The Physiological Roles of Amyloid-β Peptide Hint at New Ways to Treat Alzheimer’s Disease

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Amyloid-β (Aβ) is best known as the misfolded peptide that is involved in the pathogenesis of Alzheimer’s disease (AD), and it is currently the primary therapeutic target in attempts to arrest the course of this disease. This notoriety has overshadowed evidence that Aβ serves several important physiological functions. Aβ is present throughout the lifespan, it has been found in all vertebrates examined thus far, and its molecular sequence shows a high degree of conservation. These features are typical of a factor that contributes significantly to biological fitness, and this suggestion has been supported by evidence of functions that are beneficial for the brain. The putative roles of Aβ include protecting the body from infections, repairing leaks in the blood-brain barrier, promoting recovery from injury, and regulating synaptic function. Evidence for these beneficial roles comes from in vitro and in vivo studies, which have shown that the cellular production of Aβ rapidly increases in response to a physiological challenge and often diminishes upon recovery. These roles are further supported by the adverse outcomes of clinical trials that have attempted to deplete Aβ in order to treat AD. We suggest that anti-Aβ therapies will produce fewer adverse effects if the known triggers of Aβ deposition (e.g., pathogens, hypertension, and diabetes) are addressed first.

Keywords: infection, antimicrobial, cancer, traumatic injury, cerebrovascular, immune system, seizure, ARIA

INTRODUCTION

The presence of large numbers of “senile plaques” in the hippocampus and overlying cortical regions is one of the definitive features of Alzheimer’s disease (AD). These spherical proteinaceous deposits consist primarily of a 38–42 amino acid long peptide known as amyloid-β (Aβ). The Aβ peptide is derived from a transmembrane protein called amyloid-β precursor protein (APP). β-site APP cleaving enzyme 1 (BACE1) cleaves APP to release the C99 fragment of APP. This fragment gives rise to various species of Aβ peptide during subsequent cleavage by γ-secretase. In the brain, Aβ is produced by astrocytes and neurons; however, non-neural tissues such as skin, skeletal muscle and intestinal epithelium also secrete Aβ (Puig and Combs, 2013). Normally present in a soluble form, Aβ is secreted into the extracellular space of the brain and then cleared by the cerebrospinal fluid (CSF) and vascular system. In the CSF of cognitively normal humans, the most abundant isof orm is 40 amino acids long (Aβ40; 2–3 ng/mL), while the second most common isof orm (Aβ42) is present at approximately 0.75 ng/mL (Ida et al., 1996; Mo et al., 2015). Experiments with transgenic mice that overexpress Aβ have revealed that the turnover of soluble
Aβ is rapid, and it is cleared from the extracellular space and CSF with a half-life of just 0.7–2.0 h (Savage et al., 1998; Abramowski et al., 2008). Radioactive tracer studies have shown that Aβ is removed from the circulation by the capillary beds of the kidneys, liver, gastrointestinal tract, and skin (Xiang et al., 2015).

Solute Aβ can bind to other molecules of Aβ to form oligomers that are cleared more slowly from the brain, or which can accrete to form insoluble Aβ plaques. Numerous in vivo and in vitro experiments demonstrated that the oligomeric and insoluble forms of Aβ are toxic to brain cells. These findings have led to the prevailing view that Aβ exhibits a “toxic gain-of-function” when it forms oligomers and aggregates into plaques, thereby directly contributing to the pathogenesis of AD, and making it the logical target for therapeutic intervention (Masters and Selkoe, 2012). However, of more than 200 clinical trials that specifically targeted Aβ between 1984 and 2013, none improved clinical outcomes in AD patients (Schneider et al., 2014). Indeed, some of these trials were associated with adverse outcomes. This situation has continued through to the present day, with not a single clinical trial between 2012 and 2017 producing a significant cognitive benefit. This frustrating lack of progress has led to suggestions that Aβ needs to be targeted at an earlier stage of the disease, prior to the onset of dementia or even before any cognitive changes are detectable (Tarawneh and Holtzman, 2009).

The term “amyloidogenic” is applied to any soluble peptide or protein that has the capacity to interact with similar molecules to self-assemble into insoluble fibrils, which then bond with other fibrils to form a regular β-pleated sheet. The molecular conformation of these amyloid sheets makes them strongly resistant to degradation by proteolytic enzymes. Functional amyloids and amyloidogenic peptides are common in biological systems. For instance, colonial bacteria utilize amyloids to aggregate, attach to a substrate, and improve the strength of their protective biofilms (Dueholm et al., 2013). Plants produce amyloids with strong antifungal and antimicrobial properties (Villar-Piqué et al., 2010; Garvey et al., 2013).

A meta-analysis of APP-like and Aβ-like sequences in living species has found that these sequences are present in hydra and sea anemones, indicating that the sequences must have evolved prior to the evolution of arthropods, around 500 million years ago (Tharp and Sarkar, 2013). All vertebrates produce APP, β-secretase, and Aβ; Aβ in birds, reptiles and amphibians has a >90% sequence homology with human Aβ, while in mammals the sequence homology exceeds 95% (Tharp and Sarkar, 2013). The conservation of the Aβ molecular sequence throughout vertebrate evolution implies that it must confer a selective advantage for species survival. This notion is further supported by evidence that depletion of endogenous Aβ has adverse consequences in a variety of species and animal models (summarized in Table 1). Although this concept runs counter to research that has focused on Aβ’s neurotoxic potential in AD, enough evidence has accumulated to suggest that Aβ serves a beneficial role in human physiology, where it may contribute to:

- **Antimicrobial activity**: Aβ has antibacterial, antifungal, and antiviral properties that are effective against at least eleven species of microbes.
- **Tumor suppression**: Aβ may intercept oncogenic viruses and suppress tumor growth.
- **Sealing leaks in the blood-brain barrier (BBB)**: Aβ binds blood-borne solutes together to form a plug that prevents the spread of neuroactive and toxic components into the brain.
- **Promoting recovery from brain injury**: The presence of Aβ results in better outcomes in animal models of controlled cortical impact, spinal cord injury, hypoxia, and autoimmune disease.
- **Regulating synaptic function**: Aβ regulates the responsiveness of glutamatergic and cholinergic synapses in the hippocampus, thereby contributing to memory consolidation.

Such beneficial properties may explain the persistence of Aβ throughout the vertebrate series. The following sections consider the evidence that supports each of these putative functions.

### Aβ Has Antimicrobial Properties

Among the first physiological functions of Aβ to be proposed was the “Bioflocculant hypothesis” (Bishop and Robinson, 2002; Robinson and Bishop, 2002), where we noted that the widespread occurrence of Aβ in healthy individuals suggests that Aβ plays a natural physiological role, one that is most probably protective. We suggested that “Aβ may have a broader role as a general chelator and flocculant of potentially toxic agents that are dissolved in the extracellular fluid. In addition to metal ions, this would include bacteria and viruses, proteins, and neuroactive molecules that have been inadvertently released into the extracellular fluid.”

Once bound and taken out of solution, we envisaged that these pathogens could be phagocytosed and cleared by microglia and macrophages. In our review of the recent evidence for Aβ’s role as an antimicrobial peptide (AMP), a class of innate immune molecules with broad-spectrum antimicrobial properties, we noted that Aβ not only binds and intercepts microbial pathogens, as suggested by the Bioflocculant hypothesis, but also possesses microbicidal activity that enables it to directly kill bacteria and viruses (Gosztyla et al., 2018).

The notion that Aβ is an AMP is consistent with reports that several other amyloid peptides have antimicrobial properties, including serum amyloid A, microcin E492, temporins, and protegrin-1 (for reviews see Bishop and Robinson, 2004a; Kagan et al., 2012). Their antimicrobial activity may be partly due to the capacity of these peptides to form fibrils that insert into cell membranes and create pores that permit the unregulated passage of solutes into and out of microbes, leading to the death of these cells (Kagan et al., 2012). Similarly, Aβ may capture and perforate microbes with its hairpin loop, while aggregates of Aβ may immobilize microbes, akin to neutrophil extracellular traps.

**Abbreviations:** Aβ, Amyloid-β; AD, Alzheimer’s disease; APP, amyloid-β precursor protein; AMP, antimicrobial protein; BACE1, β-site APP cleaving enzyme 1; HSV1, herpes simplex virus-1; APOE, apolipoprotein; CSF, cerebrospinal fluid; ARIA, amyloid-related imaging abnormalities; BBB, blood-brain barrier; TBI, traumatic brain injury; LTP, long-term potentiation.
TABLE 1 | Adverse consequences of endogenous Aβ depletion.

| Experiment | Model (Strain) | Results | References |
|------------|----------------|---------|-------------|
| BACE1 knockout | Mice (C57BL/6) | Worse motor performance following controlled cortical impact | Mannix et al., 2011a |
| BACE1 knockout or γ-secretase inhibition | Mice (C57BL/6) | More white matter damage and impaired locomotor recovery following spinal cord injury | Pajooshesh-Ganjii et al., 2014 |
| APP or BACE1 knockout | Mice (C57BL/6) | No compensatory increase in blood flow after cerebral ischemia, resulting in increased acute mortality | Koike et al., 2012 |
| APP knockout | Mice (C57BL/6) | Worse progression of experimental autoimmune encephalomyelitis | Grant et al., 2012 |
| Aβ immunodepletion, blocking of Aβ binding, or APP knockdown | Mice (CD-1 or C57BL/6) | Reduced hippocampal LTP and PTP, impaired spatial and contextual fear memory; rescued by treatment with human Aβ42 | Morley et al., 2010; Puzzo et al., 2011 |
| BACE1 knockout | Mice (C57BL/6) | Spontaneous epileptic seizures, impaired spatial memory | Hu et al., 2010 |
| BACE1 and BACE2 double knockout | Mice (mixed 129S5 and 129P2) | Increased mortality, reduced weight, hyperactive behavior | Dominguez et al., 2005 |
| Aβ immunodepletion | Rats (Long-Evans) | Impaired short- and long-term memory retention, rescued by treatment with human Aβ42 | Garcia-Osta and Alberini, 2009 |
| BACE1 or γ-secretase inhibition or Aβ immunodepletion | Rat (Wistar) cortical or cerebellar granule neurons, human SH-SY5Y cells | Reduced cell viability, rescued by incubation with human Aβ40 | Plant et al., 2003 |
| Aβ immunodepletion | Mouse lemur primates | Microhemorrhages, iron accumulation in the choroid plexus | Joseph-Mathurin et al., 2013 |
| Anti-APP morpholino or 8-secretase inhibition | Zebrafish | Cerebrovascular defects, rescued by treatment with human Aβ40 | Luna et al., 2013 |

APP, Aβ precursor protein; BACE1, B-site APP cleaving enzyme 1; PTP, post-tetanic potentiation; LTP, long-term potentiation.

and the destruction of microbes may be accelerated by increased oxidation in the presence of iron from ferritin-rich cells like microglia (Batton et al., 1997; Robinson et al., 2003; Bishop and Robinson, 2004b; Wang et al., 2012).

The antimicrobial activity of human Aβ was confirmed by Soscia et al. who demonstrated that the addition of 25 μg/mL of synthetic Aβ42 slowed the proliferation of seven different bacteria and one fungal species in culture as effectively or better than the innate defensin LL-37. Aβ42 was found to be slightly more potent than Aβ40 when delivered at the same concentrations. It may be argued that this antimicrobial effect is not representative of the in vivo situation, because the concentrations of Aβ used by Soscia et al. exceeded the physiological range by 4–5 orders of magnitude. However, this limitation was addressed by demonstrating that homogenates of temporal cortex from AD brain are more effective at inhibiting the growth of Candida albicans cultures than homogenates from cognitively normal subjects. This inhibitive effect was neutralized by pre-incubating the homogenates with anti-Aβ antisera, indicating that the antimicrobial activity was probably due to the higher Aβ burden in the AD brains (Soscia et al., 2010). Additionally, if Aβ responds to pathogens, it is likely that the concentration of Aβ in the immediate vicinity would far exceed the concentration of Aβ averaged across a given brain region. These findings were confirmed by Spitzer et al. who found that 25–50 μg/mL of Aβ42 agglutinated and reduced the viability of four bacterial species and the yeast C. albicans (Spitzer et al., 2016). Direct evidence for Aβ’s antimicrobial activity in vivo was reported in a recent study by Kumar et al. Here, mice and nematodes that overexpressed human Aβ demonstrated enhanced resistance to bacterial or yeast infections. Electron microscopy images revealed that Aβ fibrils entrapped bacterial and yeast cells in vitro and in vivo (Kumar et al., 2016).

In addition to bactericidal and fungicidal activity, Aβ has virucidal properties (reviewed by Bourgade et al., 2016a). Lukiw et al. demonstrated that high concentrations of Aβ42 inhibit the infection of human neuron-glia co-cultures by herpes simplex virus 1 (HSV1) as effectively as the antiviral agent acyclovir (Lukiw et al., 2010). An in vitro study by Bourgade et al. solidified this finding by demonstrating that Aβ42 and Aβ40 prevent HSV1 infection as effectively as LL-37, by binding to the virus and preventing its uptake into cells (Bourgade et al., 2015). This team further demonstrated that human H4 neuroglioma cells produce Aβ upon exposure to HSV1 and that transfer of cell media containing Aβ to naive H4 cells prevented HSV1 infection (Bourgade et al., 2016b). Aβ was ineffective against the non-enveloped human adenovirus, leading Bourgade et al. to conclude that the antiviral activity of Aβ is associated with a capacity to interact with viral coat proteins.

This conclusion is consistent with the findings of White et al. who showed that Aβ42, and to a lesser extent Aβ40, are effective at preventing infection of cultured cells by the pandemic strains H1N1 and H3N2 of the influenza virus (an enveloped virus) (White et al., 2014). The primary antiviral mechanism involves...
AB binding viral particles into extracellular aggregates that were then precipitated from the supernatant and unable to infect cultured fibroblasts. Furthermore, pre-incubation of the virus with soluble AB stimulated the subsequent uptake of virus by phagocytes but the virus did not replicate within these cells, indicating that the aggregated viral particles had been neutralized by the AB. The strength of these effects increased as a function of AB concentration. It appears that the antimicrobial property of AB is largely due to its capacities to permeabilize cells and to bind and aggregate pathogens. A recent study by the same group found that the AB42 C-terminal amino acids 41 and 42 are critical for this function, as fragments lacking these amino acids show an impaired ability to flocculate and promote neutrophil uptake of viruses and bacteria (White et al., 2018).

Indirect evidence from animal studies has shown that the production of AB waxes and wanes in response to immune challenge and healthy resolution. For example, AB deposits have been noted in wild-type mice infected with Chlamydia pneumoniae (Little et al., 2004, 2014; Boelen et al., 2007), HSV1 (Wozniak et al., 2007), pseudorabies virus (Tanaka and Nagashima, 2017), or Toxoplasma gondii (Torres et al., 2018), while transgenic-AD mice infected with Porphyromonas gingivalis showed increased AB deposition (Ishida et al., 2017). Notably, AB returned to normal levels after the C. pneumoniae infection had resolved. In addition, wild-type mice infected with persistent cerebral toxocariasis acquire insoluble AB deposits in the hippocampus at concentrations 10–20-fold higher than in uninfected mice (Chou et al., 2017). The presence of AB deposits in non-transgenic mice is significant because it may provide insight into the presence of AB in the 95% or more AD patients who have non-hereditary “sporadic” AD. This interpretation is further supported by evidence from human studies. CSF levels of soluble APP or AB decrease during CNS infection (Sjögren et al., 2001; Gisslén et al., 2009; Jesse et al., 2010; Mattsson et al., 2010; Angel et al., 2012; Krut et al., 2013), indicating that APP and AB42 are sequestered within the brain during this time. After resolution of Lyme neuroborreliosis and bacterial meningitis, CSF levels of APP, or AB42 return to normal (Sjögren et al., 2001; Angel et al., 2012).

Several researchers have championed the “Pathogen hypothesis” of AD (for review see Robinson et al., 2004b; Itzhaki et al., 2016), which postulates that AD may be caused by a cerebral infection of HSV1 (Ball, 1982; Ball et al., 2013; Itzhaki, 2014), Borrelia (Miklossy, 2015), or C. pneumoniae (Balín et al., 2008). While a discussion of that literature is beyond the scope of the present review, it is pertinent to note a variety of microbial species have been observed in AB plaques or AD brains. Specifically, HSV1 DNA (Wozniak et al., 2009), and Borrelia antigen and DNA (Miklossy, 2016) have been found in plaque cores, both Borrelia and C. pneumoniae have been cultured from AD brain tissue (Balín et al., 1998; Gérard et al., 2006; Dreses-Werringloer et al., 2009), and extracellular and intracellular C. pneumoniae and various intraneuronal fungal infections have been reported in AD brain tissue (Hammond et al., 2010; Alonso et al., 2014, 2015; Pisa et al., 2015a,b). These observations can be viewed within the context of work by Michael D’Andrea and others, which have demonstrated that intracellular accumulations of AB can burst out following cell death to produce extracellular dense-core plaques (reviewed by D’Andrea, 2014, 2016). A viral infection could contribute to intraneuronal deposition of AB, resulting in cell lysis, and the release of dense-core plaques containing viral DNA into the extracellular space. In contrast, extracellular AB accumulation could be attributed to the interception of bacterial or fungal pathogens. Taken together, these data suggest that AB responds to and limits various types of infections in cells, animals, and humans (Figure 1).

Since AB acts as an AMP, depletion of AB would be expected to increase infection rates or infection severity. Indeed, clinical trials that have targeted AB in AD patients have provided support for this notion (Table 2). For instance, approximately 6% of trial participants that received AN-1792, an active anti-AB immunization, developed meningoencephalitis (Orgogozo et al., 2003; Robinson et al., 2004a; Gilman et al., 2005; Patton et al., 2006), Increased infection rates, including orolabial herpes relapse, and upper respiratory infections, have been reported in clinical trials of β- or γ-secretase inhibitors [Green et al., 2009; Doody et al., 2013; AlzForum (n.d.-d, h, m)] and the AB-binding compound ELND005 (Salloway et al., 2011; Alonso et al., 2014). A recent meta-analysis of ten clinical trials concluded that γ-secretase inhibitors are associated with an increased risk of infections (Penninkinkampi et al., 2016). While these observations are not direct evidence of an antimicrobial role for AB, they are certainly consistent with this possibility and indicate that future clinical trials should be alert to the potential for such outcomes.

### Aβ MAY PROTECT AGAINST SOME FORMS OF CANCER

There is an impressive inverse relationship between AD and cancer. One interesting example is the naked mole rat, a notoriously cancer-resistant rodent that accumulates AB at levels similar to AD-mice bearing at least three human transgenes without developing memory impairment (Edrey et al., 2013; Deweerdt, 2014). Multiple studies have demonstrated that cognitively normal elderly patients who are diagnosed with cancer are less likely to subsequently develop AD, whereas patients who have been diagnosed with probable AD are half as likely to have had cancer or to develop cancer compared to age-matched, cognitively-normal peers (Driver et al., 2012; White et al., 2013; Catalá-López et al., et al., 2014; Ma et al., 2014; Shi et al., 2015; Yarchoon et al., 2017). While some reports have suggested that this relationship may be due to ascertainment bias (Freedman et al., 2016; Bowles et al., 2017; Hanson et al., 2017), a recent examination of nearly 3.5 million veterans found that the risk of several types of cancer is lower in AD patients, even after accounting for bias (Frain et al., 2017).

AD patients have significantly lower incidences of non-melanoma skin cancer, head and neck cancer, colorectal cancer, lung cancer, breast cancer, bladder cancer, and hematologic malignancies (reviewed by Shi et al., 2015). A recent analysis...
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FIGURE 1 | Aβ is antimicrobial against bacteria, fungi, and viruses. Aβ has the mechanical properties to trap microbes, insert into and permeabilize their membranes, and create a toxic oxidative response that is likely accelerated in the presence of iron obtained from nearby ferritin-rich cells.

of 4,357 subjects observed a reduced risk of AD following a diagnosis with incident cancer, though no difference in AD risk was found for prevalent cancers. However, when the analysis was restricted to late-stage prevalent cancers, diagnosis was associated with a 50% reduction in AD or dementia risk (Bowles et al., 2017). The fact that patients with vascular dementia have incidences of cancer that are comparable to those in the general elderly population (Roe et al., 2010) implies that there is something specific about AD that confers protection against cancer. This conclusion is supported by a meta-analysis of over 50 clinical studies involving more than half a million participants, in which it was found that AD is associated with a greatly reduced risk of cancer (Catalá-López et al., 2014).

While the basis of the protection against cancer is unknown, the outcomes of the AD clinical trials do not support a direct role for Aβ in the repression of cancer. While some of the trials reported increased rates of cancer, such trials involved γ-secretase inhibitors, rather than inhibitors of BACE1 or immunotherapy against Aβ (Table 2). For instance, clinical trials of the γ-secretase inhibitor Avagacestat were halted early, in part because seven patients developed squamous-cell or basal-cell carcinomas of the skin, compared to none in the placebo group (Coric et al., 2012, 2015). Similarly, a phase III trial of the γ-secretase inhibitor Semagacestat was discontinued after 5–6% of patients developed squamous-cell or basal-cell carcinomas of the skin, compared to none in the placebo group (Doody et al., 2013). A meta-analysis found that γ-secretase inhibitors are associated with a nearly five-fold increase in skin cancer risk (Penninkilampi et al., 2016). It should be noted that increased rates of cancer have not been reported for clinical trials that have specifically targeted Aβ, so it is likely that the adverse effects were related to functions of γ-secretase that are separate from its cleavage of Aβ, such as a loss of the APP cleavage product, Notch (Roperch et al., 1998; Paris et al., 2005).

Although the evidence from clinical trials does not support an active role for Aβ in the suppression of cancer, it is possible that circulating Aβ plays an indirect role by intercepting oncogenic viruses. Up to 18% of cancers are thought to be induced by oncogenic viruses (Parkin, 2006). For example, most non-melanoma skin cancers, including squamous-cell and basal cell carcinomas, contain human papillomavirus (Arroyo Mühr et al., 2015). It is notable that these forms of cancer are underrepresented in AD. The finding that the oncogenic virus Epstein-Barr stimulates the production of anti-Aβ antibodies, raises the possibility that some viruses may benefit from the elimination of Aβ (Xu and Gaskin, 1997). Since high titers of anti-Epstein-Barr virus antibodies in patients with mild cognitive impairment are predictive of future cognitive decline (Shim et al., 2017), it is tempting to speculate that AD may involve attempts by oncogenic viruses to neutralize the defenses provided by Aβ, which are then countered by increased production of antibodies against the virus. Such counter-responses could account for the lower rate of some cancers in AD.

Experimental evidence indicates that Aβ is capable of inhibiting tumor cell growth. For instance, the treatment of cultured cancer cell lines with conditioned media containing Aβ significantly reduced the rate of proliferation of human glioblastoma, human breast adenocarcinoma, and mouse melanoma cells (Zhao et al., 2009). The extent of the reduction was associated with the concentration of Aβ present in the medium and was not linked to the presence of APP. In mice, Aβ suppresses tumor growth when injected directly into human glioblastoma and human lung adenocarcinoma xenografts (Paris et al., 2004). Similarly, Aβ delivered into the
peritoneal cavity reduces the growth of lung adenocarcinoma xenografts (Paris et al., 2004). In transgenic mouse lines that overexpress Aβ, the rates of growth of implanted glioma tumor masses are suppressed by 40–50% at 8 months of age compared to tumor masses in wild-type mice (Paris et al., 2010).

Paris et al. demonstrated that high concentrations of Aβ inhibit capillary growth both in vivo and in vitro, and when present at very high concentrations it causes capillaries to degenerate. They concluded that Aβ may slow tumor growth by retarding neovascularization (Paris et al., 2004, 2010). An alternative possibility, suggested by the present authors, relates to the exceptionally high binding affinity of Aβ for iron, copper, and zinc (Bishop and Robinson, 2002; Robinson and Bishop, 2002). By scavenging free metal ions, Aβ may limit the availability of these essential micronutrients and slow the proliferation of tumor cells. Evidently there are several potential mechanisms that could account for the inverse relationship between AD and some forms

### TABLE 2 | Adverse events in Aβ-targeted clinical trials.

| Drug (Mechanism)                        | Aβ endpoints | Relevant adverse effects                                                                                                                                                                                                 | References |
|-----------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Aducanumab (Anti-Aβ immunization, Passive) | ↓ Aβ plaques | ARIA, ↑ Urinary tract infection, ↑ Upper respiratory tract infection                                                                                                                                                  | AbetaPro   |
| Aflitpoe AD02 (Anti-Aβ immunization, Active) | ↓ Aβ plaques | ↑ Atrophy and worsened cognition compared to unexpectedly beneficial placebo                                                                                                                                              | AbetaPro   |
| Alzhermed (Aβ-binding)                  | ↓ Focal plaques | ↑ Hippocampal atrophy, ↑ GI reactions                                                                                                                                                                                | Aflitpoe AD02 |
| AN-1792 (Anti-Aβ immunization, Active)  | ↓ CSF Aβ    | ↑ Atrophy transiently                                                                                                                                                                                                     | AbetaPro   |
| Avagacestat (γ-secretase inhibitor)     | ↑ Fibrillar Aβ | ARIA (~33% in APOE4/4, 7% in APOE4/3, 4% non-APOE4), ↑ Seizures, ↑ Paranoid, ↑ Skin/GI/vascular reactions                                                                                                          | Aflitpoe AD02 |
| B11181181 (BACE-inhibitor)             | ↓ CSF Aβ ~80% | ↑ ARIA in strong responders, ~8% Attrition for safety concerns, ↑ Acute psychosis, ↑ Skin/GI/vascular reactions                                                                                                        | AbetaPro   |
| CAD106 (Anti-Aβ immunization, Active)   | ↓ Brain Aβ | ARIA (temporary and in areas with the most Aβ reduction), “Futility”                                                                                                                                                     | AbetaPro   |
| ELIND005 (Aβ-binding)                   | ↓ Plasma Aβ | ↑ Infections, ↑ Relapse of orolabial herpes, ↑ Ventricular volume, ↑ Infections, ↑ Liver toxicity                                                                                                                                 | AbetaPro   |
| Gantenerumab (Anti-Aβ immunization, Passive) | ↓ Aβ ~11% | ARIA (temporary and in areas with the most Aβ reduction), “Futility”                                                                                                                                                     | AbetaPro   |
| LY2886721 (BACE-inhibitor)             | ↓ BACE activity 50–75% | ARIA (permanent and in areas with the most Aβ reduction), “Futility”                                                                                                                                                     | AbetaPro   |
| RG7129 (BACE-inhibitor)                | ↓ AβAβ2 ~72% | ↑ Liver toxicity                                                                                                                                                                                                           | AbetaPro   |
| Semagacestat (γ-secretase inhibitor)   | ↑ Plasma AβAβ2 38–72% | ↑ ARIA (permanent and in areas with the most Aβ reduction), “Futility”                                                                                                                                                   | AbetaPro   |

Documented negative outcomes from clinical trials that have targeted Aβ. Not all results are reported. Only drugs with reported effects or side-effects outside of Aβ modulation are included on this table. ARIA, Amyloid-related imaging abnormalities; APOE, apolipoprotein; NE, no effect.
of cancer, and until further research has been conducted, the basis of this relationship will remain a matter for speculation.

Aβ SEALS LEAKS IN THE BLOOD-BRAIN BARRIER

In contrast to cancer, the link between Aβ and the integrity of the BBB is firmly established. Aβ plaques in AD brain tissue contain many different blood proteins and peptides, including serum albumin, fibrinogen, thrombin, IgG, von Willebrand factor, collagen IV, and hemin (Cullen et al., 2006), which are normally foreign to the brain. Hemoglobin also binds to Aβ in an iron-dependent manner and colocalizes with Aβ plaques and vascular deposits in post-mortem AD brains (Oyama et al., 2000; Wu et al., 2004; Chuang et al., 2012). In 2002, one of us proposed that if the BBB becomes leaky, allowing pro-inflammatory and neuroactive compounds to enter the brain, soluble Aβ will bind these compounds into an insoluble mass to prevent their spread through the neuropil (Bishop and Robinson, 2002). Other researchers have built on this idea. Stone demonstrated that practically all plaques in AD are closely associated with a capillary, thereby supporting a causal link between a leaky BBB and Aβ deposition (Stone, 2008), while Atwood et al. (2003) proposed that Aβ may serve as a vascular “scab” that seals breaches of the BBB.

Aβ may slow bleeding with filamentous aggregates that pull the walls of the capillary endothelial cells back together (Atwood et al., 2003). In fact, incorporation of Aβ into the surface of either red blood cells or endothelial cells increases the probability that the cells will adhere to the microvasculature (Ravi et al., 2004; Figure 2). Viewed from this perspective, the heavier plaque burden in AD may be because the BBB is more porous than in non-demented elders. A recent imaging study reported that the BBB becomes more permeable in the human hippocampus with age, and that permeability is more pronounced in individuals with mild cognitive impairment than in age-matched controls or those with multiple sclerosis (Montagne et al., 2015). In support of this hypothesis, cortical superficial siderosis is seven times more common in AD than in age-matched controls (Dubissy et al., 2012; Wollenweber et al., 2014); this condition is due to the accumulation of iron from extravasated hemoglobin, and its presence is indicative of a history of micro-hemorrhages (Charidimou et al., 2015). It follows that removal of Aβ in AD is likely to lead to increased BBB permeability and an increase in micro-hemorrhages and subsequent brain edema.

Clinical trials targeting Aβ have provided dramatic confirmation of this hypothesis. The most common adverse side-effect of these trials has been MRI evidence of brain edema and/or micro-hemorrhages, sometimes accompanied by increased confusion and disorientation. This pattern of pathological change, so characteristic of amyloid depletion, has been termed “Amyloid-Related Imaging Abnormalities” (ARIA). The prevalence of ARIA has been very high in clinical trials of passive immunotherapies (e.g., Bapineuzumab, Solenezumab, Aducanumab, and Gantenerumab) (reviewed by Lanning et al., 2014; DiFrancesco et al., 2015). In the clinical trials with Bapineuzumab for instance, the incidence of ARIA with edema increased from 7.1% of patients on the lowest dose of the drug to 30.8% of patients on the highest dose; 47.2% of these patients also exhibited evidence of micro-hemorrhages, while a further 4% had micro-hemorrhages without evidence of increased edema (Sperling et al., 2012). In the Aducanumab trials, the incidence of ARIA was even higher, at 47–55% of participants in the highest dosage group (AlzForum (n.d.-a); DiFrancesco et al., 2015; Sevigny et al., 2016). A meta-analysis of fourteen clinical trials found that anti-Aβ immunotherapies are associated with a nearly five-fold increase in ARIA (Penninkilampi et al., 2017). Unlike trials targeting secretases, these immunotherapies targeted Aβ without altering APP processing, suggesting that ARIA is directly related to the loss of Aβ. ARIA resulting from the targeting of Aβ is more likely to occur in carriers of the apolipoprotein ε4 (APOE ε4) allele AlzForum (n.d.-e), and imaging confirms that the edema occurs at focal sites that exhibit the greatest reductions in Aβ (Ostrowitzki et al., 2012). The edema results from the entry of blood solutes into the neuropil, followed by an influx of water into the brain along the osmotic gradient.

Although ARIA was not observed in the early experiments with transgenic mice, subsequent experiments have confirmed that the link exists. For instance, anti-Aβ immunotherapy of PDAPP mice, which overexpress APP, leads to an increase in BBB permeability in a subset of mice that is accompanied by cerebral microbleeds, siderosis, and localized edema, which are the hallmarks of ARIA (Blockx et al., 2016). Similarly, aged mouse lemur primates, which exhibit an age-associated accumulation of endogenous Aβ with a peptide sequence that is similar to that in humans, also develop ARIA following anti-Aβ immunotherapy (Joseph-Mathurin et al., 2013).

Several lines of experimental evidence from mice indicate that BBB breakdown leads to increased Aβ deposition. Mice that overexpress endothelin-1, resulting in a weakened BBB, show increased astrocytic secretion of Aβ following an ischemic stroke (Hung et al., 2015). Micro-hemorrhages created with Rose Bengal dye in transgenic-AD mice drove transient increases in Aβ plaques in infarcted and adjacent areas (Garcia-Alloza et al., 2011). Similarly, micro-hemorrhages created with diet-induced hyperhomocysteinemia in transgenic-AD mice shifted the distribution of Aβ deposits from the parenchyma to the vasculature (Sudduth et al., 2014). Furthermore, hemorrhages induced by needle stick lesions in wild-type rats led to a transient up-regulation of APP, Aβ, and phosphorylated tau near the lesion site and a longer-lasting deposition of Aβ along the needle tract (Purushothuman et al., 2013). Mice that have been chronically subjected to high blood pressure develop Aβ deposits around their cerebral blood vessels and display learning impairments (Carnevale et al., 2016).

Collectively, the preceding observations provide powerful support for the view that Aβ seals leaks in the BBB, a role that probably becomes increasingly important as the aging BBB gradually loses its integrity. Viewed from this perspective, comorbid conditions that are likely to enhance the permeability...
FIGURE 2 | Aβ seals leaky vessels. Traumatic brain injury and cerebrovascular insults stimulate Aβ production and draw Aβ to the vasculature. Aβ binds to red blood cells (RBCs), blood proteins, and to iron (Fe) and copper (Cu) ions. These interactions cause Aβ to aggregate at the site of hemorrhage or breaches of the BBB. Aβ anchors into cell membranes and increases adherence between RBCs and vascular endothelial cells, helping to seal leaks in the vasculature.

of the BBB, such as diabetes and vascular hypertension, should be correlated with a heavier plaque burden. Indeed, a diabetic phenotype does increase the expression of Aβ in AD-Tg mice (Ho et al., 2004), is sufficient to do the same in wild-type rabbits (Bitel et al., 2012), and is associated with greater plaque pathology in the subset of diabetic AD patients with an APOE ε4 genotype (Malek-Ahmadi et al., 2013). Similarly, vascular hypertension is associated with higher Aβ burdens in wild-type animal models (Gentile et al., 2009; Schreiber et al., 2014; reviewed by Bueche et al., 2014), increased Aβ aggregates in the human placenta (Kalkunte et al., 2013; Buhimschi et al., 2014), and increased Aβ deposits in the AD brain (Ashby et al., 2016).

Aβ MAY IMPROVE RECOVERY FROM BRAIN INJURY

The presence of Aβ plaques in the hippocampus and cerebral cortex has become synonymous with AD, to the point where cognitively normal persons with significant Aβ burdens are assumed to have incipient AD. However, as was seen in the preceding sections, the presence of Aβ deposits does not necessarily indicate AD; they may indicate sites where pathogens have been intercepted and neutralized or where a leaky BBB has been repaired. Another well-documented role of Aβ is in assisting the brain to recover from traumatic and ischemic injuries.

In humans, a traumatic brain injury (TBI) elevates APP levels in the brain within 2 h (McKenzie et al., 1996) and Aβ plaques become evident within 4 h (Roberts et al., 1994; Graham et al., 1995; Johnson et al., 2010). Two microdialysis studies of brain extracellular fluid from TBI patients found that those with the higher titers of Aβ experienced better outcomes (Brody et al., 2008; Magnoni et al., 2012). Aβ plaques form routinely after a head injury, even in children as young as 10 years, who presumably would not otherwise have plaques (Roberts et al., 1994; Graham et al., 1995), and they are more likely to form in APOE ε4 carriers (Nicoll et al., 1995; Zunarelli et al., 1996; Mauri et al., 2006; Abu Hamdeh et al., 2017). A PET study of TBI patients found that while Aβ deposits colocalized with areas of white matter damage, the Aβ burden was not significantly correlated with the extent of neuropsychological impairment (Scott et al., 2016). Though Aβ accumulation occurs immediately after a traumatic injury and can persist in damaged axons for years (Johnson et al., 2012; Scott et al., 2016; Bagnato et al., 2017), the brains of long-term survivors of head injury do not have greater plaque numbers or increased APP expression when compared to age- and APOE-matched controls (Macfarlane et al., 1999; Chen et al., 2009). This suggests that Aβ accumulates transiently in response to injury.

Evidence from animal models also shows that Aβ expression responds rapidly to injury, resolves over time, and may be necessary for a good recovery. A recent meta-analysis of 19 animal studies reported that Aβ expression consistently increases within 24 h of TBI, including in models that lack AD-related transgenes (Bird et al., 2016). For example, controlled cortical impact leads to an upregulation of APP and BACE1 expression in wild-type rats (Blasko et al., 2004; Acosta et al., 2017) and accelerates Aβ deposition in transgenic-AD mice (Tajiri et al., 2013; Washington et al., 2014; Shishido et al., 2016). Controlled cortical impact increases the expression of Aβ40 and Aβ42 in transgenic-AD mice within one day, with levels returning to baseline within one week (Washington et al., 2014). During this early period, post-injury macrophage activation is suppressed (Kokiko-Cochran et al., 2016), which may provide
injured neurons with time to repair and recover, instead of being phagocytosed.

It is notable that controlled cortical impact results in worse motor performance in mice that are deficient in BACE1 compared to wild-type mice (Mannix et al., 2011a), and when the mice are treated with intra-ventricular injections of Aβ40 after the injury, motor performance improves in the knock-out mice but worsens in the wild-type mice (Mannix et al., 2013). These results suggest that the level of Aβ production in wild-type mice affects controlled cortical impact was tuned and appropriate. Recovery after controlled cortical impact is also modulated by age and APOE genotype; in immature and adult mice expressing human APOE ε4, only adults showed worse spatial memory performance compared to wild-type, as well as high Aβ40 levels 1 month after injury (Mannix et al., 2011b). Similarly, Aβ expression increases during the first 3 days after spinal cord injury, and if Aβ production is prevented by BACE1 knock-out or by treatment with a γ-secretase inhibitor, the mice develop more white matter damage, and display impaired recovery from locomotor deficits (Pajooshesh-Ganj et al., 2014).

Steinman et al. noted that Aβ42 is prominent in cerebral lesions and in the damaged axons of patients with multiple sclerosis, and postulated that this might represent a protective response to injury (Ferguson et al., 1997; Trapp et al., 1998; Han et al., 2008). Steinman’s group delivered intraperitoneal injections of Aβ40 or Aβ42 into four different animal models of multiple sclerosis. Astonishingly, they found that the treatment attenuated motor paralysis, reduced the extent of demyelinated lesions, suppressed lymphocyte activation, and lowered pro-inflammatory cytokine expression in blood. In contrast, APP knockout mice fared much worse than wild-type mice. It is important to note that protection in this model was associated with a hexameric form of Aβ that reduces T-cell activation (Grant et al., 2012).

Another example of the protection that Aβ affords from brain injury comes from experimental models of stroke. In wild-type mice, occlusion of the common carotid artery drives a compensatory increase in blood flow in the cerebral arteries, but this compensatory increase is attenuated in APP knock-out mice (Koike et al., 2012). This reduction of compensatory blood flow is lethal, and consequently APP knock-out mice die shortly after bilateral occlusion of the common carotid artery, whereas wild-type mice survive; since BACE1 knockout mice suffer the same fate, this loss of viability is likely due to the absence of Aβ rather than other products of APP cleavage (Koike et al., 2012). Further evidence that Aβ is protective during a stroke comes from a rat model of middle cerebral artery occlusion, in which the mean infarct volume is significantly reduced in transgenic-AD rats compared to wild-type rats (Clarke et al., 2007).

The preceding observations show that the presence of Aβ improves outcomes after injury to the central nervous system. Consequently, pre-emptive anti-Aβ treatments for AD are likely to increase the probability that the treated individuals will display poorer prognoses if they have the misfortune of sustaining a TBI (e.g., from a fall) or a stroke.

**Aβ MAY REGULATE ACTIVITY AT HIPPOCAMPAL SYNAPSES**

A growing body of evidence demonstrates that soluble Aβ is necessary for synaptic plasticity and memory (reviewed by Puzzo and Arancio, 2013; Morley and Farr, 2014). During periods of neuronal activity, APP is transported anterogradely to synapses, where Aβ is cleared and released along with neurotransmitter into the synaptic cleft (Kamnetz et al., 2003; Cirrito et al., 2005; Tampellini et al., 2009). Aβ then acts on presynaptic neurons to increase the probability of further neurotransmitter release (Fedele et al., 2015; Puzzo et al., 2015). Depletion of endogenous Aβ in rodents greatly reduces LTP and short- and long-term memory; this can be rescued by the addition of human Aβ42 (Garcia-Osta and Alberini, 2009; Morley et al., 2010; Puzzo et al., 2011). Additionally, rodents treated with picomolar concentrations of human Aβ42 show enhanced memory compared to a scrambled control peptide or vehicle (Garcia-Osta and Alberini, 2009; Morley et al., 2010). The duration of Aβ exposure seems to be important for this process. Mouse hippocampal neurons exposed to physiological concentrations of oligomeric Aβ42 show enhanced plasticity within minutes, but reduced plasticity with prolonged exposure (Koppensteiner et al., 2016). This was confirmed in vivo, as brief hippocampal infusions of Aβ42 enhanced contextual memory in mice, while longer infusions impaired memory (Koppensteiner et al., 2016).

Aβ may enhance long-term potentiation (LTP) by increasing the amount of acetylcholine released into the synaptic cleft and increasing the probability that the postsynaptic neuron will depolarize. Mice injected with low concentrations of Aβ into the hippocampus showed enhanced memory retention in two memory tasks and increased acetylcholine production in the hippocampus (Morley et al., 2010). Picomolar concentrations of Aβ directly activate α7-nicotinic acetylcholine receptors, whereas nanomolar concentrations of Aβ block and inactivate the receptors. Similarly, picomolar concentrations of Aβ42 enhance LTP and memory consolidation in mice, while nanomolar concentrations impair memory (Fedele et al., 2015; Puzzo et al., 2015; Ricciarelli and Fedele, 2017). Furthermore, Aβ-mediated enhancement of memory is ineffective in the absence of α7-nicotinic acetylcholine receptors (Fedele et al., 2015; Puzzo et al., 2015; Ricciarelli and Fedele, 2017).

In addition to interacting with acetylcholine signaling, Aβ can also stimulate glutamatergic receptors. Nanomolar concentrations of Aβ facilitate NMDA (N-methyl-D-aspartate) receptor-mediated LTP, while picomolar concentrations enhance contextual fear memories. When Aβ is present at high picomolar concentrations (which are pathological), it can disrupt the clearance of glutamate from the extracellular space by astrocytes, leading to a build-up of extracellular glutamate that then causes aberrant activation of NMDA receptors and eventual synaptic dysfunction (Tu et al., 2014).

Some clinical trials that have depleted patients’ brains of Aβ have reported increased rates of adverse events that might be attributable to synaptic dysfunction. For instance,
increased seizure activity was reported in clinical trials of the anti-\(\beta\)-immunotherapy Bapineuzumab (AlzForum (n.d.-e)). In other clinical trials the removal of A\(\beta\) has been accompanied by worse cognitive outcomes. For example, the \(\gamma\)-secretase inhibitor Semagacestat caused significantly lower scores on tests of cognitive status, functional status, and dementia in a dose-dependent manner, which did not resolve until 32 weeks after termination of drug dosing (Doody et al., 2013). Avagacestat, another \(\gamma\)-secretase inhibitor, was also associated with a decrease in performance on these same cognitive tests, though it did not reach statistical significance (Coric et al., 2012, 2015). In trials of active anti-\(\beta\) immunotherapies, Affitope AD02 counteracted the surprisingly beneficial effect of the placebo on cognitive function (AlzForum (n.d.-b); Schneeberger et al., 2009; AlzForum, 2014b), while CAD106 caused an increase in acute psychosis (AlzForum (n.d.-g); AlzForum, 2014a). The negative cognitive effects of anti-\(\beta\) immunotherapies support a direct role of A\(\beta\) depletion in contributing to synaptic dysfunction in these trials.

While most animal studies have not reported adverse cognitive or behavioral effects after immunization with A\(\beta\), two anti-A\(\beta\) immunotherapies (one was the rodent equivalent of Bapineuzumab) were recently tested in two transgenic mouse models of AD and all four conditions resulted in neuronal hyperactivity and dysfunction, independent of the effects of these antibodies on the clearance of A\(\beta\) plaques (Busche et al., 2015). Notably, however, others have reported that anti-APP/\(\beta\) immunotherapy successfully reduced neuronal hyperexcitability and epileptiform discharges in triple transgenic-AD mice (Kazim et al., 2017). This may be explained by the use of older mice in the former study, compared to younger pre-plaque mice in the latter. Additionally, the inability of the antibody used in the latter study to differentiate between APP and A\(\beta\) could also be a contributing factor to the discrepancy. Other studies have reported that the absence of APP and A\(\beta\), due to the knockout of APP or BACE1, increases spontaneous seizure activity and potentiates elicited seizures (Steinbach et al., 1998; Hu et al., 2010). Finally, the treatment of healthy wild-type mice with A\(\beta\) immunotherapy or with antisense directed at APP significantly impaired their learning on a T-maze foot-shock avoidance task (Morley et al., 2010). Collectively, the evidence reviewed in this section provide strong evidence for A\(\beta\) serving a physiological role in hippocampal LTP and memory retention.

**CONCLUSION**

The research reviewed in the current paper reveals that the A\(\beta\) peptide is involved in the protection and repair of the central nervous system. A\(\beta\) regulates synaptic function and contributes to memory consolidation; it may also protect from some forms of cancer and aid recovery from TBI. There is solid evidence that pathogens or a breach in the BBB trigger soluble A\(\beta\) to aggregate into insoluble deposits in order to intercept the pathogen or seal the leak. Some of the adverse outcomes associated with clinical trials can be understood from this perspective: a reduction in the capacity to intercept pathogens leads to a higher incidence of infections, while a loss of capacity to seal leaks in the BBB leads to increased numbers of micro-bleeds and brain edema (ARIA). This being the case, targeting the production or removal of A\(\beta\) earlier in the course of AD is likely to be associated with the same adverse events, except that the longer duration between start of treatment and patient death will increase the likelihood of these adverse events occurring during the lifetime of the patient and may reduce the patients’ capacity to recover.

More favorable outcomes might be achieved by treating the known triggers of A\(\beta\) deposition before targeting A\(\beta\) production. This would involve screening patients for potential causes of BBB leakage (such as diabetes or vascular hypertension) and/or for evidence of latent microbial infections, and then treating accordingly. Such treatments should slow the rate of A\(\beta\) deposition, with corresponding benefits for cognition. Once these known sources of A\(\beta\) deposition have been addressed, we would expect subsequent anti-\(\beta\) therapies to be associated with fewer instances of ARIA or brain infection. However, it remains possible that anti-\(\beta\) therapies will adversely affect learning and memory, recovery from TBI or the incidence of some forms of cancer.

**AUTHOR CONTRIBUTIONS**

HB: Wrote the first draft of the manuscript; MG and SR: Substantially revised subsequent drafts. All authors have read and approved the final manuscript.

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