Therapeutic Potential of FGF21 in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common form of dementia which mostly affects persons younger than 65 years old. Mounting findings showed that amyloid-β (Aβ) peptides, oxidative stress, neuroinflammation and insulin resistance may play central role in the pathogenesis of AD. There are very many methods to slow it through affecting these aforementioned factors. However, more efficient prevention of the progression of AD is still ambiguous. Fibroblast growth factor 21 (FGF21) is an endocrine hormone that is expressed by several organs. It increases insulin sensitivity and regulates lipid metabolism and energy homeostasis. Emerging evidence demonstrates that FGF21 has potential effects in the brain involving metabolic regulation, neuroprotection and cognition. Hence, we hypothesize that FGF21 may be a protective factor in AD by attenuating Aβ generation, inflammation, oxidative stress, and insulin resistance. Our hypothesis will shed new light on the understanding of pathogenesis of AD and help to find a new way to prevent the genesis and progress of AD.

Keywords

FGF21, Alzheimer' Disease, Amyloid-β (Aβ), Oxidative Stress, Inflammation, Insulin Resistance

1. Introduction

Alzheimer's disease (AD) is an insidious, progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration, progressive

impairment of daily life activities, and as well as a variety of neuropsychiatric symptoms and behavioral disturbances [1]. It is the most common form of dementia, with an estimated 5.2 million people diagnosed in the United States in 2013, of which approximately 200,000 individuals are younger than 65 [1] and 50% of people over 85 years old are affected by various degrees of AD [2]. There are more than 47 million people living with dementia worldwide in 2016, and the total estimated worldwide cost of dementia is more than 818 billion USD. It will become a trillion dollar disease by 2018 [3]. By 2050, the distribution of dementia cases is 67.2 million in Asia (51.5% of total), 15.8 million in Africa (12%), 29.9 in Americas (22.7%) and 18.6 in Europe (14.2%), (Table 1). Nearly 68% of all people living with dementia will live in low and middle income countries [4]. The etiology and pathogenesis of AD is complicated, but currently known pathological hallmarks of AD include the presence of neuritic plaques, neurofibrillary tangles, synaptic loss, ultimately neuronal death [5] [6] [7] [8] [9]. Methods to block the progression of the disease and prevent neuronal loss or even cure it are still ambiguous.

2. Pathogenesis of Alzheimer's Disease

2.1. Amyloid-β (Aβ) Peptides

Mounting evidence showed that amyloid-β (Aβ) peptides play a central role in the pathogenesis of AD. The initial "amyloid cascade" hypothesis suggested that Aβ peptides drive the neuropathological cascade responses leading to dementia [10]. The revised amyloid cascade hypothesis suggested that soluble Aβ oligomers initiate the pathological cascade of AD leading to synaptic dysfunction, neuronal cell death, and dementia [11]. Moreover, transgenic mice with overexpression of the human amyloid precursor protein (APP-tg mice) have learning and memory deficits, as well as neuritic plaques similar to those seen in humans with AD [12]. In view of this, several immunization programs have successfully cleared the amyloid in APP-tg mice [13] [14]. However, the immunization programs attempted to clear AD patients brain amyloid through monoclonal antibodies, AN1792 [15], Solanezumab (LY2062430) and Bapineuzumab [16] [17], were terminated because of adverse effects 14 and lack of clinical treatment effect [16] [17]. The results of concurrent neuropsychological tests and magnetic resonance imaging (MRI) tests were surprising and disappointing, the brain

Table 1. People living with dementia around the world (million).

| Continent＼Year	2015	2030	2050
Americas	9.4 (20.1%)	15.8 (21.2%)	29.9 (22.7%)
Europe	10.5 (22.5%)	13.4 (17.9%)	18.6 (14.2%)
Asia	22.9 (48.9%)	38.5 (51.5%)	67.2 (51.1%)
Africa	4.0 (8.5%)	7.0 (9.4%)	15.8 (12%)
World	46.8	74.7	131.5
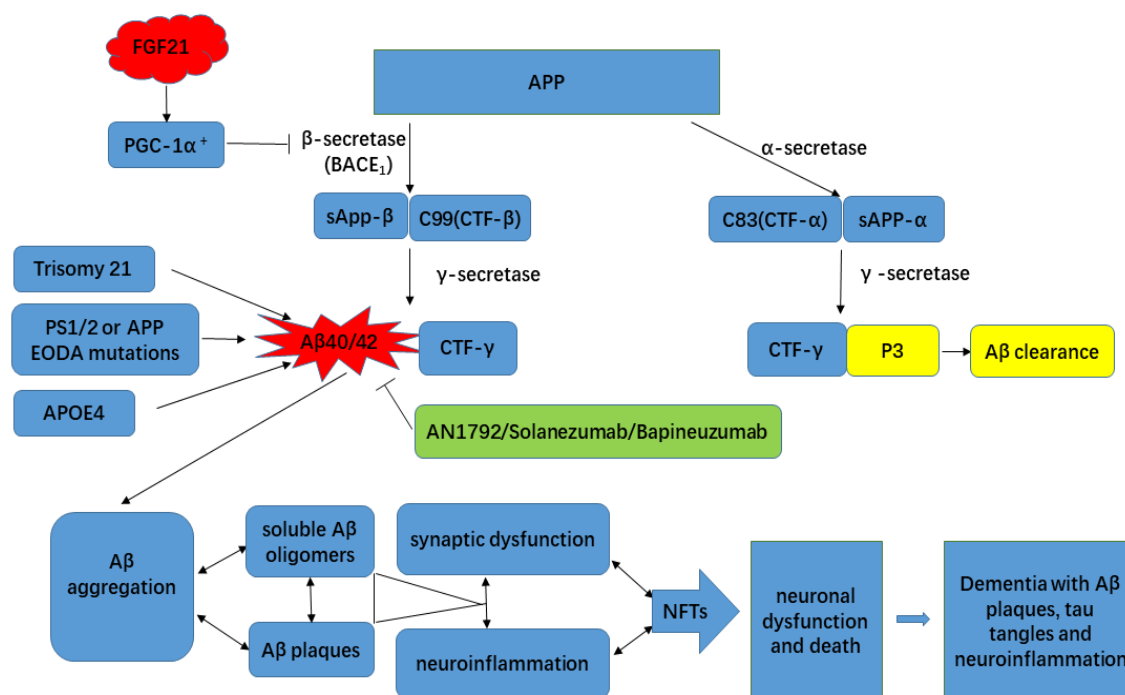
Figure 1. The potential mechanisms of Aβ in AD and the potential targets of FGF21. 1) Aβ derives from the amyloid precursor protein (APP), which is cleaved by β secretase (BACE$_1$) and γ secretase to yield Aβ. The Aβ_{40} form is the more common isoform, but Aβ_{42} is the more fibrillogenic and is thus associated with disease states. It is generally believed that Aβ oligomers are the most toxic. It leads to synaptic dysfunction, neuroinflammation, neurofibrillary tangles, then causes neuronal dysfunction and death, ultimately result in learning and memory deficits which displayed by AD. 2) Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding APP and presenilins 1 and 2 (PS1/2), while the apolipoprotein E4 (APOE4) is the major genetic risk factor for sporadic AD. People with trisomy 21 (Down Syndrome) almost universally exhibit at least the earliest symptoms of AD by 40 years of age. All these factors can lead to Aβ buildup, Aβ aggregation, and the sequential changes and symptoms we mentioned above. 3) There are some immunization programs attempted to clear AD patients brain amyloid through monoclonal antibodies, AN1792, Solanezumab (LY2062430) and Bapineuzumab, but they were terminated because of adverse effects and lack of clinical treatment effect. 4) FGF21 can activate peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), then decrease Aβ generation by reducing BACE1 transcription.

atrophy in immunized patients was worse than that of placebo-controlled patients [18]. These findings suggested that amyloid deposition is not the only one pathogenic cause of AD (**Figure 1**).

2.2. Oxidative Stress

Other research indicated that oxidative stress may be involved in the pathogenesis of AD. Further study showed that oxidative stress markedly elevated in preclinical AD patients and amnestic mild cognitive impairment (aMCI) patients [19] [20]. The mechanism may be that the oxidative stress leads to membrane damage, cytoskeleton alterations [21] and destroy the synaptic homeostasis in the hippocampus early in the AD process and ultimately speeding up the progression of AD [19]. Growing evidence indicates that many oxidative markers are increased in the AD brain, including protein oxidation [22], lipid peroxida-

tion [23], and nucleic acid oxidation [21]. Reactive oxygen species (ROS), which are cytotoxic byproducts of oxygen metabolism, are accumulated during aging, hyperglycemia, hypoxic insults and inflammation [24]. In the AD brain, these may induce synaptic loss and eventually promote neurofibrillary tangles and neuritic plaques formation [25]. Moreover, there is a positive feedback loop between oxidative stress and Aβ, which contributes to the pathologic progress of AD [26] [27] [28]. This is because ROS alter the expression of β-APP cleaving enzyme (BACE$_1$), the rate-limiting enzyme of AD [29] [30], and Presenilins1 (PS1), the catalytic submit of the γ-secretase [26], thereby promoting Aβ production in AD. Meanwhile, Aβ induces oxidative stress and the generation of HNE, which is a neurotoxic lipid peroxidation product and associated with Aβ pathology in AD [26]. Several studies suggested that antioxidants vitamin E and vitamin C play a role in delaying the onset of AD [31] [32] [33] [34]. These studies further confirmed that oxidative stress is involved in the occurrence and progression of AD (**Figure 2**).
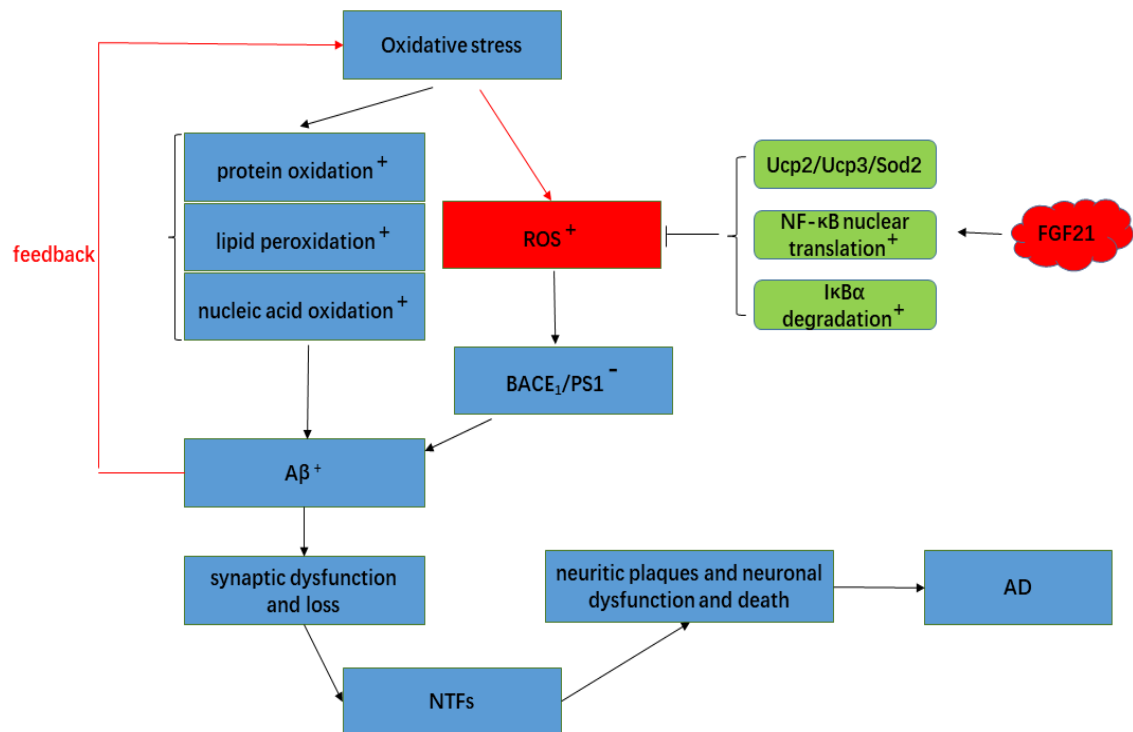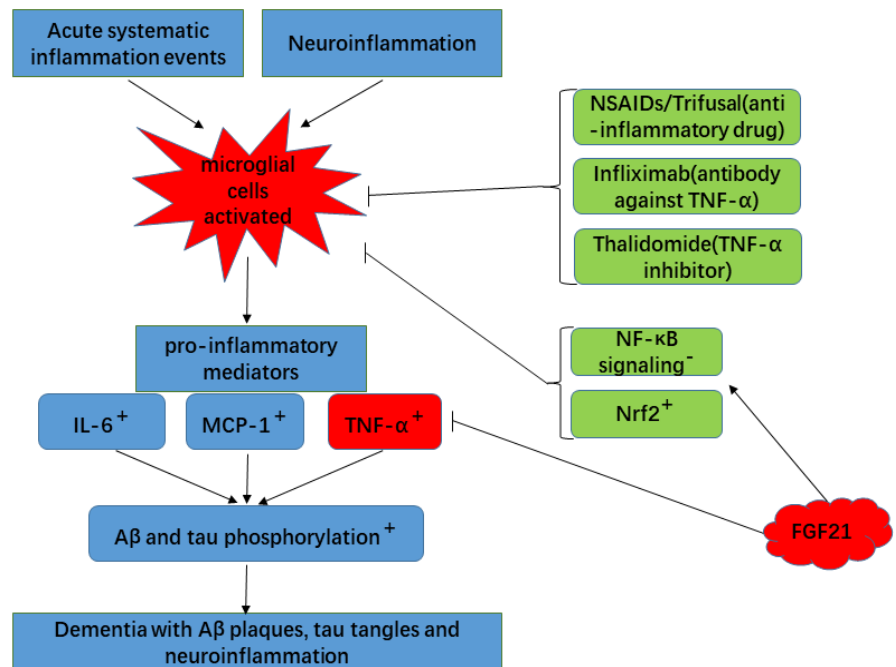

Figure 2. The potential mechanisms of oxidative stress in AD and the potential targets of FGF21. 1) Oxidative stress leads to membrane damage, cytoskeleton alterations and destroy the synaptic homeostasis in the hippocampus early in the AD process and ultimately speeding up the progression of AD. During these process, there are many oxidative markers are increased in the AD brain, including protein oxidation, lipid peroxidation, and nucleic acid oxidation. 2) Oxidative stress can also increase the production of ROS which alter the expression of BACE1 and PS1, then promote the production of Aβ in AD. 3) There is a positive feedback loop between oxidative stress and Aβ. All the factors mentioned above will finally lead to AD which illustrated in **Figure 1**. 4) FGF21 can upregulate the expression of genes encoding proteins involved in antioxidative pathways, including mitochondrial uncoupling proteins (Ucp2 and Ucp3), superoxide dismutase-2 (Sod2), reduced ROS production. It also could inhibit D-galactose-induced ROS production in a dose dependent manner, through preventing NF-κB nuclear translation and IκBα degradation.

2.3. Neuroinflammation

Besides the amyloid plaques and oxidative stress, neuroinflammation in the central nervous system (CNS) also causes neuronal injury, and pro-inflammatory changes exist in early stages of the disease in AD patients, when microglial cells are activated and produce pro-inflammatory mediators [35]. Acute systemic inflammatory events with increased levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), were associated with an increasing rate of cognitive decline in mild to severe dementia [36]. Animal models of lipopolysaccharide (LPS) induced sepsis showed CNS inflammation, neuronal death and cognitive decline [37] [38] [39]. Correspondingly, non-steroidal anti-inflammatory drugs (NSAIDs) can ameliorate behavioral and pathology deficits in AD transgenic mouse models [40] [41]. Although clinical trials have failed to reproduce the beneficial effects of NSAIDs in AD patients, they may be beneficial when administered in the early stage of the disease [42]. The anti-inflammatory effects of NSAIDs may be that NSAIDs directly bind to peroxisome proliferator-activated receptor γ (PPAR γ) [42], which expressed in human brain [43] and inhibited microglial activation and the expression of a wide range of proinflammatory genes [42] [44] [45], and activate its transcriptional regulatory activities [42]. Other anti-inflammatory drugs such as trifusal showed a significant low rate of conversion to dementia in clinical trials with mild cognitive impairment patients [37] [46]. The diversity of effects may depend on the drug, because different anti-inflammatory drugs may have different molecular targets. And anti-TNFα treatment with the antibody against TNFα, infliximab, reduced Aβ and tau phosphorylation in transgenic mice [41]. In addition, the TNFα inhibitor thalidomide can decrease the activation of both astrocytes and microglia, Aβ load, plaque formation and tau phosphorylation [41] (**Figure 3**). Further studies assessing the potential for targeting these specific inflammatory processes are needed to elucidate more effective treatments and provide a clearer understanding of the complexities of inflammatory signaling in AD [41].
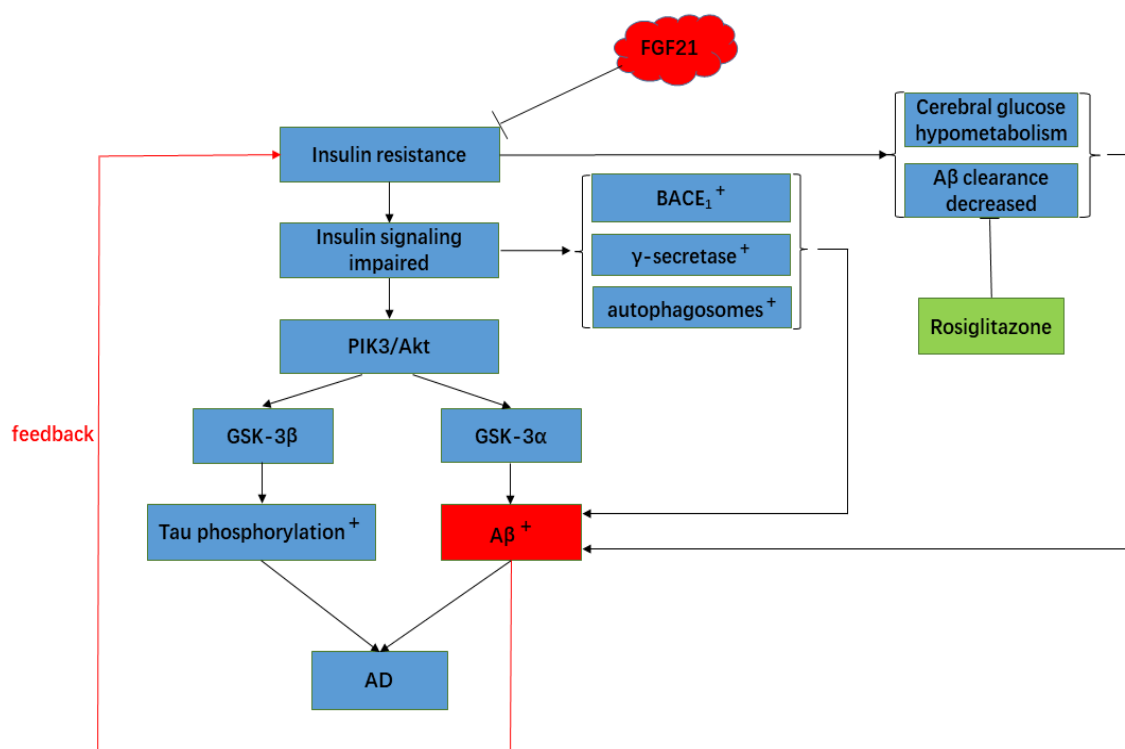
2.4. Insulin Resistance

Accumulating evidence also suggests that insulin resistance acts as a known risk factor for AD [2] [47]. Brain insulin signaling plays a critical role in the regulation of food intake, body weight, reproduction, and learning and memory [48] [49]. Defective insulin signaling is associated with decreased cognitive ability and the development of dementia and AD [2] [50]. Insulin resistance, induced by peripheral metabolic syndrome, impairs the insulin signaling in the brain, which mainly impacts the PIK3/Akt pathway, then reduces Aβ and tau phosphorylation by inhibiting the activation of glycogen synthase kinase 3-α and -β separately, which are the key signaling molecules downstream of Akt [51]. There is a feed-forward interaction between impaired insulin signaling and Aβ production, which contributes to the pathologic progress of the AD and cognitive decline [2] [52]. Insulin resistance also can promote Aβ generation through altering

Figure 3. The potential mechanisms of neuroinflammation in AD and the potential targets of FGF21. 1) Neuroinflammation and acute systemic inflammatory events in the CNS causes neuronal injury, then activate the microglia cells and produce pro-inflammatory factors (TNF-α, IL-6, MCP1) exist in early stages of the disease in AD patients. The pro-inflammatory factors increase Aβ formation and tau phosphorylation, then lead to dementia with Aβ plaques and tau tangles. 2) The anti-inflammatory drugs (NSAIDs, trifusal), directly bind to PPARγ, then inhibit microglial activation and the expression of a wide range of proinflammatory genes. Infliximab, the antibody against TNFα, can reduce Aβ and tau phosphorylation. Thalidomide, the TNFα inhibitor, can decrease the activation of both astrocytes and microglia, Aβ load, plaque formation and tau phosphorylation. All the factors mentioned above can improve AD through different pathways. 3) FGF21 could significantly reduce the mRNA expression level of TNFα. It also can inhibit macrophage-mediated inflammation, by activating the nuclear transcription factor-E2-related factor 2 (Nrf2) and suppressing the NF-κB signaling pathway.

insulin signal transduction, increasing BACE1 and γ-secretase activities, and accumulation of autophagosomes [52] [53]. Moreover, insulin resistance causes both cerebral glucose hypometabolism and a systemic hyperinsulinemic state [49]. Brain glucose hypometabolism was found even at the preclinical stage of AD [49]. Peripheral insulin resistance not only reduced cerebral glucose metabolism, but also decreased Aβ clearance in the CNS [47] [48]. Rosiglitazone, a ligand for peroxisome proliferator-activated receptors (PPARs), improve cognitive function by facilitating Aβ clearance, reducing amyloid plaques and tau phosphorylation in AD mouse models [2] [54] [55]. Rosiglitazone can also protect cognitive decline in MCI patients [56] [57] [58], while pioglitazone can improve cognitive deficiency and stabilize the disease in the individuals with mild AD [59] [60]. Treatments to enhance cerebral glucose metabolism showed improvement in cognition and AD symptomatology [61]. Collectively, insulin resistance is closely related with the pathologic process of AD (**Figure 4**).

Figure 4. The potential mechanisms of insulin resistance in AD and the potential targets of FGF21. 1) Insulin resistance impairs the insulin signaling in the brain, which mainly impacts the PIK3/Akt pathway, then reduces $A\beta$ and tau phosphorylation by inhibiting the activation of glycogen synthase kinase 3-α and -β separately. It also can promote $A\beta$ generation through altering insulin signal transduction, increasing BACE1 and γ-secretase activities, and accumulation of autophagosomes. 2) There is a positive feedback loop between insulin resistance and $A\beta$. All the factors mentioned above will finally cause AD. 3) Rosiglitazone, a ligand for peroxisome proliferator-activated receptors (PPARs), improve cognitive function by facilitating $A\beta$ clearance, reducing amyloid plaques and tau phosphorylation in AD. 4) FGF21 can potentially ameliorate cognition through improving insulin resistance and cerebral glucose hypometabolism.

In summary, $A\beta$ peptides play a central role in the pathogenesis of AD, while oxidative stress, neuroinflammation and insulin resistance participate in the pathogenic process of AD.

3. Fibroblast Growth Factor 21(FGF21) in Alzheimer's Disease

FGF21 is one member of the FGF family. It acts as either a paracrine or an endocrine hormone, and is expressed by adipose tissue, muscles, liver, pancreas, heart, and brain [62] [63]. FGF21 can lower glucose and lipid levels, increase insulin sensitivity and regulate energy homeostasis in rodents [64]. Its activity occurs when FGF21 binds to the fibroblast growth factor receptor (FGFR) and β-klotho (KLB), a single-pass transmembrane protein [64] and an essential co-receptor for FGF21 [65] [66]. There are seven major isoforms of FGFR, including 1b, 1c, 2b, 2c, 3b, 3c and 4. *In vivo* study, FGFR1c is the primary receptor to mediate its activity [67] [68] [69]. In fact, FGF21 is expressed in several areas of the brain, including the substantia nigra, striatum, hippocampus and

cortex [70]. It can enter the brain from blood and can also be detected in human cerebrospinal fluid [71] [72] [73]. Moreover, FGFs and KLB have been found in several brain areas [74] [75] [76]. These findings indicate that FGF21 may have potential regulating roles in the CNS.

3.1. FGF21 and Amyloid-β (Aβ) Peptides

Growing evidence demonstrates that FGF21 activated peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) [70] [77] [78] [79] [80], which is abundantly expressed in the brain [81] [82]. The expression of PGC-1α is reduced in the brain of AD patients. Exogenous human PGC-1α (hPGC-1α) expressed in primary neurons from the Tg2576 mouse of AD decreased Aβ generation by reducing BACE1 transcription which was dependent on PPAR γ [83] [84]. In accordance with this result, gene delivery of hPGC-1α in the brain of transgenic APP23 mice reduced amyloid deposition, which correlated with a decrease in BACE1 expression [85]. These findings suggest that FGF21 may reduce Aβ generation by decreasing BACE1 expression, as illustrated in Figure 1.

3.2. FGF21 and Oxidative Stress

As widely known, ROS, the cytotoxic byproducts of oxygen metabolism, could induce synaptic loss, promote neurofibrillary tangles, form neuritic plaques and finally cause neuron death [24]. This plays an essential role in the pathologic progress of AD. Recent work has shown that FGF21 participates in regulating oxidative stress [86] [87] [88]. It upregulated the expression of genes encoding proteins involved in antioxidative pathways, including mitochondrial uncoupling proteins (Ucp2 and Ucp3), superoxide dismutase-2 (Sod2), reduced ROS production in cardiomyocytes, and ameliorated cardiac tissue injury [86] [87]. In the brain of aging mice, FGF21could inhibit D-galactose-induced ROS production in a dose dependent manner [87], through preventing NF-κB nuclear translation and IκBα degradation [88]. Hence, as showed in Figure 2, FGF21 may ameliorate the oxidative stress of AD by enhancing the activities of SOD and reducing the production of ROS.

3.3. FGF21 and Inflammation

Increasing evidences demonstrated that inflammatory process play a critical role in AD progression [89] [90] [91]. However, FGF21 was demonstrated a modulatory role in the inflammatory processes [61] [73]. As demonstrated in Figure 3, it acted as a positive acute phase response (APR) protein and protected mice from the challenge of LPS and sepsis [61]. The inflammatory genes such as interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) were significantly higher in FGF21 knockout mice [86]. While in db/db mice models, FGF21 treatment significantly reduced the mRNA expression level of TNFα [92]. FGF21 inhibited macrophage-mediated inflammation, by activating the nuclear transcription factor-E2-related factor 2 (Nrf2) and suppressing the NF-κB sig-

naling pathway [93].

3.4. FGF21 and Insulin Resistance

A growing body of findings suggests that insulin resistance is closely related with the pathologic process of AD [2] [50] [51]. FGF21 acts as one of the metabolic regulators. It has been demonstrated as a potent regulator of glycemia, lipid metabolism and energy homeostasis [94] [95]. Recombinant FGF21 treatment can improve whole-body insulin sensitivity and reduce plasma levels of glucose and triglycerides in diabetic mice [94], while loss of endogenous FGF21 *in vivo* led to increased insulin resistance and pancreatic islet hyperplasia and dysfunction [95]. As presented in Figure 4, FGF21 can potentially ameliorate cognition through improving insulin resistance and cerebral glucose hypometabolism.

4. Conclusions

Here, we hypothesize that the FGF21 may be a protective factor in AD by attenuating Aβ generation, inflammation, oxidative stress, and insulin resistance.

FGF21 increased energy expenditure and insulin sensitivity in obese rats, and intracerebroventricular injection of FGF21 into rats increased metabolic rate and insulin sensitivity [96]. FGF21 also acts as a robust neuroprotective factor and a potentially new therapeutic target for CNS disorders. For example, exogenous FGF21 protein completely protected aging neurons from glutamate challenge [97]. The serumal FGF21 levels increased significantly in patients with schizophrenia [96]. It may be involved in regulating glucose metabolism in schizophrenia, with positive correlations with pyruvate, lactate, 2-oxoglutarate, and malate in the schizophrenia group [96]. On the other hand, FGF21 activated PGC-1α and increased mitochondrial efficacy in human dopaminergic neurons which suggest that FGF21 could potentially play a role in dopaminergic neuron viability and in Parkinson's disease [70].

Moreover, increasing evidence indicates that FGF21 has beneficial roles on behavior and cognition. The activity of transgenic overexpression of FGF21 mice (TgFgf21) increased during light phase, but decreased during dark phase. This circadian behavior in mice can also be altered by genetically deleting KLB in the brain [75]. The locomotor activity of FGF21 transgenic mice was reduced after a 24 hours fast [98]. D-galactose-induced aging mice, which were administrated with FGF21, had preserved cognitive function. This may be related to FGF21's ability to reduce brain cell damage in hippocampus by attenuating oxidative stress, increasing anti-oxidant activity, decreasing the enhanced total cholinesterase activity in the brain and reducing the expression of pro-inflammation cytokines such as IL-6 and TNF-α [63] [88].

Taken together, FGF21 acts as a neuroprotective factor, performs its decreased Aβ generation, anti-inflammatory, anti-oxidative stress, and glucose homeostatic effects. In view of the complex pathogenesis of AD, we propose that FGF21 may be a protective factor in AD by attenuating Aβ generation, inflammation, oxida-

tive stress, and insulin resistance. It may be a potential therapeutic for AD.

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Abbreviations

Aβ	amyloid-β
AD	Alzheimer's disease
APOE4	apolipoprotein E4
APP	amyloid precursor protein
APR	acute phase response
BACE1	β-APP cleaving enzyme
CNS	central nervous system
FGF21	fibroblast growth factor 21
FGFR	fibroblast growth factor receptor
hPGC-1α	human PGC-1α
IL-6	interleukin-6
KLB	β-klotho
LPS	lipopolysaccharide
MCI	mild cognitive impairment
MCP-1	monocyte chemoattractant protein-1
MRI	magnetic resonance imaging
Nrf2	nuclear transcription factor-E2-related factor 2
NSAIDs	non-steroidal anti-inflammatory drugs
PS1/2	presenilins 1 and 2
PGC-1α	peroxisome proliferator-activated receptor γ coactivator-1α
PPAR γ	peroxisome proliferator-activated receptor γ
PPARs	peroxisome proliferator-activated receptors
ROS	reactive oxygen species
Sod2	superoxide dismutase-2
TgFgf21	transgenic overexpression of FGF21 mice
TNF-α	tumor necrosis factor-α
Ucp2/Ucp3	uncoupling proteins2/3