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Cerebral Hypoperfusion and Other Shared Brain Pathologies in Ischemic Stroke and Alzheimer's Disease

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Abstract

Newly emerged evidence reveals that ischemic stroke and Alzheimer's disease (AD) share pathophysiological changes in brain tissue including hypoperfusion, oxidative stress, immune exhaustion, and inflammation. A mechanistic link between hypoperfusion and amyloid β accumulation can lead to cell damage as well as to motor and cognitive deficits. This review will discuss decreased cerebral perfusion and other related pathophysiological changes common to both ischemic stroke and AD, such as vascular damages, cerebral blood flow alteration, abnormal expression of amyloid β and tau proteins, as well as behavioral and cognitive deficits. Furthermore, this review highlights current treatment options and potential therapeutic targets that warrant further investigation.

Keywords

Alzheimer's disease; Amyloid β; Cerebral blood flow; Hypoperfusion; Stroke; Tau protein; Treatment

Introduction

Alzheimer's disease (AD) and ischemic stroke have in common several cerebral pathophysiological alterations. AD, a neurodegenerative disorder, is the most common cause of dementia. It causes neuronal damage that leads to poor memory and learning difficulty [1–3]. AD is becoming increasingly ubiquitous, with prevalence at about 3.9% in people over 60 years old worldwide [4, 5]. The characteristic neurological changes

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seen in AD are often accompanied by additional vascular pathologies and features of other neurodegenerative diseases [6, 7]. Clinical studies have indicated that the burden of cerebrovascular disease in AD is higher than that in elderly controls [8], and both occlusion of cerebral large vessels and chronic cerebral hypoperfusion (CCH) contribute to the pathogenesis of AD [9, 10]. Similarly, ischemic stroke is also an age-related disease and a leading cause of morbidity, mortality, and disability worldwide [11–14]. Recently, ischemic stroke has been implicated as an exacerbating factor for AD [15, 16]. Compared to the damage ischemic stroke and AD each inflict, their co-morbidity results in worsened stroke-related motor control and AD-related cognitive deficits [17]. The complex interrelations between AD and ischemic stroke include cerebral hypoperfusion, energy deficit, inflammation, capillary dysfunction, immune exhaustion, oxidative stress, and change in the expression of some proteins, such as β-amyloid and tau protein. This review will discuss cerebral hypoperfusion and related shared pathologies in ischemic stroke and Alzheimer's disease, and will also highlight potential targets for therapeutic intervention.

Decreased Cerebral Perfusion and Metabolic Dysfunction in Ischemic Stroke

Vascular Obstruction and Hypoperfusion in Ischemic Stroke

An initiating event of acute stroke is the occlusion of a blood vessel that impairs blood flow to a certain degree, leading to infarction of brain tissue in the part of the brain supplied by that blood vessel [18]. Changes in the blood-oxygen-level-dependent (BOLD) signal provide a noninvasive measure of blood flow. Recent investigation of the relationship between BOLD signal temporal delay and dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) in stroke patients found that BOLD delay is related to macrovascular delay and microvascular hypoperfusion, and thus, BOLD signal can identify severely hypoperfused tissue in acute stroke [19]. Many factors participate in acute ischemic stroke, including thrombosis, embolism, and stenosis [20]. Ischemic strokes can be divided into embolic and thrombotic, the latter of which is the most common. An embolic stroke is caused by a blood clot or plaque fragment that blocks a cerebral blood vessel, while thrombotic stroke largely occurs secondary to atherosclerosis [21]. The vessel occlusion can occur in relation to a local vessel blockage typically in patients with intracranial atherosclerosis, artery-to-artery embolization from an internal carotid artery (ICA) plaque, or secondary to embolization of a thrombus from the heart to a brain vessel, in cases of atrial fibrillation [22, 23].

In acute ischemic stroke, critical hypoperfusion is a frequent cause of hypoxic brain injury. One report revealed that there was a significantly lower cerebral blood flow (CBF) velocity in the affected hemisphere within 72 h after stroke compared to controls. In addition, both cerebral autoregulation and the regulatory mechanisms responsible for neurovascular coupling deteriorated initially following stroke onset but returned to control levels during the recovery period [24]. A study of 40 acute stroke patients showed that within ischemic regions, mean CBF was lowest in the ischemic core (17 ± 23 mL/100 g/min), followed by regions of early (21 ± 26 mL/100 g/min) and late infarct growth (25 ± 35 mL/100

g/min; ANOVA $P < 0.0001$) [25]. It is reported that hemispheres with acute stroke had a significantly lower CBF and cerebral metabolic rate of oxygen and a significantly higher oxygen extraction fraction than the contra-lateral hemisphere [26].

The limited blood supply to the brain after focal ischemia can lead to oxygen starvation at the level of neuronal and endothelial cells. Moreover, hypoxic-induced capillary dysfunction can hinder the ability to extract oxygen, further causing tissue hypoxia and ischemia [27]. In response to the ischemic insult, the neurovascular coupling mechanisms will alter CBF to meet the oxygen demands of the cerebral tissue. Should supply be compromised, either by a clot or capillary dysfunction, the neurovascular junction compensates by increasing CBF. This can be accomplished, among other mechanisms, by stimulating pericytes, the contractile cells in the basement membrane of capillaries, to dilate and increase flow [28]. Thus, in the early stages of brain hypoxia, hyperemia is induced as a compensatory mechanism, via flow-metabolism coupling [27]. However, in conditions of prolonged ischemia, oxidative-nitrative stress occurs in cerebral vasculature, leading to persistent constriction of the pericytes [29]. When reperfusion occurred after 2 h of ischemia, pericytes remained contracted, contributing to capillary dysfunction and reduced CBF [30].

Cerebral Hypoperfusion-Mediated Changes in Ischemic Brains

As CBF falls below the ischemic threshold of 20 mL/100 mg/min, neurologic symptoms develop and hypoxic tissue injury evolves within minutes or hours, unless the oxygen supply is restored. Regions of cerebral ischemic injury in stroke can be divided into the ischemic core and the ischemic penumbra, both of which can be identified by computed tomography (CT) and magnetic resonance imaging (MRI) techniques [31]. There is little or no residual cerebral blood flow in the ischemic core, and energy failure occurs within minutes [32]. Conversely, there is initially moderate CBF reduction in the ischemic penumbra region, and there is the possibility to salvage the ischemic brain tissue so that infarction may not develop for several hours in this area [33].

In the event that blood flow to the brain is impeded or the cell is unable to extract the oxygen it needs, brain cells (especially neurons) fail to synthesize ATP via mitochondrial aerobic metabolism, and to compensate, they use the less efficient anaerobic glucose metabolism to generate energy [34]. Without sufficient ATP in the neurons, the sodium-potassium pump function is inhibited, causing intracellular Na^+ buildup within the neurons and osmotic-obligated water influx, resulting in cytotoxic edema [35]. The deficiency of ATP results in the release of excitatory neurotransmitters such as glutamate into the synapse, causing excitotoxicity [34]. The accumulation of intracellular Ca^{2+} also activates proteases and lipases, increases production of free radicals and reactive oxygen species (ROS), and stimulates the release of mitochondrial apoptotic factors into the cytoplasm [36]. Therefore, neuronal hypoxia sets off a cascade of events, culminating in neuron death [27].

β-Amyloid Deposition and Hyper-Phosphorylated Tau Protein in Ischemic Brains

Studies conducted during the last decade suggest that β-amyloid levels are inherently linked to brain ischemia. Lee et al. reported increased serum levels of β-amyloid, corresponding with the spread of infarction [37]. Another related protein that correlates to clinical

outcome is amyloid precursor protein (APP), a transmembrane protein with an intracellular C-terminal domain and an extracellular N-terminal domain [38]. APP is embedded in the axonal and somatodendritic compartments of the neuronal membrane, and can be cleaved and become insoluble monomer amyloid β (Aβ) after cleavage by β-secretase along with γ-secretase [1]. In a three-year longitudinal study assessing the influence of Aβ on cognitive decline after stroke/transient ischemic attack in subjects without Parkinson's disease (PD), patients with Aβ deposition experienced a more severe and rapid cognitive decline over 3 years after stroke compared with subjects without Alzheimer's disease-like Aβ deposition.

Aβ is associated with changes in multiple cognitive domains, when studied using murine models [30]. Most mouse models replicate AD conditions by upregulating APP to increase Aβ formation, a key mediator of pathology. However, the problem with this method of simulating AD is that other APP fragments, with unknown functions, besides Aβ are also overproduced. In 2014, Saito et al. developed APP knock-in mice, in which they introduced Swedish and Beyreuther/Iberian mutations to the APP gene (mutations demonstrated in AD progression), instead of simply upregulating the gene [39].

In follow-up studies, these mice displayed Aβ accrual, neuroinflammation, and progressive cognitive deficits that worsened with age, all classic hallmarks of AD. It was previously proposed that memory loss in AD occurs as a result of disruption in mushroom synaptic spines, located in hippocampal neurons, which are involved in long-term memory storage. Synaptic spine stability relies on synaptic Ca^{2+}/calmodulin kinase II (CaMKII), implying a dependence on maintaining appropriate Ca^{2+} levels within the neuron. Entry of Ca^{2+} into neurons is regulated by neuronal store-operated Ca^{2+} entry (nSOC) channel, which works alongside stromal interaction molecule 2 (STIM2). Sun et al. demonstrated, using a presenilinupregulated mouse model, that extracellular $Aβ_{42}$ upregulated the mGluR5 receptor, prompting increased Ca^{2+} in the endoplasmic reticulum (ER) and subsequent reduction of STIM2. This decreased influx of Ca^{2+} via nSOC and, thus, decreased CaMKII activity. The overall effect was destabilization of the mushroom post-synaptic spines [40]. In a follow-up study using APP knock-in mice, loss of mushroom spines in hippocampal neurons was prevented by inducing increased STIM2 expression and also by inhibiting mGlur45 receptor [41].

Another study investigated the effects of soluble oligomers of Aβ, increasingly thought to increase synaptotoxicity, on neuron and synapse stability. They used the APP E693Q "Dutch" murine model of AD, which allowed intracellular accrual of soluble Aβ, without forming any detectable plaques. The results demonstrated a significant decrease in the arborization of dendrites along with a decrease in dendrite length. Furthermore, there was a clear decrease in post-synaptic density (PSD) length of synapses on mushroom spines in the hippocampus. These findings support the theory that early cognitive deficits seen in AD are due to accumulation of soluble Aβ and the structural disturbances it causes [42].

In another study, approximately 30% of subjects with post-stroke/transient ischemic attack cognitive impairment demonstrated Alzheimer's pathology [43]. One study in experimental focal ischemia in female rats investigated the effects of comparatively small changes of cerebral blood flow on the expression of APP mRNA, and showed a twofold increase in

focal transient ischemic brain injury that remained elevated for 7 days following the insult [44]. Mice subjected to focal ischemia and also exposed to chronic unpredictable restraint stress exhibited an additional increase in multiple forms of Aβ oligomers (25 and 50 kDa oligomers) localized within the thalami of both hemispheres. Furthermore, Aβ oligomers, most notably the 30–40 and 50 kDa oligomers, are suggested to correlate with accelerated cognitive decline [45].

In addition, tau protein is found in the blood of 40–50% of patients in the acute phase of a stroke, caused by the degradation of neurons and damage to the blood-brain barrier (BBB) [46]. Compared with patients without tau protein, patients in whom tau protein was detected in serum developed more severe neurological deficits, had worse functional status measured in the early and late phases of ischemic stroke, and were found to have larger volumes of infarction. It was thus concluded that detection of tau protein in the serum of patients with ischemic stroke can be considered a prognostic factor for worse clinical outcome in early and late phases of ischemic stroke [47]. Another study in primary cortical neurons showed that tau proteins had blocked transport of APP from the neuron body into the axons and dendrites, causing APP accumulation in the soma [48]. One study reports that hyper-phosphorylated tau protein accumulation in cortical neurons co-localizes with markers of apoptosis. Similarly, ptau-positive cells increased in the CA1 region of the hippocampus in a time-dependent manner in rats with cognitive dysfunction induced by cerebral hypoperfusion. Cerebral hypoperfusion can cause and aggravate the phosphorylation of tau protein in the brain, leading to cognitive dysfunction [49]. Chronic cerebral hypoperfusion for 2.5 months in mice caused significant short-term memory deficits, mild long-term spatial memory impairment, as well as increased level of tau phosphorylation, suggesting that chronic cerebral hypoperfusion causes cognitive impairment and contributes to Alzheimer’s pathology [50].

The sudden death of neurons occurs due to inadequate blood flow in the ischemic stroke brain [51]. After a stroke, significant impairment in language, cognition, motor, and sensory skills develops [52]. The mechanisms of post-stroke cognitive impairment are not fully understood. Some suggest that post-stroke cognitive impairment is secondary to either ischemia or Alzheimer’s disease promoted by stroke, while others suggest the two mechanisms work synergistically to cause neurological deficits [53].

Alzheimer’s Disease

AD can be classified as sporadic or familial. Sporadic AD accounts for 90–95% of cases, is late-onset, and thought to be the result of genetic and environmental factors. Genetic studies have implicated the e4 allele of apolipoprotein E (apoE4) as contributing to increased risk of AD. Apolipoprotein E helps degrade β-amyloid plaques; however, the e4 allele, in patients predisposed to AD, is shown to be less effective at clearance than the e2 allele, seen more prevalently in the general population. Specifically, apoE4 is the target of neuron-specific proteolysis, resulting in damaging byproducts that enter the neuron, weaken its infrastructure, and damage the mitochondria, ultimately contributing to neuronal death [54]. Patients that inherit one allele of e4 are at an increased risk for AD as well as cerebral amyloid angiopathy (CAA), a disorder defined by the deposition of fibrillar Aβ within

cerebral vasculature. Furthermore, patients that inherit two alleles of e4, one from each parent, are very likely to develop AD [55].

Familial AD is seen in 5–10% of cases, is early-onset, and results from several possible gene mutations that escalate progression of disease. The PSEN-1 gene on chromosome 14 and the PSEN-2 gene on chromosome 1 encode presenilin 1 and presenilin 2 proteins, respectively. Presenilin 1 and 2 are the protein subunits of γ-secretase, the enzyme that cleaves the transmembrane domain of APP. Mutations in the genes encoding these proteins alter the activity of γ-secretase, which cleaves APP yielding longer Aβ monomers in its altered form. These modified fragments are more conducive for aggregation and plaque formation, contributing to the pathogenicity of this gene mutation [1]. Another possible gene mutation that can cause AD is trisomy 21 (Down syndrome). The gene that encodes APP is located on chromosome 21, and thus, individuals with Down syndrome, having an extra gene, have increased neuronal expression of APP, causing increased Aβ formation. The predisposition of patients with Down syndrome to form Aβ (and subsequently β-amyloid plaques) contributes to their onset of familial AD by age 40 [55].

The Role of Aβ in the Pathophysiology of AD

APP is thought to aid in neuronal growth as well as repair after a CNS insult; however, its function in the CNS is not entirely elucidated [56]. α-Secretase is the enzyme that cleaves the extracellular domain of APP, yielding two fragments: the secreted soluble APP α (APPsα) as well as the APP intracellular domain (AICD). γ-Secretase acts on the transmembrane component of APP. The products of α-secretase and γ-secretase are peptide fragments that are soluble and non-binding, and can be recycled into forming APP on the neuronal cell membrane. However, if β-secretase cleaves APP along with γ-secretase, the resulting protein fragment is the insoluble monomer Aβ [1].

There are two variations of Aβ, Aβ40 and Aβ42, which adhere together extracellularly, forming β-amyloid plaques. These plaques can build up between neurons as well as form sheaths around neurons [56]. Pathology arises when the plaques are dense enough to hinder transmission of impulses and neuron-neuron signaling, ultimately impairing brain function. β-Amyloid plaque formation stimulates microglia activity, which phagocytose the plaques. In doing so, microglia secrete cytokines triggering an inflammatory response that causes further damage to the strained neurons in the region [1]. In addition to depositing on and around neurons, β-amyloid plaques can accumulate around the vasculature in the brain, usually around the intracortical and leptomeningeal arteries, arterioles, capillaries, and sometimes the veins. As a result of plaque deposition, vessel walls weaken from fibrinoid necrosis and are more prone to aneurysms. The plaque forms a hard, proteinaceous sheath around the blood vessel, physically impairing its ability to constrict or dilate [56]. The smooth muscle in the endothelium works harder under this strain, resulting in thickening of the tunica intima. Thus, the accumulation of β-amyloid plaques around vasculature in the brain causes CAA [57].

Contribution of Tau Protein to the Progression of AD

Increasing evidence suggests that phosphorylated tau is involved in the loss of synapses, defective axonal transport, and cognitive decline in patients with AD [58]. The recent development of in vivo tau PET radiotracers showed that Aβ and tau are associated with different aspects of memory encoding, leading to aberrant neural activity that is behaviorally detrimental. Additionally, there is evidence linking Aβ and tau-associated neural dysfunction to brain atrophy [59]. Increasing evidence suggests that serine/aspartyl proteasescaspases are activated in the AD brain. Previous studies identified a caspase-3 cleavage site within APP and caspase-3-mediated cleavage of tau as mechanisms involved in the development of Aβ and tau neuropathology, respectively [60].

Under physiological conditions, tau proteins serve an integral role in the maintenance of neuron structure and are not pathologic. The neuron is supported by its cytoskeleton, which provides its shape and aids in the delivery of nutrients and the transport of waste [61]. Composed of microtubules, the neuron cytoskeleton is stabilized by tau protein, which ensures that the skeleton will not degrade. As the β-amyloid plaques accrue outside the neuron, certain cellular pathways inside the neuron are stimulated, resulting in the phosphorylation of tau protein via a serine/threonine kinase. This modification induces tau proteins to change conformation, dissociate from the microtubules, and aggregate with other modified tau proteins to form neurofibrillary tangles in the cell body of the neuron. Loss of the stabilization of tau protein weakens the microtubules, making nutrient delivery and waste removal less effective, as well as hindering signaling between neurons [62]. Eventually, the neuron cannot bear the injury of tangles and metabolic waste products within the cell, undergoing apoptosis [1].

Tau protein aggregates are not restricted to the implicated neuron; in fact, it was first discovered in 2009 that dysfunctional tau proteins can spread in a “prion-like” fashion [63]. Essentially, intracellular aggregates of two or more tau molecules, called tau oligomers, are able to propagate in the brain, causing further neurodegeneration [64]. This occurs through a process called seeding: tau oligomers are formed within the neuron and released in endosomal vesicles; once in the extracellular environment, they can spread to other neurons, where their uptake is determined by the presence of heparan sulfate proteoglycans on the cell membrane [63]. The secretion of tau into the extracellular environment is thought to occur as a physiological answer to elevated buildup of neurofibrillary tangles in the neuron during progression of tauopathy [65]. Another mechanism of tau propagation is the translocation of tau oligomers through tunneling nanotubes between neurons [63]. Pathology occurs once these newly seeded tau oligomers promote phosphorylation and misfolding of functional tau proteins present on the neuron cytoskeleton [64].

Correlating Pathologic Neurodegeneration to Symptoms Observed in AD

Widespread neuronal death causes gross alterations to brain. First, the brain atrophies, causing narrowed gyri and widened sulci, and results in enlargement of the ventricles. The earliest areas affected are the temporal lobe, impacting learning and memory. The disease progresses to the frontal lobe, affecting thinking and planning. Next, the posterior temporal

lobe is modified, causing impaired communication. At severe stages of AD, the parietal lobe is damaged, causing disorientation [57].

Hypoperfusion in AD

Vasoconstriction and Capillary Dysfunction in AD

Blood flow to the brain is tightly regulated to coordinate the metabolic requirements of the tissue with the oxygenation it receives. This occurs through two mechanisms: at the micro-circulatory level through neurovascular coupling, while in larger vessels through autoregulation. Neurovascular coupling controls perfusion to small pericapillary areas, providing the capacity for each neuron to receive the nutrients it needs. Autoregulation assures the maintenance of relatively constant blood flow independent of blood pressure variations. AD modifies these pathways by inducing vasoconstriction and, ultimately, hypoperfusion. Specifically, the plaque buildup acts on the smooth muscle cells of the tunica media of the arterioles, leading to the narrowing of the lumen, and reduced blood flow to the tissue [55].

In addition to impacting the function of the smooth muscle cells in vasculature, patients with AD are prone to pericyte degeneration as well. These contractile cells express β-amyloid receptors. As the pathology of AD spreads and β-amyloid production is increased, β-amyloid peptides are internalized by pericytes, causing pericyte death. Pericytes are located on the periphery of capillaries, so the death of these cells surrounding capillaries, and the resulting fibrosis, causes a thickening around the vasculature and consequent vasoconstriction [55].

Animal models have demonstrated that application of Aβ40 and Aβ42 topically can cause vascular dysfunction. Mice genetically altered to have increased expression of APP on their neuron membranes have evidence of cerebral vasoconstriction secondary to the increase of endogenous Aβ40 and Aβ42 monomers, before they began to aggregate into β-amyloid plaques. This change occurs at the age of 2 months, impairing inherent autoregulation and neurovascular mechanisms that would compensate for this loss. Additionally, these mice have nicotinamide adenine di-nucleotide phosphate oxidase (NADPH oxidase) inhibited or inactivated by the deletion of Nox2, and demonstrate substantially more vasoconstriction than the mice with functional NADPH oxidase [55].

Presence of Aβ Impairs Nutrient Uptake and Neuron Metabolism

In patients with AD, multiple vascular mechanisms contribute to decreased blood flow and impaired nutrient uptake and neuronal metabolism. Cholinergic nerves from the basal nucleus innervate the pial arterioles of the cerebral cortex, causing vasodilation and increased blood flow. One study found that in patients with AD, these vessels of the cerebral cortex were denervated and, thus, more constricted. With less blood flow to the cerebral cortex, the neurons are not receiving the nutrients and oxygen they need to meet their metabolic demands, resulting in neurologic deficits like memory impairment [66]. Additionally, Aβ40 and Aβ42 monomers impair endothelial nitric oxide synthase (eNOS), which ordinarily produces nitric oxide to induce vasodilation. In fact,

these monomers enhance the production of endothelin-1 (EDN1), a vasoconstrictor, by upregulating expression of the ECE1 and ECE2 genes. It is also thought that accumulation of Aβ42 contributes to the enhanced synthesis of another vasoconstrictor angiotensin II, leading to hypoperfusion of the frontal cortex [55].

The functionality of neurons depends entirely on their ability to access and utilize glucose. When one region of the brain is activated, blood flow is increased to the region to meet the increased metabolic demand. Astrocytes are the supporting cells of the central nervous system, monitoring the level of neuron activity. Their endfeet surround blood vessels: should there be an increase in neuron activity, astrocytes can regulate the diameter of the blood vessel and regulate blood flow to the region. Blood vessels with β-amyloid plaques forming a constricting sheath around their diameter displace the astrocyte endfeet, hindering the ability of the brain cells to regulate blood flow as needed [47]. Patients with an autosomal dominant mutation predisposing them to familial AD were found to have a decrease in glucose uptake by brain vasculature a decade before disease onset, as evaluated by FDG-PET. The reduction of glucose uptake started in the precuneus and progressed along the cingulate gyrus, moving onto the parietal lobe and anterior occipital lobe, before spreading to the rest of the cerebrum. Similar results were observed in carriers of the ApoE e4 allele and patients with sporadic AD using arterial spin-labeled perfusion magnetic resonance imaging (ASLMRI) [55].

The hypoperfusion and deficits in glucose metabolism typically manifest in AD patients several years before the cognitive regression. Part of the damage they inflict involves triggering oxidative-nitrative stress, causing damage to neuron macromolecules, such as DNA and proteins, and mitochondria [67]. Mitochondria are the primary source for energy generation in the cell in the form of ATP. It has been hypothesized that deficits in this organelle may be at the heart of the progression of AD itself, as impaired production of ATP promotes production of ROS [68]. Increased presence of these toxic molecules in the neuron contributes to metabolic dysfunction and neurodegeneration [67].

It seems that a variety of factors including genetic predisposition, capillary morphology, and age contribute to the degree of capillary dysfunction. Initially, capillary transit time heterogeneity (CTH) rises, contributing the pathogenesis of AD as it decreases oxygenation to tissues. The resulting hypoxia and subsequent decrease in glucose uptake induce inflammation in the affected regions, prompting Aβ deposition and neurofibrillary Tau tangles. Clearance mechanisms are also disrupted, creating the progressively deteriorating state seen in AD patients [27]. In addition, a greater concentration of white matter hyperintensities (WMH) was seen in patients with familial AD years prior to onset of disease. The importance of cerebral hypoperfusion in the pathogenesis of AD is thus demonstrated by its correlation with the rate of cognitive decline seen in AD patients [55].

In addition to hypoperfusion, vascular cognitive impairment is recognized as a distinct group of interrelated vascular-based neurological insults that can accumulate and lead to dementia. Importantly, the pathology of vascular cognitive impairment extends far beyond brain destruction brought on by major stroke and also includes subclinical stroke, white matter changes such as hyperintensities and lipohyalinosis, small lacunar infarcts, cerebral

hypoperfusion, and compromise of the BBB [69]. Thus, the damage caused by vascular cognitive impairment can progress, culminating in dementia.

Shared Pathologies of Ischemic Stroke and AD

Risk Factors Predisposing Patients to Ischemic Stroke and/or AD

Given the similarities in hypoperfusion and cognitive decline seen during disease progression of both ischemic stroke and AD, several studies have tried to determine whether having one of the diseases affects a patient's predisposition to the other. Zhou et al. conducted a large meta-analysis and concluded that the risk of AD increases 1.6-fold in ischemic stroke patients [70]. Another such study, conducted over 12 years and with over 6000 patients, affirmed these findings, showing that patients who have suffered an ischemic stroke were more likely to also have AD, regardless of individual genetic factors [71]. The data on whether AD patients are at an increased risk to suffer ischemic stroke is less definitive. Chi et al. conducted a cohort study with 980 AD patients and reported that these patients were more likely to suffer intracranial hemorrhage and ischemic stroke [72]. This claim was not corroborated by the meta-analysis by Zhou et al. who could not conclusively determine an association between AD patients and an increased likelihood of stroke [70].

Ischemic stroke and AD have several risk factors in common including age, diabetes, hypertension, smoking, and hypercholesterolemia [27]. Additional shared risk factors include homocystinemia and ApoE e4 isoforms [72]. However, the most obvious shared condition shared by ischemic stroke and AD is of a cerebrovascular pathology, leading to hypoxia and neurodegeneration.

Cerebral Hypoperfusion-Mediated Changes in Affected Patients

Cerebrovascular deficit in both diseases occurs, in large part, because of capillary dysfunction. Initially, this loss is compensated for by increasing CBF, so even as capillaries become progressively less functional, the metabolic needs of the tissue are met. Because of the strain increased CBF causes with chronic hypoperfusion, a new adaptation is introduced, wherein the body shunts oxygenated blood from the capillaries to arterioles. This functional shunting allows more oxygen to be available to the brain. Thus, the initial hyperperfusion seen in the acute stages of the disease is replaced with hypoperfusion in cerebral capillaries [54].

The resulting hypoperfusion lowers oxygenation levels below what is needed to maintain metabolic function, eventually compromising neuron operation. In an animal study in rodents, CCH was induced by occluding arterial supply. This caused severe dysfunction within the neurons, including mitochondrial damage and impaired protein synthesis. The subsequent imbalance of metabolites and ROS formation created oxidative stress to the neurons, as well as to the supporting glial cells and epithelial cells. These deficits led to the neurovascular unit being compromised, resulting in further hypoperfusion, and a cycle of neuron function impairment and cognitive decline. In most cases of cognitive function loss, cerebrovasculature damage is observed, just as is seen in ischemic stroke [73].

Protein Kinase C in Ischemic Stroke and AD

In AD, the memory loss and progressive cognitive loss are attributed to neuron death, from aggregation of neurofibrillary tangles and senile plaques. Similarly, in ischemic stroke, lack of oxygenation in tissue leads to an increasing dependence on anaerobic metabolism by the neuron, depleting glucose levels, the only energy source the brain uses. Chronic strain leads to neuron and glial cell damage, causing irreversible injury and subsequent neurological deficits. Therefore, in both AD and ischemic stroke, neurodegeneration is evident during the progression of the disease, commonly brought on by lack of blood flow and nourishment to the tissue [54].

A potential target for therapeutic consideration in both AD and ischemic stroke is protein kinase C (PKC), which has several known functions including BBB maintenance, initiating restoration mechanisms, and being crucial to learning and formation of memory. There are several isoforms of PKC, which can be arranged as conventional (α, β, γ), novel (δ, ε, η, θ), and atypical (ι, ζ, N1–N3). Neuronal dysfunction and cognitive deficits have been linked to mutations of PKC. PKC mutations or conditions that impair the ability of PKC to migrate to appropriate locations in the cell have been shown to increase Aβ formation as well as contribute to the likelihood of the patient suffering from an ischemic stroke [74].

PKCα is associated with initiating protein synthesis, contributing to the support of the synaptic terminal and, thus, improving the formation of memory. It increases the risk of hemorrhage after an ischemic stroke, and has also been demonstrated to upregulate α-secretase, the enzyme that functions to degrade APP into soluble monomers, preventing Aβ aggregation. PKCβ has an active site with a Cα backbone, which contributes to its role in cognition. It also helps resolve disruption in the tight junctions of the BBB during hypoxia and tissue injury. PKCδ facilitates the release of ROS and consequent apoptosis following prolonged ischemia; essentially, it activates the matrix metalloproteinase-9 (MMP-9), increasing the permeability of the BBB, and leaving the tissue vulnerable to toxins and inflammation. PKCζ has a similar mechanism of action, also promoting disruption of the BBB during hypoxia, allowing a greater concentration of inflammatory mediators and cytokines to enter the previously restricted cerebrovasculature. PKCε has a catalytic domain which aids PKC migration from plasma membrane to nuclear membrane. It is thought that this function assists with object recognition and spatial memory formation. In addition, PKCε stimulates endothelin-converting enzyme to further break down Aβ40 and Aβ42, improving clearance of Aβ, and, thus, improves recovery of neurologic function. The greatest influence of the PKCs appears to be within the neurovascular unit. PKC clearly has an influence in the regulation of tight junction proteins, allowing dangerous toxins to enter and accumulate within the brain, damaging not only neurons, but supporting pericytes, astrocytes, and endothelial cells. With its vast therapeutic implications, PKC is a target for further investigation to benefit both ischemic stroke and AD [74].

Inflammation and Immune Exhaustion in Ischemic Stroke and AD

Neuroinflammation is thought to play a pivotal role in many diseases affecting the brain, including AD and stroke [75]. Decades of research investigating neuroinflammatory processes have supported the involvement of resident-surveying CNS cells (microglia/

astrocytes) in initiating innate immune responses that contribute to neurodegenerative disease pathology. Coordinated glial reactivity is required for efficient removal of pathogenic insults and cellular debris arising from tissue injury, as dysregulation of this CNS neuroinflammatory response contributes to the progression of neurodegenerative disorders including stroke [76] and AD [77].

Neuroinflammation is characterized predominantly by microglial activation, which can be visualized using positron emission tomography (PET). As resident brain macrophages, microglia are activated in stroke, where they exhibit their beneficial phagocytic function in clearing blood components released into the brain parenchyma. Under normal physiological conditions, macrophages from outside the CNS are unable to access the brain microenvironment. However, in cases where the CNS is responding to an insult, like the damage caused in neurodegenerative disorders like stroke, macrophage entry is facilitated into the brain parenchyma. Macrophages have the unique ability to express two activation states, depending on the environment it enters. Ordinarily, macrophages have restorative capacities, functioning mainly to eliminate debris and phagocytose invaders. However, upon encountering an inflammatory microenvironment, macrophages adopt the pro-inflammatory phenotype M1 [78]. Pro-inflammatory microglia activation worsens brain damage by activation of blood-derived leukocytes [79]. In addition, MI macrophages mediate the release of inflammatory molecules, including tumor necrosis factor α (TNF-α), growth factors, adhesion molecules, NADPH oxidase, and chemokines like interleukin 1β (Il-1β) [80]. The increased Aβ aggregation and burden of neurofibrillary tangles in the AD brain can stimulate the immune system and induce further inflammatory stress. Stabilization of the inflammatory cascade induces a positive feedback process, resulting in irreversible damage to brain cells [81–83].

An inflammatory response consists of activated macrophages and microglia, and innate immune cells, which has demonstrated to be both beneficial and detrimental in neurological repair [84]. Most responses of macrophages are self-limiting and diminish with senescence, but activated microglia’s increased expression of pro-inflammatory cytokines is maintained while chemotactic and phagocytic activities are downregulated. The senescence of macrophages and microglia has a negative impact on several neurological diseases, and the mechanisms underlying their age-dependent phenotypic changes vary from extrinsic microenvironmental changes to intrinsic changes in genomic integrity. Evidence now suggests that complex bilateral communication between the peripheral immune status and central immunity plays a key role in influencing various neuroinflammatory processes, including microglial activation [85]. This response involves biochemical, physiological, and morphological changes and is associated with the production of cytokines and secondary mediators that influence synaptic plasticity, cognition, and behavior [86].

Therapeutic Considerations

Although the hope to find a unified cure seems elusive, shared pathological mechanisms in ischemic stroke and AD imply that discovery of common leverage points for novel drugs may be feasible. In animal models of ischemic stroke or AD, several drugs have shown beneficial effects on reducing ischemic infarct, clearing Aβ40 and Aβ42 plaque

accumulation, or reversing cognitive deficits. These include melatonin, PKC-activator bryostatin-1 and yessotoxin, which inhibits the tau kinase, GSK3β, thereby reducing the concentration of phosphorylated tau protein and decreasing Aβ accumulation [74]. Additional therapeutic studies are summarized below.

Alleviating Hypoperfusion by Increasing Blood Flow and Reducing Capillary Dysfunction

Current therapies available include acetylcholinesterase inhibitors like donepezil and rivastigmine, which have been shown to increase cerebral perfusion and improve cognitive function. Additionally, the angiotensin receptor antagonist losartan also seems to increase blood flow to the region and improve neurologic response. Zibotentan targets the END1 receptor associated with vasoconstriction of the cerebral arterioles, as well as the pericytes that surround the capillaries. It is a selective inhibitor, meaning that while the modulatory function of the receptor would not be lost, the amount of vasoconstriction that contributes to disease progression would be lessened. By reducing the amount of vasoconstriction, zibotentan could provide therapeutic benefit by increasing blood flow to an ischemic region of the brain, improving cognitive function [65].

Targeting β-Amyloid by Reducing its Accumulation and Increasing its Clearance

It has been suggested that APP could be a potential therapeutic target, as documented by interactions between APP and proteins necessary to maintain cell structure after sustaining an injury, like calcium channels, glutamate receptors, and gene regulatory pathways. APP is also upregulated following both hypoxia and ischemic stroke. The soluble cleavage product of APP, APPsα, facilitates many of APP's neuroprotective functions [1].

APPsα confers neuronal protection through several of its interactions. First, it downregulates the activity of β-secretase, thus preventing the formation of Aβ40 and Aβ42, the monomers which aggregate to form plaques. Furthermore, APPsα has been shown to recruit microglia and influence calcium homeostasis and survival mechanisms, all of which facilitate the clearance of plaque. Thus, APPsα reduces the formation of plaque as well as enhances its clearance from the microenvironment. APPsα promotes anti-apoptotic pathways, such as activating CREB and NF-κB, modulating the activity of cyclin-dependent kinase 5 (CDK-5), and upregulating immediate early gene transcription factors. It also inhibits GSK-3β, reducing the phosphorylation of tau protein and, thus, reducing the formation of neurofibrillary tangles. In murine models, the intraventricular application of APPsα enhanced memory. Over-expression of ADAM-10, and the consequent increase in APPsα levels, leads to enhanced cortical synaptogenesis in vivo. Therefore, APPsα is suggested to have protective function following cellular injury and stimulates cognition [1].

The other soluble product of APP, its intracellular domain AICD, is also involved in several signaling mechanisms involving the MAPK pathway and Ras proteins. It also forms a complex with the Fe65 protein, after translocating to the nucleus. This complex mediates genes with survival and anti-apoptotic function. Interestingly, in the hippocampus, APPsα stimulated neuronal proliferation, whereas AICD actually hinders it. This suggests that the pathogenesis of AD may be reliant upon the balance between these APP fragments, a balance between neurogenesis and neurodegeneration [1].

The different secretases that stimulate APP catalysis may also prove to be promising therapeutic targets. Activation of the α-secretase promotes non-amyloidogenic pathways to yield the soluble monomers of APP. Melatonin activates α-secretase, while simultaneously inhibiting β-secretase and γ-secretase. Additionally, the activation of muscarinic acetylcholine receptors also increases α-secretase activity. Besides promoting α-secretase, studies are being conducted to understand the efficacy of inhibiting β-secretase and γ-secretase. However, complications arise in this situation because these secretases have more than one target and help mediate reactions besides APP catalysis [1]. Gambierol, a β-secretase inhibitor, was illustrated to decrease Aβ levels as well as reduce the phosphorylation of Tau.

The *N*-methyl-D-aspartate receptor (NMDAR) plays an important role in neuronal function. An established drug for AD, memantine, has been shown to inhibit NMDAR, but it also protects against cytotoxicity, proving to be beneficial in ischemic stroke. Other established therapies include L-type calcium channel blockers like nifedipine and nimodipine, which inhibit Aβ accumulation and ameliorate cognitive decline related to amyloid buildup in animal models [87].

Utilizing Neuroprotective Agents to Reduce Cognitive Decline

ROS have been demonstrated to play an intrinsic role in the progression of both ischemic stroke and AD. One of the major sources of ROS is NADPH oxidase, making it a potential therapeutic target. In murine models of cerebral hypoperfusion mediated by occluding the common carotid arteries, inhibition of NADPH oxidase showed promising results and improved cognitive function [88]. In Japan, edaravone, a free radical scavenger that can cross the BBB, has been approved to proactively treat infarct and cognitive insufficiency in ischemic stroke in part via reducing oxidative damage to the neurovascular unit [89]. Given that both ischemic stroke and AD share the elements of vascular damage and hypoperfusion and that edaravone has already been demonstrated to be beneficial in prophylactically treating ischemic stroke, it may prove to be beneficial against AD as well.

The therapeutic polyphenol resveratrol defends against cellular injury and death and slows the progression of diseases associated with aging. In a CCH rat model, resveratrol reduced synaptic plasticity and acted as a neuroprotective agent, lessening neuron damage and cognitive decline. Its mechanism of action and induction of neuroprotection was hypothesized to involve PKA-CREB activation [90].

Another possible avenue for therapeutics in the shared pathology of AD and ischemic stroke is the restoration of folates, which are nutrients needed for cerebral function. A genetic defect, methylenetetrahydrofolate reductase (MTHFR) dysfunction results in elevated homocysteine levels, which contributes to the progression of dementia. In a murine model, mice were placed on control diets or folic acid-deficient diets (FADD). Mice with MTHFR deficiency and on the FADD diet showed cognition defects and slower memory recall, as evidenced by the Morris water maze, as compared to the mice with the MTHFR deficiency and control diet. The mice on the FADD diet had folate insufficiency that was not compensated for by their diets, leading to elevated homocysteine levels.

Elevated homocysteine is indicative of nutrient starvation in the cortical tissue and reduced acetylcholine levels, increasing the probability of neurodegeneration [91].

To understand the effect of autophagy on cognitive deficits, mice were subjected to bilateral common carotid artery occlusion (BCCAO) to simulate CCH. The concentration of the autophagy proteins Beclin-1, light chain 3b, and P62 increased, and impairments in cognition were seen, along with neuronal damage in the hippocampus, which included white matter injury and Aβ deposition. These abnormalities persisted even after restoration of CBF [92]. It was thought that these effects may be neutralized by impairing the process of autophagy. Thus, the impact of fatty acid amide hydrolase (FAAH) inhibitor URB597 was tested in a murine CCH model to study cognition, evaluated by the Morris water maze. The autophagy proteins and mammalian target of rapamycin (mTOR) signaling pathway proteins were measured using Western blot and immunofluorescence. mTOR signaling proteins quantified the autophagy induced by CCH, which was reduced upon URB597 involvement and improved the cognitive function. Repeated treatment of URB597 demonstrated improvement of the damage caused by CCH, thus indicating that inhibiting autophagy has therapeutic benefit in slowing the progression of neurodegeneration and improving cognitive facilities [93].

Current Therapeutic Options

Currently, the administration of tissue-type plasminogen activator (tPA) within 4.5 h of stroke onset is the standard therapy for intravenous thrombolysis of the implicated clot and restoration of cerebral blood flow in ischemic stroke. In addition to this established treatment, several trials have shown the efficacy of using an intraarterial device within 6 h of suffering a stroke in patients with smaller ischemic cores. With the promise of intraarterial device intervention, it is warranted to study combination therapy with neuroprotective agents to prevent against reperfusion injury as well to increase its efficiency in patients who receive delayed treatment [18].

Another consideration is varying the doses of tPA, as higher doses have also been correlated to an increased hemorrhagic transformation (HT) rate. Ong et al. conducted a study with 274 patients who received tPA; the parameters measured were early neurological improvement (ENI) and early neurological deterioration (END) within the first 24 h. There was a 6-month follow-up for 260 patients. The standard dose of tPA at 0.9 mg/kg body weight and lower doses of 0.7 mg/kg body weight and 0.8 mg/kg body weight were compared. While the ENI and END of the lower doses did not vary significantly from those of the standard dose, the 6-month outcome was more promising for patients receiving the lower dose, likely because of decreased HT rate [94].

In addition to varying the dose of tPA, other studies investigated the use of other thrombolytic agents following stroke to aid in reperfusion. Li et al. conducted a study with 1071 patients to study the efficacy of intravenous desmoteplase administered 3–9 h after stroke. Parameters included reperfusion 4–8 h after administration of treatment, clinical outcome at 90 days, and predisposition to hemorrhage. Desmoteplase increased reperfusion following stroke, but it had no overt benefit compared with tPA in long-term outcome at 90

days. Interestingly, desmoteplase had higher rates of asymptomatic intracerebral hemorrhage but no change in symptomatic intracerebral hemorrhage when compared to tPA [95].

The accumulation of Aβ is one of the biggest contributors to the neurodegeneration in AD; so, agents that promote its clearance are widely researched. Abushouk et al. conducted a meta-analysis on 2380 patients to study the effects of the monoclonal antibody bapineuzumab, which targets Aβ for destruction. While the cerebrospinal fluid (CSF) concentrations of phosphorylated tau proteins were significantly reduced, there was little evidence to suggest bapineuzumab enhanced Aβ clearance. There was no clear improvement compared with the placebo group when patients were assessed using the Alzheimer's disease assessment scale (ADAS)-Cog11 or the mini-mental state examination (MMSE). In addition, there was an increased risk of cerebral edema in the group treated with the drug bapineuzumab [96].

The usage of vitamin E supplements (dose-independent) was investigated in patients with AD and mild cognitive impairment (MCI). Vitamin E is obtained through diet and has antioxidant functions. Three hundred and four patients with AD and 516 patients with MCI were involved in a trial measuring the efficacy to counteract neurological decline. There were no changes from baseline when using the ADAS-Cog subscale over 6–48 months, but less cognitive deficit was seen in AD patients using vitamin E over those using placebos when assessing with the Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory [97].

The effects of the agent latrepiridine on cognition and function were assessed in patients with mild to severe AD. Latrepiridine can modify a number of targets seen in the progression of AD, like correcting mitochondrial permeability and moderating voltage-gated Ca^{2+} channels. However, there was little clinical benefit using latrepiridine vs. placebo, as there was little improvement in cognition when measured with the ADAS-Cog or the MMSE. Interestingly, there was some behavioral benefit when the Neuropsychiatric Inventory (NPI) was used to assess the effectiveness of the drug, and there was no enhanced risk of adverse events vs. placebo [98].

Conclusion

AD and ischemic stroke are both age-related neurodegenerative diseases that have several associated pathologies including hypoperfusion, capillary dysfunction, oxidative stress, and production of toxic substances like Aβ. Given the intricacies of disease progression in both ischemic stroke and AD, a single, united cure may not be probable. However, as the two share a great deal of similarities in their pathologies, developing therapies that address these issues may benefit treatments of both diseases.

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