HHS Public Access

Author manuscript

J Neuroendocrinol. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

J Neuroendocrinol. 2022 January ; 34(1): e13074. doi:10.1111/jne.13074.

Breakdown of the blood-brain barrier: a mediator of increased Alzheimer's risk in patients with metabolic disorders?

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Abstract

Metabolic disorders (MDs), including type-1 and 2 diabetes (T2DM) and chronic obesity, are among the faster growing diseases globally and are a primary risk factor for Alzheimer's disease (AD). The term "type-3 diabetes" has been proposed for AD due to the interrelated cellular, metabolic, and immune features shared by diabetes, insulin resistance (IR), and the cognitive impairment and neurodegeneration found in AD. Patients with MDs and/or AD commonly exhibit altered glucose homeostasis and IR; systemic chronic inflammation encompassing all of the periphery, blood-brain barrier (BBB), and central nervous system (CNS); pathological vascular remodeling; and increased BBB permeability which allows transfusion of neurotoxic molecules from the blood to the brain. This review summarizes the components of the BBB, mechanisms through which MDs alter BBB permeability via immune and metabolic pathways, the contribution of BBB dysfunction to the manifestation and progression of AD, and current avenues of therapeutic research which address BBB permeability. In addition, issues with the translational applicability of current animal models of AD regarding BBB dysfunction and proposals for future directions of research that address the relationship between MDs, BBB dysfunction, and AD are discussed.

Article Summary:

This review summarizes the components of the blood-brain barrier (BBB), mechanisms through which metabolic disorders alter BBB permeability via immune and metabolic pathways, the contribution of BBB dysfunction to the manifestation and progression of Alzheimer's disease, and current avenues of therapeutic research which address BBB permeability

The incidence of metabolic disorders, such as obesity and diabetes, is increasing globally with a corresponding increase in AD. Diabetes is defined by hyperglycemia caused by impaired insulin secretion (type-1), resistance to insulin (type-2), or both[1]. The number of individuals with diabetes worldwide has quadrupled since 1980, making diabetes the 4th most common cause of death from non-communicable disease. Obesity rates in the United states are three times the global average, with 39.8% of adults having a body-mass index of 30 or greater[2] and globally since 1975, the number of individuals classified as obese has tripled to 650 million adults, or 13% of the population[3]. Obesity is also

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associated with IR, as well as dyslipidemia, and hypertension[4]. At the same time, in the United States AD is the sixth most common cause of death. There are 5.8 million patients currently diagnosed with AD in the US, a number that may grow to over 13 million people by 2050 as the baby-boomer generation ages[5]. AD is characterized by functional cognitive impairment coupled with increased deposition of beta amyloid protein (Aβ) and aggregation of hyperphosphorylated tau protein[6]. Unfortunately, shared causal mechanisms between MDs and AD lead to significant comorbidity, with some researchers referring to AD as "type-3 diabetes"[7–9] due to the commonalities. Understanding the metabolic, immunological, and vascular complications of MDs and AD is an essential component of developing and implementing interventions aimed at reducing the number of individuals who develop AD, identifying those in the early stage of the disease, slowing or stopping its progression, and alleviating symptoms such as cognitive impairment. Many of these commonalities occur at the BBB, the selectively permeable series of membranes and cells that protect the CNS.

Role of the BBB

The BBB regulates the transport of ions and molecules (including nutrients) to and from the brain. The barrier regulates adequate supply of oxygen, glucose, and trace elements while excluding toxic plasma components and leukocytes which could damage neural tissue if not excluded[10]. The endothelial layer that comprises the barrier has four primary components: endothelial cells, mural cells, cells of the basal lamina, and glia. The endothelial cells of the barrier are highly polarized and held together in tight junctions that exclude large and hydrophilic molecules and regulate passage of smaller molecules and ions. Tight junctions are composed of integral proteins such as occludins, claudins, zonula occludens protein-1, and alpha and beta-catenin which form the tight junctions or adhere the junctions to the cytoarchitecture[11]. Importantly, the BBB endothelial layer protects the CNS from peripheral immune cells and other immune factors which would cause inflammation and damage within the brain[12]. The inner/abluminal membrane contains two types of mural cells: pericytes and vascular smooth muscle cells. Pericytes support remodeling and tone of the approximately 600–700km (in an adult human) of cerebral vasculature, forming tendrils that ensheath the capillary wall[13]. Vascular smooth muscle cells surround arteries and contract or expand to control blood flow[14] and hence provide oxygen. Constant oxygen supply is vital as hypoxia damages neurons within minutes[10]. Two layers of basal lamina surround the abluminal surface and provide a structural framework: an endothelial membrane that is secreted by endothelial cells and a parenchymal membrane secreted by astrocytes[15]. The basal lamina is selectively permeable to, and regulates concentrations of, growth factors, hormones, and essential nutrients[16,17]. Both layers function to maintain barrier integrity, and the parenchymal layer further connects astrocyte processes to the membrane[15]. Among glial cells functioning at the BBB, astrocytes are particularly important. Astrocytes regulate blood flow, ionic concentration (including potassium and calcium), and glucose transport from periphery facing endothelial cells to neurons[18,19]. Under healthy conditions the components of the BBB work together to maintain homeostasis and efficiently regulate influx and efflux of essential materials in the CNS. However, MDs can impede healthy functioning and compromise the BBB.

Metabolic disorders: disruptions of the BBB relevant to AD

MDs impair molecular transport, vascular structure, and tight junction integrity[20–23]. Chronic obesity and T2DM damage the tight junctions of the barrier and increase permeability to larger peripheral blood products[22,23]. These effects are particularly robust in the hippocampus[24]; this is potentially important because cognitive and metabolic processes specifically in the hippocampus are also markedly impaired by IR, so that hippocampal cognitive dysfunction is a key symptom of T2DM and obesity[25,26]. In patients with T2DM, which is defined by systemic insulin resistance, specifically hippocampal damage is evident early in the development of the disease and persists throughout disease progression[27–29]. Insulin resistance within the brain and specifically within the hippocampus causes cognitive impairment: in particular, insulin regulates glucose metabolism in the hippocampus (as well as in the periphery)[30,31] and is an essential component of hippocampal memory including regulation of local glucose metabolism via the insulin sensitive glucose transporter 4[32–34]. Rats perform better on spatial memory tasks after intrahippocampal administration of insulin and performance is impaired by blocking intrahippocampal insulin signaling[25,35]. IR is manifest in the hippocampus of individuals with MDs and AD and is correlated with cognitive impairment[36]; moreover, IR is apparent in hippocampal and cortical cells derived from AD patients postmortem even without a prior MD diagnosis[37]. Hence, MDs appear likely to have effects on the BBB that correlate with, but may precede, cognitive and brain-metabolic impacts.

Consistent with this, BBB dysfunction is apparent in IR mice before any cognitive effects of a high-fat diet (HFD)[38]. Diet-induced obese (DIO) mice exhibit early BBB dysfunction at the hippocampus and hypothalamus due to increased production of reactive oxygen species, causing cellular stress and a decrease in the tight junction proteins claudin-5 and zonula occludens-1[39,40]. Other rodent models of T2DM, such as Zucker diabetic fatty rats, natively show the same decrease in occludins and claudin-5, most significantly in the hippocampus[23]. Tight junction disruption at the hippocampus corresponds with increased hippocampal expression of the proinflammatory signaling molecules interferon-gamma (IFN-γ) and interleukin-1beta (IL-1β)[41]. Further, hyperglycemia, as manifest in T2DM, increases production of protein kinase C (PKC) causing a reduction of bioavailable nitric oxide (NO) and a thickening of basement membranes, respectively impairing vasorelaxation and inducing vasoconstriction[42,43]. Alterations in glucose transport across the BBB is evident in the early phases of AD and may be another link between pathological metabolic changes and AD development and progression. The primary glucose transporter at the brain endothelium, glucose transporter-1 (GLUT-1) is reduced in AD patients[44–46] as is GLUT-3, an important neuronal glucose transporter[47]. GLUT-1 deficient transgenic mice overexpressing human APP Swedish mutation exhibit increased amyloidosis, reduced cerebral vascularization and blood-flow, and decreased GLUT-1 expression, despite showing no changes in blood glucose levels[48]. Hypoglycemia, a common side-effect of insulin treatment, decreases claudin-5 expression and disrupts the functioning of zona occluden-1[49], and even among elderly patients with T2DM, the number of hypoglycemic events is associated with increased risk of dementia[50]. Dyslipidemia, a component of central obesity, contributes to a chronic inflammatory response[51] and, among patients with AD, is associated

with significantly increased incidence of BBB dysfunction[52]. In both diabetes and obesity, metabolic and immune changes at the BBB contribute to an inflammatory cascade that increases the risk of cognitive impairment via impaired molecular transport and vascular changes[53].

Chronically elevated inflammation damages the cerebral vasculature and is a key factor linking metabolic disorders, BBB degeneration, and AD (figure 1)[54,55]. Inflammation is an immune mechanism that is a key component of the body's adaptive response to pathogens and injury[56], but severe or chronic inflammation can lead to pathology[57,58]. T2DM causes endothelial cells at the BBB to increase expression of receptor for advanced glycation end-products (RAGE) which activates the proinflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway and leads to further increased production of pro-inflammatory cytokines interleukin-6 (Il-6) and tumor-necrosis factor alpha (TNF-α)[53,55,59] causing an impaired endothelial vasodilatory response[42]. BBB inflammation induces vascular remodeling leading to hypoxia and increases secretion of hypoxia-induced factor 1a (HIF1a)[60] which enhances Aβ toxicity and continues to increase the production of inflammatory cytokines locally[61]. Over time, these vascular impairments lead to chronic cerebral hypoperfusion and upregulated expression of RAGE, leading to increased Aβ deposition in the brain and further neuroinflammation via the NF-κB pathway[62]. Hypoperfusion also causes pericytes to detach from the basement membrane, increasing vascular permeability to large, and potentially neurotoxic, molecules from the periphery[63]. The resulting reduction in pericyte coverage correlates with cortical and hippocampal capillary and BBB dysfunction and occurs secondarily to decreases in cerebral blood-flow, indicating that hypoxia and hypoperfusion instigate the change[63]. Hypoperfusion, inflammation, and reduced pericyte coverage at the hippocampus contributes to a loss of hippocampal volume in conjunction with progressive cognitive impairment in both T2DM and AD[24,64]. AD is associated with cerebral, and specifically hippocampal, hypometabolism[65,66]; hence, reduction in supply of glucose and/or oxygen subsequent to hypoperfusion is likely to be a major causal link between MDs and AD. Through the process of inflammation and hypoxia induced vascular damage, MDs cause chronic damage to the BBB and increase AD risk via hypometabolism and increased concentration of Aβ.

Contribution of BBB breakdown to AD progression

BBB breakdown is a critical component of AD pathology (reviewed in table 1). A low level of BBB breakdown in medial temporal regions is a normal aspect of aging; during the etiology of AD, however, this breakdown increases (initially prior to cognitive impairment) with the extent of barrier dysfunction predictive of the magnitude of cognitive impairment[67–73]. Nation et al (2019) found that increased permeability is not correlated with an increase in CSF amyloid or tau in patients with early cognitive impairment[69], suggesting the possibility of multiple converging mechanisms and specifically that BBB breakdown may be a causal factor for AD independent of abnormal central protein factors. A similar result is shown in transgenic mice expressing the AD risk factor gene apolipoprotein 4 (*APOE4*) and 5 AD risk factor transgenes altering amyloid precursor protein (APP) and presenillin-1 (PS1) (*APOE4*;5xFAD). These mice display increased BBB permeability along with reduced cerebral blood-flow and pericyte coverage in the cortex and hippocampus[74].

APOE4;5xFAD mice and AD patients also display increased concentrations of fibrinogen in the brain, a key clotting factor in the periphery which incites neuroinflammation and demyelination upon infiltration to the CNS[74–78]. The BBB impairment shown in *APOE4*;5xFAD mice is due, at least in part, to activity in the inflammatory cyclophilin A/matrix metalloproteinase 9 (CyA/MMP9) pathway, as pharmacological inhibition of the pathway attenuated neuronal loss and improved cognitive performance[74], again suggesting that proinflammatory cascades contribute significantly to barrier dysfunction. As in the proinflammatory cascade observed in MDs, BBB breakdown throughout AD progression is due in part to the impact of increased Aβ on the brain endothelium[67–69,71,73]. One of the first neural structures to be adversely impacted by AD is the hippocampus which is both a target of the early impact of MDs and a site of early BBB permeability[70–73]. Dysregulated molecular transport at the BBB increases AD pathology risk: hyperinsulinemia, as seen in MDs, damages the vasculature of the BBB while decreasing clearance of toxic $A\beta_{42}$ oligomers and increasing permeability of the barrier to peripheral $A\beta_{42}$[79]. Neuronal Aβ accumulation is a hallmark of AD pathology, and Aβ oligomers specifically are neurotoxic and cause a pronounced inflammatory response[80,81]. Simultaneously, increased expression of vasoconstrictive endothillin-1 and Aβ accumulation in vessel walls causes a thinning of neuronal capillaries and a reduction in total vascularization in the brains of patients with AD and T2DM causing chronic hypoperfusion[82] and DIO mice display a similar vascular insufficiency and are at increased risk for transient ischemic strokes causing acute hypoperfusion[83]. These factors incite a feed-forward mechanism in BBB dysfunction whereby metabolic dysregulation and inflammation cause hypoperfusion and impair Aβ clearance; these in turn induce vascular changes, worsen cerebral hypoperfusion, further degrade the barrier, and increase inflammation[61]. Aβ efflux is dependent on both concentration and active transport via RAGE and low density lipoprotein receptor-1 (LRP-1) and estimates for total Aβ clearance across the BBB range from 25–85% of total efflux[84–86]. Therefore, any reduction in Aβ transport may contribute to AD. This is supported by observed reductions in LRP-1 in both AD patients and APOE knockout mice[84] and by impairment in Aβ clearance in mice injected with radiolabeled $A\beta_{1–40}$ and an anti-LRP-1 antibody[85]. In vitro models using human AD cultured neurons exposed to Aβ found that barrier permeability increased along with increased levels of reactive oxygen species (ROS), MMP2, and IFN-y as well as decreased expression of the tight junction-regulating proteins Claudin-1,5, and VE-cadherin[87]. Although the effect of Aβ to increase permeability of the BBB has been shown several times, work analyzing cognitive impairment and barrier integrity in patients with AD and several other neurodegenerative disorders found that it may be a secondary effect in many cases: barrier permeability was more strongly associated with diabetes and damage to the brain microvasculature than amyloid burden or genetic risk factors[88]. It is likely that several overlapping dysfunctions cause BBB breakdown in patients with both MDs and (pre-)AD. Overall, converging evidence indicates that BBB breakdown may be a critical component in the progression from MDs to AD.

Genotype can also contribute to BBB degradation relevant to AD. Carriers of the *APOE4* isoform are at increased risk for the development of AD partially due to alterations at the BBB. Although *APOE4* and low-density lipoproteins do not cross the BBB[89,90], trans-BBB transport of insulin[91] and Aβ[92] is partially regulated by *APOE4* and is impaired

in *APOE4* carriers. *APOE4* carriers have increased activity in the proinflammatory CyA/MMP9 pathway in pericytes and endothelial cells, leading to apoptosis, increased barrier permeability, and impaired barrier repair when compared to APOE3 carriers[68,93–95]. *APOE4* mice displayed a 29% reduction in glucose transport and a 41.3% increase in RAGE expression at the BBB[96]. Decreased brain glucose metabolism is a hallmark symptom of AD[65,66] which is pronounced in positron emission tomography scans of *APOE4* carriers prior to symptoms of cognitive impairment[97,98], during mild cognitive impairment (MCI)[99], and after progression to AD[65], indicating a relationship between *APOE4* genotype, cerebral metabolic dysfunction, and AD risk. In cognitively unimpaired subjects, *APOE4* carriers exhibit increased permeability of the BBB at the hippocampus and parahippocampal gyrus which is not explained by elevated Aβ or tau[68]. Within AD patients, *APOE4* status predicts increased accumulation of the peripheral clotting factor prothrombin, an indicator of BBB leakage and vascular damage, in both prefrontal cortex and CSF[100]. The complexity of the interrelation between metabolic factors, immune functioning, and *APOE* genotype limits the utility of approaches which account only for one aspect and is likely a significant reason why effective treatment strategies for AD have been elusive to-date.

Therapeutic targets: insulin resistance and the BBB.

The BBB is both a critical target for, and a significant barrier to, the development of therapeutic agents for the treatment of AD[101]. To date, therapeutics targeting amyloid and tau have failed to slow progression and/or reduce symptoms of AD[102]. Hence, novel therapies targeting other aspects of the disease including aberrant inflammation, hypometabolism, and BBB permeability are required. Drugs currently approved to treat metabolic dysfunction have promise to improve BBB function and reduce the pace of cognitive impairment. The glucagon-like peptide-1 (GLP-1) analogue liraglutide crosses the BBB[103] and improves cognition in animal models[104,105] and an exploratory trial of the GLP-1 analog dulaglutide found potential for slowing cognitive decline in T2DM patients[106]. Central delivery of insulin is another treatment for brain metabolic dysfunction that shows promise in treating AD. Insulin transport into the brain is reduced in both patients with obesity and AD[107,108]. In DIO mice, exogenous insulin increased efflux and decreased influx of Aβ across the BBB, thereby reducing Aβ accumulation, and improved cognitive performance[109]. However, as insulin influx to the brain is saturable, the amount of insulin that can be transported across the BBB is inherently limited[110]. To overcome this limitation, insulin may be administered intranasally, thereby bypassing the BBB and entering the brain alongside the olfactory and trigeminal neural pathways[111,112]. By administering insulin intranasally rather than peripherally, therapeutically relevant doses may be delivered directly to the CNS and avoid potential side effects of large doses of insulin administered to the periphery[113]. In mice overexpressing APP and PS1, intranasal insulin reduced Aβ plaque formation, reduced Aβ production, improved insulin signaling, and alleviated cognitive impairments[114]. In both wild-type and senescence-prone accelerated mice (a model of accelerated and sporadic AD), intranasal insulin is detected in the brain within 5 minutes of administration and remains increased for up to 60 minutes post-administration[115]. In clinical trials, patients with MCI to moderate AD symptoms receiving a daily dose of

intranasal insulin over the course of 4 months improved cognitive functioning and decreased hyper-phosphorylated Tau and Aβ42 ratios[116].

There are, however, caveats to the use of insulin in restoring brain metabolism, improving cognition, and decreasing Aβ load. These issues include sex differences in the BBB's response to inflammation[117,118] and the impact of *APOE* genotype on BBB integrity as discussed above. One study found that intranasal insulin improved cognition in *APOE4* negative males but worsened cognition in *APOE4* negative females[119] while a subsequent study in the same lab found that four months of intranasal insulin improved cognition for *APOE4* carriers but worsened cognition for non-*APOE4* carriers[120]. It is possible, therefore, that intranasal insulin may only be an efficacious therapy for a subset of AD patients at most. Exogenous insulin may also be less effective in the context of MDs. DIO rats required an order of magnitude higher dose of intrahippocampal insulin than control and diet-resistant rats in order to display cognitive enhancement[121]. Chronic systemic insulin therapy can also result in recurrent hypoglycemia which, when severe enough to require hospitalization or emergency intervention, is itself associated with an increased risk of dementias, both AD and vascular[122]. Moreover, insulin and Aβ compete for a common breakdown pathway[123,124], so that hyperinsulinemia is associated with impaired degradation of Aβ[125] and chronic insulin therapy at clinically useful doses may potentially lead to an unwelcome increase in brain amyloid burden. There is convincing evidence that some level of insulin is produced in the brain, rather than being transported from the periphery[34]; speculatively, a further potential therapeutic approach would be to support and/or increase such production.

Targeting the neuroinflammatory response is a viable, if complex, alternative avenue of therapeutic development which has the potential to attenuate damage to the BBB and retard development of AD. Administration of non-steroidal anti-inflammatory drugs (NSAIDs), a once-promising avenue of treatment[126], has unfortunately been unsuccessful. A randomized clinical trial (RCT) administering 220mg of Naproxen or placebo twice daily for two years concluded that Naproxen was ineffective at slowing AD symptom progression and was associated with adverse health events[127]. Similar results have been found with other NSAIDs[128]. The lack of clinical efficacy and increase in adverse events may be due to NSAIDs' common affinity for inhibition of cyclooxygenase 1/prostaglandin G/H 1 (COX-1) which has numerous positive homeostatic functions besides the inflammatory response, and lower affinity for COX-2, which functions much more exclusively as a proinflammatory regulator[128]. These results indicate that more specific modulation of the immune system may be required. Treatments involving administration of exogenous anti-inflammatory cytokines and their agonists, or antagonists to pro-inflammatory cytokine activity, are currently being investigated. The regulatory/anti-inflammatory cytokine interleukin-10 (IL-10) regulates microglia morphology and the production of IL-6/TNF-α: upregulations of IL-10 attenuates BBB impairment and improves cognition[129]. Targeting RAGE is another viable avenue of therapeutic intervention currently under development which may reduce inflammation, improve vascular function, and slow cognitive decline in T2DM and AD. The RAGE inhibitor FPS-AM1 passes through the BBB and reduces microglial activation, oxidative stress, and proinflammatory cytokine signalling[130], while the RAGE inhibitor Azeliragon slows cognitive deterioration in patients with mild to moderate AD[131]. As RAGE

is a binding target for Aβ, administration of soluble RAGE binds to Aβ in the periphery and prevents RAGE mediated translocation across the BBB[132]

In clinical trials, resveratrol, a naturally occurring polyphenol found naturally in grapes, has been shown to be well tolerated, improve cognitive outcomes, and preserve BBB integrity while upregulating IL-10 gene expression and concentrations[133]. Resveratrol also attenuates BBB permeability due to HFD[39]. Longitudinal epidemiological studies and animal models also indicate that caffeine protects against BBB degenerations and decreases risk of AD development, likely through reducing the effects of oxidative stress and increasing insulin sensitivity[134,135]. Caffeine also protects against HFD-induced reduction of brain-derived neurotrophic factor (BDNF) and cognitive impairment[136]. Preliminary animal models have also indicated a benefit from the use of interferon-β1a (IFNβ1a), a regulatory cytokine commonly used to treat multiple sclerosis and a potent inhibitor of IL-6, IL-1β, TNF-α, and IFN-γ[137]. Dietary interventions aimed at controlling the specific inflammatory factors which impair BBB integrity therefore have potential to delay or prevent AD by preserving normal molecular transport and protecting against vascular injury.

Lifestyle factors should also be addressed with the goal of reducing risk or severity of AD. Regular exercise improves insulin sensitivity, cognitive performance, and endothelial function and decreases inflammatory reactivity at the BBB[138,139], and while the exact mechanism of action is not known, the improvement likely involves increased expression of BDNF which promotes neuronal survival and synaptic integrity and stabilizes the vasculature[140]. In longitudinal studies and RCTs involving chronically obese individuals, taking part in a voluntary weight-loss intervention (diet, exercise, or bariatric surgery) was associated with significant improvement in memory and attention[141]. Following a weight-loss intervention, neuroinflammation and IR decreased while BBB transport of insulin and leptin increased[22]. This suggests that treatment for chronic obesity may also reduce risk for the development of AD via improvement of BBB functioning. From a dietary perspective, a procognitive and anti-inflammatory diet such as The Mediterranean-Dietary Approach to Systolic Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) prevents cognitive decline[142] and is associated with a reduce AD risk[143]. Patients with T2DM adhering to the Mediterranean diet show improved glycemic control[144] and reduced high-density lipoprotein and overall adiposity[145] and patients with cardiovascular disease on the Mediterranean diet or DASH show reduced biomarkers of inflammation[146,147]. This suggests that the neuroprotective effect of the MIND diet occurs via beneficial metabolic and immune changes[148]. Preservation of BBB integrity through non-pharmacological or lifestyle interventions will likely delay or prevent the onset of AD.

Importance of accurate models and early identification

In evaluating models for AD research, attention should be paid to the function of the BBB to ensure translational accuracy. For instance, a comparison of double transgenic *APP/PS1* with control B6/SJL mice did not find any difference in barrier permeability to albumin, insulin, or Aβ40[149]. Another study using *APP/PS2*, human Tau, and *APOE4* knock-in mice lines failed to detect significant alteration in BBB permeability to radiolabeled tracers and albumin[150]. These findings may suggest that the models do not accurately recapitulate the

impact of AD in humans[10,68,151]. It is also possible that the failure to observe differences is due to methodological issues, as brain perfusion prior to tissue collection may remove non-immune antibodies from the brain and radiolabeled tracers may lack the sensitivity and resolution to detect BBB changes in the context of neurodegenerative disease[152]. Administration of intranasal insulin increased glucose metabolism in the hippocampus only in wild-type, but not *APP/PS1* mice[153] indicating that *APP/PS1* mice may have altered metabolism in a non-translationally relevant manner. Taken together, this may indicate a limitation of the transgenic models themselves. A potential explanation is that the various transgenic mouse lines do not capture the long-term immunological and metabolic alterations leading to a chronic inflammatory state and vascular changes seen in most AD patients. Due to these inconsistencies, it may be beneficial to concentrate on animal models of AD which include the metabolic and immunological risk antecedents, such as HFD-induced obesity and T2DM.

Patients with MDs exhibit peripheral and CNS IR, chronic systemic inflammation in the CNS, BBB, and periphery, and marked impairment of the cerebrovasculature. Cerebrovascular impairment causes hypoxia and hypoperfusion leading to pericyte loss, damage to tight-junctions, and a further exacerbated inflammatory response. These factors combine to increase AD risk by increasing permeability of the BBB to cytotoxic peripheral blood products, impairing transport of insulin into and Aβ out of the brain, and damaging regions such as the hippocampus and prefrontal cortex. In order to identify patients with MDs who are at risk for developing AD early enough for the progression to be slowed by non-pharmacological lifestyle interventions, health screenings should include rigorous assessment for cognitive impairments[154]. Given the cascade nature of the inflammatory response, BBB breakdown, and amyloid accumulation in AD, early identification of at-risk individuals before the onset of severe symptoms is an important step in slowing disease progression. Awareness of the interrelation between metabolic, immune, and vascular functioning may also open new treatment modalities in the future.

Acknowledgements:

This work was funded by NIH R01AG050598. The authors would like to thank Angelina Tassone for her help producing figure 1.

Data Availability Statement:

Data sharing is not applicable to this article as no new data were created or analyzed in the current study.

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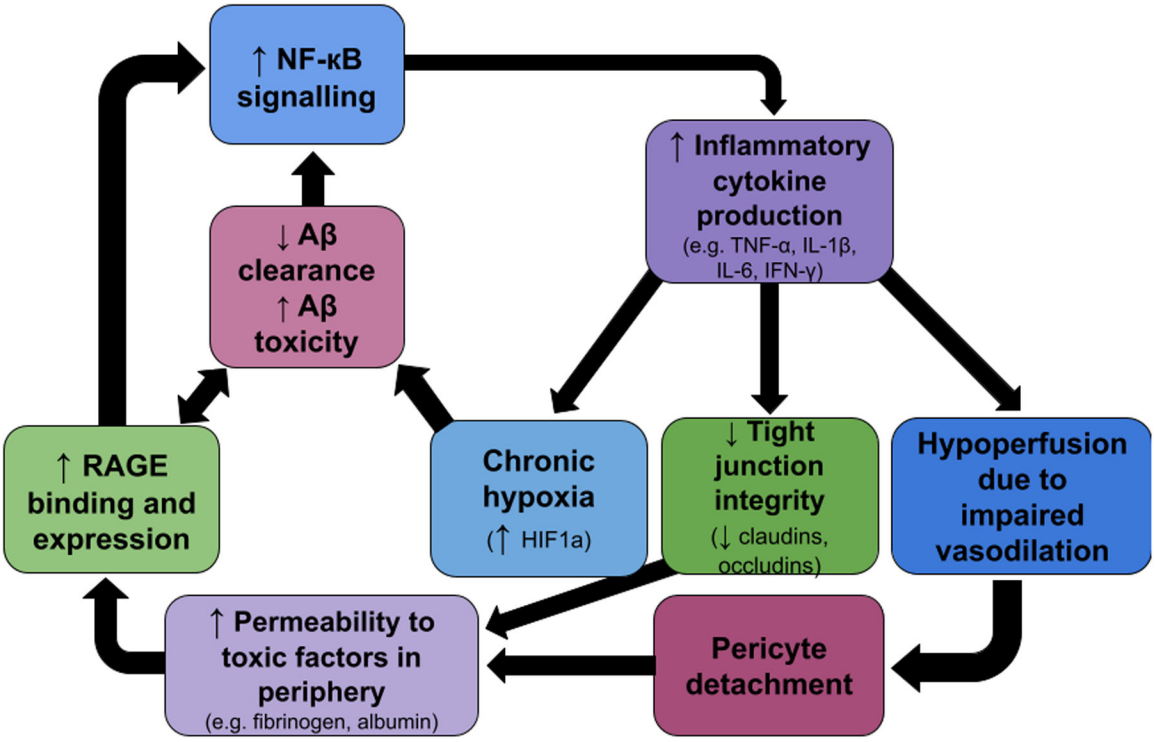

Figure 1:

A simplified schematic representing some of the cascading positive feedback loops connecting inflammatory responses, vascular damage, BBB changes, and increased amyloid toxicity.

Table 1:

summary of cited literature regarding metabolic dysfunction at the BBB and AD and the role of BBB dysfunction in AD.

Metabolic dysfunction at the BBB	Mooradian (1997)[21]	Diabetes is associated with pathological changes to BBB microvasculature
	Rhea et al. (2017)[22]	Review: obesity decreases expression of TJ proteins, thins cerebrovasculature, and increases neuroinflammation
	Chang et al. (2014)[39]	HFD disrupts BBB function and increases neuronal apoptosis
	Salameh et al. (2019)[40]	DIO disrupts hippocampal and hypothalamic BBB
	Roy et al. (2010)[43]	Diabetes causes thickening of vascular basement membrane
	Sajja et al. (2014)[59]	Hypoglycemia reduces claudin-5 and disrupts zona occluden-1 function
	Serlin et al. (2011)[53]	Diabetes induces vascular damage, impairs glucose transport, and increases RAGE signaling
	Yamagishi and Imaizumi (2005)[55]	Hyperglycemia increases productions of advanced glycation end products and reactive oxygen species, resulting in vascular
	Li et al. (2016)[83]	BBB disruption is more severe in obese mice following ischemic stroke
Metabolic dysfunction in AD	Allen et al. (2004)[20]	Meta-analysis: T2DM is associated with increased risk and faster progression of AD
	Roberts et al. (2014)[24]	Mid-life diabetes is associated with loss of brain volume and increased cognitive impairment
	McNay et al. (2010)[25], McNay & Recknagel (2011)[26]	Central insulin resistance impairs spatial working memory
	Bruel et al. (2011)[27]	T2DM is associated with reduction in HPC volume in obese adolescents
	den Heijer et al. (2003)[28]	T2DM is associated with reduction in HPC volume
	Gold et al. (2007)[29]	T2DM associated with reduced HPC volume and impaired cognitive performance in middle aged
	McNay and Pearson-Leary (2020)[33]	Reduced glucose transport associated with cognitive impairment in rats
	Biessels & Reagan (2015)[36]	IR is evident in brains of patients with T2DM and AD
	Talbot et al. (2012)[37]	Reduced insulin signaling evident in the HPC in AD patients without T2DM
	Hardigan et al. (2016)[42]	Diabetes induces cerebrovascular dysfunction resulting in cognitive impairment
	Mosconi et al. (2010)[66], (2013)[65]	Decreased brain glucose utilization occurs early in AD disease progression and correlates with severity
	Swaminathan et al. (2018)[79]	Peripheral insulin administration alters the clearance of Aβ40 and Aβ42
	Small et al. (1995)[98]	APOE4 carriers display reduced parietal metabolism
BBB dysfunction in AD	Rhea et al. (2020)[91]	Review of the impact of APOE4 and insulin on the BBB
	Takechi et al. (2017)[38]	Cognitive decline is preceded by BBB dysfunction in IR mice
	Horwood and Davies (1994)[44], Kalaria and Harik (1989)[46], Mooriadian (1997)[21], Simpson et al. (1994)[47]	BBB glucose transport reduced in AD
	Bowman et al. (2018)[52]	AD patients with dyslipidemia exhibit increased BBB permeability
	Chakraborty et al. (2017)[61]	Review: vascular disturbance impairs BBB function and increased AD risk

	Yang et al. (2020)[62]	Cerebral hypoperfusion increases neuroinflammation, Aβ accumulation, and BBB permeability
	Liu et al. (2019)[63]	Chronic hypoperfusion reduces BBB integrity and decreases pericyte coverage
	Montagne et al. (2015)[67]	BBB breakdown is evident in early AD and correlates with degree of cognitive impairment
	Montagne et al. (2020)[68]	BBB breakdown in APOE4 carriers precedes and predicts cognitive decline independent of Aβ or tau
	Nation et al. (2019)[69]	BBB breakdown is evident in individuals with early mild cognitive impairment independent of Aβ or tau
	Montagne et al. (2021)[74], Bell et al. (2012)[93], Halliday et al. (2016)[94]	APOE4 accelerated BBB dysfunction is dependent on the Cyclophilin A/MMP9 pathway and independent of Aβ
	Cortes-Canteli et al. (2010)[75]	Fibrinogen clots colocalize with Aβ, and fibrinogen depletion improves cognitive performance
	Hultman et al. (2013)[76]	APOE4 exacerbates Aβ associated fibrinogen deposition
	Miners et al. (2018)[77]	Decreased BBB integrity and pericyte marker PDGFRβ is associated with increased fibrinogen deposition and Aβ accumulation in the brain.
	Ryu and McLarnon (2009)[78]	Co-administration of Aβ42 and fibrinogen cause pronounced neuroinflammation which can be reduced by blocking microglial activation
	Bailey et al. (2004)[82]	Review of the contributions of microvascular pathology to AD
	Nelson et al. (2017)[85], Shibata et al. (2000)[84]	Aβ influx/efflux is dependent on BBB RAGE and LRP1/2
	Zlokovic (2013)[92]	Review of the cerebrovascular effects of APOE4
	Main et al. (2018)[95]	BBB regeneration is impaired by APOE4 following traumatic brain injury
	Alata et al. (2015)[96]	APOE4 mice display decreased cerebral vascularization and glucose transport across the BBB
	Zipser et al. (2007)[100]	Prothrombin levels in the cortex correlate with Braak stage

Abbreviations: Aβ, beta amyloid protein; AD, Alzheimer's disease; APOE, apolipoprotein E; BBB, blood–brain barrier; DIO, diet-induced obese; HFD, high-fat diet; HPC, hematopoietic progenitor cell; IR, insulin resistance; LRP, low density lipoprotein receptor; MMP, metalloproteinase; PDFGR, platelet-derived growth factor receptor; RAGE, receptor for advanced glycation end-products; T2DM, type 2 diabetes; TJ, tight junction.