Vascular hypothesis of Alzheimer disease topical review of mouse models

Scheffer, S.; Hermkens, D.M.A.; Weerd, L. van der; Vries, H.E. de; Daemen, M.J.A.P.

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Vascular Hypothesis of Alzheimer Disease

Topical Review of Mouse Models

Sanny Scheffer, Dorien M.A. Hermkens, Louise van der Weerd, Helga E. de Vries, Mat J.A.P. Daemen

ABSTRACT: Alzheimer disease (AD) is marked by profound neurodegeneration, neuroinflammation, and cognitive decline. Pathologically, AD is characterized by the accumulation of extracellular amyloid and intraneuronal tangles, consisting of hyperphosphorylated tau. To date, factors leading to disease onset and progression are still an important topic of investigation. Various epidemiological studies revealed cardiovascular disease as an important contributor to the development and progression of AD, leading to the so-called vascular hypothesis. Vascular risk factors, such as hypertension, diabetes, and hyperhomocysteinemia, are associated with a significantly increased chance of developing AD, suggesting an additive or even synergistic effect. These vascular risk factors are often linked to a reduction in cerebral blood flow and the resulting chronic cerebral hypoperfusion is suggested to play a key role in the onset of AD. However, the causal effects of such vascular risk factors for AD onset remain largely unknown. Evidence from animal studies support that chronic cerebral hypoperfusion induction causes a strong aggravation of AD-related pathology, but a comprehensive overview of how the various cardiovascular disease risk factors contribute to disease is lacking. Therefore, we here critically review current literature, to unravel the existing evidence derived from in vivo mouse studies and define the role of cardiovascular disease and chronic cerebral hypoperfusion in AD development. We conclude that, although many aspects of the vascular hypothesis are well supported by observational studies, in-depth mechanistic studies and well-designed randomized controlled trials are highly needed to establish temporal and causal relationships. Described new insights can have major prospective potential for therapeutic interventions.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: Alzheimer disease ■ cardiovascular disease ■ cerebral hemodynamics ■ dementia ■ vascular risk factors

Over the past 2 decades, the so-called amyloid hypothesis dominated the field of Alzheimer disease (AD) research. This theory states that AD pathology starts by the sequential cleavage of APP (amyloid precursor protein), which results in Aβ (amyloid β) accumulation, as plaques in brain parenchyma or as vascular deposits leading to cerebral amyloid angiopathy (CAA).[1] An imbalance in Aβ production and clearance leads to Aβ-induced neuronal toxicity, neuronal tau hyperphosphorylation, and the formation of neurofibrillary tangles, major hallmarks of AD pathology.[2] However, clinical interventions based on the reduction of Aβ toxicity, mediating APP processing, or removing amyloid plaques or neurofibrillary tangles, have not been successful.[3] The lack of success can be explained by observations that amyloid burden does not always correlate with neurodegeneration and cognitive decline.[4,5] These findings, combined with a growing number of contradictions surrounding the amyloid hypothesis, suggest that other key mechanisms contribute to AD pathogenesis.[6]

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Recently, the 2020 Lancet Commission on dementia prevention, intervention, and care published evidence supporting that at least 12 potentially modifiable risk factors (ie, less education, hypertension, hearing impairment,

Correspondence to: Sanny Scheffer, MSc, Department of Pathology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, Amsterdam, the Netherlands. Email s.scheffer@amsterdamumc.nl

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Nonstandard Abbreviations and Acronyms

AD	Alzheimer disease
ANGII	angiotensin II
APP	amyloid precursor protein
Aβ	amyloid β
BBB	blood-brain barrier
BCAS	bilateral common carotid artery stenosis
CAA	cerebral amyloid angiopathy
CBF	cerebral blood flow
CCH	chronic cerebral hypoperfusion
CVD	cardiovascular disease
HHcy	hyperhomocysteinemia
LRP1	low-density lipoprotein receptor-related protein-1
MCA	middle cerebral artery
MI	myocardial infarction
MMP	matrix metalloproteinase
Nrf2	nuclear factor E2-related factor 2
PS1	presenilin-1
RAGE	receptor for advanced glycation end products
ROS	reactive oxygen species
SAMP8	senescence-accelerated mouse strain 8
TAC	transverse aortic constriction

Highlights

- Cardiovascular disease is an important contributor to the development and progression of Alzheimer disease. Vascular risk factors like hypertension, diabetes, and hyperhomocysteinemia, significantly increase risk of developing Alzheimer disease, suggesting an additive or even synergistic effect.
- Cardiovascular disease is often linked to a reduction in cerebral blood flow and the resulting chronic cerebral hypoperfusion likely plays a pivotal role in the onset of Alzheimer disease.
- This review provides a comprehensive overview of in vivo studies modeling individual vascular risk factors, as well as cerebral hemodynamic disruptions in Alzheimer disease transgenic mouse models.
- Experimentally inducing long-term cardiovascular risk factors or disrupting cerebral hemodynamics accelerates or aggravates Alzheimer disease-like brain pathology and cognitive decline in relevant transgenic mice, characterized by changes across 5 domains (ie, amyloid and tau pathology, neuroinflammation, neurodegeneration, and cognitive decline).
- The Alzheimer disease field should focus on developing animal models that better represent the human disease, as well as implementing a universal set of well-defined methodological guidelines, to facilitate crucial translational steps from preclinical studies to clinical trials.
- Long-term global vascular disruption is a driving force in the full range of Alzheimer disease pathology, probably acting within a network of cellular processes, of which oxidative stress and inflammation are considered key propagating components.

smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution), account for around 40% of worldwide dementias, including AD.[7] Four of these established risk factors are also known risk factors for cardiovascular disease,[8] namely hypertension, diabetes, obesity, and physical inactivity. Based on the Lancet report they contribute a cumulative 6% to increased dementia risk, which is likely even higher when multiple cardiovascular risk factors cluster in individual people.[7] To define the causality of established risk factors, we here aim to highlight specifically their cardiovascular consequences to support the vascular hypothesis, thereby challenging the classic amyloid hypothesis (overview in Figure 1).

One essential player in AD pathogenesis is cerebrovascular impairment, including disrupted cerebral blood flow (CBF) and dysfunction of the so-called neurovascular unit.[9,10] The neurovascular unit consists of specialized brain endothelial cells of the blood-brain barrier (BBB) that are supported in their neuroprotective barrier properties by surrounding glial cells, such as astrocytes and microglia, pericytes, and vascular smooth muscle cells. Proper function of the BBB is critical for brain homeostasis by controlling the environment of the central nervous system, as it prevents the entry of neurotoxic molecules into the central nervous system through tight junctions and efflux transporters. Vice versa, the BBB actively supplies the brain with its essential nutrients.[11] BBB dysfunction promotes or even precedes the neurodegenerative process in AD, evidenced by epidemiological, pharmacological, and neuroimaging studies.[12–14] Brain capillary damage and hippocampal BBB breakdown are associated with early cognitive decline, irrespective of changes in the classical pathological hallmarks such as amyloid and tau accumulation, indicating BBB damage as an early marker of cognitive dysfunction.[15] Importantly, BBB dysfunction also reduces the efflux of amyloid from the brain through the dedicated transporters, such as P-glycoprotein and LRP1 (lipoprotein receptor-related protein-1).[16,17] Together this leads to amyloid deposits onto the vasculature (a pathological process referred to as [capillary] cerebral amyloid angiopathy), further impairing vascular function.[18,19] Various mechanisms are thought to contribute to brain endothelial dysfunction, which includes inflammatory events, effect of genetic differences between patients, and the altered interaction and dysfunction of surrounding pericytes, reviewed in-depth elsewhere.[20–22]

Importantly, early BBB breakdown is linked to impaired white matter microcirculation, causing progressive blood

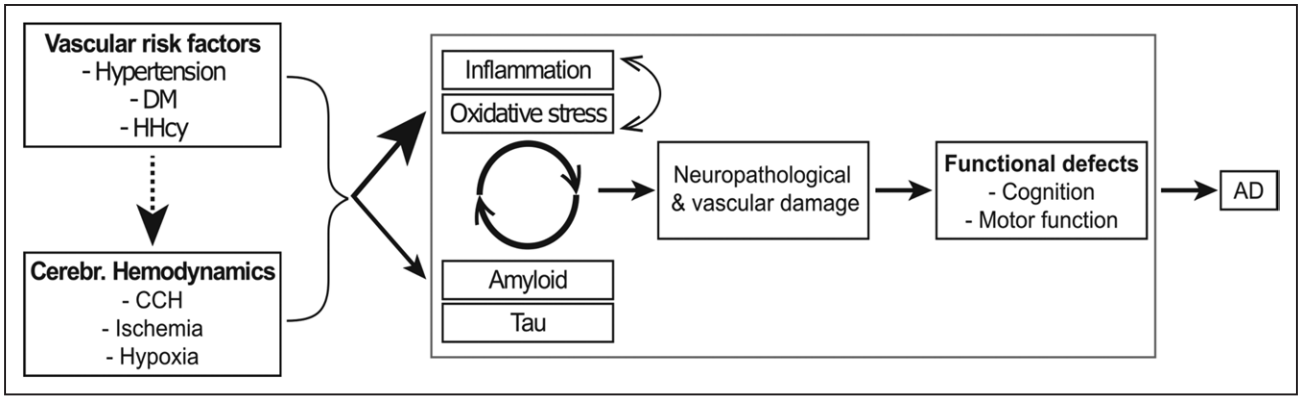

Figure 1. The link between cardiovascular disease (CVD) and Alzheimer disease (AD).
Vascular risk factors (eg, hypertension, diabetes [DM], and hyperhomocysteinemia [HHcy]) can disrupt normal cerebral hemodynamics, causing, for example, chronic cerebral hypoperfusion (CCH), ischemia, or hypoxia. All are known to cause oxidative stress intimately linked to neuroinflammation, which can chronically lead to abnormal amyloid and tau protein aggregation. Inherent predisposition to aberrant amyloid processing and tau phosphorylation, enhanced by CVD, has an additive effect. These combined factors can then impair neurovascular function, ultimately resulting in functional defects typical for advanced AD.

flow reductions.[23] This could result in chronic cerebral hypoperfusion (CCH), which is suspected to play a key role in AD pathogenesis.[24–26] In this context, cardiovascular risk factors (eg, hypertension, hyperhomocysteinemia [HHcy], and diabetes) are often linked to AD development, as they are associated with BBB dysfunction and hemodynamic abnormalities, often resulting in reduced CBF, promoting cerebral hypoperfusion-hypoxia (Figure 1).[27] However, the exact underlying mechanisms are poorly understood.

One mechanism proposed to play a pivotal role in AD pathogenesis is oxidative damage (Figure 2), caused by an imbalance in the production and detoxification of reactive oxygen species and reactive nitrogen species.[28] Along with neuroinflammation and mitochondrial dysfunction, oxidative stress induces cellular damage and disruption of the DNA repair system.[29] Oxidative stress is hypothesized to be an early event in AD pathogenesis and closely interacts with amyloid in the brain.[30] The cerebral vasculature is especially susceptible to oxidative stress, where it is closely associated with CCH and profound deficits in neurovascular regulation.[31] Collectively, a vicious cycle appears to exist, with vascular factors promoting oxidative stress and microvascular inflammation, leading to disruption of Aβ clearance and further impairment of neurovascular function. However, causal and temporal relationships have yet to be established, and in this context, many studies are conducted using a wide variety of mouse models.

The aim of this review is, therefore, to identify the validity of the current evidence derived from these mouse studies, substantiating the vascular hypothesis of AD with a specific focus on the role of oxidative stress. We are aware of the wide range of available human studies and recognize the importance of using this data to create a broader, more comprehensive picture. However, these studies are reviewed elsewhere and go beyond the scope of the current review nor can they provide causal or mechanistic data. Therefore, we focus on critically assessing existing literature and provide a comprehensive overview of in vivo studies specifically implementing different types of disease models in AD transgenic mice, starting with individual cardiovascular risk factors, followed by studies focusing on compromised hemodynamics. We will discuss the different types of models used in the field and provide a rundown of the main findings, highlighting reported results relevant to AD-like pathology and cognitive decline.

SEARCH METHOD AND SELECTION CRITERIA

Electronic databases (PubMed, Web of Science, Science Direct, Google Scholar) were searched without any year restrictions, but limited to literature published in the English language. Different combinations and spellings/abbreviations of the following MeSH terms were used: "Alzheimer disease," "mouse model," "transgenic," "cerebral hypoperfusion," "cerebral hemodynamics," "cerebral blood flow," "hypoxia," "ischemia," "bilateral carotid artery stenosis," "artery occlusion," "myocardial infarction," "transverse aortic ligation," "cardiovascular disease," "vascular risk factors," "diabetes mellitus," "hypertension," "hyperhomocysteinemia." The reference lists from relevant publications were used to identify further relevant literature. The last search was conducted on May 6, 2020. Studies included in Tables 1 and 2 were limited to in vivo studies, experimentally inducing either a vascular risk factor or disrupting normal cerebral hemodynamics in an Alzheimer disease transgenic mouse model.

VASCULAR RISK FACTORS AND AD

Adherence to the American Heart Association ideal cardiovascular health index is reported to be associated

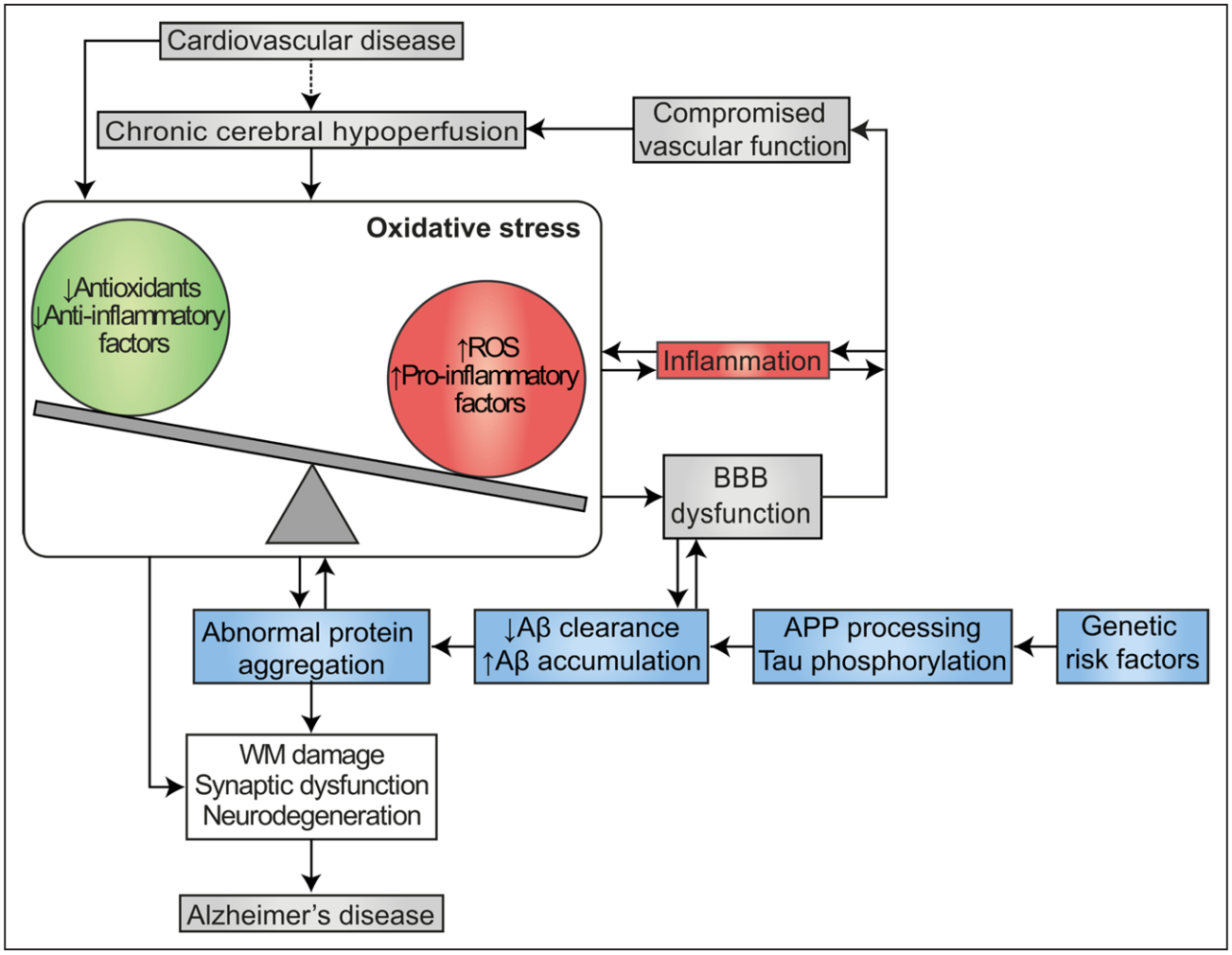

Figure 2. The proposed role of oxidative stress in the association between cardiovascular disease (CVD) and Alzheimer disease (AD).

CVD can cause hemodynamic changes, possibly leading to chronic cerebral hypoperfusion (CCH), which disturbs redox homeostasis due to an increase in reactive oxygen species (ROS) and proinflammatory mediators, whereas antioxidants and anti-inflammatory mediators are decreased. The resulting oxidative stress is closely linked to neuroinflammation in a positive feedback loop that can chronically impair blood-brain barrier (BBB) function, causing reduced Aβ (amyloid-β) clearance and thereby elevated Aβ accumulation and abnormal protein aggregation. Genetic predisposition to aberrant APP (amyloid precursor protein) processing and tau phosphorylation has an additive effect. Aβ neurotoxicity aggravates BBB dysfunction, enhancing oxidative stress and neuroinflammation, which can then lead to impaired vascular function, further disrupting cerebral circulation. Ultimately, oxidative stress can cause white matter (WM) damage, synaptic dysfunction, and progressive neurodegeneration, resulting in advanced AD.

with a lower 10-year risk of all-cause dementia, vascular dementia, and AD.[32] Epidemiological and biological evidence show a strong association between modifiable vascular risk factors, such as hypertension, diabetes, HHcy, and a highly increased risk of developing AD.[33–35] On the basis of population attributable risks, a statistic that takes into account prevalence in addition to strength of association, it is estimated that ≈1% to 2% of AD cases worldwide are currently attributable to diabetes and 1% to 5% to midlife hypertension.[7,36] For Hhcy, risk ranges from 4.3% to 31%.[37] Several in vivo studies investigated the downstream effects of vascular risk factors on AD pathogenesis using different transgenic mouse models for amyloidosis with mutations in APP or PS1 (presenilin 1). Alternatively, models for tauopathy or mixed pathology were used. The studies included in this review pharmacologically induced hypertension, mostly by chronically infusing the animals with ANGII (angiotensin II), a component of the renin-angiotensin system that has a prominent role in blood pressure regulation. Alternative methods use mineralocorticoid deoxycorticosterone acetate salt, which results in renin-independent hypertension, or L-N^G-Nitro arginine methyl ester to create a NO-deficient model.[38] All diabetes mouse studies discussed below used streptozotocin injections, an alkylating agent that targets insulin-producing beta cells in the pancreas, mimicking type 1 diabetes in mice.[39] HHcy was induced through a dietary approach that disrupts the metabolic pathways of homocysteine. This can be done using diets either deficient in folate, vitamin B6, B12, or a combination, or by adding

an excess amount of methionine.[40] Below we discuss the main findings for the different models. Findings from included studies are summarized in Table 1.

Experimentally inducing hypertension,[41–45] diabetes,[46–54] or HHcy[55–61] enhances cerebro(vascular) Aβ levels and intraneuronal Aβ accumulation, often leading to cortical amyloid deposition and CAA development, next to changes in amyloidogenic pathways. Hypertension causes an increase in cerebrovascular Aβ deposition, but not in the parenchyma.[45] Diabetes leads to a shift in Aβ soluble/insoluble levels, promoting the formation of toxic soluble species.[51] However, a few studies using HHcy models observe no effect of HHcy on Aβ levels or amyloidogenic pathways,[58,61,62] perhaps because of the use of different dietary interventions or mouse strains. Additionally, both HHcy[57] and diabetes enhance deposition of phosphorylated tau in amyloidosis mouse models.[46,48,51] This is also found in mixed amyloidosis and tau pathology 3×Tg-AD mice[54] and in a mouse model for tauopathy.[53] Hypertension does not significantly increase tau species immunoreactivity in P301L-tau Tg mice.[42] Nor does diabetes affect brain tau levels 3×Tg-AD mice; however, the mice do exhibit a trend towards elevation.[47] Collectively, all 3 vascular risk factors are associated with aggravated amyloid and tau pathology in AD transgenic mouse models.

Importantly, all 3 are also linked to an increased (neuro)inflammatory response and result in both vascular and neurodegenerative changes. Hypertension leads to increased BBB dysfunction and enhanced vascular inflammation, often surrounding CAA-affected vessels. Increased CAA contributes to loss of pericyte interaction with the vasculature, thereby disturbing neurovascular coupling.[44] Indeed, several cerebrovascular impairments are observed after induction of hypertension.[41,43,45] neurovascular unit dysfunction may, in turn, affect neuronal health and advance (hippocampal) neurodegeneration, detected already at an early age in hypertensive amyloidosis mice.[44,45] Similar to hypertension, inducing diabetes in amyloidosis and in 3×Tg-AD mice also results in an exacerbated inflammatory response, both in close proximity to plaques and in plaque-free areas.[51,52,54] Although no necrotic or apoptotic changes are observed in the brain following experimental diabetes induction,[48] synaptic plasticity does decrease[54] and postmortem assessment shows brain atrophy and hemorrhages.[51] Diabetes is also associated with increased mortality.[48] Although diabetes leads to only slight decreases in the amount of cerebrovascular pericyte and endothelium cells, it is suggested that BBB dysfunction is involved in AD pathogenesis.[51,63] In addition, the expression of 20 AD-associated risk genes, including those involved in APP processing, cytoskeleton, synaptic function, protein kinases, and apoptosis are significantly altered after inducting diabetes in 3×Tg-AD mice, indicating disruption of multiple signaling pathways.[54] HHcy induces cerebral oxidative stress[59,60] and an exacerbated neuroinflammatory response, accompanied by an activation of MMP2 (matrix metalloproteinases 2) and MMP9,[61] both implicated in cerebrovascular pathophysiology.[64] Induction of HHcy in amyloidosis mice also increases cerebral microhemorrhages compared with wild-type mice, which may be CAA-related.[61]

Finally, experimental induction of these 3 risk factors also causes significant cognitive deficits. Hypertension does not always result in spatial learning impairments,[42] but does disrupt spatial reference and temporal order memory,[41,44,45] even at the early stage of AD progression.[41] deoxycorticosterone acetate salt also affects motor function in a mouse model for tauopathy.[42] Diabetes results in reduced spatial cognition,[46,48] with exacerbated short-term and spatial reference memory deficits both in an amyloidosis and a mixed pathology mouse model[49,54] and an aggravation of episodic and working memory impairment.[51] These diabetes-related cognitive deficits correlate negatively with the increased cerebral Aβ levels.[48] Several HHcy dietary combinations also result in significant cognitive decline and behavioral impairments, even at a preplaque age.[56,58,59,61]

The number of mouse studies addressing this topic is relatively limited and mechanistic, longitudinal data are rare. Nevertheless, these findings indicate that hypertension, diabetes, and HHcy affect AD-related pathology and cognitive performance to a similar extent and cerebrovascular dysfunction may be the common denominator in this process. Epidemiological studies of vascular risk factors, together with imaging tools in preclinical models for AD, implicated CCH as one of the earliest mechanistic factors involved in the development of AD-related cognitive decline.[65] Indeed, most, if not all, of the vascular risk factors are associated with cerebrovascular dysfunction and disturbed cerebral hemodynamics,[66–68] leading to the hypothesis that CCH is an important link between vascular disease and AD. Since cerebral hemodynamic changes were not assessed in these animals, no data are available on whether CCH is indeed the main mediating factor. Mechanistic studies, including CBF measurements, are needed to fully grasp the underlying pathways involved in AD pathogenesis.

REDUCTION OF CEREBRAL PERFUSION AND AD

CCH in humans is thought to result from 1 of 3 main direct causes (1) structural vascular lesions as a consequence of large artery occlusion or stenosis; (2) cerebral hemodynamic changes through disruptions of the micro- and microvasculature, possibly caused by pericyte degeneration and subsequent BBB dysfunction; and (3) alterations in blood composition resulting in increased blood viscosity.[23,25] Clinical studies using a range of imaging techniques, such as transcranial doppler, single-photon emission computed tomography, and perfusion-weighted magnetic resonance imaging,

Table 1. Overview of Structural and Functional Brain Changes in AD Mice With Cardiovascular Risk Factors

	Model (duration intervention)	Animals (age start experiment, sex)	AD mouse model (genes mutated)	Amyloid and tau pathology	Inflammation and oxidative stress	Degenerative changes	Vasculature changes	Cerebral hemodynamic changes	Behavior	References
HT	ANGII (600 ng/[kg·min]); 14 d	Tg2576, 3 mo+6 mo, M	Amyloidosis; APP	↑ CAA ↑ Aβ pathway changes	…	…	No change in vascular reactivity	…	…	Faraco et al[43]
		APPS*w*DI, 3 mo, M	Amyloidosis; APP	…	…	…	↓ Vascular reactivity	…	…	Faraco et al[43]
	ANGII (1.1 mg/kg/d); 8 wk	Tg2576, 5 mo, F	Amyloidosis; APP	↑ $A\beta_{40,42\ (brain)}$ ↓ $A\beta_{40,42\ (serum)}$	…	…	…	…	No cognitive deficit	Díaz-Ruiz et al[42]
	DOCA-salt; 8 mo	P301L-tauTg, 5.5 mo, F	Tauopathy; MAPT	No abnormal tau species	…	…	…	…	↓ Motor function	Díaz-Ruiz et al[42]
	ANGII (1000 ng/[kg·min]); 2.5 mo	APP/PS1, 2 mo, M	Amyloidosis; APP, PS1	↑ $A\beta_{42\ (S)}$ No change in $A\beta_{40\ (S)}$ ↑ Plaques ↑ CAA	No inflammatory changes	↓ Cerebral microvessel density	↓ VEGF-A ↓ NO production	…	↓ Cognition No motor defects	Cifuentes et al[41]
	L-NAME (100 mg/kg); 3 mo or 6 mo	APPS*w*DI, 3–4 mo, M+F	Amyloidosis; APP	No change in $A\beta_{40,42}$ levels ↓ Plaques ↑ CAA	↑ Microgliosis No astrogliosis	↑ Neuronal and pericyte loss No changes in vessel number	↓ BBB integrity	…	↓ Cognition No motor defects	Kruyer et al[44]
	ANGII (1000 ng/[kg·min]); 4 wk	5×FAD, 6 mo, M	Amyloidosis; APP, PS1	↑ Aβ cerebrovascular deposition No change parenchymal $A\beta_{40/42}$ deposits	↑ Microgliosis	↑ Neuronal loss	…	↓ CBF	↓ Cognition No motor defects?	Cao et al[45]
Diabetes	STZ (200 mg/kg), 1× IP; 2 mo	P301L-tauTg (pR5 model), 4 mo, ?	Tauopathy; MAPT	↑ Phospho-tau ↑ NFTs	…	…	…	…	…	Ke et al[53]
	STZ (90 mg/kg), 1×/d/2 d IP; 12 wk	hAPP, 4 mo, ?	Amyloidosis; APP	↑ $A\beta_{42\ (S)}$ No change in $A\beta_{40\ (S)}$ ↑ Plaques ↑ Aβ pathway changes ↑ Phospho-tau	…	↑ Neuronal loss ↑ Synapse loss	…	…	↓ Cognition No motor defects	Jolivalt et al[46]
	STZ (90 mg/kg), 1×/d/2 d IP; 20 wk	APPS*w*/PS1/ΔE9, 3 mo, M	Amyloidosis; APP, PS1	↑Plaques	↑ NF-κB ↑ AGEs/RAGE	…	…	…	…	Wang et al[52]
	STZ (90 mg/kg), 1×/d/2 d IP; 20 wk	APP/PS1, 3 mo, ?	Amyloidosis; APP, PS1	↑ $A\beta_{42}$ ↑ Plaques ↑ Aβ pathway changes	…	…	…	…	↓ Cognition No motility or vision defects	Wang et al[49]
	STZ (90 mg/kg), 1×/d/2 d IP; 2.5 mo	5×FAD, 1.5 mo, ?	Amyloidosis; APP, PS1	↑ $A\beta_{40,42}$ ↑ Aβ pathway changes	…	…	…	…	…	Devi et al[50]
	STZ (40 mg/kg), 1×/d/5 d IP; 8 wk	APPS*w*/PS1/ΔE9, 18 wk, ?	Amyloidosis; APP, PS1	↑ $A\beta_{40\ (S)}$ ↓ $A\beta_{40\ (IS)}$ ↓ Plaques ↓ CAA No Aβ pathway changes ↑ Phospho-tau	↑ Microgliosis	↑ Brain atrophy	↑ Hemorrhages	…	↓ Cognition No motor defects	Ramos-Rodriguez et al[51]
	STZ (50 mg/kg), 1×/d/5 d IP; 16 wk	3×Tg-AD, 11–12.5 mo, F	Amyloidosis+ tauopathy; APP, PS1, MAPT	↑ $A\beta_{\ (S)}$ ↑ Aβ pathway changes Trend elevated tau	…	…	…	…	…	Li et al[47]
	STZ (1.25 mg/kg), 1×/ICV; 6 mo	Tg2576, 3 mo, M+F	Amyloidosis; APP	↑ $A\beta_{40,42\ (S+IS)}$ ↑ Plaques ↑ Tau	…	No apoptosis	…	…	↓ Cognition No motor defects	Plaschke et al[48]

(*Continued*)

Table 1. Continued

	Model (duration intervention)	Animals (age start experiment, sex)	AD mouse model (genes mutated)	Amyloid and tau pathology	Inflammation and oxidative stress	Degenerative changes	Vasculature changes	Cerebral hemodynamic changes	Behavior	References
	STZ $_{(3\ mg/kg)}$, 1×/ ICV; 3–6 wk	3×Tg-AD, 6 mo, F	Amyloidosis+ tauopathy; APP, PS1, MAPT	↓ $A\beta_{40}$ No change in $A\beta_{42/40}$ Changes in 20 AD-related genes ↑ Phospho-tau	↑ Microgliosis ↑ Astrogliosis	↓ Synaptic plasticity	…	…	↓ Cognition Slight motor defects	Chen et al[54]
HHcy	Diet $_{(-\ folate,\ vitamin\ B6,\ vitamin\ B12)}$; 60 d	TgCRND8, 3 wk, M+F	Amyloidosis; APP	↑ $A\beta_{40,42}$ ↑ Plaques ↑ Aβ pathway changes	…	No apoptosis	…	…	Slight cognitive deficit	Fuso et al[56]
	Diet $_{(-\ folate,\ vitamin\ B12,\ vitamin\ B6)}$; 60 d	TgCRND8, 3 wk, ?	Amyloidosis; APP	…	↑ Oxidative stress markers Changes in antioxidant activity	…	…	…		Cavallaro et al[60]
	Diet $_{(-\ vitamin\ B)}$; 60 d	TgCRND8, 3 wk, M+F	Amyloidosis; APP	↑ $A\beta_{40,42}$ ↑ Plaques ↑ Aβ pathway changes ↑ Phospho-tau	…	…	…	…	No cognitive deficit	Fuso et al[57]
	Diet $_{(+\ methionine)}$; 3 m+11 m	ArcAβ, 3 mo, M+F	Amyloidosis; APP	↑ $A\beta_{40\ (IS;\ 11\ m,f)}$	…	…	…	…	…	Farkas et al[55]
	Diet $_{(+\ methionine)}$; 5 m	Tg2576, 9 mo, F	Amyloidosis; APP	↑$A\beta_{40\ (IS)}$ ↑$A\beta_{42\ (S+IS)}$ ↑ Plaques No Aβ pathway changes	↑ Oxidative stress markers	…	…	…	↓ Cognition	Zhuo et al[59]
	Diet $_{(+\ methionine)}$; 7 mo	Tg2576, 8 mo, F	Amyloidosis; APP	↑$A\beta_{40\ (IS)}$ ↑$A\beta_{42\ (S+IS)}$ ↑ Plaques No Aβ pathway changes	…	…	…	…	↓ Cognition	Zhuo et al[58]
	Diet $_{(+\ methionine;\ -\ folate,\ vitamin\ B6,\ vitamin\ B12)}$; 7 mo	Tg2576, 8 mo, F	Amyloidosis; APP	No changes in $A\beta_{40,42\ (S+IS)}$ No change in plaques No Aβ pathway changes	…	…	…	…	…	Zhuo et al[62]
	Diet $_{(+\ methionine;\ -\ folate,\ vitamin\ B6,\ vitamin\ B12)}$; 6 mo	APP/PS1, 6 mo, M+F	Amyloidosis; APP, PS1	No change in $A\beta_{38'40,42\ (S+IS)}$ ↓ Plaques ↑ CAA	↑ Microgliosis Switch M2a to M1-biased state	…	↑ Hemorrhages ↑ MMP2, MMP9	…	↓ Cognition	Sudduth et al[61]

? indicates unknown, not published data; ↑, increase; ↓, decrease; AD Alzheimer disease; AGEs, advanced glycation end products; ANGII, angiotensin II; APP, amyloid precursor protein; Aβ, amyloid β; APPSwDI, APP-Swedish, Dutch, Iowa; ArcAβ, arctic Abeta; BBB, blood-brain barrier; CAA, cerebral amyloid angiopathy; CBF, cerebral blood flow; DOCA-salt, deoxycorticosterone acetate salt; F, female; FAD, familial Alzheimer disease; h, human; Hhcy, hyperhomocysteinemia; HT, hypertension; ICV, intracerebroventricular; IP, intraperitoneal; IS, insoluble; L-NAME, L-NG-nitroarginine methyl ester; M, male; M1, macrophage M1 subtype; M2a, macrophage M2a subtype; MAPT, microtubule-associated protein tau; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; NFT, neurofibrillary tangles; Phospho-tau, phosphorylated tau; PS1, presenilin 1; RAGE, receptor for advanced glycation end products; S, soluble; STZ, Streptozotocin; Tg, transgenic; TgCRND8, APP (Swedish/Indian) CRND8; and VEGF-a, vascular endothelial growth factor A.

reported a marked reduction in CBF in patients with AD, already in early stages of disease development.[69–71] This suggests an early, perhaps even causal, role for CCH in AD pathogenesis. To define the impact of disrupted cerebral hemodynamics on the development of AD, several studies have surgically or chemically reduced CBF or oxygen levels in AD transgenic mouse models. Below (and summarized in Table 2) we focus on data from animal models and interventions with 4 distinct alterations in cerebral flow reduction ranging from chronic cerebral hypoperfusion, hypoxia, mild ischemia (and reperfusion), and severe ischemia.

Table 2. Overview of Structural and Functional Brain Changes in AD Mice With Flow or Oxygen Disruption

	Model (duration intervention)	Animals (age start experiment, sex)	AD mouse model (genes mutated)	Amyloid and tau pathology	Inflammation and oxidative stress	Degenerative changes	Vasculature changes	Behavior	References
CCH	BCAS (0.18 mm); 12 wk	APPS*w*DI, 10 wk +16 wk +20 wk, M	Amyloidosis; APP	↑ CAA	…	Some microinfarcts	…	…	Okamoto et al[74]
	BCAS (0.18 mm); 1 mo+9 mo	APPS*w*I, 5 mo+8 mo+11 mo, M	Amyloidosis; APP	↑$A\beta_{40,42\ (S+IS)}$	↑ Astrogliosis	↑ WM rarefaction	…	…	Kitaguchi et al[81]
	BCAS (0.18 mm); 6 mo	APPS*w*I, 2 mo, M	Amyloidosis; APP	↓$A\beta_{42\ (IS)}$ ↓ Plaques ↑$A\beta_{(S)}$	…	↓ Neuronal density	…	↓ Cognition	Yamada et al[86]
	BCAS (0.18 mm); 28 d	T44 Tg, 8 mo, M	Tau; T44	↑ Phospho-tau	…	…	…	…	Shimada et al[79]
	BCAS (0.18 mm); 50 d	APPswe/PS1dE9, 10–11 wk, M+F	Amyloidosis; APP, PS1	↑ Aβ plaque growth No Aβ pathway changes Shift Aβ species	…	Refraction of WM without apoptosis	Changes in CSF dynamics	…	Bannai et al[85]
	BCAS (ac, 0.75 mm); 15 d	APP23, 6 mo+ 12 mo, M	Amyloidosis; APP	↑$A\beta_{(12M)}$ ↑ Phospho-tau $_{(12M)}$	↑ Oxidative stress (12M) ↑ Mitochondrial fission, ↓ fusion	…	…	…	Feng et al[78]
	BCAS (ac, 0.75 mm); 8 mo	APP23, 4 mo, M+F	Amyloidosis; APP	↑ Plaques ↑ CAA	↑ Neuroinflammation ↑ Oxidative stress	↓ Neuronal density	…	↓ Cognition $_{(>8\ mo)}$ ↓ Motor function $_{(>5\ mo)}$	Liu et al[82]
	BCAS (ac, 0.75 mm); 8 mo	APP23, 4 mo, M+F	Amyloidosis; APP	↑ Phospho-tau+phospho-α-synuclein	…	…	↑ MMP9 ↑ NVU remodeling ↓ NV tropic coupling	…	Liu et al[80]
	BCAS (ac, 0.75 mm); 8 mo	APP23, 4 mo, M+F	Amyloidosis; APP	…	↑ Complement cascade	…	↑ Coagulation cascade	…	Shi et al[95]
	BCAS (ac; 0.75 mm); 8 mo	APP23, 4 mo, M+F	Amyloidosis; APP	…	Changes (neuro) inflammatory markers	…	…	…	Shi et al[96]
	BCAS (ac, 0.75 mm); 8 mo	APP23, 4 mo, M	Amyloidosis; APP	↑ Plaques ↑ CAA Imbalanced Aβ transport receptors	↑ Oxidative stress	…	↓ Vital nutrient transporter proteins (BBB integrity)	…	Shang et al[84]
	BCAS (ac, 0.75 mm); 8 mo	APP23, 4 mo, M	Amyloidosis; APP	↑ Plaques	↑ NLRP3 inflammasome	…	NVU dissociation	…	Shang et al[83]
	TAC; 1.5 mo+3 mo	APP/S*w*DL, 6 mo, M	Amyloidosis; APP	↑$A\beta_{40,42\ (S+IS;\ 3\ mo)}$ ↑ Plaques $_{(3\ mo)}$ ↑ CAA $_{(3\ mo)}$	…	No hemorrhages	…	…	Li et al[92]
	TAC; 6 wk	APP/PS1, 4.5 mo, M	Amyloidosis; APP, PS1	↑ Plaques No change $A\beta_{40,42\ (S+IS)}$	↑ Astrogliosis	↓ Microvascular density ↑ Microhemorrhages ↑ Apoptosis+ senescence ECs ↓ Endothelial dilatory function ↓ BBB integrity	↓ CBF	↓ Cognition	de Montgolfier et al[93]
	MI; 1 mo	APPS*w*/PS1/ΔE9, 20 wk, M	…	↑ Plaques ↑ Phospho- tau	↑ Proinflammatory microglia ↑ Oxidative stress	…	…	↓ Cognition	Zhang et al[94]
Hypoxia	10% O_2, 72 h	APPS*w*/PS1/ΔE, 9 mo, ?	Amyloidosis; APP, PS1	…	…	↑ Neurogenesis	…	…	Varela-Nallar et al[106]

(*Continued*)

Table 2. Continued

	Model (duration intervention)	Animals (age start experiment, sex)	AD mouse model (genes mutated)	Amyloid and tau pathology	Inflammation and oxidative stress	Degenerative changes	Vasculature changes	Behavior	References
	8% O_2,16 h/day; 1 mo	APP23, 8 mo, ?	Amyloidosis; APP	↑ $A\beta_{40,42}$ ↑ Plaques ↑ Aβ pathway changes	…	…	…	↓ Cognition	Sun et al[101]
	11.1 % O_2, 6 h/d; 30 d	APPS*w*/PS1/ΔE9, 3 mo, ?	Amyloidosis; APP, PS1	↑ $A\beta_{42}/A\beta_{40}$ ratio ↑ Plaques ↑ Aβ pathway changes ↑ Phospho-tau	…	↓ Synaptic density ↑ Demethylation genomic DNA	…	↓ Cognition	Liu et al[100]
	5% or 21% O_2, every 10 min, 8 h/d; 4 wk	3×Tg-AD, 6 m, M	Amyloidosis+ tauopathy; APP, PS1, MAPT	↑ $A\beta_{42}$ No change in $A\beta_{40}$ No change in plaques ↑ Intracellular Aβ No Aβ pathway changes	…	…	…	No cognitive deficit	Shiota et al[104]
	10% O_2, 10 h/d; 4 wk	APP/PS1,10–11 mo, M+F	Amyloidosis; APP, PS1	No changes $A\beta_{40,42\ (S+IS)}$ No changes in plaques	↑ Astrogliosis	…	…	…	Macheda et al[105]
	Hypoxic pressure chamber; 15 d	APP/PS1, 9 mo, M	Amyloidosis; APP, PS1	↓ $A\beta_{40,42}$ ↓ Plaques	…	↑ Neurogenesis ↓ Apoptosis	…	↑ Cognitive performance, decreased anxiety	Meng et al[107]
	Jar 1×/d; until first gasping breath; 60 d	APPS*w*/PS1, 9 mo, F	Amyloidosis; APP, PS1	↑ $A\beta_{42\ (S)}$ ↑ Plaques ↑Aβ pathway changes	↑ Macroautophagy	…	…	…	Li et al[99]
	Jar 1×/d; until first gasping breath; 2 mo	APP/PS1, 6 mo, F	Amyloidosis; APP, PS1	↑ Plaques ↑ Phospho-tau	…	↑ Neuronal apoptosis	…	↓ Cognition No motility or vision defects	Wang et al[103]
	Jar 1×/d; until first gasping breath; 60 d	APP/PS1, 6 mo, ?	Amyloidosis; APP, PS1	↑ $A\beta_{42}$ ↑ Plaques ↑ Phospho-tau	…	…	…	↓ Cognition No motor defects	Gao et al[98]
	Jar 1×/d; until first gasping breath; 2 mo	APPS*w*/PS1/ΔE9, 2 mo+6 mo+12 mo, M	Amyloidosis; APP, PS1	↑ $A\beta_{40,42\ (S+IS;\ 8+14\ mo)}$ ↑ Plaques $_{(8+14\ mo)}$ ↑ Aβ pathway changes $_{(8+14\ mo)}$	↑ Cytokines $_{(8+14\ mo)}$ ↑ ROS levels $_{(8+14\ mo)}$ ↑ Oxidative stress markers $_{(8+14\ mo)}$ ↓ Antioxidant activity $_{(8+14\ mo)}$ ↑ Nuclear Nrf2 $_{(4\ mo)}$ ↓ Nuclear Nrf2 $_{(8+14\ mo)}$ ↓ Nrf2/ARE pathway changes $_{(8+14\ mo)}$	↓ Synaptic markers $_{(8+14\ mo)}$	…	↓ Cognition $_{(8+14\ mo)}$	Wang et al[102]
Transient ischemia (reperfusion)	BCCAO 3 min; 10 d	Tg2576, 4–6 mo, ?	Amyloidosis; APP	↑ $A\beta_{40,42}$ No change in plaques	…	No neuronal loss	…	↓ Cognition	Watanabe et al[110]
	BCCAO 4 min; 48 h	3×Tg-AD, 3 mo, M	Amyloidosis+ tauopathy; APP, PS1, MAPT	↑ $A\beta_{42\ (S+IS)}$ ↑ Aβ pathway changes ↑ Phospho-tau	↑ Macroautophagy	No cell death	…	…	Koike et al[111]

(*Continued*)

Table 2. Continued

	Model (duration intervention)	Animals (age start experiment, sex)	AD mouse model (genes mutated)	Amyloid and tau pathology	Inflammation and oxidative stress	Degenerative changes	Vasculature changes	Behavior	References
	BCCAO 12 min; 24 h+48 h+3 mo	3×Tg-AD, 12 mo+15 mo, M	Amyloidosis+ tauopathy; APP, PS1, MAPT	No change in $A\beta_{40,42\ (S+IS)}$ ↑ Aβ pathway changes ↓ Phospho-tau $_{(3\ mo)}$ ↑ Tau $_{(IS)}$	…	↑ Ischemic infarct $_{(24\ h)}$ No ongoing cell death $_{(3\ mo)}$	…	…	Koike et al[112]
	BCCAO 17 min; 2–5 wk	APPS*w*/PS1/ΔE9, 3.5 mo, M	Amyloidosis; APP, PS1		↑ Microgliosis ↑ Astrogliosis	↑ Neuronal loss	…	↓ Cognition ↓ Motor function	Kemppainen et al[113]
	BCCAO 17 min; 5 wk	APPS*w*/PS1/ΔE9, 9 mo, M	Amyloidosis; APP, PS1	↓ Plaques	↑ Microgliosis ↑ Astrogliosis ↑ Blood-derived monocytes	↑ Neuronal loss ↑ Neurogenesis	…	…	Heikkinen et al[114]
Severe ischemia	MCAO 45 min; 3 d	Tg2576, 6 mo+15 mo, M	Amyloidosis; APP	No change in plaques $_{(15\ mo)}$ No change in CAA $_{(15\ mo)}$	…	↑ Infarct size	↓ Vascular reactivity $_{(15\ mo)}$	↓ Sensorimotor function	Milner et al[117]
	MCAO 1 h; 7 d	APPS*w*/PS1/ΔE9, 6–7 mo, M	Amyloidosis; APP, PS1	↑ Plaques	…	↑ Infarct size	…	…	Garcia-Alloza et al[121]
	pMCAO; 24 h	APPS*w*, 3–4 mo, ?	Amyloidosis; APP	No Aβ changes in ischemic area	…	↑ Infarct size	↓ Vascular reactivity	…	Zhang et al[118]
	pMCAO; 24 h	APP, 8 mo, M	Amyloidosis; APP	…	↑ Microglial p38 MAPK activity	↑ Infarct size	No change in vascular reactivity	…	Koistinaho et al[123]
	pMCAO; 24 h	3×Tg-AD, 3 mo+12 mo, M+F	Amyloidosis+ tauopathy; APP, PS1, MAPT	No change in phospho-tau	↑ Microglial changes	↑ Degeneration ECs and astrocyte endfeet	↑ Collagen IV and laminin No STL change	↑ Neurobehavioral deficit	Hawkes et al[115]
	pMCAO; 24 h	APPS*w*/PS1/ΔE9, 9 mo, M	Amyloidosis; APP, PS1	…	…	↑ Infarct size	No change in vascular reactivity	…	Heikkinen et al[114]
	pUCCAO; 3 d+5–6 wk	APPS*w*/PS1, 4 mo, M	Amyloidosis; APP, PS1	No change in plaques	↑ Microgliosis No changes in blood monocytes ↑ Ratio $Ly6C^{hi}$/$Ly6C^{low}$ monocytes	No neuronal loss	…	↓ Cognition $_{(5\ wk)}$ No cognitive flexibility deficit $_{(5\ wk)}$ No motor defects $_{(5\ wk)}$	Pimentel-Coelho et al[24]
	pUCCAO; 8 wk	Tg2576, 14–15 mo, F	Amyloidosis; APP	No change in plaques	…	No neuronal loss No WM damage ↑ Metabolic deficits	…	↓ Cognition No motor defects	Lee et al[116]
	pUCCAO; 1 wk +5 wk+5 mo	PS1V97L, 3 mo, ?	Amyloidosis; PS1	↑ Aβ accumulation	↑ NF-κB ↑ Inflammatory cytokines	…	↓ BBB integrity	↓ Learning	Yang et al[119]
	Photo-induced; 1 d+7 d+21 d	APPS*w*DI, 12 mo, ?	Amyloidosis; APP	↓ Aβ $_{(7\ d+21\ d)}$	↑ Microgliosis $_{(7\ d+21\ d)}$ ↑ Macrophages $_{(7\ d+21\ d)}$	…	…	…	Van Nostrand et al[122]
	Endothelin-1 unilateral injection; 21 d	APP23, 6 mo, ?	Amyloidosis; APP	↑ APP ↑ Tau	↑ Microgliosis ↑ NF-κB	…	…	↓ Cognition	Whitehead et al[120]
	Rose bengal injection; during	APPS*w*/PS1/ΔE9, 6–7 mo, ? + Tg2576, 11–13 mo, ?	Amyloidosis; APP, PS1	↑ Plaques $_{(transient)}$ ↑ CAA No Aβ pathway changes	…	↑ Morphological changes to neurites	…	…	Garcia-Alloza et al[121]

? indicates unknown, not published data; ↑, increase; ↓, decrease; ac, ameroid constrictor; AD, Alzheimer disease; APP, amyloid precursor protein; ARE, antioxidant response element; Aβ, amyloid β; APPSwDI, APP-Swedish, Dutch, Iowa; BBB, blood-brain barrier; BCAS, bilateral common carotid artery stenosis; BCCAO, bilateral common carotid artery occlusion; CAA, cerebral amyloid angiopathy; CBF, cerebral blood flow; ECs, endothelial cells; F, female; IS, insoluble; M, male; MAPT, microtubule-associated protein tau; MCAO, middle cerebral artery occlusion; MI, myocardial infarction; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; Nrf2, Nuclear factor E2-related factor 2; NV, neurovascular; NVU, neurovascular unit; p38 MAPK, p38 mitogen-activated protein kinases; Phospho-tau, phosphorylated tau; pMCAO, permanent middle cerebral artery occlusion; PS1, presenilin 1; pUCCAO, permanent unilateral common carotid artery occlusion; ROS, reactive oxygen species; S, soluble; STL, Solanum tuberosum lectin; TAC, transverse aortic constriction; Tg, transgenic; and WM, white matter.

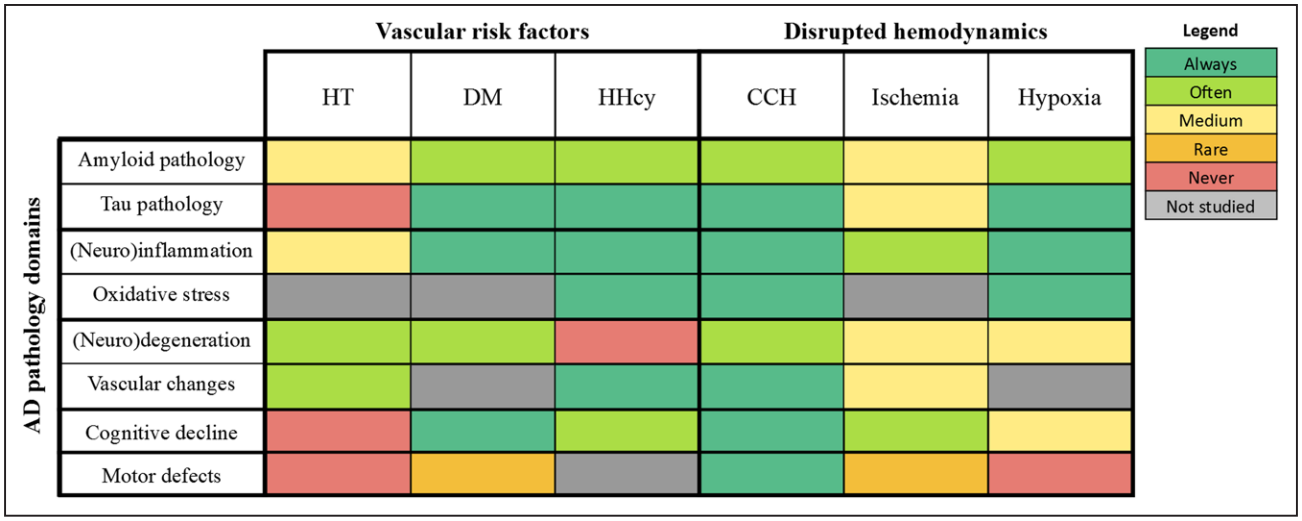

Figure 3. Heatmap of the findings described in Tables 1 and 2, providing an overview of the effects of experimentally inducing vascular risk factors (hypertension [HT], diabetes [DM], or hyperhomocysteinemia [Hhcy]) or disrupting cerebral hemodynamics (chronic cerebral hypoperfusion (CCH), ischemia, or hypoxia) on Alzheimer disease (AD) pathology domains.
Occurrence (as reflected by the colors) of the reported detrimental effects were calculated with the aim to indicate the strength of the evidence summarized in Tables 1 and 2. Not studied (gray) means that none of the studies included investigated the effect of their intervention on this particular domain. Never (red) means that when studies researched the effect of their intervention on this domain, an effect was not found/present/shown. Always (dark green) indicates that all studies investigating the effect of the intervention on this domain, reported a detrimental effect.

Chronic Cerebral Hypoperfusion

The bilateral common carotid artery stenosis (BCAS) model is most frequently used to surgically induce CCH by placing partially occluding external microcoils around both carotid arteries.[72] BCAS, commonly using 0.18 mm-internal-diameter-microcoils, induces a marked reduction of 15% to 26% in CBF in amyloidosis mice up to 12 weeks.[73,74] Alternatively, gradually occluding external ameroid constrictors can be employed to narrow the lumen of the carotids. All ameroid constrictor studies discussed below are conducted by the group of Zhai et al,[75] consistently demonstrating a slow progressive stenosis and a gradually decreasing CBF by ≈50% during the first 14 days postsurgery. Two less often used models are the transverse aortic constriction (TAC) and myocardial infarction (MI) model. TAC causes CCH, hypertension, left ventricular hypertrophy, and cardiac failure.[76] MI, induced by permanent ligation of the left anterior descending artery, is reported to cause a reduction of CBF after 4 to 6 weeks.[77] However, the effects on cerebral function using these models are less well characterized.

Several studies clearly show an exacerbating effect of BCAS on AD-like pathology in AD transgenic mice, using microcoils as well as ameroid constrictors. Microcoil-induced BCAS increases tau phosphorylation in both amyloidosis and tau transgenic mice[78–80] and enhances Aβ pathology in amyloidosis mice. CCH significantly increases Aβ accumulation and Aβ fibrils in the intracellular compartment, as soon as one month after BCAS. These changes are accompanied by astroglial proliferation in the cerebral cortices, hippocampus, and white matter,[81] indicative of ongoing neuroinflammation. An acceleration in leptomeningeal Aβ deposition is observed 12 weeks postsurgery, whereas sham-operated mice exhibit virtually no leptomeningeal Aβ depositions.[74] These findings are consistently confirmed in the ameroid constrictor model, reporting an increased formation of Aβ plaques and CAA.[78,82–84] Not only is Aβ plaque growth enhanced, but there is also a shift towards the formation of neurotoxic Aβ soluble species with high molecular weight, without changing the total amount of PBS-soluble Aβ. This may be attributed to a microcoil-induced change in interstitial fluid dynamics, leading to congestion and facilitation of Aβ accumulation.[85] A shift in amyloid metabolism is also reported, controversially showing that the degree of Aβ deposition and plaque formation is suppressed following microcoil-induced CCH. However, as the amount of extracellular soluble Aβ increases, this suggests that perhaps the soluble, rather than the insoluble species, play a key role in neurotoxicity and cognitive decline.[86] Another potential mechanism underlying CCH-induced amyloid accumulation is an imbalance in 2 main Aβ receptors, LRP1 and RAGE (receptor for advanced glycation end products), as reported in the ameroid constrictor model.[84] These receptors are involved in regulating efflux and influx across the BBB.[87,88] As the majority of cerebral Aβ is cleared through transport across the BBB, and only a small part via passive interstitial fluid bulk flow, defective transvascular clearance of Aβ plays a major factor in the accumulation of parenchymal and cerebrovascular amyloid.[87] This is repeatedly shown to be mediated in particular by LRP1.[89–91] Chronic reduction of CBF by TAC or MI induction also significantly exacerbates amyloid plaque deposition, CAA, and tau phosphorylation[92–94] and leads

to increased levels of both soluble and insoluble Aβ after 3 months,[92] but not 6 weeks.[93]

Interestingly, several ameroid constrictor studies report a detrimental effect of CCH on BBB integrity and neurovascular unit function, accompanied by alterations of both coagulation and complement cascade components indicative of BBB damage.[80,83,95] These findings are associated with a robust neuroinflammatory and oxidative stress response.[82–84,96] CCH is reported to affect mitochondrial function by shifting the balance in mitochondrial morphology from fusion to fission with increasing amyloid and tau pathology. Defective mitochondria are a major source of reactive oxygen species production in the brain, thereby potentially forming a vicious cycle of oxidative stress.[78] CCH-induced AD-like pathology can be significantly ameliorated by Edaravone treatment, a potent free-radical scavenger, highlighting the importance of oxidative stress as a main driver of CCH-induced progression of AD.[84] Several transgenic mice develops microinfarcts after 12 weeks of BCAS-induced CCH, a phenomenon not shown in the control mice.[74] CCH leads to increased leukoaraiosis in amyloidosis mice[81,85] and a significant correlation is found between decreased neuronal density and cognitive impairments s.[82,86] An impairment in cerebrovascular and BBB function, linked to exacerbated astrogliosis, is also reported after TAC.[93] Microglia acquire a more proinflammatory phenotype after MI and an upregulation of oxidative stress markers can be seen.[94] In parallel, cognitive function is negatively impacted in both TAC and MI surgical models.

Despite variations in experimental design and a relatively small number of studies, results consistently show altered amyloid and tau metabolism, increased neuroinflammation and oxidative stress, and BBB damage resulting in neuronal damage and cognitive decline in AD mouse models in which CCH is induced surgically.

Hypoxia

Hypoxia, possibly resulting from hypertension, atherosclerosis, diabetes (ischemic) brain trauma, or stroke, is a known risk factor for AD.[97] Hypoxia can be induced in mice by placing the animals daily in a sealed jar until the first gasping breath is observed. Alternatively, animals can be placed in a chamber that allows for the precise control of oxygen concentration, so the animals can be intermittently exposed to cycles of normoxia or hypoxia. Exposure to hypoxic circumstances in a jar or chamber enhances amyloidogenic pathway activity, resulting in increased Aβ production and neuritic plaque formation in several amyloidosis AD mouse models[98–103] and mixed pathology 3×Tg-AD mice.[104] However, changes in Aβ levels or plaque load are not always detected using a hypoxia chamber.[105] This may be due to the use of a milder, intermittent hypoxia model compared with other studies with a stronger hypoxic exposure like a sealed jar. Another factor can be the differences in amyloid overexpression patterns between transgenic mice strains. Tau phosphorylation is increased in hypoxic amyloidosis mice.[98,100,103] Hypoxia enhances macroautophagy activity, which may contribute to Aβ production, and exacerbates inflammation.[99,102,105] Hypoxia also inhibits Aβ degradation. Microglia from hypoxic animals exhibit decreased CD36 expression, which is a class B scavenger receptor involved in oxidative and proinflammatory processes. Hypoxia treatment increases reactive oxygen species levels and reduces transactivation of transcription factor Nrf2 (nuclear factor E2-related factor 2) target genes in the AD mouse brain,[102] a known antioxidant signaling pathway. Hypoxia further induces apoptotic markers in the brains of amyloidosis mice. Additionally, hypoxia induced demethylation of genomic DNA and decreased DNA methyltransferase 3b expression, which may lead to enhanced β-amyloidogenesis, accelerating AD neuropathology.[100] Exposing amyloidosis mice to chronic hypoxia leads to marked spatial learning and memory deficits.[98,100–103] However, exposing 3×Tg-AD mice to chronic intermittent hypoxia using a oxygen-controlled chamber does not affect cognitive performance, despite increased cerebral Aβ levels and intracellular amyloid levels.[104] Hypoxia also stimulates activation of the Wnt (wingless-related integration site)/β-catenin signaling pathway, a known positive modulator of adult neurogenesis and angiogenesis. Accordingly, hypoxic amyloidosis mice demonstrate increased neurogenesis, suggesting a compensatory mechanism.[106] Decreased Aβ pathology, an improvement in cognition and anxiety levels, accompanied by increased neurogenesis and reduced presence of apoptotic markers is found in amyloidosis mice placed in a hypoxic pressure chamber.[107]

The different experimental methods used to induce hypoxia and the level thereof should be considered when drawing conclusions. Overall, it appears that using a sealed jar to induce hypoxia strongly exacerbates AD-like pathology and cognitive decline compared to milder, intermittent methods. Unfortunately, it remains unknown whether the degree of hypoxia in these animal models is representative of the degree of hypoxia in the brains of patients with AD. Despite this important limitation, the discussed results are in accordance with a large body of literature implicating a role for hypoxia in AD progression in mice and humans. In terms of mechanisms, hypoxia is often linked to CCH-induced reduced delivery of oxygen and glucose to the brain.[108] In addition, it may particularly stimulate APP processing and Aβ production in endothelial cells and neighboring neurons, promoting CAA and vascular dysfunction.[109] In summary, the described findings indicate that intermittent or milder forms of hypoxia do not impact AD pathogenesis as much and can even have a stimulating effect on neurogenesis, whereas chronic hypoxia seems to exacerbate AD neuropathology and cognitive functioning.

Mild Ischemia (and Reperfusion)

Mild global ischemia, a procedure that refers to a transient episode of low blood flow resulting in molecular changes without causing an infarct, is induced by transiently occluding both common carotid arteries. Duration of ischemia varies in the included studies, ranging from 3 to 17 minutes, followed by reperfusion. Mild global ischemia induces an increase in Aβ levels by enhancing β-secretase protein expression, without affecting plaque deposition in amyloidosis mice[110] or 3-month-old 3×Tg-AD mice.[111] In contrast, no changes in Aβ levels are found in older (12–15-month-old) 3×Tg-AD animals.[112] Mild global ischemia in 3×Tg-AD mice decreases total tau levels, coincident with activation of macroautophagy and ubiquitin-proteasome pathways.[111] Tau phosphorylation increases at specific tau epitopes, persisting up to several weeks.[111,112] Bilateral common carotid artery occlusion followed by reperfusion impairs motor coordination and causes spatial learning and memory deficits,[110,113] which correlates with marked neuronal loss in the hippocampus of amyloidosis mice up to 5 weeks after the initial insult. This is accompanied by increased microgliosis, astrogliosis, and infiltration of blood-derived monocytic cells.[113,114] Although shorter transient cerebral ischemia does not induce neuronal loss in AD transgenic mice, marked memory deficits are observed following surgery as well as decreased high-K^+-evoked acetylcholine release, suggesting that the observed memory impairments may be due to Aβ-induced cholinergic dysfunction.[110] Similar to hypoxia, neurogenesis increases in mild ischemic amyloidosis mice.[114]

Importantly, there are substantial differences in the duration of BCAAO and time points studied, possibly explaining some of the contradictory results. Nonetheless, the results indicate that a single, mild, and transient ischemic insult can have an acute detrimental effect on AD neuropathology, marked by increased Aβ levels, inflammation, neurodegeneration, and cognitive decline.

Severe Ischemia

Severe ischemia can be induced in mice by permanently and unilaterally occluding a common carotid or middle cerebral artery (MCA), by photo-induced cerebral infarcts, or by injecting endothelin-1 or the photosensitive dye Rose Bengal. Permanent MCA occlusion in mixed pathology mice does not affect tau phosphorylation,[115] nor does it exacerbate amyloid plaque or CAA deposition.[24,116,117] No difference in Aβ levels is found between the ischemic and nonischemic hemisphere, although relatively high levels of Aβ are measured in the brains of the ischemic mice.[118] Occlusion of the right common carotid artery does not affect amyloid deposition in an APP mouse model,[116] whereas it does lead to an increase in Aβ brain accumulation in a PS1 mouse model.[119] Injections with endothelin-1, a potent vasoconstrictor, targeting the right striatum to mimic small lacunar infarcts, also does not affect congophilic plaques in young mice; however, plaque-bearing mice have not been studied with this model to date. Endothelin-1 injections do potentiate APP immunostaining and increase tau levels with an additional increase in the ipsilateral hemisphere, along with an enhanced inflammatory response.[120]

An increased senile plaque deposition is observed after MCA occlusion. Real-time intravital multiphoton microscopy demonstrates that induction of cerebral microstrokes in amyloidosis mice using Rose Bengal also causes a striking number of new plaques and CAA in the area immediately adjacent to the infarcted area. However, this effect appears to be transient and returns to baseline within 1 week. No alterations in candidate proteins related to Aβ generation or degradation are found. The researchers also investigated human infarcted brain tissue in the same study and could not confirm an increase in amyloid burden associated with cerebral infarcts. This may be explained by the potential transient nature of the effect on amyloid in response to ischemia, as observed in the mice.[121] Photo-induced unilateral focal cerebral ischemia on the other hand dramatically reduces amyloid deposition, also associated with an increase in the presence of microgliosis and macrophages in the ischemic hemisphere. The authors conclude that focal ischemia may lead to clearance of deposited Aβ initiated at 7 days with almost complete removal in the ischemic brain area by 21 days, which might involve the infiltration of activated immune cells.[122] In line with these findings, several studies show that severe ischemia robustly elicits an immune response and increased microglial activation in AD transgenic mice.[24,115,119,123]

Upon MCA occlusion amyloidosis mice consistently suffer from larger reductions in CBF and enlarged infarcts or stroke volumes, compared with their littermate controls, suggesting an increased susceptibility to ischemic injury.[114,117,118,121,123] Severe ischemia also disrupts BBB integrity.[119] Accordingly, MCA occlusion is associated with pronounced degeneration of endothelial cells and astrocyte endfeet as described in 3×Tg-AD mice.[115] Some studies also report decreased vascular reactivity,[117,118] however this can not be confirmed by other studies, which may be related to the various mouse strains used in such studies.[114,123] Finally, chronic cerebral ischemia induces marked neurological and cognitive deficits.[24,115–117,119,120] Right common carotid artery significantly impairs learning curves, which correlate robustly with the amount of cortical Aβ plaques, the mobilization of blood-derived monocytes, and the number of bone marrow-derived microglia in the brain. This indicates that a slight decrease in CBF can selectively impair cognitive performance already in an early phase of amyloid pathology, accompanied by a cellular innate immune response.[24] Interestingly, cognitive decline is not related to neuronal

loss or white matter damage and may instead be caused by more subtle alterations of neuronal function, such as synaptic dysfunction or cerebral hypometabolism.[24,115,116]

Again, one should keep in mind that there are large differences between the experimental models discussed in this section, which is a likely explanation for some of the contradictory results described. Nevertheless, these findings suggest that severe ischemia can lead to detrimental shifts in amyloid metabolic pathways next to an increased inflammatory response, and cognitive impairments.

LIMITATIONS AND RECOMMENDATIONS

To date, a large majority of mechanistic and therapeutic research in the field of AD relies on animal models, using transgenic mice expressing human genes including those discussed in this review. Transgenic mice reflect features of pathological hallmarks in patients with AD, such as amyloid plaque pathology in brain areas typical for AD, often linked to gliosis, synaptic impairments, and cognitive deficits, mostly in spatial learning and memory.[124] However, successful AD therapeutics preclinical studies subsequently fail to show clinical efficacy in patients with AD. Thus, several points must be considered regarding the (preclinical) validity of transgenic mouse models for AD drug testing.

One clear limitation of AD transgenic mice is that their pathological phenotype does not fully resemble human AD pathology. AD transgenic mice lack regional brain atrophy and widespread neurodegeneration that is typical for AD. Usually, only very old animals show (minor) neurodegeneration limited to specific brain areas.[125,126] Differences also exist in the neuroinflammatory response[127] and in amyloid pathology. For example, most AD transgenic mice develop compact core plaques, whereas patients show a more amorphous morphology with lower core density.[128] The vascular amyloid distribution and composition seen in human AD is also not entirely mirrored in mice, which could be a consequence of differences in the drainage of cerebral interstitial fluid,[129] as well as a lack of suitable mouse models to study the smaller vessels and the BBB in the context of AD. In AD transgenic mice, mutant APP genes are overexpressed in the brain; however, in humans, the Aβ peptides are also produced outside of the central nervous system.[129] Importantly, not many AD transgenic mice form both plaques and tangles, although the presence of both is a defining characteristic of human AD and crosstalk between amyloid and tau significantly impacts neurotoxicity.[130] Moreover, cognitive deficits in AD transgenic mice usually coincides with, or sometimes even precedes, the onset of plaque formation, which is much earlier than in patients with AD where it only occurs after decades of plaque development.[124] Another important problem with the AD transgenic models is that most are (partial) representations of the more infrequent familial form of AD (familial Alzheimer disease), rather than the more prevalent sporadic Alzheimer disease form. Although there are similarities between familial Alzheimer disease and sporadic Alzheimer disease, there are some important differences in manifestation of pathology and underlying cause, which could explain some of the missing translation between preclinical research and human clinical trials.[124] It is also expected that endogenous rodent proteins and protein pathways have a different response to the nonphysiological expression of human proteins, which may result in downstream effects that would not occur in humans or a lack of effects that should. Both species do share some similarities at the cellular or pathway level, even at the gene expression level, but the extent and significance of these similarities are highly debated.[131,132] Normal brain aging appears to be more comparable between mice and humans, whilst the transcriptional profile in AD transgenic mice might not recapitulate that of the human disease.[133]

Clearly, AD mouse models have added valuable information to our current understanding; however, it is important to remember that these animals do not actually have the human disease. They are designed to capture specific pathological elements in a nonphysiological way that allows for optimal experimental testing. With a good understanding of the exact neuropathology represented by each model and the correlation to the human disease, a better interpretation and translation to human studies will become possible. Some improvements can potentially be made by using the nontransgenic senescence-accelerated mouse strain 8 (SAMP8), which is thought to more closely model sporadic Alzheimer disease.[134] Also some more physiological knock-in mice exist that show cognitive decline months after plaque formation, more resembling patients with AD.[135] For future research, new transgenic models overexpressing a combination of human genes should be generated and characterized. Newly identified risk genes derived from genome-wide association studies could be incorporated in the construction of new models to more accurately mimic the pathological phenotype of human AD. Apart from the intrinsic problems with current AD mouse models discussed above, the preclinical field of AD is dramatically lacking a consensus regarding the ideal experimental design. Currently, there are a near-infinite number of methodological variations and no consistency, even in the use of scientific language and terms to describe for example study outcomes. This also becomes apparent when viewing the wide range of models, methodologies, and scientific terms used to describe the studies included in this review. The field would benefit strongly from a set of clearly defined and universally implemented guidelines, similar to the Stroke Therapy Academic Industry Roundtable, published in 2009.[136] Like the Stroke Therapy Academic Industry Roundtable, this should include recommendations including, but not limited to, study design, exact characteristics of animal models, anesthesia and physiological monitoring protocols, therapeutic drug dose, and outcome parameters. This, together with the use of improved AD mouse models,

could help overcome the barriers in the translation of preclinical studies to human clinical trials.

CONCLUSIONS

Based on the substantial body of in vivo studies described above and summarized in Figure 2, it is evident that experimentally inducing long-term cardiovascular risk factors or disrupting cerebral hemodynamics accelerates or aggravates AD-like brain pathology and cognitive decline in relevant AD transgenic mice.

Despite differences between mouse strains and disease models used, each of the 4 categories of disrupted hemodynamics (ie, CCH, hypoxia, mild ischemia, severe ischemia) separately demonstrates a clear association between vascular risk factors and CCH to AD, supporting the vascular hypothesis of AD. Hence, future studies should address how the 4 overarching categories induce comparable consequences and if a common denominator can be identified or whether each of the 4 induce a differential effect on AD pathology. We acknowledge the large differences between the methods used, limiting our conclusions. However, we think that certain overarching patterns can be identified. It appears that CCH, hypoxia, mild, and severe ischemia are all linked to cognitive decline and an increased inflammatory and oxidative stress response. However, where CCH often results in global neurodegeneration and cerebrovascular dysfunction, ischemia seems to cause more localized damage in the ischemic or infarcted area, suggesting that a regional stimulus will mostly have a regional effect. Indeed, region-specific vascular patterns are shown to be characterized by distinct pathophysiological responses to ischemia.[137] In addition, CCH seems to robustly aggravate amyloid and tau pathology, which is less apparent in ischemic models, perhaps due to a more transient nature of induced pathology. Severe hypoxia appears to have a similar effect on AD pathology as CCH, whereas intermittent or milder hypoxia may exert beneficial effects leading to enhanced neurogenesis and improved cognition.

All taken together, it does appear that a long-term global vascular disruption drives the full range of AD pathology, at least in AD transgenic mice. However, as vascular function is not measured in most of the studies, it is difficult to pinpoint the exact extent of the vascular disruption. To date, no solid evidence exists on any causal relations between CCH and AD development or progression, nor to conclusively identify underlying mechanisms. In addition, it remains to be established during which stage of AD pathogenesis vascular risk factors and cerebral hemodynamic disturbances contribute the most to AD pathology. As can be deduced from Figure 2, a multitude of processes are affected. Undoubtedly cardiovascular disease and CCH interact with a wide range of cellular processes, most likely not in a cascade but in a network of events, of which oxidative stress and inflammation are considered key propagating components.[138,139] Future multidimensional mechanistic and therapeutic intervention studies are needed to identify causal relationships and to gain more insight into the temporal sequence of events. Longitudinal multimodal imaging across neurovascular dysfunction in patients with AD, as well as recent developments in AD genetic, omics, and biomarkers should be explored. Importantly, studies using more representative mouse models and human studies are needed so important translational steps can be taken to advance AD therapeutic strategies.

ARTICLE INFORMATION

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Affiliations

Department of Pathology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, the Netherlands (S.S., D.M.A.H., M.J.A.P.D.). Departments of Radiology & Human Genetics, Leiden University Medical Center, the Netherlands (L.v.d.W.). Department of Molecular Cell Biology and Immunology, Amsterdam Neuroscience, Amsterdam UMC, Vrije University of Amsterdam, the Netherlands (H.E.d.V.).

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Disclosures

None.

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