Chapter 2

Alzheimer's Disease: Beyond the Neuron

Aradhana Verma and Matthew Zabel

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Abstract

This chapter describes the various systems beyond the central nervous system that are associated with Alzheimer's disease (AD). There is strong evidence to believe that while AD has symptoms of memory and cognitive impairment—undoubtedly domains of the central nervous system—the primary insult that causes this condition may arise systemically. We describe associations with the immune system, gut microbiome, and endocrine abnormalities that may be at play. Our goal is to incorporate a multi-system approach to understand the pathogenesis of AD. Our body does not function as soloed organ systems, and we hypothesize that the mechanisms described herein are similarly contributing to the progression of cognitive impairment in AD.

Keywords: microglia, inflammation, metabolism, diet, gut microbiota, amyloid

1. Introduction

No scientific problem has seen more heartbreak and frustration than the challenges of Alzheimer's disease (AD). This is not surprising—we are dealing with a disease that progressively degenerates a complex biological system. A century has passed since the symptoms were first recorded by Dr. Alois Alzheimer, yet we lack meaningful treatments. We propose that this is not a weakness of past research, but a misguided approach that focuses on specific aspects of disease pathogenesis centering within the brain and out of context from other systems involved. In other words, we suggest that the seemingly elusive nature of piecing together this tragic disease is due to viewing it through the lens of only one or two potential mechanisms at a time. Our goal is to synthesize several mechanisms into an explanation of disease pathogenesis that incorporates neurons, the immune system, and even the gastrointestinal tract and its microbial inhabitants. We will show that the pathology seen in AD is

a result of multiple hits contributed by systems within and outside the brain parenchyma and thus prompt the search for novel therapies that address the multi-organ etiology of AD pathology.

2. The amyloid cascade hypothesis

The most widely accepted theory of AD etiology is the amyloid cascade hypothesis [1], which maintains that overproduction and/or decreased clearance leads to extracellular aggregation of the presumably toxic amyloid-beta (Aβ) peptide. These extracellular Aβ aggregates act to increase neuronal kinase activity, resulting in phosphorylation of the microtubule-associated protein tau. Hyperphosphorylation of tau induces formation of intracellular aggregates known as neurofibrillary tangles and alters intracellular transport along microtubule tracks. This in turn abolishes neuronal communication, resulting in cell death in a spatially conserved pattern and producing deficits in networks that subserve memory and cognition. Aggregation of Aβ and tau is well-established pathological characteristics of AD brain tissue at autopsy. It is also known that in familial forms of AD, mutations in amyloid precursor protein (APP), Presenilin 1, or Presenilin 2 accelerate Aβ production and accumulation and lead to cognitive decline at a much earlier age. Presinilins function as part of the gamma secretase protein complex, one of three proteolytic enzymes responsible for cleaving APP into Aβ or nonaggregating amyloid peptides. Autopsy samples from brain parenchyma of patients with familial AD, which account for less than 1% of all AD cases, present with exorbitant Aβ and Tau accumulation similar to sporadic AD. Additionally, since the APP gene is located on chromosome 21, individuals with Down syndrome (trisomy 21) invariably develop AD-like dementia, also at a younger age than sporadic cases. This intuitively makes sense: an extra copy of APP on chromosome 21 will inevitably lead to the generation of more Aβ. However, it is highly uncertain to what degree familial AD and Down syndrome recapitulate the initial stages of sporadic AD, which accounts for the vast majority of AD cases. This is the core of the debate surrounding the amyloid cascade hypothesis: Is Aβ aggregation the start of AD or a downstream effect of an earlier insult? Additionally, and of considerable concern, to the day of writing this chapter, multiple immunotherapy clinical trials that target and clear Aβ as well as trials to block the activity of the secretases have failed to reverse cognitive loss and, in some cases, have accelerated it [2]. In this chapter, we will describe Aβ aggregation only as surrogate for the final common pathway of multiple disease mechanisms leading to the established end pathology of AD and not as a direct, initiating cause of clinical demise.

3. Microglia in brain homeostasis

3.1. Microglia and brain development

Microglia are the endogenous immune cells of the central nervous system. Over the past decade, the ontogeny of microglial cells has been controversial. Their developmental progression has

gone through several interesting iterations leading to our current understanding of how these peripherally derived cells come to reside in the central nervous system [3]. During development, myeloid precursors travel to the brain and then differentiate into microglia (CNS parenchymal macrophages). These tissue-specific macrophages make their way to the brain through the circulation from the embryonic yolk sac [4]. They grow concurrently with neurons, before the development of astrocytes and oligodendrocytes, participating in key neurodevelopmental events such as neurogenesis, synaptic pruning, and thus the development and remodeling of neuronal circuits. There is evidence that microglia need to adapt to their quickly changing environment and modify their functions as needed [5]. It seems logical, then, that aberrant or impaired microglial activation during development would be implicated in CNS disease later on in life.

Early brain development involves a vast amount of axon and synaptic growth—a process known as exuberant synaptogenesis. During early childhood and puberty, these synapses are slowly eliminated in a regulatory process called synaptic pruning. Interestingly, the mechanisms responsible for synaptic pruning are related to peripheral immune mediators such as major histocompatibility complex [6] and complement proteins [7, 8]. As described in a review by our group [9] and briefly summarized below, the reemergence of these molecules in the aging brain may lead to inappropriate synaptic pruning and uncontrolled neuroinflammation.

3.2. Microglia and AD

The role of microglia in the body is the story of Goldilocks. Much like the body's peripheral immune system, diseased or dystrophic microglia have diminished capacity to fight exogenous infections, clear endogenous cellular waste products, or promote homeostasis after an injurious insult. On the other hand, too much activation can severely harm the brain, much like how autoimmunity or graft rejection occurs in the periphery. In the brain, microglia contribute to Aβ clearance [10, 11]. However, the ability of microglial clearance appears to deteriorate and, in some cases, negatively change with age [12, 13]. At late stages of AD, microglia are thought to become overstimulated and paradoxically contribute to the disease by releasing proinflammatory cytokines in response to Aβ deposition [14, 15] or actively phagocytosing damaged, but live neurons [16]. Recent studies have consistently shown complement cascade proteins C1q and C3b—both normally associated with peripheral inflammation—upregulated on synapses induced by Aβ plaques in a mouse model of AD. Microglia then eliminated these C1q- or C3b-tagged synapses, leading to neurodegeneration and behavioral impairment [17, 18]. Immunohistochemistry studies reveal that Ig-positive neurons were C1q and C5b-9-positive and appeared degenerative [19]. These data suggest that neurons in AD brains are dying from an antibody-induced classical complement process. Additionally, newly discovered genetic risk factors are based on microglial phagocytosis, including CD33 [20], TREM2 [21, 22], and complement receptor 1 [23]. A full description of these mechanisms is out of the scope of this chapter, but the reader is encouraged to read more exhaustive reviews on this topic [24–26]. Nonetheless, it is a fascinating prospect that a peripherally derived cell plays such a large part in a central nervous system disease and that many of the processes used for brain development resurface to wreak havoc during degeneration. This shall segue into our next section discussing purely systemic mechanisms of AD pathogenesis.

4. Peripheral manifestations of a central nervous system disease

Over the past two to three decades, significant research effort has attempted to characterize the peripheral contributions to brain disease. This is a fascinating notion, considering the apparent impermeability of the central nervous system. However, even this impermeability depends on the environment to which the brain is subjected and may be under the influence of factors important during development. Unlike most other organs (with the exception of the retina and testes), the brain is highly susceptible to injury by chemical stressors normally present outside the confines of the blood-brain barrier (BBB). Neurons, despite their seemingly robust ability to work throughout the human lifespan, constant firing during that lifespan and frequent turnover of their signal transmitting elements (synapses), are a delicate class of cells. For this, neurons are accompanied by three other cell types termed glial cells, which are supportive in nature. These consist of the myelinating oligodendroglia, the jack of all trades astroglia and the aforementioned specialized immune cells of the CNS called microglia. All of these cells—count approximately 172 billion [27]—are separated from the nearly 500 miles of brain vasculature and capillary networks by the tight junction-lined and sealed BBB [28]. Most of the protection afforded to neurons is performed by the BBB, microglial cells, and astrocytes. Dysfunction of any of these components leads to some form of neuronal compromise. In this section, we will concentrate specifically on the BBB and microglia and how peripheral insults, including an unsuspecting role of the resident microflora, may influence their ability to protect neurons.

4.1. Systemic inflammation

Recent studies reveal that a cross-pollination between molecules thought to be exclusively involved with either the CNS or the immune system. Cytokines, complement proteins, and major histocompatibility complex (MHC) class 1 proteins have all been implicated in brain development [29–31] and neurological disease.

We know that bacterial, viral, fungal, and parasitic infections that target the CNS are associated with an increased risk of AD. These infections likely trigger a chronic, systemic inflammatory state in the CNS, leading to neurodegeneration. For example, it has been shown that a bacterial infection can induce amyloidosis and thus lead to the development of AD [32]. A recent study in mice showed that memory impairment after West Nile virus infection was dependent on microglia and complement-induced synaptic pruning within the CA3 region of the hippocampus [33]. However, the big question that many in the field of AD have asked is: What are the contributions of the immunological effectors that exist solely in the peripheral blood, and how do they wreak havoc within the tightly regulated brain parenchyma?

The start of this research began even before the discovery that established Aβ as the composition of the senile plaques that are the hallmark pathology seen in postmortem AD brains [34]. Eikelenboom and Stam found both immunoglobulins and complement proteins resided within senile plaques using basic immunoperoxidase techniques [35]. This study, along with continued confirmatory experiments led to the subsequent study of non-steroidal anti-inflammatory drugs

(NSAIDs) in randomized control trials [36–40]. Unfortunately, a relatively recent meta-analysis demonstrated no clinically significant slowing of AD progression when these data were aggregated [41]. However, many of the studies included in the meta-analysis were done well before the establishment of a thorough understanding of AD clinical progression [42, 43]. In other words, could it be that therapy needs to be initiated during prodromal clinical stages of the disease—a time when the pathology has not yet reached a saturation threshold and may be more effectively halted? A corollary to this is whether we should begin battling neurodegeneration even in the first years of life, as we will discuss below. These questions are being actively studied in current trials of both anti-amyloid and anti-inflammatory therapies.

Research still continues to produce good studies implicating a peripheral source of immunological and inflammatory mediators of disease. Of particular interest in this regard is a series of studies using a parabiotic model of AD pathogenesis. Villeda and colleagues demonstrated that connecting the circulatory systems of old and young mice could alter cognitive function in both groups, but in opposite directions [44]. For example, blood transferred from old to young mice reduced synaptic plasticity and neurogenesis and thus decreased spatial learning and memory and fear conditioning. In addition, the authors were able to isolate several chemokine differences between the two groups of mice (specifically CCL11) and when injected intraperitoneal or into the dentate gyrus of young mice, a similar decrease in cognitive function ensued. Conversely, and further proof of concept, the same group then exposed older mice to young blood and found a reversal of the effects seen in their previous study (i.e. increased dendritic spine density, stabilization of synaptic plasticity, and reversal of age-related cognitive dysfunction) [45]. This positive regulation also seems to be mediated by remodeling of the cerebrovasculature, which ultimately increases blood flow [46] and additionally lends credence to vasculopathic origins of neurodegenerative diseases.

Preclinical studies of this possible therapeutic modality in AD mouse models are ongoing and have so far shown some promise. For example, aged mice harboring an APP mutation that underwent heterochronic parabiosis to young wild-type mice or injection of young plasma showed a complete restoration of markers of synaptic function compared to old APP isochronic parabiotic mice [47]. Important to the overarching theme of this chapter is that these effects were independent of changes in amyloid between the groups, suggesting Aβ is not involved to the degree that the field often perpetuates. However, results of cognitive and behavioral testing were not as impressive suggesting more work will need to be done to determine the specific factors involved in the synaptic changes and thus the efficacy of this treatment option.

Another interesting set of data that supports a peripheral cause for AD comes out of the field of sepsis and critical care. Sepsis is an exacerbated and uncontrolled peripheral inflammatory response to an infectious agent via the release of proinflammatory cytokines such as IL-1 and TNF-alpha as well as complement proteins. Although sepsis is an acute event, it could be an enlightening lens through which to view the link between peripheral inflammation and cognitive dysfunction. For example, one study compared relatively young ICU patients (mean age 55) with and without sepsis and found that those who had survived sepsis 6 to 24 months prior demonstrated cognitive dysfunction equivalent to mild cognitive impairment on a battery of neuropsychological tests [48]. Additionally, volumetric magnetic

resonance imaging showed reduction in hippocampal volume in sepsis patients compared to nonsepsis patients, but no evidence of vasculopathy. Confounding factors such as depression, systemic infection that is not sepsis and quality of life were all controlled for. This was corroborated by a separate group that showed a decrease in whole brain volumes at least 3 months after sepsis, which was associated with long-term cognitive impairment at least 12 months post sepsis [49]. Another study in older individuals (mean age 77) demonstrated that patients with sepsis 3 years prior were three times more likely to become cognitively impaired compared to nonsepsis patients [50]. These data suggest that cognitive impairment persists several months to years after a peripheral blood insult, although it would be interesting to follow these patients even further, even to autopsy. Even studies looking at nonsepsis patients, systemic infections show that an increased infectious burden with common pathogens (including bacteria such as *Chlamydia pneumoniae* and *Helicobacter pylori* and viruses such as cytomegalovirus and herpes simplex viruses 1 and 2) conferred a higher risk of memory decline that is independent of vascular risk factors [51].

More recent studies have tried to delineate some of the molecular and cellular mechanisms of sepsis-induced cognitive decline, and many are unsurprisingly similar to those proposed for the etiology of AD. One very interesting study compared the neuropathology of a rat model of sepsis-associated encephalopathy to that of deceased patients with sepsis and found two patterns of brain damage: diffuse axonal injury and ischemic damage [52]. Pathologically, human sepsis specimens demonstrated Aβ-positive plaques and neurofibrillary tangles, which corresponded to increased levels of βAPP and altered axonal morphology in the rat model. Both pathological hallmarks were absent in control specimens of both humans and rats. Furthermore, MRI was able to demonstrate either diffuse axonal injury or ischemic brain injury in 9 of the 13 sepsis patients, although several of the patients were of advanced age making it difficult to determine if these lesions are truly a result of sepsis or a separate underlying pathology. However, this is a unique study, and larger numbers of patients with more quantitation would be of great value for future clinical management. This may be prudent sooner rather than later as a recent preclinical study has shown that statins may be beneficial in preventing this cognitive decline in mice with experimental sepsis-associated encephalopathy [53]. The authors showed that this cognitive protection (not necessarily prevention of death from sepsis) was due to reduction in peripheral and brain proinflammatory cytokines, oxidative stress, and even microglial activation, in addition to increased capillary density and subsequent increase in blood flow. These results coincide nicely with findings demonstrated in clinical studies, as discussed above.

4.2. Diabetes mellitus: the effect of peripheral blood glucose

To have a discussion linking peripheral inflammation and other peripheral stressors to brain disease, one must discuss the effect of diet and exercise on neuronal homeostasis. Just as AD has become an epidemic in the aging population, there is an increasing prevalence of obesity and type 2 diabetes mellitus (T2DM). T2DM is related to chronically elevated blood glucose. Both T2DM and metabolic syndrome are highly associated with aberrant insulin signaling. The association of AD with impaired insulin signaling suggests that a similar pathological pathway may be at play here.

Epidemiologic and basic science research has found a shared link between the pathophysiology of AD and T2DM. This is a difficult association to make since both conditions are common in aging. However, several key animal and human studies have shown that the connection may be deeper than just that of aging. Some have even suggested identifying Alzheimer's disease as type 3 diabetes mellitus.

Chronically elevated glucose levels are a known risk factor for dementia and Alzheimer's disease in individuals with and without a diagnosis of diabetes [54]. This literature highlights the various deleterious consequences of chronically elevated glucose on the aging brain. A 2015 study compared the brains of individuals with T2DM and those without T2DM to identify any possible effects on the brain. The brains of individuals with T2DM was associated with higher levels of total tau and phosphorylated tau in the CSF, suggesting an increased level of neuronal damage in the brain, although no significant association was made with regards to the brain Aβ load. The study concluded that T2DM may promote neurodegeneration by promoting tau hyperphosphorylation [55]. As with all studies between two separate conditions, we should be cautious if these types of studies demonstrate correlation or in fact a causation. More research is needed to support either conclusion.

On a mechanistic level, the insulin receptor and the insulin-like growth factor-1 (IGF-1) receptor have been found to be impaired in AD neurons, suggesting that CNS cells in persons with AD may be resistant to insulin signaling. One possible mechanism for the impaired signaling pathway is due to aberrant phosphorylation of Ser/Thr sites, IGF-1, and insulin receptor resistance. The increased levels of phosphorylation sites were found primarily in neurons with neurofibrillary tangles of AD brains [56]. A disruption of insulin signaling to the brain would have significant consequences to the brain as it could lead to a compromised source of energy. It would impair important neurotrophic and metabolic brain functions and contribute to AD pathology.

Switching gears from causes to treatment, recent studies have shown an interesting connection between therapeutic targets of T2DM and AD. Medications such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide that have shown to improve glucose control in patients with diabetes also show evidence of memory improvement in mice models of Alzheimer's disease. Amyloid plaque load, neuroinflammation, and oxidative stress have been shown to be reduced by these anti-diabetic drugs [57]. The results are still early, and it remains unclear if these treatments will demonstrate similar results in humans. Further clinical research and potential clinical trials will bring us one step closer to understanding the link between diabetes and Alzheimer's disease. Importantly, it may open doors for new, innovative approaches to treatment of AD and other forms of dementia.

The benefit of regular physical activity and exercise is clearly recognized in the neurological wellbeing of a population. Multiple cohort studies have found that high physical activity is associated with a reduced risk of AD and dementia [58–60]. The connection of T2DM and obesity with AD is a compelling reason to explore the effects of exercise since there is robust evidence that demonstrates the efficacy of exercise on reducing the progression of insulin resistance. Physical activity and exercise stimulates release of particular neurotransmitters and growth factors, specifically brain-derived neurotrophic factor (BDNF) and insulin-like

growth factor (IGF-1), and increases circulating testosterone levels. All of these effects have been shown to reduce the levels of Aβ in the brain, both by decreased production and increased clearance in the brain. The reduced Aβ was even found in individuals that carried the ApoE4 allele, which put them at greater risk for Alzheimer's disease [61]. These findings suggest the observation that Alzheimer's disease is linked to metabolism and the body's hormonal signaling system. The Aβ found in AD may be the result, but not the true culprit of the condition.

4.3. The microbiome

The human microbiome—the complement of microbial species (or microbial genes) and communities inhabiting the human organism—has been the subject of intense research interest in the context of brain development and dysfunction [62]. The influence of microflora on external and internal cues in brain development has been known for some time through population-based studies. As part of normal physiology, crosstalk between the gut and the brain plays a critical role in modulating brain homeostasis and behavior. Several neurological and psychiatric disorders (e.g. multiple sclerosis, Parkinson's disease, spinal cord injury, autism, and Alzheimer's disease) have been associated with dysbiosis or the disruption of normal gut flora. For example, children with late onset autism were found to have significantly more and different species of *Clostridium* in their fecal flora than control subjects without autism [63], and oral vancomycin improved several neurocognitive parameters when given to late-onset autistic children [64]. Experimental studies in rodents have shown that germ-free (GF) mice have increased serotonin, norepinephrine, and dopamine turnover and a decrease in their receptor levels, as well as reduced anxiety [65, 66]. Interestingly, changes to the microflora due to high-fat diet during pregnancy can have detrimental effects on the fetus when compared to normal chow diet [67]. Maternal obesity seems to also correlate with changes to the microflora (i.e. increase in *Bacteroides and Staphylococcus*) [68], which may predispose the mother to neurological disease and increase the risk of future neurodegeneration in her offspring. Additionally, gut bacterial infection early in life can alter memory formation in the young [69] and later in life, especially after a subsequent inflammatory insult [70].

At the cellular level of brain development, the resident microflora can alter the development and thus the permeability of the BBB. In GF mothers, BBB permeability was increased in the fetus [71]. Mice born to GF mothers demonstrated decreased BBB integrity beginning *in utero* with decreased levels of tight junction proteins in the hippocampus, frontal cortex, and striatum. Interestingly, pericyte coverage and vascular density were not altered in this model, but the authors did not investigate the role that GF status had on astrocyte physiology, which are an important cellular component of the BBB. The mechanism of decreased tight junction components was due to the lack of short-chain fatty acids (SCFAs) normally produced by commensal organisms. Considering the importance of the BBB in keeping neurotoxic molecules out of the brain parenchyma, this developmental flaw makes the brain vulnerable to a number of insults from the periphery increasing neuronal stress.

Of particular interest here is that SCFAs produced by bacteria in the gut also have the potential to inhibit Aβ aggregation in cell culture [72] and guide the proper development of microglial

cells, as discussed later. At the genetic level, Apolipoprotein E (ApoE)—one of the most important risk factors in AD—may play a role in selecting for a microflora more prone to generating SCFAs. For example, 5xFAD mice harboring the ApoE2 allele, which is considered protective, contained higher numbers of the *Ruminococcaceae* family of bacteria, which are known to produce high levels of SCFAs [73]. However, ApoE4 mice (the best characterized genetic risk factor for AD) contained higher levels of *Lactobacillaceae*, which are considered a pro-health microflora, making these results difficult to interpret, but may highlight the importance of SCFAs in CNS protection. As might be expected, the neutral ApoE3 mice contained a mixture of both families of bacteria. These results were independent of 5xFAD status.

An altered microbiome may be a source of proinflammatory molecules that are toxic to the brain. For example, in humans, it has recently been demonstrated that elderly patients with higher levels of Aβ based on ^{18}F-Florbetapir positron emission tomography (PET) contained higher levels of proinflammatory microbiota (e.g. *Escherichia* and *Shigella*), as well as proinflammatory cytokines, while also containing lower levels of anti-inflammatory microbiota (e.g. *Eubacterium rectale, Eubacterium hallii,* and *Bacteroides fragilis*) [74]. Interestingly, even cognitively impaired individuals without PET evidence of amyloidosis showed a similar increase in proinflammatory microbiota and peripheral cytokines and decreased anti-inflammatory microbiota, although the effect was smaller. This corroborated findings in the first PET study show that periodontal disease was associated with amyloidosis in AD-specific brain regions. However, the authors did not characterize the clinical characteristics of the study subjects, so it is difficult to know if these findings are relevant to cognitive decline. In addition, peripheral inflammation was implicated in the increased rate of cognitive decline in a cohort of mild to moderate AD patients who had periodontitis [75], which was not seen in patients without it, although the relative changes were not that robust. However, other studies have shown a positive relationship between the levels of TNF-α and immunoglobulins to periodontal bacteria in AD patients with periodontal disease that was absent in normal controls [76]. In fact, serum immunoglobulins to a wide variety of periodontal pathogens were present in patients before they converted to clinical AD [77], implying an increased risk of AD due to peripheral inflammation mediated by oral microflora.

Experimental and preclinical models of AD have also shown that changes to the microbiome have an effect on the progression of disease pathology. In the first study to show this, the authors used a well-characterized AD mouse model harboring the Swedish APP mutation and the PS1 tau mutation [78]. The experimental group (ABX) of these mice was given a cocktail of antibiotics after postnatal day 14 for the entirety of their lifespan. As might be expected, the ABX group had a distinctly different microbial profile than the control group, but also demonstrated a lower Aβ plaque burden and smaller plaque size. Additionally, insoluble levels of Aβ40 and Aβ42 were decreased, but soluble forms of these two peptides were actually increased, although it is not clear as to why this was. A subsequent study in the same model of AD, but with a different method of GF group generation, obtained similar findings of reduced Aβ plaque burden in GF-APP mice [79]. Interestingly, when the authors cross-colonized the GF-APP mice with the microbiota from the conventionally raised APP-PS1 group, the Aβ levels increased in the GF-APP group. Conversely, colonization of the GF-APP group with microbiota from wild-type mice (a separate group of mice conventionally raised

and without the APP-PS1 mutations) contained less Aβ pathology than conventionally raised APP-PS1 mice. This last set of data is congruent with human findings that the specific microbial populations involved in AD pathogenesis are more important than simply whether microorganisms are present or not. The authors attempted to demonstrate this idea by looking at the differences in microbial populations between conventionally raised APP-PS1 mice and GF-APP mice. However, because the variable being changed in this circumstance is the APP status, their results would suggest that APP mutation effects microbial diversity and not necessarily that microbial diversity effects Aβ generation. In other words, any mouse model starting with a mutation that increases Aβ levels in the first place has already conceded that an overproduction of Aβ is the cause of pathology in that model, which in humans has shown to be inaccurate for 95% of AD cases (i.e. the sporadic, non-Mendelian cases make up the vast majority of human cases). For now, thought, the data suggests that microbial products and the immune response to microbiota contribute to specific pathological outcomes implicated in AD—namely APP metabolism. Unfortunately, the experimental studies described in the previous paragraph lack a clinical surrogate. For example, the studies by Minter et al. and Harach et al. did not characterize neuronal degeneration or cognitive decline in their identical models, so we cannot know if there was any clinically relevant change to neuronal integrity. It is well known within the field of AD that neuronal degeneration is a better predictor of cognitive decline than is Aβ pathology.

One mechanism that may link the microflora with neurodegeneration involves the immune cells of the brain. As one might expect of a peripherally derived immune cell, a complex gut microbiota promotes microglial development, while the lack of rich microbiota leads to impaired microglial maturation, differentiation, and function. In the first of its kind, one study compared the immune responses and its association within the brain by studying GF mouse models [80]. Moreover, the same study found that the reintroduction of complex microbiota may largely, but not entirely, restore microglia. Interestingly, the authors of the study suggest that the wide complexity of the microbiota, not the bacterial load, is associated with restored microglial function.

This seems like a good time to revisit another interpretation of the amyloid cascade hypothesis put forth by Bishop and Robinson over two decades ago and, unfortunately, largely forgotten. They named it the bioflocculant hypothesis of AD [81]. It is an alternative way to look at the production of Aβ, not as much as the start of a pathological cascade, but as a way to halt the sequence of events beginning with a previous injury or stressor that leads to neurodegeneration. It views Aβ production as a response to exogenous insults since Aβ is produced after a variety of brain injuries [82–85]. They compare the production of Aβ, and subsequent aggregation into plaques, to a web constructed to trap any offending agents that may enter the brain in a pathological state. They convincingly describe a situation in which neurons may use the sticky properties of Aβ as a way to contain pathogens, toxic metals, or other products of blood in a trap much like a spider's web. It is then easy to imagine microglia as the spider in this scenario engulfing anything trapped within the web and disposing of it. We would add to this list of functions, a means to plug up holes in the microvasculature as might be seen

in the microbleeds of cerebral amyloid angiopathy. In support of their hypothesis, a recent paper demonstrated Aβ's role in trapping infiltrating bacteria (specifically *Salmonella typhi* and *Candida albicans*), which coaggregated in 5xFAD mice by binding to the bacterial cell wall via heparin-binding domains [86].

One could easily imagine such a scenario playing out in the etiology of AD starting even with risk factors present in the early years of life: (1) early embryonic changes to host microbiota may predispose a person to a leaky BBB and all of the consequences of that derangement later in life (**Figure 1a**). (2) BBB malfunction may either contribute to or coincide with the microbiota-dependent alterations to networks responsible for memory formation—AD is a disease of memory formation after all. (3) Although in its beginning phases of understanding, the SCFAs that are responsible for maintaining components of BBB tight junctions during development seem to also decrease the toxic effects of the Aβ peptide later in life. (4) The brain's immune cells, if not exposed to the appropriate milieu of microorganisms (and their metabolites such as SCFAs) during development, may be unable to protect the brain against invading pathogens in adulthood and/or contribute directly to inappropriate neuronal network remodeling in development and disease (**Figure 1a**, **b**). (5) Changes to the normal microflora during adulthood, either through systemic infection (e.g. sepsis, periodontal disease, or any other form of peripheral increase in the proinflammatory state) or antibiotic use, can increase the risk of conversion to AD, especially in the elderly (**Figure 1c**). (6) Lastly, all of these steps leading to neuronal demise are also dependent on the metabolic perturbations seen in disorders of glucose control and obesity (**Figure 1d**).

4.4. Role of probiotics and antibiotics

The gut microbiota-brain axis is still insufficiently understood. There is a need for more research to better identify the unique combination of microbiota that is implicated in the disease process. The logical next step would be the development of antibiotic or probiotic treatments with the goal of reducing the disease burden.

An important study to answer the question of the microflora's influence on AD pathology and cognitive function did so by feeding an AD mouse model a probiotic formulation rather than depleting them of bacteria [87]. The study authors found that cognitive dysfunction was ameliorated with the use of probiotics and this was dependent on reduction in peripheral proinflammatory cytokines, increased anti-inflammatory cytokines, and replenishment of autophagic and proteasomal function within neurons. These are two important ways for the body to regulate itself and remove old or damaged proteins. Aberrant proteasome function then leads to neurotoxicity and favors the development of misfolded proteins in the brain [88, 89]. In addition, several studies presented at this year's annual Neuroscience meeting using probiotics containing *Lactobacilli* and *Bifidobacteria* improved memory in several mouse models of AD [90]. Although it is early, these data lend credence to the importance of correcting the composition of the microflora after use of antibiotics and the possible importance of taking a probiotic to maintain both brain and overall health.

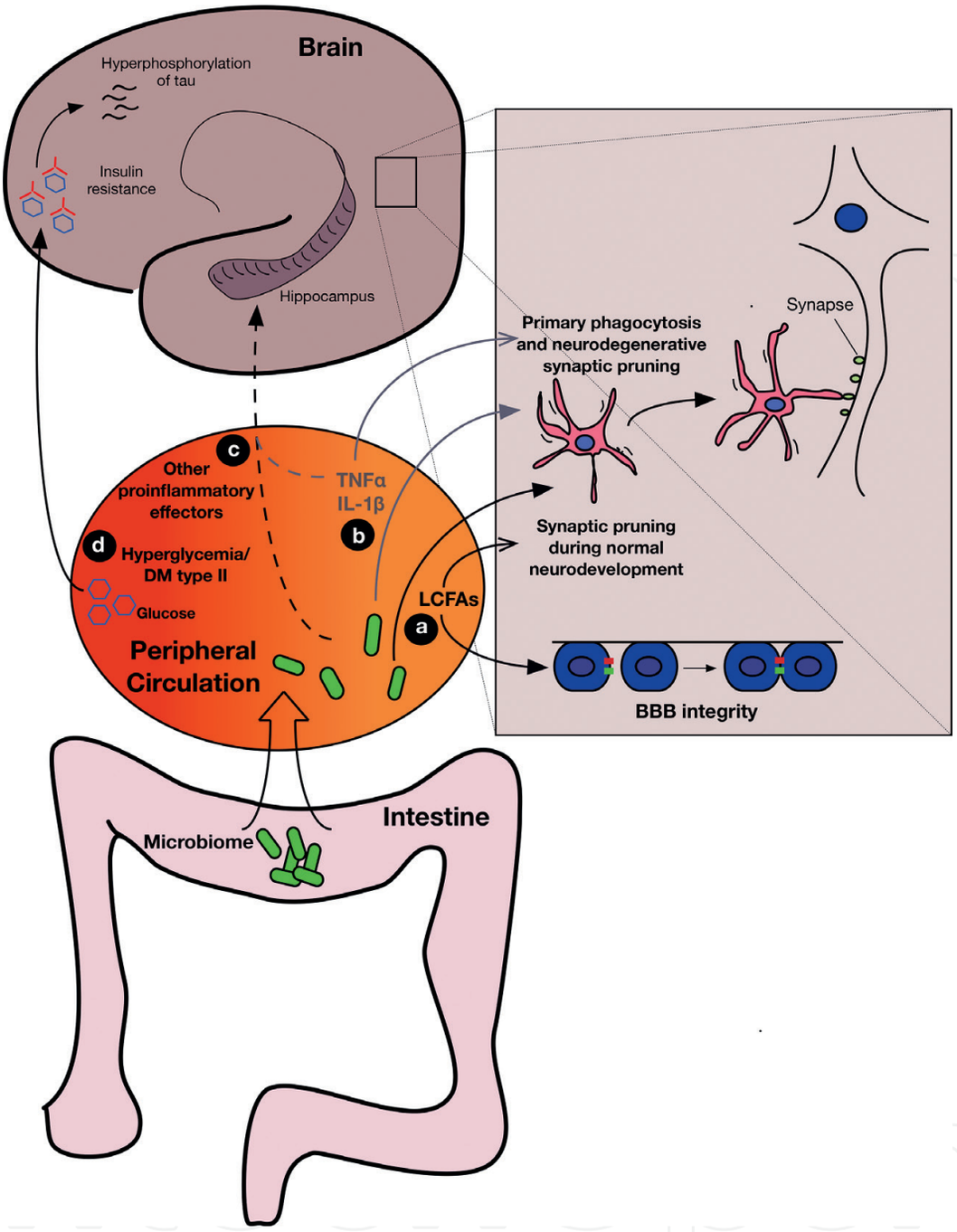

Figure 1. Summary figure of proposed involvement of the microbiome in brain development and dysfunction. **(a)** Short-chain fatty acids (SCFAs) produced as bacterial metabolites by anti-inflammatory bacteria exert their influence both on the development of the blood-brain barrier (BBB) and on the development of microglia. Dysfunction of either of these processes may lead to neurodevelopmental disorders early in life or neurodegenerative disorders in adults. On the other hand, proinflammatory bacteria are recognized by the immune system as such during a state of sepsis, which elicits the overproduction of proinflammatory cytokines. These effectors may **(b)** activate microglia in adults leading to aberrant synaptic pruning and primary phagocytosis of live neurons or **(c)** have a direct effect on memory forming networks during development as well as memory formation and/or retrieval in the adult. development as well as memory formation and/or retrieval in the adult. **(d)** Chronically elevated peripheral glucose levels may lead to insulin resistance and aberrant phosphorylation of the insulin receptor and concomitant hyperphosphorylation of the microtubule-binding protein tau, which is a hallmark pathology of the AD brain and correlates more specifically with the progression of neurodegeneration.

5. Conclusion

In this chapter, we described several concurrent mechanisms of AD pathogenesis, including the effects of systemic inflammation, metabolic dysfunction, and the gut microbiome. Since there seems to be no cure for AD and current established and experimental therapies are suboptimal at best, we suggest that more research should focus on minimizing peripheral inflammation and maintaining an anti-inflammatory complement of microbiota as early as possible. Targeting these two entities appears to positively affect the plethora of mechanisms implicated in AD (i.e. Aβ aggregation, tau hyperphosphorylation, microglial and complement activation, and BBB breakdown). There is reason to believe that AD arises from a manifestation of multiple hits within and outside of the central nervous system. A multi-system strategy will thus be most efficacious for prevention and treatment.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Author details

Aradhana Verma and Matthew Zabel*

*Address all correspondence to: matthew.zabel9352@cnsu.edu

College of Medicine, California Northstate University College of Medicine, Elk Grove, CA, United States

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