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Review article

Glycative stress and anti-aging: 12. Glycative stress and dementia

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Abstract

As of 2010, the number of dementia patients aged 60 and over is estimated to be 35.56 million worldwide. Also, the number of dementia patients aged 65 and over in Japan was estimated to be 4.62 million in 2012. The number of dementia patients in Japan continues to increase, reaching 8.02 million in 2030 and is estimated to afflict more than 1 person in 5 people (20.7% prevalence rate) aged 65 and above. Dementia indicates a state of decline in the persistence of normal cognitive function due to acquired brain damage, which hinders daily life and social life and refers to symptoms that are observed when there is no loss of consciousness. Dementia is classified into four types: Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy bodies (DLB), and dementia due to other diseases. Among these, AD is the direct cause of more than 60% of dementia cases. AD symptoms include "Mild cognitive impairment (MCI)" and "Behavioral and psychological symptoms of dementia (BPSD)". Glycation may be involved in the onset and progression of dementia from the perspective of protein denaturation and enhanced crosslinking due to the formation of AGEs and RAGE-mediated induction of inflammation. Incidence of MCI is observed to be high in people with significant accumulation of AGEs in the skin. The prevalence of dementia is known to be more among diabetic patients. The neuropathological characteristics of an AD patient's brain include senile plaques. The senile plaques are composed of amyloid-β protein (Aβ). Aβ forms AGEs and aggregates in the presence of glucose. The Aβ AGE formation may be related as a factor promoting the formation of protein crosslinks and aggregation of Aβ. Pentosidine, CML, and RAGE (receptor for AGEs) are found in the microglia and astrocytes present in the brain of AD patients, and the levels are elevated compared to healthy elderly people. Generation and accumulation of AGEs associated with the accumulation of Aβ and senile plaques in the brain induce inflammation and apoptosis through Aβ neurotoxicity and RAGE and are presumed to be involved in the promotion and enhancement of neuronal cell death, which is a pathological condition of AD.

***KEY WORDS*:** dementia, Alzheimer's disease, mild cognitive impairment (MCI), amyloid-β protein, advanced glycation end products (AGEs)

1. Introduction: Dementia and Alzheimer's Disease

As of 2010, the number of dementia patients aged 60 and over is estimated to be 35.56 million (4.7% prevalence) worldwide [1]. The number of people with dementia is expected to increase to 65.69 million by 2030. In Japan, the number of dementia patients aged 65 and over in Japan was estimated to be 4.62 million (15.0% prevalence) in 2012 [2]. If the prevalence rate of dementia in each age group is assumed to remain constant after 2012, dementia patients will continue to increase thereafter, reaching 6.75 million in 2025 (18.5% prevalence) and 8.02 million in 2030 (20.7% prevalence) and it is estimated that more than 1 person in 5 people aged 65 and above will be a dementia patient.

Dementia indicates a state of decline in the persistence of normal cognitive function due to acquired brain damage, which hinders daily life and social life, and refers to symptoms that are observed when there is no loss of consciousness [3]. According to the 10th edition of the International Classification of Diseases (ICD-10) by the World Health Organization (WHO), dementia is said to be "usually caused by chronic or progressive brain disease, and is a syndrome arising from the dysfunction of memory, thought, orientation, understanding, computation, learning, language, judgment and many other higher brain functions". Dementia is classified into four types: Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy bodies (DLB), and dementia due to other diseases.

According to a survey conducted in Ama town, Shimane

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Prefecture, dementia was observed in 104 out of 943 people aged 65 or above [4]. The types were AD 63.5%, VD 15.4%, DLB 4.8%, Parkinson's disease dementia (PDD) 6.7%, Progressive supranuclear palsy (PSP) 1.9%, and Frontotemporal lobar degeneration (FTLD) 0.96%, where AD was a direct cause accounting for more than 60% of the dementia cases.

AD symptoms include "Mild cognitive impairment (MCI)" and "Behavioral and psychological symptoms of dementia (BPSD)". The symptoms of MCI are memory disturbance, disorientation, impaired judgment, aphasia, apraxia and agnosia, together referred to as the core symptoms. BPSD includes excitement, yelling, restlessness, uneasiness, jealousy, socio-culturally inappropriate behavior, sexual disinhibition, collectomania, swearing, stalking, anxiety, depression, delusions, and hallucinations. BPSD can be divided into positive symptoms such as excitement, easy stimulability, impatience, hallucinations, and delusions, and negative symptoms such as apathy, indifference, and depression. About 60 to 90% of dementia patients have multiple BPSD symptoms, and they commonly have indifference, excitement, irritability, and depression [5].

As a neuropathological feature of AD, atrophy is observed in the hippocampus and the cerebral cortex in the brain, and neuronal loss, senile plaques and neurofibrillary tangle (NFT) deposition are extensively observed microscopically [6]. The electron microscope image of NFT is a unique fiber bundle called paired helical filament (PHF). Amyloid β protein (Aβ) and hyperphosphorylated tau protein are identified as the main structural components of senile plaques and PHF. Tau protein is a protein bound to microtubules with a molecular weight of about 50,000 that are present in the nerve axon and has the function of promoting and stabilizing the polymerization of microtubules. Microtubules form a cytoskeleton and function as a transport rail for intracellular proteins and intracellular organelles. Phosphorylation of tau protein causes destabilization of microtubules, leading to a decline in the intracellular transport mechanism.

Senile plaques, which are the deposition sites of Aβ, are more specific to AD than NFT. Diffuse plaques, which are mainly characterized by non-fibrous Aβ deposition, are the lesions identified at the earliest stage of the AD brain. Also, in the familial AD of the autosomal dominant inheritance form, point mutations and duplications of the Aβ Amyloid precursor (Amyloid precursor protein (APP)) are associated with the disease. Polymerized Aβ aggregates (amyloid-β aggregates) have neurotoxicity. These characteristics suggest that deposition of Aβ in the brain takes place before the phosphorylation of tau protein in the onset of AD and is closely associated with the pathogenesis of AD. The onset mechanism theory of AD that focuses on Aβ is called the "Amyloid cascade hypothesis" [7].

AD patients have reduced choline acetyltransferase (ChAT) activity in the cerebral cortex compared with the normal control group. The cerebral cortex ChAT activity of AD patients is correlated with the global cognitive score. In AD, a remarkable loss in cholinergic neurons is observed in the nucleus basalis of Meynert (NBM) of the basal forebrain, and there is a disorder in the cholinergic neural pathways that project from the central nervous system cells present in the basal forebrain to the cerebral cortex and hippocampus. Acetylcholinesterase (AChE) inhibitors and nicotine stimulate acetylcholine neurotransmission in the brain. The administration of atropine and scopolamine blocks acetylcholine neurotransmission in the brain and affects learning and memory behavior. These facts suggest that the dysfunction of cholinergic nerves is closely related to the cognitive function, including learning and memory. The theory on the pathogenesis of AD due to failure in the production of acetylcholine is called "Cholinergic hypothesis" [8].

On the other hand, observations suggest that the deposition of senile plaques in AD patients is not correlated with neuronal loss. Based on these findings, one theory considers tau protein as the main causative agent of dementia, and disappearance of tau protein, which is a microtubule stabilizing factor, and formation of PHF in the axons of neurons to form NFT causing the degeneration of the cytoskeleton to be the pathogenesis of dementia. This theory on the pathogenesis of AD is called "Tau hypothesis" [9,10]. Which occurs first, hyperphosphorylation of tau protein or formation of PHF, is still under debate.

Glycation may be involved in the onset and progression of dementia from the perspective of protein denaturation and enhanced crosslinking due to the formation of advanced glycation end products (AGEs) and RAGE-mediated induction of inflammation [11]. As a result of measuring the levels of accumulated AGEs in the skin of 226 subjects who underwent anti-aging medical examination using AGE Reader, subjects with a measurement value of 2.27 or more are observed to have a higher occurrence of MCI than those with lesser values (***Fig. 1***) [12].

2. Alzheimer's Disease and Diabetes

The complications of diabetes include neuropathy, retinopathy, nephropathy, and cardiovascular disease. The incidence of dementia is known to be high among diabetic patients (***Fig. 2***) [13]. A large-scale epidemiological study by the University of Rotterdam (The Rotterdam Study) examined the relationship between dementia and diabetes among 6,370 people (692 patients with type-2 diabetes (T2DM) and 5,678 non-diabetic patients) with an average age of 55 and older [14]. The findings of the study showed that 126 people (2.0%) developed dementia, out of which 27.0% had T2DM. Among the 126 patients with dementia, 89 (70.6%) had AD, and of the 6,244 patients who did not develop dementia, 10.5% had T2DM. The risk of AD for patients with T2DM was estimated to be 1.9 times higher compared to non-diabetic patients.

In Hisayama, Fukuoka Prefecture, a survey was conducted for 232 people without dementia (153 women and 79 men) aged 60 and older regarding the relationship between glucose metabolic capacity and dementia [15]. In this survey, research was conducted on the relationship between glucose metabolic capacity and the onset of dementia using the 75 g oral glucose tolerance test (OGTT). When the normal glucose tolerance group (control) was set to 1.0 (n = 115), the impaired fasting glycemia group was 0.63 (n = 13), the impaired glucose tolerance group was 1.35 (n = 63), and the diabetes group was 1.74 (n = 41), and the lower the glucose metabolic capacity, the higher was the risk of dementia (after adjustment for gender and age). The involvement of diabetes

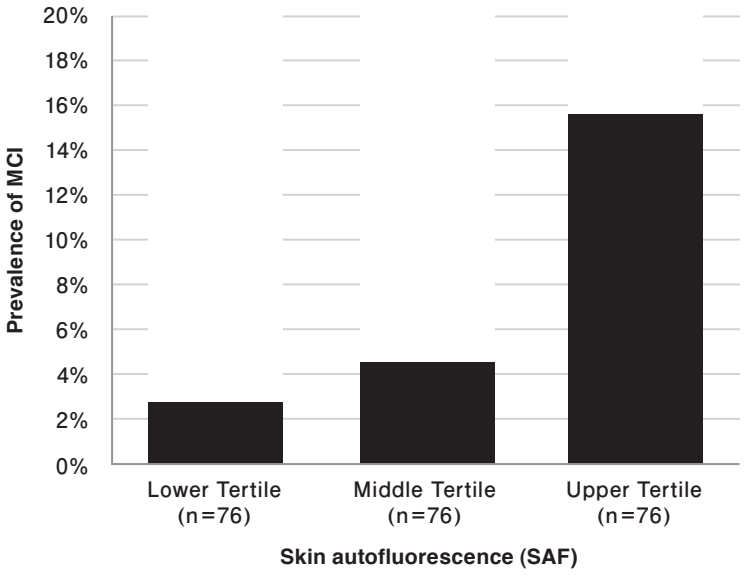

Fig. 1.

Analysis of MCI prevalence by participant's profile index.

Prevalence of MCI is analyzed using the tertile method (n = 226); Existence of MCI, SAF ≥ 2.27, odds ratio 6.402; 95%Cl, 1.590 – 25.773, p = 0.009. The figure is adapted from Reference 12. MCI, mild cognitive impairment; SAF, skin autofluorescence measured AGE Reader; 95%Cl, 95 % confidence interval.

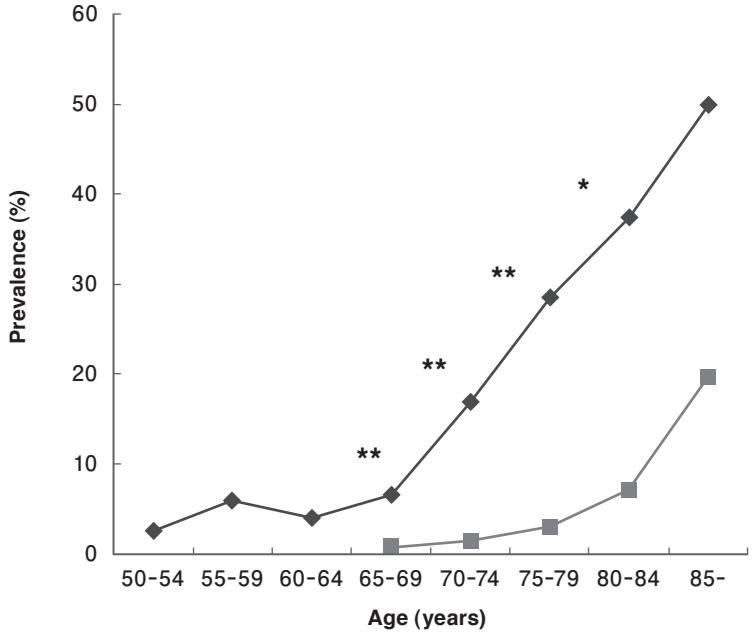

Fig. 2.

Prevalence of dementia in diabetes.

◆, diabetes; ■, ordinary subjects; *, $p < 0.01$; **, $p < 0.001$, compared with ordinary subjects within each age category. The figure is adapted from Reference 13.

and glucose metabolic capacity, especially postprandial hyperglycemia in the onset of dementia has also been reported from other surveys [13].

3. Alzheimer's Disease and AGEs

The neuropathological characteristics of an AD patient's brain include brain atrophy, senile plaques, and neurofibrillary tangles. Senile plaques are composed of Aβ. Aβ is a peptide (Aβ40, Aβ42) composed of around 40 amino acids having a molecular weight of 4,300 to 4,500. Aβ is a cleavage product of the amyloid-β protein precursor (APP) formed by the action of β- and γ-secretase. In AD, Aβ clumps together to form insoluble fibers and gets deposited.

Aβ is glycated and formed into AGEs (AGE-Aβ) when incubated in the presence of glucose. The Aβ amino acid sequence has lysine residues (Lys; K) at the 16th and 28th sites, and arginine residues (Arg; R) at the 5th site, and these amino acid sequence sites are involved in glycation. Also, AGE-Aβ may be contributing as a "seed" to accelerate the aggregation of Aβ since Aβ clumps together when incubated in the presence of glucose [16].

The amount of AGEs in the frontal lobe tissue proteins having senile plaques has been reported to be three times more in AD patients as compared to healthy elderly people [17]. On the other hand, adding aminoguanidine, a glycation reaction inhibitor, to the Aβ-glucose reaction system and then incubating, suppressed the formation of Aβ aggregates [17]. The presence of AGEs such as pentosidine, pyrraline and CML (N^{ε}-carboxymethyl lysine) has been observed in senile plaques [18, 19]. Aβ-AGE formation by glycation may be related as a factor promoting the formation of protein crosslinks and aggregation of Aβ.

The tau protein in PHF that is obtained from the brain of an AD patient is converted into AGEs. On the other hand, the soluble tau protein obtained from the brain of a non-AD patient or the brain of a person without dementia is not converted into AGEs. There are 13 lysine residues in the

amino acid sequence of tau protein, and it is reported that 6 of them have been glycated [19]. Since the glycation site of tau protein corresponds to the binding site for microtubules, the binding function gets impaired. The glycated tau protein induces oxidative stress such as active oxygen and IL-6 and causes damage to neuronal functions [20].

Through an *in vitro* experimental setup of tau protein, it has been shown that glycated tau protein forms PHF-like fibers, and non-glycated tau proteins do not form fibers [21]. In PHF, AGEs such as pentosidine, pyrraline and CML are observed. Glycated tau protein induces the formation of APP and Aβ. The intracellular transportability of cells reduces due to phosphorylation and glycation of tau protein, making extracellular secretion of APP impossible. This results in the accumulation of APP inside the cells. Glycation of Aβ and tau protein facilitates the deposition and aggregation of Aβ and accelerates the deposition of tau protein at the same time.

Pentosidine, CML, and RAGE, which is a receptor for AGEs, are found in the microglia and astrocytes present in the brain of AD patients, and have elevated levels as compared to healthy elderly people [22, 23]. Microglia, which is also referred to as resident macrophages, are a type of cell present in the central nervous system having functions such as removal or repair of neurons. Activation of microglia is linked to the production of inflammatory cytokines such as tumor necrosis factor (TNFα), interleukin (IL)-1β and interferon (IFN) and may cause damage to neurons [24]. Astrocytes are star-shaped glial cells specifically present in the brain and spinal cord, which maintain the functions of the central nervous system such as regulating blood flow, supplying energy to neurons, involvement in synaptic functions and regulating neurotransmitters [25]. When chicken egg albumin-AGE is added to cultured microglia cells, RAGE-mediated production of nitric oxide (NO), IL-6, TNF-α, through RAGE is observed [26].

In experiments where various AGEs were added to culture systems of rat cortical neuronal cells, it is observed that apoptosis is more strongly induced in glyceraldehyde-derived AGEs than Amadori products, glycolaldehyde-derived AGEs, methylglyoxal-derived AGEs and glyoxal-derived AGEs [27]. On the other hand, CML and CEL did not induce cell death. These results show that the generation and accumulation of AGEs associated with the accumulation of Aβ and senile plaques in the brain induces Aβ neurotoxicity and RAGE-mediated inflammation and apoptosis, and is presumed to be involved in the promotion and enhancement of neuronal cell death, which is a pathological condition of AD (***Fig. 3***) [28, 29].

Conflict of Interest Statement

The authors claim no conflict of interest in this study.

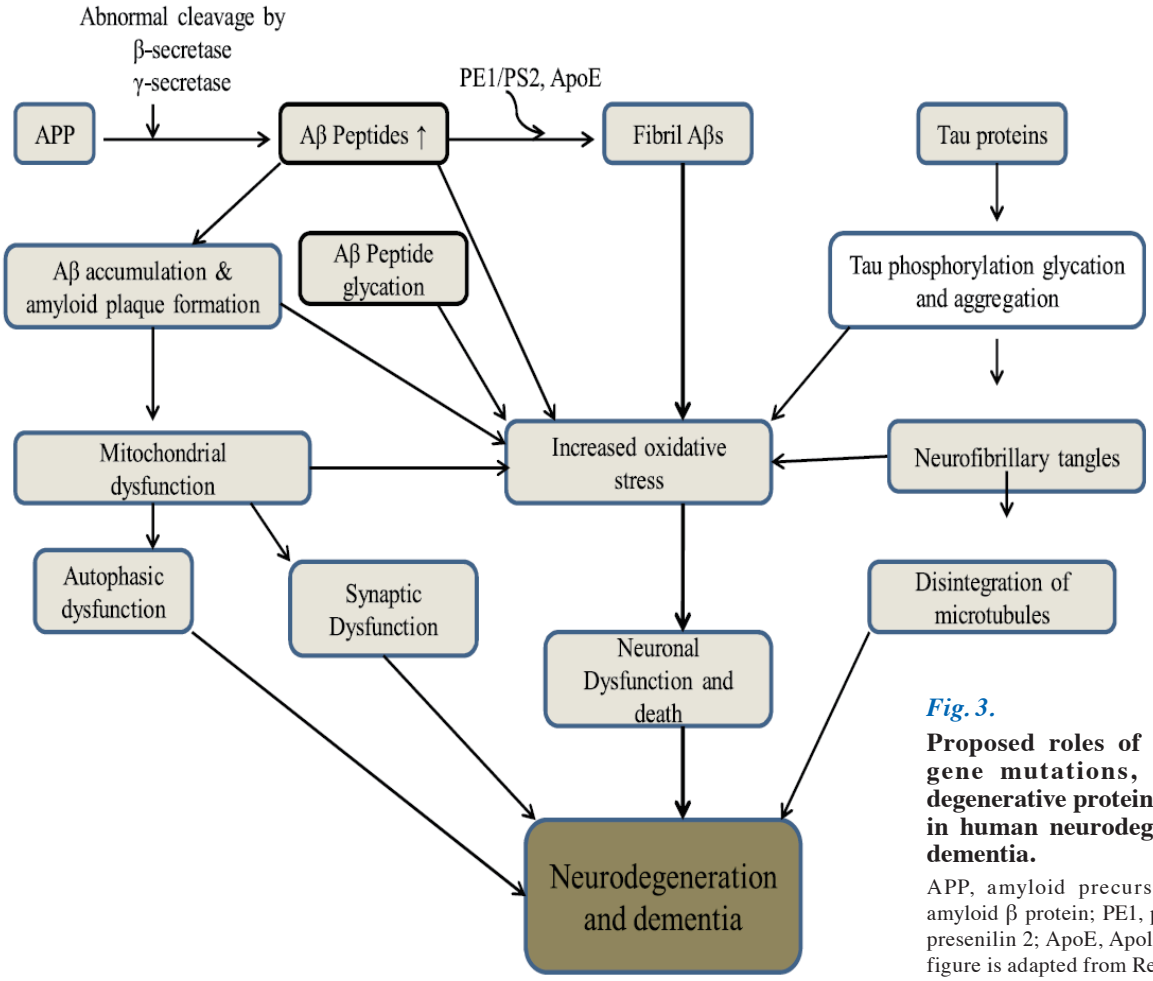

Fig. 3.

Proposed roles of APP, specific gene mutations, and various degenerative protein modifications in human neurodegeneration and dementia.

APP, amyloid precursor protein; Aβ, amyloid β protein; PE1, presenilin 1; PS2, presenilin 2; ApoE, Apolipoprotein E. The figure is adapted from Reference 28.

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