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# Current updates on latest basic research of scientific relevance in hypertensive dementia

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In Japan, there is an urgent need to respond to dementia, and the Basic Act on Dementia to Promote an Inclusive Society [1] was enacted in January 2024. Among the basic policies, the importance of promoting research on dementia and preventing dementia is emphasized. Hypertension is one of the modifiable risk factors for dementia, and, in particular, midlife hypertension is attracting attention from an epidemiological perspective [2]. It has become clear that hypertension-induced dementia ("hypertensive dementia") is associated with disturbance in the balance of the neurovascular unit (NVU), which is composed of the three elements of blood vessels, astrocytes, and neurons, in not only vascular dementia (VaD) but also Alzheimer's disease (AD) [3]; thus, it has been proposed that the accumulation of cardiovascular burden over the life course induces dementia in older age [4]. Although the concept of "hypertensive dementia" has been established clinically, basic research is also progressing to elucidate the mechanisms and to find emerging concepts in particular, since the American Heart Association issued a scientific statement on blood pressure and dementia in 2016 [5]. After introducing the statement, a number of papers related to hypertensive dementia have been reported each year, and attention to this condition has been increasing. The Japanese Society of Hypertension has focused on the importance of hypertension management for the prevention of dementia, and established the Prevention of Cognitive Impairment by Hypertension Management (PCIHM) Working Group to investigate the relationship between hypertension and dementia through both basic and clinical research. This review summarizes the latest developments in basic research on hypertensive dementia. We hope that this will be useful not only for basic researchers in dementia but also for general practitioners who treat hypertension worldwide.

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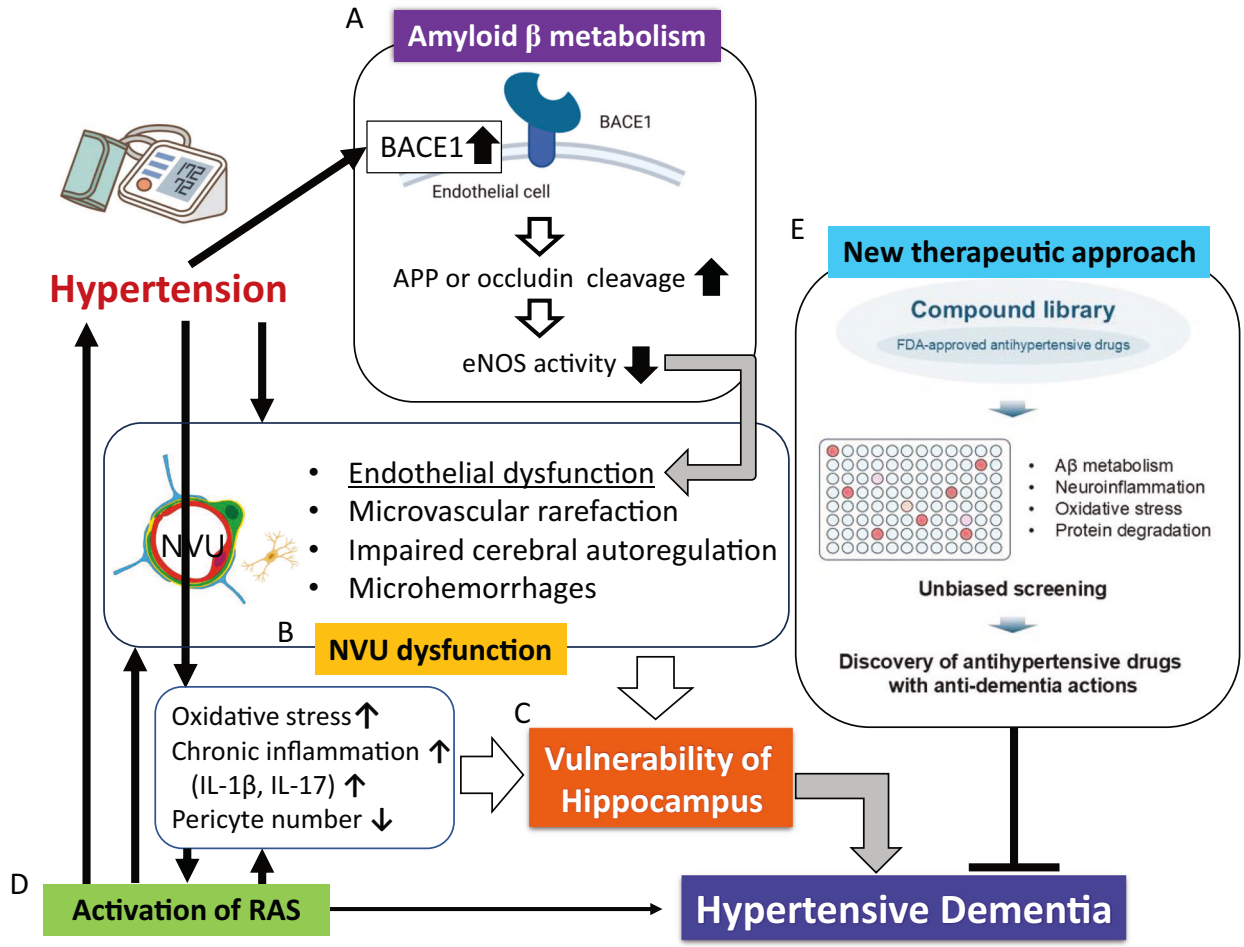
**Graphical Abstract**

Schematic presentation of possible mechanisms of hypertensive dementia, including amyloid beta metabolism (A), NVU dysfunction (B), vulnerability of the hippocampus (C), and activation of RAS (D), and possible new therapeutic approaches for discovering antihypertensive drugs with anti-dementia actions (E). See text for details. Aβ, amyloid β; APP, amyloid β precursor protein; BACE1, β-site amyloid precursor protein cleaving enzyme 1; BBB, blood-brain barrier; CBF, cerebral blood flow; eNOS, endothelial nitric oxide synthase; FDA, Food and Drug Administration; IL, interleukin; NOX, NADPH oxidase; NVU, neurovascular unit; RAS, renin-angiotensin system; ROS, reactive oxygen species




## Hypertensive dementia

Hypertension is widely recognized as a major risk factor for cardiovascular disease, particularly stroke, and is consequently considered a contributing factor to VaD. Recent advances in understanding the NVU highlight the intricate interplay among blood vessels, neurons, and astrocytes [3]. Hypertension, by inducing structural and functional alterations in the cerebral vasculature, is increasingly regarded as a potential driver of NVU dysfunction and subsequent neurodegeneration through vascular injury. From this integrated perspective, hypertension is thought to influence both the onset and progression of various forms of dementia, including AD. Notably, prolonged hypertension results in accumulation of vascular stress over time. Numerous epidemiological studies have shown that midlife hypertension significantly increases the risk of developing dementia in later life [6, 7]. While recent evidence suggests that appropriate antihypertensive treatment initiated in midlife may have a preventive effect on dementia, definitive conclusions have yet to be reached [4, 7–9]. Conversely, the relationship between hypertension and dementia in older adults remains inconsistent, confounded by factors such as age-related heterogeneity and the potential cognitive consequences of hypotension [7, 10] or blood pressure variability [11–14]. Both low blood pressure and fluctuating blood pressure levels have been associated with reduced cerebral perfusion, which may exacerbate cognitive decline.

When examining dementia subtypes, dementia with Lewy bodies (DLB) frequently presents with orthostatic hypotension due to autonomic dysfunction. Javanshiri et al. reported that cardiovascular comorbidities, including hypertension, were significantly less prevalent in DLB compared to VaD [15]. Nonetheless, a systematic review by Chin et al. identified an association between cerebral microbleeds (CMBs) and dementia, reporting that in AD, CMBs were linked to both a history of hypertension and amyloid-β (Aβ) burden. Similarly, a relationship between hypertension and CMBs has also been observed in DLB [16]. Thus, while the role of hypertension may be less prominent in certain dementia types, such as DLB, its contribution, particularly through blood-brain barrier (BBB) disruption, cannot be dismissed when considering neurodegenerative diseases more broadly.

Hypertension-induced BBB disruption may trigger neuroinflammation, increase oxidative stress via activation of the renin-angiotensin system (RAS), and impair Aβ clearance, collectively worsening the neural environment and contributing to dementia pathogenesis. Therefore, we propose the term "hypertensive dementia" to encompass dementia arising from vascular impairment and hypertension-related neuropathological mechanisms, such as inflammation and BBB breakdown. In this review, we present recent basic research on the pathophysiology of dementia associated with hypertension and its related factors. We further re-examine the mechanisms underlying hypertensive dementia and explore the potential for its prevention through optimized blood pressure control.

## Possible mechanisms of hypertensive dementia

### Neurovascular unit dysfunction

#### Impact of hypertension on cerebral circulation

Hypertension significantly alters the cerebral circulation through changes in both the structure and function of blood vessels. It induces arteriolosclerosis, which is characterized by thickening of the arterial wall and narrowing of the lumen due to hypertrophy and hyperplasia of vascular smooth muscle cells (VSMC). Such changes include the phenotypic switching of VSMC from a contractile form toward a synthetic state. Consequently, vessels become stiffer and less responsive to fluctuations in blood pressure, compromising the blood supply to the brain. This structural rigidity increases the brain's susceptibility to ischemic events, especially when cerebral autoregulation fails [3]. The functional impairment of cerebral autoregulation in hypertension stems from a loss of endothelial function and increased vascular stiffness. Under normal conditions, the NVU maintains cerebral blood flow (CBF) through a balance of vasodilation and vasoconstriction. In hypertension, this balance skews in favor of vasoconstrictor factors such as angiotensin II (Ang II) and endothelin-1 (ET-1), leading to excessive vasoconstriction, reduced CBF, and exacerbation of conditions like white matter lesions and cognitive decline [17]. Even modest sustained hypertension induces cerebrovascular remodeling and inflammatory changes, driven by mechanical and oxidative stress, inflammation, and neurohumoral factors like Ang II, leading to neuronal injury and cognitive decline through hypoxia and oxidative stress [18]. Hypertension impairs vasodilation by increasing protein kinase C (PKC) activity, which inhibits Rab11A-mediated trafficking of large conductance calcium-activated potassium (BK) channel β1 subunits in arterial myocytes. This leads to reduced nitric oxide (NO)-induced BK channel activation and vasodilation in hypertensive rats, altering arterial contractility and contributing to the risk of cerebrovascular diseases associated with hypertension [19]. Impaired cerebral vasoreactivity and autoregulation have also been observed in transgenic mouse models expressing mutant neurogenic locus notch homolog protein 3 (NOTCH3), which mimic features of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), highlighting the role of vascular dysfunction in exacerbating ischemic brain injury [20]. Transient receptor potential vanilloid 4 (TRPV4) channels are non-selective $Ca^{2+}$ permeable channels expressed in endothelial cells, smooth muscle cells, astrocytes and neurons [21], all of which are included in the NVU and act together to regulate cerebral perfusion [22]. Hypertension impairs TRPV4-mediated dilation of cerebral parenchymal arterioles, reducing cerebral perfusion and contributing to cognitive decline, as shown in both TRPV4 knockout rats and hypertensive mice. TRPV4 channels are influenced by mineralocorticoid receptor activation, and blocking this receptor improves cerebrovascular function and cognition, highlighting its therapeutic potential [23, 24]. Notably, agonistic autoantibodies targeting the alpha 1-adrenergic receptor, which are detected in patients with widespread conditions like hypertension and type 2 diabetes, induce cerebrovascular damage in rats. Magnetic resonance imaging (MRI) revealed reduced vascular area and blood flow in the brain in antibody-exposed rats, suggesting that these antibodies may contribute to central nervous system diseases such as stroke and dementia [25]. Neurovascular coupling (NVC), the mechanism that links neuronal activity to localized increases in CBF, plays a critical role in ensuring the metabolic demands of active neurons are met. Capillary endothelial cells are central to NVC, using inward-rectifier $K^+$ (Kir2.1)-mediated retrograde hyperpolarization to regulate CBF in response to neural activity [26]. In hypertension, this critical Kir2.1

channel-mediated signaling pathway is disrupted by angiotensin II type 1 receptor blocker (ARB)-induced aldosterone breakthrough, impairing functional hyperemia and exacerbating neurovascular uncoupling [27]. This mechanism highlights the importance of Kir2.1 channels in maintaining NVC and underscores their therapeutic potential in preventing cognitive decline linked to vascular dysfunction.

### Hypertension-induced neurovascular unit dysfunction

The NVU plays a vital role in maintaining brain homeostasis, controlling the entry of molecules into the brain via the BBB, regulating cerebral blood flow, and responding to neural activity. It consists of vascular endothelial cells, pericytes, astrocyte endfeet, microglia, neurons, and the extracellular matrix. The integrity of the NVU is essential for protecting the brain from potentially harmful substances in the bloodstream and for regulating cerebral perfusion in response to neuronal demands. Hypertension profoundly affects the NVU through multiple mechanisms, including endothelial dysfunction, vascular remodeling, BBB breakdown, and chronic cerebral hypoperfusion [28].

Endothelial cells in the NVU are highly sensitive to changes in blood pressure. Under hypertensive conditions, these cells experience oxidative stress, which disrupts NO signaling—a critical regulator of vascular tone. Reduced NO bioavailability leads to impaired vasodilation, increased vascular resistance, and cerebral hypoperfusion. This contributes to cognitive decline, as sustained reductions in CBF result in neuronal injury and accumulation of toxic metabolites [28]. Hyperhomocysteinemia has been shown to impair regional CBF by reducing NO bioavailability and increasing oxidative stress, exacerbating endothelial dysfunction and NVU damage in hypertensive conditions [29]. Hypertension models have consistently demonstrated that hypertension reduces endothelial nitric oxide synthase (eNOS) expression and activity, leading to a deterioration in cerebrovascular function. This reduction in NO availability contributes to increased vascular resistance, BBB disruption, and impaired Aβ clearance, mechanisms that are closely associated with the pathophysiology of AD. The compromised vascular function exacerbates the accumulation of Aβ, thereby linking cerebrovascular dysfunction to the progression of AD [30].

The BBB is a selective barrier that prevents the entry of potentially harmful substances into the brain. BBB dysfunction is recognized as an early biomarker of cognitive dysfunction in AD, associated with hippocampal damage and occurring independently of amyloid and tau biomarkers [31]. Hypertension-induced mechanical and oxidative stress weaken tight junctions between endothelial cells, leading to increased BBB permeability. This allows plasma proteins, inflammatory mediators, and other neurotoxic substances to infiltrate the brain parenchyma, initiating neuroinflammation and contributing to neuronal damage [28]. Hypertension-induced BBB damage is particularly pronounced in the hippocampus, while chronic hypoperfusion leads to white matter lesions, both of which contribute to cognitive decline and link vascular dysfunction to AD [32]. Capillary dysfunction plays a significant role in impairing oxygen extraction and CBF, further linking microvascular damage to the progression of both stroke and dementia [33]. Over-expression of endothelial ET-1 also exacerbates BBB breakdown, increases oxidative stress, and promotes neuronal apoptosis, further contributing to cognitive deficits in ischemic conditions [34]. The role of perivascular macrophages in BBB dysfunction has been highlighted in hypertension models, where crosstalk between endothelial cells and macrophages aggravates BBB permeability through Ang II receptor signaling, underscoring the immune-vascular interaction in NVU damage [35]. Furthermore, in Ang II-induced hypertensive mice, depletion of microglia and perivascular macrophages using a colony-stimulating factor 1 receptor inhibitor, PLX5622, has been shown to attenuate cognitive decline by suppressing pro-inflammatory activation at sites of BBB disruption [36]. This indicates that targeting immune cells may provide a therapeutic avenue to mitigate hypertension-induced NVU damage and cognitive impairment. Notably, elevated endothelial β-site amyloid precursor protein cleaving enzyme 1 (BACE1) induced by hypertension contributes to cerebral small vessel damage by cleaving tight junction proteins, leading to BBB breakdown, endothelial dysfunction, and cognitive impairment [37]. Intriguingly, chronic hypertension has also been shown to cause more pronounced defects in the integrity of the blood–cerebrospinal fluid (CSF) barrier than in the BBB, particularly in the spontaneously hypertensive rat (SHR). Studies have demonstrated that SHR exhibit increased permeability between the choroid plexus and CSF, indicating significant blood-CSF barrier disruption. These findings highlight the extensive impact of hypertension on NVU dysfunction and underscore the greater susceptibility of the blood-CSF barrier to hypertensive damage compared to the BBB [38].

### Mechanisms linking NVU dysfunction to dementia

The cumulative effects of hypertension on NVU-endothelial dysfunction, BBB disruption, and cerebral hypoperfusion create a pro-inflammatory, hypoxic environment conducive to neurodegeneration [39]. Hypertension-induced NVU dysfunction results in reduced CBF, leading to neuronal injury and accumulation of toxic metabolites. One of the key factors contributing to NVU dysfunction is the age-related decline in circulating insulin-like growth factor 1 (IGF-1) level. IGF-1 deficiency exacerbates hypertension-

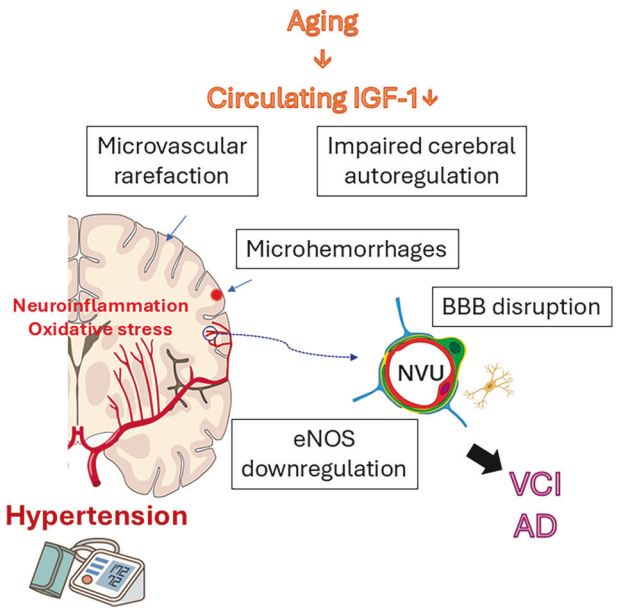



**Fig. 1** Age-related decline of circulating IGF-1 and neurovascular unit (NVU) dysfunction in hypertension. IGF-1 deficiency exacerbates 1) hypertension-induced microvascular rarefaction in the hippocampus and neocortex, leading to reduced microvascular density and an anti-angiogenic gene expression profile; 2) impaired neurovascular coupling, increased BBB disruption, and neuroinflammation, contributing to VCI pathogenesis; 3) enhanced cerebral microhemorrhages due to oxidative stress-mediated matrix metalloproteinase activation and arteriolar fragility; 4) VSMC dysfunction, impairing cerebral autoregulation and contributing to cognitive decline; and 5) eNOS downregulation, exacerbating hypertension-induced AD pathology, with exercise-mediated IGF-1/PI3K/p-Akt pathway activation promoting eNOS expression to mitigate cognitive impairment. AD Alzheimer's disease, BBB blood-brain barrier, eNOS endothelial nitric oxide synthase, IGF-1 insulin-like growth factor I, VCI vascular cognitive impairment

induced microvascular rarefaction in the hippocampus and neocortex, decreasing microvascular density and promoting an anti-angiogenic gene expression profile [40]. This impairment leads to neurovascular uncoupling, increased BBB disruption, and neuroinflammation, contributing to the pathogenesis of vascular cognitive impairment (VCI) [40, 41]. IGF-1 deficiency also enhances cerebral microhemorrhages by increasing oxidative stress-mediated matrix metalloproteinase activation and impairing vascular remodeling, thus increasing arteriolar fragility [42]. VSMC are integral to IGF-1's vasoprotective effects; VSMC-specific IGF-1 receptor deficiency impairs cerebral myogenic autoregulation and leads to cognitive dysfunction, highlighting the role of VSMC dysfunction in VCI [43]. Additionally, eNOS downregulation associated with IGF-1 deficiency contributes to hypertension-induced AD pathology; long-term exercise promotes eNOS and IGF-1 expression, activating the PI3K/Akt pathway and ameliorating cognitive impairment in the stroke-prone spontaneously hypertensive (SHRSP) rat [44]. These findings underscore IGF-1's crucial role in cerebrovascular health and suggest targeting IGF-1 signaling as a therapeutic strategy to prevent or mitigate VCI and AD in elderly hypertensive individuals (Fig. 1).

Moreover, the phenotypic switching of VSMC from a contractile form toward a synthetic state plays an important role in the progression of atherosclerosis with vascular remodeling such as vascular arterial wall thickening and narrowing of the lumen which reduces CBF and alter CBF autoregulation. A recent study highlighted the role of protein arginine methyltransferase 5 (PRMT5) in VSMC phenotypic switching. PRMT5 expression is upregulated in response to platelet-derived growth factor (PDGF) stimulation and vascular injury. This upregulation leads to histone modifications that suppress the expression of contractile genes while promoting proliferation and migration of VSMC, facilitating the transition to a synthetic phenotype. Inhibition of PRMT5 was found to attenuate neointimal formation, suggesting its potential as a therapeutic target [45]. Another study demonstrated that the combination of increased blood pressure and matrix stiffness synergistically induces VSMC phenotypic switching. This mechanical stress leads to cytoskeletal remodeling and the formation of matrix-degrading structures called podosomes, which are characteristic of the synthetic phenotype. These findings underscore the importance of mechanical cues in vascular remodeling associated with hypertension [46].

Adducin 3 (ADD3) is a subunit of the adducin protein complex involved in actin cytoskeleton regulation, particularly in VSMC. The K572Q mutation in ADD3 disrupts its actin-binding domain, destabilizing the cytoskeleton and impairing autoregulation of CBF. This dysfunction exacerbates NVU damage, increases BBB permeability, and contributes to cognitive decline, particularly in models of hypertension-induced dementia [47].

Hypertension induces chronic oxidative stress in the NVU, primarily through activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) and the production of reactive oxygen species (ROS). ROS directly damage endothelial cells and promote the activation of inflammatory pathways, exacerbating vascular dysfunction and contributing to neuronal injury. Chronic oxidative stress, driven by NOX and inducible nitric oxide synthase (iNOS), exacerbates vascular dysfunction and neuronal injury. Pharmacological inhibition of iNOS and NOX has been shown to attenuate oxidative damage and cognitive deficits in hypertension-induced VaD models [48].

## Effects of Alzheimer's disease pathology

### Hypertension and amyloid beta metabolism

Stress-induced hormonal and behavioral reactions may also participate in the development of hypertension,

atherosclerosis, insulin resistance, and other peripheral disturbances that may indirectly induce neuropathological processes participating in the development and progression of AD [49, 50]. Microanatomical, neurochemical and behavioral data on SHR favor the hypothesis that this strain is a suitable model of vascular brain disorder [51]. SHR, along with patients with established hypertension, also develop astrogliosis in the brain [52]. Importantly, stress-induced detrimental effects are attractive as etiological factors in AD because they can be reduced by several approaches including behavioral intervention such as exercise [50] and pharmacological interventions such as antihypertensive agents. Antihypertensive intervention is considered to be effective because hypertension is known to induce intracerebral hemorrhage in Tg2576 mice, a model of cerebral amyloid angiopathy (CAA) that recapitulates common vascular changes in AD [53, 54]. CAA and hypertension-induced cerebral small vessel disease (CSVD) share some features but are mechanistically different because a transgenic rat model of CAA type 1 (rTg-DI) and the SHRSP, a rat model of hypertension, show distinct brain proteomic signatures at 12 months of age [55]. In SHRSP, age-dependent extracellular deposition of Aβ is observed from approximately 20-30 weeks onwards [56, 57]. SHRSP treated with N-acetylcysteine (NAC) show an age-dependent increase in BBB breakdown and small perivascular bleeds, accompanied by increased Aβ plaque load in the cerebral cortex [58]. The microvascular and brain injury observed in SHR-SP may be explained by a combination of neurological, inflammatory and vascular functional pathways [59]. In a mouse model of hypertension induced by chronic pressure overload, early cerebrovascular damage develops and is sustained by $CD8^{+}$IFN-gamma+T lymphocytes [60]. Depletion of perivascular macrophages (PVM) via intracerebroventricular injection of clodronate in two models of hypertension—chronic fourteen-day Ang II infusion and BPH/2 J mice that have life-long hypertension—revealed that PVM are critical for impairing cerebral cortical arteriolar function in hypertension. These effects involve crosstalk between PVM and cerebral endothelial cells, interaction with circulating immune cells, and/or production of reactive oxygen species (ROS) [61]. An experimental study showed that Ang II-induced hypertension with aging (24 months) upregulated expression of Aβ precursor protein (APP), beta secretase, and gamma-secretase in C57BL/6 mice but rather changed hippocampal expression of several APP binding proteins [62]. However, another study showed that Ang II in the Tg2576 model did induce microvascular amyloid deposition and enhanced beta-secretase APP cleavage [63]. In different APP-overexpressing mice bearing Swedish and Indiana mutations, Ang II enhanced Aβ generation and gamma-secretase APP cleavage [64]. In addition, chronic hypertension induces impairment of blood–brain barrier permeability with deposition of Aβ in brain tissue, and passive immunotherapy prevents this latter phenomenon [65]. Thus, the conflicting results regarding the association between spontaneous or Ang II-induced hypertension and Aβ accumulation suggest that hypertension accelerates AD pathology in a context-dependent manner.

## Plausible mechanisms of hypertension-induced AD

Several different mechanisms by which hypertension induces AD pathology are proposed. In SHR, water content in the brain is increased, at least partially due to decreased expression of aquaporin 4 [66], a molecule involved in the glymphatic Aβ clearance pathway. In the same model, a high fluorescent molecular weight tracer released passively into the hippocampus showed markedly enhanced spreading and accumulated at interstitial fluid-CSF borders, around arteries surrounded by astrocytes positive for aquaporin 4 [67]. Sieving of high molecular weight solutes at these sites may promote aggregation of Aβ. In the hippocampus of SHR, expression of occludin and zonula occludens-1 was decreased with blood brain barrier disruption, which may facilitate Aβ influx into the brain [68]. Aβ influx may be facilitated by the receptor for advanced glycation end product (RAGE), which may be upregulated by hypertension [69]. RAGE activation in cerebral vessels is a crucial pathogenetic event in a hypertension-induced Aβ accumulation model (transverse aortic coarctation (TAC) mice), suggesting that inhibiting this target could limit the onset of vascular-related AD [21]. In addition, Tg-SwDI mice, a CAA model, showed exacerbation of microvascular Aβ accumulation, vascular inflammation, blood-brain barrier disruption, and pericyte loss, thus accelerating cognitive deficits after 3-6 months of chemically induced chronic hypertension [70]. Transient hypertension, induced by one-month treatment with L-NG-nitroarginine methyl ester (L-NAME), also aggravated CAA and induced loss of cortical myelin in the cingulate cortex in F344TgAD [71]. Rho-associated coiled-coil-containing protein kinase (ROCK) 1 and ROCK2 were found to modulate different aspects of vascular remodeling following hypertension, suggesting that ROCK1 and ROCK2 signaling are a molecular signature of hypertension-induced vascular degeneration in AD [71].

Immune response represents a pivotal and genetically variable modifying factor that may influence vulnerability to neurodegeneration. Microglial cells in SHR overexpressing human truncated tau protein showed lowered expression of MHCII level with a robust phagocytic phenotype compared to those in counterpart WKY rats overexpressing the same construct [72, 73]. At the early stage of hypertension in SHR-SP, hippocampal microglia exhibited

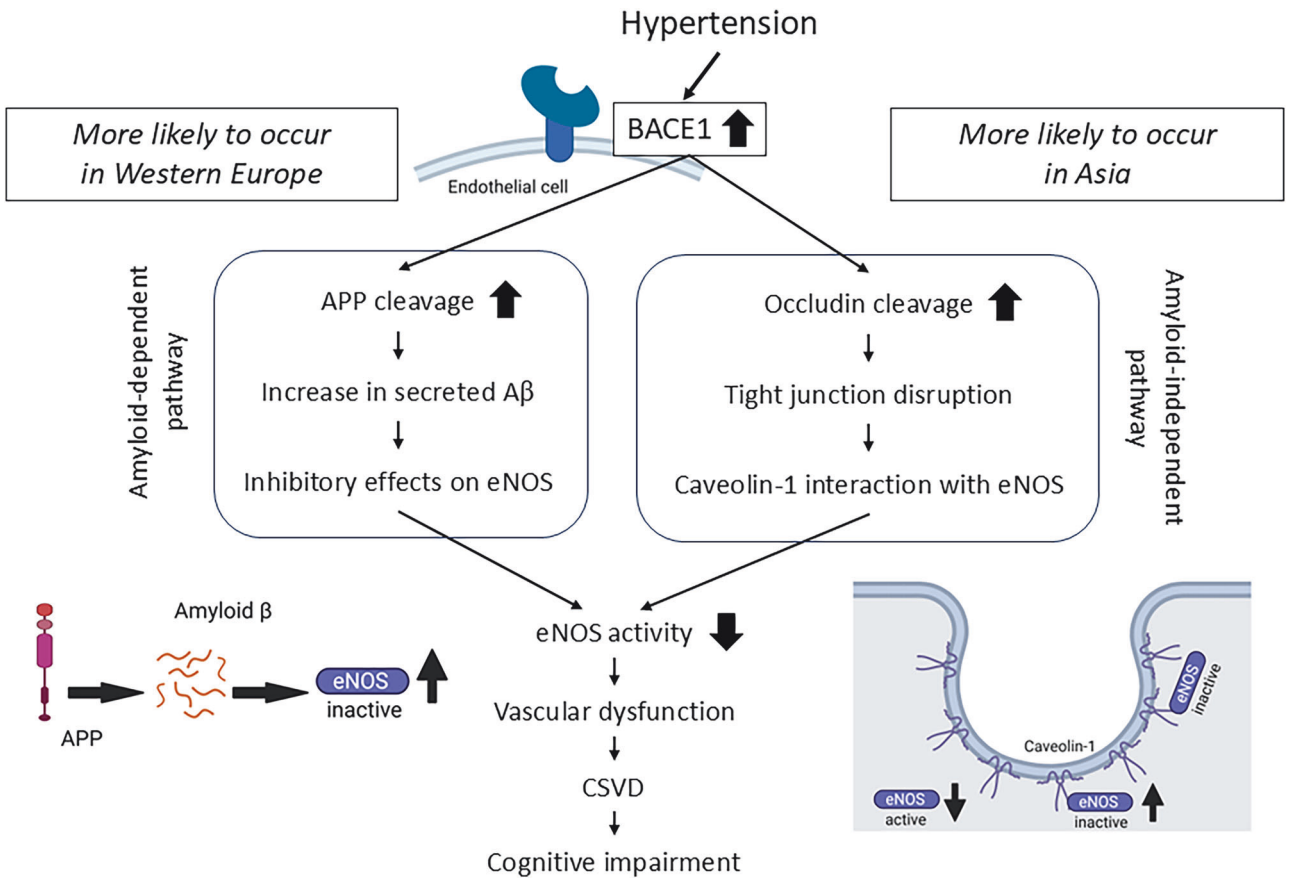



**Fig. 2** Plausible mechanism underlying development of hypertension-induced cerebral small vessel disease (CSVD) through BACE1 upregulation. Hypertension is associated with increased expression of endothelial BACE1, which then cleaves APP (resulting in Aβ synthesis; amyloid-dependent pathway) and occludin (resulting in tight junction disruption; amyloid-independent pathway); both of these phenomena culminate in eNOS inactivation and induction of CSVD. The amyloid-dependent pathway is associated with the amyloid form of CSVD (left), which may be more common in Western populations, and the amyloid-independent pathway is associated with hypertension-related CSVD (right), which may be more common in Asian populations. Aβ amyloid β, APP Aβ precursor protein, BACE1 β-site amyloid precursor protein cleaving enzyme 1, CSVD cerebral small vessel disease, eNOS endothelial nitric oxide synthase

upregulated inflammation-associated markers CD11b/c, CD200R, and CD86 [74]. In a TAC model of hypertension, microglial cell activation and interleukin (IL)-1beta upregulation occurred at 3 weeks, followed by Aβ deposition at 4 weeks. However, immune system activation by lipopolysaccharide (LPS) significantly suppressed amyloid burden, suggesting that stimulation in the appropriate time window may be protective [75]. Pro-inflammatory IL-1beta [76, 77] and Toll-like receptor 4 [76] were significantly increased in the hippocampus of SHR [77]. These results suggest that targeting inflammation can either exacerbate or limit vascular-triggered AD pathology in a time- and context-dependent manner [78].

### Endothelial nitric oxide synthase and AD

eNOS may be involved in hypertension-induced AD pathology because beta secretase/BACE1 is upregulated in the eNOS-deficient mouse brain, potentially leading to Aβ accumulation. BACE1 is highly expressed in cerebral microvessels from patients with hypertension, and BACE1 cleaves a tight junction protein, occludin, and attenuates eNOS activity [37] (Fig. 2). Consistent with this, endothelial-specific BACE1 transgenic mice show chronic hypoperfusion, BBB leakage, tau hyperphosphorylation, synaptic loss, and cognitive impairment, while inhibition of aberrant BACE1 activity ameliorates tight junction loss, endothelial dysfunction, and memory deficits [37]. eNOS constitutes a feedback signaling loop with Pin1 and Aβ: Pin1 inhibits Aβ production and enhances eNOS activity, and Aβ and eNOS form a mutual inhibition system [79]. Once such a feedback signaling loop is disturbed, it may result in Aβ deposition, hypertension and microbleeds, synchronously leading to AD and CAA. Impaired NO bioavailability exacerbates the pathophysiology of AD in APP/PS1 (amyloid precursor protein/presenilin-1) mice, essentially impacting amyloid load and cognitive impairment, independently of L-NAME-induced hypertension, although only CAA seems to be dependent on hypertension [80].

## Renin-angiotensin system

### Direct effects of angiotensin II

Hypertension-induced brain damage is not just a direct result of damage to blood vessels, but may also be caused by a vicious cycle involving increased oxidative stress, neuroinflammation, and sympathetic nerve activation, which may intensify the damage. It is thought that activation of RAS is involved in these processes. Examination of autopsy samples from the frontal cortex showed that protein levels of Ang II type 1 ($AT_1$) receptor and phosphorylated extracellular signal-regulated kinase (ERK) were higher in AD. Protein level of $AT_1$ receptor correlated with an oxidative stress marker (protein carbonyl level) in both AD and cognitive impairment groups [81], indicating activation of RAS in the brain of AD patients. In a study using diabetic mice, swelling of astrocyte endfeet was observed, suggesting disruption of the BBB. Such a pathological change was suppressed by an ARB, telmisartan, indicating involvement of Ang II in the BBB disruption [82]. Ang II reduces the endothelium-dependent response in cerebral blood vessels by inducing oxidative stress such as NOX-dependent ROS, especially peroxynitrite [83, 84]. This endothelial dysfunction may inhibit NVC and induce microvascular damage, resulting in reduced CBF [85] and reduce the increased blood-flow response to external stimuli [86], ultimately impairing cognitive function. A more detailed mechanism has been reported by Iadecola's group. Daily subcutaneous administration of a sub-pressor dose of Ang II gradually increased blood pressure. After discontinuation of Ang II administration, blood pressure decreased; however, microvascular dysfunction did not quickly recover, indicating that Ang II-induced oxidative stress in the microvasculature significantly disrupts cerebrovascular blood flow regulation and attenuates the increase in CBF induced by neural activity and endothelium-dependent vasodilators [87]. They also showed that suppression of free radicals in the subfornical organ (SFO) by overexpression of Cu/Zn-superoxide dismutase (Cu/Zn-SOD) in a similar model reduced microvascular dysfunction, suggesting that SFO and its hypothalamic centrifugal pathway are involved in Ang II-induced cerebrovascular changes [88]. Faraco et al. also reported that perivascular macrophages (PVM) induce neurovascular dysfunction due to hypertension, leading to cognitive dysfunction [89]. Iadecola et al. summarized one of the underlying mechanisms of hypertension-induced cognitive impairment by Ang II in a review published in 2019, that Ang II activates the $AT_1$ receptor in PVM, and then activates NOX2 leading to vascular oxidative stress and neurovascular dysfunction. This indicates that PVM are an abundant source of vascular ROS production [90] (Fig. 3). Recently, Chen et al. reported a mechanism by which direct binding of Aβ42 to the $AT_1$ receptor in astrocytes activates β-arrestin signaling and induces autophagy dysfunction, leading to Aβ accumulation and inducing synaptotoxicity [91]. On the other hand, a study using two mouse models, AD, hAPP23(+/-) and hAPPswe/PSEN1dE9 mice, demonstrated that Ang II administration for 28 days was too short to induce cognitive decline and brain pathology, suggesting that long-term Ang II administration may be required to impair brain and cognitive function [92].

### Actions of ARB administration on RAS

Many basic experiments have investigated the effects of a sub-depressor dose of RAS inhibitors. Intranasal administration of losartan decreased inflammatory cytokines such as IL-12p40/p70, IL-1β, and granulocyte macrophage colony-stimulating factor (GM-CSF) while increasing IL-10, which suppressed inflammation and expression of tyrosine hydroxylase in the striatum and locus coeruleus in APP/PS1 mice [93]. Intranasal administration of losartan also increased IL-10, resulting in a decrease in perivascular β-amyloid and a decline in neurogenesis in SHRSP [94]. Coatl-Cuaya et al. showed that losartan improved cognitive function by regulating hypertension and improving neuroplasticity in chronic hypertensive mice [95]. Campos et al. showed that losartan was effective in reducing cognitive decline in ovariectomized female mice [96]. Takeda et al. reported that olmesartan treatment reduced microvascular oxidative stress in APP23 mice and suppressed cognitive decline in a blood pressure-independent manner [97]. Treatment with olmesartan also suppressed cognitive decline via suppression of oxidative stress in a 5XFAD mouse model in which bilateral common carotid artery occlusion (BCCAO) was applied for 17 minutes to induce ischemia [98]. On the other hand, telmisartan suppressed learning and memory deficits, endothelial dysfunction, and changes in various biochemical parameters in deoxycorticosterone acetate (DOCA)-saline hypertension, as did donepezil [99]. Shindo et al. also reported that telmisartan's anti-inflammatory effects mediated by the partial agonistic action of peroxisome proliferator-activated receptor (PPAR) γ prevented spatial cognitive impairment in a rat model of oligomeric or aggregated Aβ administration [100]. Liu et al. reported that telmisartan increased Aβ40 and Aβ42 production but decreased the Aβ42/Aβ40 ratio, while losartan, valsartan, and candesartan showed no change in Aβ generation and olmesartan showed a significant increase in Aβ42 generation [101]. Telmisartan has also been shown to be neuroprotective in ovariectomized mice by increasing the protective arm of RAS (angiotensin converting enzyme (ACE) 2/Ang-(1-7)/Mas receptor) when used in

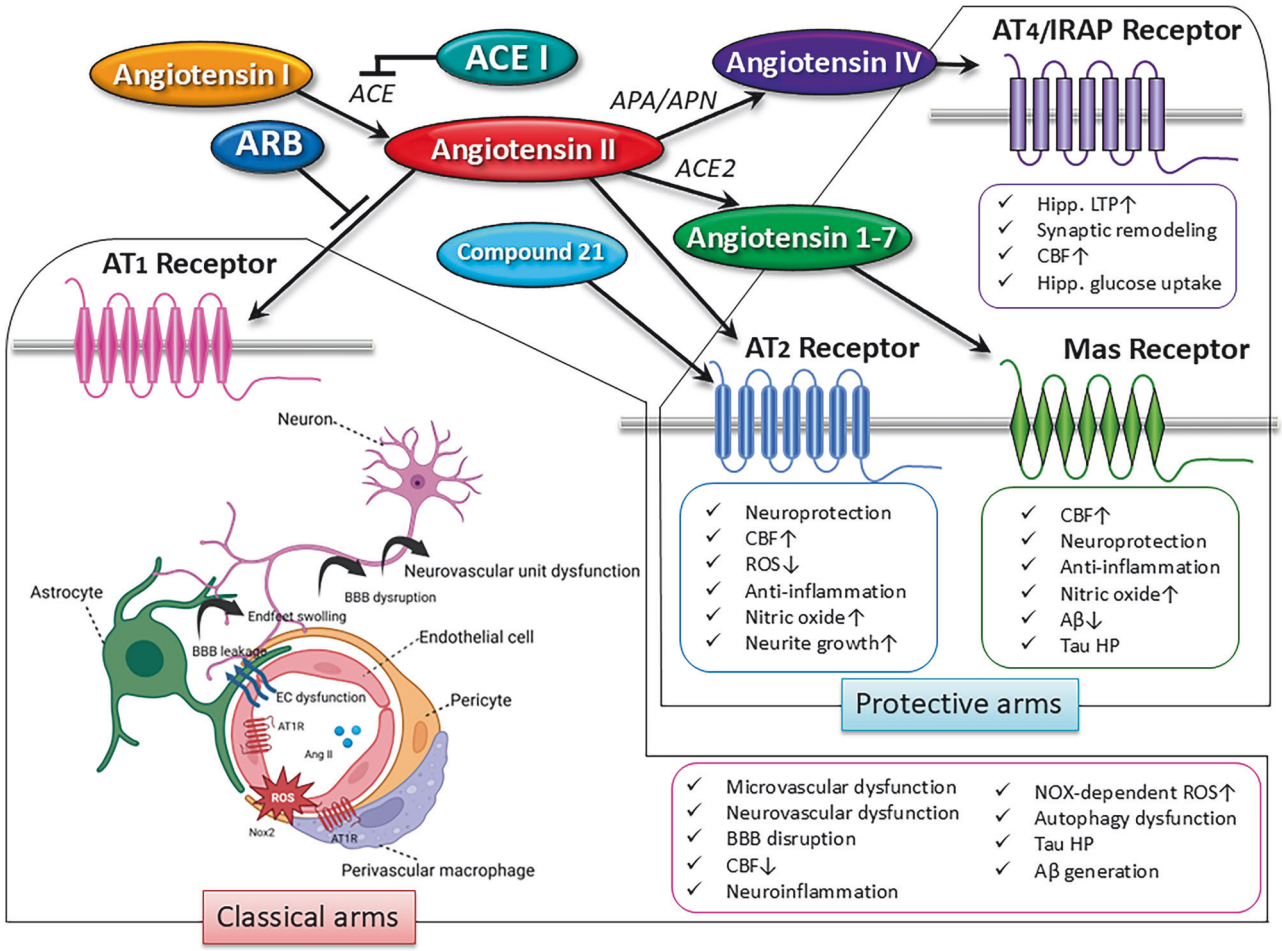



**Fig. 3** Possible mechanisms of Ang II-induced cognitive impairment via Ang II- receptors. Angiotensin II (Ang II) binds to Ang II type 1 ($AT_1$) receptors on vascular peripheral cells of the blood brain barrier (BBB) (e.g., perivascular macrophages) and produces oxidative stress, inducing cerebral vascular endothelial cell (EC) damage. This leads to disruption of the BBB, which induces neuroinflammation in the brain through the invasion of inflammatory cells and Ang II itself, which does not pass through the normal BBB. BBB disruption induces swollen astrocyte endfeet, which leads to dysfunction of the neurovascular unit. This is a possible mechanism leading to RAS-activated neurological damage. Aβ amyloid beta, BBB blood-brain barrier, CBF cerebral blood flow, Hippo hippocampus, HP hyperphosphorylation, LTP long-term potentiation, NOX nitric oxide, ROS reactive oxygen species

combination with 17β-estradiol [102]. Valsartan has been reported to potentiate spinogenesis by enhancing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking and synaptic plasticity signaling [103]. Furthermore, candesartan has been reported to improve hippocampal neurogenesis by inhibiting astrocyte and microglial activation independent of blood pressure reduction [104]. Moreover, intranasal administration of irbesartan effectively prevented LPS-induced cognitive decline by activation of PI3K/Akt pathways through neuroprotection and anti-inflammation [105]. Thus, ARB administration in experimental systems has shown brain protective effects based on different mechanisms depending on the drug (Table 1). Since no drug-drug comparisons have been made, this may indicate multiple aspects of Ang II action rather than drug-to-drug differences.

## Protective arms of RAS (AT2 agonists and ACE2/Ang-(1-7)/Mas axis)

Ang II type 2 ($AT_2$) receptor activation by ARB administration has been previously reported to protect the brain and prevent cognitive impairment via relative stimulation of the $AT_2$ receptor by unbound Ang II. Thus, a direct $AT_2$ receptor stimulator has previously been expected to be a multiple-organ protective agent. An $AT_2$ receptor agonist (Compound 21, C21) has been reported to have no anti-hypertensive effect but has shown organ-protective effects in models of AD, kidney disease, stroke, and myocardial infarction [106], and prevention of cognitive impairment [107–109]. Treatment of a 60 min transient middle cerebral artery occlusion model with C21 and/or candesartan reduced cytotoxicity and prevented chronic reactive

**Table 1** Summary of preventive drugs or compounds against hypertensive dementia

| Pharmacological action | Drug or compound | Probable mechanism | Reference# |
|---|---|---|---|
| Calcium channel blocker (CCB) | felodipine, nifedipine, amlodipine, nilvadipine, nitrendipine, nimodipine, and isradipine | Reduction of Aβ accumulation | [199] |
| | lercanidipine, manidipine, and nimodipine | Restoration of brain damage such as hyperplasia of astrocytes | [202] |
| | nicardipine | Reduction of Aβ accumulation | [197] |
| | | Prevention of neurodegeneration | [200] |
| | amlodipine | Reduction of blood pressure variability and amelioration of breakdown of blood–brain barrier | [201] |
| | | Attenuation of increase in cerebrovascular resistance | [205] |
| | nilvadipine | Inhibition of splenic tyrosine kinase (SYK) and amelioration of neuroinflammation | [203] |
| | lercanidipine | Reduction of delayed neuronal death in hippocampal neurons | [204] |
| | felodipine | Degradation of neurodegenerative disease-associated proteins | [219] |
| | azelnidipine | Suppression of oxidative stress and inflammatory responses in Aβ-stimulated microvasculature | [221] |
| Angiotensin II type 1 receptor blocker (ARB) | losartan | Decrease in inflammatory cytokines and increase in IL-10 | [93–96] |
| | olmesartan | Decrease in perivascular β-amyloid by increase in IL-10 | [97, 98] |
| | telmisartan | Improvement of neuroplasticity | [99–102] |
| | valsartan | Reduction of cognitive decline in ovariectomized female mice | [103] |
| | | Prevention of oligomerization of Aβ into neurotoxic species | [217] |
| | candesartan | Inhibition of astrocyte and microglial activation | [104] |
| | | Anti-inflammatory effect against LPS treatment | [233] |
| | Iirbesartan | Reduction of neuroinflammation by activating PI3K/AKT pathway | [105] |
| β-blocker | propranolol | Amelioration of corticosterone-induced cognitive impairment | [206] |
| | | Reduction of Aβ accumulation | [197] |
| | nebivolol | | [207] |
| | penbutolol | Reversal of biological AD signature and reduction of Aβ accumulation | [218] |
| Diuretic | indapamide | Reduction of oxidative stress and axonal injury | [220] |
| | bumetanide | Reversal of APOE4 transcriptomic brain signatures and improvement of memory deficits in APOE4 animal models of AD | [237] |
| Mineralocorticoid receptor antagonist | eplerenone | Prevention of decreased activity of Kir2.1 | [26, 27] |
| | | Alleviation of aldosterone-induced brain damage with increased cortical thinning and apoptosis | [133] |
| Angiotensin converting enzyme inhibitor (ACEi) | lisinopril | Reduction of brain total tau and phosphorylated tau (pTau)-181 levels | [129] |

**Table 1** (continued)

| Pharmacological action | Drug or compound | Probable mechanism | Reference# |
|---|---|---|---|
| Direct angiotensin II tye 2 receptor agonist | Compound 21 (C21) | Reduction of cytotoxicity and prevention of chronic reactive microgliosis | [107–109, 114] |
| Angiotensin converting enzyme 2 (ACE2) enhancement | diminazene aceturate (DIZE)) | Improvement of amyloid-related hippocampal pathology | [122] |
| Glycosylated angiotensin-(1-7) peptide | Ang-1-6-O-Ser-Glc-NH2 (PNA5) | Suppression of inflammation | [124] |
| Metabolite of angiotensin II and its receptor | angiotensin IV/insulin-regulated aminopeptidase (IRAP) | Promotion of activity-dependent glucose uptake in hippocampus | [116, 117] |
| Other compounds with antihypertensive effects | traditional Chinese medical compounds | Modification of Aβ metabolism and reduction of oxidative stress | [209–214] |
| | carotenoids | | [215] |
| | plant-related products | | [216] |
| | ifenprodil | Neuroprotective activity through effects on NMDA receptor | [232] |
| Cholinergic precursor | choline alphoscerate | Neuroprotection in SHR | [227–229] |
| Choline esterase inhibitor | galantamine | | |
| | donepezil | Reduction of brain inflammation, oxidative stress, and endothelial dysfunction with memory impairment | [239] |
| Melatonergic MT1/MT2 agonist | agomelatine | | |
| Selective ATP sensitive potassium (KATP) channel opener | nicorandil | | |
| Colony stimulating factor 1 receptor (CSF1R) inhibitor | PLX5622 | Depletion of microglia and perivascular macrophages | [36] |
| Nonselective inhibitor of nitric oxide synthetases | L-NG-nitroarginine methyl ester (L-NAME) | Aggravation of CAA and induction of loss of cortical myelin in cingulate cortex | [71] |
| Nuclear factor-kappa B (NF-kB) inhibitor | natrium diethyldithiocarbamate trihydrate (NDDCT) | Attenuation of endothelial dysfunction and changes in various biochemical levels | [128] |
| Selective cyclooxygenase-2 inhibitor | NS-398 | Preservation of cerebral blood flow | [173] |
| Specific p38 mitogen activated protein kinase inhibitor | SB202190 | Preservation cerebral blood flow in double transgenic APPsw AD model | [173] |
| Endothelin A receptor angagonist | zibotentan (ZD4054) | Reduction of baroreflex responsiveness, and accumulation of Aβ and elevated endothelin-1 | [177] |
| Chromogranin A derived peptide | catestatin | Antihypertensive and neuroprotective effects via GABAergic output in SHR | [230] |
| Natriuretic peptide hormone | atrial natriuretic peptide | Aβ inhibitor in nonaggregated state | [235] |
| Hormone cleaved from fibronectin type-III domain-containing protein 5 | irisin | Reduction of neural Aβ aggregation and phopshorylated tau | [236] |
| Serine protease inhibitor derived from human urine | ulinastatin | Suppression of renovascular hypertension-induced cognitive impairment | [238] |
| Antioxidant | quercetin | | |

**Table 1** (continued)

| Pharmacological action | Drug or compound | Probable mechanism | Reference# |
|---|---|---|---|
| Endothelin-1 antagonist | bosentan | Management of renovascular hypertension-induced VaD | [240] |
| Specific serotonin-norepinephrine reuptake inhibitor (SNRI) | venlafaxine | Suppression of brain pathology observed in 2K1C VaD model | [241] |
| | neprilysin (NEP) | Degradation of Aβ peptides | [242, 243] |
| | phytochemicals | Prevention or attenuation of progression of dementia | [245] |
| | melatonin | | [246] |
| | miR-124 inhibitor | | [247] |

*Aβ* amyloid beta, *AD* Alzheimer's disease, *APP* amyloid precursor protein, *CAA* cerebral amyloid angiopathy, *GABA* gamma-aminobutyric acid, *IL-10* interleukin 10, *LPS* lipopolysaccharide, *MT1/MT2* melatonin receptors, *NMDA* N-methyl-D-aspartate, *SHR*, spontaneously hypertensive rat, *VaD* vascular dementia, *2K2C* two-kidney, two-clip

microgliosis in SHR after stroke [110]. Although $AT_2$-related brain protective effects in female mice have been previously reported [111, 112], in ovariectomized (OVX) female SHR subjected to middle cerebral artery occlusion (MCAO), C21 prevented cognitive dysfunction after stroke, presumably through a mechanism involving vascular protection and recovery [113]. Alshammari et al. suggested that modulation of $AT_2$ receptor signaling via C21 may be a useful therapeutic option to improve sensori-motor and cognitive outcomes in aged animals [114]. Although it has been expected that Ang II, which cannot bind to the $AT_1$ receptor, would stimulate the $AT_2$ receptor and cause cerebroprotection in response to ARB administration, some reports suggest that $AT_2$ receptor-targeted therapy is not an ideal strategy to restore Aβ-associated cognitive impairment and cerebrovascular damage, considering the effects of an ARB with PD123319, an $AT_2$ receptor antagonist. [115]. The effects of Ang IV and angiotensin II type 4 ($AT_4$) receptor signaling on cognitive function have been investigated. For example, insulin-regulated aminopeptidase (IRAP), which is also the receptor for Ang IV, co-localized with the insulin-responsive glucose transporter type 4 (GLUT4), and Ang IV promoted activity-dependent glucose uptake in hippocampal sections [116], indicating that Ang IV acts as a cognitive enhancer [117]. Recent reviews have demonstrated the preventive effects of ARBs on cognitive dysfunction via activation of not only the Ang II/$AT_2$ receptor pathway but also the Ang IV/$AT_4$ receptor, Ang-(1-7)/Mas receptor pathways through other unbound Ang II metabolites by $AT_1$ receptor blockade [118, 119]. The cognitive function-related effects induced by receptor stimulation of each RAS component are summarized in Fig. 3, with reference to the content mentioned thus far and past reviews [120].

Also, the protective arms of the RAS, such as the ACE2/Ang-(1-7)/Mas axis, have been expected to prevent dementia via brain protective effects. The brain ACE2/Ang-(1-7)/Mas axis may be involved as protective factors in the etiology and progression of AD, possibly through regulation of tau hyperphosphorylation [121]. ACE2 enhancement through administration of diminazene aceturate (DIZE) improved amyloid-related hippocampal pathology and cognitive deficits in Tg2576 mice [122]. Moreover, systemic administration of Ang (1-7) to 5XFAD mice improved Ang II-induced cognitive impairment, and brain damage and skeletal muscle damage were suppressed [123]. Glycosylated angiotensin-(1-7) peptide Ang-1-6-O-Ser-Glc-NH2 (PNA5) suppressed inflammation and showed beneficial effects on vascular dementia [124]. Furthermore, chronic subcutaneous administration of iodine Ang (1-7) (non-radioactive iodine isotope) to SHR showed that neither Ang (1-7) nor iodine Ang (1-7) affected blood pressure or cognitive function [125]. If $AT_2$ receptors are present, the

absence of Mas receptors may have a protective effect against chronic cerebral ischemia [126]. Tran et al. reviewed the effects of neuroinflammation induced by chronic RAS activation on cognitive impairment with consideration of the classical arms and protective arms in the brain [127].

#### Other RAS components

The nuclear factor-kappa B (NF-kB) inhibitor, natrium diethyldithiocarbamate trihydrate (NDDCT), suppressed vascular dementia in DOCA-induced hypertensive mice as did the ACE inhibitor (ACEI), lisinopril [128]. Lisinopril also significantly reduced brain total tau and phosphorylated tau (pTau)-181 levels [129]. On the other hand, overexpression of ACE in bone marrow monocytic cells alters immune responses that defend against many different types of pathological attacks, including the cognitive decline observed in animal models of AD [130]. Cells overexpressing ACE also showed enhanced immune responses [131]. Increased expression of ACE by macrophages and neutrophils enhances the ability of these cells to respond to immune challenges such as infections, neoplasms, AD, and atherosclerosis [132].

Koide et al. found that chronic hypertension caused neurovascular uncoupling via decreased activity of Kir2.1, an inwardly rectifying potassium channel in capillary endothelial cells. This effect was prevented by amlodipine and not by losartan, but was preventable by eplerenone, suggesting the effects of aldosterone [27]. Moreover, eplerenone alleviated aldosterone-induced brain damage with increased cortical thinning and apoptosis in SHR [133].

This review's final focus is on neprilysin inhibitors. Some protease inhibitors may affect Aβ metabolism [134], such as through inhibition of neprilysin [135]. The long-term effects of neprilysin inhibitors on amyloid metabolism have been a concern because neprilysin is an amyloid-degrading enzyme [136], and it has been previously reported that neprilysin expression and activity are decreased in the cortex of elderly AD patients [137]. However, Langenickel et al. showed that spinal fluid Aβ40 and Aβ42 were unchanged after sacubitril/valsartan treatment compared to placebo in healthy volunteers [138]. Also, Brum et al. recently showed that plasma Aβ42 and Aβ40 increased significantly from baseline in the sacubitril/valsartan group, while the plasma Aβ42/Aβ40 ratio decreased significantly [139]. Moreover, from a sub-study of a recent clinical study, PARAGON-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Global Outcomes in Heart Failure with Preserved Ejection Fraction), no difference in cognitive change in patients was observed between treatment with sacubitril/valsartan and treatment with valsartan during a median follow-up of 32 months [140]. Thus, considering that sacubitril is thought to hardly cross the blood-brain barrier, the effect of sacubitril/valsartan on Aβ metabolism may not be clinically relevant.

## Basic approach to hypertensive dementia

### Mystery in dementia approach with animal models —Why is the hippocampus vulnerable?

#### Cerebrovascular network, energy supply and waste removal processes in hippocampus

The brain hippocampus is an important region that plays a central role in memory and learning, but it is also vulnerable to damage from a variety of factors. This chapter details the mechanisms of vulnerability of the brain hippocampus revealed by experimental animal models. The hippocampus is particularly dependent on blood flow in the brain and is highly vulnerable to lack of blood flow, ischemia [141, 142]. Even short periods of ischemia can damage hippocampal neurons, leading to cell death in the worst cases. Because the hippocampus has a very high energy demand compared to other brain regions, probably due to its complex functions such as memory formation and information processing, if the blood flow supply is cut off, energy deficiency quickly sets in and cellular function is impaired. Neurons in the hippocampus utilize the excitatory neurotransmitter glutamate in abundance. Ischemia causes over-release of glutamate into the extracellular space, leading to over-excitation of neurons. This is known as 'excitotoxicity' and is a major cause of neuronal death [143]. In addition, the hippocampus is a particularly frequent focus of epileptic seizures, or seizure origin, probably due to its excitotoxicity and complicated and dense neuronal network. An experimental rat model of eclampsia showed that seizures during pregnancy can cause long-lasting hippocampal dysfunction [144]. On the other hand, ageing causes a decrease in the number and function of neurons in the hippocampus, due to the effects of various age-related factors, including oxidative stress and inflammation, on the hippocampus, eventually leading to reduced memory and cognitive function [145]. The same level of hypertension can lead to significantly earlier onset and increased cerebral microhemorrhages in aged mice than in younger mice [146]. These findings suggest that impairment of the cerebrovascular network can have a strong impact on energy supply and waste removal processes in the hippocampus. Bennette et al. performed mesoscale microscopy methods and in vivo imaging to compare aged and younger murine cerebrovascular networks. They found that vasculature and pericyte densities showed significant reductions in not only the hippocampal network but also basal forebrain areas, which corresponds well with areas of obvious brain atrophy in elderly

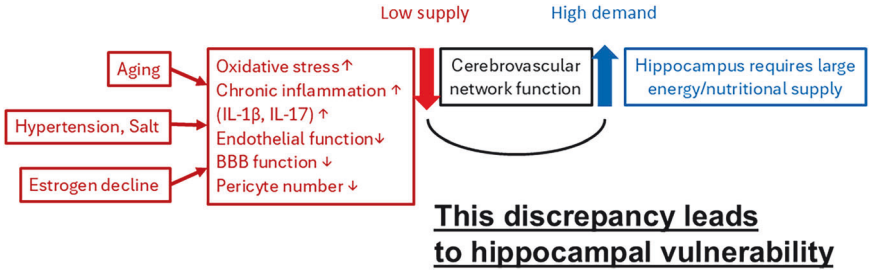



**Fig. 4** Proposed mechanism for vulnerability of hippocampus. The hippocampus, which is essential for memory and learning, has a high energy demand and requires a large amount of blood flow. On the other hand, aging, hypertension, and decline in estrogen exacerbate oxidative stress and inflammation, leading to disruption of the cerebrovascular network, including BBB leakage and pericyte damage. This mismatch between high demand and low supply ultimately renders the hippocampus highly vulnerable. IL-1β interleukin-1β, IL-17 interleukin-17, BBB blood-brain barrier

humans. In addition, the aged brain exhibited increased blood extravasation with leakage of immunoglobulin, indicating compromise of the blood-brain barrier. Of note, the oxygen-carrying capacity of blood is also reduced in the aged mouse brain [147]. Other research groups reported that mitochondrial function of isolated brain microvessels is impaired in aged mice, which could be one reason for the reduced oxygen-carrying capacity of blood [148]. What kind of mechanism contributes to the impaired cerebrovascular networks? Some evidence suggests a contribution of the immune system to cerebrovascular network damage, especially under hypertension. A study in hypertensive rhesus monkeys showed widespread activation of microglial cells and astroglial cells, with leakage of the blood-brain barrier [149]. Recent data demonstrated that perivascular macrophages are the major source of ROS, inducing the neurovascular dysfunction [61]. Kaiser et al. evaluated SHR and reported that both T cells and natural killer cells were significantly increased in the SHR brain microvasculature [150]. Microarray analysis also showed that endothelial proliferation-related genes including those for CD151 antigen and activin A receptor were upregulated in SHR [151]. Hypertension can damage the vascular network as well as the glymphatic network and result in white matter lesions. Mortensen et al. infused paramagnetic contrast into the cisterna magna under dynamic MRI to quantify glymphatic transport kinetics in SHR and age-matched normotensive Wistar-Kyoto rats. They demonstrated that glymphatic system clearance was suppressed in SHR, indicating that hypertension and aging impaired glymphatic transport, resulting in impairment of the removal processes for waste or proteins including amyloid beta in the brain [152]. In vivo MRI clearly showed that the perivascular space is enlarged in SHRSP [153]; meanwhile, white matter volume, including that of the corpus callosum, is decreased in SHR, compared with WKY rats [154]. These findings suggest that the hippocampus has a propensity to require a large energy and nutritional supply, which in itself leads to vulnerability to ageing and hypertension. Therefore, the cerebrovascular network is critically important to maintain the homeostasis of the hippocampus (Fig. 4).

## Experimental models for assessment of hypertensive dementia

### Animal models of NVU damage in hypertension

Animal models have played a crucial role in elucidating the mechanisms of NVU damage and cognitive impairment associated with hypertension. The SHR and SHRSP models closely replicate key features of human VCI, including white matter damage, oxidative stress, neuroinflammation, and BBB disruption [155]. Chronic hypertension induces early BBB dysfunction in the hippocampus of young SHR and SHRSP rats, suggesting BBB impairment in the initial stages of vascular dementia [156]. Similarly, stroke-prone renovascular hypertensive rats (RHRSP), established using the two-kidney, two-clip method, exhibit cerebral hypoperfusion, BBB disruption, white matter damage, and cognitive impairment, mirroring human CSVD pathology and validating RHRSP as a suitable preclinical model [157].
The SHR model is also characterized by sleep apnea, which is associated with microvascular rarefaction in critical brain regions, such as the pre-Bötzinger complex. This condition leads to neuronal loss, neuroinflammation, and cognitive decline. Notably, sleep apnea exacerbates hypertension, further aggravating neurovascular damage, especially in small vessels, and contributing to the development of vascular dementia [158].

Rodent models of chronic hypoperfusion, such as bilateral carotid artery occlusion, are instrumental in replicating the white matter damage and cognitive deficits observed in VCI. These models highlight essential aspects of ischemic injury, microvascular alterations, and behavioral impairments, making them effective tools for studying NVU dysfunction in the context of hypertension-induced VCI [159]. In models of cerebral hypoperfusion, SHR show

more severe cognitive deficits and white matter pathology due to worsened BBB breakdown [160] and neurodegenerative outcomes [161]. Chronic hypoxia in SHR disrupts tight junction proteins, leading to increased BBB permeability and triggering angiogenesis in white matter. Minocycline treatment has been shown to reduce BBB damage, enhance angiogenesis, and protect oligodendrocytes [162]. Recent studies utilizing models of gradual cerebral hypoperfusion in SHR have demonstrated slowly progressing white matter damage and working memory impairment, effectively modeling subcortical ischemic vascular dementia while reducing mortality rates compared to traditional models [163]. Moreover, chronic hypoxia in hypertensive rat models exacerbates NVU dysfunction by inducing tau hyperphosphorylation, neuroinflammation, and neurodegeneration, paralleling the structural brain damage and cerebral hypoperfusion seen in human vascular dementia patients [164].

Aging, hypertension, and diabetes have been shown to perturb the brain vasculome in unique ways, with significant alterations in gene expression that influence neurovascular function. Hypertension, in particular, activates pathways related to mitochondrial responses and apoptosis in the brain, contributing to vascular damage and cognitive decline [165]. However, limitations of rodent models, such as their limited white matter, highlight the need for larger species that more accurately replicate human VCI pathology, including white matter damage and cognitive impairment [166].

Transgenic models that combine hypertension with genetic mutations linked to AD, such as the APP/PS1 mouse model, have provided valuable insights into the interaction between hypertension and amyloid pathology. In aged APP/PS1 mice, increased systolic blood pressure decreases CBF and connectivity, leading to neuroinflammation and cognitive impairment, modeling the early vascular contributions to AD [167]. Hypertension accelerates amyloid plaque deposition, reduces cerebral microvessel density, and impairs NO production, thereby hastening cognitive decline in AD models [168].

The chronic elevation of pulse pressure, induced by the transverse aortic constriction model, has also been shown to promote neurovascular damage, increase Aβ accumulation, and prevent cognitive improvement in AD models [169].

Collectively, these animal models offer critical insights into the complex interplay between hypertension, NVU dysfunction, and cognitive impairment. The SHR, SHRSP, and transgenic models, in particular, demonstrate how chronic hypertension induces NVU damage through BBB disruption, neuroinflammation, white matter pathology, and ischemic injury. Such findings underscore the importance of developing therapeutic strategies targeting NVU integrity in the context of hypertension-related VCI and AD. Future research should also aim to refine these models, incorporating species with more extensive white matter to better approximate human pathology.

### In vitro models of NVU dysfunction

In vitro models have advanced our understanding of NVU dysfunction under hypertensive conditions. Co-culture systems of endothelial cells, astrocytes, and pericytes recreate the NVU and help explore the effects of hypertension on NVU function. These models reveal that hypertensive conditions increase endothelial permeability, reduce NO production, and alter astrocyte-endothelial interactions, all contributing to NVU dysfunction [159, 170].

In vitro BBB models, including co-culture systems and synthetic microvessels, simulate BBB permeability and NVU dysfunction. However, they are limited in replicating the full complexity of the NVU. Newer synthetic microvessel models show promise for mimicking vascular conditions, such as BBB dynamics, but still face challenges in reproducing full 3D interactions [159, 170].

Organ-on-a-chip technology integrates microfluidics with cell culture to replicate NVU dynamics under hypertensive conditions. These models simulate mechanical stress from elevated blood pressure, providing insights into how hypertension leads to NVU damage and cognitive decline. They also serve as platforms for testing potential therapeutic interventions aimed at preserving NVU function in hypertensive patients [171]. Although organ-on-a-chip technology is a valuable tool that more closely mimics physiological conditions, there are currently no reports of studies related to hypertension and dementia using this system. It is anticipated that future research utilizing this experimental platform will enable more detailed examination of the pathophysiology involved.

### Aβ injection as a model of hypertension

Intraarterially injected Aβ constricts cerebral vessels, which may contribute to cerebral hypoperfusion as observed in early AD [172]. Besides, freshly solubilized Aβ enhances endothelin-1-induced vasoconstriction in isolated human middle cerebral and basilar arteries [173]. These observations are consistent with the finding that Aβ (25-35) induced vasoconstriction of mouse aortic rings and coronary arteries in Langendorff-perfused rat hearts, which resulted in decreased coronary flow through alpha1-adrenergic receptor activation [174]. In addition, when injected into the cerebroventricular space, Aβ induces a progressive rise in blood pressure in rats with pre-existing hypertension produced by a high-salt diet through modulation of autonomic activity, which may be interpreted as a physiological response to hypoperfusion complicating the accumulation of Aβ within

the brain [175]. Beta-adrenergic receptors may also be involved in AD pathogenesis through effects on Aβ production or inflammation [176]. Aβ-induced vasoconstriction is ameliorated by NS-398, a selective cyclooxygenase-2 inhibitor, or by SB202190, a specific p38 mitogen activated protein kinase inhibitor, and these two agents preserved cerebral blood flow in the double transgenic APPsw AD model (PS1/APPsw) [173]. Aβ-induced hypertension with evidence of reduced baroreflex responsiveness and accumulation of Aβ and elevated endothelin-1 in Wistar rats was ameliorated by the endothelin A receptor antagonist zibotentan (ZD4054) [177].

## Therapeutic approach to hypertensive dementia

### Prevention of dementia with antihypertensive drugs

Evidence from epidemiological studies and clinical trials suggests that certain antihypertensive drugs may reduce the risk of developing dementia. Notably, some of these drugs are reported to reduce the incidence of both vascular dementia and AD through mechanisms independent of their blood pressure-lowering effects. Recently, the world's first disease-modifying therapy against AD, an immunotherapy targeting AD-related Aβ protein, has obtained full approval in East Asia, including Japan, Europe, and the United States; however, its efficacy is limited. The anti-dementia actions of generic antihypertensive medications would have a huge impact on the worldwide dementia-related socioeconomic burden.

The cellular and molecular mechanisms underlying the favorable effects of antihypertensive drugs have been extensively investigated in a variety of in vitro and in vivo models of dementia. Some researchers have focused on specific types of antihypertensive drugs and investigated their mechanisms in detail using validated experimental models. This classical approach is straightforward and enables us to elucidate multiple aspects of the actions of certain types of antihypertensive drugs. However, this kind of approach requires a priori knowledge of clinical evidence demonstrating that the target drug has been proven to exert favorable effects on dementia; therefore, this approach cannot be used to discover new drugs with unknown therapeutic potential.

To eliminate this bottleneck, some researchers have adopted comprehensive drug screening methodology to newly identify antihypertensive agents with potential therapeutic effects on dementia, focusing on their specific molecular mechanisms, such as the modulation of Aβ metabolism, neuroinflammation, axonal injury, and protein degradation.

### Mechanisms underlying anti-dementia actions of antihypertensive drugs

For certain types of antihypertensive drugs, there is considerable clinical evidence supporting their favorable effects on the pathogenesis of dementia. The cellular and molecular mechanisms underlying those effects have been investigated in a variety of experimental models.

**RAS-acting drugs** Among all pharmacological classes of antihypertensive drugs, the mechanisms of the anti-dementia actions of ACEIs and ARBs have been most thoroughly investigated, as the cerebral RAS is known to play a critical role in cognition and the pathophysiology of dementia. Evidence from a variety of in vitro and in vivo models of AD [178–182], the hypertensive [183–186]/vascular dementia model [187–191], the inflammation-induced cognitive impairment model [192], and the age-related anxiety mouse model [193] supports the concept that RAS-acting drugs could prevent the progression of dementia. The role of the cerebral RAS and its contribution to the pathogenesis of dementia are described in detail elsewhere in this review article [see section 3.1]. Of note, RAS-acting drugs do not always exert neuroprotective effects in experimental mouse models [194], and ARB-induced hypotension is reported to induce cognitive decline associated with tau phosphorylation and reduced spin density [195].

Recent studies have shown an association of ACE with AD, suggesting a potential role of ACE in Aβ degradation. Whether ACEIs exacerbate the cerebral accumulation of neurotoxic Aβ by preventing its degradation or not is a critical issue in the long-term management of hypertension in people at risk of developing dementia [196]. Indeed, some researchers have demonstrated that certain types of ACEI, such as captopril, increased Aβ level in cell culture models and in the brain of AD mouse models at a clinical dose [196]. However, this effect of captopril on Aβ production was hardly observed in other studies [197, 198]. The discrepancy in the results may be attributable to differences in the experimental systems used in each study. More evidence is needed to determine whether certain ACEIs have the property of preventing Aβ degradation and, consequently, exacerbating AD neuropathology in the brain.

**Calcium channel blockers (CCBs)** Paris et al. compared dihydropyridine (DHP) calcium channel blockers (CCBs) (felodipine, nifedipine, amlodipine, nilvadipine, nitrendipine, nimodipine, and isradipine) and non-DHP CCBs (verapamil

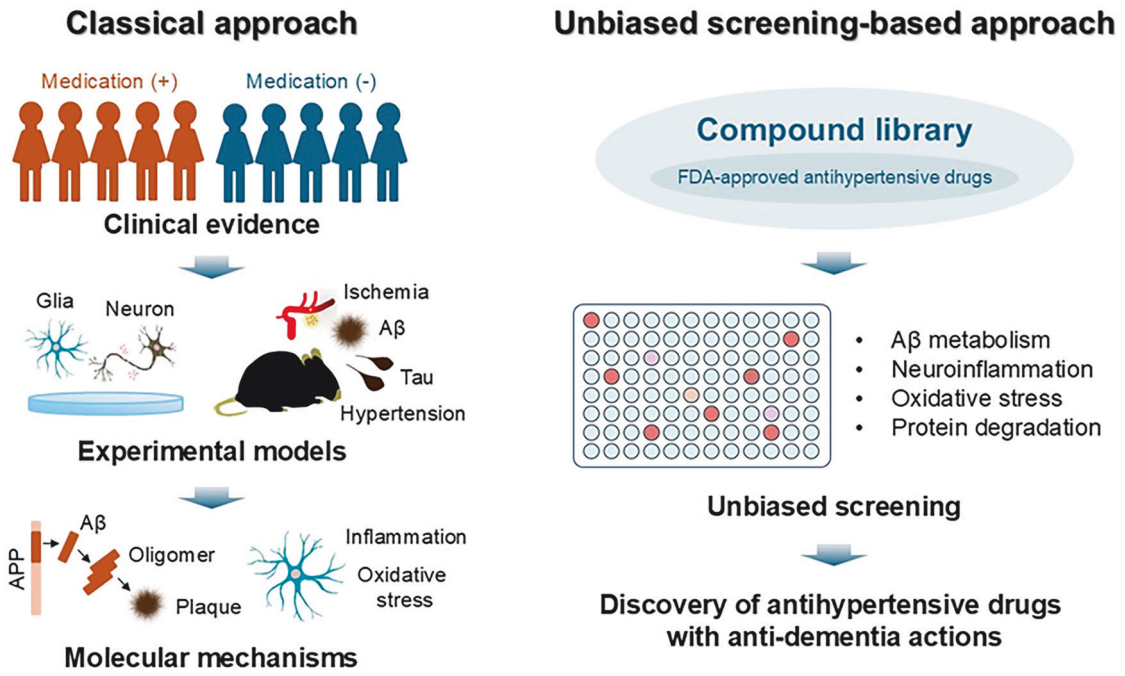



**Fig. 5** Approaches to identify antihypertensive drugs with potential therapeutic effects on dementia. The classical approach focuses on specific types of antihypertensive drugs that have been proven to exert favorable effects on dementia in clinical studies and investigates their mechanisms using validated experimental models. The screening-based approach enables us to uncover unknown effects of antihypertensive drugs on the pathogenesis of dementia without a priori knowledge of clinical evidence. APP amyloid precursor protein

and diltiazem) for their potential effect of modulating Aβ metabolism in both in vitro and in vivo AD models. They reported that DHP CCBs, but not non-DHP CCBs, significantly reduced Aβ accumulation [199]. Another type of DHP CCB (nicardipine) prevented neurodegeneration in the brain of hypertensive rats through mechanisms independent of its blood pressure-lowering effect [200]. Reducing blood pressure variability through DHP CCB (amlodipine) treatment successfully ameliorated cognitive impairment and breakdown of the blood–brain barrier in an aged hypertensive mouse model (BPH/2 J) [201]. DHP CCBs (lercanidipine, manidipine, and nimodipine) repaired hypertension-induced brain damage, such as hyperplasia of glial fibrillary acidic protein (GFAP)-positive astrocytes in the brain of hypertensive rats [202]. Memory deficit and neuroinflammation in a mouse model of traumatic brain injury (TBI) could be ameliorated by treatment with a DHP CCB (nilvadipine) through inhibition of splenic tyrosine kinase (SYK) [203]. Ischemia-induced delayed neuronal death in hippocampal neurons was prevented by treatment with a DHP CCB (lercanidipine) in a hypertensive rat model [204]. Long-term treatment with a DHP CCB (amlodipine), but not a β-blocker (atenolol), attenuated the increase in cerebrovascular resistance observed in a hypertensive rat model [205].

**β-blockers** β-adrenergic antagonists are reported to ameliorate cognitive impairment induced by chronic administration of corticosterone in mice [206] and reduce the amyloid burden in an AD mouse model [207]. However, another study using an AD mouse model reported that chronic administration of β-blockers potentiated neuroinflammation and impaired cognitive behavior [208].

**Other compounds with antihypertensive effects** Other than the above-mentioned antihypertensive medications, drugs, or compounds with a potential blood pressure-lowering effect, such as traditional Chinese medical compounds [209–214], antioxidant carotenoids [215], and other plant-related products [216], are reported to have favorable effects against dementia in cellular and animal models. Modification of Aβ metabolism and reduction of oxidative stress are proposed as putative mechanisms underlying the anti-dementia actions of these compounds.

## Unbiased screening-based approach to identify antihypertensive drugs with anti-dementia properties

In contrast to the above-mentioned classical approach targeting a specific type of antihypertensive drug, the screening-based approach enables us to uncover the unknown effects of antihypertensive drugs on the pathogenesis of dementia without a priori knowledge of clinical evidence. Here, we review recent findings derived from such unbiased screening-based approaches (Fig. 5).

Wang et al. [217] aimed to identify antihypertensive drugs, among 55 currently prescribed antihypertensive medications, that can reduce Aβ generation and its oligomerization to toxic species via a high-throughput screening system. They first found that seven of 55 antihypertensive drugs significantly reduced Aβ generation in a primary neuronal cell culture derived from an APP-Tg AD mouse model (Tg2576). These seven drugs represented six pharmacological subclasses, including a β-blocker (propranolol), an α/β-blocker (carvedilol), ARBs (valsartan and losartan), a CCB (nicardipine), a diuretic (amiloride), and a vasodilator (hydralazine). Among the seven antihypertensive drugs, valsartan was able to prevent oligomerization of Aβ into a neurotoxic species. Then, the authors evaluated the efficacy of valsartan in vivo in the APP-Tg AD mouse model (Tg2576). Valsartan treatment successfully prevented the development of amyloid neuropathology and attenuated cognitive impairment. Importantly, these effects were achieved at below the recommended human equivalent dosage of the drug, with minimal impact on blood pressure.

Furthermore, the same group of researchers has conducted more comprehensive screening assays. They screened 1600 Food and Drug Administration (FDA)-approved drugs, which included 115 cardiovascular drugs representing all pharmacological classes, to identify drugs that could potentially affect Aβ production and cerebral accumulation [197]. In the initial screening with a primary neuronal culture derived from an APP-Tg AD mouse model (Tg2576), they identified 184 FDA-approved drugs that significantly reduced Aβ production, 13 of which were related to cardiovascular treatment. They observed that seven anti-hypertensive drugs (carvedilol, propranolol, valsartan, losartan, hydralazine, nicardipine, and amiloride), representing different pharmacological subclasses, were able to reduce Aβ production in a dose-dependent manner. Among the candidate drugs, nicardipine and propranolol decreased the cerebral accumulation of both Aβ40 and Aβ42 species in the brain of APP-Tg AD mice following a one-month course of treatment.

Pauls et al. identified some anti-hypertensive drugs with therapeutic potential against AD pathogenesis using a unique unbiased data-driven approach [218]. First, they performed comprehensive transcriptomic and proteomic analyses of brain tissues from three distinct AD mouse models (AppNL-F, AppNL-G-F, and 3xTg-AD mice) at different time points and found common molecular patterns representing progression of AD pathogenesis, which they called the "biological signature of AD". Then, they screened more than 800,000 bioactive compounds to identify small molecules with the potential to reverse the biological AD signature using a computer-based machine-learning approach. This approach identified 8250 candidate compounds that could potentially reverse the AD signature; this included a number of antihypertensive drugs. Among the candidate antihypertensive drugs, bendroflumethiazide and penbutolol had the highest scores in terms of AD-signature reversing properties. Indeed, treatment with these antihypertensive drugs reversed cognitive impairment in AD mouse models. Penbutolol reversed the AD molecular signature and decreased the cerebral accumulation of Aβ in the treated animals. Notably, these drugs have not previously been tested in clinical trials or mouse models of AD.

A growing body of evidence supports the critical role of inflammation in the pathogenesis of dementia, including AD, and RAS may be involved in this neuroinflammation. Gouveia et al. [105] conducted comprehensive pharmacological in vitro and in vivo screening to investigate the effects of RAS-acting drugs on neuroinflammation. First, three ARBs (irbesartan, valsartan, and losartan) and three ACEIs (enalapril, lisinopril, and captopril) were screened in a BV-2 microglial cell culture model with LPS stimulation. Among these RAS-acting drugs, irbesartan most potently inhibited the production of inflammatory cytokines in vitro. Then, the authors evaluated the efficacy of irbesartan in vivo using an LPS-induced neuroinflammation mouse model with cognitive impairment. Intranasal administration of irbesartan significantly ameliorated LPS-induced cognitive impairment, which coincided with modification of the PI3/AKT pathway, dendritic spine density, and oxidative stress.

Siddiqi et al. [219] screened FDA-approved CCBs to identify drugs with autophagy-inducing properties that potentially degrade neurodegenerative disease-associated proteins such as tau (in tauopathy, including AD), α-synuclein (in Parkinson's disease), and mutant huntingtin (in Huntington's disease). Of note, they aimed to identify drugs capable of inducing autophagy in the brain at concentrations that are achievable in humans without side effects. They first selected five CCBs with a BBB-penetrant and a long half-time among all FDA-approved CCBs (nimodipine, isradipine, felodipine, diltiazem, and verapamil). In the primary in vitro screening using a cell culture model to evaluate autophagy activity, felodipine caused the greatest increase in the number of autophagosomes. They then confirmed that felodipine could decrease the amount of insoluble tau in two zebrafish transgenic models of tauopathy, demonstrating its in vivo efficacy. Finally, they demonstrated that felodipine reduced the cerebral accumulation of insoluble α-synuclein in a transgenic mouse model of Parkinson's disease expressing A53T mutant α-synuclein. Notably, this reduction of α-synuclein was associated with improvement of motor impairment and prevention of neuronal cell death in the substantia nigra. Felodipine treatment also improved motor function in a mouse model of Huntington's disease (B6HD mice).

Michaels et al. [220] investigated the molecular mechanisms underlying axonal loss occurring in the brain

of AD and vascular dementia models and revealed that age-related microglial NOX activation plays a critical role. They conducted systematic screening aimed at identifying candidate drugs with antioxidant properties using the drug library of the US Drug Collection. Among over 1000 compounds, they found that indapamide, a diuretic with good evidence of BBB permeability, had a significant antioxidant property. Indapamide inhibited extracellular superoxide generation in a microglia-enriched culture. Furthermore, indapamide treatment in middle-aged mice reduced demyelinated lesion volume and axonal loss in a pharmacological model of axonal injury.

## Various treatment strategies for AD in relation to hypertension

The effects of azelnidipine, a DHP CCB used for the treatment of hypertension, on oligomeric Aβ (oAβ)-induced calcium influx and its downstream pathway were assessed in immortalized mouse cerebral endothelial cells (bEND3); azelnidipine was shown to suppress oxidative stress and inflammatory responses in Aβ-stimulated microvasculature in an AD model [221]. Oxidative stress is a factor causing dementia such as AD and VaD. In VaD, NOXs are a molecular source of ROS, and inhibition of NOX activity can reduce cognitive impairment in animal models of VaD [222]. Oxidative stress-induced neuronal damage and expression of genes linked with neuroinflammation were ameliorated by African star apple fruit pulp in rats given cyclosporine (25 mg/kg.bw) to induce hypertension; it mitigated the effect of high blood pressure on brain neurochemicals associated with AD [223].

In the BPH/2 mouse, a polygenic model of hypertension, small cerebral resistance arteries that run across the surface of the brain (pial arteries) showed enhanced pressure-induced constriction due to diminished activity of BK channels—key vasodilatory ion channels of cerebral vascular smooth muscle cells [224]. This pathogenic mechanism is responsible for the observed increase in constriction and may be targeted as a possible avenue for restoring healthy CBF in vascular dementia.

SHR can be used as a model for studying learning impairment and reduced central nicotinic receptors, which persist and worsen with age [225]. SHR showed upregulation of cholinergic markers, vesicular acetylcholine transporter (VAChT) and choline acetyltransferase (ChAT), which suggests that AhE inhibition may exert beneficial effects on cholinergic neurotransmission in an animal model of VaD [226]. Galantamine and the cholinergic precursor choline alphoscerate showed neuroprotection in SHR [227–229]. The chromogranin A-derived peptide catestatin (CST) exerted potent antihypertensive and neuroprotective effects plausibly through gamma-aminobutyric acid (GABA)ergic output in SHR, and constitutes a novel potential therapeutic measure to correct impairment of blood flow control in disorders such as stroke and AD [230].

Intravenous infusion of mesenchymal stem cells (MSC) elicited functional recovery in SHRSP through restoration of BBB function via remodeling of the microvasculature and inhibition of Aβ accumulation [231]. The infused MSC activated both transforming growth factor-beta and angiopoietin 1 signaling pathways.

The anti-hypertensive agent ifenprodil has neuroprotective activity through its effects on N-methyl-D-aspartate (NMDA) receptors [232]. A centrally acting ARB, candesartan, was found to exert an anti-inflammatory effect in a model of brain inflammation induced by LPS treatment, which may be translatable to treatment of brain disorders such as AD [233]. Microglial TREM2 (triggering receptor expressed on myeloid cells 2) mitigates inflammatory responses and neuronal apoptosis in angiotensin II-induced hypertension in middle-aged mice [234]. By use of a transgenic C. elegans worm that expresses human Aβ1-42, atrial natriuretic peptide (ANP) was found to delay Aβ-induced worm paralysis, decrease Aβ plaques in the worm brain, and reduce ROS production, suggesting that ANP possesses a novel biological function as an Aβ inhibitor, in the nonaggregated state [235]. Irisin, a hormone cleaved from fibronectin type-III domain-containing protein 5 in response to exercise, was shown to repair damage caused by midlife cardiovascular risk factors such as hypertension, prevent neural Aβ aggregation, and reduce neuroinflammation. In transgenic htau mice, irisin reduced ptau in the hippocampus in only female htau mice, but not in male htau mice [236].

In silico computational strategies for drug candidate selection identified bumetanide, a loop diuretic which inhibits the kidney $Na^+$-$K^+$-2Cl- cotransporter isoform NKCC2 and is used for treatment of hypertension, as a top candidate agent that reverses APOE4 transcriptomic brain signatures and improves memory deficits in APOE4 animal models of AD [237].

2K1C (two-kidney, two-clip) renovascular hypertension-induced impairment of behavioral, biochemical, and endothelial parameters was attenuated by treatment with ulinastatin or quercetin alone as well as in combination [238]. The 2K1C hypertension model shows a significant increase in brain inflammation, oxidative stress, and endothelial dysfunction with memory impairment recapitulating VaD, which was ameliorated by agomelatine, a melatonergic MT1/MT2 agonist, nicorandil, a selective ATP sensitive potassium (KATP) channel opener, and donepezil [239]. Endothelin-1 antagonism with bosentan ameliorated renovascular hypertension-induced VaD [240]. Venlafaxine, a specific serotonin-norepinephrine

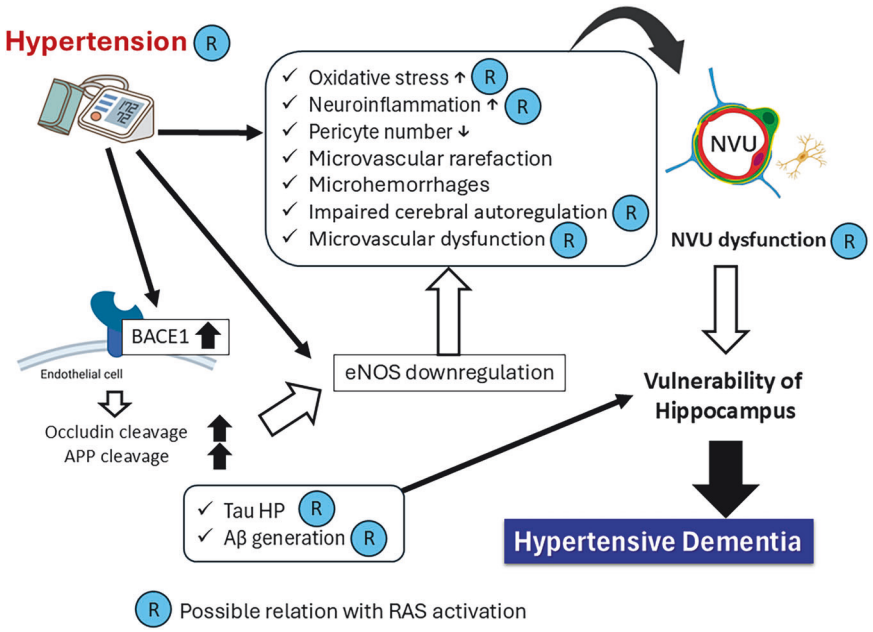



**Fig. 6** Schematic presentation providing comprehensive overview of key mechanisms of hypertensive dementia. Hypertension affects the metabolism of Aβ and induces NVU dysfunction through vascular disorders, increased oxidative stress, and neuroinflammation, leading to vulnerability of the hippocampus. Decreased eNOS affects various aspects, and activation of the renin-angiotensin system modifies each mechanism. Aβ amyloid beta, APP Aβ precursor protein, BACE1 β-site amyloid precursor protein cleaving enzyme 1, eNOS endothelial nitric oxide synthase, NVU neurovascular unit, HP hyperphosphorylation, RAS renin-angiotensin system

reuptake inhibitor (SNRI), was also shown to be effective on brain pathology observed in the 2K1C hypertension VaD model [241].

Vasopeptidases, such as neprilysin (NEP), are known to degrade Aβ peptides; therefore, NEP inhibitors used as antihypertensive drugs may induce Aβ accumulation and influence AD risk [242, 243]. Thus, the safety of the use of sacubitril/valsartan (LCZ696), a drug approved for heart failure, for cognitive function should be assessed, especially in the case of long-term administration [244].

Other drug candidates for AD include phytochemicals [245], melatonin [246], and miR-124 inhibitors [247]. These interventions may represent an important strategy for prevention or attenuation of the progression of dementia.

## Other therapeutic strategies for protection of cerebrovascular network

Bailey et al. performed mRNA microarray and found that salt exposure increased oxidative stress, activated microglia, and reduced myelin integrity in SHRSP [248]. Of note, dietary salt stimulates Th17 polarization in the gut, increased circulating IL-17. IL-17 can act as a suppressor of NO production, leading to endothelial dysfunction [249, 250]. A high-fat diet is also associated with cerebrovascular network dysfunction. In 5XFAD mice, a high-fat diet increased NOX, upregulated hippocampal oxidative stress, and enhanced cerebrovascular beta-amyloid deposition, leading to cognitive dysfunction [251]. Other research groups reported that a diet high in saturated fats, salt and refined sugar induced hypertension, blockage of brain microvessels and white matter atrophy in Sprague-Dawley rats [252]. On the other hand, a diet supplemented with high acetate and butyrate, releasing high amounts of short-chain fatty acids, regulated intestinal energy metabolism, suppressed immune cell recruitment, and delayed cognitive decline in 5XFAD mice [253].

A sex hormone, estrogen, is also related to cerebral blood flow and increases glucose transport across the blood-brain-barrier. In addition, estrogen decline can suppress the inflammatory response such as increased TNF-alpha and stimulation of TH17 T-cells [254]. Pradhyumnan et al. administered estrogen receptor subtype-beta in a transient MCAO (tMCAO) model of elderly Sprague-Dawley female rats, and found that this treatment decreased hippocampal neuronal death and improved cognitive function, suggesting that estrogen treatment has potential for future clinical investigation [255].

As another therapeutic agent to protect the cerebral vascular network, glucagon-like peptide 1 (GLP-1) has attracted attention. GLP-1 is involved in cellular energy metabolism, and some studies have shown that GLP-1 treatment improves brain glucose metabolism in AD [256]. Recently, Zheng et al. reported that GLP-1 treatment improved cognition in 5xFAD mice through enhancing aerobic glycolysis and suppression of oxidative stress [257]. Resveratrol is a natural polyphenol with anti-inflammatory properties. Interestingly, there is some evidence that resveratrol treatment increases GLP-1, which is secreted by intestinal L cells, attenuates the gut microbiome pattern, and suppresses inflammation in the brain [258]. Treatment with resveratrol attenuated hypertension-induced oxidative stress, suppressed vascular matrix metalloproteinase activation, and reduced cerebral microhemorrhages [146]. These findings indicate that both control of the

**Table 2** Summary of animal models with experimental results of hypertension-related stimulation or treatment

| Mice | | | | |
|---|---|---|---|---|
| Strains | Treatment | How to create model animals | Effects of hypertension or hypertension related stimulation or treatments | Reference |
| 3xTg-AD | | Tg mice expressing PS1M146V, APPSwe and tauP301L transgenes | Captopril does not influence cerebral Aβ level | [198] |
| 5XFAD | | Tg mice expressing both human APP carrying familial Swedish (K670N, M671L), Florida (I716V) and London (V717I) mutations and and human PS1 harboring two FAD mutations, M146L and L286V. | Intranasal administration of captopril reduces brain inflammation and amyloid burden | [179] |
| | Ang II infusion | 5XFAD with 4 weeks Ang II infusion | Ang-(1-7) counteracts Ang II-induced cognitive impairment | [123] |
| | BCCAO | 5XFAD with transient cerebral ischemia induced by BCCAO | Olmesartan suppresses cognitive decline via reduced oxidative stress | [98] |
| AKR/J | Corticosterone Tx | AKR/J mice received 100 μg/ml corticosterone in drinking water for 4 weeks | Propranolol restores cognitive deficits associated with reduced Aβ and tau phosphorylation | [206] |
| APP23 | | Tg mice expressing human APP carrying familial Swedish (K670N, M671L) mutations | Olmesartan treatment reduced microvascular oxidative stress and suppressed cognitive decline | [97] |
| | | | Metoprolol induces synaptic phagocytosis and impairs cognitive function | [208] |
| APP J20 | | Tg mice expressing human APP carrying familial Swedish (K670N, M671L) and Indiana (V717F) mutations | AT2 receptor agonist (Compound 21) normalizes neurovascular coupling, and reduces astrogliosis and dense core Aβ plaques | [115] |
| | | | Candesartan reduces neuroinflammation but does not change amyloid burden or cognitive function | [180] |
| APP J20 and Tg2576 | | Transgenic mice with mutant APP associated with FAD | Captopril increases brain amyloid deposition | [196] |
| APP/PS1 | | Transgenic mice expressing a chimeric mouse/human APP (Mo/HuAPP695swe) and a mutant human PS1 (PS1-dE9) | Intranasal losartan exerts direct neuroprotective effects via Aβ-reducing and anti-inflammatory effects | [93] |
| | | | Telmisartan alleviates cognitive impairment by reducing Aβ accumulation | [182] |
| | Aging | APP/PS1 mice aged 16–18 months, when they naturally develop hypertension and AD-like pathology | Elevated systolic blood pressure reduces cerebral blood flow and functional connectivity, promotes neuroinflammation, and impairs cognition, modeling early vascular contributions to AD | [167] |
| | Ang II infusion | Subcutaneous infusion of hypertensive dose of angiotensin II via osmotic minipumps in APP/PS1 mice starting at 2 months of age | Enhanced amyloid plaque deposition, reduced cerebral microvessel density, impaired NO production, and early-onset cognitive deficits | [168] |
| APP/PS1 and APP23 | | Ang II (1 μg/kg/min for 28 days) via an osmotic minipump | Learning and memory and pathological cerebral amyloid load were not further impaired in both mice | [92] |
| APP/PS1 and C57BL/6 J | | Ang II (500 ng/kg per minute for 4 weeks) infusion | Impairment of CBF, functional connectivity, and cognition only in AD model mice | [85] |
| APP/PS1 and WT | TAC | TAC surgery performed to chronically increase pulse pressure in right carotid artery, mimicking localized systolic hypertension both in WT and APP/PS1 TAC-mice | Induced cerebral endothelial dysfunction, BBB breakdown, microvascular rarefaction, neuroinflammation, increased Aβ deposition, and cognitive decline | [169] |

**Table 2** (continued)

| Mice | | | | |
|---|---|---|---|---|
| APP/PS1 and Tg2576 | | Tg mice with mutant APP associated with FAD | Nilvadipine decreases Aβ burden in brain and improves memory function | [199] |
| Appwt/NL-F | | AppNL-F mice contain a humanized Aβ sequence with Swedish "NL" (KM670/671NL) and Beyreuther/Iberian "F" (I716F) mutations. | Penbutolol and bendroflumethiazide reduce Aβ plaques in brain and restores molecular signature of AD | [218] |
| Appwt/NL-G-F | | AppNL-G-F mice contain a humanized Aβ sequence with Swedish "NL" (KM670/671NL) and Beyreuther/Iberian "F" (I716F) mutations and Arctic mutation "G" (E693G). | Penbutolol and bendroflumethiazide reduce Aβ plaques in brain and restore molecular signature of AD | [218] |
| Astrocyte-specific AT1RKO | Aβ ICV injection | Aβ1–42 oligomers (400 pmol/3 μl/5 min) were stereotaxically administered right intracerebroventricularly in astrocyte-specific AT1RKO | Astrocytic AT1R contributes to Aβ-induced cognitive deficits and synaptotoxicity through β-arrestin2 signaling | [91] |
| AT2R KO | BCAS | BCAS performed by applying micro coils in AT2RKO | Cognitive impairment was more marked in AT2RKO than in C57BL6J | [108] |
| BPH/2 J | | Genetic model of spontaneous hypertension | Amlodipine attenuates memory impairment associated with reduced microglial activation | [201] |
| C57BL/6 J | Aging | Ten-month-old C57Bl/6 J mice used as middle-aged mouse model | Atorvastatin and captopril improved behavioral deficits | [193] |
| | High-fat, high-fructose diet | Wild-type mice maintained on high-fat, high-fructose diet for 24 weeks | Candesartan or UDCA did not alter BBB and cognitive function | [194] |
| | BCAS | BCAS performed by applying micro coils | AT2 receptor agonist (Compound 21) prevents cognitive impairment | [108] |
| | Ang II infusion | Ang II (250 ng/kg per minute for 30 to 45 minutes) infusion | Impairment of endothelial regulation of cerebral microcirculation by Ang II | [84] |
| | | Repetitive arousals (for 10 s every 2 min) during 12 h light-on for 30 consecutive days with or without Ang II (1000 ng/kg per min at infusion rate of 11 μl/h) | Hypertension sensitizes vascular responsiveness | [86] |
| C57BL/6 | | Ang II (600 ng/kg per minute for 2 weeks) infusion | Perivascular macrophages produce ROS and alter neurovascular regulation and affect cognitive impairment | [89] |
| | | Nonpressor dose of Ang II (200 ng/kg per minute for 2 weeks) infusion | Induction of cerebrovascular dysfunction and oxidative stress without elevating arterial pressure | [87] |
| | | | Induction of vasomotor dysfunction by inducing vascular oxidative stress involving subfornical organ | [88] |
| | LCA ligation | LCA ligation to induce myocardial infarction which induces VCID and HF | Glycosylated Ang-(1-7) peptide has cognitive protective effects via anti-inflammative effects | [124] |
| | LPS injection | Single intraperitoneal injection of LPS (1 mg/kg) | Intranasal irbesartan prevents cognitive decline by neuroprotection and anti-inflammatory effects | [105] |
| | Lysolecithin injection | Middle-aged (8–10 months of age) wild-type mice underwent experimental demyelination induced with toxin lysolecithin injected into white matter | Indapamide alleviates axon and myelin injury associated with decreased oxidative stress | [220] |

**Table 2** (continued)

| Mice | | | | |
|---|---|---|---|---|
| ddY | Aβ ICV injection | ICV injection of Aβ 1-40 into ddY mice | Telmisartan improves cognitive deficit partly due to PPARγ activation | [181] |
| hTau | TBI | hTau mice were subjected to repetitive brain injury (total of 5 hits with inter-concussion interval of 48 h), resulting in expression of six isoforms of human tau, but no expression of mouse tau | Nilvadipine reduces neuroinflammation via inhibition of P-SYK | [203] |
| KKAy | | Polygenic mouse model of T2DM | BBB disruption with swelling of astrocyte endfeet via overactivity of Ang II | [82] |
| P301S | | Mice overexpressing T34 isoform of tau | Phosphorylated tau isoforms level is decreased by lisinopril | [129] |
| SAMP8 | | Model of accelerated aging with features of sporadic AD | Ang-(1-7) is reduced and inversely correlates with Tau hyperphosphorylation | [121] |
| SNCA | | Tg mice expressing Parkinson's disease-causing A53T mutant α-synuclein protein | Felodipine induces autophagy and reduces α-synuclein level | [219] |
| Tg2576 | | Tg mice expressing human APP carrying familial Swedish (K670N, M671L) mutations | Some antihypertensive drugs differentially modulate Aβ production and accumulation | [197] |
| | | | Nebivolol reduces amyloid neuropathology in brain | [207] |
| | | | Valsartan lowers cerebral Aβ level and improves cognitive function | [217] |
| | | | ACE2 enhancer, DIZE, improved amyloid-related hippocampal pathology and cognitive deficits | [122] |
| Rats | | | | |
| Strains | Treatment | How to create model animals | Effects of hypertension or hypertension related stimulation or treatments | Reference |
| Long Evans | OVX | Ovariectomized female Long Evans rats at 3 months of age | Losartan was effective in reducing cognitive decline | [96] |
| OLETF | | Genetic model of metabolic syndrome | Olmesartan alleviated neurodegenerative processes including blood-brain barrier breakdown and synaptic reduction | [191] |
| SHR | | Genetically modified rat model of severe HT | Losartan improved cognitive function by regulating hypertension and improving neuroplasticity | [95] |
| | | | Neither Ang (1-7) nor iodine Ang (1-7) had an effect on cognitive function | [125] |
| | | | Eplerenone alleviated aldosterone-induced brain damage with increased cortical thinning and apoptosis | [133] |
| | | | Nicardipine alleviated microanatomical changes such as glial activation | [200] |
| | | | Dihydropyridine-type $Ca^{2+}$ channel blockers alleviated microanatomical changes such as glial activation | [202] |
| | | | Amlodipine and atenolol did not prevent brain damage | [205] |

**Table 2** (continued)

| Mice | | | | |
|---|---|---|---|---|
| | | | Induced sleep apnea, preBötzinger complex damage, neuroinflammation, and cognitive decline; worsened small vessel pathology and VaD | [158] |
| | | | Early BBB disruption in hippocampus prior to neuronal loss | [156] |
| | 4-VO/ICA | Stepwise bilateral occlusion of vertebral and internal carotid arteries is performed in young SHR and normotensive rats | SHR exhibited greater hippocampal and cortical neurodegeneration and persistent memory impairment compared to normotensive controls | [161] |
| | BCCAO | BCCAO surgery is performed in adult SHR and normotensive Wistar rats | SHR exhibited more severe BBB disruption, white matter injury, and spatial memory impairment compared to normotensive controls | [160] |
| | 2VGO | Bilateral placement of ameroid constrictors on common carotid arteries in SHR | Induced progressive white matter damage and working memory impairment with low mortality; replicated features of subcortical ischemic vascular dementia (SIVD) | [163] |
| | MCAO | Ten-week-old SHR underwent middle cerebral artery occlusion | Telmisartan prevented cognitive deficits via peroxisome proliferator-activated receptor-γ pathway | [190] |
| | tMCAO | 18-month-old SHR after 30-min tMCAO | AT2 receptor agonist (Compound 21) enhanced sensorimotor recovery and ischemic lesion resolution | [114] |
| | | 60-min tMCAO in SHR | RAS modulators preserved cognitive function, reduced cytotoxicity, and prevented chronic reactive microgliosis | [110] |
| | MCAO after OVX | 1 h MCAO in female SHR 3 months after OVX | AT2 receptor agonist (Compound 21) prevented cognitive impairment through vascular protection and restoration | [113] |
| | LPS injection | SHR received ICV injections of LPS | Perindopril attenuated cognitive impairment by reducing oxidative stress and RAGE activation | [192] |
| SHRSP | | Genetically modified rat model of severe HT with high risk of stroke | Early BBB disruption in hippocampus prior to neuronal loss | [156] |
| | | | Induced white matter damage, oxidative stress, neuroinflammation, and BBB disruption | [155] |
| | | | Intranasal losartan had neuroprotective, neurogenesis-inducing, and Aβ-decreasing effects through IL-10 pathway | [94] |
| | | | Telmisartan protected against cognitive decline via up-regulation of brain-derived neurotrophic factor | [183] |
| | tBCCAO | SHRSP underwent bilateral carotid occlusion for 10 min | Lercanidipine prevented ischemia-induced delayed neuronal death | [204] |
| | UCAO and high-salt diet | UCAO is performed at 12 weeks in SHR/SP rats fed JPD (16% protein, 0.75% potassium, 4% sodium) with 1% sodium chloride added to drinking water | Chronic hypoxia degraded tight junction proteins, increased BBB permeability, induced angiogenesis, and caused white matter injury; minocycline mitigated BBB disruption and promoted angiogenesis and oligodendrocyte survival | [162] |
| | High-salt, low-protein diet | SHRSP rats are fed JPD (consisting of 16% protein, 0.75% potassium, 4% sodium) with 1% saline in drinking water starting at | Induced tau hyperphosphorylation, neuroinflammation, and neurodegeneration; replicated structural brain damage and hypoperfusion observed in human VaD | [164] |

**Table 2** (continued)

| Mice | | | | |
|---|---|---|---|---|
| | | 11 weeks of age for 4 weeks to induce chronic cerebral hypoxia and hypertension-related vascular injury | | |
| SHR-SR | | Genetic model of severe hypertension | Telmisartan reduced accumulation of Aβ and phosphorylated tau | [184] |
| | | | Telmisartan protected neurovascular unit by reducing inflammatory reactions | [185] |
| | | | Telmisartan improved neuronal lipid metabolism in brain | [186] |
| | tMCAO | Twelve-week-old SHR-SR underwent tMCAO for 90 minutes | Telmisartan protected neurovascular function associated with reduced neuroinflammation | [188] |
| | tMCAO | Three-month-old SHR-SR underwent tMCAO for 90 min | Telmisartan reduced intracellular and extracellular Aβ accumulation | [189] |
| Sprague-Dawley | 2K2C | 2K2C surgery in Sprague-Dawley rats, named RHRSP | Induced cerebral hypoperfusion, BBB leakage, white matter injury, and cognitive decline | [157] |
| Wistar | BCCAO | Bilateral occlusion of common carotid arterie in rats | Centrally active ACE inhibitors including perindopril ameliorated cognitive impairment by inhibiting brain ACE activitiy | [178] |
| | | | Perindopril ameliorated cognitive impairment by augmenting cholinergic neurotransmission | [187] |
| | | | Induced chronic cerebral hypoperfusion, white matter damage, microvascular injury, and cognitive impairment | [159] |
| | DOCA-Tx | Chronic administration of DOCA (20 mg/ kg s.c., twice weekly for 90 days) | Nuclear factor kappa-B (NF-κB) inhibitor, NDDCT, as well as lisinopril attenuated hypertension-induced impairment of learning and memory, and endothelial dysfunction | [128] |
| | | | Telmisartan suppressed learning and memory deficits with endothelial dysfunction | [99] |
| | OVX | Seven days after OVX, D-gal (100 mg/kg/day i.p.) treatment daily for 6 weeks | Telmisartan had neuroprotective effects by increasing protective arm of RAS when used in combination with 17β-estradiol | [102] |
| | Aβ ICV injection | ICVr injection of Aβ (oligomeric Aβ; 200 pmol/20 μL, aggregated Aβ; 600 pmol/20 μL) after four-vessel transient cerebral ischemia | Telmisartan ameliorated impairment of spatial memory via its anti-inflammatory effect | [100] |

*Aβ* amyloid beta, *ACE* angiotensin converting enzyme, *AD* Alzheimer's disease, *Ang-(1-7)* angiotensin 1-7, *Ang II* angiotensin II, *APP* amyloid precursor protein, *AT1R* angiotensin II type 1 receptor, *AT2R* angiotensin II type 2 receptor, *BBB* blood brain barrier, *BCCAO* bilateral common carotid artery occlusion, *CBF* cerebral blood flow, *DIZE* diminazene aceturate, *DOCA* deoxycorticosterone acetate, *FAD* familial Alzheimer's disease, *HF* heart failure, *HT* hypertension, *ICV* intracerebroventricular, *JPD* Japanese permissive diet, *LCA* left coronary artery, *LPS* lipopolysaccharide, *MCAO* middle cerebral artery occlusion, *NDDCT* natrium diethyldithiocarbamate trihydrate, *NO* nitric oxide, *NT* normotension, *OLETF* Otsuka Long-Evans Tokushima Fatty, *OVX* ovariectomy, *PPARγ* peroxisome proliferator-activated receptor γ, *PS1* presenilin 1, *P-SYK* phosphorylated spleen tyrosine kinase, *RAGE* receptor for advanced glycation end products, *RAS* renin-angiotensin system, *RHRSP* stroke-prone renovascular hypertensive rat, *ROS* reactive oxygen species, *SAMP8* senescence-accelerated mouse prone 8, *SHR* spontaneously hypertensive rat, *SHRSP* stroke-prone spontaneously hypertensive rat, *SHR-SR* spontaneously hypertensive stroke resistant, *SNCA* α-synuclein, *SOVD* subcortical ischemic vascular dementia, *TAC* transverse aortic constriction, *TBI* traumatic brain injury, *Tg* transgenic, *tMCAO* transient middle cerebral artery occlusion, *Tx* treatment, *T2DM* type 2 diabetes mellitus, *UCAO* unilateral carotid artery occlusion, *UDCA* ursodeoxycholic acid, *VCID* vascular cognitive impairment and dementia, *VaD* vascular dementia, *VO* vessel occlusion, *WT* wild type, *2K2C* two-kidney, two-clip, *2VGO* 2-vessel gradual occlusion, *4-VO/ICA* 4-vessel occlusion/internal carotid artery

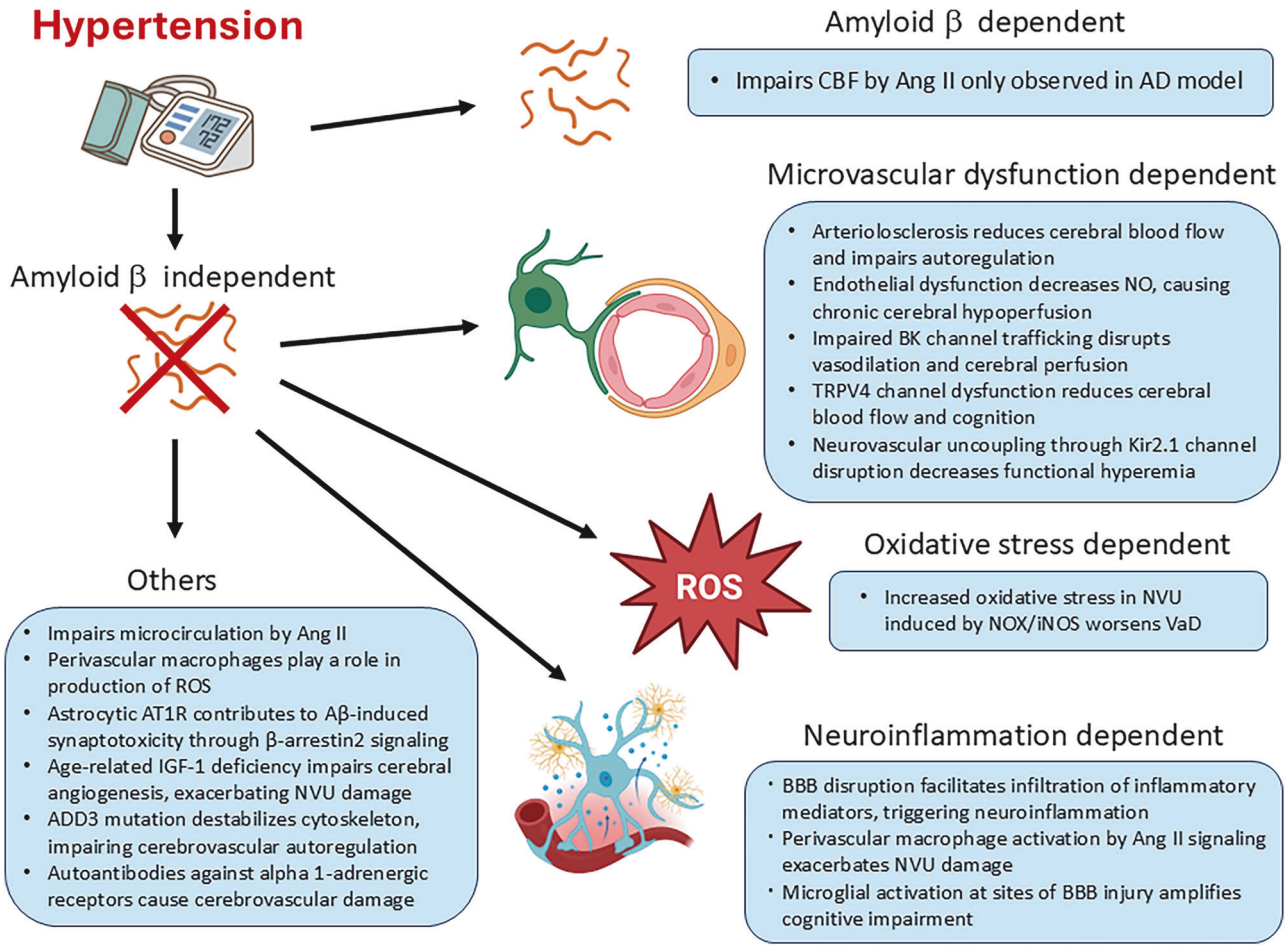



**Fig. 7** Visual summary of complexity and variety of molecular and cellular mechanisms of hypertensive dementia categorized based on key mechanisms. Functional, pathophysiological, and molecular-cellular research findings that induce hypertensive dementia through each key mechanism have been reported. Here is a summary of each key mechanism. Aβ amyloid beta, AD Alzheimer's disease, ADD3 adducin 3, Ang II angiotensin II, AT1R Ang II type 1 receptor, BBB blood brain barrier, BK channel large conductance calcium-activated potassium channel, IGF-1 insulin-like growth factor 1, iNOS inducible nitric oxide synthase, NO nitric oxide, NOX NADPH oxidase, NVU neurovascular unit, ROS reactive oxygen species, TRPV4 transient receptor potential vanilloid 4, VaD vascular dementia

oxidative stress/inflammatory response and maintenance of endothelial function are important to maintain the cerebrovascular network in a good condition. Potential drugs and compounds to prevent hypertensive dementia are summarized in Table 1, in the order in which they appear in the text.

### Asian perspectives

Taking into account clinical considerations, there may be differences in the mechanism of induction of hypertensive dementia between Asians and Westerners, as shown in Fig. 2; there may be more amyloid-independent mechanisms underlying the development of small vessel injury in Asians. In addition, the incidence of stroke is higher in Asia than in Europe and the United States, suggesting that cerebrovascular disease is more likely to occur in Asians than in Westerners [259]. Moreover, RAS activity in Asian subjects may differ from that in Western subjects due to differences in salt intake and salt sensitivity [260]. It is possible that certain diseases may be more likely to occur in Asians, and the presence of these diseases, combined with hypertension, may lead to the development of dementia. We anticipate that more effective preventive measures will be developed in consideration of the basic mechanisms of hypertensive dementia.

## Conclusions and perspectives

We herein present an update summary of basic research on hypertensive dementia, describing the factors and mechanisms and how they may induce hippocampal vulnerability,

and present a new screening method for anti-dementia drugs. We present a summary that provides an integrative and factor-specific view of the mechanisms of hypertensive dementia (Fig. 6). Table 2 summarizes the animal models included in the text and the effects of stimulation or treatment related to hypertension, as well as a comprehensive review of the molecular and cellular mechanisms of hypertensive dementia from basic research to date (Fig. 7). Unfortunately, it is frustrating that there is currently no conclusive interventional trial that can demonstrate whether treating hypertension can reduce the onset or progression of dementia, but there are numerous studies that have demonstrated that endothelial BACE1 increases and eNOS decreases albumin leakage, microglial activation, and inflammatory cytokines such as IL-1 beta, which will contribute to elucidation of the pathophysiology and early treatment of hypertensive dementia. The establishment of characteristic biomarkers for hypertensive dementia is also desirable. We hope this review will help in this regard. To confront the ongoing dementia pandemic, we should continue to make progress in basic research and develop clinically beneficial prevention and treatment methods based on the results of such research.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.



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