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Emerging approaches for the treatment of Alzheimer disease: Targeting NF-ϰB pathway

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July 16, 2020

Abstract

Alzheimer's disease (AD) is the most predominant neurodegenerative disorder and form of dementia around the globe. Despite its prevalence, only a few drugs approved for AD and all concerned with the symptoms rather than the underlying cause of the disorder. Classic neuropathological disease hallmarks (β-amyloid & NFT) and sporadic AD risk genes APOE that activate NF-ϰB, yet may incite pathology. NF-ϰB inhibition is a current strategy to counter neuroinflammation and neurodegeneration in the brain of individuals with AD, and numbers of NF-ϰB modulators are being examined in clinical trials. Modification of the NF-ϰB system focuses mainly on preventing oxidative stress with the pathway to cell death and managing the levels of neurotransmitters. This review summarizes several shreds of evidence indicating the upregulation of NF-ϰB in AD and illustrates its function in current efforts for a therapeutic approach. The goal of innovative research strategies is to modulate NF-ϰB, providing an alternate treatment that may help individuals with AD and generate hope for potential clinical advancements in AD.

Keywords:

Alzheimer's disease, β-amyloid, neurofibrillary tangles, oxidative stress, neurodegeneration, neuroinflammation, neurotransmitters, NF-ϰB, p50/p65, canonical pathway

Abbreviations:

AD- Alzheimer disease; NFTs- Neurofibrillary tangles; APP- Amyloid-β protein precursor; ERK- Extracellular Signal-Regulated Kinase; JNK- c-Jun N-terminal kinase; PI3K- Phosphatidylinositol 3-kinase; Akt- Protein Kinase B; MAPK- mitogen-activated protein kinase; NF-ϰB- Nuclear factor kappa B; JAK/STAT- Janus kinase/signal transducers and activators of transcription; NBM- Nucleus basalis of Meynert; ATP- Adenosine triphosphate; ETC- Electron transfer chain; ROS- Reactive oxygen species; RNS- Reactive nitrogen species; HNE- 4-hydroxyl-2-nonenal; LTP- Long-term potentiation; NMDA- N-methyl-D-aspartate; AMPA- γ-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MHC- major histocompatibility complex; TLR- Toll-like receptor; TNF-α- Tumor necrosis factor-α· IFN-γ- Interferon-γ· APCs- Antigen-presenting cells; mTOR- Mechanistic target rapamycin; BBB - blood-brain barrier; IR- Insulin receptor; IRS- Insulin receptor substrates; IGF-1- Insulin-like growth factor-1; RHD- Rel Homlogy Domain; RHR- Rel Homlogy Region; DRG- Dorsal root ganglion; NLS- Nuclear localization sequence; NES- Nuclear export sequence; NADPH- Nicotinamide adenine dinucleotide phosphate; ALS- Amyotrophic lateral sclerosis; HD- Huntington's disease; PD- Parkinson's disease; MS- Multiple sclerosis; VCAM- Vascular cell adhesion molecule; ICAM- Intercellular adhesion molecule; ELAM- Endothelial-leukocyte adhesion molecule; MMPs- matrix metalloproteinases; PSA- Prostate-specific antigen; VEGF- Vascular endothelial growth factor; STAT- Signal transducer and activator of transcription; nAchRs- nicotinic acetylcholine receptors; mAchRs- metabotropic muscarinic acetylcholine receptors; VTA- Ventral tegmental area; THp- Tyrosine hydroxylase-positive; LC- Locus Coeruleus; ssDNA- Single stranded DNA; BACE1- β-secretase β-site APP-cleaving enzyme 1; Aph1-

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anterior pharynx defective-1; NGF- Nerve growth factor; GDNF- Glial cell line-derived neurotrophic factor; AGE- Advanced glycation endproducts; RAGE- Receptor for advanced glycation endproducts; GLAP- Glyceraldehyde related pyridinium; GSK- Glycogen synthase kinase

Introduction

Alzheimer's disease (AD) is recognized as a peculiar neurological disease associated with the degeneration of neurons, mainly characterized by dementia. This neurodegenerative disease typically begins with the loss of memory (amnesia), language impairment (aphasia), loss of muscle control and balance (ataxia), poor judgments, visual complaints, and impairment in other cognitive skills affecting everyday activities accompanied by agitation and hallucinations. Sporadically, there is an increase in muscle tone along with incontinence and mutism (Bird, 2018). AD is an age-related neurological condition that mainly affects to elderly worldwide. In 2017, the official death records have reported 121,404 deaths, making AD the 6^{th} - largest cause of death in the United States (US) and 5^{th}-largest cause of death within Americans over age 65. Deaths from cardiovascular disease and prostate cancer declined between 2000 and 2017, while deaths from AD are jumped by 145 %. During 2018, individuals with AD or other dementias implement an additional 18.5 billion hours of treatment from over 16 million family members and other unpaid relatives. This treatment is estimated at nearly $234 billion, but its expense leads to the increased risk of emotional distress to family members and negative outcomes of physical and mental health. Average medicare premiums per beneficiary for Alzheimer's and some other dementias services over 65 years are often more than three times higher than compensation to beneficiaries without such diseases.

Net 2019 expenses on hospitals, lengthy-term care, and nursing home programs for people 65 years with dementia is forecast to be $290 billion (Alzheimer's Association, 2019). The underlying cause of AD pathogenesis is still poorly understood due to this reason there is no specific therapies are available that can completely stop or counteract its development. (Pimplikar et al., 2014). Early intervention of AD may be an essential key to avoid, delay, and cure the disease, but neurological changes occur before the symptoms appear as memory impairment, the decline in thinking capability (Gaugler *et al.* , 2016). During AD, neuronal damage and destruction eventually affect various parts of the brain like the hippocampus, entorhinal cortex, cingulate gyrus, amygdala, thalamus, motor cortex, sensory cortex, etc which are believed to be the major regions for memory as well as swallowing, and walking. Available evidence had reported that the vulnerable brain regions of an individual having AD contain insoluble amyloid β (Aβ) peptide deposited extracellularly in a grey matter as neuritic or senile plaques. Similarly, hyperphosphorylated tau (p-tau) protein accumulated intracellularly as NFT causes the destruction of cholinergic neurons through oxidative stress, excitotoxicity, and neuroinflammation (Reitz and Mayeux, 2014a). Individuals suffering from the end stage of AD are bed-bound and need complete clock-time treatment. Numerous novel clinical strategies to address AD explicitly arise and make this condition render. It is well known that the upregulation of the p65 subunit of NF-ϰB mediates neuroinflammation and apoptosis of neuronal cells via the canonical pathway which is responsible for the progression of AD (Srinivasan and Lahiri, 2015a).

Etiopathological factors

The etiology of AD is diverse because various putative factors endure the progression of AD which includes genetic factors, aging, environmental pollutants, toxic metals, and various other disease states like hypertension, head trauma, diabetes mellitus, cardiovascular disease (Reitz and Mayeux, 2014). Some other factors such as body weight; plasma lipid levels (Michikawa, 2003) also may constitute a prevalent risk factor for cognitive health in previous studies. These factors are responsible for the AD via different mechanisms. Some of the symptoms which develop in AD are getting lost in familiar places, difficulty in concentrating and thinking, problem in multitasking, decline in the ability to make reasonable decisions, and judgments (Shetty and Bates, 2015), struggling in once-routine activities like cooking, etc. Additionally, there are some changes in personality and behavior like apathy, depression, distrust in others, aggressiveness, mood swings, social withdrawal, irritability, wandering, changes in sleeping habits, and delusions (Lyketsos et al., 2011). (Figure 1)

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Pathophysiology of Alzheimer's disease

Evidence reported that the excessive pairing of Aβ40 and Aβ42 peptides in the hippocampus produces neuronal toxicity and affect synaptic plasticity (Amakiri et al., 2019). Furthermore, AD is also exacerbated by mutations in genes like APP, Presenilin-1 (PS1), and Presenilin-2 (PS2), APOE 4 which enhance Aβ1-42 formation and accumulation (Wolfe, 2018). Similarly, some environmental toxins and physical factors such as environmental toxins such as pesticides, chemicals, and insecticides, alcohol consumption, obesity, smoking, viral infection with viruses (HHV-6a and HHV-7), and diet are associated with increased risk of AD (Reitz and Mayeux, 2014). Several lines of concrete evidence indicate the participation of aluminum along with other metals in AD etiopathogenesis (Exley et al., 2017). Numerous molecular mechanisms like ERK, PI3K, JNK, MAPK, Akt, Wnt signaling pathway, NF-ϰB, JAK/STAT, and increased expression of activated glial cells is typically seen in postmortem AD reports (Srinivasan and Lahiri, 2015). Increased production of IL-1β, IL-6 along with TNF-α in serum and cerebrospinal fluid of AD patients has been recorded, which is due to the upregulation of the canonical NF-ϰB expression (Wang et al., 2015).

On the other hand, five fundamental factors can be derived from a comprehensive framework that captures all recognized risk factors: cholinergic dysfunction, mitochondrial dysfunction (MtD), oxidative stress (OS), glial cell activation, and insulin desensitization. Each factor has a distinct and direct interacting impact on AD, etiopathogenetic, genetics, and serves as the secondary pathogenic mechanism for other known risk factors. Acetylcholine (Ach), a key neurotransmitter in the brain, has function across the cortex, basal ganglia, and forebrain. Cholinergic neuron number is high in the thalamus, neocortex, limbic system, and striatum, suggesting the cholinergic activity is an essential for memory, thought, learning, and other more essential cognitive functions. The primary cause of dysfunction and extinction of cholinergic neurons in the forebrain is suspected to be neurofibrillary degeneration in the basal forebrain, grant a generalized presynaptic cholinergic impairment (Hampel et al., 2020). NBM is the source of cortical cholinergic innervations in the basal forebrain and undergoes severe neurodegeneration in the AD. NFTs in the NBM is likely to cause the loss of the cortical cholinergic innervations. Cholinergic deficiency then adds to the cognitive decline, which eventually results in neuronal death (Hampel et al., 2020).

In addition, the impairment of mitochondrial energy metabolism, abnormal mitochondrial morphology, decreased mitochondrial membrane potential ($\Delta\psi m$) and reduced levels of ATP are strongly linked to AD (Calkins et al., 2011). In fact, enzymatic processes associated with AD pathogenesis are affected by the mitochondrial Electron transport chain (ETC). In the transgenic mouse model of AD, a reduction in complex I function is reported (Derungs et al., 2017). It has been shown that Aβ42 decreases complex III activity in SY5Y cells without affecting complex I and II activities (Kwon et al., 2015). A decrease in plaque-associated complex IV staining has recently been observed in a mouse model of AD (Xie et al., 2013). In line with this finding, brain mitochondria isolated from Thy-1 AβPPSL mice display decreased complex levels of IV, possibly $\Delta\psi m$, and ATP along with increased intracellular Aβ accumulation (Pohland et al., 2018). Furthermore, reactive oxygen species (ROS) are examples of senescent or weakened mitochondria.

Accumulation of Aβ and hyperphosphorylated tau induces oxidative stress, although ROS has often been proven to promote tau hyperphosphorylation (Maryam, Naini, and Soussi-yanicostas, 2015). Oxidative stress caused by free radicals leads to lipid peroxidation resulted in the production of major end products HNE, malondialdehyde, and acrolein trigger neurotoxicity (Pamplona, 2008). HNE interacts through proteins that form sustainable covalent adducts to residues of lysine, histidine, and cysteine, thus generating carbonyl action on proteins, resulting in oxidative damage, namely protein oxidation. All these protein carbonyls are most common in the frontal, occipital, hippocampus, temporal, and lower parietal lobes (Gonos et al., 2018). RNS-like peroxynitrite makes protein tyrosine (3-nitrotyrosine and di tyrosine) nitrate. Extended measurements of such proteins may be observed in the hippocampal and cortical regions. Higher protein amounts of 3-nitrotyrosine and protein carbonyl change, antioxidant enzymes, such as glutathione peroxidase, glutathione reductase, and catalase (Peroxidation and Involving, 2002). ROS overproduction damages proteins, lipids, and nucleic acids, contributing to the development of progressive AD-related neurodegeneration.

Excitatory action of glutamate is primarily found in prefrontal and hippocampal division implicated in

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neuronal functions such as memory and learning, and also has lower micromolar amounts under ideal circumstances, yet its concentration raises from μM to mM during synaptic transmission due to its ability to have synaptic plasticity, i.e. LTP (Danysz and Parsons, 2012). Glutamate receptors are metabotropic and ionotropic types structurally and functionally. The ionotropic receptors further classified into NMDA, AMPA, and kainite. NMDA receptors i.e. NMDARs, are essentially necessary for activation of LTP. The synthesis of glutamate is severely impaired by ROS-caused pathological modifications and

the lipid peroxidation end product HNE in the amino acid transporter 2 (EAAT2), that is localized in the cell membrane of perisynaptic astrocytes and plays a crucial role in removing unnecessary glutamate from the extracellular fluid, thus reducing activation of NMDAR. LTP inhibition induces a fast and sustained glutamate release in the synaptic cleft, and this excess glutamate can allow the NMDARs to overactive (Zhou and Sheng, 2013). In AD, NMDARs are overactivated which then results in more influxes of Ca2+ ions, and there has been an overloading of Ca2+, which eventually triggers excitotoxicity.

Neuroinflammation is a specific or unspecific immunological reaction induced by microglial activation. Therefore, adequate modulation of the activated microglial cells is essential for neuroinflammation inhibition. Microglial cells are the CNS endogenous macrophages and are thus responsible to track and respond to damage and attack well into the developing brain, serving as the natural defense system of the brain (Dani et al., 2018). Activated microglia expresses various kinds of cell surface proteins, comprising scavenger receptors, Fc receptors, chemokine and cytokine receptors, and MHC molecules, and has a broad range of TLR group, pattern recognition receptors that recognize microbial intruders (Doens and Fernández, 2014). Upon activation, TLRs triggers a signal sequence including the primary myeloid differentiation reaction 88 and also the induction of transcription factors such as NF-ϰB and the protein Activator-1. Microglia can induce a pro-inflammatory cascade after activation, which results in the production of molecules like cytokines, which are complementary considerations (Nardo, 2015). Microglia expresses cytokines [tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-1, IL-6, IL-10, IL-12, IL-16, IL-23]; chemokines [CC(CCL2/MCP-1, CCL3/MIP-1β, CL4/MIP-1, CCL5/RANTES]; CXC (CXCL8/IL8, CXCL9/MIG, CXCL10/IP-10, CXCL12/SDF-1α); CX3C (CX3CL1/fractalkine)]; metalloproteinase matrix (MMP-2, MMP-3, MMP-9); and eicosanoid (leukotriene C4, prostaglandin D2, complement factors C1, C3, and C4 and cathepsins B and L) that also cause astrocyte chemotaxis across NFT. Astrocytes allow IFN-γ activation, which stimulates the release of class I or II MHC molecules; microglia express antigens in CD8+ cells, whereas astrocytes reveal them in CD4+ cells. Microglia has a greater performance as APCs when triggered with IFN-γ previously. Astrocytes are however known as pseudo-professional APCs (Cabezas, Batista, and Rol, 2014).

Insulin is known to play several roles at the molecular levels within CNS, including controlling neuronal viability and cognition (Tumminia et al., 2018). Changes in levels of peripheral insulin may cause changes in insulin signaling for CNS and may correspond to cognitive dysfunction and pathogenesis. CNS insulin regulation deficiency is due to decreased neural levels of insulin, e.g. reduced peripheral development or impaired insulin ability to penetrate the BBB, or decreased CNS IR reaction (e.g. IR desensitization caused by enhanced insulin levels). IRs are distributed differently in different regions of the brain, such as the hippocampus, amygdala, and cerebral cortex (Griffith et al., 2018). Under physiologic circumstances whenever insulin adheres to the IR, a cascade governs key downstream serine/threonine kinases including AKT/PKB, mTOR, and ERK which gradually phosphorylate serine/threonine residues of IRS then inhibit insulin signals in a negative feedback mechanism. Declining insulin gene expression and protein levels, IGF-1 receptors, and several other downstream agents contribute to a decreased synthesis of acetylcholine including cognitive function in LOAD brains (Folch et al., 2018). IR stimulation results in the amplification of signaling pathways by phosphorylated IRS proteins including PI3K and ERK (Saltiel, 2001). PI3K -Akt cascade activation enhances neural development and viability (Rodgers and Theibert, 2002), and Akt inactivates GSK-3β, which in turn prevents phosphorylation of tau (Zhao et al., 2004). Various studies indicate insulin-regulated tau phosphorylation and a higher rate of development of NFTs (Schubert et al., 2003). Insulin and IGF-1 control tau phosphorylation by inhibiting GSK-3β via the signaling channel of PI3K-protein kinase B (PI3K-PKB) (Ma et al., 2009). In the hippocampus, insulin resistance can induce a neuroplasticity defect

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which includes spatial learning and memory deficits. When discussed, various pathways are implicated in AD's pathophysiology, from which the pathway that is our main concern is NF-ϰB as its upregulation is highly responsible for AD's trigger. (Figure 2)

NΦ-ϰB Pathway

NFB is a transcription factor which was identified in 1986 as a nuclear factor that binds the enhancer part the kappa immunoglobulin light-chain of activated B cells (Flood et al., 2011; Wuertz et al., 2012). NF-ϰB is not a single gene, but a family of closely related transcription factors in eukaryotes that includes five genes which are NF-ϰB 1, NF-ϰB 2, Rel A, C-Rel & Rel B. NF-ϰB proteins are further divided into two types; out of which one contains Rel A, C-Rel, Rel B which are synthesized in their mature form and contain a transactivation domain which interacts with the transcriptional apparatus and the other type contains NF-ϰB 1- p105/p50 and NF-ϰB 2- p100/p52 and these are synthesized in a precursor form (Dolcet et al., 2005). Each gene provides a sequence of ankyrin copies that sequester NF-ϰB throughout the cytosol via concealing its NLS or even by obscuring its DNA-binding domain (R. H. Shih, Wang, and Yang, 2015). Furthermore, seven proteins are raised by these five genes that share an RHD in their sequence. The RHD mediates their dimerization, interaction with their specific inhibitors, and DNA binding (Karin and Ben-neriah, 2000). NF-ϰB was postulated as a crucial transcription factor for the development of B cells and some other cells for their functioning and development which includes T-cells thymocytes, macrophages dendritic cells, and fibroblasts. NF-ϰB is related to increased transcription of almost 500 different genes, including all those codings for adhesion molecules, chemokines (IL-8), and cytokines (IL-1, IL-2, TNF-a, and IL-12). These would be the key components of the innate immune response to penetrating microorganisms and are also essential to transfer inflammatory and phagocytic cells to tissues (Tripathi and Aggarwal, 2006). NF-ϰB is regulated via commuting into the nucleus from the cytoplasm in response to cell stimulation (Birbach et al., 2002). Usually, the activation of NF-ϰB occurs in the spinal cord and dorsal root ganglion (DRG) and they both are entangled in the processing and transmission of nociceptive information (Lee et al., 2004).

Furthermore, the activation of NF-ϰB may result from different signaling pathways that are triggered by a variety of cytokines, tyrosine kinase, growth factors, etc such as Ras/MAPK and PI3K/AKT pathway (Manea et al., 2007). NF-ϰB regulates many processes such as cellular processes and immunological response (Ahmed et al., 2016), proliferation, migration & apoptosis. Depending upon the level of Rel A & C-Rel, NF-ϰB may exert a binary function, either as an inhibitor or an activator of apoptotic cell death (Chen et al., 2003). It also stimulates the expression of enzymes including the inducible form of cyclo-oxygenase (COX-2) that generates prostanoid and the inducible nitric oxide synthase (iNOS) that produces nitrous oxide (NO) (Yamamoto and Gaynor, 2005). NF-ϰB pathway is found to be activated in response to a number of stimuli which includes UV light, H2O2, cigarette smoke, viral and bacterial products, free radicals, carcinogens, neurotrophin, depolarization, developmental changes, cytokines (IL-1, TNF), ceramide, glutamate, neurotoxic peptide, oxidative stress, phorbol ester, intracellular stresses such as endoplasmic reticulum protein overload (Bowie and O'Neill, 2000) , environmental pollutants, etc (Sethi and Tergaonkar, 2009) and the activation of NF-ϰB pathway by various means is responsible for various diseases and disorders such as diabetic neuropathy and renal dysfunction, gastric cancer, intervertebral disc disease (Wuertz et al., 2012), hepatocellular carcinoma, ulcerative colitis and crohn's disease (Sun and Zhang, 2007), lung injury (You et al., 2012), rheumatoid arthritis, osteosarcoma, multiple myeloma, ovarian cancer, leukemia and lymphoma, myocardial injury, asthma, irritable bowel disease, atherosclerosis (Serasanambati and Chilakapati, 2016), memory impairment along with neuroinflammation and neurodegeneration (Ali et al., 2015), incontinentia pigmenti (Yamamoto and Gaynor, 2005), etc. Efforts to promote NF-ϰB modulators have resulted in several candidates, some of which are presently in clinical trials and several drugs are currently being approved owing to their ability to influence the NF-ϰB pathway.

Στρυςτυρε οφ ΝΦ-ϰΒ ανδ ΙϰΒ

The butterfly-like crystal structure of various forms of NF-ϰB attached to DNA has identified the molecular bases of the transcription factors sequence and dimerization specificities (Chen, 1998). The RHR comprises two Ig-like folds linked using a flexible linker region. These folds interact with the DNA; loops are mainly

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responsible for sequence-specific recognition throughout the N terminal fold, although the dimer interface is contained in the C-terminal fold (Yong-Qing Chen, 1998). Dimerization is driven by intense hydrophobic interactions across the substrate surface, generated by three-stranded β-sheet trapping in the opposing molecule against a similar sheet. Two separate structure determinations for NF-κB have recently been reported: IκB ternary complexes comprising of the p65 RHR, the p50 C-terminal Ig-like fold [including the NLS], and IκBa ankyrin repeats (Huxford, Huang and Malek, 1998). IκBα's ankyrin repeats form a flattened a-helical stack, which discontinuously connects the RHRs' folds to the C terminal Ig-like folds. The NES on IκBα is revealed in both systems and disruption of NF-κB DNA binding tends to be mainly mediated by residues C-terminal to the IκBα ankyrin repeats (Jacobs and Harrison, 1998). Although these mechanisms give new insight into IκBs control of NF-κB, sadly the details do not unambiguously answer the way IκBα covers the NF-κB's NLS. This is partially due to variations amongst two p65 NLS structures and the paucity of adequate ordered structure in the p50 NLS. Therefore, both systems lack the essential IκBα regulatory N-terminal domain (Karin and Ben-neriah, 2000). Though, one possible conclusion is that IκBa's N-terminal ankyrin repeats sterically obstruct karyopherin binding to NF-κB's NLS. (Figure 3)

Μυλτιπατηολογιςαλ ασπεςτς οφ ΝΦ-κΒ ιν Αλζηειμερ Δισεασε

Role of NF-κB and oxidative stress in AD

Oxidative stress is described as a physiological state where the ROS generated inundated the antioxidant metabolites which are further responsible for high levels of free radicals (Forcados et al., 2017) that may be due to amplified ROS generation, vitiate antioxidant system, alone or amalgamation of both (H. Chen et al., 2011). ROS and other free radicals play significant roles in cell signaling pathways and are components of normal cellular metabolism (Alpay et al., 2015). The foremost etymology of ROS comprehends the mitochondrial electron transport system and various oxidase enzymes including NADPH oxidase, COX, xanthine oxidase, P450 enzymes, LOX, glucose oxidase, and uncoupled NO synthases among others (Kim et al., 2015). Most of the reactive species are emanated in the mitochondria, predominantly the electrons react with O2 during the generation of ATP, eliciting the development of the O2· which further reacts with the other molecules like Fe2+, proceeding the formation of other reactive species like OH·, H2O2, and organic peroxides (Pisoschi and Pop, 2015). The respiratory chain of mitochondria contain NO, that evoke RNS (Valko et al., 2007) and promote lipid peroxidation by reacting with cellular macromolecules (lipids) produce highly toxic reactive intermediates: 4-hydroxynonenal and malondialdehyde (Liou and Storz, 2010). Literature reports stipulated that ROS can activate the NF-κB transcription factor which has been evidenced by cell lines studies (A. C. H. Chen et al., 2011). ROS and RNS are known to upsurged in response to various factors (T-cell receptors, co-receptor CD28 etc) that also trigger NF-κB in some cell types (Thaker and Rudd, 2015). Schreck et al. revealed that overexploitation of the O2- consuming SOD enzyme potentiated NF-κB activation regulated by TNF in MCF-7 cells (Schreck et al., 1992). On NF-κB activation, the effects of ROS is additionally supported by the experiments which demonstrated that the antioxidants can impede the initiation of NF-κB, like L-cysteine, N-acetylcysteine, thiols, polyphenols, green tea, and vitamin E, etc (Forcados et al., 2017). In response to agents that activate NF-κB, H2O2 has also been shown to be generated. This eventually led to the manifesto of H2O2 as the key second messenger to NF-κB activation (Byun et al., 2018). Interestingly, there is a conditional function of oxidative stress on NF-κB in a way that NF-κB which is activated by the oxidative stress itself also increases the level of inflammatory cytokines and enzymes intracellularly such as TNF α, IL-1β, IL-6, iNOS, COX-2 (Chen, Zhang and Wu, 2017) which is further responsible for the neuroinflammation, neuronal death and other neurodegenerative diseases (Sivandzade et al., 2019).

Role of NF-κB besides Neuroinflammation and Neurodegeneration in AD

Neuroinflammation, the inflammation of neurons is a condemnatory feature in the pathophysiology of neurodegenerative disorders such as AD, PD, ALS, MS, and frontotemporal dementia, etc (Muhammad et al., 2019). Various studies suggested that in case of trauma the external stress is responsible for neurons to generate inflammatory mediators (Fischer and Maier, 2015). Furthermore, activated microglia and astrocytes are the main initiators of inflammatory mediators that can provoke secondary neurotoxicity, which eventually

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leads to neuroinflammation-mediated neurodegeneration (Liu et al., 2019). Regulation of inflammation is done by numerous molecules and factors which involves adhesion molecules [VCAM-1, ICAM-1, ELAM-1], cytokines (IL-1, IL-2, IL- 6, IL-12, TNF-α, TNF-β), chemokines (such as monocyte chemoattractant protein 1, IL-8), proinflammatory enzymes [MMPs, COX-2, 5-LOX, 12-LOX, C-reactive protein, PSA], VEGF, STAT-3, and proinflammatory transcription factors NF-ϰB (R. Shih, Wang and Yang, 2015). Among these mediators, NF-ϰB is recommended to be the most extensively studied target for its critical role in neuroinflammation which is further also responsible for neurodegeneration (Nafees et al., 2015). Ample evidence indicates that in CNS, the stimulation of NF-ϰB triggers various multicellular responses genes transactivation which is involved in the commencement and propagation of neurodegenerative diseases. NF-ϰB regulates more than 500 genes, which are implicated in inflammation-related responses by which it plays an important role in various diseases (Gupta, Kim, and Prasad, 2010).

In inactive cells, NF-ϰB dimers interact with IϰBα to give inactive complexes that are localized to the cytoplasm. When the cells are exposed to anoxia or any other extracellular inflammatory stimuli like acute alcohol exposure or any chemical stress, NF-ϰB is transiently activated via rapid phosphorylation, ubiquitinylation, and eventually proteolytic degradation of IϰBα, by which the translocation of NF-ϰB from the cytoplasm to the nucleus takes place where inflammatory cytokine gene transcription and the expression of proinflammatory cytokines are regulated which further instigates neuroinflammatory responses (Li et al., 2019). These functional deflections are depending upon the involvement of specific components of the NF-ϰB dimer formation. Especially, c-Rel containing NF-ϰB dimers can instigate the MnSOD and Bcl-xL expression and employ as anti-apoptotic effects (Pizzi et al., 2009) while the pro-apoptotic effect induced by NF-ϰB p50/RelA dimer. The misproportion of NF-ϰB dimer formation between c-Rel and RelA might result in the pathological process in certain neurons. Notably, RelA is illustrated as a most imparting subunit in neurodegenerative changes (Tilstra et al., 2012).

Various endogenous and exogenous stimuli are accountable for the upregulation of NF-ϰB, with which expression of a large number of proinflammatory cytokines and enzymes, including TNF-α, iNOS, IL-1β, and COX-2 can be regulated positively which is further responsible for neuroinflammation and this inflammation of neurons in excess further leads to neurodegeneration (Umesalma and Sudhandiran, 2010). Endotoxins like lipopolysaccharides (LPS) are also responsible for activating NF-ϰB signaling which have been shown to actuate inflammatory target protein COX-2 and PGE2 development likely to lead cerebral vascular inflammation (Muhammad et al., 2019). Studies suggest that NF-ϰB is activated after cerebral ischemia in cerebral vascular endothelial cells, glial cells and neurons, which triggers a phenomenal increase in the expression of inflammatory cytokines that lead to an inflammatory cascade reaction and exasperating brain damage (Yang and Chen, 2014). Several in vivo and in vitro studies manifested that PPARγ decreases proinflammatory cytokines release by suppressing the nuclear transcription factor NF-ϰB (Sauer, 2015). Therefore, the critical linkage of the activation of NF-ϰB with the regulation of neuroinflammation-associated pathogenesis of disease has been found which includes AD, PD, ALS, MS, etc. (Figure 4)

Role of NF-ϰB and Neurotransmitter abnormalities in AD

Neurotransmitters (NTs) are widely acknowledged for making contact with CNS diseases as close as possible. Eccentric neurotransmitter changes have been shown to be almost amalgamated with several neurological diseases including AD (Reddy, 2017), HD (Huntington and States, 2018), PD (Moghaddam et al., 2017), ALS (Volonté et al., 2019), MS (Micu et al., 2017), etc. Neurotransmitters and their metabolites are enormously present in mammalian CNS and peripheral biofluids, including amino acid neurotransmitters such as Tyrosine, Acetylcholine (Ach), Glutamate and γ-aminobutyric acid (GABA), and monoamine neurotransmitters such as Dopamine (DA), and Norepinephrine (NE), serotonin (5-HT), and also their acidic 5-hydroxy indole acetic acid (5-HIAA) metabolite (Xu et al., 2018). In this, we predominantly focus on the changes on neurotransmitters indicatively in AD and neurotransmitters that we discuss here include Serotonin, Dopamine, Norepinephrine, Acetylcholine, GABA, Glutamate, etc. In addition, the NF-ϰB pathway plays a vital role in the above-mentioned changes in neurotransmitters that are considered to be an important marker for the detection of Alzheimer's disease.

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AD's major hallmark is cholinergic hypofunction or decline in acetylcholine level. By stimulating either ionotropic nicotinic acetylcholine receptors (nAchRs) or metabotropic muscarinic acetylcholine receptors (mAchRs), the neurotransmitter acetylcholine strives its physiological functions. It has been declared that in AD brains there are (1) decreased rates of choline acetyltransferase supersede by decreased Ach synthesis; (2) expressive loss of cholinergic neurons; (3) decreased neuronal and axonal cholinergic abnormalities; (Geula et al., 2008) (4) decreased numbers of postsynaptic neurons susceptible to acetylcholine; and (5) decreased levels of nAchRs (Chen, Xiong and Yan, 2013). Recent study has suggested that cholinergic hypofunction is closely associated with Aβ and tau pathology and that mAchRs has also been involved in AD pathophysiology (Jiang et al., 2014). There is a dispute that whether the lack of cholinergic feedback is responsible for NF-ϰB activation or NF-ϰB upregulation is responsible for acetylcholine failure in the brain, especially in the hippocampus. Notably, in both scenarios when NF-ϰB is hyperactivated, there is a loss of cholinergic input as these are interrelated, taking into account NF-ϰB's function in AD (Lim et al., 2011).

In CNS, GABA and glutamic acid (Glu) are identified as major inhibitory and excitatory neurotransmitters respectively and is uniformly distributed in large amounts in the CNS. One of the causes of some neurological diseases such as AD is the paucity of transition from Glutamate to GABA leading to high excitation and poor inhibition (Lanctôt et al., 2004). GABA interneurons play a crucial role in controlling hippocampal activation rates via inhibition, and furthermore, the learning and memory forming processes include consolidation of stimulating and inhibitory neuronal network activity (Shetty and Bates, 2015). Consequently, loss or impaired activity of GABA-ergic interneurons may lead to impairment in learning and memory (Limon, Reyes-ruiz, and Miledi, 2012). Changes in the role of GABA-ergic interneurons results in increased neural activity in the aged hippocampus CA3 region which leads to memory loss, as the hyperactive pyramidal neurons of CA3 are ineffectual to encode new information in a manner typically done in the young hippocampus (Shetty and Bates, 2015).

Additionally, glutamic acid or glutamate has been documented to increase in various neurological diseases, peculiarly in the case of AD as it is unable to transit into GABA. Therefore, an exciting-inhibitory imbalance in the hippocampus likely contributes to both aging and AD memory loss. Due to the hyperactivation of NF-ϰB, there is a dysregulation of GABAergic and glutamatergic neurons which can be easily seen in the case of AD (Xu and Li, 2015). Recent studies in transgenic mice have observed a critical function of NF-ϰB in inhibitory GABAergic interneurons where the expression of glutamate decarboxylase, a rate-limiting enzyme necessary for the synthesis of the inhibitory neurotransmitter, GABA, has been down-regulated in these mice due to which level of GABA is decreased and it is also observed that glutamate levels are increased with the NF-ϰB upregulation as glutamate is unable to transit into GABA and remain as such (Mahony et al., 2006). A model in which the learning motor is the exciting neurons, and the brake is given by GABAergic neurons may also clear these conclusions. Blocking the brake will result in overactivation of the motor (excitatory neurons); leading to the assumption that the upregulation of the NF-ϰB pathway is associated with decreased levels of GABA and increased Glutamate levels.

5-HT, a biogenic amine derived from tryptophan, is widely distributed in the whole brain. Besides the 5-HT transporter, which is commonly spread in the brain and mimics 5-HT innervation, certain specific 5-HT receptors, such as 5-HT1A, 5-HT1B, 5-HT2, and 5-HT4, are potentially implicated in memory processes, based on their anatomical position mainly found in the hippocampus, the raphe nucleus, the septum, substantia niagra, the dorsal subiculum, along with cortical regions (Buhot et al., 2000). 5-HT eventually endures oxidative deamination to form 5-HIAA, was found to decrease significantly in AD brains (Yun et al., 2015). It is reported that the serotonin agonist is responsible for the inhibition of the NF-ϰB pathway which proposed that the high serotonin level is responsible for the downregulation of the NF-ϰB pathway, and likewise conversely (Herr, Bode, and Duerschmied, 2017), it has been said that there should be a decreased serotonin level in the hyperactivation state of the NF-ϰB pathway as in AD.

DA, a catecholamine, the metabolites of tyrosine (Tyr), is one of the main neurotransmitters involved in dementia, necessitate in sleep-wake cycles, learning, memory, and emotion. (i) Aβ plaque-induced dopaminergic dysfunction has been identified in the AD affected brain (Martorana and Koch, 2014) (ii) Specific deteriora-

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tion of dopaminergic neurons in the ventral tegmental area (VTA) culpable for the release of dopamine to the hippocampus has been reported; (Nobili et al., 2017) and (iii) Restoration of synaptic plasticity and memory has been observed after treatment with DA. In conjunction with these findings, a variety of dopaminergic (DAergic) system alterations has already been identified in patients of AD including decreased DA levels and their receptors. A study showed a remarkable depletion of THp dopaminergic neurons in Tg2576 mice VTA, along with a reduction in hippocampus basal outflow of DA, presumably leading to deficiencies in cognitive and non-cognitive mesolimbic symptoms (Nobili et al., 2017). Dopaminergic neurons exhibit intermediate features, having an ambiguous relationship to Aβ pathology anyway. In the case of dopamine, after treatment with MPTP in a study, a noteworthy increase in NF-ϰB p65 immunoreactivity was observed predominantly in substantia nigra glial cells. Following MPTP therapy, a significant increase in immunopositive apoptotic neurons with ssDNA was also observed in the substantia nigra (Aoki et al., 2009). These results show that dopaminergic neuronal failure may be induced by apoptosis due to upsurged cytokines and apoptosis-related proteins via the upregulation of NF-ϰB in substantia nigra's reactive astrocytes after treatment with MPTP in mice. This study ultimately leads to the outcome that the level of dopamine is decreased in the case of AD specifically due to hyperactivation of NF-ϰB. In case of dopamine, it is stated that the dopamine agonist is liable for inhibiting NF-ϰB pathway which indicates that, elevated dopamine level is accountable for the downregulation of NF-ϰB pathway (Sun et al., 2015).

The strong correlation between Norepinephrine depletion and AD severity in patients has prompted multiple studies of LC dysfunction's contribution to AD development by using animal models (Chalermpalanupap et al., 2013). Norepinephrine has several strong influences on microglial activity, and typically suppresses pro-inflammatory cytokines development and encourages the production of anti-inflammatory molecules (Mei et al., 2015a). Such results suggest that the loss of NE itself impairs synaptic plasticity and cognitive performance and exacerbates neuropathology similar to AD. It is also found that the increase in Norepinephrine transporter (NET) level, which is further correlated with the increased NE level is responsible for the down-regulation of the NF-ϰB pathway (Chavan, Pavlov and Tracey, 2017) and also the other way round it can be stated that there should be a low NE level in the upregulation state of the NF-ϰB pathway as seen in AD (Mei et al., 2015b).

It was found that most of the researches had only inspected that the neurotransmitters are either increasing or decreasing in AD respectively, rather than disclosing neurotransmitter differences and similarities from a global perspective. The assessment of neurotransmitters and their metabolite levels in animal brain tissues is therefore a prerequisite tool for investigating the similarities and differences in the pathophysiology of this disease and also a good approach for researching the differences in the essence of these interrelated neuropsychiatric disorders.

Role of NF-ϰB and Aβ accumulation in AD

AD-affected brains have extracellular deposits; senile plaques consisting primarily of a group of hydrophobic peptides, known as amyloid β-peptides (Aβ). Such peptides are at the heart of the theory of the amyloid cascade which suggests Aβ, a primary etiological cause of neurodegeneration arising at the late stages of pathology (Arber et al., 2019). Therefore, one of the major therapeutic tracks appears as a strategy aimed at circumcising Aβ overload. Aβ is a premium product of the synthesis of APP arising from the concurrent cleavage of APP by two distinguishable enzyme activities: γ-secretase and β-secretase 1 or β-site APP-cleaving enzyme 1 (BACE1), consisting mainly of a complex of high molecular weight protein comprising anterior pharynx defective-1 (Aph1), presenilin enhancer-2 (Pen2), presenilin 1 or 2 (PS1, PS2), and nicastrin (NCT) (Wolfe, 2018). Aβ clearance pathways involve ubiquitin-proteasome process, proteases, autophagy-lysosome, microglial phagocytosis, and transportation from the brain to the blood through the blood-brain barrier (BBB), arachnoid villi, and blood-CSF barrier, that can be called blood circulatory clearance. Lymphatic clearance has recently been shown to play a crucial function in the movement of Aβ through the cervical lymph nodes. Another strong reason for lymphatic clearance within the brain is the identification of meningeal lymphatic channels. In fact, peripheral clearance also leads to clearance of Aβ (Xin et al., 2018). Many sources of evidence indicate inflammation and oxidative stress may lead to the

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pathology of AD. To some degree, this can affect Aβ development, since the expression of BACE1 tends to be modulated by stress (Cervellati et al., 2019). Oxidative stress and inflammation are distinguished by cytokines and ROS releases, which are believed to activate the NF-ϰB (Morgan and Liu, 2011).

Numerous in vitro experiments have shown that Aβ peptides in primary cultured neurons that may induce NF-ϰB. This finding is partially indicative of the fact that NF-ϰB was found in adjacent cells or in plaques of amyloids (Chen et al., 2012). Such studies report stimulation of the canonical pathway in a feedback regulation through which Aβ activates NF-ϰB, which then manages the development of Aβ peptides (Chen et al., 2012). Ironically, inhibition of NF-ϰB activation decreases Aβ secretion in vitro, and it was proposed that this can happen by interacting with APP production (Paris et al., 2011). Several earlier studies demonstrate a concentration-dependent Aβ regulation of APP as well as the components of the γ-secretase complex by NF-ϰB. This study shows that, under physiological circumstances, by suppressing the protein APP level and transcriptional activities of β-and γ-secretase, NF-ϰB reduces Aβ production. In comparison, supraphysiological Aβ concentrations directed at imitating the pathological condition, NF-ϰB stimulates Aβ development by increasing the activity of APP and processing enzymes. A data set from this analysis reflects a differential regulation of APP, β-and γ-secretases by NF-ϰB which relies on the physiological or supraphysiological situations of development of Aβ (Chami et al., 2012).

Available findings suggest that NF-ϰB may usually regulate homeostasis of Aβ under physiological constraints or lead to a degenerative process through which Aβ supports its own development in the pathological sense and is also shown in several invivo studies. They also demonstrated that an increase in BACE1 transactivation mediated by Aβ42 was dependent on NF-ϰB. NF-ϰB increases APP levels in transgenic mice; BACE1 promotes activity, expression, and enzymatic activity (Paris et al., 2010), the activity of γ-secretase; and production of Aβ. In fact, NF-ϰB inhibition decreased plaque burden in mice. NF-ϰB has been shown to suppress BACE1 promoter in neuronal and resting glial cells while activating BACE1 promoter in neuronal and activated glial cells that are exposed to Aβ (Bourne et al., 2007). This can also be elucidated by the existence of the NF-ϰB dimers implicated as p52/c-Rel exists in resting environments, although p50/p65, p52/p65, and p52/c-Rel are accountable for NF-ϰB-mediated BACE1 transactivation in triggered neurons and glia (Bourne et al., 2007). It is notable in this sense that Valerio et al. showed that Aβ40 can trigger NF-ϰB by supporting the nuclear translocation of subunits p50 and p65 (Valerio et al., 2006). Ironically, it has been shown that hiring components of NF-ϰB and building up the separate heterodimeric network may be linked to Aβ levels. Therefore, Arevalo et al. found that a low concentration of Aβ40 activates an NGF -like phenotype while a 40-fold higher concentration hampers NGF-induced NF-ϰB activation (Maria-Angeles Arevalo, Pedro M. Roldan, 2009). Accordingly, it has been stated that mostly low concentrations of Aβ could activate a protective phenotype that is dependent on NF-ϰB. This set of results supports our statement that physiological and supraphysiological concentrations of Aβ could contribute separately to their own production by modulating their precursor chemicals and secretases through a mechanism dependent on NF-ϰB. In addition to conventional approaches designed at diminishing production of Aβ by precisely harmonizing either β- or γ-secretases from pharmacological samples or even by the counterbalance of Aβ-associated results through a vaccinal strategy (Strooper, Vassar and Golde, 2010), alternative therapeutic routes aimed at NF-ϰB could also be potentially envisaged.

Signaling Cascades

Extracellular mediators control NF-ϰB by triggering numerous signaling cascades within cells contributing to survival or death of neurons and ultimate activity of the nervous system, in which MAPK, AGE/RAGE/GSK-3, PI3K/AKT plays a key role in NF-ϰB activation and serve as potential targets (Shi et al., 2016).

PI3K/AKT

AKT serves as a key PI3K signal mediator that plays a major role in cell proliferation, development, metabolism, and longevity. Sustained expression of NF-ϰB in neuronal cells has been shown to cause neuroprotection by modulation of the PI3-kinase-PKB/AKT pathway (Granic et al., 2009). AKT stimulation

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enhances the transactivating process and induces increased nuclear concentrations of p65-NF-κB that is essential for neuroprotection. Attachment of p65 to the putative NF-κB regulatory sequence adapts cells to persist in the existence of oxidative stress, because PC12 pheochromocytoma cells possessing active AKT have lower concentrations of ROS in reaction to H2O2 (Rojo et al., 2004) The PI3K inhibitors (Buparlisib, XL147, GDC-0032) effectively blocks the translocation of the NF-κB p65/p52 complex by the GDNF and the blockade of AKT prevents the binding action of NF-κB (Dhandapani et al., 2005). PI3K/AKT signaling activation implies the function of neuroprotection through the in vitro analysis by modifying the binding process and the nuclear translocation of NF-κB.

MAPK

The family MAPK contains three subtypes: p38, JNK, and ERK. Reports suggested inappropriate activation of the MAPK signaling pathways in AD. Studies have also shown that the ERK pathway can activate NF-κB (Reber et al., 2009). The pharmacological repression of ERK and p38 MAPK and the dominant-negative modification of both enzymes prevented Aβ-induced NF-κB transactivation and therefore neurotoxicity by Aβ (Jang and T, 2005). P38 inhibitor therapy, SB239063, inhibits downstream phosphorylation of IκBα and p65 translocation into the ventral midbrain nucleus. In comparison, treatment with SP600125, a JNK inhibitor, improves nucleus-dependent p38 MAPK phosphorylation of the p65 NF-κB subunit (Wagley et al., 2013). In comparison to JNK, ERK and p38 MAPK will play the opposite function of NF-κB. Neuroprotection may be offered by clinical approaches that reduce mitochondrial activation of proapoptotic MAPK modules.

AGE/RAGE/GSK3

Aβ and tau may be exposed to non-enzymatic glycation and form AGE. Such AGEs bind with the so-called RAGE, a multi-ligand receptor belonging to the superfamily of the immunoglobulin, act as a cell surface acceptor for Aβ that transmits the signal. AGEs cause tau hyperphosphorylation, memory loss, synaptic protein degradation, and long-term cognitive disability in rats (Granic et al., 2009). In an Alzheimer-type pathology model, evidence showed that RAGE is a cofactor for neuronal perturbation triggered by Aβ (Arancio et al., 2004). Two AGEs, like those of pentosidine and GLAP, both reported to rise in AD brains, were known to upregulate BACE1 by interacting with RAGE and thereby activating NF-κB, establishing a pathological link among diabetes and AD (Guglielmotto et al., 2012). It was observed that RAGE expression increased significantly in the cerebral cortex of APP/PS1 mice, there was also a massive increase in the phosphorylation of IκBα and the nuclear translocation of NF-κB/p65 in the same model. The process involves modifications in behavior of inflammation, glucose and ROS, as ligands such as AGEs, Aβ, S100b, and amphoterin engaged with RAGE i.e. HMGB 1, activate the multiple signaling pathways. Then the activation of RAGE can trigger MAPK signaling cascades that converge to phosphorylate IκB in IκB kinase complex, thus freeing and stimulating NF-κB, thus initiating the transcription of the dependent gene, namely IL-1β and TNF-α, that in effect causes the translocation of NF-κB to the nucleus (Ma et al., 2015). GSK-3 is a proline-directed serine/threonine-protein kinase typically suspected for having a significant role in glycogen metabolism, comprising two GSK-3 isoforms GSK-3α protein and GSK-3β protein, with that of the β isoform found at higher concentrations in neuronal tissues. Arousal of GSK-3β and not GSK-3α facilitated the expression of the BACE1 gene and BACE1-mediated APP production in vitro by controlling the function of the BACE1 gene promoter, which was based on the NF-κB p65-binding components in the BACE1 promoter (Ly et al., 2013). Interruption of expression of NF-κB p65 in RelA-KO cells has excluded the effect of GSK-3β on the human BACE1 gene promoter transcriptional activation. Collaboratively, primary plaque-associated inflammation activators are the major component of plaques and AGEs.

ΝΦ-κΒ ας α τηεραπευτις ταργετ ιν ΑΔ

As already discussed, NF-κB is regulated in neural and glial cells that mediate neuroinflammation and neurodegeneration by Aβ aggregates and other endogenous CNS molecules along with exogenous factors such as oxidative stress, etc that can be due to environmental toxins, physical and chemical stress, etc which is mainly due to the imbalance between the level of Rel A & C-Rel genes. Neurodegeneration reduction and enhancement of neuroprotection after neuroinflammation suppression have been shown in animal models of

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AD (Huang et al., 2011). The following is a review of recent progress in the treatment of AD by means of natural products, their synthetic derivatives, and other disease-modifying agents with an emphasis on NF-κB as a mechanistic target. (Table 1)

Conclusion and Future perspectives

The worldwide strain of treating the condition has identified brain and nervous system diseases as major health threats. Despite significant advancements in elucidating the underlying molecular mechanisms, there are few therapies that can alter or delay the progression of chronic neurological illnesses. The specific inflammatory role in the development of multiple progressive neurodegenerative diseases with varying clinical symptoms is evidenced by considerable evidence. The upregulation of NF-κB, which results in a self-sustaining and self-propagating vicious cycle of uncontrolled, sustained inflammation that drives the neurodegenerative mechanism, is a prevalent outcome of increased inflammatory signaling. So, disrupting this vicious cycle by addressing the NF-κB signaling pathway is an appealing disease-modifying therapeutic approach for neurodegenerative pathologies. Caution should however be practiced in designing and assessing possible NF-κB inhibitors for CNS diseases as constitutively active NF-κB in neurons is essential to neuronal development and survival. In fact, the wide range of inductive NF-κB responses from neuroprotection to neurodegeneration depending on the severity of the initiating event(s) and the form of triggered NF-κB dimers adds to the difficulty of the therapeutic protocol. The positive effects of anti-NF-κB therapeutic approaches are likely to be effective in strongly activated NF-κB pathological disorders that impair homeostatic activity such as intermittent or rapidly advancing AD.

For therapeutic regulation of neuroinflammation and neurodegeneration, a better understanding of the molecular processes that decide the conversion point(s) of NF-κB activities from being defensive to mediating harmful effects is necessary.

Expert opinion

Multiple studies confirm the vital role of chronic inflammation with various clinical characteristics as a unifying theme in Alzheimer's disease. Sustained or unregulated NF-κB activation is crucial to inflammation survival making the NF-κB pathway a significant therapeutic aim. Even as part of their therapeutic effects, some USFDA-approved medicines like dexamethasone and donepezil block NF-κB signaling. Considerable attempts by clinical and scientific drug discovery teams are directed at improving targeted NF-κB inhibitors. It has been shown that approaches that disrupt molecules upstream of the NF-κB pathway or the related signaling interfaces or others who bind IκB inhibitory proteins produce a significant potential for systemic and off-target toxicity. The double and opposite activities of active NF-κB in neuronal survival and apoptosis are an extra level of complexity to remember when addressing NF-κB in the CNS. Recent articulation of NF-κB pathways indicates that, though amplification of C-Rel containing dimers mediates neuroprotective effects through the upregulation of neurotrophic and anti-apoptotic genes, enhanced expression of p65/p50 dimers precipitates primarily neurodegeneration by enhancing the transactivation of pro-apoptotic and neurotoxic mediators in the CNS. Under physiological conditions, there is a homeostatic equilibrium among the dimer-containing proportions of activated C-Rel and RelA/p50 dimers, which sustain neuroprotection while avoiding neurotoxicity. Superimposition of secondary stress factors such as aging, elevated oxidative stress or damage in susceptible populations, enhanced activated RelA/p50 dimers and shifted the focus towards inflammation and neurodegeneration.

Strategies that hit RelA/p50 dimers specifically are likely to get back homeostasis. Specific targeting of this NF-κB subunit can produce therapeutic drugs with an improved safety profile, as augmented p65 is highly expressed only in pathologically active cells. Chemical variants of natural compounds inhibiting NF-κB have been tested in previous years for therapeutic benefits in neurodegenerative diseases. Pharmacologically, the active chemical moiety of several natural compounds, like those of diterpenes, has shown to form adducts with specific residues of p65, undermining their ability to bind DNA and transactivate. The widening arrays of NF-κB interactors have significantly increased the ability to recognize newer targets for precise inhibition. The goal is to reach large interfaces of protein-protein and protein—DNA associations. Moreover, devel-

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opments in high-throughput screening tools, structural biology, computational biology, and rational drug design approaches improve the discovery and production of select therapeutically useful NF-ϰB inhibitors. Characterizing synthetic variants of natural compounds as well as rationally designed products will facilitate the production of RelA's small-molecule inhibitors with greater benefit to the risk ratio for human therapy.

Conflict of Interest

The authors declare that they have no conflict of interests regarding the publication of this article.

Acknowledgement

The authors thank Mr. Parveen Garg, chairman of ISF College of Pharmacy and Dr. Shamsher Singh, HOD of Department of Pharmacology for helping and critically reading the paper.

Bibliography

Ahmed, S. *et al.* (2016) 'Diosmin Modulates the NF-kB Signal Transduction Pathways and Downregulation of Various Oxidative Stress Markers in Alloxan-Induced Diabetic Nephropathy', *Inflammation* . Inflammation. doi: 10.1007/s10753-016-0413-4.

Ali, T. *et al.* (2015) 'Melatonin attenuates D-galactose-induced memory impairment, neuroinflammation and neurodegeneration via RAGE/NF-KB/JNK signaling pathway in aging mouse model', *Journal of Pineal Research* , 58(1), pp. 71–85. doi: 10.1111/jpi.12194.

Alpay, M. *et al.* (2015) 'Oxidative stress shapes breast cancer phenotype through chronic activation of ATM-dependent signaling',*Breast Cancer Research and Treatment* . Springer US, pp. 75–87. doi: 10.1007/s10549-015-3368-5.

Alzheimer's Association (2019) '2014 Alzheimer's disease facts and figures.', *Alzheimer's & dementia : the journal of the Alzheimer's Association* . Elsevier Inc., 10(2), pp. 321–387. doi: 10.1016/j.jalz.2019.01.010.

Amakiri, N. *et al.* (2019) 'Amyloid beta and micrornas in Alzheimer's disease', *Frontiers in Neuroscience* , 13(MAY). doi: 10.3389/fnins.2019.00430.

Aoki, E. *et al.* (2009) 'Role of nuclear transcription factor kappa B (NF-kappaB) for MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine)-induced apoptosis in nigral neurons of mice', *Experimental and Molecular Pathology* . Elsevier Inc., 86(1), pp. 57–64. doi: 10.1016/j.yexmp.2008.10.004.

Arancio, O. *et al.* (2004) 'RAGE potentiates A b -induced perturbation of neuronal function in transgenic mice', 23(20), pp. 4096–4105. doi: 10.1038/sj.emboj.7600415.

Arber, C. *et al.* (2019) 'Familial Alzheimer ' s disease patient-derived neurons reveal distinct mutation-speci fi c effects on amyloid beta', *Molecular Psychiatry* . Springer US. doi: 10.1038/s41380-019-0410-8.

Birbach, A. *et al.* (2002) 'Signaling molecules of the NF-ϰB pathway shuttle constitutively between cytoplasm and nucleus',*Journal of Biological Chemistry* , 277(13), pp. 10842–10851. doi: 10.1074/jbc.M112475200.

Bird, T. D. (2018) 'Alzheimer Disease Overview 1 . Clinical Characteristics of Alzheimer Disease', *Gene Reviews* , pp. 1–12.

Bourne, K. Z. *et al.* (2007) 'Differential Regulation of BACE1 Promoter Activity by Nuclear Factor- j B in Neurons and Glia Upon Exposure to b -Amyloid Peptides', 1204(March), pp. 1194–1204. doi: 10.1002/jnr.

Bowie, A. and O'Neill, L. A. J. (2000) 'Oxidative stress and nuclear factor-ϰB activation: A reassessment of the evidence in the light of recent discoveries', *Biochemical Pharmacology* , 59(1), pp. 13–23. doi: 10.1016/S0006-2952(99)00296-8.

Buhot, M.C., Martin, S. and Segu, L., 2000. Role of serotonin in memory impairment. *Annals of medicine* , *32* (3), pp.210-221.

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Byun, Eui-baek *et al.* (2018) 'Neuroprotective effect of polysaccharide separated from Perilla frutescens Britton var . acuta Kudo against H 2 O 2 -induced oxidative stress in HT22 hippocampus cells', *Bioscience, Biotechnology, and Biochemistry* . Taylor & Francis, 8451, pp. 1–15. doi: 10.1080/09168451.2018.1460572.

Cabezas, I. L., Batista, A. H. and Rol, G. P. (2014) 'The role of glial cells in Alzheimer disease : potential therapeutic', *Neurología (English Edition)* . SEGO, 29(5), pp. 305–309. doi: 10.1016/j.nrleng.2012.10.009.

Calkins, M. J. *et al.* (2011) 'Impaired mitochondrial biogenesis , defective axonal transport of mitochondria , abnormal mitochondrial dynamics and synaptic degeneration in a mouse model of Alzheimer ' s disease', 20(23), pp. 4515–4529. doi: 10.1093/hmg/ddr381.

Cervellati, C. *et al.* (2019) 'Serum beta-secretase 1 (BACE1) activity as candidate biomarker for late-onset Alzheimer ' s disease'. GeroScience, 1.

Chalermpalanupap, T. *et al.* (2013) 'Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease', *Alzheimer's Research and Therapy* , 5(2). doi: 10.1186/alzrt175.

Chami, L. *et al.* (2012) 'Nuclear Factor- B Regulates APP and - and -Secretases Differently at Physiological and Supraphysiological A ', 287(29), pp. 24573–24584. doi: 10.1074/jbc.M111.333054.

Chavan, S. S., Pavlov, V. A. and Tracey, K. J. (2017) 'Mechanisms and Therapeutic Relevance of Neuro-immune Communication', *Immunity* . Elsevier Inc., 46(6), pp. 927–942. doi: 10.1016/j.immuni.2017.06.008.

Chen, A. C. H. *et al.* (2011) 'Low-Level laser therapy activates NF-kB via generation of reactive oxygen species in mouse embryonic fibroblasts', *PLoS ONE* , 6(7), pp. 1–8. doi: 10.1371/journal.pone.0022453.

Chen, C. H. *et al.* (2012) 'Increased NF-ϰB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease', *International Journal of Neuropsychopharmacology* , 15(1), pp. 77–90. doi: 10.1017/S1461145711000149.

Chen, F. *et al.* (2003) 'Phosphorylation of PPAR g via Active ERK1 / 2 Leads to its Physical Association With p65 and Inhibition of NF- kb', 744, pp. 732–744. doi: 10.1002/jcb.10668.

Chen, F. E. (1998) 'Crystal structure of p50/p65 heterodimer of transcription factor NF- B bound to DNA', 391(January), pp. 1996–1999.

Chen, G., Xiong, Z. and Yan, Z. (2013) 'A β impairs nicotinic regulation of inhibitory synaptic transmission and interneuron excitability in prefrontal cortex', pp. 1–12.

Chen, H. *et al.* (2011) 'Oxidative Stress in Ischemic Brain Damage : Mechanisms of Cell Death and Potential Molecular Targets for Neuroprotection', 14(8), pp. 1505–1517. doi: 10.1089=ars.2010.3576.

Chen, X., Zhang, J. and Wu, L. (2017) 'Plumbagin inhibits neuronal apoptosis, intimal hyperplasia and also suppresses TNF-α/NF-κB pathway induced inflammation and matrix metalloproteinase-2/9 expression in rat cerebral ischemia', *Saudi Journal of Biological Sciences* . King Saud University. doi: 10.1016/j.sjbs.2017.03.006.

Dani, M. *et al.* (2018) 'Microglial activation correlates in vivo with both tau and amyloid in Alzheimer ' s disease', (July), pp. 1–15. doi: 10.1093/brain/awy188.

Danysz, W. and Parsons, C. G. (2012) 'Alzheimer ' s disease , b -amyloid , glutamate , NMDA receptors and memantine – searching for the connections'. doi: 10.1111/j.1476-5381.2012.02057.x.

Derungs, R. *et al.* (2017) 'Genetic ablation of the p66 Shc adaptor protein reverses cognitive de fi cits and improves mitochondrial function in an APP transgenic mouse model of Alzheimer ' s disease', (July 2016), pp. 605–614. doi: 10.1038/mp.2016.112.

Dhandapani, K. M. *et al.* (2005) 'Neuroprotection by stem cell factor in rat cortical neurons involves AKT and NF j B', pp. 9–19. doi: 10.1111/j.1471-4159.2005.03319.x.

Posted on Authorea 16 Jul 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.159493419.94920936 — This a preprint and has not been peer reviewed. Data may be preliminary.

Doens, D. and Fernández, P. L. (2014) 'Microglia receptors and their implications in the response to amyloid β for Alzheimer ' s disease pathogenesis', pp. 1–14.

Dolcet, X. *et al.* (2005) 'NF-kB in development and progression of human cancer', *Virchows Archiv* , 446(5), pp. 475–482. doi: 10.1007/s00428-005-1264-9.

Exley, C. (2017) 'Aluminum Should Now Be Considered a Primary Etiological Factor in Alzheimer's Disease', *Journal of Alzheimer's Disease Reports* , 1(1), pp. 23–25. doi: 10.3233/adr-170010.

Fischer, R. and Maier, O. (2015) 'Interrelation of oxidative stress and inflammation in neurodegenerative disease: Role of TNF', *Oxidative Medicine and Cellular Longevity* , 2015. doi: 10.1155/2015/610813.

Flood, P. M. *et al.* (2011) 'Transcriptional Factor NF- ϰ B as a Target for Therapy in Parkinson ' s Disease', 2011, pp. 11–14. doi: 10.4061/2011/216298.

Folch, J. *et al.* (2018) 'The Implication of the Brain Insulin Receptor in Late Onset Alzheimer ' s Disease Dementia', pp. 1–16. doi: 10.3390/ph11010011.

Forcados, G. E. *et al.* (2017) 'Oxidative Stress and Carcinogenesis : Potential of Phytochemicals in Breast Cancer Therapy Oxidative Stress and Carcinogenesis : Potential of Phytochemicals in Breast Cancer', 5581(January). doi: 10.1080/01635581.2017.1267777.

Gaugler, J. *et al.* (2016) '2016 Alzheimer's disease facts and figures', *Alzheimer's and Dementia* . Elsevier Inc., 12(4), pp. 459–509. doi: 10.1016/j.jalz.2016.03.001.

Geula, C. *et al.* (2008) 'Cholinergic Neuronal and Axonal Abnormalities Are Present Early in Aging and in Alzheimer Disease', 67(4), pp. 309–318.

Gonos, E. S. *et al.* (2018) 'Origin and pathophysiology of protein carbonylation , nitration and chlorination in age - related brain diseases and aging', 10(5), pp. 868–901.

Granic, I. *et al.* (2009) 'Inflammation and NF- ϰ B in Alzheimer ' s Disease and Diabetes', 16, pp. 809–821. doi: 10.3233/JAD-2009-0976.

Griffith, C. M. *et al.* (2018) 'Evidence for altered insulin receptor signaling in Alzheimer's disease', *Neuropharmacology* . Elsevier Ltd. doi: 10.1016/j.neuropharm.2018.01.008.

Guglielmotto, M. *et al.* (2012) 'AGEs / RAGE complex upregulates BACE1 via NF- B pathway activation', *NBA* . Elsevier Inc., 33(1), pp. 196.e13-196.e27. doi: 10.1016/j.neurobiolaging.2010.05.026.

Gupta, S. C., Kim, J. H. and Prasad, S. (2010) 'Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals', pp. 405–434. doi: 10.1007/s10555-010-9235-2.

Hampel, H. *et al.* (2020) 'The cholinergic system in the pathophysiology and treatment of Alzheimer ' s disease', (May 2018). doi: 10.1093/brain/awy132.

Herr, N., Bode, C. and Duerschmied, D. (2017) 'The effects of Serotonin in immune Cells', 4(July), pp. 1–11. doi: 10.3389/fcvm.2017.00048.

Huang, T. *et al.* (2011) 'Resveratrol Protects Rats from A b -induced Neurotoxicity by the Reduction of iNOS Expression and Lipid Peroxidation', 6(12). doi: 10.1371/journal.pone.0029102.

Huntington, G. and States, U. (2018) 'Huntington ' s disease : From basic science to therapeutics Huntington ' s disease', pp. 247–249. doi: 10.1111/cns.12841.

Huxford, T., Huang, D. and Malek, S. (1998) 'The Crystal Structure of the I B / NF- B Complex Reveals Mechanisms of NF- B Inactivation', 95, pp. 759–770.

Jacobs, M. D. and Harrison, S. C. (1998) 'Structure of an I B / NF- B Complex', 95, pp. 749–758.

Posted on Authorea 16 Jul 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.159493419.94920936 — This a preprint and has not been peer reviewed. Data may be preliminary.

Jang, J. and T, Y. S. (2005) 'h -Amyloid-induced apoptosis is associated with cyclooxygenase-2 up-regulation via the mitogen-activated protein kinase – NF- n B signaling pathway', 38, pp. 1604–1613. doi: 10.1016/j.freeradbiomed.2005.02.023.

Jiang, S. *et al.* (2014) 'M1 muscarinic acetylcholine receptor in Alzheimer ' s disease', 30(2), pp. 295–307. doi: 10.1007/s12264-013-1406-z.

Karin, M. and Ben-neriah, Y. (2000) 'P HOSPHORYLATION M EETS U BIQUITINATION : The Control of NF- j B Activity', pp. 621–663.

Kim, G. H. *et al.* (2015) 'The Role of Oxidative Stress in Neurodegenerative Diseases', 24(4), pp. 325–340.

Kwon, B. *et al.* (2015) 'Biochimica et Biophysica Acta Synergistic effects of β -amyloid and ceramide-induced insulin resistance on mitochondrial metabolism in neuronal cells', *BBA - Molecular Basis of Disease* . Elsevier B.V., 1852(9), pp. 1810–1823. doi: 10.1016/j.bbadis.2015.05.012.

Lanctôt, K. L. *et al.* (2004) 'GABAergic function in Alzheimer's disease: Evidence for dysfunction and potential as a therapeutic target for the treatment of behavioral and psychological symptoms of dementia',*Canadian Journal of Psychiatry* , 49(7), pp. 439–453. doi: 10.1177/070674370404900705.

Lee, K. M. *et al.* (2004) 'Spinal NF-kB activation induces COX-2 upregulation and contributes to inflammatory pain hypersensitivity',*European Journal of Neuroscience* , 19(12), pp. 3375–3381. doi: 10.1111/j.0953-816X.2004.03441.x.

Li, Q. *et al.* (2019) 'Luteoloside attenuates neuroin fl ammation in focal cerebral ischemia in rats via regulation of the PPAR γ / Nrf2 / NF- ϰ B signaling pathway', *International Immunopharmacology* . Elsevier, 66(November 2018), pp. 309–316. doi: 10.1016/j.intimp.2018.11.044.

Lim, C. S. *et al.* (2011) 'INCREASED INTERACTIONS BETWEEN PKA AND NF- B SIGNALING IN THE HIPPOCAMPUS FOLLOWING LOSS OF CHOLINERGIC INPUT', *NSC* . Elsevier Inc., 192, pp. 485–493. doi: 10.1016/j.neuroscience.2011.05.074.

Limon, A., Reyes-ruiz, J. M. and Miledi, R. (2012) 'Loss of functional GABA A receptors in the Alzheimer diseased brain', 109(25), pp. 10071–10076. doi: 10.1073/pnas.1204606109.

Liou, G. and Storz, P. (2010) 'Reactive oxygen species in cancer', 44(January), pp. 479–496. doi: 10.3109/10715761003667554.

Liu, J. *et al.* (2019) 'Propofol reduces microglia activation and neurotoxicity through inhibition of extracellular vesicle release',*Journal of Neuroimmunology* . Elsevier, 333, p. 476962. doi: 10.1016/j.jneuroim.2019.05.003.

Ly, P. T. T. *et al.* (2013) 'Inhibition of GSK3 b -mediated BACE1 expression reduces Alzheimer-associated phenotypes Find the latest version : Inhibition of GSK3 β -mediated BACE1 expression reduces Alzheimer-associated phenotypes', 123(1), pp. 224–235. doi: 10.1172/JCI64516.224.

Lyketsos, C. G. *et al.* (2011) 'Neuropsychiatric symptoms in Alzheimer's disease', *Alzheimer's and Dementia* . Elsevier Ltd, 7(5), pp. 532–539. doi: 10.1016/j.jalz.2011.05.2410.

Ma, Q. *et al.* (2009) 'beta -Amyloid Oligomers Induce Phosphorylation of Tau and Inactivation of Insulin Receptor Substrate via c-Jun N-Terminal Kinase Signaling : Suppression by Omega-3 Fatty Acids and Curcumin', 29(28), pp. 9078–9089. doi: 10.1523/JNEUROSCI.1071-09.2009.

Ma, X. *et al.* (2015) 'Large-Scale Transportation Network Congestion Evolution Prediction Using Deep Learning Theory', pp. 1–17. doi: 10.1371/journal.pone.0119044.

Mahony, A. O. *et al.* (2006) 'NF- B / Rel Regulates Inhibitory and Excitatory Neuronal Function and Synaptic Plasticity', 26(19), pp. 7283–7298. doi: 10.1128/MCB.00510-06.

Posted on Authorea 16 Jul 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.159493419.94920936 — This a preprint and has not been peer reviewed. Data may be preliminary.

Manea, A. *et al.* (2007) 'Regulation of NADPH oxidase subunit p22phox by NF-kB in human aortic smooth muscle cells', *Archives of Physiology and Biochemistry* , 113(4–5), pp. 163–172. doi: 10.1080/13813450701531235.

Maria-Angeles Arevalo, Pedro M. Roldan, P. J. C. and A. R.-T. (2009) 'Amyloid-beta serves as an NGF-like neurotrophic factor or act as a NGF antagonist depending on its concentration', pp. 1425–1433. doi: 10.1111/j.1471-4159.2009.06412.x.

Martorana, A. and Koch, G. (2014) "' Is dopamine involved in Alzheimer ' s disease ?"', 6(September), pp. 1–6. doi: 10.3389/fnagi.2014.00252.

Maryam, S., Naini, A. and Soussi-yanicostas, N. (2015) 'Tau Hyperphosphorylation and Oxidative Stress , a Critical Vicious Circle in Neurodegenerative Tauopathies ?', 2015.

Mei, Y. *et al.* (2015a) 'Aging-associated formaldehyde-induced norepinephrine deficiency contributes to age-related memory decline',*aging cell* , pp. 659–668. doi: 10.1111/acel.12345.

Mei, Y. *et al.* (2015b) 'Aging-associated formaldehyde-induced norepinephrine deficiency contributes to age-related memory decline', pp. 659–668. doi: 10.1111/acel.12345.

Michikawa, M. (2003) 'Cholesterol paradox: Is high total or low HDL cholesterol level a risk for Alzheimer's disease?', *Journal of Neuroscience Research* , 72(2), pp. 141–146. doi: 10.1002/jnr.10585.

Micu, I. *et al.* (2017) 'Axo-myelinic neurotransmission: a novel mode of cell signalling in the central nervous system',*NEUROSCIENCE* , pp. 1–9.

Moghaddam, H. S. *et al.* (2017) 'Neurotransmission systems in Parkinson ' s disease Neurotransmission systems'. doi: 10.1515/revneuro-2016-0068.

Morgan, M. J. and Liu, Z. (2011) 'Crosstalk of reactive oxygen species and NF- ϰ B signaling', *Nature Publishing Group* . Nature Publishing Group, pp. 103–115. doi: 10.1038/cr.2010.178.

Muhammad, T. *et al.* (2019) 'Hesperetin, a citrus flavonoid, attenuates LPS-induced neuroinflammation, apoptosis and memory impairments by modulating TLR4/NF-ϰB signaling', *Nutrients* , 11(3), pp. 1–20. doi: 10.3390/nu11030648.

Nafees, S. *et al.* (2015) 'Rutin ameliorates cyclophosphamide induced oxidative stress and inflammation in Wistar rats : Role of NF ϰ B / MAPK pathway', *CHEMICO-BIOLOGICAL INTERACTIONS* . Elsevier Ireland Ltd. doi: 10.1016/j.cbi.2015.02.021.

Nardo, D. De (2015) 'Cytokine Toll-like receptors : Activation , signalling and transcriptional modulation', *CYTOKINE* . Elsevier Ltd. doi: 10.1016/j.cyto.2015.02.025.

Nobili, A. *et al.* (2017) 'Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease'. doi: 10.1038/ncomms14727.

Pamplona, R. (2008) 'Biochimica et Biophysica Acta Membrane phospholipids , lipoxidative damage and molecular integrity : A causal role in aging and longevity', 1777, pp. 1249–1262. doi: 10.1016/j.bbabio.2008.07.003.

Paris, D. *et al.* (2010) 'Reduction of b -amyloid pathology by celastrol in a transgenic mouse model of Alzheimer ' s disease', pp. 1–15.

Paris, D. *et al.* (2011) 'Anatabine lowers Alzheimer ' s A β production in vitro and in vivo', *European Journal of Pharmacology* . Elsevier B.V., 670(2–3), pp. 384–391. doi: 10.1016/j.ejphar.2011.09.019.

Peroxidation, L. and Involving, C. (2002) 'Serial Review : Causes and Consequences of Oxidative Stress in Alzheimer ' s Disease Guest Editors : Mark A . Smith and George Perry DISEASE BRAIN : POTENTIAL CAUSES AND CONSEQUENCES INVOLVING', 32(11), pp. 1050–1060.

Posted on Authorea 16 Jul 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.159493419.94920936 — This a preprint and has not been peer reviewed. Data may be preliminary.

Pimplikar, S. W. (2014) 'Neuroinflammation in Alzheimer's disease: From pathogenesis to a therapeutic target', *Journal of Clinical Immunology* , 34(SUPPL. 1). doi: 10.1007/s10875-014-0032-5.

Pisoschi, A. M. and Pop, A. (2015) 'European Journal of Medicinal Chemistry The role of antioxidants in the chemistry of oxidative stress : A review', *European Journal of Medicinal Chemistry* . Elsevier Masson SAS, 97, pp. 55–74. doi: 10.1016/j.ejmech.2015.04.040.

Pizzi, M. *et al.* (2009) 'Post-ischemic brain damage : NF- j B dimer heterogeneity as a molecular determinant of neuron vulnerability', 276, pp. 27–35. doi: 10.1111/j.1742-4658.2008.06767.x.

Pohland, M. *et al.* (2018) 'MH84 improves mitochondrial dysfunction in a mouse model of early Alzheimer ' s disease'. Alzheimer's Research & Therapy, pp. 1–12. doi: 10.1186/s13195-018-0342-6.

Reber, L. *et al.* (2009) 'Ser276 Phosphorylation of NF-kB p65 by MSK1 Controls SCF Expression in Inflammation', 4(2). doi: 10.1371/journal.pone.0004393.

Reddy, P. H. (2017) 'A Critical Assessment of Research on Neurotransmitters in Alzheimer ' s Disease', 57, pp. 969–974. doi: 10.3233/JAD-170256.

Reitz, C. and Mayeux, R. (2014a) 'Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers', *Biochemical Pharmacology* . Elsevier Inc., 88(4), pp. 640–651. doi: 10.1016/j.bcp.2013.12.024.

Reitz, C. and Mayeux, R. (2014b) 'Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers', *Biochemical Pharmacology* . Elsevier Inc., 88(4), pp. 640–651. doi: 10.1016/j.bcp.2013.12.024.

Rodgers, E. E. and Theibert, A. B. (2002) 'Functions of PI 3-kinase in development of the nervous system', 20(April), pp. 187–197.

Rojo, A. I. *et al.* (2004) 'Regulation of Cu / Zn-Superoxide Dismutase Expression via the Phosphatidylinositol 3 Kinase / Akt Pathway and Nuclear Factor- B', 24(33), pp. 7324–7334. doi: 10.1523/JNEUROSCI.2111-04.2004.

Saltiel, A. R. (2001) 'New Perspectives into the Molecular Pathogenesis and Treatment of Type 2 Diabetes', 104, pp. 517–529.

Sauer, S. (2015) 'Ligands for the Nuclear Peroxisome Proliferator- Activated Receptor Gamma', *Trends in Pharmacological Sciences* . Elsevier Ltd, 36(10), pp. 688–704. doi: 10.1016/j.tips.2015.06.010.

Schreck, R. *et al.* (1992) 'Dithiocarbamates as potent inhibitors of nuclear factor κb activation in intact cells', *Journal of Experimental Medicine* , 175(5), pp. 1181–1194. doi: 10.1084/jem.175.5.1181.

Schubert, M. *et al.* (2003) 'Insulin Receptor Substrate-2 Deficiency Impairs Brain Growth and Promotes Tau Phosphorylation', 23(18), pp. 7084–7092.

Serasanambati, M. and Chilakapati, S. R. (2016) 'Function of Nuclear Factor kappa B (NF-kB) in human diseases-A Review', (November). doi: 10.22205/sijbs/2016/v2/i4/103443.

Sethi, G. and Tergaonkar, V. (2009) 'Potential pharmacological control of the NF-κB pathway', *Trends in Pharmacological Sciences* , 30(6), pp. 313–321. doi: 10.1016/j.tips.2009.03.004.

Shetty, A. K. and Bates, A. (2015) 'Potential of GABA-ergic cell therapy for schizophrenia , neuropathic pain , and Alzheimer ' s and Parkinson ' s diseases', *Brain Research* . Elsevier. doi: 10.1016/j.brainres.2015.09.019.

Shi, Z. *et al.* (2016) 'Journal of the Neurological Sciences Upstream regulators and downstream effectors of NF- κ B in Alzheimer ' s disease', *Journal of the Neurological Sciences* . Elsevier B.V., 366, pp. 127–134. doi: 10.1016/j.jns.2016.05.022.

Shih, R. H., Wang, C. Y. and Yang, C. M. (2015) 'NF-kappaB signaling pathways in neurological inflammation: A mini review', *Frontiers in Molecular Neuroscience* , 8(DEC), pp. 1–8. doi: 10.3389/fnmol.2015.00077.

Posted on Authorea 16 Jul 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.159493419.94920936 — This a preprint and has not been peer reviewed. Data may be preliminary.

Shih, R., Wang, C. and Yang, C. (2015) 'NF-kappaB Signaling Pathways in Neurological Inflammation : A Mini Review', 8(December), pp. 1–8. doi: 10.3389/fnmol.2015.00077.

Sivandzade, F. *et al.* (2019) 'Redox Biology NRF2 and NF- κ B interplay in cerebrovascular and neurodegenerative disorders : Molecular mechanisms and possible therapeutic approaches', *Redox Biology* . Elsevier B.V., 21(October 2018), p. 101059. doi: 10.1016/j.redox.2018.11.017.

Srinivasan, M. and Lahiri, D. K. (2015a) 'Significance of NF-κB as a pivotal therapeutic target in the neurodegenerative pathologies of Alzheimer's disease and multiple sclerosis', *Expert Opinion on Therapeutic Targets* , 19(4), pp. 471–487. doi: 10.1517/14728222.2014.989834.

Srinivasan, M. and Lahiri, D. K. (2015b) 'Significance of NF-κB as a pivotal therapeutic target in the neurodegenerative pathologies of Alzheimer's disease and multiple sclerosis', *Expert Opinion on Therapeutic Targets* . Informa UK, Ltd., 19(4), pp. 471–487. doi: 10.1517/14728222.2014.989834.

Strooper, B. De, Vassar, R. and Golde, T. (2010) 'foCuS on DemenTiA The secretases : enzymes with therapeutic potential in Alzheimer disease',*Nature Reviews Neurology* . Nature Publishing Group, 6(2), pp. 99–107. doi: 10.1038/nrneurol.2009.218.

Sun, C. *et al.* (2015) 'Dopamine Impairs Functional Integrity of Rat Hepatocytes Through Nuclear Factor Kappa B Activity Modulation : An In Vivo , Ex Vivo , and In Vitro Study', pp. 1520–1532. doi: 10.1002/lt.

Sun, X. F. and Zhang, H. (2007) 'NFKB and NFKBI polymorphisms in relation to susceptibility of tumour and other diseases',*Histology and Histopathology* , 22(10–12), pp. 1387–1398. doi: 10.14670/HH-22.1387.

Thaker, Y. R. and Rudd, C. E. (2015) 'Distinct NF-kB activation pathways engaged by T-cell receptor and co-receptor CD28 on T-cells',*Inflammation and Cell Signaling* , pp. 1–6. doi: 10.14800/ics.613.

Tilstra, J. S. *et al.* (2012) 'NF- k B inhibition delays DNA damage – induced senescence and aging in mice Find the latest version : NF- κ B inhibition delays DNA damage – induced senescence and aging in mice', 122(7), pp. 2601–2612. doi: 10.1172/JCI45785.most.

Tripathi, P. and Aggarwal, A. (2006) 'NF-kB transcription factor: A key player in the generation of immune response', *Current Science* , 90(4), pp. 519–531.

Tumminia, A. *et al.* (2018) 'Type 2 Diabetes Mellitus and Alzheimer ' s Disease : Role of Insulin Signalling and Therapeutic Implications'. doi: 10.3390/ijms19113306.

Umesalma, S. and Sudhandiran, G. (2010) 'Differential Inhibitory Effects of the Polyphenol Ellagic Acid on Inflammatory Mediators NF- j B , iNOS , COX-2 , TNF- a , and IL-6 in 1 , 2-Dimethylhydrazine-Induced Rat Colon Carcinogenesis', pp. 650–655. doi: 10.1111/j.1742-7843.2010.00565.x.

Valerio, A. *et al.* (2006) 'NF- j B pathway : a target for preventing b -amyloid (A b) - induced neuronal damage and A b 42 production', 23(September 2005), pp. 1711–1720. doi: 10.1111/j.1460-9568.2006.04722.x.

Valko, M. *et al.* (2007) 'Free radicals and antioxidants in normal physiological functions and human disease', 39, pp. 44–84. doi: 10.1016/j.biocel.2006.07.001.

Volonté, C. *et al.* (2019) 'Seminars in Cell & Developmental Biology Functional microglia neurotransmitters in amyotrophic lateral sclerosis', *Seminars in Cell and Developmental Biology* . Elsevier, 94(April), pp. 121–128. doi: 10.1016/j.semcdb.2019.04.014.

Wagley, Y. *et al.* (2013) 'Inhibition of c-Jun NH 2 -terminal kinase stimulates mu opioid receptor expression via p38 MAPK-mediated nuclear NF- κ B activation in neuronal and non-neuronal cells',*BBA - Molecular Cell Research* . Elsevier B.V., 1833(6), pp. 1476–1488. doi: 10.1016/j.bbamcr.2013.02.017.

Wang, W. *et al.* (2015) 'Role of pro-inflammatory cytokines released from microglia in Alzheimer ' s disease', 3(10), pp. 1–15. doi: 10.3978/j.issn.2305-5839.2015.03.49.

Posted on Authorea 16 Jul 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.159493419.94920936 — This a preprint and has not been peer reviewed. Data may be preliminary.

Wolfe, M. S. (2018) 'Dysfunctional γ-Secretase in Familial Alzheimer ' s Disease', *Neurochemical Research* . Springer US, 0(0), p. 0. doi: 10.1007/s11064-018-2511-1.

Wuertz, K. *et al.* (2012) 'Inflammatory and catabolic signalling in intervertebral discs: The roles of NF-KB and map kinases',*European Cells and Materials* , 23(Ivd), pp. 103–120. doi: 10.22203/ecm.v023a08.

Xie, H. *et al.* (2013) 'Mitochondrial Alterations near Amyloid Plaques in an Alzheimer ' s Disease Mouse Model', 33(43), pp. 17042–17051. doi: 10.1523/JNEUROSCI.1836-13.2013.

Xin, S. H. *et al.* (2018) 'Clearance of Amyloid Beta and Tau in Alzheimer's Disease: from Mechanisms to Therapy', *Neurotoxicity Research* . Neurotoxicity Research, 34(3), pp. 733–748. doi: 10.1007/s12640-018-9895-1.

Xu, B. I. N. and Li, H. (2015) 'Brain mechanisms of sympathetic activation in heart failure : Roles of the renin - angiotensin system , nitric oxide and pro - inflammatory cytokines (Review)', pp. 7823–7829. doi: 10.3892/mmr.2015.4434.

Xu, H. *et al.* (2018) 'Targeted neurotransmitters profiling identifies metabolic signatures in rat brain by LC-MS/MS: Application in insomnia, depression and Alzheimer's Disease', *Molecules* , 23(9), pp. 1–14. doi: 10.3390/molecules23092375.

Yamamoto, Y. and Gaynor, R. (2005) 'Role of the NF-kB Pathway in the Pathogenesis of Human Disease States', *Current Molecular Medicine* , 1(3), pp. 287–296. doi: 10.2174/1566524013363816.

Yang, S. S. W. and Chen, Y. (2014) 'Propofol Reduces Inflammatory Reaction and Ischemic Brain Damage in Cerebral Ischemia in Rats', pp. 793–799. doi: 10.1007/s11064-014-1272-8.

Yong-Qing Chen, S. G. and G. G. (1998) 'A novel DNA recognition mode by the NF-kB p65 homodimer', 5, pp. 67–73.

You, Z. *et al.* (2012) 'Nuclear Factor-Kappa B Mediates One-Lung Ventilation-Induced Acute Lung Injury in Rabbits', pp. 78–85. doi: 10.3109/08941939.2011.603817.

Yun, H. *et al.* (2015) 'Serotonin 6 depression receptor controls alzheimer ' s disease and', 6(29).

Zhao, L. *et al.* (2004) 'Insulin-Degrading Enzyme as a Downstream Target of Insulin Receptor Signaling Cascade : Implications for Alzheimer ' s Disease Intervention', 24(49), pp. 11120–11126. doi: 10.1523/JNEUROSCI.2860-04.2004.

Zhou, Q. and Sheng, M. (2013) 'NMDA receptors in nervous system diseases', *Neuropharmacology* . Elsevier Ltd, 74, pp. 69–75. doi: 10.1016/j.neuropharm.2013.03.030.

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Figure 1: Etiological factors and their mechanistic role in the pathogenesis of Alzheimer's disease.

Figure 2: Role of mitochondrial failure, oxidative stress, and neuroinflammation associated

to multipathological insult in Alzheimer's disease.

LPO- Lipid peroxidation; MDA- Malondialdehyde; TSPAN 12- Tetraspanin-12; IRAK 1- Interleukin 1 Receptor Associated Kinase; CREB- cAMP response element-binding.

Figure 3: Physiological role of canonical and non-canonical pathway in regulating basic cellular functions.

TLRs- Toll-like receptors; TOLLIP- Toll interacting protein; MYD88- Myeloid differentiation primary response 88; IRAK- Interleukin Receptor Associated Kinase; TCR- T-cell receptor; ZAP-70- Zeta-chain-associated protein kinase 70; PKC- Protein kinase C; TRAF- Tumor necrosis factor receptor (TNFR)-associated factor; TRADD- TNFR1-associated death domain; FADD- Fas-Associated protein with Death Domain; IKK- IκB kinase; IL-1R- Interleukin-1 receptor; BAFFR- B-cell activating factor receptor; LTβ-

Leukotriene β· RANK- Receptor activator of nuclear factor-ϰB; BCR- B-cell receptor; GFR- Growth factor receptor; RIPK- Receptor-interacting serine/threonine-protein kinase; MAP3K14- Mitogen- Activated Protein Kinase Kinase Kinase 14; TAB- TGF-Beta Activated Kinase 1 (MAP3K7) Binding Protein; PKR- Protein kinase R; PI3K- Phosphatidylinositol 3-Kinase; BTK- Bruton's tyrosine kinase; BCL10- B-cell CLL/lymphoma 10; MALT1- Mucosa-associated lymphoid tissue lymphoma translocation protein 1; CARMA 1- CARD-containing MAGUK protein 1; CARD11- Caspase recruitment domain-containing protein 11; cIAP1- Cellular inhibitor of apoptosis protein-1.

Figure 4: Ligand based upregulation of canonical pathway and neurodegeneration in Alzheimer's disease.

TLRs- Toll-like receptors; TOLLIP- Toll interacting protein; MYD88- Myeloid differentiation primary response 88; IRAK- Interleukin Receptor Associated Kinase; TCR- T-cell receptor; ZAP-70- Zeta-chain-associated protein kinase 70; PKC- Protein kinase C; TRAF- Tumor necrosis factor receptor (TNFR)-associated Factor; TRADD- TNFR1-associated death domain; FADD- Fas-Associated protein with Death Domain; IKK- IϰB kinase; IL-1R- Interleukin-1 receptor

Table 1: Various herbal drugs targeting NF-kB as protective strategy.

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