Perspective

Recent Developments in Understanding Brain Aging: Implications for Alzheimer’s Disease and Vascular Cognitive Impairment

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Received July 15, 2015; Accepted October 22, 2015

Decision Editor: Rafael de Cabo, PhD

Abstract

As the population of the Western world is aging, there is increasing awareness of age-related impairments in cognitive function and a rising interest in finding novel approaches to preserve cerebral health. A special collection of articles in The Journals of Gerontology: Biological Sciences and Medical Sciences brings together information of different aspects of brain aging, from latest developments in the field of neurodegenerative disorders to cerebral microvascular mechanisms of cognitive decline. It is emphasized that although the cellular changes that occur within aging neurons have been widely studied, more research is required as new signaling pathways are discovered that can potentially protect cells. New avenues for research targeting cellular senescence, epigenetics, and endocrine mechanisms of brain aging are also discussed. Based on the current literature it is clear that understanding brain aging and reducing risk for neurological disease with age requires searching for mechanisms and treatment options beyond the age-related changes in neuronal function. Thus, comprehensive approaches need to be developed that address the multiple, interrelated mechanisms of brain aging. Attention is brought to the importance of maintenance of cerebromicrovascular health, restoring neuroendocrine balance, and the pressing need for funding more innovative research into the interactions of neuronal, neuroendocrine, inflammatory and microvascular mechanisms of cognitive impairment, and Alzheimer’s disease.

Key Words: Brain aging—Alzheimer’s disease—Cerebrovasculature

The aging of human populations is a critical challenge to health care systems and age-related changes in cognitive ability are of particular importance. For aging subjects who experience cognitive impairment, the reduction in function can be disabling and affects social interactions, independence, and health span. Currently, a large percentage of the otherwise healthy population older than 60 years is affected by learning and memory impairments. Importantly, many age-related conditions including obesity, hypertension, and diabetes interact with age to exacerbate impairments in learning and memory. The number of individuals affected by cognitive decline is expected to rise considerably as the aging population increases imparting a significant socioeconomic impact to the country. Although studies suggest that age-related cognitive decline may be reversible, the etiology remains unknown, preventing the development of effective therapeutic interventions.

The general consensus in the field is that brain aging and the resulting cognitive impairments are not the result of changes in a single factor but rather are the consequence of multiple interacting cellular and molecular events. The cellular changes that occur within neurons and glia have been widely studied but these cells also require an intact cerebrovasculature as well as factors within the circulation including key nutrients, trophic factors, and substrates that are...
necessary for normal function. Here we present an update on recent key studies into the mechanisms of brain aging with an emphasis on several articles published in *Journals of Gerontology* that are part of the exciting developments in the field.

**Cognitive Decline and Neurodegeneration in Aging**

Age-related cognitive decline has multiple underlying causes but most of the current efforts are focused on advancing diagnosis, progression, and therapy for Alzheimer’s disease (AD) that is the primary cause for dementia in the elderly adults. Highlights from this field noted below illustrate the current trends.

**Alzheimer’s Disease: Variable Results From Clinical Trials and the Shift in Focus to Prevention and Early Diagnosis**

The failure of clinical trials based on gamma secretase inhibitors (1), antibodies to amyloid (2), and other drugs targeted toward amyloid precursor protein processing (eg, R-flurbiprofen (3)) represented an important finding in the field and focused attention on early intervention. Two recent trials of solanezumab, a humanized monoclonal antibody that binds to the soluble form of beta amyloid (Aβ), failed to show significant improvement in primary outcome measures in mild-to-moderate Alzheimer disease (2). Importantly, when results from the pooled mild AD population were combined, there was a 34% reduction in the rate of decline in the Alzheimer’s Disease Assessment Scale (ADAS-Cog14) and Mini-Mental State Examination (MMSE) scores in the solanezumab treatment group versus placebo (4). Although plasma levels of both Aβ1–40 and Aβ1–42 rose many hundred-folds in the treated group compared with the placebo group, no statistically significant improvement was seen in the pooled moderate AD cases with solanezumab treatment. Other monoclonal anti-Aβeta antibodies undergoing clinical testing had also been evaluated for safety. For instance, anti-Aβ mAb GSK933776 administered intravenously at doses of 1–6 mg increased total amyloid and Aβeta42 levels in plasma and cerebrospinal fluid (CSF) (5). GSK933776 exhibited a favorable safety profile in the Phase I trial with no brain edema or hemorrhage in the 18 patients tested. Also, bapineuzumab, a humanized monoclonal antibody directed against amyloid β was associated with enhanced amyloid-related magnetic resonance imaging abnormalities due to hemosiderin deposition (ARIA-H) that appears to be related to impaired vascular integrity (6). In their study Arrighi et al. (6) concluded that presence of the apolipoprotein (APOE) ε4 allele or preexisting hemosiderin deposition, as well as treatment with bapineuzumab and use of antithrombotic agents increased risk for ARIA-H, probably resulting from loss of integrity of cerebral vessels due to amyloid burden. In addition, a Phase II trial of a promising inhibitor of the beta-site amyloid precursor protein-cleaving enzyme (BACE1, LY2886721) was suspended due to liver toxicity. It was suggested that the liver toxicity was not simply an off-target effect of the drug but rather a specific effect of BACE inhibition at sites other than the brain (7). An important conclusion that has emerged from all these studies is that better clinical trial designs are urgently needed to measure protection from cognitive decline and that intervention early during the disease process is necessary because most trials focus on very advanced (late) stage AD patients creating a “treatment versus prevention dilemma” (8).

Early diagnosis of AD in the general population requires that assays be developed using reliable biomarkers in plasma. A recent study independently confirmed that a decrease in circulating Aβ42/Aβ40 occurs in patients with AD and is inversely correlated with neocortical amyloid burden. Although inflammatory and renal function covariates undoubtedly influence plasma Aβ levels during the 18 months of this study, the overall conclusion was that plasma Aβ42 decreased in subjects with established mild cognitive impairment (MCI) and in those transitioning to MCI (9). In another study, three (3) candidate CSF biomarkers that reflect AD pathology were assessed: amyloid-beta, total tau protein (t-tau), and tau protein phosphorylated at AD-specific epitopes (p-tau) (10). These markers were useful in supporting the AD diagnosis and have predictive value for AD when patients experience MCI. In addition, De Leon et al. (11) conclude that the combined use of conventional imaging (magnetic resonance imaging or fluorescein-glucose-emission tomography) with selected CSF biomarkers can incrementally contribute to an early and specific diagnosis of AD. 231P-tau offers diagnostic specificity for AD and the levels of 231P-tau, but not t-tau, are consistently elevated in AD when compared to controls or those with fronto-temporal dementia, Lewy body dementia, or vascular dementia patients (12). Although the usefulness of circulating biomarkers in the diagnosis of memory impairment and dementia is still debated, the Food and Drug Administration indicated that further research would be required before the effect of an intervention on a single biomarker alone could be considered an adequate surrogate measure for AD or used to approve a candidate drug for early AD (13).

The suspected gender differences in dementia risk and AD prognosis acquired more validation. Results from the Framingham study indicated that women have twice the remaining lifetime risk of AD and dementia than men at the age of 65 years (14). New reports from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) conclude that annual cortical atrophy rates were faster in women than in men (15) and correlated with amyloid-beta and tau changes in CSF and with ApoE4 allele status. In another study cognitive abilities of women with MCI declined twice as fast as men’s (16) with contribution of female gender being equal to the effect of ApoE4. In another study, Banks et al. (17) investigated the importance of adiposity as a contributing factor in AD and concluded that brain levels of amyloid precursor protein were more closely related to body weight and serum levels of gastrointestinal hormones than to brain weight, chronological age, or cytokine levels. This research complements previous findings indicating that increased levels of C-reactive protein and interleukin-6 (both associated with body fat) contribute to increased risk of all-cause dementia (18). For more results from the ADNI study we refer to the recently published excellent review (19) summarizing key findings in the field.

Novel pathways have been recently associated with risk of cognitive impairment and AD. The process of endocytosis was implicated in amyloidogenesis and AD risk using multiple genetic and functional studies (20–26). Repressor element 1-silencing transcription factor (REST; also known as neuron-restrictive silencer factor, NRSF) was originally described as a master negative regulator of neurogenesis that represses neuronal gene transcription in non-neuronal cells (27). In an elegant article Lu et al. (28) provided evidence for increased expression of REST in the aging brain.
and data showing that Wnt/beta-catenin signaling may contribute to the induction of REST in the ageing brain. REST effectively repressed amyloidogenesis and cell death-associated genes and thus its normal function might be neuroprotective. Indeed, REST levels in specific hippocampal and other neuron populations in human brain correlated with memory and longevity. In accordance with this view cultured neurons lacking REST expression were more vulnerable than control neurons to oxidative stress induced cell death and degeneration induced by incubation with toxic amyloid oligomers (28). Importantly, they described an almost total absence of REST in the nuclei of neurons from AD patients. Interestingly, low-density lipoprotein receptor-related protein 6 (lrp6) was determined to be an essential co-receptor for Wnt signaling and genetic variants in this gene were also associated with AD risk (29,30). Using a novel lrp6 knockout mouse, lrp6 deletion resulted in a marked increase in amyloid production and memory impairments with age (31). Based on these studies, age-related changes in the Wnt-lrp6-REST pathway appear to be a promising area for further investigation.

Important findings also have been reported related to mitochondrial dysfunction and the regulation of NAD levels (32). Mitochondrial impairments have been implicated in AD since it was reported that Aβ oligomers interfere with the physiological function of the mitochondrial protein, drp1 (also known as dynamin1-like, DNM1L). Importantly, drp1 mediates mitochondrial and peroxisomal division (33,34). In the presence of Aβ oligomers, drp1 is activated leading to aberrant mitochondrial fission (35,36), which can be prevented by GSK3beta inhibition (37). These studies suggest that Aβ oligomers, in addition to their other known actions (38), may regulate mitochondrial dysfunction and thus impair neuronal metabolism.

Alternative Approaches to Prevent and Treat Cognitive Impairment, Intranasal Insulin, and Cognitive Function

AD and aging are associated with insulin resistance in the brain (39). Recently clinical trials have been conducted demonstrating that intranasal insulin may improve both memory performance and metabolic integrity of the brain in patients suffering from AD or MCI (40–42). These articles discuss the results of intranasal insulin studies and suggest possible molecular pathways through which insulin is able to improve memory and learning processes in both cognitively healthy and impaired humans. Importantly, insulin signaling pathways were shown to prevent Aβ oligomer toxicity (43). It is noteworthy that intranasal insulin treatment may act to modulate neuronal calcium dependent after-hyperpolarization as reported by Maimaiti et al. (44). Their results suggest that the after-hyperpolarization may be a novel cellular target of insulin in the brain that could have a role in improved cognitive performance following intranasal insulin therapy.

Combined approaches to prevent and treat cognitive impairment in the elderly adults are illustrated by the findings of Garcia-Mesa et al. (45). These investigators report a substantial protective effect of physical exercise in the 3xTg mouse model of AD. Voluntary wheel running from 12 to 15 months of age lowered elevated reactive oxygen species and it was suggested that oxidative stress was a central event in the disease process, which correlated with AD-like pathology and anxiety, apathy, and cognitive loss that occurs with progression of the disease. Although the study corroborates the importance of redox mechanisms in the neuroprotective effect of physical exercise, additional studies need to be undertaken to examine the specific functional improvements that occur in response to exercise.

Cognitive Training

Computer-based memory and attention training methods have been reported to improve episodic memory in patients with MCI, but the long-term effect has not been well studied. In a review of the neural networks rehabilitated by current cognitive training methods and those affected in AD, researchers suggest that a consistent training-related increase in brain activity occurs in the medial temporal, prefrontal, and posterior default mode networks, as well as an increase in gray matter structure in the fronto-parietal and entorhinal regions (46,47). The type of activation pattern described above was independent of that observed in healthy older adults (46), suggesting that cognitive training in persons at risk of developing AD could improve compensatory mechanisms and partially restore function. Evidently, changes in neuronal networks may be result of functional changes of individual neurons induced by aging or neurodegeneration but more studies are required to close the knowledge gap between human magnetic resonance imaging and PET trials and in vitro cellular experiments.

Epilepsy and Dementia—Deep Brain Stimulation as a Possible Therapeutic Approach

Interesting insight about the role of human cortical networks in learning and memory were reported from seven subjects undergoing epilepsy surgery with implantation of intracranial electrodes (48) followed by a spatial learning task. Entorhinal stimulation applied while the subjects were learning specific landmarks enhanced their memory of these locations. Direct hippocampal stimulation was not effective. In a Phase I trial, deep brain stimulation of the fornix/hypothalamic area in six patients for 6–12 months reversed impairments in glucose metabolism and slowed cognitive decline (49,50). Based on these results, further investigation of deep brain stimulation to treat memory deficits is warranted.

Neuroepigenetics

A new avenue for understanding the regulation of brain aging, neuroepigenetics, has continued to develop as a field (51). Neuroepigenetics includes studies of regulation of gene expression at the genomic level without changes in DNA sequence, namely histone and DNA modifications, that are key regulators of genomic structure and gene expression (52). Recent studies suggest that DNA methylation at specific sites in the genome may be a quantitative biological-marker of aging (53–55). These recent reports received considerable attention in the research community and DNA methylation may be a quantifiable endpoint for studies of anti-aging therapies. More broadly, age-related changes in DNA methylation may contribute to susceptibility/risk for a wide range of age-related diseases (56,57).

Recent studies of note include the finding that centenarians may have a slower rate of neuroepigenetic aging (58). Additionally, in a detailed study, one of the first examples of regulation of age-related neuroinflammation by DNA methylation levels points to the wide range of studies to be performed to understand the potentially central role of the neuroepigenome in aging (59). With the relative youth of this field a great deal of phenomenological work remains to be performed to understand the effects of aging on specific cell types in the central nervous system (60,61) and the field
will be driven by rapid advances in technology designed to analyze the epigenome (62,63).

Cerebrovascular Aging

The brain vasculature has consistently been an under-investigated area of brain aging. Although the brain comprises only about 2% of body mass, it receives close to 20% of total cardiac output. The high metabolic needs of the brain, which relies heavily on oxidative metabolism, require an immense network of microvessels with a total length of approximately 600 km. The cerebral microcirculation is not only responsible for delivering oxygen and nutrients used for metabolism in the brain, but also for the wash-out of toxic by-products, providing an appropriate ionic milieu for neuronal function and water and solute transport from the blood into the brain parenchyma. Due to the key role of the cerebral microcirculation in preservation of brain health, there is increasing research into the role of age-related structural and functional alterations in the cerebral microcirculation in brain aging (26,64–76).

Previous studies demonstrate that aging impairs endothelial angiogenic capacity (77–81) and promotes structural alterations in the cerebral microcirculation, which include cerebromicrovascular rarefaction (67,82,83). Microvascular rarefaction in the hippocampus has been causally linked to decreased performance in hippocampally dependent behavioral tests (84). Importantly, microvascular endothelial cells represent the largest endocrine organ in the body, secreting a wide range of growth factors and cytokines, which regulate the function of perivascular cells. A prominent example is the recently discovered role of microvascular endothelial cells in maintenance of neurogenic niches (85). Aging is known to alter the secretory phenotype of endothelial cells (77,80), and promote pro-inflammatory phenotypic changes in the microvascular endothelium, which likely contribute to age-related neuroinflammation (86).

Endothelial cells also produce highly diffusible gasotransmitters, including nitric oxide, which regulate a number of cellular functions, including mitochondrial biogenesis, in neighboring cells (87). Microvascular endothelial dysfunction and impaired bioavailability of nitric oxide have been well documented in the aged cerebro-microcirculation (86,88), offering important new directions for future studies exploring age-related changes in brain metabolism. Furthermore, the cerebromicrovascular endothelial cells are a key component of the blood brain barrier, and recent studies provide evidence that disruption of the blood brain barrier occurs both in humans (71) and experimental animals (76,83). Blood brain barrier disruption has been proposed to have a pathophysiological role in neurodegeneration (73,89,90). Therefore, additional studies are warranted to elucidate the molecular mechanisms responsible for the age-related breakdown of blood brain barrier integrity, its functional consequences and develop therapeutic approaches targeting the blood brain barrier for the preservation of brain health.

Blood flow through the microcirculation is tightly regulated by complex, interacting mechanisms. The key regulatory paradigms include: (i) cerebral pressure autoregulation, which maintains a constant flow in the presence of changing cerebral perfusion pressure, and (2) neuro-vascular/glial-vascular coupling, which adjusts local blood flow to changes in neuronal activity in a moment-to-moment manner. There is increasing evidence that adaptation of cerebral autoregulation to high pressure is compromised in aging (65,83), which likely has an important role in exacerbating the deleterious pathophysiological effects of hypertension in aging (64,83,91) and the development of microvascular injury, including cerebral microhemorrhages (65). Recent studies also demonstrate that aging leads to profound neurovascular dysregulation (88,92,93), characterized by impaired cerebral blood flow responses induced by synaptic activity. Age-related impairment of neurovascular coupling mechanisms is also manifest in elderly patients (94–96) and has been causally linked to the decline in higher cortical functions including cognition (97,98). Also, there is increasing evidence linking neurovascular uncoupling to cognitive impairment (99). Recent evidence suggests that the aging-induced decrease in neurovascular coupling can be restored by pharmacological interventions (88), offering a potential target for pharmacological interventions to promote brain health in the elderly patients. Restoration of a key homeostatic mechanism matching energy supply with the needs of active neuronal tissue is expected to have beneficial effects on multiple aspects of brain function (17,100–114) in aging.

The glymphatic system, formed by astroglial cells, is a recently discovered paravascular waste clearance system in the brain that facilitates convective exchange of water and soluble contents (including macromolecules) between CSF and the interstitial fluid compartment (115–117). There is growing evidence that the glymphatic system significantly contributes to neurotoxic protein waste removal, including clearance of β-amyloid, from the brain (116). In addition to β-amyloid clearance, the glymphatic system also facilitates transport of nutrients, lipids, hormones, growth factors, and neuromodulators in the brain parenchyma (118). Recent studies demonstrate that advancing age in laboratory rodents is associated with a dramatic decline in clearance of intraparenchymally injected β-amyloid from the brain (119), raising the possibility that impaired glymphatic clearance contributes to the pathogenesis of AD.

Age-related alterations of the cerebral circulation, ranging from subclinical microvascular alterations and impaired glymphatic clearance to full-blown dementia, will eventually affect every individual. Yet, studies investigating cerebromicrovascular aging are chronically underfunded. One can only hope that with recent evidence emerging that sporadic AD is primarily a vascular rather than a neurodegenerative disorder (73), research into age-related cerebromicrovascular pathophysiologic alterations will receive more attention. Indeed, epidemiological studies demonstrate that practically all risk factors for AD have a vascular component that reduces cerebral perfusion, that hypertension exacerbates development of AD both in animal models and humans (68) and that AD patients exhibit cerebral microvascular pathologies before cognitive and neurodegenerative alterations.

Endocrine Circulating Factors

There is a long history of research demonstrating that alterations in circulating factors can influence cognitive function. Increased levels of glucocorticoids have been shown to impair learning and memory and are the mediator for the effects of increased stress on cognitive impairment (120). In addition, there are substantial data that circulating insulin-like growth factor-1 (IGF-1) regulates learning and memory and that the loss of IGF-1 with age contributes to cognitive decline (121). Many of the actions of IGF-1 are compounded by alterations of paracrine or local IGF-1 secretion and in some cases loss of circulating IGF-1 results in an increase in paracrine IGF-1 levels that compensate for the changes in circulating hormone levels. This is best seen in models of growth hormone deficiency induced in utero and has led to confusion related to the “beneficial” effects of IGF-1 deficiency in specific models that were indeed not deficient in IGF-1 (121). IGF-1...
appears to have a wide range of actions on the brain. Direct effects of IGF-1 on neurons, astrocytes, and endothelial cells have been reported and the most recent data suggest that IGF-1 effects cerebrovascular autoregulation and neurovascular coupling that are critical for the regulation of cognitive function (66,122,123). Although the role of circulating endocrine factors in the maintenance of learning and memory processes have been recognized for several decades, only recently have the molecular mechanisms been studied. Investigations into the actions of IGF-1 already have provided an improved understanding of brain aging and the pathways that are capable of improving function. Additional studies are likely to improve our understanding of brain aging and result in the genesis of novel interventions.

In addition to modulating glucocorticoids and IGF-1 levels, recent data indicate that heterochronic parabiosis, or the joining of a blood supply between young and old animals, is capable of reversing several age-related functional impairments. This procedure includes the rescue of muscle function after damage (124) as well as neurogenesis in the aged brain (125–128). Although there is controversy related to the specific circulating factors that are altered in the parabiotic, a recent study indicates that beta-2 microglobulin increases with age and that parabiosis lowers levels of this factor in the older animals, resulting in a “rejuvenated” phenotype. These are important findings and the investigators support their conclusions by showing increases in beta-2 microglobulin in the human population and improved cognitive function of aged animals with a beta-2 microglobulin genetic knockout. These results provide important insight into the interactions between immune and cognitive function. Nevertheless, the heterochronic parabiosis model is highly complex and issues related to nonspecific stress and the exchange of other endocrine factors that naturally occur in the model have not been resolved. Importantly, the levels of thyroid hormones, IGF-1, and glucocorticoids in these models have not been reported and it is likely that multiple mechanisms contribute to restoration of function.

Conclusions

Based on the current studies, it is clear that our understanding of brain aging in general and neurological diseases associated with age are progressing at a rapid pace. Nevertheless, many challenges remain. For clinical studies, early detection and diagnosis of neurologic disease are paramount for the assessment of interventions that can delay or perhaps even prevent AD. This will require the continued logical disease are paramount for the assessment of interventions that can delay or perhaps even prevent AD. This will require the continued investigation of function.

Additional studies are likely to improve our understanding of brain aging and the pathways that are capable of improving function. As noted in the beginning of this overview, the multiple mechanisms of brain aging and generate novel interventions. Studies of the basic mechanisms of brain aging and improve the health of the aging population.

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