Successful brain aging: plasticity, environmental enrichment, and lifestyle

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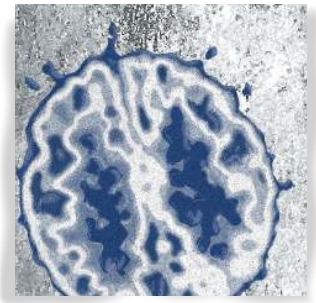

Aging is a physiological process that can develop without the appearance of concurrent diseases. However, very frequently, older people suffer from memory loss and an accelerated cognitive decline. Studies of the neurobiology of aging are beginning to decipher the mechanisms underlying not only the physiology of aging of the brain but also the mechanisms that make people more vulnerable to cognitive dysfunction and neurodegenerative diseases. Today we know that the aging brain retains a considerable functional plasticity, and that this plasticity is positively promoted by genes activated by different lifestyle factors. In this article some of these lifestyle factors and their mechanisms of action are reviewed, including environmental enrichment and the importance of food intake and some nutrients. Aerobic physical exercise and reduction of chronic stress are also briefly reviewed. It is proposed that lifestyle factors are powerful instruments to promote healthy and successful aging of the brain and delay the appearance of age-related cognitive deficits in elderly people.

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Introduction

Aging of the brain is a very complex biological process associated with declines in sensory, motor, and cognitive functions. However, aging is not a disease. Aging is a normal physiological process that can develop without the appearance of concurrent diseases. When this occurs, the process is referred as "successful aging."[1] Nonetheless, with advanced age, the possibility of individuals suffering from dementia, as a consequence of that physiological process of aging, has been postulated. In fact, it has been suggested that around 120 years of age, without concomitant diseases, the population of neocortical synapses could decline to the level found in Alzheimer's disease, with a loss of intracerebral connectivity of around 40%. This loss can result in true primary senile dementia without the presence of the plaques and tangles that characterize Alzheimer's disease.[2] Although these data are open to discussion and also clearly refer to a very old age, which in fact is at the upper limit of human longevity, they nevertheless reveal the intimate relationship between age and disease.

Life expectancy is continuing to increase, thus making longevity "one of humanity's most astonishing successes."[3] Thus, it is important to decipher not only the mechanisms

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underlying this prolonged human longevity, but also the complex factors that make humans more vulnerable to pathology and neurodegenerative diseases. It is also important to understand the factors that delay pathological aging, because by so doing we can emphasize a lifestyle that promotes healthy aging of the entire body, including the brain. Current research provides an increasing body of evidence supporting the existence of an environment-dependent plasticity of the brain and the relevance of this plasticity for aging and neurodegenerative diseases.[1,4-6]

The aim of this article is to first review the anatomical and functional changes of the aging brain, and second to review the reported plastic effects of environmental enrichment on different neurobiological parameters. This article will also review the effects of caloric restriction, physical exercise, and stress, with special emphasis on glucocorticoids on the aging brain. It will be proposed that lifestyle factors are powerful instruments that promote a delay in the appearance of age-related deficits and lead to a healthy and successful aging of the brain.

Genome, ambiome, and longevity

Aging is an endogenous, progressive, and deleterious process that does not seem to be genetically programmed, but rather results from many molecular events that cause an accumulation of damaged cellular components including proteins, DNA, and cell membranes.[7,8] This deleterious process is mostly due to an increase in oxidative stress free radicals and mitochondrial instability, which results in a lower production of ATP, which would render less energy available to invest in the maintenance and repair of the organism.[9]

Longevity, which refers to how long the process of aging will continue, is in part governed by genes that promote molecular mechanisms controlling antioxidant activity and the maintenance and repair of damage induced by free radicals.[7] Nonetheless, today we are starting to understand that the increase in longevity that we are currently witnessing does not seem to rely as much on those genes already mentioned, but rather on genes that become activated during aging by different lifestyle features and the proteins encoded by these activated genes.[9,10,11]

Lifestyle factors seem to be of crucial importance, not because they can determine how long we will live, but rather because they can determine how healthily we will age and thus maintain an independent life during aging. In fact a key point in our society, and the goal we are currently trying to achieve through the field of biogerontology, is how long we can grow old "gracefully" and with full emotional involvement in life.[12]

All of this is in line with current research which is providing evidence indicating that the aging brain retains a considerable functional plasticity which is very much dependent on the environment and, as mentioned, on the lifestyles of the individuals.[1,9] In fact, we coined the term "ambiome" (ambiens-ambientis = environment) to describe that "set of physical, psychological, and cultural factors that change the biochemistry, anatomy, and physiology of the brain during the lifespan of an individual or can determine the clinical expression of a disease." [13]

For instance, caloric restriction and aerobic physical exercise have been shown to promote not only healthy aging of the brain, but also slow down the progression of neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease.[14-17]

Anatomical and functional changes in the aging brain

During aging the brain changes its structure and function, and these changes are in fact modulated by the interaction of the individuals with their environment.[1] Today we know that the plastic changes of the brain during aging are not homogeneous throughout the entire brain, but are related to the neuronal-synaptic-molecular substrates found in each area. This hypothesis is supported by findings showing that, during aging, changes in the morphology of neurons, as well as changes in the tissue density, are specific to each area of the brain.[18,19] Also, dendritic and spine densities and dynamics and functional interactions among different neurotransmitters do change differently among specific areas of the brain during aging.[19-22]

Particularly relevant for understanding plasticity of the aging brain are data showing that, with the exception of neurons from the monoamine cell groups in the midbrain and basal forebrain[23,24] and some areas of the dorsolateral prefrontal cortex,[25] there is no significant loss of neurons during the normal process of aging. This has been shown primarily in brain areas related to learning and memory and other cognitive functions that are centered in the hippocampus and the cerebral cortex of rodents, primates, and humans.[18,26] Also, dendritic branching in the cerebral cortex and hippocampus does not

seem to change during aging in rats, primates, and humans.[18] However, other brain regions, particularly some areas of the prefrontal cortex and hippocampus, suffer a volume decline with aging, and this decline may be produced by a decrease in synaptic density.[2,19,27]

In contrast to the scarce morphological changes that occur in the cerebral cortex and hippocampus during aging, functional changes in these two areas of the brain have been reported. For example, deficits in long-term potentiation induction or reversal, as well as long-term depression induction, have been reported in old rats. These deficits have been suggested to be the neural basis of cognitive and motor dysfunctions observed in aged animals.[4,18] Also, normal aging is accompanied by alterations in neuronal calcium homeostasis.[8,28] which could be related to oxidation of proteins that are involved in cellular ion homeostasis. This is important, since sustained elevations of intracellular calcium concentrations can cause neuritic degeneration and cell death, and by so doing form the bases for age-related impairments in learning and memory.[29]

Neurotrophic factors seem to be very much relevant in the aging brain because of their involvement in a high-order of brain plasticity such as learning. In fact, the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), in the hippocampus has been reported to decrease with age, and these decreases might contribute to age-related cognitive impairments in rats.[1,30,31] Also, a deficit in the expression of genes that encode for neurotrophic factors that promote neuronal survival, dendritic branching, and outgrowth of synaptic plasticity, has been shown to be associated with increased cell vulnerability during aging and neurodegenerative diseases.[4]

With regard to neurotransmission and aging of the brain, we reported that in the prefrontal cortex the release of dopamine induced by a mild stressor and the increases of dopamine and γ-aminobutyric acid (GABA) in the nucleus accumbens by activation of glutamate receptors decrease with age.[1,32,33] Moreover, we have recently proposed that the interaction between neurotransmitters in specific areas of the brain could provide new clues to understanding the age-related changes in specific circuits of the brain.[21,34] For instance, we have found that the interaction between glutamate and dopamine decreases with age in the nucleus accumbens, but not in the dorsal striatum of aged rats.[34] These results reinforce the idea already expressed in this review that the effects of aging on the brain are regionally specific, and further highlight the relevance of studies to investigate the potential interactions between neurotransmitters in specific neural networks during the normal process of aging.[1,34]

An experimental setting that provides evidence for the plasticity of the brain in both adult and aged animals is referred to as "environmental enrichment." This will be discussed below.

Environmental enrichment and aging of the brain

Environmental enrichment refers to an experimental setting in which animals experience enhanced cognitive and social interactions as well as sensory and motor abilities, and this potentiates learning and memory.[1] Several studies have shown that this experimental model facilitates the study of plastic changes that occur in the brains of young as well as aged animals. Animals living in these environmental conditions exhibit improved learning and memory and have a reduction in the responses of several neurotransmitters to stress, enhanced neurogenesis in the dentate gyrus of the hippocampus, increased brain weight and size, and enhanced gliogenesis, as well as dendritic branching and new synapse formation in several areas of the brain.[1,6,35-37] Animals living in enriched environments show increased expression of the genes for nerve growth factor NGF, glial derived neurotrophic factor (GDNF) and BDNF in several areas of the brain.[6,38] BDNF, in particular, seems to be required for the improvement in learning and the neurogenesis produced in the hippocampus of animals living in these enriched environments.[39]

Several experimental studies have shown, specifically in aged animals, that environmental enrichment attenuates the age-related changes in cortical thickness, dendritic branching, spine density, neurogenesis, and gliogenesis.[1,40-42] All these effects have been correlated with an improved performance of old animals in different learning tasks.[1,43] These experimental data are indicative of the plastic capacities of the aged brain. Taken collectively they reinforce the idea that the aged brain is highly responsive to challenges, and they may also help to explain why cognitive and physical exercise make individuals resistant to developing Alzheimer's disease and other types of dementia.[14,44]

The studies reviewed here on animals living in an enriched environment provide powerful evidence for the effects of different lifestyle elements on the anatomy and

physiology of the brain and particularly on the aged brain and its plasticity. Several other lines of research in animal models and also humans further emphasize the intimate relationship between lifestyle and successful brain aging (see below).

Lifestyle and successful brain aging

It is becoming apparent that successful brain aging is possible if people maintain certain healthy lifestyle habits throughout their lives. These lifestyle factors include: the number of calories ingested, composition and quality of diet, physical as well as mental exercise, not smoking, active social life, effective use of technical innovations for social communication, maintenance of an active emotional life, and control of a stressful lifestyle.[10] Some of these are briefly reviewed below, and are also summarized in *Table I*.

Reduction in food intake and the effects of specific nutrients

Caloric restriction a reduction of food intake by 20% to 40% without malnutrition has been shown to decrease the rate of aging of the brain, probably due in part to a significant decrease in the production of mitochondrial reactive oxygen species and a corresponding decrease in their detrimental effects on different cellular macromolecules including proteins, lipids, and DNA.[45] This dietary manipulation has powerful effects on the health of many species, including monkeys and humans.[17,46-48] Caloric restriction has protective effects, particularly in the aging brain. Some of these effects are: reduction in motor and cognitive deficits, improvements in metabolic functions including insulin sensitivity and glucose homeostasis, and reductions in the appearance of tumors and the incidence of cardiovascular diseases.[9,49,50] The underlying mechanisms for these protective effects of caloric restriction, particularly the improvement in learning and memory in aged animals, includes changes in synaptic plasticity reduction in spine loss and increased neurogenesis in the hippocampus.[51]

The effects of caloric restriction on the brain, particularly the aging brain, are regionally specific and very much dependent on the neuronal and synaptic substrates of that specific area and its neuronal circuits.[1] For example, it has been shown that the gray matter volume in the caudate nucleus decreases with age in control animals, but is preserved in calorie-restricted monkeys.[46] In contrast, other areas of the monkey brain, including the

Current research is providing evidence for some lifestyle features that can be modified by individuals to help decrease the risk of cognitive dysfunctions. Some of these lifestyle factors may produce their effects through convergent molecular mechanisms.[10,67,68]
Cognitive exercise
Experiments in rats living in enriched environments which enhance cognitive and social interactions provide indications of possible mechanisms for the benefits of cognitive stimulation in humans. Environmental enrichment produces improvements in learning and memory, enhances neurogenesis, increases brain weight, dendritic branching, and new synapse formation, and increases the expression of genes for neurotrophic factors.[1,6,11,38,75,76]
Reduction of food intake and healthy diet
Caloric restriction has protective effects in the aging brain. These effects include improvements in learning and memory, reduction of spine loss, and increased neurogenesis. Caloric restriction may be protective in Alzheimer's disease and Parkinson's disease. Specific nutrients such as omega-3-fatty acids and vitamins E and C may decrease the rate of brain aging by protecting membranes from oxidative damage and slowing down the rate of cognitive decline and also progression of Alzheimer's disease.[46,49,51,52,53,55,57,77]
Aerobic physical exercise
Aerobic physical exercise maintains brain health and plasticity throughout life. Exercise improves cognitive function in humans, produces increases in brain volume, stimulates neurogenesis and synaptogenesis, and increases neurotrophic factors in different areas of the brain. Physical exercise may protect the brain against reduction in cognitive functions in the elderly and delay the onset and slow down the progression of Alzheimer disease.[14,16,58,59,62,68,78]
Reduction in chronic stress
Chronic stress may produce cognitive dysfunction in the elderly and may increase the rate of cognitive decline in Alzheimer's patients. Stressful lifestyles have been suggested to increase glucocorticoid levels in the brain and this be neurotoxic, affecting neuronal energy balance and producing a decline in cognitive functions. Minimizing life stress has been recommended.[11,69,74]

Table I. Lifestyle factors that may facilitate successful aging of the brain.

frontal and temporal cortex, are characterized by a significant reduction in gray matter volume that is not decreased by a reduction in food intake.[46] Several studies have shown that caloric restriction elevates the levels of BDNF in several areas of the brain, particularly the hippocampus.[51] These increases in BDNF levels seem to be regionally specific, as suggested by a recent study that evaluated the release of neurotransmitters and BDNF levels in rats subjected to a 40% restriction in food intake throughout their entire lifespan.[17]

Caloric restriction may also be protective in Alzheimer's disease and Parkinson's disease, as well as in other neurodegenerative disorders.[52,53] For instance, in mouse models of Alzheimer's disease, caloric restriction has been shown to reverse the deficits in learning and memory typically found in these animals.[54] Also, the motor impairment detected in a monkey model of Parkinson's disease has been shown to be attenuated by caloric restriction.[52] A major role of neurotrophic factors as well as other proteins and enzymes on these protective effects of caloric restriction has been suggested.[9]

Several studies highlight the role of certain nutrients for normal brain function, and these nutrients may influence the activities of specific molecular substrates important for learning, memory, and other cognitive functions.[55] An example of one of those nutrients is the omega-3 fatty acids, which are considered essential for maintaining synaptic function and plasticity.[55] In fact, the omega-3 fatty acid, docosahexaenoic acid, is an important component of neuronal membranes and it has been found that dietary supplementation with this fatty acid elevates the levels of BDNF in the hippocampus and counteracts rat learning disabilities after traumatic brain injury.[56] Other micronutrients, such as vitamin E, have been shown to have the specific capacity to protect synaptic membranes from oxidative damage. Thus there are micronutrients that protect the brain against aging by promoting neuronal plasticity.[55] Moreover, different micronutrients, including flavonoids, contained in fruits and vegetables may counteract the aging process by improving cognitive functions.[57]

Aerobic physical exercise

Frequent aerobic physical exercise is a way of maintaining brain health and plasticity throughout life, and particularly during aging.[10,58-60] Earlier studies showed the benefits of exercise on the brain, more specifically cognitive function, during aging in humans.[61] More recent research in animals has given support to this emphasis on the beneficial effects of exercise by showing that it has the capacity to stimulate neurogenesis in the hippocampus and enhance learning, synaptogenesis, and agiogenesis.[49,62,63] Neurotrophic factors such as BDNF, nerve growth factor, and fibroblast growth factor are important mediators of these brain effects mediated by physical exercise. In particular and most importantly, BDNF has emerged as one of the most relevant mediators for synaptic plasticity and neuronal connectivity, and therefore this factor is being considered a key element for mediating the protective effects of physical exercise on the brain.[49,64] All these effects provide convincing support to the idea that the practice of regular physical activity has a protective effect on brain function that may be of particular relevance during aging.[9]

Several recent studies have reported the benefits of physical exercise, both in terms of cognitive functions and reducing the risk of impairment of these functions in the elderly and in patients with Alzheimer's disease and psychiatric diseases such as depression.[14,65] In fact, in Alzheimer's disease physical exercise has been suggested to not only delay the onset of the disease but also slow down the course of the disease.[14] Moreover, physical exercise can improve the motor impairments that occur in Parkinson's disease patients, and may also have beneficial effects on slowing down the progression of other neurodegenerative diseases, as has been shown recently in an animal model of spinocerebellar ataxia.[16,66] Interestingly, the effects of aerobic physical exercise, caloric restriction, and enriched environments all seem to converge in terms of their abilities to enhance neuronal plasticity via a mechanism involving BDNF.[67] More specifically, flavonoids and exercise may both enhance synaptic plasticity and learning by increasing BDNF levels and activating similar molecular pathways.[68] In summary, it can be stated that aerobic exercise and dietary restriction, through similar molecular mechanisms, may make neurons more resistant to oxidative stress and less susceptible to mitochondrial impairment; therefore both of these factors may protect against neurodegenerative diseases.

Stress reduction

Human beings living in societies experience various forms of stress. There is a permanent organic response

to this chronic social stress, with implications for the brain, and particularly for the aging brain.[10,69] From a physiological perspective, and among the many different hormones and neuromodulators that are released from both the brain itself and other organs and glands in the body under a situation of stress, glucocorticoids are probably the most relevant.[11] In fact glucocorticoids, which are released from the adrenal gland into the bloodstream during stress, enter the brain through the blood-brain barrier and are distributed throughout different areas of the brain, including the prefrontal cortex, amygdala, and hippocampus.[70] Glucocorticoids do interact with neurons and astrocytes in those specific areas and produce changes, both at the functional neurotransmitter and anatomic levels.[12,71,72]

Of special relevance for aging of the brain are the effects mediated by glucocorticoids in the hippocampus,[11,73] where they seem to be neurotoxic, affecting neuronal energy balance and the neuronal substrates for learning and memory.[73] Moreover, the reduction in the number of neurons in this area of the brain produced by glucocorticoids has been correlated with a decline in cognitive functions.[74] Interestingly, environmental enrichment is effective in attenuating the increases of glucocorticoids produced by acute stress in the prefrontal cortex of adult rats.[1,11]

Recent experimental findings are relevant for further understand the chronic effects of stress and glucocorticoids, with particular implications for the aged brain. Up until recently the deleterious effects of glucocorticoids, particularly in the hippocampus, were mainly ascribed to the effects mediated by their elevated levels that result as a consequence of acute stress, rather than to chronic increases in the basal levels of these steroids. However, we and others have proposed that a permanent increase of the "basal" levels of glucocorticoids that results from a stressful lifestyle could also contribute to the neuronal damage that occurs in the these areas of the brain during aging.[11,71]

Conclusions

Aging is a highly complex process influenced by a large number of factors that vary from individual to individual. It is clear that many factors, including controlling the amount of food we ingest as well as the components of our diet, the incorporation of aerobic physical activity into our daily routine, and the attenuation of stress, are essential components for a successful aging of the brain. As reviewed here, aging of the brain is a process that is not only intrinsic to the neuronal mechanisms within the brain but also influenced by important hormones and neuromodulators that are released from peripheral organs and endocrine glands. Especially relevant in this context are the glucocorticoid hormones. During aging and with a chronic stressful lifestyle, corticosterone in rats or cortisol in humans could potentially change the function of specific neuronal circuits in the brain. These effects could be modulated and attenuated in animals living in enriched environmental conditions, which emphasizes the importance of lifestyles in maintaining health during aging of the brain.

A major problem facing modern societies is how to change lifestyle and habits, particularly in the older population. Yet research is providing powerful evidence for the idea that prevention of many diseases can be diminished by a healthy diet and lifestyle that includes cognitive exercise, stress management, and a reduction in cardiovascular risk through regular physical exercise. Prevention of the cognitive decline and dementia that occurs during aging could well be a decisive argument to support the modification of public health policies. ❑

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Envejecimiento cerebral exitoso: plasticidad, enriquecimiento ambiental y estilo de vida

El envejecimiento es un proceso fisiológico que puede desarrollarse sin la aparición de enfermedades en forma concomitante. Sin embargo, muy frecuentemente, las personas de edad avanzada sufren de pérdida de memoria y de una declinación cognitiva acelerada. Los estudios sobre la neurobiología del envejecimiento están comenzando a descifrar los mecanismos subyacentes no sólo a la fisiología del envejecimiento, sino también los mecanismos que hacen que las personas sean más vulnerables a la disfunción cognitiva y a las enfermedades neurodegenerativas. Hoy en día se sabe que el envejecimiento cerebral mantiene una considerable plasticidad funcional, la cual está impulsada por genes que son activados por diferentes factores del estilo de vida. En este artículo se revisan algunos de estos factores del estilo de vida y sus mecanismos de acción, incluyendo el enriquecimiento ambiental y la importancia de la ingesta de alimentos y de algunos nutrientes. También se revisan brevemente el ejercicio físico aeróbico y la reducción del estrés crónico. Se propone que los factores del estilo de vida son instrumentos poderosos para promover un envejecimiento cerebral saludable y exitoso y retardar la aparición de los déficit cognitivos relacionados con la edad en las personas mayores.

Pour un bon vieillissement cérébral : plasticité, enrichissement environnemental et style de vie

Le vieillissement est un processus physiologique qui peut survenir sans maladies simultanées. Très souvent cependant, les personnes âgées souffrent d'une perte de mémoire et d'un déclin cognitif accéléré. Des études sur la neurobiologie du vieillissement commencent à permettre de déchiffrer les mécanismes sous-jacents de la physiologie du vieillissement cérébral ainsi que les mécanismes rendant certains sujets plus vulnérables au dysfonctionnement cognitif et aux maladies neurodégénératives. Nous savons aujourd'hui que le cerveau vieillissant conserve une plasticité fonctionnelle considérable et que cette plasticité est favorisée par des gènes activés par différents facteurs de style de vie. Nous exposons dans cet article quelques facteurs de style de vie ainsi que leurs mécanismes d'action, incluant l'enrichissement environnemental et l'importance de l'alimentation et de certains nutriments. Nous analysons aussi brièvement l'exercice physique aérobie et la diminution du stress chronique. Les facteurs de style de vie seraient des outils puissants pour favoriser un vieillissement cérébral sain et réussi et permettraient de différer l'apparition des déficits cognitifs liés à l'âge chez les personnes âgées.

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