicity is an established environmental risk factor for sporadic AD, and aluminium sulphate exposed human astroglial cells exhibit upregulation of several NF-κB responsive miRNA like miRNA 125b and miRNA 146a, which are also overexpressed in AD brain [104]. This effect of aluminium sulfate can be prevented by antioxidants like phenyl butyl nitrone (PBN) and PDTC indicating the involvement of ROS in aluminium induced NF-κB activation [104]. In murine brain mixed co-culture of astrocytes-neurons-microglia, amyloid beta peptide induces inflammatory response and apoptosis through activation of double-stranded RNA dependent kinase (PKR) and NF-κB signaling, and specific inhibitors of PKR prevent the amyloid beta toxicity [105]. Thus, the results from these various studies do clearly show that the activation of NF-κB by ROS or inflammatory mediators could be either neuroprotective or neurotoxic under different conditions which imply that the regulation could be really complex under *in vivo* scenario. Thus, the increased NF-κB activation in post-mortem AD brain could either be a protective response or a trigger for neurodegeneration and apoptosis, and at least one reason for this uncertainty lies in the fact that NF-κB activation leads to both upregulation of pro-survival and pro-apoptotic genes or pro-oxidant and antioxidant genes [52]. Another important issue in the NF-κB and AD connection is the regulation of amyloid beta homeostasis through transcriptional upregulation of various related enzymes and proteins especially APP and BACE1 [106]. The type 1 integral protein APP is coded by a gene located in chromosome 21and undergoes alternative splicing to generate several isoforms of the protein of which the one with 695 amino acids is present in the brain [107]. The 5' regulatory regions of APP gene in rat and human have considerable homology and contain the binding sites for Sp1, AP-1, AP-2, AP-4, GCF etc. [108,109]. Further, a binding site for NF-κB family of proteins has been mapped in the regulatory region of APP gene [110]. The BACE1 enzyme plays a critical role in amyloidogenic processing of APP, and an increased activity of this enzyme is seen in AD post-mortem brain and correlated with increased Aβ peptide load [111,112]. The transcriptional regulation of BACE1 gene by NF-κB is complex, but under conditions of Aβ overload the upregulation of BACE1 gene may occur through NF-κB activation [113,114]. A recent study has shown that in HEK293 cell line under physiological conditions, NF-κB actually downregulates the expression rates of genes for APP, BACE1 and several components of γ-secretase complex, but when these cells are overexpressing wild-type or mutated APP gene and having an overload of Aβ peptides, NF-κB activation positively modulates all these genes [115]. Thus, NF-κB upregulation in AD brain actually sustains a vicious cycle where increased Aβ peptide load further enhances its synthesis from the precursor protein (Fig. **2**). The upregulation of BACE 1 by 27-hydroxycholesterol, an oxidation product of cholesterol, in SHSY5Y cells also requires NF-κB activation as well as the involvement of the gadd153 gene (growth arrest and DNA damage induced gene 153), and in triple transgenic AD mice the deposition of amyloid β peptide is preceded by the increased activity of NF-κB and gadd153 [116].

Inhibitors of NF-κB: Therapeutic Potential in AD

The complexity of NF-κB activation apparent from the discussion already presented, makes it a little uncertain whether the inhibitors or activators of NF-κB would be effective in halting the progression of AD pathology [117]. Agents targeting the NF-κB pathway can act at various levels. One possible site would be upstream of NF-κB where triggering stimuli like ROS, viruses, Aβ, cytokines and many others act. Downstream miRNAs, inflammatory mediators, pro-oxidant gene products may also serve as potential targets, while a third approach would be to target NF-κB itself [118,119].

Inhibiting the triggers of NF-κB signaling cascade by antioxidants or specific antagonists of cytokines have been attempted in experimental models and clinical trials of AD. However, ROS and cytokines act at various levels in AD pathogenesis and not exclusively through NF-κB signaling cascade. Although varieties of antioxidants, synthetic or present in natural products, have shown promise in mitigating the disease pathology in experimental models of AD, the large scale clinical trials have been disappointing [3,120,121]. IL-1 receptor antagonist has given good results in stroke models, but there is no convincing evidence of their usefulness in AD **[**122**].** Compounds like etanercept targeting TNF-α have shown improvement in the clinical profile of AD but on a limited scale with improvement of aphasia and verbal fluency following cerebrospinal fluid administration of etanercept [123,124].

The direct inhibition of NF-κB by various means has provided some encouraging results in cell based AD models. This can be accomplished in many ways like preventing activation of IKK, inhibiting the phosphorylation of IkB, targeting proteosome mediated degradation of IkB, interfering with the translocation of RelA-p50 dimer to nucleus, oxidizing p65 subunit at critical cysteine residues or deacetylating p65 subunit and using decoy nucleotides which competitively inhibit the binding of p65/p50 dimer to the consensus sequence of NF-κB DNA binding site [118,119,125]. For example, Aβ40 induced translocation of NF-κB to nucleus and degeneration of cells in primary culture of neurons has been blocked by the decoy oligonucleotide of kB site on DNA, the specific inhibitor of IKK AS602868 and the anti-inflammatory agent aspirin [126]. The compound, xyloco-side G, present in a Chinese medicinal plant, protects amyloid beta induced apoptosis in SHSY5Y cells and primary neurons by preventing nuclear translocation of NF-κB [127]. Oridonin, obtained from Rabdosia rubescence, prevents apoptosis, glial activation, release of cytokines and inflammation in the hippocampus of Aβ42 induced AD mice and also prevents NF-κB activation [128]. Many natural compounds like curcumin, resveratrol, epigallocatechin-3-gallate etc. can prevent microglial activation and inflammatory response in various models including AD experimental models, and NF-κB inhibition partly accounts for their beneficial action [129,130]. Several studies have shown that NF-κB

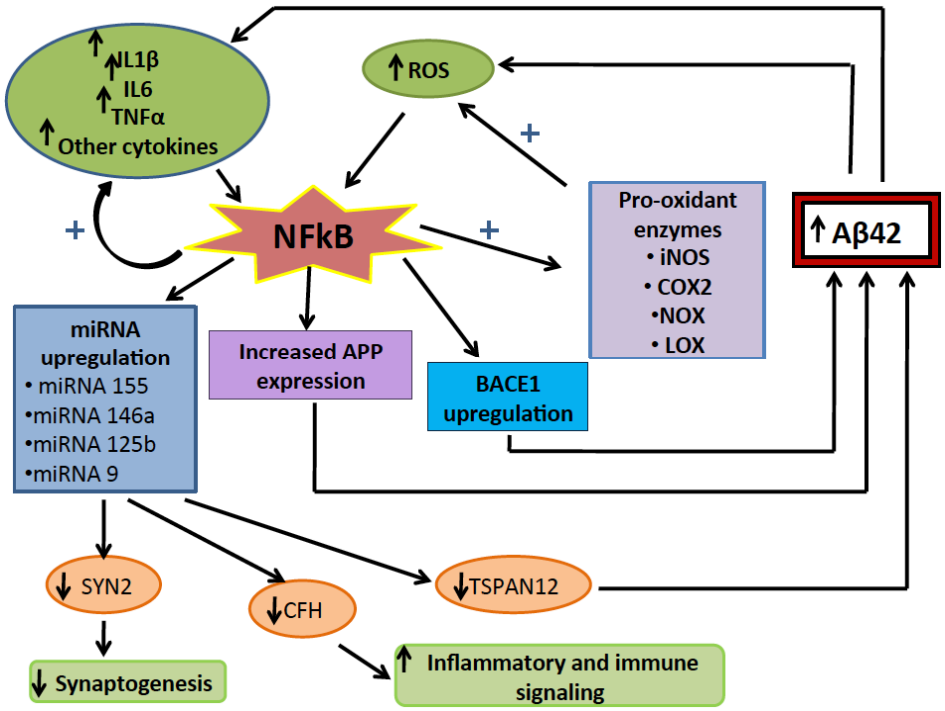

Fig. (2). NFκB in AD pathogenesis. This simplified diagram shows the different interactions of ROS and inflammatory mediators with AD pathogenesis through NF-κB activation. NF-κB induced upregulation of APP and BACE1 occurs under conditions of Aβ overload. SYN2- Synapsin2; CFH- Complement factor H ; TSPAN12- Tetraspanin 12; LOX- Lipoxygenase.

inhibitors which are known to prevent Aβ induced toxicity in experimental models can also reduce amyloid peptide load of the cells overexpressing APP or of brain in experimental AD models [131,132]. We have provided examples where NF-κB inhibitors have been useful in preventing amyloid beta related toxicity or altering amyloid beta load in different experimental models, and some of these may lead to the development of new therapeutic agents against AD. However, there are other specific NF-κB inhibitors e.g. IKK-NBD, TAT-NBD, selective 5-lipoxygenase inhibitor etc. which have shown promise in preventing ischemic brain injury in different experimental systems and their efficacy should also be tested in AD animal or cell-based models [133-135]. It has been shown that p38 MAP kinase activity regulates transcriptional activity of NF-kB, and in AD brain p38 activity is increased [136,137]. An orally active p38 inhibitor MW01-2-069A-SRM is found to inhibit cytokine production, prevent loss of synaptophysin and improve behavioral deficit in a mouse model of AD [138].

NF-κB not only regulates a large number of protein-coding genes, but also many miRNAs including some like mi146a, mi125b which are upregulated in PD brain and implicated in PD pathogenesis [88,89]. A relatively novel approach for neuroprotection that may be useful in AD is to shut down the NF-κB dependent miRNAs activated by NF-κB using anti-miRNA or antagomir i.e. a 100% complementary oligonucleotide sequence to miRNA [139]. The biggest advantage of targeting miRNAs rather than NF-κB is that "culprit" miRNAs are effectively inhibited without having much impact on the critical functions of the cell. Though not devoid of 'off target' effects, the approach is relatively more specific than inhibiting NF-κB which is often met with homeostatic disturbances.

CONCLUSION

AD not only impairs the quality of life of the patient but poses a great burden to economy and society. The nature of primary mediators of the AD cascade is still shrouded in mystery, but ROS signaling and inflammatory response play crucial roles. Various studies have focused on the inflammatory and oxidative components of AD that are linked to the transcription factor NF-κB. So far, the approved therapies for AD including cholinesterase inhibitors and memantine have not lived up to the expectation of disease modifying agents. Therein lies the enthusiasm of targeting the NF-κB signaling cascade to gain new insight into disease pathogenesis and identify potential disease modifying agents.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors wish to thank the Department of Science and Technology, Indian Council of Medical Research and Department of Biotechnology, New Delhi for their continued support to the communicating author for research in the field of neurodegenerative disorders.

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Received: ????????????????? Revised: ????????????????? Accepted: ?????????????????