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# The Function of A $\beta$ in the Healthy Brain: Beta Amyloid as an Antimicrobial Protein

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**Abstract:** *There is no question as to whether or not the beta amyloid (A $\beta$ ) peptide plays a role in the exacerbation and onset of AD. There are very evident correlations between the volume of A $\beta$  deposition in the AD brain and the severity of the symptoms of AD-typical neurodegeneration. There are certainly many factors involved in the progression of AD, of which the aggregation of A $\beta$  peptides is only one. While many have ruminated on the mechanism by which A $\beta$  serves to impair synaptic function and contribute to neurodegeneration, the role of this protein has yet to be fully uncovered, not just in the AD brain, but in the normally functioning brain as well. Recent research has shed light on the role of A $\beta$  in the normal brain, offering evidence for the fact that beta amyloid functions as an antimicrobial protein, with its primary objective being to serve an immunoresponsive purpose. This text will highlight some of the critical studies on the topic, and illuminate the role that A $\beta$  most likely plays in the functioning of the normal brain, and how this influences its pathological deposition in the AD brain.*

## I. INTRODUCTION

Alzheimer's Disease (AD), The neurodegenerative ailment that affects one in every nine Americans and is the sixth leading cause of death, has thus far proven to be an irreversible degradation of neuronal function which is characterized principally by the aggregation of beta amyloid (A $\beta$ ) peptides (Frost & Li, 2017). While it is known that there is a correlation between A $\beta$  accumulation and the onset of AD (Frost & Li, 2017; Iacobelli, 2021), the specific mechanism by which the peptide turns pathological and impairs neuronal function, thus contributing to synaptic toxicity remains a topic on which the medical community is starkly divided. Aside from a general lack of understanding of the specific mechanisms that serve to exacerbate AD, our misunderstanding of the role that A $\beta$  plays in the onset and progression of AD derives from the fact that there is little understanding as to the role that the protein plays in the normally functioning brain. This leaves researchers with no starting point from which a mechanism for its pathological mutation in the AD brain can be intuited. Some have proposed that the aggregation of A $\beta$  into plaques simply blocks synaptic pathways and limits neuronal plasticity, while others argue that the protein is directly toxic to the neurons or the myelin sheaths that surround them (Frost & Li, 2017). Regardless of the means to the neurodegenerative ends that is AD and eventually death, a better understanding of the role that A $\beta$  plays in the AD brain certainly must come via a better understanding of the role it plays in the healthy brain, if any at all. This text will review the relevant research on the topic, with the aim to illuminate the most probable function for A $\beta$  presence in the healthy brain, and seek to explain how this normative function can mutate to such a dangerously pathological extent, as is the case with AD.

## II. BETA AMYLOID AS AN ANTIMICROBIAL PROTEIN

Antimicrobial proteins and peptides, described by Battersby et al., as an adaptive immune response which are variable and each specialized to serve as anti-infectives (Battersby et al., 2016), are critical to immune function in the mind and body, and the leading theory on the role that A $\beta$  plays in the healthy brain is that the substance is indeed an antimicrobial protein thus serving an immunological function, before it aggregates to a detrimental degree in the AD brain.

This theory is primarily substantiated by the deposition patterns and tendencies of A $\beta$  in the diseased brain, as it has been revealed that astrocytes, which are the primary agents in the astrogliosis immune response that is triggered by cerebral pathogens, secrete A $\beta$  as they become active (Frost & Li, 2017). That said, while correlated, a specific mechanism of causality has yet to be determined. In fact, one of the only reasons, aside from the correlation, that A $\beta$  has historically been thought of as a causal factor of AD is the fact that there has been no established role for A $\beta$  in a normally functioning brain. Physiologically speaking, much of the scientific community has operated under the assumption that it played no role other than exacerbating AD, and it is only in recent years that it has been thought to be an antimicrobial protein.

Battersby et al., went on to show that antimicrobial proteins play a significant, immunoprotective role in newborn infants, as broad spectrum antibiotics which serve as a defense against common infections such as sepsis or meningitis (Battersby et al., 2016), a finding that is directly in line with studies that have shown that reduced expression of genetic components necessary for the production of A $\beta$  will lead to higher mortality rates in transgenic mice.

$\beta$ -secretase (BACE), is a key genetic component in the production of A $\beta$ , as it cleaves APP prior to a second cleavage by  $\gamma$ -secretase after which the intracellular domain for APP and A $\beta$  peptides are released into the brain, all of which constitutes the amyloidogenic pathway, which Hussain et al., uncovered as the only mechanism by which A $\beta$  could be produced. Hence, BACE is wholly necessary for the production and secretion of A $\beta$  (Hussain et al., 1999). This allowed Dominguez et al., to transgenically modify mice such that BACE1 and BACE 2 were knocked out, to study how a lack of A $\beta$  production would affect their mortality rates (Dominguez et al., 2005).

Because it is well established that antimicrobial proteins, as a class of immune cells, are antibiotics which serve a broad range of functions and protect against bacteria, fungi, viruses, and a diverse panoply of pathogens (Zaiou et al., 2007), it is safe to assume that a reduction in a specific kind of antimicrobial protein would leave one vulnerable to infection, which as we know from Battersby et al., the young are particularly vulnerable to (Battersby et al., 2016).

In keeping with this assumption, it was discovered that these BACE1 and BACE2 double knockout mice had a significantly higher mortality rate than the control mice, but this wasn't the most interesting of the findings. When the studied mice were moved to a different, pathogen-free facility, their mortality rate returned to normal (Dominguez et al., 2005). This implies that the lack of BACE1 and BACE2 expression, and hence the reduced production of A $\beta$  itself was not the causal factor behind the increased mortality levels, but instead, the lack of  $\beta$ -secretase expression in mice facilitated an increased vulnerability to pathogens that allowed infections which would otherwise be handled by the immune systems of the mice, to run rampant and kill them at increased rates. This is presumably due to a lack of A $\beta$  which would in other cases serve as an antimicrobial protective agent to stave off the pathogens. While it is possible that other factors were at play, this study established an important link between a lack of A $\beta$  presence, and an increased susceptibility to deadly pathogens.

In an effort to further establish the antimicrobial classification of the A $\beta$  peptide, Soscia et al. compared the protein to a known antimicrobial protein, LL-37, which is one of many antimicrobial proteins in the Cathelicidin family (Soscia et al., 2010). The study showed an increased level of activity of A $\beta$  proteins in response to eight of the twelve pathogens to which it was introduced, a rate similar to that of LL-37 (Soscia et al., 2010; Frost & Li, 2017).

Perhaps most indicative of A $\beta$ 's antimicrobial function however is the historically observed responsiveness to the Herpes Simplex 1 (HSV-1) virus, that is a well established characteristic of A $\beta$  in a normally functioning brain (Frost & Li, 2017). HSV-1 is a known risk factor for AD and in many cases has been shown to predetermine the onset of sporadic AD, with its viral cells later bunching around A $\beta$  plaques (Wozniak, Mee, & Itzhaki, 2009). In an effort to examine this relationship, Bourgade et al. exposed fibroblasts, epithelial cells, and neuronal cell lines to A $\beta$  isoforms before later exposing those same cells to HSV-1. They found that, whether or not the A $\beta$  was added at the same time as the HSV-1, or two hours before the HSV-1, A $\beta$  effectively inhibited the replication of HSV-1 cells by preventing the entry of the virus into healthy cells, which is thought to be done by A $\beta$  insertion to the envelope of HSV-1 cells (Bourgade et al., 2014). It should be noted that A $\beta$  was not able to inhibit the replication of HSV-1 when it was added two or more hours after the cell lines were exposed to the virus, although the aforementioned antimicrobial protein, LL-37 was able to inhibit HSV-1 replication independent of its time of addition relative to the HSV-1 exposure. Nonetheless, the study concluded that A $\beta$  could be reclassified as a novel antimicrobial protein, evolved specifically to enveloped, neurotropic viruses such as HSV-1 (Bourgade et al., 2014).

Based on these findings, it is entirely likely that the reason HSV-1 is a relatively reliable predictor for the later onset of AD is that the latent, viral infection is in a constant state of combatance by the antimicrobial protein that is A $\beta$ , and the constant production and secretion of this protein, which is also such a fundamental component of AD, leads to aggregation which triggers the onset of the neurodegenerative ailment in question, although more study on this subject must be done.

But, this finding was backed through the more recent study, Powell-Doherty et al., which once again examined the predictive nature of HSV-1 for the future onset of AD, this time examining the responsiveness of A $\beta$ , as well as the tau protein, which is another protein correlated with the onset and progression of AD, equivalent to A $\beta$  in terms of both progressive deposition as well as implied causality, yet much like its fellow protein, there is little to no evidence that tau plays a causal role in the exacerbation of AD. As for now, all that can definitively be said of the protein is that its presence and aggregation into neurofibrillary tangles (NFTs), is correlated with the progression of AD. But although little can be said with certainty of its role in AD it is, much like A $\beta$ , overwhelmingly likely that tau plays some causal, or at least exacerbational, role in the onset and progression of the disease.

This study explores the function of A $\beta$  and tau as antimicrobial proteins utilizing HSV-1 and murine hippocampal neurons in adult mice. Cultures of these hippocampal neurons were exposed to HSV-1 and after seven days, were studied in search of A $\beta$  and tau expression, both of which were observed at elevated levels, with A $\beta$  characteristically colocalizing with HSV-1 (Powell-Doherty et al., 2020). This study, at the very least, shows that A $\beta$  peptides, as well as tau, are involved in immunal responses to both acute and chronic threats by pathogens, implying that they are immune cells, an idea once again reinforced by the study of astrogliosis and A $\beta$  secretion by Frost & Li, 2017 (Frost & Li, 2017; Iacobelli, 2021).

This study, briefly touched on earlier, is important not for describing the function of A $\beta$  as an antimicrobial protein, but for linking A $\beta$  to an immunoreactive response that is present, but not exclusive to AD. In short, astrogliosis is an immune response of the CNS that involves the presence of astrocytes, a type of glial cell, which serve to combat pathogens and neural insults, especially those that are characteristic of neurotropic diseases, i.e. HSV-1. In the study, Frost & Li showed that active astrocytes express  $\beta$ -secretase (BACE1) with a higher prevalence than astrocytes at rest, and because this is the genetic complex necessary for the amyloid precursor protein (APP), which is the protein from which A $\beta$  is derived, to be cleaved along with  $\gamma$ -secretase via the amyloidogenic pathway, these astrocytes will secrete A $\beta$  (Frost & Li, 2017, Iacobelli, 2021). Because astrocytic glial cells outnumber neurons by a ratio of nearly ten to one, even minor secretion of A $\beta$  by astrocytes will facilitate rapid accumulation of the protein (Iacobelli, 2021). So, it is easy to see how this process plays an important role in the onset and progression of AD, but more important to this study is the fact that astrogliosis, a CNS immune response, yields A $\beta$  in such massive quantities. From an evolutionary perspective, an immune response so critical to our survival as astrogliosis would have evolved this mechanism of A $\beta$  secretion purposefully, and evidence explored thus far in this paper indicates that that purpose is to serve as an antimicrobial protein.

In further support of the antimicrobial nature of A $\beta$ , a 2012 study sought to establish links between astrocytic activity and viral infections which have been shown to facilitate the onset of viral encephalitis, a disease closely related in its physiology to AD (Bender, Frik, & Gomez, 2012). As we have examined, astrogliosis is a fundamental immune reaction for AD, but the same is true of most infections which attack the central nervous system. Various subtypes of viral infection including neurotropic herpesviruses (of which HSV-1 is a part), enteroviruses, retroviruses, and paramyxoviruses among others have been shown to trigger an astroglial response, and the astrocytes and microglia that serve as the constituent pieces in this defense against pathogens trigger inflammation and immune combatance against whatever viral infection is in question (Bender, Frik, & Gomez, 2012). Toll-like receptors, which are a type of protein that are amongst a class of pattern recognition receptors, play an important role in the proper function of the innate immune responses to CNS infections of any kind, and astrocytes which are active express these receptors at higher rates than astrocytes at rest (Bender, Frik, and Gomez, 2012). Recall that when active, astrocytes tend to express  $\beta$ -secretase (BACE), which is necessary for APP to be cleaved and propagate through the amyloidogenic pathway. Hence, active astrocytes tend to produce A $\beta$  in greater quantities.

Because the toll-like receptors on active astrocytes are implicated in the immune response, astrocytes will be activated in every astrogliosis immune response to CNS infections, and because these astrocytes are active, they will secrete A $\beta$ . There is no way to avoid the secretion of A $\beta$  peptides and intracellular APP domain (which will facilitate further secretion of A $\beta$ ) in conjunction with an immune response to pathogens that threaten the CNS. While we know that a pathological abuse of this immune response will undoubtedly catalyze the pathological abnormalities observed in AD patients, the 2012 study by Bender, Frik, and Gomez shows that, although more study of the relationship between astrocytes and viral infections is necessary, it can at least be inferred that astrocytic activation in response to CNS infections is regular, and by extension, A $\beta$  secretion is a normal, immunoreactive activity (Soscia et al., 2004).

It can now be observed that A $\beta$  secretion by astrocytes, which themselves are activated by the presence of a pathogen in the CNS, is a fundamental component of the neural system's immune response. Linking this revelation with the findings mentioned earlier by Dominguez et al., it can be assumed that when A $\beta$  is not available to a CNS which has been exposed to a viral pathogen, the host will be at greater risk for the exacerbation of infection, and from this it can be reasoned that A $\beta$  plays a role in the defense against that pathogen (White et al., 2014). Because no other factors in the Dominguez et al. study, nor the Bender, Frik, and Gomez study were altered, aside from the allowed expression of BACE in the former, it is safe to assume that the immune response observed in the Bender, Frik, and Gomez study is wholly necessary for the survival of the host as opposed to the success of the pathogen, and it is purely because this response was not available to the transgenically modified mice in the Dominguez et al. study that their mortality rate shot up. Thus, while not directly necessary for survival, it is safe to assume that A $\beta$  is necessary for defense against viral pathogens, thus substantiating an earlier cited claim by Bourgade et al. that A $\beta$  represents a novel class of antimicrobial proteins (Bourgade et al., 2014).

Kumar et al. showed, once again using transgenic mice, that an intracerebral injection of *Salmonella typhimurium*, in mice which had been transgenically modified to overexpress amyloid precursor protein (APP) and presenilin 1 (PSN1), both of which are genetic complexes whose expression is directly correlated to A $\beta$ , had a higher survival rate at four weeks of age than wild type mice, implying that increased production of A $\beta$  in youth actually serves to increase the survivability of mice, rather than present any type of danger as would be expected if A $\beta$  only played a pathological role as it does in the AD brain (Dominguez et al., 2005). Instead, increased A $\beta$  levels in the transgenically modified mice likely imply that the protein offers increased immunoprotective function to the transgenically modified mice that is not available to the wild type mice, and so the transgenically modified mice who have higher A $\beta$  levels as a result of their increased APP and PSN1 expression will be better able to combat infections and pathogenic agents who may otherwise fatally compromise the CNS of wild type mice (Kumar et al., 2016).

While further study must be done to solidify the notion that A $\beta$  serves as an antimicrobial protein, the link between its secretion and activity of astrocytes pretty clearly implicates the protein in the immunoreactive processes of the CNS. In addition, studies on transgenically modified mice have shown that A $\beta$  levels, dependent on the age of the subject, have a direct influence on the mortality rate of the mice, and are likely involved in immunoprotective functions of the CNS.

### III. PATHOLOGICAL TRANSFORMATION OF BETA AMYLOID IN AD PATIENTS

Once again, further study of A $\beta$  in the human immune system is required to say with any certainty whether or not A $\beta$  is an immunologically involved protein, but the mounting body of evidence on the subject certainly seems to indicate that A $\beta$  does in fact represent a novel class of antimicrobial proteins. Study in mice has shown that when A $\beta$  levels in youth are increased, they increase the survivability of young mice who overexpress APP and PSN1 (Dominguez et al., 2005), but as we know from historical analysis of the role that A $\beta$  plays in the onset and progression of AD, there is a universally observed correlation between the aggregation of A $\beta$  into plaques, and the worsening of AD's behavioral ramifications such as reduced cognition and loss of motor function (Zanetti, 2004; Soscia et al., 2010). This means that AD is an age dependent disease, but also that increased levels of A $\beta$  are not the only factor involved in the neurodegenerative process of AD. Neither of these facts are novel revelations, but are nonetheless important to reinforce.

The question is then not one of whether or not A $\beta$  is helpful or harmful, as we have come to understand that it can be both. Instead, the mechanism by which A $\beta$  turns from helpful to harmful should be called into question, and once again, astrogliosis is heavily involved in this process.

While there are many theories on the methods which render A $\beta$  neurotoxic in AD patients, the process can be thought of simply as a process in which the immunoreactive nature of glial cells in response to perceived pathogens is utilized to a pathological extent. There are several steps to this process, the first of which involves a trigger, that is variable, and may involve the expression of the apolipoprotein E4 isoform, which impairs the rate at which A $\beta$  is cleared from the brain (Iacobelli, 2021; Lin et al., 2018; Abramov, Cannevari & Duchon 2003). The clearance is rerouted from the LRP-1 receptor to the VLDLR, which clears the pathological A $\beta$  at a significantly slower rate. Whereas the E2 and E3 isoforms of this apolipoprotein are known to clear A $\beta$  through LRP-1 and VLDLR at a much quicker rate than the E4 isoform (Deane et al., 2008). Up to 65% of AD cases are predicted by the presence of the ApoE4 isoform, and thus this trigger, which simply causes aggregation by rerouting the channel through which A $\beta$  is cleared from the brain, may serve as the initial step in the onset of up to two thirds of AD cases.

The other possible trigger involves the preclinical myelin damage which triggers an initial immune response, which, as we have reiterated time and again throughout the text, is mediated by astrocytes that, when active, secrete A $\beta$  at substantial volumes (Frost & Li, 2017).

Either of these triggers will elicit an astrogliosis immune response, in which astrocytes rush to the scene of either the preclinical myelin damage or the A $\beta$  plaques which have accumulated due to impaired clearance as a result of ApoE4 expression. As they act on the sites, this astroglial response will lead to a deposition of A $\beta$  that is greater in volume than what preceded it, triggering more astrocytes to the scene which will in turn leave behind even more A $\beta$ , thus trapping the brain in a cycle through which an astroglial response is continually elicited, and the astrocytes involved continue to secrete significantly more A $\beta$  than they clear, thereby propagating the progression of AD (Iacobelli, 2021; Frost & Li, 2017).

While there are other theories proposed which have led to ideas such as the Tau Propagation Hypothesis or the Amyloid Cascade Hypothesis, this is thus far the best model to explain the pathology of A $\beta$  in an AD brain, and recent study has suggested that it all starts with the normal functioning of A $\beta$  as an antimicrobial protein in a healthy brain.

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