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Perspective

Potential role of antimicrobial peptides in the early onset of Alzheimer's disease

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Abstract Cerebral aggregation of amyloid-β (Aβ) is thought to play a major role in the etiology of Alzheimer's disease. Environmental influences, including chronic bacterial or viral infections, are thought to alter the permeability of the blood-brain barrier (BBB) and thereby facilitate cerebral colonization by opportunistic pathogens. This may eventually trigger Aβ overproduction and aggregation. Host biomolecules that target and combat these pathogens, for instance, antimicrobial peptides (AMPs) such as Aβ itself, are an interesting option for the detection and diagnostic follow-up of such cerebral infections. As part of the innate immune system, AMPs are defensive peptides that efficiently penetrate infected cells and tissues beyond many endothelial barriers, most linings, including the BBB, and overall specifically target pathogens. Based on existing literature, we postulate a role for labeled AMPs as a marker to target pathogens that play a role in the aggregation of amyloid in the brain.

Keywords: Infection; Alzheimer's disease; Amyloid plaques; Antimicrobial peptides; Contrast agents

1. Introduction

Based on the existing clinical criteria, Alzheimer's disease (AD) can only be diagnosed at a late stage of the disease and with a considerable degree of uncertainty. A definitive diagnosis still requires postmortem detection of neurofibrillary tangles and amyloid plaques. Recently, the combination of cerebrospinal fluid biomarkers and nuclear imaging with positron emission tomography tracers fluorodeoxyglucose-fluor-18 and Pittsburgh compound B together with structural magnetic resonance imaging has been introduced in clinical settings to play a supporting role in diagnosing AD, as well as to increase our understanding of the disease pathogenesis [1]. Based on the neuropathologic hallmarks and in vivo biomarkers, the AD-induced neurodegeneration is estimated to start several decades before clinical onset and is believed to have reached a plateau at the actual time of clinical presentation [2,3]. The exact underlying pathogenesis responsible for the amyloid-β (Aβ) imbalance, the hyperphosphorylation of tau, and their intimate association remains one of the major unresolved questions regarding AD. Although the amyloid cascade hypothesis is widely known and accepted [2], we still know very little about what triggers plaque formation, let alone about whether their presence is a cause or only a consequence of the disease.

Besides the aforementioned amyloid cascade and tau hypothesis, some claim that the dyshomeostasis of cerebral iron plays an intricate and crucial role [4]. Increased cortical accumulation of iron is often found in the presence of amyloid plaques, and mechanistic explanations for the role of iron include neurotoxicity due to the formation of reactive oxygen species or a dysregulation of myelin maintenance. Both processes could be viewed as positive forward mechanisms as amyloid precursor protein and Aβ, tau, and demyelination in turn may contribute to the iron dyshomeostasis [4]. It is clear that as yet no clear single explanation regarding the pathogenesis of AD has been found.

In 2010, a hypothesis was postulated that brain infections with bacteria or viruses may play an initiating role in amyloid plaque formation and the development of AD [2]. Our

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perspective aims to provide evidence for the effect of chronic infections in the development of AD based on existing literature. Second, we propose a potentially novel role for antimicrobial peptides (AMPs) in AD pathology as pathogen-targeting agents for the detection and follow-up of these brain infections with respect to AD.

2. Chronic infections as an initial event in AD pathogenesis

As suggested by others, chronic systemic infections may play a crucial role in the initial pathogenesis of AD. Many inflammatory markers are indeed found to be significantly increased in AD subjects, as highlighted in a recent review by Zotova et al. [5]. Apart from chronic infection, vitamin D deficiency, obesity, rheumatism, depression, stress, or type 2 diabetes are proposed as risk factors [6–8]. These factors are known to contribute to the downregulation of the innate immune response [9] and thus increase the risk for a bacterial infection [10] (Fig. 1).

These infections lead to persistent inflammatory stimuli, regulated by cytokines that are known to induce stress and alter the immune response [11]. As these stimuli have a detrimental effect on the integrity of the blood-brain barrier (BBB) [12], they provide an opportunity for other pathogens to enter the central nervous system (CNS). Second, the inflammatory response to a systemic infection may indirectly lead to an upregulation of Aβ production, thereby initiating the amyloid cascade (Fig. 2).

3. The infiltration of pathogens into the brain

As said earlier, inflammatory stimuli may compromise the endothelial layer. Supportive for this hypothesis is the observation that for both sepsis and bacterial meningitis, the BBB is compromised because of the breakdown of intercellular tight junctions caused by the endotoxin lipopolysaccharide and peptidoglycans, particularly within the venules [13]. Moreover, chronic infections alter the integrity of the BBB and may promote the transmigration of monocytes and autoreactive T cells over the brain epithelium. As these cells are potentially infected by pathogens, monocytes and T cells may well be the vehicle to transport bacteria into the CNS [14].

Indeed, persistent subclinical CNS infections have been reported for AD patients, caused by various pathogens such as *Chlamydia*, *Borrelia spirochetes*, *Helicobacter pylori*, herpes simplex virus, and infections related to human immunodeficiency virus that causes acquired immunodeficiency syndrome [14,15]. A complete overview of recent studies regarding the incidence and role of bacterial or viral CNS pathogens in AD pathology is summarized in Table 1.

In many cases, the presence of bacterial infections in the brain was confirmed by polymerase chain reaction techniques after autopsy. Therefore, a critical remark must be made when discussing the causality of AD based only on the results of postmortem studies because from these studies, it remains unclear whether the entry of these pathogens occurred at the onset of AD or is merely the consequence of a leaky BBB caused by inflammatory processes induced by other chronic infections or secondary to AD itself [16]. Unfortunately, currently, no methods are available for in vivo detection of infectious agents in the brain, apart from an invasive brain biopsy. Specific infection imaging agents that target the CNS would be essential to further the knowledge of the causality of these mechanisms.

4. Linking chronic infections to AD onset

The (repetitive) infiltration of pathogens in the brain is thought to induce AD directly through CNS (re)infection and the resulting neuroinflammatory response, although no specific bacterial or viral pathogens have been linked conclusively to late-onset AD in humans [17]. Clinical evidence for the role of infections stems from studies on the relation between periodontitis and AD, showing that the presence of serum antibodies to periodontal bacteria associates with an AD diagnosis and even presents an independent risk factor for the future development of AD [18].

Rather than AD being the result of a single pathogen, the diverse bacterial and viral pathogens associated with the disease evoke a similar neuroinflammatory response, thereby initiating the formation of fibrillar amyloid, as will be explained in the next paragraph. Once initiated, the amyloid formation then proceeds through a self-assembling process, which may be accelerated by the neuroinflammatory status of the patient, thus creating a positive feed-forward loop. In line with our hypothesis, recently, a number of animal studies have been published showing that several pathogens (*Chlamydia pneumoniae*, herpes simplex, *Escherichia coli*, or *Cryptococcus neoformans*) play a significant role in the development of amyloid plaque formation [19–22]. These types of models will be of great value to establish the role of bacterial and viral infections in the onset of AD, as well as to test potential imaging markers aiming to detect living and virulent pathogens in the brains. In this respect, AMPs that were developed as specific tracers for imaging infections may play an important role in this [23].

5. The role of AMPs in AD

AMPs are part of the innate immune response and can be found in all living species. In humans, AMPs are produced by phagocytes, epithelial cells, endothelial cells, and many other cell types [24]. They can be expressed constitutively or be induced during inflammation or a microbial challenge. AMPs usually contain less than 50 amino acids and can be classified into three main structural categories: (1) linear peptides adopting an amphipathic α-helical structure such as cecropin, magainin, bee melittin, and human ubiquicidin and histatins; (2) peptides with 1 to 4 disulphide bridges