Aging and Stroke: The Human Condition

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Abstract

Stroke and aging-related cognitive decline are complex processes that are interconnected and influenced by immune/inflammatory processes. In this paper, we explore the relationships among the cardiovascular, immune and nervous systems that could account for the associated mechanisms between brain aging and stroke, and describe the influence of the immune system on stroke and aging-related cognitive decline and assess the potential that age-related dysfunction in mitochondria may contribute to both stroke and cognitive aging. We conclude that comorbid chronic inflammatory diseases contribute to stroke prevalence and severity and may also contribute to age-related cognitive decline, perhaps by compromising mitochondrial function.

Glossary of Abbreviations

AD: Alzheimer's Disease
aMCI: Amnestic Mild Cognitive Impairment
AMPA: α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
Aβ: Beta-Amyloid Protein
ApoE: Apolipoprotein E
APP: Amyloid Precursor Protein
ATP: Adenosine Triphosphate
BACE: Beta-Amyloid Cleavage Enzyme
BBB: Blood-Brain Barrier
DG: Dentate Gyrus
EC: Entorhinal Cortex
EPSP: Excitatory Postsynaptic Potentials
FDG: ^{18}F-fluoreodeoxyglucose
ICAM-1: Intercellular Ahesion Molecule 1
IL: Interleukin
LTP: Long-Term Potentiation
MCI: Mild Cognitive Impairment
MMPs: Matrix Metalloproteinases
NO: Nitric Oxide
OxPhos: Oxidative Phosphorylation
O_2: Oxygen
PET: Positron Emission Tomography
PSD: Postsynpatic Density
ROS: Reactive Oxygen Species
Tg: Transgenic
TNF-α: Tumor Necrosis Factor-α
VCAM-1: Vascular Cell Adhesion Molecule 1

Introduction

The Greying of America places an enormous stress on our health-care delivery system. The number of Americans in the ≥65 and ≥85-year-old categories is growing at a rate faster than younger segments of our population.[1] Because we are living longer, the number of chronic comorbid conditions is increasing in our elderly population and consumes the vast majority of health-care resources including doctor visits and prescription medications.[2] Due to their debilitating nature, Alzheimer's disease (AD) and ischemic stroke are the diseases contributing most of the health-care burden in elderly populations. AD is the leading cause of dementia and affects 5 million Americans annually at a current cost of $203 billion/year.[3] Stroke affects about 800,000 Americans annually and is estimated to cost a total of $72 billion/year.[4-6] Unfortunately, effective preventives and treatments for these conditions are not available, and the number of young stroke and AD patients is expected to rise.[7]

This review considers the effects of aging and comorbid cardiovascular diseases on cognitive decline and stroke. We will describe the normal course of cognitive aging, the effects of AD on this process, and the factors that may contribute to the effects of aging and stroke on cognition. Recent evidence suggests the relationships among cardiovascular disease, stroke and dementia are undeniable.[8]

Cognitive Aging and Alzheimer's Disease

As life expectancy has increased, the prevalence of age-associated loss of cognitive ability and memory has increased. Only a minority of aged individuals will experience successful aging, defined here as maintaining peak cognitive performance during senescence.[9] Most individuals above the age of 50 will experience declines in episodic memory relative to their prior performance.[10,11] Among individuals in their seventh and eighth decades, a range of cognitive aging occurs and can be viewed on a continuum extending from successful cognitive aging to pathological aging, with the latter sometimes leading to mild cognitive impairment (MCI) or even a debilitating and progressive neurodegenerative condition, AD. Aging is the greatest known risk factor for AD, with the likelihood of developing AD doubling every five years

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after the age of 65.[12] Though debated, MCI may represent a transition state between normal aging and AD[13,14]; individuals with amnestic mild cognitive impairment (aMCI) have an annual conversion rate from MCI to dementia three to six times higher than that observed in normal aging.[13,14] We will highlight age-related changes in the hippocampus, a critical structure for learning and memory, and how these abnormalities could contribute directly to the neurodegenerative process observed in AD.

Normal Course of Cognitive Aging

With aging, cognitive decline occurs in a number of domains, but some processes remain unimpaired. For example, verbal skills, implicit (procedural) memory and semantic memory are often unimpaired.[15] Similarly, memories of older events are often rigidly retained,[16] but there are notable age-related deficits in executive functioning, attention, spatial learning, working memory, episodic (declarative) memory, and the ability to form complex associations.[17,18] Interestingly, recent evidence suggests a common neurobiological source for many of these memory-related deficits, the hippocampus.[19] In a range of species, hippocampal lesions result in impairments in spatial and episodic memory.[20] Similarly, AD is associated with profound neuronal death in the hippocampus.[21] However, unlike amnestic patients with clear hippocampal destruction or AD, hippocampal neurons of species exhibiting age-associated memory impairment are largely intact.[22-24] Instead, age-associated memory impairments seem to arise from alterations in the functional connections of the hippocampus, particularly the cell groups of the trisynaptic loop (Figure 1).

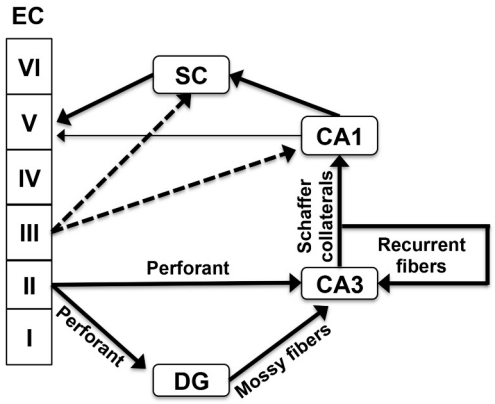

Figure 1. The trisynaptic loop of the hippocampus.
In the trisynaptic loop of the hippocampus, flow is largely unidirectional. Information enters this loop via axons of layer II of the entorhinal cortex (EC), known as the perforant pathway, and these axons connect to the dentate gyrus (DG) of the hippocampus. The mossy fibers of the DG, in turn, project to the CA3, and the CA3 connects to the CA1 region via the Schaffer collaterals. Outputs of the CA1 project to the subiculum (SC), where the SC, and to a lesser extent the CA1, project to the EC again, thereby completing the trisynaptic loop. In addition to this unidirectional flow, layer III of the EC also directly connects to the CA1 and SC (dotted lines), and layer II of the EC provides direct connections to the CA3 via the perforant pathway. CA3 neurons also receive more than 95% of their input from recurrent CA3 collaterals, referred to as "auto-associative" tracts.

Compared with young rats, the dentate gyrus (DG) of aged rats receives a fourth to a third fewer synaptic connections from the entorhinal cortex (EC),[25,26] with the reduction in synaptic connections correlating with deficits in memory performance.[26] The loss of inputs from the EC is consistent with the observation that stimulation of the perforant path generates less excitation in the DG of aged rats.[27] However, although the overall input is lower, the individual synapses become more powerful in older rats; stronger depolarizing responses are observed in aged granule cells due to an increase in quantal size.[28] Changes in long-term potentiation (LTP), believed to underlie learning and memory, have also been noted in aged mice; in synapses of the DG from the perforant pathway, the threshold for LTP induction is elevated in memory-impaired aged rats[29] and LTP decays more rapidly, with faster decays correlating with memory deficits.[27] In memory-impaired, aged humans, there also is evidence of atrophy of the perforant pathway,[30] as well as signal degradation of white matter in the region of the perforant pathway.[31] Similarly, synapses in the DG receiving input from the EC via the perforant pathway are reduced in MCI patients exhibiting memory deficits compared to age-matched control subjects with no cognitive impairment.[32]

Age-related alterations have also been noted in the CA3 region of the hippocampus. In memory-impaired aged rats, the firing rates of CA3 place cells are higher overall compared to young rats.[33] When the role of CA3 place cells in discriminating spatial representations was examined, young CA3 place cells were almost exclusively active in one arena. In contrast, aged CA3 place cells had high activity levels in both environments, suggesting aged CA3 cells failed to rapidly encode changes in the environment.[33] The hyperactivity of the CA3 may be explained by three age-related changes in hippocampal circuitry.[33] First, there is an age-associated decrease in hippocampal inhibitory interneurons.[34-36] Loss of these inhibitory interneurons may increase the susceptibility of the aged hippocampus to hyperexcitability. There also is an age-associated decrease in cholinergic modulation from basal forebrain innervation,[37,38] which releases the CA3 recurrent, autoassociation fibers from inhibition, leading to greater activity.[39] Third, there is diminished input from the EC to the DG and CA3,[25-27] yet there is no age-associated change in CA3 recurrent, autoassociation synapses.[26,40] The loss of EC to DG innervation is particularly important because DG firing increases the activation of hilar interneurons, thereby suppressing CA3 pyramidal cells;[41] removal of the perforant pathway to the DG increases CA3 activity.[41] The hyperexcitability of the CA3 is also observed in memory-impaired aged humans; aged individuals with poorer memory performance exhibit increased hippocampal

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activation.[42] Furthermore, patients with MCI exhibit greater hippocampal activation during memory encoding,[43-46] and increased activation in MCI is predictive of the degree and rate of cognitive decline and for conversion to AD.[47]

In the CA1 region, age-related memory impairments are not associated with a loss of synapses from either the CA3[23, 26] or EC inputs.[26] Rather, aged rats with memory deficits exhibit decreased excitatory postsynaptic potentials (EPSPs)[48] and a 30% reduction in the postsynaptic density (PSD) area of CA1 synapses.[49] These alterations are believed to be due to an increase in the number of nonfunctional "silent" synapses, or synapses with no AMPA receptors,[50] a hypothesis supported by findings of deficits in LTP induction at the Schaffer collaterals.[51] The number of L-type calcium channels in CA1 cells also increases with age,[52] which could explain the disruption of neuronal calcium homeostasis observed in aging.[53] The increase in L-type calcium channels may also explain why CA1 neurons are highly sensitive to excitotoxicity and susceptible to loss in AD.[54] Furthermore, the age-related excess drive from the CA3 may increase the likelihood of excitotoxicity and subsequent loss of CA1 neurons in AD.[55]

These age-related changes in hippocampal circuitry are subtle when compared to the massive neuronal loss observed in AD. Nevertheless, the impact these abnormal patterns of neural network activity may have on the development of AD could be significant and are discussed below.

Relation Between Normal Cognitive Aging and Alzheimer's Disease

AD is a neurodegenerative disorder that targets connected neuronal networks.[56] Effective regulation of activity in these neural networks is essential; over- or understimulation can erode synaptic regulation, leading to alterations in learning and memory and, more concerning, neurodegeneration throughout vulnerable networks.[57] A particularly interesting phenomenon observed in the years preceding AD diagnosis, before notable neuronal death occurs, is a hyperactivity of the distributed memory network, composed of the hippocampus, medial temporal lobe and a subset of cortical regions.[58] For example, hippocampal activation during memory tasks is abnormally high for middle-aged and elderly people with the ApoE4 allele, a known genetic risk factor for AD, and longitudinal assessment indicates the degree of hippocampal overactivation correlates with declines in memory.[59] Hyperactivity has been confirmed by multiple laboratories examining individuals at genetic or familial risk of AD,[60-63] as well as asymptomatic and minimally impaired older individuals with amyloid deposition.[64] Although this hyperactivity was once believed to be a compensatory response for deteriorating circuitry (i.e., greater cognitive effort to achieve comparable performance),[61] more recent evidence suggests this hyperactivity may signify neuronal excitotoxicity and could represent a therapeutic target.

Neural network hyperactivity may also be permissive for the development of AD. A hallmark of AD is the aggregation and accumulation of beta-amyloid (Aβ), a peptide produced by proteolytic cleavage of the amyloid precursor protein (APP). Animal studies suggest increased neural activity increases APP processing and cleavage by beta-amyloid cleavage enzyme (BACE), leading to increased production of Aβ.[65] Thus, the age-related increases in CA3 activity observed in rats,[33] as well as that found in aMCI subjects,[66,67] may well lead to an increase in Aβ production. Even in the absence of increased neuronal activity, when synaptic vesicles undergo exocytosis, extracellular Aβ levels increase. The latter might be particularly relevant for the aged DG cells, where overall input from the EC is lower yet individual synapses become more powerful due to increases in quantal size,[28] which typically represents an increase in synaptic vesicle size.[68] Additional support comes from mouse models of AD in which Aβ plaques were found specifically within the vicinity of hyperactive neurons.[69] Circumstantial human evidence also supports this view; patients with temporal lobe epilepsy, who exhibit substantially elevated neuronal activity, develop amyloid plaques as early as 30 years of age.[70]

The relation between hyperactivity and memory impairments is more than correlational; reducing hippocampal hyperactivity, either by microinjection of an inhibitory neuropeptide in the CA3 or via systemic treatment with antiepileptic agents (sodium valproate and levetiracetam), dose-dependently improved memory in aged rats[71]; despite testing the same range of doses in young rats, levetiracetam had no effect on memory performance, further supporting the view that dampening of hippocampal hyperactivity, not simply global cognitive enhancement, was responsible for the memory improvement observed in levetiracetam-treated aged rats.[71] A low dose of levetiracetam also reduced the hippocampal activation observed in aMCI and improved performance.[66] Together, these studies suggest increased hippocampal activation is not merely a compensatory response but a dysfunctional condition that may be permissive for the development of AD.

Stroke and Aging

Epidemiology of Stroke

Strokes are rare in people under the age of 18 years, then increase in prevalence as people age (Figure 2). In both men and women, prevalence of stroke increases from <0.6% in the age group of 20-39 years to nearly 14% in the >80 year old group. After the age of 55 years, there is a doubling of stroke prevalence with each passing decade of life. This greater than 23-fold increase in the prevalence of stroke over the life span indicates that aging is the greatest risk factor for stroke in our population.

In the U.S., stroke is more common in the Southeast and Appalachian regions than in the rest of the country. This is hypothesized to be the result of poor lifestyle choices that contribute to poor overall health. The Appalachia and Southeast differ from national norms in demographics, socioeconomic

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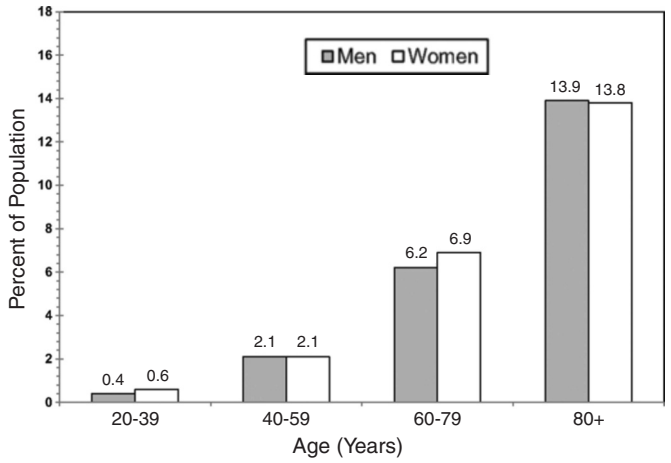

Figure 2. Prevalence of stroke by age and sex. National Health and Nutrition Examination Survey: 2007–2010. Source: National Center for Health Statistics and National Heart, Lung and Blood Institute.

characteristics, health status, health care needs, and access to care. They have low per capita and household incomes.[72,73] It is well-documented that there is a direct correlation between economic and financial stability and health status, e.g., the more economically disadvantaged a group is, the poorer the health status of that group.[74] Other reasons for poor health status and outcomes are linked and include a number of characteristics, the impact of which contributes to negative population health outcomes. One example of this is documented for the state of West Virginia. Two-thirds of its 1.8 million people live in communities with fewer than 2,500 residents, and 49 of 55 counties are designated either fully or partly as Health Professional Shortage Areas and/or Medically Underserved Areas. In 2010, the state ranked second worse in the nation in cancer deaths, fourth in heart disease-related deaths, fourth in stroke prevalence, and first in overall diabetes prevalence, heart disease and hypertension.[72] Data from 2010 indicate that 26% of West Virginians smoked cigarettes (second), 32% were obese (fifth), and the state ranked first in adult physical inactivity.[75] Collectively, these factors contribute to the unacceptably high prevalence of stroke among West Virginians. Other Southeastern states share many of these health outcome characteristics. Rural communities experience higher levels of chronic conditions (46.7%) than do urban areas (39.2%), and these populations tend to be understudied and underserved.

The potential contributing factors to this age-related increase in the prevalence of stroke are many and may be linked. Factors known to be associated with an increase in stroke prevalence are biological factors, such as hypertension, diabetes, metabolic syndrome, and obesity, and behavioral factors, such as sedate lifestyle, smoking and excess alcohol use. These identified biological factors are well-known to increase with age.[76] Less well-known factors contributing to the age-related increase in the prevalence of stroke are chronic suppression of the immune system (See Immune System, Aging and Stroke, below), the lack of adaptation of the autonomic nervous system[77] and cardiovascular system[78] with age, and the age-related alterations in the endocrine system.[79] The maladaptation of these four integrative systems, immune, autonomic, cardiovascular and endocrine, could contribute substantially to the age-related increase in stroke. However, the relative contributions of each of these systems to the age-related increase in the prevalence of stroke are not known and the mechanism(s) by which they contribute to the increase in strokes is only now being characterized.

Connection Between Stroke and Dementia

Stroke ranks as the fourth leading cause of death and the most common cause of permanent disability in the U.S. Stroke survivors must cope with ongoing neurological impairment and sensorimotor functional deficits as well as a decline in cognitive ability.[80] Epidemiological studies have shown that the prevalence of dementia in ischemic stroke patients is ninefold higher than controls at three months[81] and four to 12 times higher than controls four years after a lacuna infarct.[76] Many of these dementias develop progressively after stroke, suggesting that this cognitive decline is not a direct consequence of the initial ischemic damage.[82]

In animal models, we identified a progressive decline in spatial learning and memory after ischemic stroke that correlates with suppression of hippocampal LTP, an electrophysiological correlate of memory.[83] Additionally, we have demonstrated that stroke induces neuropathological features of AD, including tau hyperphosphorylation,[84] BACE1 activity,[85] aberrant neuronal cell cycle reentry,[86] and overproduction of APP.[87] As such, patients that experience a stroke may be at risk of developing AD-like neuropathology and subsequent cognitive decline.

No studies have assessed Aβ fibular plaques density or neurofibrillary tangles following stroke in human subjects. Such studies are needed to fill a gap in knowledge about post-stroke events that may link animal studies demonstrating AD-like neuropathology and clinical studies showing cognitive decline following stroke.

Immune System, Aging and Stroke

It was once thought that the brain was an immune-privileged organ that did not produce an inflammatory response to ischemic brain injury.[88] However, it is now well-established that cells in the brain produce and secrete cytokines, chemokines and adhesion molecules enabling the brain to mount a central and peripheral inflammatory response to ischemia.[89,90] Both central and peripheral inflammation contributes to the pathophysiology of stroke[91,92] and neurodegenerative disease.[93] There is increasing evidence that peripheral inflammation not only plays a role in the pathology of stroke but also impacts stroke etiology by increasing susceptibility.[94] In addition, altering peripheral inflammation during neurodegenerative disease significantly alters disease course.[95]

Risk factors such as atherosclerosis, obesity, diabetes, and hypertension are associated with an increased peripheral inflammatory profile, and the majority of stroke patients have at least one of these risk factors.[96] Many of these factors could participate in regulating interactions between the central and peripheral immune systems, those classically identified as immune-response mediators and those traditionally unassociated. A further understanding of the interaction between the immune and nervous systems is important to determine the contribution of maladaptive immune responses as a causative factor in both stroke and AD, resulting in disease progression and poor functional outcome.

Stroke most commonly occurs when an atherosclerotic plaque ruptures resulting in thromboembolism. The initiation and progression of plaques are driven by inflammatory cells and mediators, such as cytokines and chemokines.[97] Dysfunctional endothelial cells of the vascular wall at the site of the atherosclerotic lesion express adhesion molecules such as VCAM-1 and ICAM-1 that recruit macrophages and T cells.[98] These immune cells produce cytokines and chemokines along with vasoactive molecules that activate immune cells and smooth muscle cell proliferation resulting in the progression of the atherosclerotic lesion.[99] The continuous recruitment of immune cells and activation results in the formation of a mature plaque, and activated macrophages and T cells are a significant part of the plaque.[100] These activated immune cells secrete matrix metalloproteinases (MMPs), which are collagen-degrading proteases that destabilize the plaque and result in the rupture of the plaque, causing ischemia.[101] It is clear that inflammation is an essential contributor to the development and progression of atherosclerosis, and numerous preclinical studies demonstrate that animal models deficient in adhesion molecules, inflammatory mediators and T cells attenuate the progression of plaque formation and the instability of the plaque.[100,102-104] Clinical studies using positron emission tomography (PET) have shown patients presenting with transient ischemic attacks have high ^{18}F-fluoreodeoxyglucose (FDG) signals in atherosclerotic plaques.[105,106] FDG is taken up by macrophages and indicates the degree of macrophage activation, which further supports inflammation causing plaque instability.[107]

Increased atherosclerotic burden is a hallmark of obesity and diabetes, and these comorbid diseases cause endothelial dysfunction through insulin resistance and inflammation.[108] Thus, risk factors such as obesity and diabetes increase stroke susceptibility through proatherogenic effects. Furthermore, clinical studies have linked peripheral bacterial infections and increased stroke susceptibility during the first three days after infection.[109,110] Infection is known to increase vascular disease along with increasing inflammatory mediators, such as cytokines, to clear the infection, which can promote the formation of plaques and increase destabilization of the plaque.[111,112] Along with the proatherogenic effects of infection, infection promotes a hypercoagulable state.[113] Interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) are cytokines that increase during the inflammatory response to infections that activate the tissue factor-mediated extrinsic pathway of coagulation. Clinical studies have observed in stroke patients with infections increased platelet activation and decreased concentrations of anticoagulatory molecules, such as antithrombin, activated protein C and free protein S.[114,115] Preclinical studies confirm these findings and demonstrate that systemic administration of proinflammatory cytokines mimic characteristics of infection. Obese animal models and animal models with other comorbid diseases, such as diabetic mice and spontaneously hypertensive rats, exhibit larger infarcts and more severe neurological deficits.[116,117] These preclinical and clinical studies support the significance of peripheral inflammation and its impact on stroke, and how the interaction between the immune system and the brain can affect neurological dysfunction after an ischemic insult.

Not only does acute and chronic inflammation preceding stroke increase susceptibility to stroke and increase brain damage after stroke, but also stroke itself initiates a local inflammatory response in the brain and peripheral inflammation that can amplify this central inflammatory reaction. Interruption of cerebral blood flow results in the deprivation of oxygen, glucose and other essential nutrients to the brain and leads to a complex, multifaceted cascade of inflammatory events. Acutely after ischemia, microglia are activated due to the increase in extracellular ATP from the depolarization of neurons and glia, and activated microglia secrete cytokines and chemokines along with developing phagocytic properties.[118] Within four to six hours after an ischemic insult, peripheral leukocytes migrate and adhere to vessel walls and infiltrate into the ischemic brain tissue producing deleterious inflammatory mediators.[92] Numerous studies have shown that neutrophils are the first blood-derived cells from the periphery to infiltrate ischemic brain tissue, and when neutrophil infiltration is inhibited, infarct size is significantly decreased.[119-121] Reperfusion of the occluded vessel generates reactive oxygen species (ROS) resulting in further activation of immune and brain cells and oxidative stress, and these activated cells secrete cytokines, chemokines, MMPs, nitric oxide (NO), more ROS, and adhesion molecules that increase cell death and disruption of the blood-brain barrier (BBB).[118,122] Moreover, reperfusion and disruption of the BBB leads to further leukocyte infiltration into the brain, amplifying the inflammatory response and enhancing damage. The peripheral and central inflammatory response after ischemia leads to an increase in neuronal death, infarct size and severity of stroke.

Adhesion molecules are essential for leukocytes to infiltrate into the brain after stroke, and notably ICAM-1 and VCAM-1, the same adhesion molecules that recruit immune cells to atherosclerotic lesions, mediate the interaction between leukocytes and the vascular endothelium.[123] Furthermore, both ICAM-1 and VCAM-1 expression increase after stimulation by cytokines, such as TNF-α and IL-1, which are increased after stroke and in obese, diabetic and atherosclerotic patients.[92] An experimental stroke study in diabetic rats showed higher expression of ICAM-1

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in diabetic rats after stroke compared to non-diabetic rats, and this increase in adhesion molecules due to comorbid diseases and infection could contribute to the exacerbation of stroke and increase susceptibility to stroke.[124] Moreover, using ICAM-1 deficient mice and inhibiting ICAM-1 and VCAM-1 in experimental stroke studies result in smaller infarct sizes.[125,126] Clinically, increased plasma and cerebral spinal fluid levels of ICAM-1 and VCAM-1 are observed in stroke patients and correlated with stroke severity.[127,128] Thus, peripheral inflammation due to infection or other comorbid factors may increase stroke severity and stroke susceptibility by increasing adhesion molecules and other inflammatory mediators, which produce an environment that enhances leukocyte activation and adhesion.

It is evident that stroke is a vascular disease that results in neurological deficits after an ischemic insult, and it is not surprising that the prevalence of stroke increases with age because aging affects the vasculature and the immune systems. Capillary networks and density decrease during aging in the cortex of adult humans and animals.[129,130] Chronic inflammation and acute infection contribute to capillary disruption and cell loss resulting in a leaky BBB, and aged rodents exhibit increased BBB disruption along with reduced neurogenesis after stroke.[131-133] In addition, age-associated immune system dysfunction increases the incidence of acute infections and comorbid factors characterized by inflammation, such as diabetes and atherosclerosis, and as discussed above, these comorbid factors greatly increase susceptibility to stroke and worsen the outcome after stroke.[134]

Aged individuals are in a chronic state of low-grade inflammation referred to as inflamm-aging, and during inflamm-aging, there is a shift in cytokines toward a proinflammatory state producing proinflammatory cytokines such as TNF-α and IL-1.[135,136] The immune dysregulation theory supports the idea that during healthy aging, anti-inflammatory mediators, such as IL-10, inhibit proinflammatory mediators; however, when the system is challenged by an acute infection, comorbid factors, genetic predisposition and environmental factors, the immune system is unable to mount an anti-inflammatory response to shift the proinflammatory state, resulting in an increased incidence of infections, stroke and possibly AD.[134,137] Thus, understanding the effect of age alone on stroke is difficult because it is likely that age is a surrogate for increased chronic inflammation associated with comorbid diseases. This creates a proatherogenic and procoagulable state responsible for the increased incidence of stroke in the aged.

Mitochondrial Role in Propensity to Stroke

Ischemic stroke represents 87% of all strokes.[4] During ischemia, there is a transient or permanent decrease in blood flow to the affected brain regions, resulting in deprivation of oxygen (O_2) and glucose. The brain represents only 2% of the body mass but consumes >20% of O_2 and glucose,[138] the result of the high-energy demand of neurons to maintain ion gradients [139-141] and the almost exclusive use of mitochondrial oxidative phosphorylation (OxPhos) for the production of ATP.[142] As such, even transient reductions in O_2 or glucose put neurons at risk of dysfunction and death.

During aging[143,144] and AD,[145,146] brain mitochondrial function is compromised, expressed as a reduction in OxPhos, transport of mitochondria from soma to energy-demanding synapses and excessive mitochondrial fission.[146] Thus, both normal aging and disease aging, like AD, set the stage for limited mitochondrial response to ischemia. These mitochondrial defects could be responsible for the increase in the prevalence of stroke, increase in severity of infarcts, and the limited recovery from stroke with advancing age.

With age and AD, the brain experiences a reduced capacity to take up and utilize glucose as an energy source.[143-146] This reduction in glucose utilization in the face of persistent energy demand means that the brain must tap into other sources of energy to supply its basic functions and to respond to ischemic events. In the absence of glucose, brain mitochondria use ketone bodies derived from endogenous sources or dietary lipids through β-oxidation to supply carbon fragments for OxPhos.[147]

The use of endogenous sources of fatty acids for fuel for mitochondria may contribute to the initiation or progression of AD. Landfield et al. reported that both aging[148] and AD[149] are associated with an upregulation of genes for myelin degradation, suggesting that the aging and diseased brain may autocatabolize this vital material to generate energy. Additionally, it is now recognized in both normal aging and AD, there is a progressive loss of white matter, a possible reflection of the digestion of myelin for fuel.[150,151] Brinton et al.[152,153] have shown that transgenic (Tg) mice contain mutations in genes for human APP, presenilins and tau, mitochondrial defects in OxPhos, and appearance of β-oxidation in very early in life, arguing that AD mutations cause an early life switch from glucose to β-oxidation of lipids in neurons.

Inasmuch as both normal aging and AD compromise mitochondrial structure, function and movement, the possibility is strong that progressive mitochondrial defects contribute to the age-related increase in stroke prevalence, severity and lack of recovery. Further, the extent to which factors known to increase the risk of stroke do so by decreasing mitochondrial function is a challenge to the field of stroke research. Finally, methods of enhancing mitochondrial functions as a therapeutic target to prevent, treat and recover from stroke have not yet been explored.

Summary and Conclusions

It is clear that nonpathological aging results in cognitive decline, primarily through loss of synapses, while cognitive decline in AD is associated with both synaptic and neuronal losses. Further, the age-related increase in stroke incidence and severity is associated with cognitive loss. There are a number of factors that are common in both stroke and age-related cognitive decline, which

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suggests that common pathological processes may be at work in these diseases. These include chronic inflammation due to comorbid factors, such as cardiovascular disease. It is also apparent that chronic inflammation is a consequence of immune system dysfunction with age and stroke, producing an uninhibited proinflammatory phenotype. Finally, we now have evidence that with aging, mitochondrial structure, function and trafficking in neurons is compromised, a condition that could account for part of the age-related increase in stroke prevalence and severity as well as age-related cognitive decline, and perhaps AD. As such, targeting mitochondria for intervention could be a promising new area for research.

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