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ATVB IN FOCUS

Vascular Components of Cognitive Disorders

Series Editor: Mat Daemen

Vascular Hypothesis of Alzheimer Disease

Topical Review of Mouse Models

Sanny Scheffer¹, Dorien M.A. Hermkens¹, Louise van der Weerd, Helga E. de Vries, Mat J.A.P. Daemen¹

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 A β (amyloid β) accumulation, as plaques in brain parenchyma or as vascular deposits leading to cerebral amyloid angiopathy (CAA).¹ An imbalance in A β production and clearance leads to A β -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 A β 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,

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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

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

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.

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

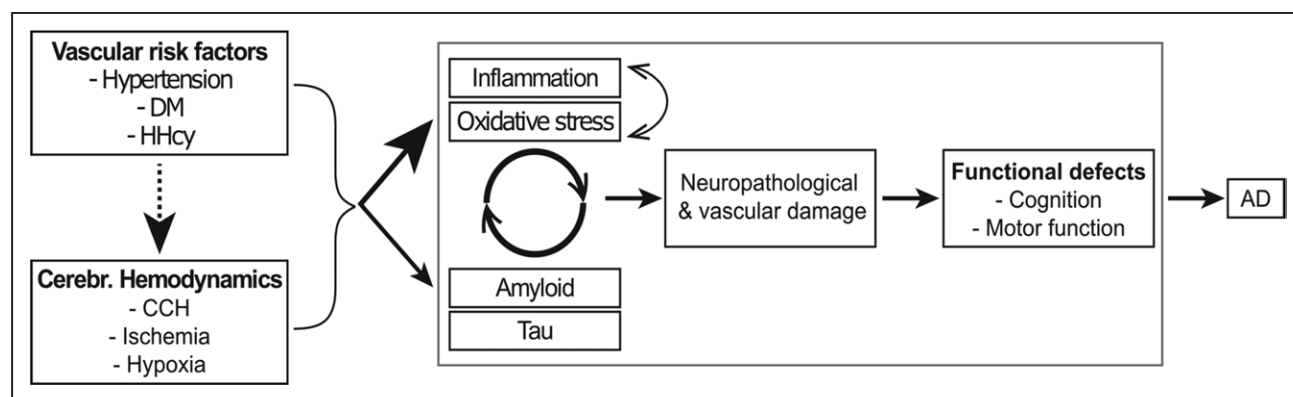


Figure 1. The link between cardiovascular disease (CVD) and Alzheimer disease (AD).

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 A β 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

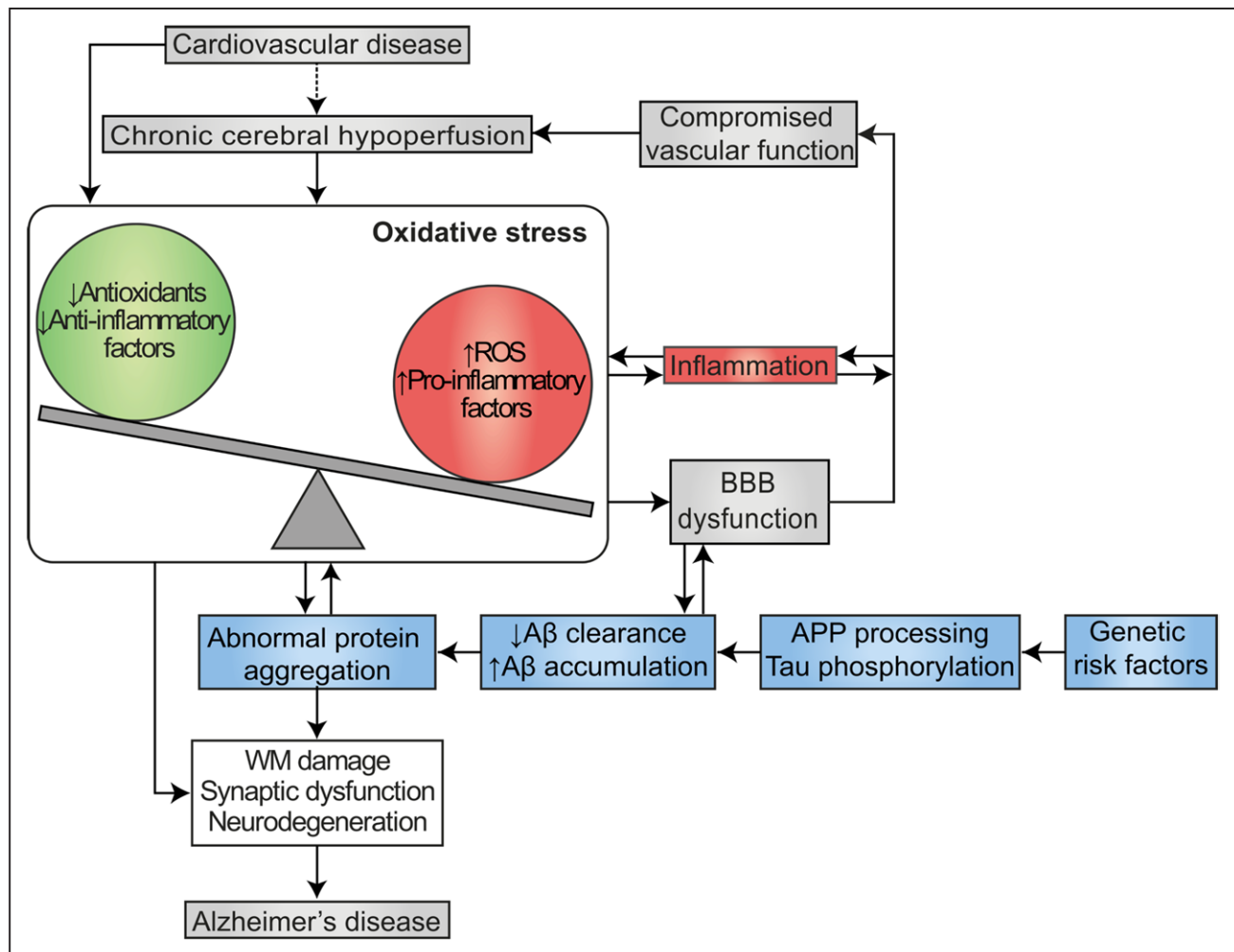


Figure 2. The proposed role of oxidative stress in the association between cardiovascular disease (CVD) and Alzheimer disease (AD).

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 A β (amyloid- β) clearance and thereby elevated A β accumulation and abnormal protein aggregation. Genetic predisposition to aberrant APP (amyloid precursor protein) processing and tau phosphorylation has an additive effect. A β 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 $\approx 1\%$ 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) A β levels and intraneuronal A β accumulation, often leading to cortical amyloid deposition and CAA development, next to changes in amyloidogenic pathways. Hypertension causes an increase in cerebrovascular A β deposition, but not in the parenchyma.⁴⁵ Diabetes leads to a shift in A β soluble/insoluble levels, promoting the formation of toxic soluble species.⁵¹ However, a few studies using HHcy models observe no effect of HHcy on A β levels or amyloidogenic pathways,^{58,61,62} perhaps because of the use of different dietary interventions or mouse strains. Additionally, both HHcy⁵⁷ 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 $\times$ Tg-AD mice⁵⁴ 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 $\times$ 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 $\times$ 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 decrease⁵⁴ 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 inducing diabetes in 3 $\times$ 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 A β 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
		APPSwDI, 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	↑ Aβ _{40,42} (brain) ↓ Aβ _{40,42} (serum)	...	...	...	...	No cognitive deficit	Diaz-Ruiz et al ⁴²
	DOCA-salt; 8 mo	P301L-tauTg, 5.5 mo, F	Tauopathy; MAPT	No abnormal tau species	...	...	...	...	↓ Motor function	Diaz-Ruiz et al ⁴²
	ANGII (1000 ng/kg/min) [†] 2.5 mo	APP/PS1, 2 mo, M	Amyloidosis; APP, PS1	↑ Aβ ₄₂ (S) No change in Aβ 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	APPSwDI, 3–4 mo, M+F	Amyloidosis; APP	No change in Aβ _{40,42} ↓ Plaques ↑ CAA	↑ Microglial No astroglial	↑ 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	5xFAD, 6 mo, M	Amyloidosis; APP, PS1	↑ Aβ cerebrovascular deposition No change parenchymal Aβ _{40/42} deposits	↑ Microglial	↑ 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	↑ Aβ ₄₂ (S) No change in Aβ ₄₀ (S) ↑ Plaques ↑ Aβ pathway changes ↑ Phospho-tau	...	↑ Neuronal loss ↑ Synapse loss	...	...	↓ Cognition No motor defects	Jolival et al ⁴⁶
	STZ (90 mg/kg) [†] 1×/d/2 d IP; 20 wk	APPSw/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	↑ Aβ 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	5xFAD, 1.5 mo, ?	Amyloidosis; APP, PS1	↑ Aβ _{40,42} ↑ Aβ pathway changes	...	...	...	...	...	Devi et al ⁵⁰
	STZ (40 mg/kg) [†] 1×/d/5 d IP; 8 wk	APPSw/PS1/ΔE9, 18 wk, ?	Amyloidosis; APP, PS1	↑ Aβ ₄₀ (S) ↓ Aβ ₄₀ (S) ↓ Plaques ↓ CAA No Aβ pathway changes ↑ Phospho-tau	↑ Microglial	↑ 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	↑ Aβ (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	↑ Aβ _{40,42} (S+I) ↑ 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	↓ Aβ ₄₀ No change in Aβ _{42/40} Changes in 20 AD-related genes ↑ Phospho-tau	↑ Microgliosis ↑ Astrogliosis	↓ Synaptic plasticity	...	...	↓ Cognition Slight motor defects	Chen et al ⁵⁴
	HHcy (- folate, vitamin B6, vitamin B12) [†] 60 d	TgCRND8, 3 wk, M+F	Amyloidosis; APP	↑ Aβ _{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	↑ Aβ _{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	↑ Aβ ₄₀ (IS; 11 m,f)	...	...	...	...	...	Farkas et al ⁵⁵
	Diet (+ methionine) [†] 5 m	Tg2576, 9 mo, F	Amyloidosis; APP	↑ Aβ ₄₀ (IS) ↑ Aβ 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	↑ Aβ ₄₀ (IS) ↑ Aβ 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 Aβ _{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 Aβ _{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 DL, 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 DL, 5 mo+8 mo+11 mo, M	Amyloidosis; APP	↑ Aβ _{40,42} (S+IS)	↑ Astrogliosis	↑ WM rarefaction	...	...	Kitaguchi et al ⁸¹
	BCAS (0.18 mm); 6 mo	APPS _w DL, 2 mo, M	Amyloidosis; APP	↓ Aβ ₄₂ (IS) ↓ Plaques ↑ Aβ _{IS}	...	↓ 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	APPS _w DL/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	↑ Aβ _(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 ⁸⁵
	BCAS (ac; 0.75 mm); 8 mo	APP23, 4 mo, M+F	Amyloidosis; APP	...	Changes (neuro) inflammatory markers	...	...	...	Shi et al ⁸⁶
	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/SwDL, 6 mo, M	Amyloidosis; APP	↑ Aβ _{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 Aβ _{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 DL/PS1/ΔE9, 20 wk, M	...	↑ Plaques ↑ Phospho-tau	↑ Proinflammatory microglia ↑ Oxidative stress	...	...	↓ Cognition	Zhang et al ⁸⁴
Hypoxia	10% O ₂ , 72 h	APPS _w DL/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	↑ Aβ _{40,42} ↑ Plaques ↑ Aβ pathway changes	...	...	...	↓ Cognition	Sun et al ¹⁰¹
	11.1 % O ₂ , 6 h/d; 30 d	APPSw/PS1/ΔE9, 3 mo, ?	Amyloidosis; APP, PS1	↑ Aβ ₄₂ /Aβ 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	3xTg-AD, 6 m, M	Amyloidosis+tauopathy; APP, PS1, MAPT	↑ Aβ ₄₂ No change in Aβ 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 Aβ _{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	↓ Aβ _{40,42} ↓ Plaques	...	↑ Neurogenesis ↓ Apoptosis	...	↑ Cognitive performance, decreased anxiety	Meng et al ¹⁰⁷
	Jar 1x/d; until first gasping breath; 60 d	APPSw/PS1, 9 mo, F	Amyloidosis; APP, PS1	↑ Aβ ₄₂ (S) ↑ Plaques ↑ Aβ pathway changes	↑ Macroautophagy	...	...	...	Li et al ⁹⁹
	Jar 1x/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 1x/d; until first gasping breath; 60 d	APP/PS1, 6 mo, ?	Amyloidosis; APP, PS1	↑ Aβ ₄₂ ↑ Plaques ↑ Phospho-tau	...	...	...	↓ Cognition No motor defects	Gao et al ⁹⁸
	Jar 1x/d; until first gasping breath; 2 mo	APPSw/PS1/ΔE9, 2 mo+6 mo+12 mo, M	Amyloidosis; APP, PS1	↑ Aβ _{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	↑ Aβ _{40,42} No change in plaques	...	No neuronal loss	...	↓ Cognition	Watanabe et al ¹¹⁰
	BCCAO 4 min; 48 h	3xTg-AD, 3 mo, M	Amyloidosis+tauopathy; APP, PS1, MAPT	↑ Aβ 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	3xTg-AD, 12 mo+15 mo, M	Amyloidosis+tauopathy; APP, PS1, MAPT	No change in A β _{40,42} (S+IS) ↑ A β 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	APPSw/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	APPSw/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	APPSw/PS1/ΔE9, 6–7 mo, M	Amyloidosis; APP, PS1	↑ Plaques	...	↑ Infarct size	...	...	Garcia-Alloza et al ¹²¹
	pMCAO; 24 h	APPSw, 3–4 mo, ?	Amyloidosis; APP	No A β 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	3xTg-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	APPSw/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	APPSw/PS1, 4 mo, M	Amyloidosis; APP, PS1	No change in plaques	↑ Microgliosis No changes in blood monocytes ↑ Ratio LyC ^{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	↑ A β accumulation	↑ NF- κ B ↑ Inflammatory cytokines	...	↓ BBB integrity	↓ Learning	Yang et al ¹¹⁹
	Photo-induced; 1 d+7 d+21 d	APPSwDI, 12 mo, ?	Amyloidosis; APP	↓ A β (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- κ B	...	...	↓ Cognition	Whitehead et al ²⁰
	Rose bengal injection; during	APPSw/PS1/ΔE9, 6–7 mo, ? + Tg2576, 11–13 mo, ?	Amyloidosis; APP, PS1	↑ Plaques (transient) ↑ CAA No A β 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; A β , 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- κ B, 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.

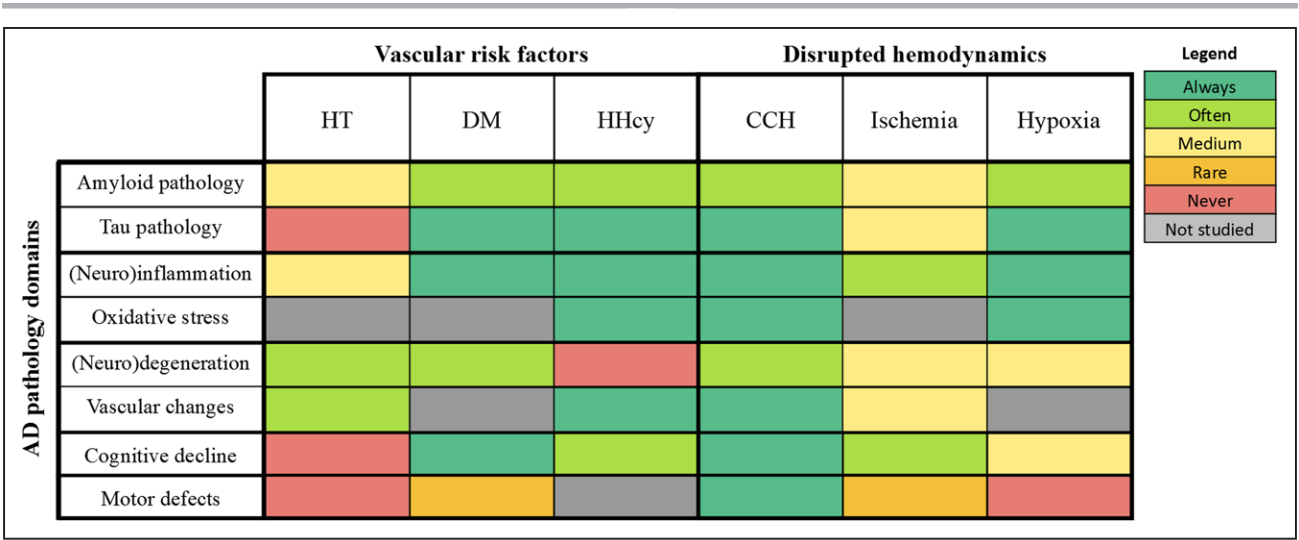


Figure 3. Heatmap of the findings described in Tables 1 and 2, providing an overview of the effects of experimentally inducing vascular risk factors (hypertension [HT], diabetes [DM], or hyperhomocysteinemia [HHcy]) or disrupting cerebral hemodynamics (chronic cerebral hypoperfusion (CCH), ischemia, 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 A β 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 develop 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.^{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 A β production and neuritic plaque formation in several amyloidosis AD mouse models^{98–103} and mixed pathology 3 $\times$ Tg-AD mice.¹⁰⁴ However, changes in A β 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 A β production, and exacerbates inflammation.^{99,102,105} Hypoxia also inhibits A β 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 $\times$ Tg-AD mice to chronic intermittent hypoxia using an oxygen-controlled chamber does not affect cognitive performance, despite increased cerebral A β 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 A β 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 A β 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 A β levels by enhancing β -secretase protein expression, without affecting plaque deposition in amyloidosis mice¹¹⁰ or 3-month-old 3 $\times$ Tg-AD mice.¹¹¹ In contrast, no changes in A β levels are found in older (12–15-month-old) 3 $\times$ Tg-AD animals.¹¹² Mild global ischemia in 3 $\times$ 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 A β -induced cholinergic dysfunction.¹¹⁰ Similar to hypoxia, neurogenesis increases in mild ischemic amyloidosis mice.¹¹⁴

Importantly, there are substantial differences in the duration of BCAA 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 A β 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 A β levels is found between the ischemic and nonischemic hemisphere, although relatively high levels of A β 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 A β 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 A β 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 A β 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 $\times$ 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 A β 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 response¹²⁷ 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 A β 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 pre-clinical 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.

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Disclosures

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REFERENCES

- Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256:184–185. doi: 10.1126/science.1566067
- Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297:353–356. doi: 10.1126/science.1072994
- Amul Z. Why therapies for Alzheimer's disease do not work: do we have consensus over the path to follow? *Ageing Res Rev*. 2016;25:70–84. doi: 10.1016/j.arr.2015.09.003
- Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolkowski SK, James JA, Snitz BE, Houck PR, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol*. 2008;65:1509–1517. doi: 10.1001/archneur.65.11.1509
- Villemagne VL, Pike KE, Chételat G, Ellis KA, Mulligan RS, Bourgeat P, Ackermann U, Jones G, Szoeke C, Salvado O, et al. Longitudinal assessment of A β and cognition in aging and Alzheimer disease. *Ann Neurol*. 2011;69:181–192. doi: 10.1002/ana.22248
- Morris GP, Clark IA, Vissel B. Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. *Acta Neuropathol Commun*. 2014;2:135. doi: 10.1186/s40478-014-0135-5
- Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413–446. doi: 10.1016/S0140-6736(20)30367-6
- Francula-Zaninovic S, Nola IA. Management of measurable variable cardiovascular disease risk factors. *Curr Cardiol Rev*. 2018;14:153–163. doi: 10.2174/1573403X14666180222102312
- Love S, Miners JS. Cerebrovascular disease in ageing and Alzheimer's disease. *Acta Neuropathol*. 2016;131:645–658. doi: 10.1007/s00401-015-1522-0
- de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol*. 2004;3:184–190. doi: 10.1016/S1474-4422(04)00683-0

11. de Wit NM, Vanmol J, Kamermans A, Hendriks J, de Vries HE. Inflammation at the blood-brain barrier: the role of liver X receptors. *Neurobiol Dis*. 2017;107:57–65. doi: 10.1016/j.nbd.2016.09.015
12. Kapasi A, Schneider JA. Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. *Biochim Biophys Acta*. 2016;1862:878–86. doi: 10.1016/j.bbdis.2015.12.023
13. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, Toga AW, Jacobs RE, Liu CY, Amezcua L, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85:296–302. doi: 10.1016/j.neuron.2014.12.032
14. van de Haar HJ, Burgmans S, Jansen JFA, van Osch MJ, van Buchem MA, Muller M, Hofman PAM, Verhey FRJ, Backes WH. Blood-Brain Barrier Leakage in Patients with Early Alzheimer Disease. *Radiology*. 2016;281(2):527–535. doi: 10.1148/radiol.2016152244
15. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, Sepehrband F, Nelson AR, Buennagel DP, Harrington MG, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med*. 2019;25:270–276. doi: 10.1038/s41591-018-0297-y
16. Van Gool B, Storck SE, Reekmans SM, Lechat B, Gordts PL, Pradier L, Pietrzik CU, Roebroek AJM. LRP1 has a predominant role in production over clearance of A β in a mouse model of Alzheimer's disease. *Mol Neurobiol*. 2019;56:7234–7245. doi: 10.1007/s12035-019-1594-2
17. Carraro A, Snkhchyan H, Kooij G, van der Pol S, van Horssen J, Veerhuis R, Hoozemans J, Rozemuller A, de Vries HE. ATP-binding cassette transporters P-glycoprotein and breast cancer related protein are reduced in capillary cerebral amyloid angiopathy. *Neurobiol Aging*. 2014;35:565–575. doi: 10.1016/j.neurobiolaging.2013.09.015
18. Chakraborty A, de Wit NM, van der Flier WM, de Vries HE. The blood brain barrier in Alzheimer's disease. *Vascul Pharmacol*. 2017;89:12–18. doi: 10.1016/j.vph.2016.11.008
19. Paris D, Patel N, DelleDonne A, Quadros A, Smeed R, Mullan M. Impaired angiogenesis in a transgenic mouse model of cerebral amyloidosis. *Neurosci Lett*. 2004;366:80–85. doi: 10.1016/j.neulet.2004.05.017
20. Graves SL, Baker DJ. Implicating endothelial cell senescence to dysfunction in the ageing and diseased brain. *Basic Clin Pharmacol Toxicol*. 2020;127:102–110. doi: 10.1111/bcpt.13403
21. Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: is Alzheimer's a vascular disorder? *Am J Cardiovasc Dis*. 2013;3:197–226.
22. Winkler EA, Sagare AP, Zlokovic BV. The pericyte: a forgotten cell type with important implications for Alzheimer's disease? *Brain Pathol*. 2014;24:371–386. doi: 10.1111/bpa.12152
23. Montagne A, Nikolakopoulou AM, Zhao Z, Sagare AP, Si G, Lazic D, Barnes SR, Daianu M, Ramanathan A, Go A, et al. Pericyte degeneration causes white matter dysfunction in the mouse central nervous system. *Nat Med*. 2018;24:326–337. doi: 10.1038/nm.4482
24. Pimentel-Coelho PM, Michaud JP, Rivest S. Effects of mild chronic cerebral hypoperfusion and early amyloid pathology on spatial learning and the cellular innate immune response in mice. *Neurobiol Aging*. 2013;34:679–693. doi: 10.1016/j.neurobiolaging.2012.06.025
25. Zhao Y, Gong CX. From chronic cerebral hypoperfusion to Alzheimer-like brain pathology and neurodegeneration. *Cell Mol Neurobiol*. 2015;35:101–110. doi: 10.1007/s10571-014-0127-9
26. Duncombe J, Kitamura A, Hase Y, Ihara M, Kalaria RN, Horsburgh K. Chronic cerebral hypoperfusion: a key mechanism leading to vascular cognitive impairment and dementia. Closing the translational gap between rodent models and human vascular cognitive impairment and dementia. *Clin Sci Lond Engl*. 2017;131:2451–2468. doi: 10.1042/CS20160727
27. Tini G, Scagliola R, Monacelli F, La Malfa G, Porto I, Brunelli C, Rosa GM. Alzheimer's disease and cardiovascular disease: a particular association. *Cardiol Res Pract*. 2020;2020:2617970. doi: 10.1155/2020/2617970
28. Cobb CA, Cole MP. Oxidative and nitrate stress in neurodegeneration. *Neurobiol Dis*. 2015;84:4–21. doi: 10.1016/j.nbd.2015.04.020
29. Alvarez LM, Pacheco GJ, Palacios H, Walrafen B, Obrenovich ME, Qasimov E, LaManna JC, Aliev G. Oxidative stress-induced mitochondrial failure and vasoactive substances as key initiators of pathology favor the reclassification of Alzheimer Disease as a vasocognopathy. *Nova*. 2008;6:101–236.
30. Federico A, Cardaioli E, Da Pozzo P, Formichi P, Gallus GN, Radi E. Mitochondria, oxidative stress and neurodegeneration. *J Neurol Sci*. 2012;322:254–262. doi: 10.1016/j.jns.2012.05.030
31. Liu H, Zhang J. Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. *Int J Neurosci*. 2012;122:494–499. doi: 10.3109/00207454.2012.686543
32. Pase MP, Beiser A, Enserro D, Xanthakis V, Aparicio H, Satizabal CL, Himali JJ, Kase CS, Vasan RS, DeCarli C, et al. Association of ideal cardiovascular health with vascular brain injury and incident dementia. *Stroke*. 2016;47:1201–1206. doi: 10.1161/STROKEAHA.115.012608
33. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neural Res*. 2006;28:605–611. doi: 10.1179/016164106X130506
34. Kroner Z. The relationship between Alzheimer's disease and diabetes: type 3 diabetes? *Altern Med Rev*. 2009;14:373–379.
35. Morris MS. Homocysteine and Alzheimer's disease. *Lancet Neurol*. 2003;2:425–428. doi: 10.1016/s1474-4422(03)00438-1
36. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10:819–828. doi: 10.1016/S1474-4422(11)70072-2
37. Smith AD, Refsum H, Bottiglieri T, Fenech M, Hooshmand B, McCaddon A, Miller JW, Rosenberg IH, Obeid R. Homocysteine and dementia: an international consensus statement. *J Alzheimers Dis*. 2018;62:561–570. doi: 10.3233/JAD-171042
38. Lerman LO, Kurtz TW, Touyz RM, Ellison DH, Chade AR, Crowley SD, Mattson DL, Mullins JJ, Osborn J, Eirin A, et al. Animal models of hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2019;73:e87–e120. doi: 10.1161/HYP.0000000000000090
39. Wu KK, Huan Y. Streptozotocin-induced diabetic models in mice and rats. *Curr Protoc Pharmacol*. 2008;Chapter 5:Unit 5.47. doi: 10.1002/0471141755.ph0547s40
40. Dayal S, Arning E, Bottiglieri T, Böger RH, Sigmund CD, Faraci FM, Lentz SR. Cerebral vascular dysfunction mediated by superoxide in hyperhomocysteinemic mice. *Stroke*. 2004;35:1957–1962. doi: 10.1161/01.STR.0000131749.81508.18
41. Cifuentes D, Poitvin M, Dere E, Broquères-You D, Bonnin P, Benessiano J, Pocard M, Mariani J, Kubis N, Merkulova-Rainon T, et al. Hypertension accelerates the progression of Alzheimer-like pathology in a mouse model of the disease. *Hypertension*. 2015;65:218–224. doi: 10.1161/HYPERTENSIONAHA.114.04139
42. Diaz-Ruiz C, Wang J, Ksiezak-Reding H, Ho L, Qian X, Humala N, Thomas S, Martínez-Martín P, Pasinetti GM. Role of hypertension in aggravating abeta neuropathology of AD type and tau-mediated motor impairment. *Cardiovasc Psychiatry Neurol*. 2009;2009:107286. doi: 10.1155/2009/107286
43. Faraco G, Park L, Zhou P, Luo W, Paul SM, Anrather J, Iadecola C. Hypertension enhances A β -induced neurovascular dysfunction, promotes β -secretase activity, and leads to amyloidogenic processing of APP. *J Cereb Blood Flow Metab*. 2015;36:241–52. doi: 10.1038/jcbfm.2015.79
44. Krueyer A, Soplop N, Strickland S, Norris EH. Chronic hypertension leads to neurodegeneration in the TgSwDI mouse model of Alzheimer's disease. *Hypertension*. 2015;66:175–182. doi: 10.1161/HYPERTENSIONAHA.115.05524
45. Cao C, Hasegawa Y, Hayashi K, Takemoto Y, Kim-Mitsuyama S. Chronic angiotensin 1-7 infusion prevents angiotensin-II-induced cognitive dysfunction and skeletal muscle injury in a mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2019;69:297–309. doi: 10.3233/JAD-181000
46. Jolivalt CG, Hurford R, Lee CA, Dumaop W, Rockenstein E, Masliah E. Type 1 diabetes exaggerates features of Alzheimer's disease in APP transgenic mice. *Exp Neurol*. 2010;223:422–431. doi: 10.1016/j.expneurol.2009.11.005
47. Li Y, Duffy KB, Ottinger MA, Ray B, Bailey JA, Holloway HW, Tweedie D, Perry T, Mattson MP, Kapogiannis D, et al. GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. *J Alzheimers Dis*. 2010;19:1205–1219. doi: 10.3233/JAD-2010-1314
48. Plaschke K, Kopitz J, Siegelin M, Schliebs R, Salkovic-Petrisic M, Riederer P, Hoyer S. Insulin-resistant brain state after intracerebroventricular streptozotocin injection exacerbates Alzheimer-like changes in Tg2576 AbetaPP-overexpressing mice. *J Alzheimers Dis*. 2010;19:691–704. doi: 10.3233/JAD-2010-1270
49. Wang X, Zheng W, Xie JW, Wang T, Wang SL, Teng WP, Wang ZY. Insulin deficiency exacerbates cerebral amyloidosis and behavioral deficits in an Alzheimer transgenic mouse model. *Mol Neurodegener*. 2010;5:46. doi: 10.1186/1750-1326-5-46
50. Devi L, Alldred MJ, Ginsberg SD, Ohno M. Mechanisms underlying insulin deficiency-induced acceleration of β -amyloidosis in a mouse model of Alzheimer's disease. *PLoS One*. 2012;7:e32792. doi: 10.1371/journal.pone.0032792
51. Ramos-Rodriguez JJ, Infante-Garcia C, Galindo-Gonzalez L, Garcia-Molina Y, Lechuga-Sancho A, Garcia-Alloza M. Increased spontaneous central bleeding and cognition impairment in APP/PS1 mice with poorly

- controlled diabetes mellitus. *Mol Neurobiol*. 2015;53:2685–97. doi: 10.1007/s12035-015-9311-2
52. Wang X, Yu S, Hu JP, Wang CY, Wang Y, Liu HX, Liu YL. Streptozotocin-induced diabetes increases amyloid plaque deposition in AD transgenic mice through modulating AGEs/RAGE/NF- κ B pathway. *Int J Neurosci*. 2014;124:601–608. doi: 10.3109/00207454.2013.866110
 53. Ke YD, Delerue F, Gladbach A, Götz J, Ittner LM. Experimental diabetes mellitus exacerbates tau pathology in a transgenic mouse model of Alzheimer's disease. *PLoS One*. 2009;4:e7917. doi: 10.1371/journal.pone.0007917
 54. Chen Y, Liang Z, Tian Z, Blanchard J, Dai CL, Chalbot S, Iqbal K, Liu F, Gong CX. Intracerebroventricular streptozotocin exacerbates Alzheimer-like changes of 3xTg-AD mice. *Mol Neurobiol*. 2014;49:547–562. doi: 10.1007/s12035-013-8539-y
 55. Farkas M, Keskitalo S, Smith DE, Bain N, Semmler A, Ineichen B, Smulders Y, Blom H, Kulic L, Linnebank M. Hyperhomocysteinemia in Alzheimer's disease: the hen and the egg? *J Alzheimers Dis*. 2013;33:1097–1104. doi: 10.3233/JAD-2012-121378
 56. Fuso A, Nicolai V, Cavallaro RA, Ricceri L, D'Anselmi F, Coluccia P, Calamandrei G, Scarpa S. B-vitamin deprivation induces hyperhomocysteinemia and brain S-adenosylhomocysteine, depletes brain S-adenosylmethionine, and enhances PS1 and BACE expression and amyloid-beta deposition in mice. *Mol Cell Neurosci*. 2008;37:731–746. doi: 10.1016/j.mcn.2007.12.018
 57. Fuso A, Nicolai V, Ricceri L, Cavallaro RA, Isopi E, Mangia F, Fiorenza MT, Scarpa S. S-adenosylmethionine reduces the progress of the Alzheimer-like features induced by B-vitamin deficiency in mice. *Neurobiol Aging*. 2012;33:1482.e1–1482.16. doi: 10.1016/j.neurobiolaging.2011.12.013
 58. Zhuo JM, Portugal GS, Kruger WD, Wang H, Gould TJ, Pratico D. Diet-induced hyperhomocysteinemia increases amyloid-beta formation and deposition in a mouse model of Alzheimer's disease. *Curr Alzheimer Res*. 2010;7:140–149. doi: 10.2174/156720510790691326
 59. Zhuo JM, Pratico D. Normalization of hyperhomocysteinemia improves cognitive deficits and ameliorates brain amyloidosis of a transgenic mouse model of Alzheimer's disease. *FASEB J*. 2010;24:3895–3902. doi: 10.1096/fj.10-161828
 60. Cavallaro RA, Fuso A, Nicolai V, Scarpa S. S-adenosylmethionine prevents oxidative stress and modulates glutathione metabolism in TgCRND8 mice fed a B-vitamin deficient diet. *J Alzheimers Dis*. 2010;20:997–1002. doi: 10.3233/JAD-2010-091666
 61. Sudduth TL, Weekman EM, Brothers HM, Braun K, Wilcock DM. β -amyloid deposition is shifted to the vasculature and memory impairment is exacerbated when hyperhomocysteinemia is induced in APP/PS1 transgenic mice. *Alzheimers Res Ther*. 2014;6:32. doi: 10.1186/alzrt262
 62. Zhuo JM, Pratico D. Severe In vivo hyper-homocysteinemia is not associated with elevation of amyloid-beta peptides in the Tg2576 mice. *J Alzheimers Dis*. 2010;21:133–140. doi: 10.3233/JAD-2010-100171
 63. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol*. 2018;14:133–150. doi: 10.1038/nrneurol.2017.188
 64. Chen Q, Jin M, Yang F, Zhu J, Xiao Q, Zhang L. Matrix metalloproteinases: inflammatory regulators of cell behaviors in vascular formation and remodeling. *Mediators Inflamm*. 2013;2013:928315. doi: 10.1155/2013/928315
 65. Pimentel-Coelho PM, Rivest S. The early contribution of cerebrovascular factors to the pathogenesis of Alzheimer's disease. *Eur J Neurosci*. 2012;35:1917–1937. doi: 10.1111/j.1460-9568.2012.08126.x
 66. Toda N, Okamura T. Hyperhomocysteinemia impairs regional blood flow: involvements of endothelial and neuronal nitric oxide. *Pflug Arch - Eur J Physiol*. 2016;468:1517–25. doi: 10.1007/s00424-016-1849-y
 67. Daulatzai MA. Cerebral hypoperfusion and glucose hypometabolism: key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. *J Neurosci Res*. 2016;95:943–972. doi: 10.1002/jnr.23777
 68. de la Torre JC. Cerebral hemodynamics and vascular risk factors: setting the stage for Alzheimer's disease. *J Alzheimers Dis JAD*. 2012;32:553–567. doi: 10.3233/JAD-2012-120793
 69. Ruitenberga A, den Heijer T, Bakker SL, van Swieten JC, Koudstaal PJ, Hofman A, Breteler MM. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. *Ann Neurol*. 2005;57:789–794. doi: 10.1002/ana.20493
 70. Huang C, Eidelberg D, Habeck C, Moeller J, Svensson L, Tarabula T, Julin P. Imaging markers of mild cognitive impairment: multivariate analysis of CBF SPECT. *Neurobiol Aging*. 2007;28:1062–1069. doi: 10.1016/j.neurobiolaging.2006.05.017
 71. Luckhaus C, Fließ MO, Wittsack HJ, Grass-Kapanke B, Jänner M, Khalili-Amiri R, Friedrich W, Supprian T, Gaebel W, Mödder U, et al. Detection of changed regional cerebral blood flow in mild cognitive impairment and early Alzheimer's dementia by perfusion-weighted magnetic resonance imaging. *Neuroimage*. 2008;40:495–503. doi: 10.1016/j.neuroimage.2007.11.053
 72. Shibata M, Ohtani R, Ihara M, Tomimoto H. White matter lesions and glial activation in a novel mouse model of chronic cerebral hypoperfusion. *Stroke*. 2004;35:2598–2603. doi: 10.1161/01.STR.0000143725.19053.60
 73. Hattori Y, Enmi J, Iguchi S, Saito S, Yamamoto Y, Nagatsuka K, Iida H, Ihara M. Substantial reduction of parenchymal cerebral blood flow in mice with bilateral common carotid artery stenosis. *Sci Rep*. 2016;6:32179. doi: 10.1038/srep32179
 74. Okamoto Y, Yamamoto T, Kalaria RN, Senzaki H, Maki T, Hase Y, Kitamura A, Washida K, Yamada M, Ito H, et al. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. *Acta Neuropathol*. 2012;123:381–394. doi: 10.1007/s00401-011-0925-9
 75. Zhai Y, Yamashita T, Nakano Y, Sun Z, Shang J, Feng T, Morihara R, Fukui Y, Ohta Y, Hishikawa N, et al. Chronic cerebral hypoperfusion accelerates Alzheimer's disease pathology with cerebrovascular remodeling in a novel mouse model. *J Alzheimers Dis*. 2016;53:893–905. doi: 10.3233/JAD-160345
 76. Bink DI, Ritz K, Aronica E, van der Weerd L, Daemen MJ. Mouse models to study the effect of cardiovascular risk factors on brain structure and cognition. *J Cereb Blood Flow Metab*. 2013;33:1666–1684. doi: 10.1038/jcbfm.2013.140
 77. Yang J, Noyan-Ashraf MH, Meissner A, Voigtlaender-Bolz J, Kroetsch JT, Foltz W, Jaffray D, Kapoor A, Momen A, Heximer SP, et al. Proximal cerebral arteries develop myogenic responsiveness in heart failure via tumor necrosis factor- α -dependent activation of sphingosine-1-phosphate signaling. *Circulation*. 2012;126:196–206. doi: 10.1161/CIRCULATIONAHA.111.039644
 78. Feng T, Yamashita T, Zhai Y, Shang J, Nakano Y, Morihara R, Fukui Y, Hishikawa N, Ohta Y, Abe K. Chronic cerebral hypoperfusion accelerates Alzheimer's disease pathology with the change of mitochondrial fission and fusion proteins expression in a novel mouse model. *Brain Res*. 2018;1696:63–70. doi: 10.1016/j.brainres.2018.06.003
 79. Shimada T, Shindo A, Matsuyama H, Yata K, Niwa A, Sasaki R, Ayaki T, Maki T, Wakita H, Tomimoto H. Chronic cerebral hypoperfusion upregulates leptin receptor expression in astrocytes and tau phosphorylation in tau transgenic mice. *Neurosci Lett*. 2019;704:133–140. doi: 10.1016/j.neulet.2019.04.009
 80. Liu X, Yamashita T, Shang J, Shi X, Morihara R, Huang Y, Sato K, Takemoto M, Hishikawa N, Ohta Y, et al. Twendee X ameliorates phosphorylated tau, α -synuclein and neurovascular dysfunction in Alzheimer's disease transgenic mice with chronic cerebral hypoperfusion. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc*. 2019;28:104310. doi: 10.1016/j.jstrokecerebrovasdis.2019.104310
 81. Kitaguchi H, Tomimoto H, Ihara M, Shibata M, Uemura K, Kalaria RN, Kihara T, Asada-Utsugi M, Kinoshita A, Takahashi R. Chronic cerebral hypoperfusion accelerates amyloid beta deposition in APPSwInd transgenic mice. *Brain Res*. 2009;1294:202–210. doi: 10.1016/j.brainres.2009.07.078
 82. Liu X, Yamashita T, Shang J, Shi X, Morihara R, Huang Y, Sato K, Takemoto M, Hishikawa N, Ohta Y, et al. Clinical and pathological benefit of twendee X in Alzheimer's disease transgenic mice with chronic cerebral hypoperfusion. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc*. 2019;28:1993–2002. doi: 10.1016/j.jstrokecerebrovasdis.2019.03.029
 83. Shang J, Yamashita T, Zhai Y, Nakano Y, Morihara R, Li X, Tian F, Liu X, Huang Y, Shi X, et al. Acceleration of NLRP3 inflammasome by chronic cerebral hypoperfusion in Alzheimer's disease model mouse. *Neurosci Res*. 2019;143:61–70. doi: 10.1016/j.neures.2018.06.002
 84. Shang J, Yamashita T, Tian F, Li X, Liu X, Shi X, Nakano Y, Tsunoda K, Nomura E, Sasaki R, et al. Chronic cerebral hypoperfusion alters amyloid- β transport related proteins in the cortical blood vessels of Alzheimer's disease model mouse. *Brain Res*. 2019;1723:146379. doi: 10.1016/j.brainres.2019.146379
 85. Bannai T, Mano T, Chen X, Ohtomo G, Ohtomo R, Tsuchida T, Koshi-Mano K, Hashimoto T, Okazawa H, Iwatsubo T, et al. Chronic cerebral hypoperfusion shifts the equilibrium of amyloid β oligomers to aggregation-prone species with higher molecular weight. *Sci Rep*. 2019;9:2827. doi: 10.1038/s41598-019-39494-7
 86. Yamada M, Ihara M, Okamoto Y, Maki T, Washida K, Kitamura A, Hase Y, Ito H, Takao K, Miyakawa T, et al. The influence of chronic cerebral hypoperfusion on cognitive function and amyloid β metabolism in APP overexpressing mice. *PLoS One*. 2011;6:e16567. doi: 10.1371/journal.pone.0016567
 87. Shibata M, Yamada S, Kumar SR, Calero M, Bading J, Frangione B, Holtzman DM, Miller CA, Strickland DK, Ghiso J, et al. Clearance of Alzheimer's amyloid-ss(1–40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier. *J Clin Invest*. 2000;106:1489–1499. doi: 10.1172/JCI10498

88. Deane R, Du Yan S, Subramanyam RK, LaRue B, Jovanovic S, Hogg E, Welch D, Manness L, Lin C, Yu J, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. *Nat Med*. 2003;9:907–913. doi: 10.1038/nm890
89. Deane R, Wu Z, Sagare A, Davis J, Du Yan S, Hamm K, Xu F, Parisi M, LaRue B, Hu HW, et al. LRP/amyloid beta-peptide interaction mediates differential brain efflux of Abeta isoforms. *Neuron*. 2004;43:333–344. doi: 10.1016/j.neuron.2004.07.017
90. Nelson AR, Sagare AP, Zlokovic BV. Role of clusterin in the brain vascular clearance of amyloid- β . *Proc Natl Acad Sci U S A*. 2017;114:8681–8682. doi: 10.1073/pnas.1711357114
91. Storck SE, Meister S, Nahrath J, Meißner JN, Schubert N, Di Spiezio A, Baches S, Vandenbroucke RE, Bouter Y, Prikulis I, et al. Endothelial LRP1 transports amyloid- β (1–42) across the blood-brain barrier. *J Clin Invest*. 2016;126:123–136. doi: 10.1172/JCI81108
92. Li H, Guo Q, Inoue T, Polito VA, Tabuchi K, Hammer RE, Pautler RG, Taffet GE, Zheng H. Vascular and parenchymal amyloid pathology in an Alzheimer disease knock-in mouse model: interplay with cerebral blood flow. *Mol Neurodegener*. 2014;9:28. doi: 10.1186/1750-1326-9-28
93. de Montgolfier O, Pinçon A, Pouliot P, Gillis MA, Bishop J, Sled JG, Villeneuve L, Ferland G, Lévy BI, Lesage F, et al. High systolic blood pressure induces cerebral microvascular endothelial dysfunction, neurovascular unit damage, and cognitive decline in mice. *Hypertens Dallas Tex*. 2019;73:217–228. doi: 10.1161/HYPERTENSIONAHA.118.12048
94. Zhang W, Luo P. Myocardial infarction predisposes neurodegenerative diseases. *J Alzheimers Dis*. 2020;74:579–587. doi: 10.3233/JAD-191225
95. Shi X, Ohta Y, Liu X, Shang J, Morihara R, Nakano Y, Feng T, Huang Y, Sato K, Takemoto M, et al. Chronic cerebral hypoperfusion activates the coagulation and complement cascades in Alzheimer's disease mice. *Neuroscience*. 2019;416:126–136. doi: 10.1016/j.neuroscience.2019.07.050
96. Shi X, Ohta Y, Liu X, Shang J, Morihara R, Nakano Y, Feng T, Huang Y, Sato K, Takemoto M, et al. Acute anti-inflammatory markers ITIH4 and AHSR in mice brain of a novel Alzheimer's disease model. *J Alzheimers Dis*. 2019;68:1667–1675. doi: 10.3233/JAD-181218
97. Peers C, Pearson HA, Boyle JP. Hypoxia and Alzheimer's disease. *Essays Biochem*. 2007;43:153–164. doi: 10.1042/BSE0430153
98. Gao L, Tian S, Gao H, Xu Y. Hypoxia increases A β -induced tau phosphorylation by calpain and promotes behavioral consequences in AD transgenic mice. *J Mol Neurosci*. 2013;51:138–147. doi: 10.1007/s12031-013-9966-y
99. Li L, Zhang X, Yang D, Luo G, Chen S, Le W. Hypoxia increases A β generation by altering β - and γ -cleavage of APP. *Neurobiol Aging*. 2009;30:1091–1098. doi: 10.1016/j.neurobiolaging.2007.10.011
100. Liu H, Qiu H, Yang J, Ni J, Le W. Chronic hypoxia facilitates Alzheimer's disease through demethylation of γ -secretase by downregulating DNA methyltransferase 3b. *Alzheimers Dement J Alzheimers Assoc*. 2015;12:130–143. doi: 10.1016/j.jalz.2015.05.019
101. Sun X, He G, Qing H, Zhou W, Dobie F, Cai F, Staufenbiel M, Huang LE, Song W. Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. *Proc Natl Acad Sci U S A*. 2006;103:18727–18732. doi: 10.1073/pnas.0606298103
102. Wang CY, Wang ZY, Xie JW, Cai JH, Wang T, Xu Y, Wang X, An L. CD36 upregulation mediated by intranasal LV-NRF2 treatment mitigates hypoxia-induced progression of Alzheimer's-like pathogenesis. *Antioxid Redox Signal*. 2014;21:2208–2230. doi: 10.1089/ars.2014.5845
103. Wang CY, Xie JW, Wang T, Xu Y, Cai JH, Wang X, Zhao BL, An L, Wang ZY. Hypoxia-triggered m-calpain activation evokes endoplasmic reticulum stress and neuropathogenesis in a transgenic mouse model of Alzheimer's disease. *CNS Neurosci Ther*. 2013;19:820–833. doi: 10.1111/cns.12151
104. Shiota S, Takekawa H, Matsumoto SE, Takeda K, Nurwidya F, Yoshioka Y, Takahashi F, Hattori N, Tabira T, Mochizuki H, et al. Chronic intermittent hypoxia/reoxygenation facilitate amyloid- β generation in mice. *J Alzheimers Dis*. 2013;37:325–333. doi: 10.3233/JAD-130419
105. Macheda T, Roberts K, Lyons DN, Higgins E, Ritter KJ, Lin AL, Alilain WJ, Bachstetter AD. Chronic intermittent hypoxia induces robust astrogliosis in an Alzheimer's disease-relevant mouse model. *Neuroscience*. 2019;398:55–63. doi: 10.1016/j.neuroscience.2018.11.040
106. Varela-Nallar L, Rojas-Abalos M, Abbott AC, Moya EA, Iturriaga R, Inestrosa NC. Chronic hypoxia induces the activation of the Wnt/ β -catenin signaling pathway and stimulates hippocampal neurogenesis in wild-type and APPswe-PS1 Δ E9 transgenic mice in vivo. *Front Cell Neurosci*. 2014;8:17. doi: 10.3389/fncel.2014.00017
107. Meng SX, Wang B, Li WT. Intermittent hypoxia improves cognition and reduces anxiety-related behavior in APP/PS1 mice. *Brain Behav*. 2020;10:e01513. doi: 10.1002/brb3.1513
108. Zhang X, Le W. Pathological role of hypoxia in Alzheimer's disease. *Exp Neurol*. 2010;223:299–303. doi: 10.1016/j.expneurol.2009.07.033
109. Salminen A, Kauppinen A, Kaarniranta K. Hypoxia/ischemia activate processing of Amyloid Precursor Protein: impact of vascular dysfunction in the pathogenesis of Alzheimer's disease. *J Neurochem*. 2017;140:536–549. doi: 10.1111/jnc.13932
110. Watanabe T, Takasaki K, Yamagata N, Fujiwara M, Iwasaki K. Facilitation of memory impairment and cholinergic disturbance in a mouse model of Alzheimer's disease by mild ischemic burden. *Neurosci Lett*. 2013;536:74–79. doi: 10.1016/j.neulet.2012.12.041
111. Koike MA, Green KN, Blurton-Jones M, Laferla FM. Oligemic hypoperfusion differentially affects tau and amyloid- β . *Am J Pathol*. 2010;177:300–310. doi: 10.2353/ajpath.2010.090750
112. Koike MA, Garcia FG, Kitazawa M, Green KN, Laferla FM. Long term changes in phospho-APP and tau aggregation in the 3xTg-AD mice following cerebral ischemia. *Neurosci Lett*. 2011;495:55–59. doi: 10.1016/j.neulet.2011.03.034
113. Kempainen S, Hämäläinen E, Miettinen PO, Koistinaho J, Tanila H. Behavioral and neuropathological consequences of transient global ischemia in APP/PS1 Alzheimer model mice. *Behav Brain Res*. 2014;275:15–26. doi: 10.1016/j.bbr.2014.08.050
114. Heikkinen R, Malm T, Heikkilä J, Muona A, Tanila H, Koistinaho M, Koistinaho J. Susceptibility to focal and global brain ischemia of Alzheimer mice displaying A β deposits: effect of immunoglobulin. *Aging Dis*. 2014;5:76–87. doi: 10.14336/AD.2014.050076
115. Hawkes CA, Michalski D, Anders R, Nissel S, Grosche J, Bechmann I, Carare RO, Härtig W. Stroke-induced opposite and age-dependent changes of vessel-associated markers in co-morbid transgenic mice with Alzheimer-like alterations. *Exp Neurol*. 2013;250:270–281. doi: 10.1016/j.expneurol.2013.09.020
116. Lee JS, Im DS, An YS, Hong JM, Gwag BJ, Joo IS. Chronic cerebral hypoperfusion in a mouse model of Alzheimer's disease: an additional contributing factor of cognitive impairment. *Neurosci Lett*. 2011;489:84–88. doi: 10.1016/j.neulet.2010.11.071
117. Milner E, Zhou ML, Johnson AW, Vellimana AK, Greenberg JK, Holtzman DM, Han BH, Zipfel GJ. Cerebral amyloid angiopathy increases susceptibility to infarction after focal cerebral ischemia in Tg2576 mice. *Stroke*. 2014;45:3064–3069. doi: 10.1161/STROKEAHA.114.006078
118. Zhang F, Eckman C, Younkin S, Hsiao KK, Iadecola C. Increased susceptibility to ischemic brain damage in transgenic mice overexpressing the amyloid precursor protein. *J Neurosci*. 1997;17:7655–7661.
119. Yang H, Wang W, Jia L, Qin W, Hou T, Wu Q, Li H, Tian Y, Jia J. The effect of chronic cerebral hypoperfusion on blood-brain barrier permeability in a transgenic Alzheimer's disease mouse model (PS1V97L). *J Alzheimers Dis*. 2020;74:261–275. doi: 10.3233/JAD-191045
120. Whitehead SN, Massoni E, Cheng G, Hachinski VC, Cimino M, Balduini W, Cechetto DF. Triflusal reduces cerebral ischemia induced inflammation in a combined mouse model of Alzheimer's disease and stroke. *Brain Res*. 2010;1366:246–256. doi: 10.1016/j.brainres.2010.10.008
121. Garcia-Alloza M, Gregory J, Kuchibhotla KV, Fine S, Wei Y, Ayata C, Frosch MP, Greenberg SM, Bacskaí BJ. Cerebrovascular lesions induce transient β -amyloid deposition. *Brain*. 2011;134(pt 12):3697–3707. doi: 10.1093/brain/awr300
122. Van Nostrand WE, Davis J, Previti ML, Xu F. Clearance of amyloid- β protein deposits in transgenic mice following focal cerebral ischemia. *Neurodegener Dis*. 2012;10:108–111. doi: 10.1159/000334763
123. Koistinaho M, Kettunen M, Goldsteins G, Keinänen R, Salminen A, Ort M, Bures J, Liu D, Kauppinen RA, Higgins LS, et al. Beta-amyloid precursor protein transgenic mice that harbor diffuse A beta deposits but do not form plaques show increased ischemic vulnerability: role of inflammation. *Proc Natl Acad Sci U S A*. 2002;99:1610–1615. doi: 10.1073/pnas.032670899
124. Drummond E, Wisniewski T. Alzheimer's disease: experimental models and reality. *Acta Neuropathol (Berl)*. 2017;133:155–175. doi: 10.1007/s00401-016-1662-x
125. Balducci C, Forloni G. APP transgenic mice: their use and limitations. *Neuromolecular Med*. 2011;13:117–137. doi: 10.1007/s12017-010-8141-7
126. Irizarry MC, Soriano F, McNamara M, Page KJ, Schenk D, Games D, Hyman BT. Abeta deposition is associated with neuropil changes, but not with overt neuronal loss in the human amyloid precursor protein V717F (PDAPP) transgenic mouse. *J Neurosci*. 1997;17:7053–7059.
127. Nazem A, Sankowski R, Bacher M, Al-Abed Y. Rodent models of neuroinflammation for Alzheimer's disease. *J Neuroinflammation*. 2015;12:74. doi: 10.1186/s12974-015-0291-y

128. Roher AE, Kokjohn TA. Of mice and men: the relevance of transgenic mice Abeta immunizations to Alzheimer's disease. *J Alzheimers Dis.* 2002;4:431–434. doi: 10.3233/jad-2002-4509
129. Kokjohn TA, Roher AE. Amyloid precursor protein transgenic mouse models and Alzheimer's disease: understanding the paradigms, limitations, and contributions. *Alzheimers Dement.* 2009;5:340–347. doi: 10.1016/j.jalz.2009.03.002
130. Nisbet RM, Polanco JC, Ittner LM, Götz J. Tau aggregation and its interplay with amyloid- β . *Acta Neuropathol.* 2015;129:207–220. doi: 10.1007/s00401-014-1371-2
131. Warren HS, Tompkins RG, Moldawer LL, Seok J, Xu W, Mindrinos MN, Maier RV, Xiao W, Davis RW. Mice are not men. *Proc Natl Acad Sci U S A.* 2015;112:E345. doi: 10.1073/pnas.1414857111
132. Takao K, Miyakawa T. Genomic responses in mouse models greatly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A.* 2015;112:1167–1172. doi: 10.1073/pnas.1401965111
133. Hargis KE, Blalock EM. Transcriptional signatures of brain aging and Alzheimer's disease: what are our rodent models telling us? *Behav Brain Res.* 2017;322(Pt B):311–328. doi: 10.1016/j.bbr.2016.05.007
134. Pallas M, Camins A, Smith MA, Perry G, Lee HG, Casadesus G. From aging to Alzheimer's disease: unveiling "the switch" with the senescence-accelerated mouse model (SAMP8). *J Alzheimers Dis.* 2008;15:615–624. doi: 10.3233/jad-2008-15408
135. Saito T, Matsuba Y, Yamazaki N, Hashimoto S, Saido TC. Calpain activation in Alzheimer's model mice is an artifact of APP and presenilin overexpression. *J Neurosci.* 2016;36:9933–9936. doi: 10.1523/JNEUROSCI.1907-16.2016
136. Fisher M, Feuerstein G, Howells DW, Hurn PD, Kent TA, Savitz SI, Lo EH. Update of the stroke therapy academic industry roundtable pre-clinical recommendations. *Stroke J Cereb Circ.* 2009;40:2244–2250. doi: 10.1161/STROKEAHA.108.541128
137. Cavaglia M, Dombrowski SM, Drazba J, Vasanji A, Bokesch PM, Janigro D. Regional variation in brain capillary density and vascular response to ischemia. *Brain Res.* 2001;910:81–93. doi: 10.1016/s0006-8993(01)02637-3
138. von Bernhardt R, Eugeni J. Alzheimer's disease: redox dysregulation as a common denominator for diverse pathogenic mechanisms. *Antioxid Redox Signal.* 2012;16:974–1031. doi: 10.1089/ars.2011.4082
139. Wadley AJ, Veldhuijzen van Zanten JJ, Aldred S. The interactions of oxidative stress and inflammation with vascular dysfunction in ageing: the vascular health triad. *Age (Dordt).* 2013;35:705–718. doi: 10.1007/s11357-012-9402-1