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Potential role of recombinant growth differentiation factor 11 in Alzheimer's disease treatment

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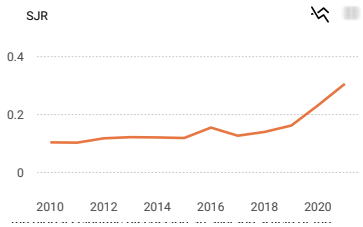

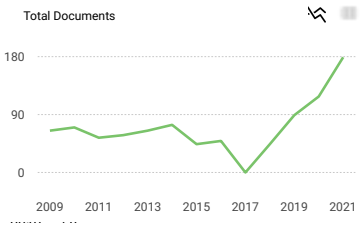

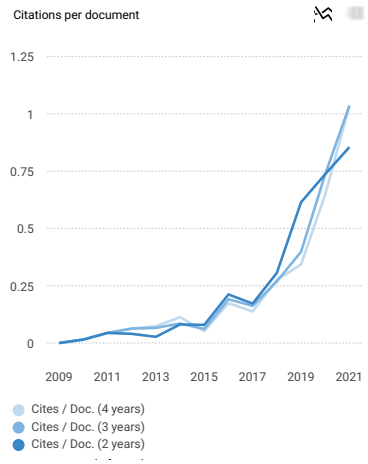

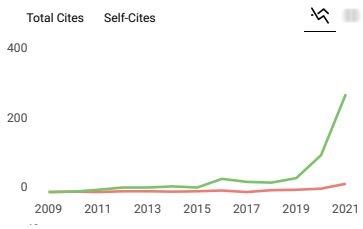

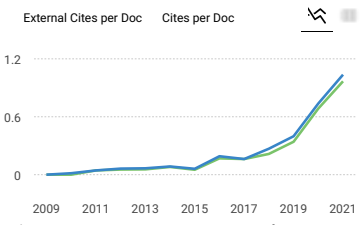

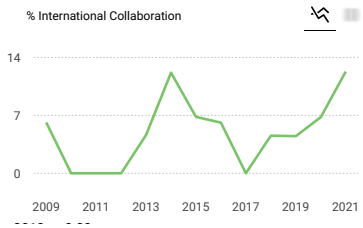

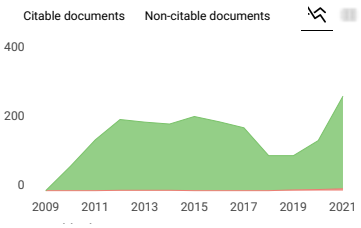

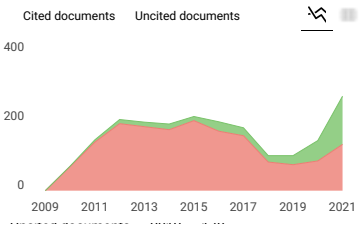

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REVIEW

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Potential role of recombinant growth differentiation factor 11 in Alzheimer's disease treatment

Bryan Gervais de Liyis[1*], Wilson Halim[1] and I. Putu Eka Widyadharma[2]

Abstract

Alzheimer's disease (AD) is a neurodegenerative disease closely related to the accumulation of beta-amyloid (Aβ) plaques. Growth differentiation factor 11 (GDF11) is one of the proteins that play a role in the aggravation of AD. Decreased concentration of GDF11 disrupts regenerative nervous system, blood vessels, and various vital systems. Low levels of GDF11 with age can be overcome with recombinant GDF11 (rGDF11) to rejuvenate the regenerative effect. Based on research results, rGDF11 enhance the proliferation rate of neuronal precursor cells as well as angiogenesis. rGDF11 can replace lost levels of GDF11, overcome astrogliosis and activation of nerve cell microglia. Therapeutic effect of rGDF11 leads to an improved prognosis in AD patients by neurogenesis and angiogenesis. The prospects of rGDF11 in the treatment of AD have great potential for further research in the future.

Keywords: Alzheimer's disease, Angiogenesis, GDF11, Neurogenesis

Background

Alzheimer's disease is a prominent neurodegenerative disease characterized by the progressive loss of cognitive abilities and disorganization of basic functions, such as walking, talking, attention as well as memory [1]. The term describes a combination of clinical syndrome that is associated with a distinct neuropathological process bound by two hallmark features: cumulation of extracellular neurotic plaques composed of 42-amino acid amyloid-beta (Aβ1-42), a cleavage product of amyloid precursor protein (APP), and intracellular neurofibrillary tangles collections composed of hyper-phosphorylated species of the microtubule-associated protein tau (MAPT) [2]. Currently, AD is the 5th leading cause of mortality and affects around 44 million people worldwide [3]. Around two-thirds of those diagnosed with AD are women [4]. Cases of AD show a growing trend as the world population progresses [1–3]. Prevalence of AD increases with age by a percentage of 10–30% in those over 65 years old and the frequency doubles every 10 years after the age of 60 [5].

The conventional Food and Drug Administration (FDA) also approved treatments for AD rejuvenate cholinergic and glutamatergic neuronal function to reestablish cognitive regulation, but do not alter the underlying course of neurodegeneration itself [6]. AD is one of the least well-served drug treatments despite the high prevalence, only five therapeutic drugs are availably approved namely memantine, donepezil, galantamine, rivastigmine, and N-methyl-D-aspartate receptor antagonist [7]. Cholinesterase inhibitors (ChEIs) such as donepezil, galantamine and rivastigmine increase acetylcholine at brain synapses and have been proven clinically useful in the treatment [6]. Unfortunately, as AD is a progressive illness, patients treated with symptomatic drugs, such as ChEIs, will continue to decline [8]. A cohort study by Hong Xu found that long-term use of ChEIs is associated with progressive cognitive decline (0.18 MMSE points/year, CI 0.07, 0.28) [9].

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Growth differentiation factor 11, a protein in transforming growth factor-β (TGF-β) superfamily of growth and differentiation factors, came to prominence in recent age-related researches [10]. It is found to decrease with age and progressive illness [11]. Research by Jacob et al., on individuals aged 60 and 75 years and over showed a significant difference in the concentration of GDF11 with age [12]. Interestingly, new findings have proven the regenerative factors of GDF11 in the brain [13], heart [14], skeletal muscle [15], kidney [16], bone [17], and skin [18]. More extensive studies found that the pro-proliferation and differentiation effects of systemically administrated GDF11 elevate the number of neural stem cells, improve vasculature in the subventricular zone and increase neuronal activity markers as well as plasticity in the hippocampus and cortex [19].

This review aims to highlight the therapeutic prospects of GDF11 in the management of Alzheimer's disease.

Material and methods

The review method used is literature review. The literature references are of relevant journals from entrusted search engines PubMed and ScienceDirect with keywords such as "Alzheimer's disease", "angiogenesis", "GDF11" and "neurogenesis". The criteria of inclusion are that of all studies related to GDF11 therapeutics. Studies should be at least 10 years old. From 82 journals that are reviewed, 62 are found to be appropriate as reference for this paper. The evaluated information, analyzed for credibility and reliability, is assembled into one scientific literature review.

Pathophysiology of Alzheimer's disease

The loss of synapses, dendrites and neurons found in AD is of consequence of abnormal amyloid-β in plaques and hyper-phosphorylated-tau in neurofibrillary tangles deposition [20]. These pathological hallmarks have a complex complementary association with the cholinergic lesion as the loss of cortical cholinergic innervation is found to be caused by the neurofibrillary tangles in the nucleus basalis of Meynert (NBM) [21, 22]. There is a long-established relationship between cholinergic abnormalities and amyloid-β pathology [23]. Research in post mortem AD patients has shown "diminishing responsiveness of the acetylcholine-synthesizing enzyme choline acetyltransferase with increasing neurotic plaques" [23]. The cholinergic depletion promotes amyloid-β deposition and tau pathology in paths that correlate to cognitive impairment [24].

Amyloid precursor protein is a single-pass transmembrane protein composed of a large ectodomain consisting of an intramembranous portion with a short intracellular tail and is expressed at high levels in the brain [25, 26]. In the non-amyloidogenic pathway, APP is cleaved by α- and γ-secretases producing neuroprotective solute peptide APPα [27]. However, cleavage via the β- and γ-secretases in the amyloidogenic pathway produces extraneural amyloid-β fragments leading to deposition (Fig. 1) [27, 28]. Furthermore, this notion is also congruent with finding from Dominici et al. which found increased levels of β2 microglobulin in AD patients compared to non-AD MCI and healthy controls (2063 ng/mL ± 852 versus 1613 ± 503 and 1832 ± 382 ng/mL, $p < 0.001$ and < 0.033, respectively) [29].

Deposition of extracellular amyloid-β into insoluble plaques in the brain is associated with the aggregation of protein tau into intracellular neurofibrillary tangles [30]. The decline of neuronal function and subsequent persistent progressive neurodegeneration are caused by the irreversible nature of pathological tau hyperphosphorylation in AD [31]. Increase of tau phosphorylation diminished microtubules affinity resulting in unusual levels of the unbound tau molecules increment [31]. Build-up of pre-tangles is followed by structural rearrangement involving the formation of the characteristic pleated β-sheet structures, subsequently forming neurofibrillary tangles by self-assemble [30–32]. Cytoskeletal microtubules disruption act as the imminent cause of progressive synaptic loss by interfering with axoplasmic as well as dendritic transport [33]. Therefore, starvation of the trophic support cells subsequently manifests as neural death and clinically as cognitive impairment [34].

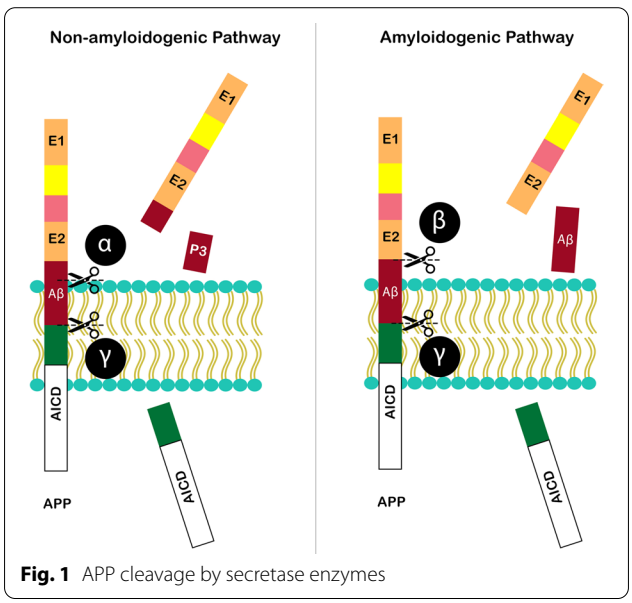

Fig. 1 APP cleavage by secretase enzymes

Signaling cascade of GDF11

The signaling cascade (Fig. 2) is divided into canonical pathway and non-canonical pathway. The difference between these two pathways is the intracellular accumulation of β-catenin and the resulting translocation in the nucleus that regulates the expression of target genes in the canonical pathway. Meanwhile, in the non-canonical pathway, β-catenin-independent fully controls the expression of genes that are not affected by the nucleus [35]. In the canonical pathway, GDF11 signaling utilizes the canonical receptors and the small mothers against decapentaplegic (SMAD) proteins of TGF-β [36, 37]. The GDF11 dimer binds to the Activin Receptors type IIA or IIB (ActRIIA/B), serine/thionine kinase activity protein, and leads to the recruitment and transphosphorylation of Activin-Like Kinase receptors (ALK) 4, 5, or 7 [36, 38]. The transphosphorylated ALK activates the Receptor-regulated SMAD (R-SMAD) 2 and 3 [36, 39, 40]. The co-SMAD, SMAD4, is recruited by the R-SMAD dimer to form a trimeric complex that ultimately translocate to the nucleus to regulate gene expression [41]. In the non-canonical pathway, mitogen-activated protein kinases (MAPKs) are the main non-SMAD pathways activating protein kinase B (AKT) and c-Jun N-terminal kinase (JNK) routes [42]. Transforming growth factor-β-activated kinase 1 (TAK1), also known as MAPKKK7, has been shown to transduce the family via MEK6, a member of the p38 kinase cascade. [43]. The tumor necrosis factor receptor-associated factor (TRAF) 2 or 6 are involved in the activation of the TAK1 complex [43]. Finally, autophosphorylation of TAK1 activates the downstream targets, which include members of the MAPK and nuclear factor kappa B (NF-kB) signaling pathways [44]. Moreover, a study found that microRNA-125b-5p (miR-125b-5p) may play a role in neuroprotection in patient with ischemic stroke mediated by upregulated circularRNA-UCK2 (circUCK2) that was discovered to function as a sponge for miR-125b-5p, boosting the production of GDF11, which decreases neuronal damage and therefore contributes to neuroprotection. The role of miRNA is not directly in signaling the production of GDF11, but circUCK2 is able to inhibit the activity of miR-125b-5p, which increases GDF11 expression. [45]. This is supported by bioinformatics analysis which revealed that GDF11 is the target gene for miR-129-5p [46].

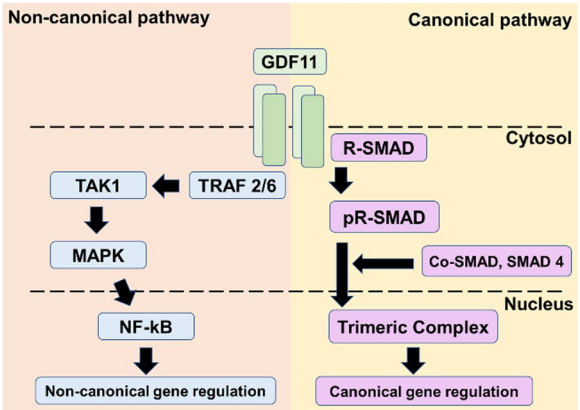

Fig. 2 GDF11 signaling cascade

Recombinant GDF11 neurogenic properties

GDF11, a circulating protein present in the blood of young mammals has been shown to promote vascular remodeling and regeneration, as well as improving cognitive performance and synaptic plasticity in the elder mice [47]. The expression of GDF11 appears to be inversely linked to neurogenesis deterioration with age [48]. GDF11 was shown to be expressed in almost all neurons, astrocytes and ependymal cells in the brain and spinal cord, indicating that it may play a vital role [49].

Only recently that it has been found that GDF11 aids the temporal development of neurogenesis in the developing spinal cord [50]. In the hippocampus and cortex of old mice, GDF11 increased hippocampal neurogenesis and plasticity by increasing the number of neural stem cells and positively affects vasculature in the subventricular zone by exerting rejuvenating effects on brain endothelial cells [19, 49]. Changes in synaptic plasticity and neuron damage, present in AD, have been confirmed in a significant number of trials [51]. Neurons rely heavily on mitochondrial oxidative phosphorylation for energy production [52]. Apoptosis and inflammation are decreased after exogenous injection of rGDF11 as it protects mitochondria from oxidative stress [52, 53]. Production of the proinflammatory cytokine interleukin-18 by microglia was also slowly decreased upon rGDF11 administration, as was interleukin-15. It is found that GDF11 also reduces injuries of white matter and promotes presynaptic plasticity, which directly supports improvement in AD symptoms [12]. A study has found that GDF11 acts by activating central nervous system (CNS) active factors in vitro that induce endothelial cells and neurogenesis. It should be noted that GDF11 cannot penetrate the blood–brain barrier [19].

rGDF11 role in Alzheimer's disease

Zhang et al. found that twice daily treatment with rGDF11 (0.1 mg/kg) improved cognition, had little effect on amyloid, increased vascular endothelial growth factor (VEGF) expression across brain blood vessels, increased blood vessel density and cerebral blood flow, reduced expression of inflammatory proteins (glial fibrillary acidic

protein [GFAP] and ionized calcium-binding adaptor protein [Iba-1]) in the brain, and increased expression of vascular-related proteins in Alzheimer's mice [13]. This hypothesis is also supported by a study conducted by Lu et al., who observed an increase in peri-infarct cortex brain-derived neurotrophic factor (BDNF) in rGDF11 treatment. Significant increases were also observed in the proangiogenic factors Angiotensin-2 and VEGF receptor-2 phosphorylation in stroke-induced mice [57]. With its ability to increase angiogenesis, GDF11 plays a role in increasing cerebral vasculature which plays an important role in neurogenesis. This is evidenced by a study by Ceren, et.al., using mice in the hippocampus area that GDF11 increased blood vessel-occupied area, number of blood vessels, blood vessel branching. This finding was found in middle age-mice aged 22–23 months. In contrast to the 2- to 3-month-old test group that did not show any changes, which indicates that GDF11 exerts a broader influence on CNS function through changes in cerebral vasculature [19]. A similar study was conducted on 8- to 10-month-old rats induced by stroke. Investigation of angiogenesis was carried out 14 days after stroke and found an increase in $BrdU^+/CD31^+$ endothelial cells length and area, as well as significantly increased vascular branches. Tomato-lectin staining showed a similar effect, that the treatment with GDF11 significantly increased lectin-perfused vessel length and area around the peri-infarct cortical area of the test samples [57]. Another similar study also found a significant decrease in $GFAP^+$ cells that decreased astrogliosis and decreased Iba-1^+ cells that inhibit microglia activation. Another marker, $CD31^+$ endothelial cells, has also been detected to have increased levels that support rapid angiogenesis [12]. Other than that, GDF11 therapy can decreased cerebral vascular Aβ in AD model mice. ELISAs for soluble and insoluble levels of Aβ40 and Aβ42 in the brain tissue and plasma show a lower Aβ40/Aβ42 ratio in GDF11-treated mice's brain tissue and plasma. In the same study also explained that gross insoluble Aβ42 was unaffected by western blot of prefrontal cortex tissue. There was also an increase in VEGF expression in the blood vessel walls which decreased plaque and density of Iba^+ microglia cells [13]. Other than that, GDF11 as a molecule that can target vascular degradation, restore age-related loss in neurogenesis, and potentially alleviate cognitive dysfunction can be of great therapeutic value [58].

Experiments on rats by Ma et al., tested neurobehavioral levels through two tests using the modified neurological severity score (mNSS) test and the adhesive removal somatosensory test. Administration of rGDF11 injected on day 7 (first step) and day 14 (second step) showed good manifestations after mice were induced with right middle cerebral artery occlusion/reperfusion (MCAO/R) models. In the same study, phosphor-Smad2/3 and CD31 + levels were also tested and it was concluded that angiogenesis affects neuro behavioral prognostic improvement [59]. An experiment by Zhang et al., using mice, found that there was an increase in phosphorylated-Smad2/3 (phosphor-Smad2/3) in both the young age (1.5 months of age) and middle age (9 months of age). Immunofluorescence was performed on all three brain sections; cortex, dentate gyrus, and thalamus. There was a significant increase in the concentration of phospho-Smad2/3 in young age mice compared to the middle age group in rGDF11 treatment, which makes the therapeutic effect of rGDF11 promising as a preventive modality of AD [55, 60]. A study also found that GDF11 regulation could improve cognitive function and cerebrovascular function as a treatment in cerebral amyloid angiopathy (CAA) which is present in more than 90% of patients with AD. Intravenous administration of rGDF11 also enhances angiogenesis (marked by a significant increase in expression of the endothelial cell marker $CD31^+$) in mice with AD complicated by CAA as seen by increased expression of VGEF/VGEFR, CD31, Collagen IV, and laminin [13]. Moreover, similar study reported that mice subject also showed decreased glial activation accompanied by a decrease in the ratio of A40/42 in brain parenchyma and lower expression of inflammation markers in the vasculature [61]. Another study using the same population setting was also found that GDF11 regulation associated with a lower damaged in intima and organelles in endothelial cells, such as mitochondria via VEGF pathway that serve a role in mediating specific cell death pathways [62].

Several studies targeting a variety of enzymes for the development of novel medicines to treat Alzheimer's disease have recently begun. In recent decades, there has been a growing emphasis on discovering new putative and unique protein or enzymatic targets for Alzheimer's disease with promising result. Some in vivo studies found that protein-based targeting such as GDF11 has shown a large benefit on Alzheimer's including effect on neurogenesis, angiogenesis, brain perfusion, and cognitive function (Table 1). These results are achieved through the injection of GDF11 protein or receptor; or even by regulating protein transcription and translation using miRNA than mRNA. Based on previous evidence, GDF11 could be a novel therapeutic target protein for humans that focused as curative than preventive intervention. However, this approach is generally not to be administered as a monotherapy because of the complex and multi-faceted pathophysiology of Alzheimer's. Moreover, this kind of approach could be permanent and lifelong because it involves continuous drug administration to get optimal results and prevent disease recurrence. Studies and

Table 1 In vivo studies of GDF11

Dosage	Time	Sample	Results	
40 ng/mL	6 days	15-month-old mice	Brain cells neurogenesis and angiogenesis	[54]
1 mg/kg	28 days	22-month-old mice	Neural activation and angiogenesis	[19]
0.1 mg/kg	1 day	9-month-old mice	Neurogenesis and increase short-term memory	[55]
40 ng/mL	1 day	–	Cell migration and angiogenesis	[56]
0.1 mg/kg	13 days	10-week-old mice	Elevated neuronal precursor cells, microvascular length and area, and brain capillary perfusion	[57]
0.1 mg/kg	28 days	12-month-old mice	Rejuvenated cognitive function, angiogenesis and elevate Aβ burden	[13]

research are still needed to develop this method, including drug dosage, duration of therapy, presence or absence of mutation effects, and possible polypharmacy effects, as well as the costs required.

Conclusion

In our study, based on the reviews of several journals, recombinant GDF11 can be utilized to rejuvenate normal cognitive function of Alzheimer's patients' brains through its pro-neurogenesis and pro-angiogenesis properties. Moreover, its potential in maintaining the stability of neural progenitors makes rGDF11 act as a curative as well as a secondary preventive for neuronal damage in the brain. These results provide promising results for rGDF11 as AD therapy.

Abbreviations

AD: Alzheimer's disease; Aβ: Beta-amyloid; GDF11: Growth differentiation factor 11; rGDF11: Recombinant GDF11; Aβ1-42: 42-Amino-acid amyloid-beta; APP: Amyloid precursor protein; MAPT: Microtubule-Associated Protein Tau; FDA: Food and Drug Administration; ChEIs: Cholinesterase inhibitors; TGF-β: Transforming growth factor-β; NBM: Nucleus basalis of Meynert; SMAD: Small mothers against decapentaplegic; ActRIIA/B: Activin Receptors type IIA or IIB; ALK: Activin-like kinase receptors; MAPKs: Mitogen-activated protein kinases; AKT: Protein kinase B; JNK: C-Jun N-terminal kinase; TAK1: Transforming growth factor-β-activated kinase 1; TRAF: Tumor necrosis factor receptor-associated factor; NF-kB: Nuclear factor kappa B; miR-125b-5p: MicroRNA-125b-5p; circUCK2: CircularRNA-UCK2; CNS: Central nervous system; VEGF: Vascular endothelial growth factor; GFAP: Glial fibrillary acidic protein; Iba-1: Ionized calcium-binding adaptor protein; BDNF: Brain-derived neurotrophic factor; mNSS: Modified neurological severity score; MCAO/R: Middle cerebral artery occlusion/reperfusion; phosphor-Smad2/3: Phosphorylated-Smad2/3; CAA: Cerebral amyloid angiopathy.

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BGL and WH contributed to literature mining and manuscript writing. IPEW supervised the project and edited the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Consent for publication

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Competing interests

There is no conflict of interest.

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