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REVIEW

Periodontal Disease and Periodontal Disease-Related Bacteria Involved in the Pathogenesis of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia, and it exhibits pathological properties such as deposition of extracellular amyloid β (Aβ) and abnormally phosphorylated Tau in nerve cells and a decrease of synapses. Conventionally, drugs targeting Aβ and its related molecules have been developed on the basis of the amyloid cascade hypothesis, but sufficient effects on the disease have not been obtained in past clinical trials. On the other hand, it has been pointed out that chronic inflammation and microbial infection in the brain may be involved in the pathogenesis of AD. Recently, attention has been focused on the relationship between the periodontopathic bacterium *Porphylomonas gingivalis* and AD. *P. gingivalis* and its toxins have been detected in autopsy brain tissues from patients with AD. In addition, pathological conditions of AD are formed or exacerbated in mice infected with *P. gingivalis*. Compounds that target the toxins of *P. gingivalis* ameliorate the pathogenesis of AD triggered by *P. gingivalis* infection. These findings indicate that the pathological condition of AD may be regulated by controlling the bacteria in the oral cavity and the body. In the current aging society, the importance of oral and periodontal care for preventing the onset of AD will increase.

Keywords: *Porphylomonas gingivalis*, cognitive decline, amyloid β, blood-brain barrier, vascular inflammation

Introduction

Dementia is the most frequent neurological disease in the world and is recognized as a global public health priority by the World Health Organization. Although various methods for prevention and treatment of dementia have yet been studied, no effective method has been established. If risk factors for dementia and factors that suppress its onset and progression could be identified that information could be used effectively, it might be possible to prevent dementia and extend the healthy life span. Recently, the associations between dementia and systemic diseases have been focused on. The pathogenesis of Alzheimer's disease (AD), which accounts for the largest number of cases of dementia, and the relationships of the pathogenesis of AD with periodontitis and periodontitis-related bacteria are described in this review.

Alzheimer's Disease

It is estimated that about 44 million people worldwide are currently suffering from dementia. Treatment costs exceed US $600 billion annually in the United States

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alone. Due to the aging of the population, treatment costs are expected to more than triple by 2050. Dementia is a generic term for diseases that make social life difficult due to impairment of cognitive function. AD is a typical disease, but there are other types of disease such as cerebrovascular dementia, Lewy body dementia, and frontotemporal dementia. AD, the most common form of dementia, was first reported by Dr. Aloysius Alzheimer in Germany in 1907.[1] The brain of a female patient who had severe memory loss was analyzed after death. As a result of contraction of the brain, there was abnormal deposition of protein around brain neurons, and this disease was named AD. It has been reported that about 27 million people worldwide suffer from AD.

Late-onset AD may be caused by the complex interaction of genetic and environmental factors. Currently, genetic factors are considered to account for about 70% of the risk for AD, and the APOE gene, which has three variants (ε2, ε3 and ε4) is the greatest risk for sporadic AD. Compared to non-ε4 carriers, the odds ratios (ORs) for AD are up to 3-times higher in carriers of ε4 heterozygotes and up to 12-times higher in carriers ofε4 homozygotes. Previous genome-wide association studies have revealed over 20 genetic risk factors for AD including inflammation, cholesterol metabolism, and endosomal vesicle recycling pathways.[2] In particular, microglial activation by amyloid deposition plays an important role in the pathogenesis of AD. The combination of these factors is thought to significantly increase the risk of AD. The results of epidemiological studies suggest that education and exercise may be effective for preventing AD. Middle-aged hypertension and diabetes also increase the risk of AD.[3] Risk factors for vascular disease or vascular disease itself may also directly affect the progression of AD pathology.

The main features of Alzheimer's pathology are the formation of amyloid plaques[4] and formation of neurofibrillary tangles (NFTs)[5]. In these pathological processes, loss of synapses and neurons leading to macroscopic atrophy is observed.[6] Amyloid plaques are extracellular deposits composed mainly of misfolded Amyloid β (Aβ) (Aβ40 and Aβ42) with 40 or 42 amino acids that are two byproducts of APP metabolism. Aβ42 is more abundant than Aβ40 in plaques because of its rapid infiltration rate and insolubility. Neurofibrillary tangles are mainly observed as hyperphosphorylated tau paired helical filaments. Although the clinical features and severity of AD correlate well with NFT pathology, β-amyloid deposition reaches a plateau early in the symptomatic phase of AD. The amyloid hypothesis is a general theory of AD pathogenesis.[4] Specifically, accumulation of Aβ caused by sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretase enzymes in the brain is caused by an imbalance between Aβ production and its clearance. It is believed that inflammation enhances the formation of NFTs and subsequent neurological dysfunction and neurodegeneration.[7] Therapy that can cure AD does not exist. As drug therapy, acetylcholine esterase inhibitors (AChEI) (donepezil, galantamine and rivastigmine)[8] and an N-Methyl-D-aspartate (NMDA) receptor antagonist (memantine)[9] are used. However, the effects of these drugs are limited, and even if there is a temporary improvement with drug treatment, after several years, patients return to the state they were in when they started taking the drugs and they will progress in the direction of deterioration. Clinical trials of AD drug candidates are currently being conducted worldwide, but their results have not been good. Although many candidate drugs target Aβ, sufficient efficacy and safety have not been confirmed in most cases.[10] According to the results of the Dominant Inherited Alzheimer Network (DIAN) Study, a follow-up study of families who developed dominantly inherited AD, there was accumulation of Aβ from 25 years before the onset of AD and hippocampal volume started to decrease 15 years before the onset of AD. Five years before the onset, the accumulation of Aβ peaks and then accumulation of tau in neurons and volume reduction of the hippocampus progress, and "light forgetting" comes to be recognized. When cognitive function decline begins, it progresses rapidly and it will be in need of care five years after the onset. AD is a disease that progresses over a long span of 25 years or more, and at the time of onset, hippocampal atrophy has already progressed. Once AD has developed, it is difficult to treat and it is therefore considered to be very important to prevent and delay the progression.

Alzheimer's Disease and Inflammation

There is a belief that brain inflammation is involved in the pathogenesis of AD. In autopsy brains from Alzheimer's patients, accumulation of activated microglia is seen around senile plaques.[7] In addition, it has been reported that the risk of AD is reduced to about one-sixth in rheumatoid patients who have been taking NASIDs for

a long time.[11] Inflammation in the brain enhances Aβ accumulation.[12] In addition, deposition of Aβ induces an inflammatory response, which results in synaptic damage and neuronal damage.[13] Recently, mutations in the TREM2 gene, which is one of the molecules that control the inflammatory response, have been found in patients with AD, and the importance of the inflammatory response in the pathogenesis of AD has been re-recognized.[10] The immune system in the central nervous system is extremely simple, there is no acquired immune system, and the immune response is carried by the innate immune system. Microglia are resident macrophages in the CNS.[14] Microglia remain dormant when the microenvironment in the brain is stable and maintain normal CNS function.[15] When a change in the microenvironment occurs, microglia change to an activated state and perform pruning of synapses and removal of foreign substances.[16–18] In addition, microglia form an immune surveillance system in the brain that regulates key processes associated with AD pathology such as clearance of Aβ and aberrant tau protein and production of neurotrophic and neuroinflammatory factors. The activated microglia show changes in cell morphology and phenotype[19,20] and have high productivity for cytokines and inflammatory mediators. Substances that contribute to CNS infection and various neuroinflammations are involved in the activation of microglia. Bacterial lipopolysaccharide (LPS)[21] and Aβ[22,23] are activators of microglia. The activated microglia have

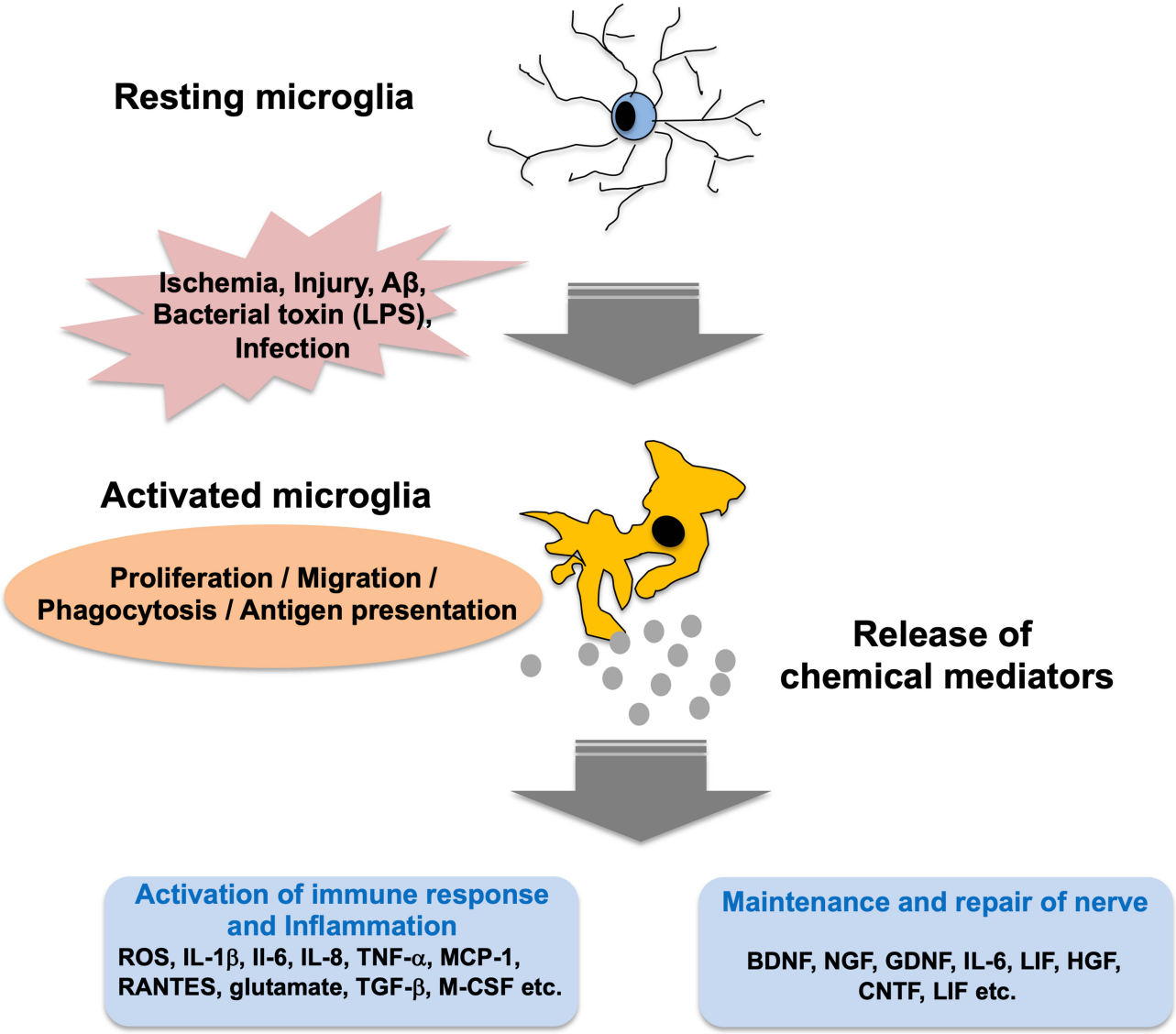

Figure 1 Activation of microglia and its role.

proliferative ability and enhance the ability of phagocytosis and antigen presentation, thereby removing damaged nerve cells in the lesion site. Activated microglia also releases various humoral factors including cytokines, chemokines, and BDNF to repair nerves. On the other hand, excessive release of these factors causes neuropathy.[24,25] In fact, it has been observed that active microglia accumulate in lesions of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Thus, microglia may be deeply involved in the pathogenesis of AD (Figure 1). It has been reported that mild systemic inflammation reduces cognitive function and decreases hippocampal capacity and that systemic inflammation increases the risk of AD.[26–28] Tumor necrosis factor (TNF)-α levels in blood are elevated in patients with AD and are also correlated with the decline in cognitive function.[29,30] LPS increases the saturable transport of insulin across the blood-brain barrier (BBB).[31] TNF-α increases the permeability of the BBB through inducing reorganization of actin filaments to stress fibers, leading to increased paracellular clearance of sucrose and inulin.[32] It is possible that these inflammatory mediators are transmitted to the brain and activate microglia in the brain.

Periodontal Disease, Periodontal Disease-Related Bacteria and AD

Correlations of the number of possessed teeth and the presence or absence of periodontal disease with cognitive function and AD have been reported. People with edentulous jaws and those with few teeth have a higher prevalence and incidence of dementia.[33] In addition, the results of a meta-analysis showed that there were significant correlations between dementia and various clinical parameters of periodontal disease such as periodontal probing depth (PPD), bleeding on probing (BOP), gingival bleeding index (GBI), clinical attachment level (CAL), and plaque index (PI).[33] After 10 years of follow-up of periodontal patients and healthy volunteers over 50 years of age, it was shown that periodontal disease patients have a 1.7-times higher risk of developing AD than do healthy people.[34] In addition, it has been reported that periodontal disease sufferers have a faster rate of decline in cognitive function than do healthy people.[35] Chronic inflammation in peripheral organs can exacerbate the molecular pathology of AD. Periodontal disease is also a chronic inflammatory disease and is involved in the development and progression of various diseases such as arteriosclerosis and diabetes as well as obesity, preterm birth and low birth weight childbirth.[36] Inflammatory cytokines including interleukin (IL)-1β, IL-6, and TNF-α are elevated in peripheral blood in periodontitis patients, and these inflammatory mediators may exacerbate cerebral inflammation in AD.

Differences in gut microbiota have been shown to be associated with lifestyle-related diseases such as obesity, cardiovascular disease, and diabetes.[37–40] Recently, an association between the gut microbiome and dementia has been confirmed,[41,42] and the gut microbiome may regulate host brain function through the microbiome–gut–brain axis.[43] Specifically, brain inflammation is caused by changes in gut microbiota,[44] which can cause deposition of amyloid β in the brain.[45,46] Therefore, enterobacteria may be involved in the pathogenesis of Alzheimer's disease. Saji et al reported that different compositions of gut microbiota were found in patients with dementia and those without dementia. Briefly, the proportion of enterotype I bacteria in the gut flora from patients with dementia was lower than that in the gut flora from patients without dementia.[47] Intestinal Bacteroides species are increased in gut microbiota in patients with mild cognitive impairment (MCI). In addition, white matter hyperintensity and parahippocampal atrophy were seen in patients with a large number of Bacteroides species.[48] These findings suggested that an increase of specific gut bacteria is involved in the pathogenesis of dementia.

It has been reported that some microorganisms were detected in autopsy brains of AD patients. HSV1, *Chlamydia pneumoni*e, spirochetes, and fungi have been reported, and these microorganisms cause brain inflammation that results in synaptic dysfunction and neuronal cell death.[49–51] In order to enclose the invading microbes in the brain, amyloid β (Aβ) is secreted from neurons and has been shown to fold and kill pathogens and protect the brain.[52,53] Thus, Aβ may function as an innate immune molecule responsible for infection in the brain. On the other hand, it is thought that Aβ-containing microorganisms are deposited in brain tissue, resulting in the formation of senile plaques that cause damage to cranial nerves and exacerbate the condition of AD.[54] In addition to these bacteria, it is thought that several periodontal pathogens such as *Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Tannerella forsythensis*, and *Eikenella corrodens* are involved in the development of several inflammatory diseases at remote organ sites like AD.[55] Especially, the association between

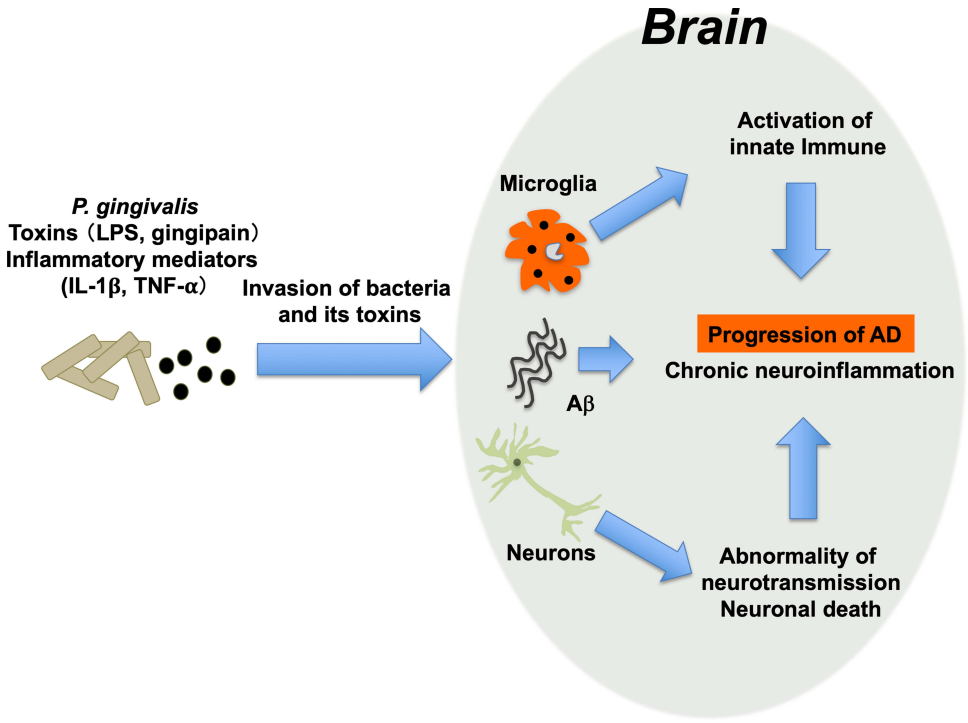

Figure 2 Possible mechanisms by which periodontal disease and *P. gingivalis* aggravate Alzheimer's disease.

Porphyromonas gingivalis and AD has attracted attention.[56,57] *P. gingivalis*, a type of periodontitis-related bacteria, was frequently detected in autopsy brain tissues of patients who died of AD. On the other hand, the bacteria were not detected in normal human brain tissue.[58] Recently, it has also been reported that gingipain, a toxin produced by

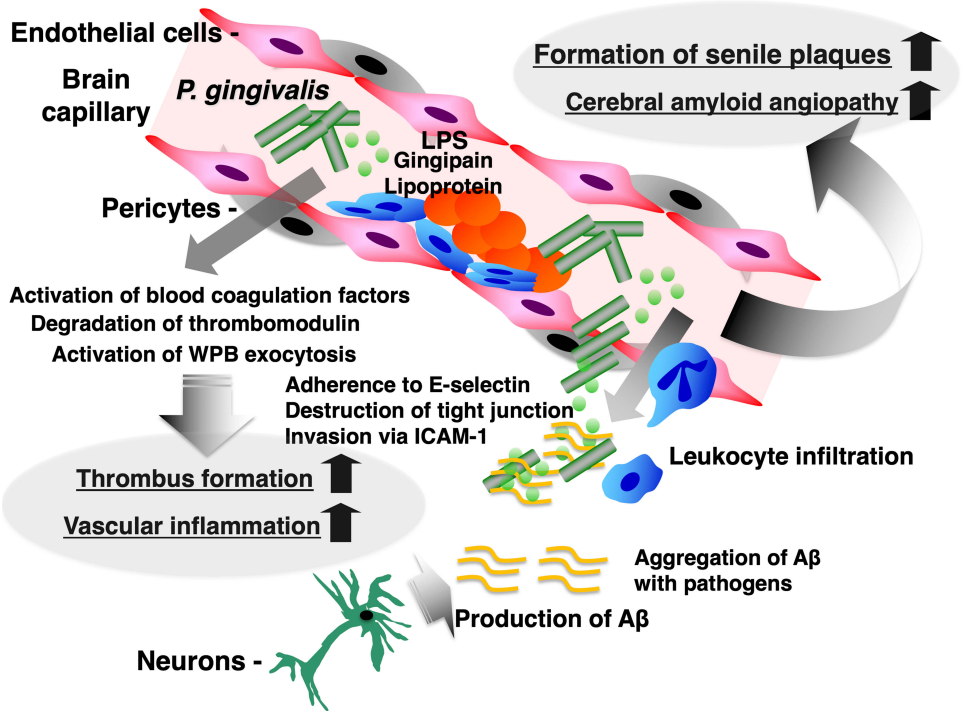

Figure 3 Induction of blood–brain barrier breakdown and amyloid deposition by *P. gingivalis* in cerebral blood capillaries.

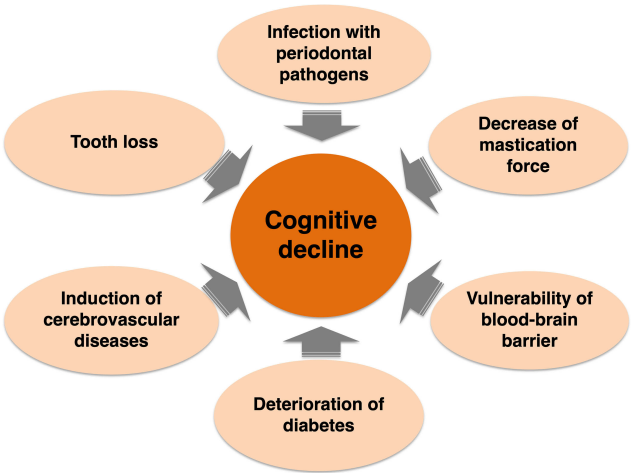

Figure 4 Deterioration of cognitive function caused by periodontal disease.

the same bacteria, was frequently detected in the brains of patients with AD and it has been shown by using a mouse model that the toxin may be involved in the pathogenesis of AD.[59] We administered *P. gingivalis* directly into the oral cavities of AD model mice (APP-Tg mice) to cause experimental periodontitis, and then we conducted a novel object recognition test to evaluate the cognitive functions in the *P. gingivalis* administration group and non-administration group.[60] We found that cognitive function in the *P. gingivalis* administration group was significantly reduced compared to that in the non-administration group. In addition, increased Aβ deposition, increased TNF-α and IL-1β production, and an increase in LPS concentration in the brain were found in the *P. gingivalis* administration group, compared to those in the non-administration group. It was also found that *P. gingivalis* LPS induced the production of Aβ in neurons and that the coexistence of LPS with Aβ enhanced the production of TNF-α and IL-1βin microglia in cultures. These results suggest that infection with *P. gingivalis* and the resulting inflammation aggravate the pathology of AD (Figure 2).

Induction of Cerebral Small Vessel Disease by *P. Gingivalis* and AD

Cerebrovascular disease is known to be an important risk factor for AD.[61] From histopathological analysis based on necropsy, 80% of patients diagnosed with AD showed cortical infarcts, lacunar infarction, cerebral microbleeds and multiple microinfarcts that are indicative of small vessel disease (SVD), intracranial atherosclerosis, and cerebral amyloid angiopathy (CAA).[62] It has been suggested that these disorders result in decreased cerebral blood flow and increased BBB permeability, exacerbating cognitive dysfunction. One of the mechanisms by which *P. gingivalis* exacerbates AD may be exacerbation of those cerebrovascular disorders. Periodontal disease has been reported to be an independent risk factor for ischemic stroke.[63] It has been reported that there is a correlation between an increase in the antibody titer to *P. gingivalis* and the onset of stroke.[64] *P. gingivalis* tends to adhere to inflamed blood vessels. *P. gingivalis* is frequently detected in peripheral arteries of patients with Burger's disease.[65] Recent studies have also shown that *P. gingivalis* is detected with 100% probability from the coronary or femoral artery in patients with atherosclerotic cardiovascular disease. *P. gingivalis* adheres to E-selectin via its outer membrane proteins (OMPs). It also invades inflamed epithelial cells and vascular endothelial cells.[66] *P. gingivalis* produces trypsin-like cysteine proteases such as gingipains (lysine gingipain (Kgp), arginine gingin dipain A (RgpA), and arginine gingin dipain B (RgpB)) and is involved in the formation of vascular lesions together with the pathogenesis of periodontal disease.[67,68] Gingipains are present in the outer membranes of bacteria, but some are released as outer membrane vesicles (OMV).[69,70] Kgp and RgpA/B are deeply involved in the survival and virulence of *P. gingivalis*.[71] Gingipains produced by the bacterium activate the blood coagulation system[72] and degrade the anticoagulant factor thrombomodulin that is expressed on vascular endothelial cells,[73] so that thrombi are easily formed in blood vessels. In addition, gingipains directly damage endothelial cells and epithelial cells.[67,68,74] Such an action of *P. gingivalis* may be involved in the pathogenesis of cerebral amyloid angiopathy (CAA), which often accompanies AD.[75] From the above, the following exacerbation mechanism of AD is inferred (Figure 2). *P. gingivalis* and its toxins in the oral cavity are transferred to the brain through the bloodstream or intestine. Normally, there is a blood-brain barrier (BBB), and so it is thought that they cannot be transferred into the brain. However, the increase of inflammatory mediators in the blood, senescence of the cerebrovasculature, or direct action of bacterial toxins on blood vessels causes vascular inflammation and thrombosis, resulting in decreased cerebral blood flow. The permeability of the BBB is also enhanced, and then the bacteria and their toxins may enter the brain. *P. gingivalis* and its toxins that have migrated to the brain parenchyma enhance the production of Aβ and activate microglia in conjunction with Aβ and Tau. Then, an innate immune response in the brain is induced and damages

neurons. Such chronic brain inflammation and neuron degeneration may exacerbate the pathological condition of AD.

Conclusions

Based on previous reports and our findings, we have described the relationships between periodontal disease, periodontal disease-related bacteria and AD (Figure 3). The conditions of periodontal disease (bacterial infection and chronic inflammation) weaken the blood-brain barrier and pose a risk for cerebrovascular disease. The conditions also cause inflammation in the brain. Periodontal disease may indirectly make AD pathology worse through exacerbation of diabetes.[76,77] Furthermore, tooth loss leads to deterioration of cognitive function.[78,79] Therefore, it is possible that periodontal disease directly and indirectly exacerbates the condition of dementia (Figure 4). Therefore, periodontal care is considered to be essential for dementia control. On the other hand, in periodontal disease patients, bacteremia often occurs due to regular brushing and chewing.[80,81] Although it is important to treat periodontitis for the prevention of AD, it is also necessary to take measures against bacteremia by invasive treatment such as scaling and root planing in the future. In addition, it may be useful for the prevention of dementia by evaluation of gut microbiota and oral microbiota as potential risk factors for dementia may be useful for prevention of dementia. Changes in bacterial flora are associated with quantitative and qualitative changes in diet.[60,82–85] By clarifying the causal relationships of nutrition with bacterial flora and dementia, the possibility of a new method for prevention of dementia by improving eating habits may be expanded.

The incidence of AD onset increases in the late 70s. On the other hand, accumulation of Aβ in the brain has started after the age of 50 years. Care for periodontal disease and control of oral bacteria in that period is important to regulate the onset and exacerbation of AD. Prevention of periodontal disease and maintenance of oral health will become increasingly important in the aging society.

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Disclosure

The authors report no conflicts of interest in this work.

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