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Is the A-beta peptide of Alzheimer's Disease an Antimicrobial Peptide?

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Introduction

As reviewed elsewhere [1], amyloids are amorphous deposits of proteins folded into stacked β-sheets in the form of long fibrils. Amyloids occur in high levels in certain human diseases and research has traditionally focused on how amyloid may cause disease. The Aβ peptide that forms the brain amyloid plaques which characterise Alzheimer's disease (AD) is one of the most intensively studied molecules in the body, yet is still very poorly understood.

The Aβ peptide was originally believed to be a pathologically abnormal species, with no physiological role, but is now known to be produced in the normal human brain and may only be pathogenic in certain folding conformations or if levels become excessive [1-4]. Evidence is appearing for roles both in normal cognition and in protective responses within the brain, as reviewed elsewhere [3,5]. One intriguing possibility is that Aβ has antimicrobial properties and may serve important innate immune functions within the brain [6].

Here we provide a commentary on a paper by Soscia and colleagues assessing this proposal *in vivo* [6], and discuss the arguments and analogies with other antimicrobial peptides on which the proposal is founded.

Anti-microbial amyloids

As reviewed elsewhere, antimicrobial peptides (AMPs) are an integral part of the innate immune system, with three main classes of AMPs in humans and other mammals–defensins, histatins and cathelicidins [4,6-8]. One property that may give a peptide antimicrobial activity is the ability to form amyloid [8]. Some bacteria produce amyloids which appear to retard growth of nearby bacteria [4] and some mammalian AMPs also form amyloid. One example is protegrin-1, a cysteine-rich peptide of the defensin family able to form β-sheets and amyloid fibrils [9,10]. Protegrins are part of the arsenal of neutrophils and macrophages and have cytotoxic effects against bacteria, fungi and enveloped viruses, as reviewed elsewhere [1]. The ability to form amyloid fibrils is proposed to be central to the antimicrobial activity of such AMPs [8,10], as described in more detail below.

Is the Alzheimer's Aβ peptide an antimicrobial peptide?

The proposal that Aβ peptide may be an antimicrobial peptide partly derives from its capacity to form both amyloid fibrils and cytotoxic oligomeric forms, features considered central to the antimicrobial properties of various AMPs [8,11]. The fibrils formed by the Aβ peptide and AMPs such as protegrin-1 or LL-37 (a prototypical member of the cathelicidin family of mammalian AMPs) have similar physiochemical properties, reflecting their b-sheet secondary structures, which are congophilic, binding avidly to the histochemical stain Congo Red, and birefringent, the classical defining properties of the amyloid plaques in AD [1,6]. Functional analogies may also exist between these peptides since, for example, when present as oligomers or protofibrils, the protegrins, LL-37 and Aβ peptide all have cytotoxic activity, as reviewed elsewhere [1,2,6,10,11].

Another example is provided by the human islet amyloid polypeptide, which aggregates in type 2 diabetes, closely resembles Aβ in its amino acid sequence and amyloidogenic properties and is able to inhibit growth of clinically relevant bacteria by bacterial membrane disruption [12].

Antimicrobial properties of Aβ *in vivo*

With regard to cytotoxicity, Soscia and colleagues report that synthetic Aβ peptide inhibits growth of 8 out of 12 common, clinically relevant pathogenic organisms, indicating antimicrobial activity similar to or greater than LL-37 [6]. Pathogens inhibited by Aβ were *Candida albicans*, *Escherichia coli*, *Staphylococcus epidermis* and *S. aureus*, *Streptococcus pneumoniae* and *S. agalactiae*, *Enterococcus faecalis* and *Listeria monocytogenes*, whereas *Pseudomonas aeruginosa* and *Streptococcus pyogenes*, *S. mitus* and *S. salivarius* were not affected under the experimental conditions used. The mechanisms involved and the factors determining whether a pathogen is inhibited by Aβ are unclear. It appears the pathogen surface carbohydrate, protein and phospholipid composition influences the ability of different antimicrobial peptides, including Aβ, to bind and attack the pathogen [6,11,13]. Since Aβ inhibited certain Gram negative and Gram positive bacteria, as well as yeast, but did not inhibit other Gram negative or Gram positive bacteria, lipopolysaccharide (LPS) is unlikely to be a primary determinant of specificity and, as far as we are aware, no direct interactions between Aβ and LPS have been reported to date. Indirect interactions may occur *in vivo* through other molecules such as the LPS receptor CD14, which is reported to bind Aβ [14], however the *in vitro* data from Soscia and colleagues [6] suggest Aβ has antimicrobial activity independent of such interactions.

In other experiments, antimicrobial activities of peptide preparations from human temporal lobe and cerebellum were tested *in vitro*. Temporal lobe samples from brains of AD patients with higher Aβ amyloid loads had higher antimicrobial activity than samples from brains of people without AD. For samples from the cerebellum, where Aβ amyloid load is low, no significant difference in antimicrobial activity was observed [6].

Further evidence for the immunoprotective capacity of Aβ comes from studies of mice producing reduced amounts of Aβ due to deficiencies in β-secretase 1 family enzymes (beta-site amyloid precursor protein cleaving enzyme; BACE). These studies reported mortality rate increases, relative to wildtype mice, of 40% and 60% respectively in BACE1 knockout mice (that produce small amounts of Aβ) and double knockout mice deficient for both BACE1 and BACE2 (that do not express Aβ). The high mortality rates appear attributable to increased vulnerability to pathogens, since maintaining mutant mice in a pathogen-free environment restored mortality rates to the levels in wild-type mice [15].

How does amyloid formation have antimicrobial effects?

Amyloid-forming peptides may protect against infection by trapping invading pathogens within a web of amyloid fibrils [13] and by binding to and disrupting pathogen surface coatings and membranes [7,8,11]. There may also be less direct cytotoxic actions, for example through modification of inflammation and other adaptive immune responses, in addition to participation in innate immune responses, reviewed elsewhere [7,11] and discussed below.

The entrapment of pathogens by fibril-forming peptides is illustrated by the AMP human α-defensin 6 (HD6), an α-defensin secreted by human small intestinal epithelial cells. Chu and colleagues [13] have recently shown that treating *Salmonella typhimurium* with HD6 entwines the bacteria and their flagella in a net-like meshwork of fibrils, termed a 'nano-net', restricting the bacteria's ability to invade intestinal epithelial cells. As HD6 can interact with very different pathogens and is not specific to a particular target, nano-nets are likely to be formed in response to invasion by diverse pathogens including fungi, some protozoan parasites and other bacteria [13].

The prevailing evidence does not appear to suggest that nano-nets 'wall off' or surround infected areas but is instead more consistent with the formation of focal nodes at sites of infection that enmesh pathogens within a tangled mass or 'net' of agglutinated peptides [8,13]. This also corresponds more closely to the typical structures displayed by Aβ amyloid plaques.

As mentioned above, besides forming fibrillar nanonets which entangle invading pathogens, AMPs may exert a range of cytotoxic actions, including increasing membrane permeability and leakiness [1,4,7,9,11]. The Aβ peptide is potentially able to act in both ways, by inducing pathogen membrane perturbations as well as by fibrillar enmeshment, since it can form ion channels within neuronal membranes [9] and also binds to bacterial membranes [6], and so may exert antimicrobial effects by creating membrane leakiness and ionic dyshomeostasis.

Other roles of Aβ relevant to cytoxicity and antimicrobial activity

Despite an extensive literature on the relationships of Aβ with oxidative and inflammatory phenomena, it remains unclear whether Aβ is a cause or a consequence of these phenomena, or both. Neuronal up-regulation of Aβ production occurs in response to oxidative stress *in vivo* and *in vitro* [3], analogous with observations that antimicrobial peptides respond to oxidation of membrane lipids, discussed elsewhere [7,11]. It is beyond the scope of this review to address these phenomena at length. Briefly, while Aβ can elicit both oxidative stress and altered expression of cytokines and other inflammation-associated responses by microglia and other CNS cells, the relationships involved are complex [16-18]. Whether microglial activation or other responses increase amyloid clearance or exacerbate AD pathology appears context-dependent, varying with disease stage and other factors, as discussed at length elsewhere [17,18].

Soscia and colleagues [6] speculate that Aβ may act in conjunction with other brain peptides with antimicrobial properties, in a concerted innate immune response to pathogens or other stimuli. Synthetic peptides based on tau protein sequences have antimicrobial properties, as do components of many other CNS peptides that may contribute to brain innate immune responses, including α-synuclein, the chromogranins and various other neuropeptides and peptide hormones such as neuropeptide Y and adrenomedullin [6].

As further discussed by these authors [6], other factors may also contribute to making Aβ an effective antimicrobial agent. For example, bacterial proteases target cationic peptides in preference to anionic peptides, making Aβ and other anionic AMPs more resistant to bacterial degradation, and oligomerization may also shield Aβ from microbial degradation.

However this resistance to degradation may ultimately prove to be a double-edged sword. While common acute and subacute infections are not typically associated with amyloid formation, amyloidosis is commonly observed in cases of chronic infections such as leprosy, tuberculosis, syphilis and osteomyelitis or in chronic inflammatory conditions such as rheumatoid arthritis, as reviewed elsewhere [19]. One possibility is that, in the short-term, aggregates of anti-microbial peptides can be cleared effectively by processes such as autophagy and subsequent intracellular degradation [20] but accumulation over longer periods may overload clearance and degradation systems and cause amyloid build-up.

Possible relationships with AD

The nature of the relationship, if any, of infection and innate immune responses with Aβ production, amyloid and AD remains unknown. Brief infections or persistent sub-acute infections may activate the innate immune system and trigger Aβ production and aggregation. For example, Aβ amyloid deposition has been reported for acquired immunodeficiency syndrome patients with brain HIV infection [21,22] and herpes simplex virus type I (HSV-I) infection can cause cellular Aβ accumulation and secretase upregulation [23]. In addition, slowly progressive syphilitic dementia manifests Aβ amyloidosis in the CNS [24].

Various studies have also reported pathogens in the CNS of AD patients, including HSV-1, *Chlamydia pneumoniae* and some fungi, as detailed elsewhere [25-28]. Different types of spirochetes have been found in AD brains [29], including *Borrelia burgdorferi* [30,31] and periodontal pathogen spirochetes [32,33]. Beta-amyloid deposition is reported to increase in mammalian glial and neuronal cell cultures exposed to spirochetes [34]. However some researchers believe that spirochetes are unlikely to be relevant in most AD patients [35,36] and more studies are required to determine the extent to which spirochetes contributes to pathogenesis across the spectrum of AD etiologies. While there is as yet little conclusive evidence from animal studies, infection of APP/PS1 mice at older ages by the Gram negative respiratory pathogen *Bordetella pertussis* has recently been reported to increase Aβ deposition [37].

Although Soscia and colleagues [6] have tested the ability of Aβ to inhibit pathogens responsible for various serious diseases, very little is yet known about the nature of the relationships between Aβ and the pathogens most frequently reported in brains of AD patients, such as *Chlamydia pneumoniae*, HSV-1, spirochetes such as *Borrelia burgdoferi* and various fungi [25-30]. While the mechanisms by which particular infections stimulate Aβ production remain to be elucidated, these pathogens may be distinguished by their ability to enter the CNS and induce chronic, persistent or latent infections in conjunction with pathogen-associated responses and pathology, possibly involving Aβ production, over protracted periods of time. For example, alphaherpesvirinae sub-family viruses such as HSV-1 are neurotropic and can enter the CNS via intra-axonal retrograde transport within neurons innervating sites of systemic infection, as reviewed elsewhere [38].

The risk of developing AD may reflect the combined burden of past pathogen infections of different kinds [39]. Moreover pathogens need not enter the brain to elicit serious or even fatal CNS sequelae, as reviewed elsewhere for the example of cerebral malaria [40]. It is also possible that even in the absence of infection, inflammatory responses by the innate immune system to either brief or persistent non-infectious events, such as traumatic brain injury, stroke or inhalation of anesthetics, may result in increased Aβ levels and AD.

Conclusions

In summary, Aβ appears likely to have antimicrobial effects in the brain and elsewhere, although it is unclear if this occurs serendipitously as a chance bystander phenomenon or if Aβ production is up-regulated as part of evolved innate immune responses to infections or other triggers. What also remains to be determined is whether particular infections or other immune response triggers contribute to Aβ pathology in AD. The prevention of amyloid formation by defensive targeting of microbial intruders and inflammatory pathways of the innate immune system may provide new therapeutic options for controlling Aβ production and aggregation.

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