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1 **Expert Review of Anti-infective Therapy**

2 **Revised version [24.06.2020](#)**

3

4 **Editorial**

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8 ***Porphyromonas gingivalis* infection may contribute to systemic and intracerebral**

9 **amyloid-beta: Implications for Alzheimer's disease onset**

10

11

12 Abstract

13 The microbiota of “chronic” periodontitis, particularly *Porphyromonas gingivalis*, have been
14 implicated in Alzheimer’s disease (AD) because this bacterium has a range of enzymes
15 (cathepsin B and gingipains) that are shown to interact with the amyloid precursor protein
16 (APP) and neuronal tau resulting in the formation of amyloid-beta ($A\beta$) and neurofibrillary
17 tangles (NFTs). These two lesions remain pivotal to explaining AD pathogenesis alongside of
18 clinical symptoms. Deposits of $A\beta$ in the brain can start 10-20 years before the clinical
19 symptoms of cognitive decline and the diagnosis of AD is established. It is rarely mentioned
20 that the AD risk doubles if the individual has received a diagnosis of periodontitis for around
21 10 years. This editorial is a review of recent but salient literature supporting the idea that
22 periodontal disease can contribute to a systemic $A\beta$ pool that may enter the brain over time. In
23 addition, intracerebral production of $A\beta$ can be initiated by *P. gingivalis*, which occurs via
24 host and bacterially derived cathepsin B acting as β -secretase to process the APP via the
25 amyloidogenic pathway yielding $A\beta_{3-42}$. These findings support a systemic and an
26 intracerebral $A\beta$ contribution from “chronic” periodontitis in subsequent AD development.

27

28 **Keywords** Inflammation; microbiota; periodontitis; systemic; amyloid; $A\beta_{3-42}$; cathepsin B;

29 Introduction

30 Generalized (“chronic”) periodontitis, a common inflammatory disease affecting the
31 supporting tissues of teeth, has been associated with several systemic diseases, e.g.
32 cardiovascular diseases, diabetes, adverse pregnancy outcomes, rheumatoid arthritis,
33 respiratory diseases, and Alzheimer’s disease (AD).¹⁻⁷ Bacteria of the periodontal pocket can
34 spread through the blood stream, which is the common but not the only way of systemic
35 bacterial dissemination in periodontitis.⁸ Dental treatment, tooth brushing, flossing, chewing,
36 and use of tooth-picks in a patient with periodontitis will release a bacteremia.⁹ This can occur
37 several times during the day and has been estimated to last for up to 3 hours.¹⁰ Tooth-related
38 bacteremia contains a wide spectrum of bacteria¹¹ among which the Gram-negative anaerobic
39 rod *Porphyromonas gingivalis* seems to have a key role in the adult form of generalized
40 periodontitis.^{12,13}

41 A plethora of studies firmly place *P. gingivalis* but not its companion species (for
42 example *Tannerella forsythia* and *Treponema denticola* in the red complex¹³) as a risk factor
43 for AD. This is because *P. gingivalis* is adept at modifying the peripheral and intracerebral
44 immune responses.¹⁴⁻¹⁶ Furthermore, this bacterium has a range of enzymes including
45 cathepsin B¹⁷ and gingipains¹⁸ that are respectively shown to interact with the amyloid
46 precursor protein (APP) and neuronal tau resulting in the formation of amyloid-beta (A β) and
47 neurofibrillary tangles (NFTs),^{19,20} which are the cardinal hallmarks of AD. Prospective,
48 retrospective population-based and nested control studies have shown that the risk of
49 developing the sporadic form of AD doubles when periodontal disease persists for about ten
50 years.²¹⁻²³ This is evident from the fact that a large section of individuals who go on to
51 developing clinical AD also suffers from periodontitis.

52 Brain inflammation, characterized by increased activation of microglia and astrocytes,
53 increases during aging and is a key feature of AD.²⁴ This has been explained in terms of the
54 hallmark lesions of AD, which are A β _{40/42} extracellular deposits in the form of plaques and
55 hyperphosphorylated tau protein associating with intraneuronal lesions called NFTs.
56 Accumulation of A β plaques results from the proteolytic cleavage of the APP by β - and γ -
57 secretase enzymes.^{25,26} These secretases are different in AD driven by bacterial infections
58 compared to the classically described site-specific secretases in the mutated APP of AD.^{27,28}
59 Similarly, toxic proteases from *P. gingivalis* called gingipains have been identified in the
60 brain of AD patients, and the levels correlated with tau and ubiquitin pathology.¹⁵

61 $A\beta$ is classically believed to be produced by neurons within the AD brain irrespective
62 of the trigger that causes its release. However, this view is changing, as some researchers
63 believe the peripheral/systemic $A\beta$ pool is also a contribution from platelets, skeletal muscle
64 cells, skin fibroblasts, and monocyte/macrophages²⁹⁻³¹ and this has implications for AD
65 pathogenesis over time. Production of inflammagens such as gingipains and
66 lipopolysaccharide (LPS) secreted by *P. gingivalis* also occurs in the periodontal pocket
67 where inflammatory macrophages are reported to bear $A\beta$.³² Gil-Montoya et al.³³ have
68 reported increased plasma $A\beta_{1-42}$ levels in individuals who have severe periodontal disease.
69 Thus Leira et al.³⁴ found when experimental periodontitis was induced in Sprague-Dawley
70 rats, a strong positive correlation between alveolar bone loss and $A\beta_{1-40}$ serum levels at 7 days
71 ($r = 0.695$, $P = 0.012$) and with serum $A\beta_{1-42}$ concentrations at 21 days ($r = 0.968$, $P = 0.002$).
72 Taken together, $A\beta$ also being generated peripherally in platelets, skin fibroblasts and skeletal
73 muscles^{29,30} may enter the circulating blood.³¹ The present editorial aims to discuss whether
74 *P. gingivalis* can contribute to systemic and intracerebral pools of $A\beta$.

75

76 ***P. gingivalis* induces systemic $A\beta$ production in infected mice**

77 Nie et al.³² recently reported that chronic, systemic *P. gingivalis* infection increased the
78 inflammatory responses and proteins associated with $A\beta$ -production in the liver of mice. The
79 liver was chosen for the peripheral $A\beta$ source in macrophages because of the general
80 abundance of these cells.³² Nie et al.³² observed that *P. gingivalis* infection in mouse liver
81 macrophages, caused a rapid production of interleukin 1-beta (IL-1 β) and thereafter an
82 intracellular accumulation of $A\beta$ through activation of Toll like receptor 2 /nuclear factor
83 kappaB (TLR2/NF- κ B) signaling. NF- κ B-dependent cathepsin B appeared crucial for
84 cleaving pro-IL-1 β and processing APP to induce the accumulation of pathogenic $A\beta_{3-42}$,
85 which was significantly increased in liver macrophages of the *P. gingivalis*-infected mice.
86 This original study demonstrated peripheral pools of $A\beta$ due to periodontitis in macrophages
87 within the periodontal tissue and in mice hepatic macrophages following *P. gingivalis*
88 infection. In a follow-up study, Zeng et al.¹⁷ induced systemic *P. gingivalis* infection in mice
89 by intraperitoneal injections containing (1×10^8 CFU/mouse every three days) for three
90 weeks. This significantly increased the expression of the advanced glycation end products
91 (RAGE) receptor in the cluster of differentiation 31 (CD31)-positive endothelial cells. This
92 implied that *P. gingivalis* systemic infection up-regulated RAGE expression in cerebral
93 endothelial cells and facilitated $A\beta$ entry into the mouse brain. Cathepsin B was suggested to
94 be a contribution from the bacterium and the host with a critical role in regulating the NF-

95 κ B/RAGE expression and in the processing of APP. This study [further](#) supported the Nie et
96 al.³² concept for the potential in systemic spread of peripheral A β to the brain from *P.*
97 *gingivalis* infection. In a proof of concept study, Bu et al.³¹ had demonstrated the plausibility
98 of peripheral A β entry to the brain being facilitated by the RAGE receptor within cerebral
99 endothelial cells.¹⁷ An alternative mode of peripheral A β entry into the brain is via
100 macrophages of the lymphatic system.³⁵

101 Another focus of Nie and colleagues³² was A β ₁₋₄₂, which is classically considered as
102 the toxic form of A β . They observed that A β ₃₋₄₂ (Fig. 1) not only occurred earlier but was also
103 two-fold higher than A β ₁₋₄₂ in the AD brain.³² In AD, Cathepsin B stimulated intracellular
104 production of A β in the brain, including the A β ₃₋₄₂. Interestingly, A β ₃₋₄₂ following *P.*
105 *gingivalis*-infection in mice generated IL-1 β , which is a proinflammatory cytokine.³² IL-1 β ,
106 participated in increasing the *in vivo* levels of A β ₃₋₄₂ in [the hepatic](#) macrophages of *P.*
107 *gingivalis*-infected mice and *in vitro* *P. gingivalis*-infected macrophages. Furthermore, A β ₃₋₄₂
108 was induced by *P. gingivalis* infection, which had caused significant death of macrophages
109 and reduced their phagocytic capacity compared to that of A β ₁₋₄₂, suggesting A β ₃₋₄₂ is very
110 toxic. A β ₃₋₄₂ was also detected exclusively in the AD brain, and this corroborates with the
111 significantly more toxic form than A β ₁₋₄₂.³² This study agreed with that of Leira et al.³⁴ who
112 reported that LPS from *P. gingivalis* increased A β protofibrils in the serum of rats. After
113 experimental periodontitis had been induced in male Sprague-Dawley rats it caused an acute
114 elevation of A β ₁₋₄₀ in serum that lasted during the whole experiment. A β ₁₋₄₂ peptide levels
115 however, peaked at the end of the study.

116

117 ***P. gingivalis* also generates A β in the [periodontium](#) and within the brain**

118 Systemically produced A β probably occurs in addition to locally generated A β in the
119 [periodontium](#) and in the brain induced by *P. gingivalis*. As mentioned, Leira et al.³⁴ found a
120 strong positive correlation between alveolar bone loss and A β ₁₋₄₀ serum levels at 7 days
121 ($r = 0.695$, $P = 0.012$) and with serum A β ₁₋₄₂ concentrations at 21 days ($r = 0.968$, $P = 0.002$).
122 Intracerebral production of A β generated by *P. gingivalis* has been seen in the brain of
123 experimental wild type animals and with AD transgenes.^{19, 30-32} Ilievski et al.¹⁹ found that
124 chronic oral application of *P. gingivalis* to wild type mice resulted in deposition of
125 extracellular A β ₁₋₄₂ together with neurodegeneration and intracerebral inflammation, as
126 demonstrated previously by Poole et al.³⁶ Similarly, Wu et al.³⁷ found that chronic exposure to

127 LPS from *P. gingivalis* for five consecutive weeks caused learning and memory deficits
128 together with intracellular accumulation of A β in neurons of middle-aged wild-type mice.
129 Taken together, these reports suggest that *P. gingivalis* can induce both a local periodontal
130 and a systemic A β production, thereby contributing to a pool of A β that can enter the brain
131 facilitated by the endothelial RAGE receptor.

132

133 ***P. gingivalis* interferes with components of the peripheral immune system aimed to** 134 **defend the brain**

135 Unexpectedly, recent research has shown that even components of the peripheral immune
136 system, such as macrophages can participate in defending the brain from insults occurring
137 outside the brain.³⁸ However, *P. gingivalis* has the ability to abolish the anaphylatoxin
138 complement component 5a (C5a) in macrophages thereby undermining TLR2/4 immunity and
139 degrade some of the complement receptor 1 (CR1) molecules that help clear amyloid via the
140 spleen.³⁹ Whether this affects other macrophages in a similar way is not known. Further
141 immune evasion strategies of *P. gingivalis* in relation to AD are discussed elsewhere.⁴⁰

142

143 **Concluding remarks**

144 We have communicated that monocytes/macrophages from the periodontium and the liver
145 may provide an additional circulating pool of unique A β ₃₋₄₂ fragments in patients with
146 periodontitis. Entry of *P. gingivalis* and/or its gingipains and LPS into the brain due to a
147 defective blood-brain barrier can lead to intracerebral deposition of A β plaques. These
148 findings support the notion that the adult form of generalized periodontitis via *P. gingivalis*,
149 contributes to both an oral and hepatic cellular source of cells that add to the systemic pool of
150 A β . This peptide can also be a contribution of other cell sources of peripheral organs like skin
151 smooth cells and platelets which have the potential to transport A β to the brain and over time
152 may play a role in AD pathogenesis. Deposits of A β in the brain can start 10-20 years before
153 cognitive decline and the diagnosis of AD. This agrees with the timeline of at least 10 years
154 required for periodontitis to initiate AD and emphasizes the need for meticulous dental
155 hygiene as a feasible prophylaxis for AD.

156

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160 Declaration of interest

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164

165 Conflict of interest

166 ~~No conflict of interest is reported by the authors.~~

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297

298 Figure legend

299 **Fig. 1** summarizes the Nie et al.³² vision as interpreted by Olsen and Singhrao for the
 300 contribution to AD of peripheral pools of A β , specifically A β ₃₋₄₂. It is generated by *P.*
 301 *gingivalis* (*Pg*) oral infection that eventually reaches the liver and the brain. The proposed
 302 signaling pathway (TLR2,4/NF- κ B) is also indicated where it is likely to act liberating
 303 interleukin-1 β (IL-1 β) cytokine that facilitates the amyloid precursor protein cleavage of A β
 304 via secretase enzymes, one of which is cathepsin B. The low-density lipoprotein
 305 receptor-related protein 1 (LRP1) is the receptor for A β transport from the brain to the
 306 peripheral blood. The A β from the systemic circulation can enter the brain using the advanced
 307 glycation end products (RAGE) receptor. Nie et al.³² have shown A β within the gingival
 308 tissues of periodontitis patients and in the liver of middle-aged mice after chronic systemic *P.*
 309 *gingivalis* infection, thereby contributing to the peripheral pools of A β . Some researchers
 310 believe the peripheral A β also comes from platelets, skeletal muscle cells, skin fibroblasts,
 311 and monocyte/macrophages. The implications of the peripheral A β is that it can also enter the
 312 brain and contribute to AD pathology as shown by Bu et al.³¹

313

314