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Dexamethasone ameliorates Alzheimer's pathological condition via inhibiting Nf-κB and mTOR signaling pathways

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ABSTRACT

Alzheimer's disease (AD) is one of the severe neurodegenerative disorders among the elderly population, so early interventions play an important role in AD progression. The deposition of amyloid-beta(Aβ) plaques and the accumulation of tau tangles within microglia and astrocytes which leads to inflammatory response due to the production of inflammatory mediators such as nitric oxide (NO), reactive oxygen species (ROS), tumor necrosis factor (TNF)-alpha that trigger the neuronal death. In the present study, we performed that dexamethasone as a synthetic anti-inflammatory agent can affect the progression of Alzheimer's dementia via nuclear factor-κB(Nf-κB) and its downstream pathways. Literature review concentrated on Nf-κB, and the mammalian target of rapamycin(mTOR) pathway was executed in addition to looking for the molecular biology aspects in the Kyoto Encyclopedia of Genes and Genomes (KEGG). According to our hypothesis, it could be suggested that dexamethasone participates in reducing oxidative stress, inflammation, insulin resistance, and deposition of Aβ through inhibiting several pathways such as Nf-κB and mTOR signaling pathways. The present hypothesis proposes that dexamethasone could be a probable candidate to improve the pathological condition of AD. It should, however, be noted that due to little evidence for dexamethasone administration in AD patients, further investigations are required.

Keywords: *Alzheimer's disease; Amyloid beta; Inflammation; Oxidative stress; Insulin resistance; Nf-κB; mTOR; Dexamethasone.*

1. INTRODUCTION

Alzheimer's disease (AD) is considered as the most prevalent form of dementia that affects elderly individuals. In the United States, the number of people aged 65 and older with AD is estimated to increase from 55 million in 2019 to about 88 million by 2050. As AD is one of the debilitating and burdensome neurodegenerative disorders among elderlies, the early diagnosis of AD provides significant advantages to the old age and whole society [1]. Alzheimer's dementia, as another common and chronic disorder, is caused by various risk factors such as aging, positive family history, and carrying of the ApoE-e4 gene. Despite the extensive effort made so far to treat AD, therapeutic approaches have merely been used to alleviate the symptoms of AD and have not led to a cure [1-3].

Microglia cells and astrocytes of the central nervous system are considered as macrophages that exhibit both toxic effects as well as supportive functions [4-5].

Pathologically, Alzheimer's disease is accompanied with the formation of beta-amyloid plaques depositing outside neurons and the accumulation of tau tangles within the brain cells which contribute to inflammatory responses. These responses are associated with the activation of microglia and astrocytes which secondarily results in the production of inflammatory mediators. Ultimately, these inflammatory mediators such as tumor necrosis factor (TNF)-alpha, nitric oxide (NO), and reactive oxygen species (ROS) stimulate neuronal death [4,6-7].

Accordingly, some evidence suggests that the AD's progression might be attributed to neuronal damage as well as the inflammatory process resulted from the accumulation of amyloid-beta (Aβ) [4].

1.1. Nf-κB signaling pathway in Alzheimer's disease.

Nf-κB is a transcriptional factor that acts in response to numerous stimuli, including lipopolysaccharide (LPS), free radicals and cytokines such as TNF-α, interleukin-2 (IL-2) in activated cells, which is involved in regulating the expression of various genes such as inducible nitric oxide synthase (iNOS), interleukin-6 (IL-6), interleukin-8 (IL-8), cyclooxygenase-2 (COX-2) and so on.

As described later, Nf-κB exacerbates inflammation by interfering with the expression of its target genes. Since inflammation is a quintessential element in the development of AD, this route could be considered as an appropriate therapeutic target in the treatment of AD [8-12].

1.2. ApoE gene has an essential role in an Aβ deposition in the brain.

ApoE is a 299 amino acid responsible for the transfer of lipoproteins and metabolism of cholesterol. The protein is mainly produced by the liver as well as macrophages. In the brain, microglia and astrocytes are responsible for the production of this glycoprotein [13-15].

The APOE gene has three alleles that express proteins apoE2, apoE3, apoE4. ApoE can alter the transportation of substrates through blood brain barrier such as Aβ [16]. Among these, the E4 allele inheritance plays a role in developing both late-onset and sporadic AD. Hence, apoE4 homozygotes are 8-10 times more susceptible to AD [14-15,17].

1.3. The role of apoE in glial activation via Nf-κB signaling pathway.

Since Nf-κB has two binding sites in the APOE promoter, it can regulate the synthesis of apoE [17]. Inflammation and

accumulation of Aβ in glial cells due to the intracellular signaling pathway of Nf-κB can lead to increased apoE synthesis. As its concentration increases, the co-aggregate of amyloid-beta with apoE is formed and leads to the development of amyloid plaques (this process occurs more with apoE4 than apoE3). Therefore, by inhibiting Nf-κB activation, the promoter activity of Aβ-mediated APOE could be suppressed and Aβ deposition could be prevented [13,17-19]

On the other hand, APOE have also a a key role in the Alzheimer's pathogenesis via the other noxious ramifications such as synaptic dysfunction, mitochondrial dysfunction, brain atrophy, severe brain inflammation, etc [14].

1.4. Nitric oxide and inducible nitric oxide synthesis in Alzheimer's disease.

NO is a small gaseous signaling molecule that is generated by nitric oxide synthase (NOS) in the presence of L-arginine and oxygen . Being inducible, nitric oxide synthase is one of the three types of NOS production pathways in many biological cells, including microglia and astrocyte in the CNS. Glial cells increase the expression of iNOS in response to the presence of microbial products, Aβ aggregation, and pro-inflammatory cytokines such as TNF-α.

Accordingly, the elevation in the expression of iNOS results in an increment in the production of NO and reactive nitrogen species (RNS). In addition, the accumulation of Aβ in the neurons leads to mitochondrial dysfunction which happens through the reduction of mitochondrial respiratory complex activity. This while metal-catalyzed oxidation of amyloid-beta precursor protein (APP) at the exterior of neurons contributes to the production and increase in the level of reactive oxygen species (ROS).

Superoxide anion (O2-) is a kind of ROS that reacts with NO to produce a very strong oxidant, peroxynitrite (ONOO-). This oxidant is responsible for the oxidation of intracellular macromolecules such as lipids, proteins and nucleic acids and results in culmination of neuronal damage and more free radicals production. iNOS, ONOO- and ROS have been highlighted in many studies on AD. Therefore, it can be claimed that inflammation and oxidative stress play important roles in the production of RNS/ROS and in the pathophysiology of AD [20-23].

Moreover, Asiimwe et al. proposed that Aβ deposition has been triggered by excessive production of NO [22].

1.5. Insulin resistance in Alzheimer's disease.

Insulin, is a peptide hormone that regulates memory, learning, and maintains neuronal survival in the central nervous system via activating several signaling pathways. Disruption of insulin signaling in the brain and insulin resistance have shown to be related to cognitive decline and Alzheimer's pathogenesis [16,24-25].

Under normal circumstances, the binding of insulin to its receptors induces insulin receptor substrate 1(IRS-1) phosphorylation in the tyrosine residue and results in cellular responses to insulin. However, in AD affected brain, the accumulation of Aβ in cerebrospinal fluid results in the secretion of inflammatory cytokines like TNF alpha from glial cells. This leads to the activation of serine kinases such as c-Jun N-terminal kinases (JNK), mTOR/S6K, and IKK followed by the binding of TNF-α to its receptors. These kinases phosphorylate the inhibitory site of IRS-1 on serine residue bringing downregulation of IRS-1 tyrosine phosphorylation and impair intracellular insulin signaling.

Ultimately, few studies support the idea that blocking of IKK/Nf-κB pathway might be an appropriate therapeutic goal to overcome insulin resistance in AD patients [24-29].

2. MATERIALS AND METHODS

Literature review concentrated on Nf-κB, and the mammalian target of rapamycin (mTOR) pathway was executed in addition to looking for the molecular biology aspects in the Kyoto Encyclopedia of Genes and Genomes (KEGG).

3. RESULTS AND DISCUSSION

3.1. Hypothesis.

Dexamethasone is a synthetic glucocorticoid that is expected to influence the inflammation process during Alzheimer's disease. Accordingly, figure 1 depicts in detail our hypothesis that dexamethasone could affect insulin resistance, oxidative stress, and Aβ plaque formation through Alzheimer's pathogenesis by inhibiting Nf-κB and its downstream pathway.

3.2. Discussion.

The data from a few studies that investigated TNF-α, and TNF-α receptor 1(TNFR1) amounts in AD, suggest increased levels in AD affected brain [30-31]. The study by Medeiros and colleagues indicate that Aβ can potentially induce TNF-α production [32].

According to the signaling pathway illustrated in Fig.1, binding of TNF-α to its receptor (TNFR1) results in the activation of IκB kinase (IKK) [9]. The activation of IKK contributes to phosphorylation of IκB protein that leads to dissociation IκBα from NF-κB. This phenomenon allows NF-κB to be translocated to the nucleus and bind to the promoter of its target genes regulating the transcription [17]. These incidents have the consequences described below:

Pathway 1: The iNOS gene is induced by NF-κB which is associated with the production of high levels of NO [32-33]. Then, reaction of NO with superoxide anion(O2-) forms peroxynitrite which may lead to oxidization of intracellular macromolecules such as proteins, lipids, and nucleic acids. This idea of macromolecule oxidization inside cells might also ascertain that NO-mediated oxidative stress may fortify neuronal damage and aggravation of Alzheimer's disease [22].

Pathway 2: As a result of Aβ overproduction, amyloid precursor protein (APP) and β-site APP cleaving enzyme 1(BACE1) are upregulated through NF-κB activation. Following this condition, an increase in Aβ generation is also expected [33].

Pathway 3: It was mentioned previously that NF-κB has two binding sites in the human Aβ promoter gene. Accordingly, it is found that the synthesis of apoE in glial cells in AD affected brain is increased through NF-κB activation followed by Aβ and cytokines overload. Moreover, Du and colleagues investigated the role of apoE in Aβ aggregation and senile plaque formation [17].

Additionally, few studies have illustrated the relationship between NF-κB inhibition and the reduction in apoE production

which was considered to contribute to a low risk of AD development [15,17].

Pathway 4: The accumulation of amyloid-beta leads to TNF-α overproduction and therefore, IKKβ activation is observed. It results in direct serine phosphorylation of IRS-1 and leads to disturbance in insulin signaling followed by inhibition of IRS-1 [26-27,34].

Tanti *et al*. have provided convincing evidence showing that during the activation of NF-κB by Aβ in the AD affected brain, upregulation of the protein tyrosine phosphatase 1B (PTB1B) happens. This is while PTB1B is responsible for downregulating insulin receptor (IR) from the cell surface. Taking all into consideration, it could be hypothesized that inflammation and amyloid-beta overproduction in AD might induce insulin resistance via IKKβ/NF-κB signaling pathway [29].

Another study conducted by O'Neill, described how excessive levels of Aβ oligomers could lead to activated mTOR and PI3K/AKT. Following this event, serine phosphorylation was observed. Therefore, a decrease in the sensitivity of insulin receptors was observed [35].

Matsumura and colleagues' investigation on the effect of dexamethasone on NO production has implied that dexamethasone may reduce iNOS mRNA expression through inhibition of NF-κB activation, which is one way of NO production reduction [36].

Another study supports the idea that dexamethasone reduces iNOS expression by inhibition of NF-κB via increasing IκBα expression [37].

Another study revealed that dexamethasone significantly downregulates cytokine synthesis like TNF-α in AD patients [38].

Furthermore, Hongmei et al. have illustrated that dexamethasone can reduce S6K phosphorylation as a downstream target of the mTOR signaling pathway. Therefore, as it is shown in Fig.1, dexamethasone is proposed to prevent IRS-1 inhibition [39].

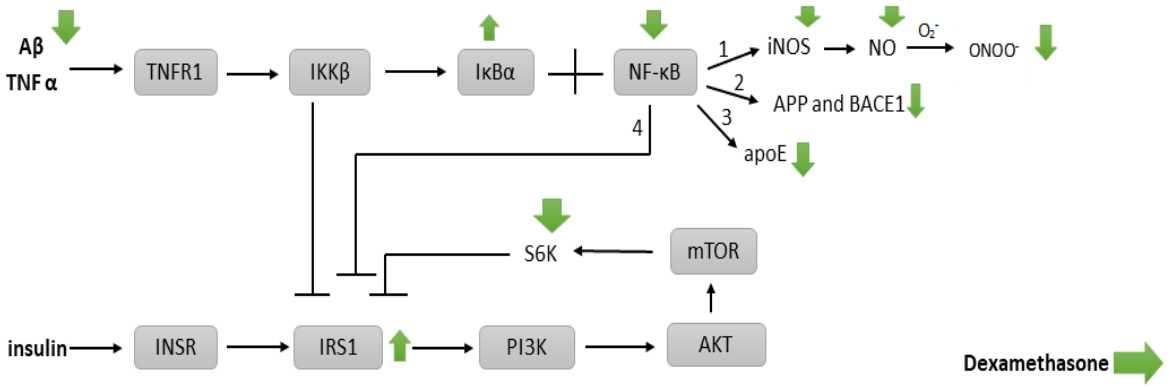

Figure 1. The schematic view of dexamethasone signaling pathways related to Alzheimer. TNFR1:tumor necrosis factor receptor 1; IKKb: inhibitory-kB kinase b; IkappaB: inhibitor of kappa B proteins; NF-kB: nuclear factor-kB; iNOS: inducible nitric oxide synthase; APP: amyloid precursor protein; BACE1: beta-site APP cleaving enzyme 1; INSR: insulin receptor; IRS-1: insulin receptor substrate 1; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; S6K: S6 kinase.

4. CONCLUSION

According to our hypothesis, dexamethasone plays a critical role in reducing inflammation, oxidative stress, generation, deposition of Aβ and insulin resistance in Alzheimer's disease through inhibiting several pathways such as NF-κB and mTOR signaling pathways.

Finally, our study suggests that dexamethasone could be a potential candidate to control the progression of AD, but due to lack of evidence of administration of dexamethasone in AD patients, further in-vitro as well as in-vivo studies are needed.

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