Effects of Aging and Stress on Hippocampal Structure and Function

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Aging is often simply defined as the decline in various body systems and functions (eg, endocrine, cognitive, motor, etc) that occur with the passage of time, although the degree of deterioration can vary greatly across individuals. Increases in average life span have brought a greater focus on brain aging. There is an emphasis on understanding how aging contributes to a decline in brain functions (eg, cognition) because such a decline adversely affects the quality of life. The hippocampus is a key brain structure for cognition and the feedback control of the stress response. Herein we describe how the hippocampus changes with age and we examine the idea that age-related changes in the secretory patterns of the hypothalamic-pituitary adrenal (HPA) axis can contribute to hippocampal aging. We also examine the proposal that cumulative stress, perhaps due to compromised HPA axis function, can contribute to hippocampal aging by subjecting it to exposure to excessive levels of glucocorticoids. The aging hippocampus does not appear to suffer a generalized loss of cells or synapses, although atrophy of the structure may occur in humans. Thus, age-related cognitive impairments are likely related to other neurobiological alterations that could include changes in the signaling, information encoding, and plastic, electrophysiological, or neurochemical properties of neurons or glia. Dysfunction of the HPA axis sometimes occurs with aging, and while excessive glucocorticoids can disrupt cognition as well as hippocampal neuronal integrity, these are not an inevitable consequence of aging. The general preservation of cells and the plastic potential of the hippocampus provide a focus for the development of pharmacological, nutritional, or life-style strategies to combat age-related declines.

AGING IS OFTEN defined as the loss of function that accompanies the advance of chronological years and for many it is the loss of reproductive and motor function that causes greatest concern. For others it is the grim specter of cognitive decline that haunts them, although there is considerable variability in how much loss of function occurs. This variability makes it difficult to define aging solely in terms of time, although it is the most convenient definition.[1] The wide spectrum of decline has generated an interest in understanding how brain structures involved in cognition change with age and whether other factors, including stress, can hasten or exacerbate the changes.[2-4] The hippocampus is crucial in memory storage and retrieval, giving it a prominent place in the many discussions of age and related changes in cognition. In humans it plays a pivotal role in declarative memory and the CA1 area of this structure is one of the first brain areas to display pathology in Alzheimer's disease (AD), a disorder synonymous with cognitive decline.[5] It also plays a crucial role in terminating the stress-related release of glucocorticoids; thus there is interest in determining the possible contribution of stress and excessive levels of glucocorticoids in the aging of this structure.[3,4,6-12] Below, we describe the changes that occur in the hippocampus with age and also examine the support for the idea that stress and glucocorticoids can contribute to these changes.

DO THE STRUCTURE AND FUNCTION OF THE HIPPOCAMPUS CHANGE WITH AGE?

The hippocampus (Fig 1) is a cytoarchitecturally distinct structure folded into the interior of the cerebral cortex. The Ammon's horn or hippocampus proper (CA3, CA2, and CA1 pyramidal cell regions) and the dentate gyrus are the 2 major parts of the hippocampus, with the entorhinal cortex providing the major source of cortical input. The cells of the entorhinal cortex project through the perforant path (PP) to the granule cells of the dentate gyrus and also provide innervation to the distal dendrites of the CA3 pyramidal cells. Input from the cortex is utilized in learning as well as the formation of short- and long-term memories. Information is conveyed throughout the hippocampus by the subfield connections of this structure.[6] As with other brain areas there has been considerable interest in determining if the hippocampus suffers a frank loss of neurons, as an individual ages. A related but distinct question concerns the types of age-related physical, biochemical, and physiological changes that may occur in hippocampal cells.

The hippocampus can be precisely and reliably identified within the 3 orthogonal anatomic planes, making it possible to evaluate the volume of the structure by magnetic resonance imaging (MRI). In humans MRI techniques have convincingly demonstrated hippocampal atrophy in certain diseases, including dementias, recurrent major depression, post-traumatic stress disorder, and Cushing's disease.[13-16] Healthy individuals also show shrinkage of the hippocampus starting in early adulthood, with the reported losses being between 0.3% to 2.1% per year.[17] Further, the loss appears to be greater in men than women, although the reported gender differences have been questioned owing to methodological issues.[17] MRI, as well as more conventional neuroanatomical assessment, suggests that hippocampus does not appear to be an atrophy-prone region in healthy aging experimental animals.[10,18]

The atrophy observed in the aged human hippocampus could be theoretically accounted for by neuronal loss. Early work in many species reported an age-related loss of neurons or a decrease in neuronal density in hippocampus, but there is still considerable controversy as to whether decreases in density reflect loss of neurons or just shrinkage of neuronal elements (dendrites, etc).[19,20] The counting methods used in these early studies required assumptions about the size, shape, and distribution of neurons, which can introduce counting biases and

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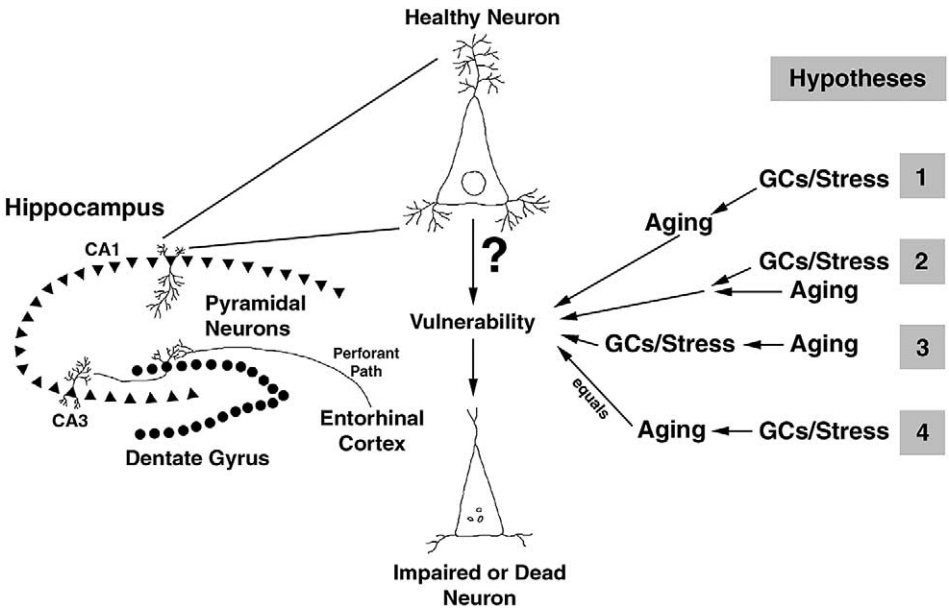

Fig 1. Schematic of the hippocampus illustrating the ways in which aging, stress and glucocorticoids may interact to increase the vulnerability of hippocampal neurons (Adapted from Miller,[66] and Porter and Landfield[10]).

errors.[21] Newer unbiased stereological approaches make no assumptions about the size or other aspects of the neurons to be counted. Studies using these design-based techniques do not provide evidence that widespread hippocampal neuron death is a natural occurrence with age.[18,22-25] While a decrease in neuronal density appears to be a reliable marker of hippocampal aging across rat strains, neuronal death and loss do not occur consistently.[19] Hippocampal neuron number is preserved throughout life in healthy subjects of many different species, including humans. Any cell loss that does occur appears very topographically restricted. Some stereology-based studies report age-related decreases in numbers of neurons in the hippocampal CA1 subfield in humans, while others report no loss.[5,26,27] Further, the CA1 loss is quite circumscribed rather than there being a general loss throughout the subfield.[27] A definitive answer to the question regarding the extent and subfield specificity of hippocampal cell loss that may occur in the human with age requires further study. This is an important question because neuron number can determine functional capacity.

Whether aging of the hippocampus normally involves a decrease in the number, density, or size of neurons and synapses remains a subject of debate. There is more support for the idea that there is synapse loss with aging of this structure.[9,28,29] There is agreement, however, that the aged hippocampus is marked by consistent changes in neurochemical and neurophysiological parameters that may contribute to the cognitive deficits. The hippocampal pyramidal cells of old rats display reduced responsiveness to acetylcholine and other neurotransmitters critical for memory processes. Old rats display lower thresholds for eliciting action potentials and the amplitude of the potential is lower. They also show reduced potassium currents, as well as impaired potentiation of synaptic activation in comparison to young rats, and many of these changes occur in the CA1 region.[30,31]

Decreased microvascular integrity and a reduction in glucose metabolism is also apparent in the hippocampus.[32,33] Reactive gliosis or astrogliosis, hallmarked by increased levels of glial fibrillary acidic protein (GFAP) (an astrocyte-localized protein), progressively increases with age throughout the brain including the hippocampus.[9,34] These increases in gene expression and protein levels occur in many species including humans and are found in healthy subjects with little or no cognitive impairment and no apparent disease. The role or the consequences of age-related astrogliosis are unknown. As these hypertrophic responses usually accompany neural injury or damage, their presence may signify a responsiveness of astrocytes to other disturbances in the aged brain including increased oxidative stress or inflammation.[35] Alternatively, astrocytes may become less responsive with age to suppressive regulatory factors (eg, glucocorticoids), or their hypertrophy may serve a role in maintaining the ionic microenvironment.[9,35,36]

In many species aging compromises learning and remembering about space and these functions are dependent on the hippocampus. With aging, deficits are displayed by rodents in performance of spatial memory tasks, by primates in performance of delayed response memory tasks, and by humans in performance of delayed recall as well as in using their memory to locate objects.[32,37] Lesions in the hippocampus produce deficits in spatial memory across species, but the actual structural basis of the age-related deficits remains unclear as neuron loss does not appear to be a common characteristic of hippocampal aging.[37] In humans, hippocampal volume is found to be related to cognitive performance with larger volumes linked to better verbal and spatial memory as well as with learning of complex spatial tasks.[38,39] In humans, atrophy, especially of the head of the right hippocampus, is associated with memory impairment and, conversely, the learning of complex spatial tasks increases the volume of the right hippocampus.[39,40]

STRESS, GLUCOCORTICOIDS, AND AGING OF THE HIPPOCAMPUS

The hippocampus has a rich abundance of glucocorticoid receptors (GR) and through their actions this brain area serves as an integral part of the feedback loop responsible for terminating glucocorticoid release during the "stress response."[3,4,8] As the hippocampus is a target for glucocorticoids, there is concern that any condition (eg, unmitigated stress, etc) resulting in excessive and uncontrolled levels of glucocorticoids poses a threat to the health of the structure. Investigators have become interested in determining whether age is one of the conditions resulting in aberrant glucocorticoid levels. Hippocampal structure and function can deteriorate with age and the excessive levels of glucocorticoids often associated with advancing age are believed to damage this brain area.[3,4,9-11]

A number of scenarios in which stress and aging interact to increase the vulnerability of the hippocampus can be envisioned (Fig 1).[10] Stress could exacerbate or hasten aging, stress and aging could act in parallel, or aging may result in excessive levels of glucocorticoids with augmented vulnerability of the hippocampus. Alternatively, but less likely, is the possibility that all of the age-related changes observed in the hippocampus are due to excessive glucocorticoid levels. To understand how stress and/or the function of the HPA axis may influence hippocampal aging, it must first be determined whether glucocorticoid levels or the efficiency of the HPA axis change with age.

As steroids can affect cognition and cognition can decline with age, a number of studies have determined if glucocorticoids increase with age to determine if excessive levels of these steroids contribute to age-associated cognitive decline.[3,4,28] Cognitive impairments occur when excessive levels of corticosteroids are attained owing to disease (eg, Cushings syndrome), exogenous corticosteroid administration, or to hypersecretion in response to a stressor.[28] As with so many other endpoints that have been evaluated in the aged, some, but not all, elderly individuals have elevated levels of glucocorticoids.[41] The affected show increased basal levels and protracted stress-induced secretion suggesting decreased responsiveness of the HPA axis negative feedback loop.[9,42,43] Further, longitudinal studies have found that higher-than-normal cortisol levels are predictive of, and are associated with, declines in hippocampally mediated tasks like those involving declarative and working memory.[2,4,28] However, excessive levels of glucocorticoids do not appear to be the norm in aging.

Excessive levels of glucocorticoids affect not only the function of the hippocampus but also its structure. However, the kinds of structural changes that ensue are not clear. There is still great controversy as to whether high protracted levels of glucocorticoids cause the death of hippocampal neurons.[2,3,9,25,28,44-47] Many studies were stimulated by Sapolsky's "glucocorticoids cascade hypothesis," and the original reports documenting that, in rats and monkeys, repeated stress or excessive exposure to glucocorticoids levels caused a decrease in the density or number of neurons in hippocampus.[11,31] In humans, excessive glucocorticoids (eg, Cushings syndrome, etc) decrease the volume of the hippocampus—an effect that is reversible with removal of the steroids.[2,28,48] However, subsequent studies have yielded conflicting findings (ie, data suggesting that excessive levels of glucocorticoids do not always cause neuronal loss and/or hippocampal atrophy). The inconsistent findings of the studies attempting to understand the impact of glucocorticoids on hippocampal neuronal viability suggest there are, as yet, undiscovered controlling variables (eg, genetic, etc) that operate in the studies reporting that excessive levels of corticosteroids cause hippocampal neuronal death.

Glucocorticoid levels also affect other aspects of hippocampal structure. Neurogenesis occurs throughout the life span in many species, including humans, and in laboratory animals high corticosteroid levels suppress neurogenesis.[9,49] Protracted stress or the administration of high levels of glucocorticoids also retards repair responses (eg, sprouting), and causes atrophy of pyramidal cell dendrites and loss of synapses; in general, it may impair the compensatory responses of otherwise normal-appearing neurons.[2] Astrocytes also are affected by glucocorticoid levels. Expression of GFAP is suppressed by excessive levels of glucocorticoids; therefore, enhanced expression of this astrocytic protein with aging may represent decreased responsiveness to glucocorticoids, possibly through a decrease in receptor number.[9,36] Thus, the changes in astrocyte-neuron interactions that occur with age may contribute to synaptic changes.[9] The fact that many of the age-related changes observed in the hippocampus are not related to outright neuron loss suggests that treatment options can be developed to reverse or retard aging of this brain area.

ANTI-AGING STRATEGIES FOR THE HIPPOCAMPUS

The hippocampus exhibits cellular, molecular, and system level plasticity that often becomes impaired with age. A lifestyle involving physical or intellectual activity appears to protect against neurodegenerative disorders and the cognitive declines often seen in the aged.[50] How activity produces this protection is unknown; nevertheless, animal studies suggest that production of trophic factors crucial to the maintenance of brain structure and function may be a key element in fostering life-long brain plasticity. Laboratory rats and mice with access to running wheels have higher levels of brain-derived neurotrophic factor in the hippocampus (see Cotman and Berchtold[51] for a discussion). Also, trophic factor gene therapy is able to reverse the shrinkage of subcortical neurons that can contribute to the hippocampal deficits observed in aged rhesus monkeys.[52]

Certain dietary constituents also appear to be protective against the deterioration that sometimes accompanies age and this knowledge has sparked interest in "nutriceuticals" or the idea of food or naturally occurring substances (eg, vitamins, amino acids, herbal supplements) as a means to promote health and to prevent or treat disease.[53] Total energy consumption may also be important inasmuch as increased vitality and longevity occur in a variety of species from invertebrates to nonhuman primates when calorie intake is restricted but adequate nutrition is maintained. The "anti-aging" properties of calorie restriction may hold promise for humans as well.[54-57] The Biosphere 2 project (although controversial) along with a number of epidemiological studies has shown that a low-calorie nutritional regimen promotes physiological changes (eg, lower

blood pressure, reduced homocysteine and cholesterol levels, etc) that can help stave off disease and prevent functional decline.[57,58] Even in individuals able to maintain a non-obese phenotype when calorie intake is excessive there appears to be a positive association between energy intake and the risk of neurodegenerative disorders.[57] The types of foods eaten also appear to be important and the beneficial properties, including brain protection, of certain types of fats and plant constituents are only beginning to be explored (eg, omega-3 polyunsaturated fatty acids, alpha-linolenic acid, folic acid, flavonoids, lutein, vitamin C, polyphenols, etc).[59,60] As with the protective effects of activity, there is little understanding of how dietary control has its actions. It does appear that many of the general age-retarding strategies described to date (exercise, ingestion of richly-colored fruits and vegetables, caloric restriction, etc) act by affecting disease development.[61] The antioxidant capacity of certain foods (eg, highly pigmented fruits and vegetables) or the reduction in oxidative stress and free radical generation that may be afforded by energy restriction are believed to be critical for neuroprotection.[57,62] It would be premature, however, to embrace free radical generation/reactive oxygen species as the basis for all age-related neurodegeneration. For example, enhanced brain oxidative activity and/or increases in free radicals do not accompany amyotrophic lateral sclerosis—a neurodegenerative disease long associated with free radical–mediated damage.[63]

There is great interest in understanding how to prevent or treat brain-specific aging as increases in longevity have accompanied the advances in medical treatment. The knowledge that most hippocampal cell types are preserved throughout life, and that this structure has the potential for extreme plasticity and neurogenesis, provides hope that effective treatment and prevention strategies will soon be developed. Indeed, it may be predicted that, in the future, pharmacological, nutritional (a "brain-healthy" diet), and life-style (reduction of stress, etc) interventions will increasingly be employed in attempts to prevent or reverse the decline in function associated with aging of the hippocampus.[19,29,51,57,64,65]

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