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Lifestyle Shapes the Dialogue between Environment, Microglia, and Adult Neurogenesis

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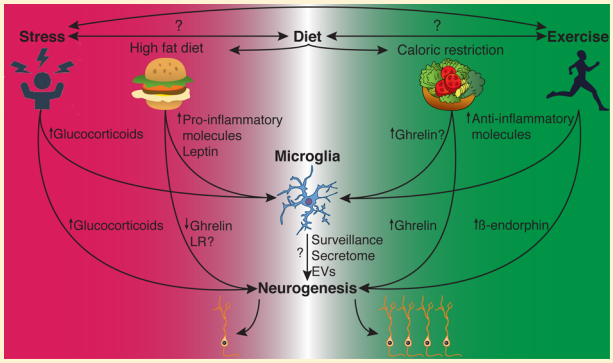
ABSTRACT: Lifestyle modulates brain function. Diet, stress levels, and physical exercise among other factors influence the "brain cognitive reserve", that is, the capacity of the brain to maintain a normal function when confronting neurodegenerative diseases, injury, and/or aging. This cognitive reserve relays on several cellular and molecular elements that contribute to brain plasticity allowing adaptive responses to cognitive demands, and one of its key components is the hippocampal neurogenic reserve. Hippocampal neural stem cells give rise to new neurons that integrate into the local circuitry and contribute to hippocampal functions such as memory and learning. Importantly, adult hippocampal neurogenesis is well-known to be modulated by the demands of the environment and lifestyle factors. Diet, stress, and physical exercise directly act on neural stem cells and/or their progeny, but, in addition, they may also indirectly affect neurogenesis by acting on microglia. Microglia, the guardians of the brain, rapidly sense changes in the brain milieu, and it has been recently shown that their function is affected by lifestyle factors. However, few studies have analyzed the modulatory effect of microglia on adult neurogenesis in these conditions. Here, we review the current knowledge about the dialogue maintained between microglia and the hippocampal neurogenic cascade. Understanding how the communication between microglia and hippocampal neurogenesis is affected by lifestyle choices is crucial to maintain the brain cognitive reserve and prevent the maladaptive responses that emerge during disease or injury through adulthood and aging.



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During the last decades, much evidence pointed to the existence of the so-called "cognitive reserve", which refers to the capacity of the brain to maintain normal functioning via compensatory or protective mechanisms while confronting injury, disease, or aging.[1,2] The concept emerged to explain the lack of correlation between the degree of neuropathological changes and the loss of cognitive functions during aging and Alzheimer's disease: while some individuals with abnormal accumulation of β-amyloid in the brain parenchyma showed clinical symptoms of dementia, others presented normal brain function.[2,3] These normally functioning individuals were speculated to have a larger cognitive reserve, possibly because of a variety of lifestyle related factors.[2] For instance, lifestyle related factors such as cognitive stimulation, exercise, healthy diet, and so forth decrease the severity or risk of suffering aging-related neurodegenerative diseases such as Parkinson's disease,[4] Huntington's disease,[5] frontotemporal dementia,[6] and the sporadic form of Alzheimer's disease.[2] However, there are also some factors that are detrimental for the cognitive reserve and lead to a more fragile central nervous system (CNS), such as stress, high fat diet, and systemic inflammation induced by infection, illness, or surgery.[7−10] Therefore, the capacity of our brain to tolerate injury, aging, or pathological burden depends on our life history.

The term cognitive reserve is a hypothetical concept that can be indirectly measured. Some quantifiable properties of the brain related to brain plasticity have been proposed to be the support of the cognitive reserve and thus may serve as objective proxies of its status: synapse density, dendritic complexity, neuronal number, or brain volume.[2] One of the brain regions that has been involved in cognitive reserve is the hippocampus due to the remarkable plasticity of its circuitry, a condition necessary to maintain memory function.[11] Therefore, the hippocampal structure and functioning reflect the plasticity of the brain and are major indicators of the state of the cognitive reserve.[1,12] One of the particular aspects of hippocampal plasticity is that new neurons are constantly added to the circuit during adulthood. Adult hippocampal neurogenesis is modulated by lifestyle factors, many of which directly act at different stages of the

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neurogenic cascade. In addition, we here propose that these factors also modulate neurogenesis by indirectly acting on microglia, the brain macrophages. Microglia are involved in neurodegenerative diseases[13] and there is growing evidence of their role on synaptic plasticity and adult neurogenesis.[14−16] Microglial cells are highly sensible to changes in the brain parenchyma[17] and thus it is possible that environmental factors regulate brain function through modulation of microglial effects on brain plasticity/adult hippocampal neurogenesis.[18]

Here, we will review the current knowledge about the interaction between lifestyle factors, microglia, and adult neurogenesis and their contribution to cognitive function, particularly learning and memory. Determining the impact of life factors on cellular elements of the neurogenic cascade will help to understand the mechanisms associated with the resistance to cognitive decline during aging, injury, or disease.

■ ADULT HIPPOCAMPAL NEUROGENESIS

Adult neurogenesis occurs in specialized regions of the mammalian brain known as neurogenic niches: the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG),[19] the subventricular zone of the lateral ventricles (SVZ),[20] and the recently described hypothalamic neurogenic niches in the medial and ventral parts of the third ventricle.[21,22] In these specialized locations, resident neural stem/progenitor cells continuously produce new neuroblasts, which migrate toward their final position to differentiate into neurons and integrate into brain circuits. This addition of new neurons to pre-established circuits has an impact on different brain functions: memory, olfaction, and appetite.[21,23] In humans, the production of newly generated neurons has been demonstrated in the DG,[24,25] while neurogenesis in the SVZ is more controversial,[26−31] and the addition of new neurons to the human striatum has been just recently described.[29] Here we will focus on the adult hippocampal neurogenic cascade because of its implication in learning and memory, and the brain cognitive reserve.[12]

The hippocampal neurogenic niche contains radial neural stem cells (rNSCs or type 1 cells) that lie in the SGZ of the DG, and are normally quiescent (i.e., not mitotic). When activated, they divide asymmetrically to generate another rNSC and an amplifying neuroprogenitor (ANP or type 2 cell). Different hypotheses on the self-renewal capacity of rNSCs have been proposed. At the populational level, rNSCs undergo three rounds of asymmetrical divisions before terminally differentiating into astrocytes.[32] This chain of events implies that the population of rNSCs is depleted over time and that this depletion may be accelerated by factors that increase the number of dividing rNSCs, as it occurs in an animal model of epilepsy in which a large pool of rNSCs become activated.[33] At the clonal level, there is evidence indicating that the population of rNSCs is heterogeneous and that some rNSCs are able to increase the number of rNSCs by symmetrical division.[34] Regardless of their self-renewal capacity, rNSCs give rise to ANPs, highly proliferative cells that divide symmetrically increasing the pool of progenitor cells and finally differentiating into neuroblasts (type 3 cells). These neuroblasts are largely postmitotic cells that migrate a short distance to reach their final position into the granular cell layer while differentiating into neurons. During the process of production of new neurons, many neuronal precursor cells and some young neurons naturally undergo apoptosis (at least 50% of newly produced cells disappear in normal conditions)[35,36] and are immediately phagocytosed by "unchallenged" microglia.[35] Young granular neurons develop an apical dendritic tree that reaches the molecular layer and extend their axons to the CA3 layer. At 2−3 weeks of age, newborn granule cells show specific electrophysiological characteristics and enhanced plasticity when compared to mature granule cells.[23,37,38] Therefore, newborn granule cells incorporated to the DG confer specific qualities to memory encoding and retrieval.[39−41]

The net production of newly integrated neurons depends on the rates of proliferation of rNSCs and ANPs, survival of newborn cells, and neuronal differentiation (including morphological and synaptic maturation), which are regulated by a multifactorial process that encloses interconnected hierarchical levels, from gene expression to behavior.[42] These processes are regulated by multiple intracellular signaling cascades, such as Wnt/β-catenin or CREB (cAMP response element-binding) signaling;[43] cellular elements of the neurogenic niche, such as the activity of surrounding mature neurons,[44] blood vessels,[45] astrocytes,[46] and microglia;[47,48] and lifestyle factors that include diet, physical activity, stress, social interaction, and sexual activity.[49]

■ MICROGLIA

Microglial cells are the only resident immune cell of the CNS and its population is maintained by self-renewal without the participation of cells from the peripheral immune system.[50,51] Microglia are of myeloid origin, unlike other glial cells such as astrocytes and oligodendrocytes, which are derived from the neuroectoderm.[52] Microglia present a plethora of receptors that allow them to respond to small variations in their surroundings, and enable them to recognize molecular patterns of pathogens and damage, that lead to their release of proinflammatory cytokines and the initiation of the innate immune response.[17] In addition, microglial highly motile processes constantly survey the brain parenchyma and maintain its homeostasis by phagocytosing pathogens, cell debris, and dead cells.[17,53] It was classically described that microglia become phagocytic when confronting pathogens or damage, but they are also highly efficient phagocytes in physiological conditions.[35,53] Furthermore, microglia maintain a tight relationship with neurons by direct contact and phagocytosis of synaptic elements, and by releasing soluble factors that modulate neuronal function.[47,53−55] Indeed, there is a constant bidirectional dialogue between microglia and neurons that affect the function of both cell types.[55] Due to their extreme sensibility to changes in the environment,[17] microglia are good candidates to be the first responders to subtle variations in the composition of the CNS environment related to changes on lifestyle. While the existence and identity of the main driver in the brain response to stress, exercise, or diet are not known, the available data suggest that microglia may act as initiators and/or amplifiers of the effects induced by lifestyle on the brain, and in turn affect the cognitive reserve.

■ MICROGLIAL CELLS AND ADULT NEUROGENESIS

Adult hippocampal neurogenesis and memory both are influenced by conditions which also alter microglia,[47,48,56] suggesting the existence of a direct or indirect relationship between the state of microglial cells, the production of new neurons, and cognitive function. Neuroinflammation linked to neurodegenerative diseases, aging, or systemic inflammatory events induces several changes in microglial function while at the same time it has a negative effect on memory and adult neurogenesis.[47,48,57,58] In addition, other factors such as stress,

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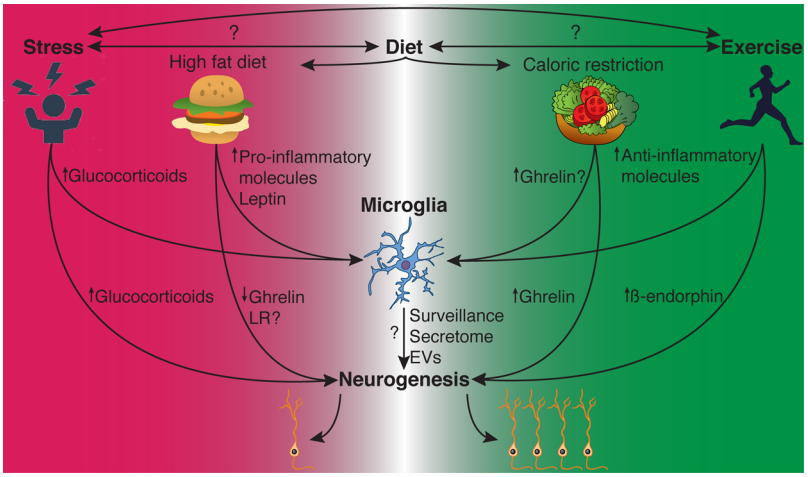

Figure 1. Effects of lifestyle (stress, diet, and exercise) on microglia and neurogenesis. Lifestyle choices affect adult hippocampal neurogenesis: stress and high fat diets are detrimental (red background), whereas caloric restriction and physical exercise are beneficial (green background). These effects are directly or indirectly mediated via glucocorticoids, ghrelin, leptin and leptin resistance (LR), and β-endorphin. Stress, diet, and exercise also affect microglial function, which may subsequently alter neurogenesis. Question marks (?) denote research areas where direct evidence is missing.

physical exercise, and diet show a concomitant effect on adult neurogenesis and microglia, as we will review in the following sections. In these conditions, microglial cells may modulate adult neurogenesis by several mechanisms: surveillance of the neurogenic niche, release of soluble factors, and release of extracellular vesicles (EVs). All of them may contribute to the net effect of microglia on adult neurogenesis and thus in memory function (Figure 1).

First, microglial processes physically survey the hippocampal neurogenic niche, where they may exert similar functions to those described in other regions of the brain.[54] For instance, it has been speculated that microglia are involved in the maturation of newborn neurons by pruning synaptic contacts between them and with more mature granule neurons.[48] In addition, microglia play an important role in the neurogenic niche of the DG by phagocytosing the excess of newborn cells that undergo apoptosis.[35] Microglial surveillance capacity is necessary for its phagocytic and synaptic pruning activity, and depends on the brain volume they scan, which is related to the density of microglial cells and the extension covered by their processes (size, complexity, and speed). Therefore, these commonly studied morphological parameters (density, size, and complexity) may reflect the potential of microglia to directly interact with cellular elements of the neurogenic cascade and modulate neurogenesis.

Second, microglial cells have the capacity to release some soluble factors that are known to modulate adult neurogenesis. Under different in vitro conditions, microglial cells may act as pro- or antineurogenic cells by releasing pro- or anti-inflammatory cytokines and neurotrophic factors.[47,48,56] Hippocampal neural precursors express receptors for the most relevant proinflammatory cytokines released by microglia, such as interleukin-1β (IL-1β) receptor (IL1R)[59] and tumor necrosis factor-α (TNFα) receptors 1 and 2 (TNFR1 and TNFR2).[60] Indeed, some evidence indicates that raised levels of IL-1β and TNFα decrease cell proliferation in the DG.[47] In addition, DG microglia have been described to produce well-known pro-neurogenic factors such as brain derived neurotrophic factor (BDNF)[61,62] or insulin-like growth factor 1 (IGF1)[63] in physiological conditions. Many other factors secreted by microglia have been shown to potentially modulate adult neurogenesis (for more details, see refs 47 and 48), although direct evidence that microglial secreted factors impact neurogenesis is largely missing. Importantly, the release of microglial soluble pro- or antineurogenic factors is modulated by neurons. Neuron−microglia communication is mediated, at least in part, by the neuronal chemokine fractalkine (CX3CL1) and its microglial receptor CX3CR1. CX3CL1 produced by neurons, either secreted or membrane-tethered, acts as an "off" signal for microglia, maintaining them in their normal surveillance state.[64] Decreased levels of CX3CR1 during aging or in knockout animals diminish the production of new hippocampal neurons,[65−67] synaptic plasticity, and memory function.[66] Importantly, the effects mediated by decreased expression of CX3CR1 have been related to increased levels of the antineurogenic cytokine IL-1β.[65,66] Interaction of neuronal fractalkine with its receptor keeps microglial expression of IL-1β low. Therefore, neuronal fractalkine signaling to microglia indirectly modulates adult neurogenesis and possibly some aspects of memory function.[64] However, there are few pieces of evidence of the modulatory potential of microglia on adult neurogenesis in vivo, and an effort should be done to properly evaluate the relevance and contribution of microglial released factors to the regulation of adult neurogenesis and memory function.

Finally, a new potential mechanism of communication between microglia and cellular elements of the neurogenic cascade is the release of extracellular vesicles containing modulatory molecules that may target cells of the neurogenic cascade, although no direct evidence of the EVs-mediated communication between microglia and elements of the neurogenic cascade has been provided. Nevertheless, microglia have been shown to release EVs with different cargos, including cytokines.[68] It has been speculated that the EV-dependent release of cytokines, such as IL-1β, may prevent the degradation and dilution of the cytokine in the extracellular environment and allow long-distance effects and specific targeting of certain cells.[69] Interestingly, microglial released EVs target neurons affecting their synaptic activity,[70,71] and thus, synaptic function of newly generated neurons may be also influenced by microglial EVs. For instance, EVs released by cultured microglia carry on their surface endocannabinoids,[71] which are known to affect neuro-

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genesis in vitro and in vivo via CB1 receptors.[72,73] Moreover, neural progenitors have been also described to release EVs.[74] These data leave open the possibility of the existence of different communication channels between microglia and cellular elements of the neurogenic cascade through direct contact, diffusible molecules, and/or EVs.

In summary, microglia present a plethora of receptors that are able to recognize changes on molecular patterns,[17] and thus, they are adequately equipped to sense changes in their environment induced by lifestyle factors and also to modulate the production of new neurons on the hippocampus.[47,48] We speculate that microglia play a key role on the cognitive reserve by mediating the changes induced by life factors in adult neurogenesis. In the next sections, we will review the evidence that suggests that stress, physical exercise, and diet, factors known to affect the cognitive reserve,[2] modulate memory function and adult neurogenesis through their influence on the state of microglia.

ROLE OF MICROGLIA ON THE EFFECTS OF STRESS ON ADULT NEUROGENESIS

Stress is the natural response to a stressor, that is, unexpected realities associated with any type of environmental or physical pressure, and is a major negative predictor of healthy aging and cognitive reserve.[75] When confronting a stressor, the response is mediated by the sympathetic nervous system, which elicits a rapid behavioral response ("fight-or-flight"). Among other changes, stress involves the release of adrenal glucocorticoids, which have an effect on gene expression. Then, the parasympathetic system returns the body's physiological conditions to homeostasis, reducing glucocorticoid levels. Importantly, the hippocampus is involved both in triggering the initial stress response and initiating the subsequent adaptive response.[76] We are habituated to cope with daily episodes of transient stress that then subside. Indeed, such acute stress episodes are usually positive and prepare our organism to overcome daily life challenges. However, when the stress response is inadequate, excessive, and/or prolonged, it may evolve into pathological conditions such as depression[77] or post-traumatic stress disorders.[78] Excessive stress is a major health problem in modern societies due to its association to cognitive impairment and mental illness, and is considered a negative regulator of the cognitive reserve due to its ability to lower brain plasticity and functioning.[76]

Stress is one of the life-factors that strongly suppress hippocampal adult neurogenesis. Both acute and chronic stress have been described to decrease adult neurogenesis by reducing neuroprogenitor proliferation and newborn cell survival.[79] However, some forms of transient stress such as the responses to sexual activity[80] or a predictable stressor[81] do not affect or even increase the production of new neurons. Importantly, stress action on adult neurogenesis has been related to an impairment of cognitive function.[49] Downregulation of adult neurogenesis upon stress conditions may lead to fear generalization, one of the effects of posttraumatic stress disorders, by increasing pattern completion and decreasing pattern separation,[78] a task in which newly generated neurons are involved.[82] Furthermore, there is an association between stress, depression, and decreased adult neurogenesis. Chronic stress may lead to depression and most animal models of chronic stress usually manifest depression-like behavior.[77] Conversely, reduced adult neurogenesis has been proposed to underlie depression.[83] Thus, several evidence indicates that sustained effects of stress on adult neurogenesis underlie stress associated pathologies, and that promoting adult neurogenesis may serve to overcome these diseases.[83]

The detrimental effect of stress on neurogenesis is mediated by elevated levels of glucocorticoids, as exogenous administration of the murine glucocorticoid corticosterone induces similar changes than stress in adult neurogenesis.[84−86] rNSCs, ANPs, and neuroblasts are susceptible of being affected by glucocorticoids, as all of them express the glucocorticoid receptor.[87] In addition, stress affects microglial function, which may in turn affect neurogenesis. Microglia express glucocorticoid receptors as well[88] and stress induces changes in microglial density, morphology, and cytokine levels in the hippocampus, which may in turn affect neurogenesis.

The effects of stress on microglia number and morphology depend on the type of stressor and timing. Chronic unpredictable stress (CUS),[89] but not repetitive exposition to the same stressor,[90] decreases the length of microglial processes in the hippocampus. Indeed, changes induced by CUS on hippocampal microglia have been described to be biphasic. CUS induces an initial decrease in the length of microglial processes and increases microglial proliferation. In contrast, in the long term, CUS causes a net decrease in the density of microglial cells, while the size of their processes remains reduced.[89] These changes in microglial morphology and density may induce alterations in their surveillance of newborn cell synaptic spines and apoptotic debris.

Cytokine release is also affected by stress. While CUS upregulates IL-1β signaling in the hippocampus,[91] a study using a despair model of stress reported elevated levels of microglial TNFα in the hippocampus of stressed animals but no changes in IL-1β levels.[92] Microglial cytokines such as IL-1β and TNFα are known to affect the neurogenic cascade during inflammatory challenge,[47,48] although it is likely that their concentration and timing of release differ in inflammation and stress paradigms. Importantly, there is some direct evidence of the connection between changes induced by stress on microglial cells and the production of new neurons in the DG. Studies on the NLRP3 (nucleotide-binding domain, leucine-rich repeat, pyrin domain containing protein 3) inflammasome indicate the existence of a link between the changes induced by stress on microglia and the neurogenic cascade. A paradigm of an acute inescapable stressor increases levels of the alarm signal HMGB1 (high mobility group box-1) in the hippocampus.[93] HMGB1 binds to microglial receptors and increase the expression of the NLRP3 inflammasome,[93] which is known to mediate the increase in the production of IL-1β induced by stress.[94] Genetic or pharmacological downregulation of NLRP3 expression in mice prevent microglial morphological changes, the increase on IL-1β, the induction of depressive-like behavior, and the reduction of adult neurogenesis mediated by different type of stressors,[94,95] supporting a link between microglia and the neurogenic cascade. Importantly, IL-1β signaling has been shown to activate the nuclear factor NF-$\kappa\beta$ signaling specifically in rNSCs[91] and to reduce hippocampal cell proliferation after acute and chronic stress.[59] Furthermore, both rats treated intracerebroventricularly with IL1R antagonist (IL1Ra) and mice genetically lacking IL1R are protected against the decrease on adult neurogenesis induced by CUS.[59] In conclusion, there is experimental evidence of an interaction between stress-affected microglia and adult neurogenesis, but further research is needed to determine the relative contribution of glucocorticoids acting directly on neurogenesis or indirectly via microglia. Therefore, further analyses are required to determine whether microglia play a direct role on the reduction of adult neurogenesis mediated by stress.

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ROLE OF MICROGLIA ON THE EFFECTS OF EXERCISE ON ADULT NEUROGENESIS

Physical activity engagement through life is considered one of the indirect indicators of the cognitive reserve state.[2] Maintaining a physically active life increases the quality of life[96] by promoting healthy aging, improving cognitive function, and decreasing the chances of suffering dementia.[96−98] Importantly, moderate aerobic exercise training during 1 year increases hippocampal volume and improves spatial memory function in nondemented elderly people.[99] In addition, engagement in physical activities is being used as a therapeutic tool to improve cognition or prevent cognitive decline in aged people.[98]

Physical activity has a clear positive impact on the production of newly generated neurons and improves memory in rodents.[49] Mice housed with free access to a running wheel (voluntary running) show higher production of new neurons mainly due to increased proliferation of ANPs through shortening of their cell cycle length.[100,101] Moreover, running also increases the survival of newly generated cells and promotes neuronal differentiation, especially during long training periods.[49,102] In addition, running seems to increase the pool of rNSCs in genetically manipulated mouse models[100,103] but not in wild-type mice.[100] However, it is not known whether this effect is mediated by induction of symmetric division of rNSCs and/or by reducing their conversion into astrocytes. Nonetheless, physical activity is also a stressor. Intense forced physical exercise has no effects in the production of new neurons in the hippocampus, likely due to the detrimental effect of the associated stress that counteracts the beneficial effect of physical activity.[104] In contrast, regular forced running increases adult neurogenesis and memory, in spite of increasing blood corticosterone levels in mice.[105] Thus, in this relationship between stress and exercise, the beneficial effects of exercise normally triumph over the detrimental effects of stress and glucocorticoids. Indeed, voluntary running is able to overcome the reduction induced by chronic stress on adult neurogenesis and memory.[106]

Finally, running simultaneously increases hippocampal adult neurogenesis and improves memory,[107,108] suggesting that adult neurogenesis, among other mechanisms such as increased synaptic plasticity and angiogenesis,[109,110] underlies the beneficial effects of running on cognition. Importantly, exercise, as expected for a cognitive reserve factor, prevents neurogenesis decline and improves memory in aged rodents and mouse models of Alzheimer's disease.[110]

Physical activity may act directly on the cells of the neurogenic cascade, or indirectly through microglia. Physical exercise increases plasma levels of β-endorphin, mainly released by the hypophysis.[111] Importantly, there is evidence suggesting that β-endorphin mediates the increase in cell proliferation induced by running in the hippocampal neurogenic niche. First, isolated adult hippocampal precursor cells express both μ-opioid and δ-opioid receptors which show high and low affinity for β-endorphin, respectively.[112,113] Although in vivo expression of opioid receptors by hippocampal precursor cells has not been demonstrated, in vitro data indicate that β-endorphin has a direct effect on hippocampal precursor cells.[112,113] Second, the increase in cell proliferation induced by exercise is abolished in the hippocampal neurogenic niche of β-endorphin-null mice, while the effect on cell survival is maintained.[114] Thus, physical activity may exert a direct effect on proliferation of hippocampal neuroprogenitors via the increase in endorphin levels. In addition, effects of running on neurogenesis are also mediated by changes on the glutamatergic system (changes in the expression of glutamate receptors *N*-methyl-D-aspartate receptors 2a and 2b), growth factors levels (such as IGF1, BDNF, and vascular endothelial growth factor), or the vasculature.[110] Furthermore, the effects on adult neurogenesis mediated by physical activity may be related to the global anti-inflammatory effect of exercise in the organism,[115,116] which in turn affects the CNS. It has been proposed that skeletal muscles release several soluble factors during contraction, such as interleukin 6 (IL-6), which affect other organs and lead to an increase in peripheral levels of anti-inflammatory molecules such as IL1Ra and interleukin 10, and a reduction in proinflammatory cytokines such as TNFα.[115−117] These peripheral changes may have consequences on the CNS affecting microglia, as cytokines may cross the blood-brain barrier and also exert an indirect effect on brain cytokine content.[118] In addition, and similarly to stress, physical exercise induces the activation of the sympathetic nervous system and increases glucocorticoid levels,[117] which may act directly on the neurogenic cascade and/or through their action on microglial cells (see above). In addition, microglia may be indirectly affected by changes induced by exercise in other cellular components of the brain such as neurons, astrocytes, and the vasculature.[109,110,119] Therefore, microglial cells may sense these changes on cytokine and glucocorticoid contents, and initiate a response to physical exercise in the brain, in turn affecting the neurogenic cascade. The indirect effect of running via microglia may be related to alterations in the contacts between microglia and cells from the neurogenic niche, and to the local release of growth factors and cytokines from microglial cells.

Several studies have pointed out the effect of physical exercise on microglia, but the data are conflicting. In vitro approaches indicate that the microglia isolated from runner mice increase the growth/survival of hippocampal neuroprogenitors cultures.[120] Interestingly, the production of neurospheres (indicative of neuroprecursor activation) is reduced when coculturing with microglia isolated from aged mice, whereas it is increased in the presence of microglia from young runners but not from young sedentary mice.[120] These data indicate that aged microglial cells exert a detrimental effect on adult neurogenesis while microglia from exercised animals have a proneurogenic potential. Whether the described effects in vitro are mediated by direct contact between microglia and precursor cells, by the release of soluble factors, or both has not been addressed. In vivo data are controversial. Young mice with free access to a running wheel have been reported to have either no changes[120] or decreased density of microglial cells,[103] and an increased microglial proliferation accompanied by no significant changes in the total number.[101] In contrast, the density of microglia is increased in mice housed in an environmental enrichment that show higher running activity.[121] Data are more consistent in old mice, in which training on a running wheel prevents the age-induced increase on proliferation and density of microglial cells in the DG.[63,103] Finally, a negative correlation has been described between the density of microglial cells and the density of proliferating cells, rNSCs, ANPs, and neuroblasts/young neurons in the DG.[103] It is thus possible that the effects of running on microglial density translate into altered surveillance capacity, subsequently affecting microglial phagocytosis of apoptotic cells or newborn cell spine monitoring.

Microglial release of proneurogenic factors such as BDNF and IGF1 may be involved in the positive effect of exercise on adult neurogenesis. Interestingly, the proportion of microglial cells

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expressing BDNF increases specifically in aged but not in adult mice with free access to a running wheel.[62] Notably, BDNF is known to promote adult neurogenesis in the hippocampus,[82] and a positive correlation has been found between the proportion of microglia expressing BDNF in the DG and the density of newly generated neurons.[62] These data suggest that an increase in microglial BDNF partially mediates the effect of exercise in the production of new neurons, although there are other sources of BDNF in the brain, including neurons,[122] astrocytes,[123] and endothelial cells.[124] On the other hand, wheel running increases the proportion of microglia expressing the pro-neurogenic growth factor IGF1, a key mediator of the neurogenesis increase induced by exercise,[125] in the DG of both adult and aged mice.[63] However, the proportion of IGF1-expressing microglia in the DG is very low (under 10%), and consequently, it is unlikely that microglial IGF1 has a global repercussion in the adult neurogenic niche, especially considering that the main source of the brain IGF1 is the blood serum.[125] Nevertheless, local effects of microglial released IGF1 may have a regional impact on adult neurogenesis, but such a possibility still needs to be explored. The communication between neurons and microglia may also be involved on the effects of exercise on adult neurogenesis. Interestingly, the effects of running on the capability of microglial cells to promote neurosphere growing have been related to the expression of the neuron-to-microglia signal CX3CL1, which is increased after prolonged running periods.[120] In addition, the CX3CL1/CX3CR1 system has been suggested to be involved in the resilience to stress promoted by exercise.[126] Exercise might decrease the production of IL-1β and other antineurogenic cytokines from microglial cells by activating CX3CR1 signaling, and thus release the cytokine brake on adult neurogenesis. Therefore, once again, the communication between neurons and microglia through the CX3CL1/CX3CR1 system seems to be involved in the effects of lifestyle factors on the neurogenic cascade. To conclude, while data from young/adult rodents are not clear, the data available from aged mice seem to be more coherent and suggest that aged microglia have a negative effect on adult neurogenesis, and that exercise promotes adult neurogenesis recovery in aged mice by modulating the functional state of microglia. Nevertheless, further studies are required to clearly demonstrate in vivo whether microglial cells play a direct role on the increase of adult neurogenesis and the associated improvement in memory function mediated by exercise.

ROLE OF MICROGLIA ON THE EFFECTS OF DIETARY HABITS ON ADULT NEUROGENESIS

Dietary habits are indicative of the state of the cognitive reserve,[2,127] and have a well-known impact on longevity and brain aging in many species, including humans.[128] Caloric intake is one of the general diet characteristics that most clearly affect cognitive capacities. Indeed, caloric restriction (CR) has a positive effect on cognition and protects from aging-related decline on brain functioning,[129] while high fat diets (HFD) have the opposite effect.[130,131] In addition, some specific components of the diet have an important impact on the cognitive reserve, such as omega-3 polyunsaturated fatty acids, which are essential for proper neuronal and brain function[128,131] and have an anti-inflammatory effect.[132] Globally, diets characterized by higher consumption of fruits, vegetables, fish, nuts, and legumes, and lower intake of meats, fat, and sweets provide the highest protection against cognitive decline.[127]

Diet has an impact on adult hippocampal neurogenesis and memory function.[133] CR potentiates the production of newly generated cells in the hippocampus, while HFD decreases adult neurogenesis.[133,134] However, the specific effects of CR and HFD on the neurogenic cascade are not clear. CR has been described to increase[135−137] or have no effect[138] on cell proliferation, and to increase cell survival in the DG.[136,138] On the contrary, HFD has been described to decrease[139] or have no effect[140] on cell proliferation, increase apoptosis,[140] and decrease cell survival in the DG.[141] The meal content also impacts neurogenesis. Rodents fed with diets rich in omega-3 fatty acids show increased proliferation[142] and survival[143] of newly generated cells. In addition, polyphenols, such as flavonoids from green tea, the curry component curcumin, or resveratrol present on the skin of red grapes, potentiate adult neurogenesis.[144] There are many other specific components on the diet such as minerals, vitamins, caffeine, and sugar that have been shown to affect adult neurogenesis, but describing all of them is out of the scope of the present review (for further information, refer to ref 133). Importantly, changes induced in adult neurogenesis by both CR and HFD appear concomitantly to increased[135] and decreased[145] memory function, respectively, suggesting that diet modulates cognition at least partially through its effects on adult neurogenesis.

Diet modulates adult neurogenesis directly by mechanisms involving soluble factors released local or systemically, or indirectly through their action on microglia. Soluble factors such as BDNF and IGF1 are also involved on the regulation of adult neurogenesis by diet. The increase on adult neurogenesis mediated by CR is smaller in heterozygous BDNF knockout mice, indicating that BDNF mediates CR-related increase on adult neurogenesis.[138] However, CR has been shown to increase levels of BDNF in the CA1 and CA3 regions of the hippocampus but not in the DG, suggesting that BDNF effect of CR on adult neurogenesis may be indirect.[146] Interestingly, the effects of HFD on neurogenesis have been associated with reduced levels of BDNF,[141] while a diet rich on omega-3 fatty acids increase hippocampal levels of BDNF.[142] These data indicate that hippocampal BDNF levels are regulated by food intake, but the mechanisms involved on diet-induced increase in BDNF are unknown. The effect of diet on neurogenesis has been associated with several other signaling pathways, including glucose-related signaling molecules such as IGF1, or glucagon-like peptide-1.[147] While it is not the aim of this paper to review the whole plethora of molecules indirectly regulated by diet that may modulate adult neurogenesis, here we will particularly focus on two molecules that stand out: ghrelin and leptin.

Ghrelin is considered the "hunger" hormone as, among other functions, it stimulates appetite[148] and is also known to mediate the CR-induced increase in neurogenesis.[136] Ghrelin is released by the empty stomach leading to daily fluctuations of its plasma levels: rising before and decreasing after meals.[149] In addition, diary global levels of plasma ghrelin are increased after diet-induced weight loss in humans[149] and reduced after long lasting HFD in rats.[150] Ghrelin is secreted into the circulation and crosses the blood-brain barrier[151] but it is also synthesized in some regions of the brain.[152] Ghrelin may exert a direct effect on cells of the neurogenic niche, which express the ghrelin receptor,[153] or an indirect effect on neurogenesis by increasing brain levels of IGF1.[154] Another molecule regulated by food intake that affects adult neurogenesis is leptin.[155] Leptin is released by adipocytes, and cells from the gastric mucosa to the bloodstream, acting in the hypothalamus to induce satiety.[156] Leptin plasma levels increase with HFD, and decrease after prolonged CR.[157] Importantly, leptin may act directly on cells of

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the neurogenic niche, as in vitro hippocampal precursor cells express the active (long) form of leptin receptor.[155] Indeed, chronic intraperitoneal administration of leptin stimulates cell proliferation and production of new-neurons in the hippocampus. Intriguingly, there is an inverse relationship between the positive and negative effects of CR and HFD in adult neurogenesis and the levels of leptin on such conditions, in spite of the positive effect of leptin on adult neurogenesis. This apparent contradiction has not been resolved yet, although it may be explained by long-term compensatory mechanisms such as leptin resistance.[158] Together, these data indicate that both ghrelin and leptin may act as direct molecular links between dietary habits and adult neurogenesis.

In addition, diet also influences microglial function and thus, may lead to changes in the microglia-neurogenic niche interactions. Obesity and HFD promote chronic systemic inflammation increasing the release of pro-inflammatory cytokines such as IL1-β or TNFα by the adipose tissue.[159] These cytokines may cross the blood brain barrier[118] and affect microglia leading to neuroinflammation.[160] The effects of CR on microglial cells have been studied in aged animals, in which CR prevents aged-related microglial neuroinflammatory priming, that is, the acquisition of a proinflammatory profile by aged microglia.[161] In addition, diets rich in omega-3 fatty acids and polyphenols revert age-related changes on microglia.[132,160] Moreover, ghrelin and leptin also have the potential of modulating microglia. Ghrelin may have a direct effect on microglia, as it reduces the production of reactive oxygen species and nerve growth factor induced by lipopolysaccharide treatment in a microglial cell line.[162] Furthermore, intraperitoneal administration of ghrelin recovers normal levels of adult neurogenesis and decrease the number of microglial cells in the hippocampus of an animal model of Alzheimer's disease.[163] These data suggest that ghrelin may affect microglial cell number and state. Nevertheless, in vivo effect of ghrelin on microglia in physiological conditions, and the presence of ghrelin receptor on microglia still need to be demonstrated. Leptin may also directly act on microglia, as the active form of the leptin receptor is expressed by primary microglial cultures.[164] Furthermore, leptin treatment induces changes in the morphology and increases TNFα, IL-1β, and IL1Ra production in primary rodent microglial cultures.[164−166] In addition, leptin deficient mice show lower number of microglial cells and these cells are less ramified in the hypothalamus.[166] In conclusion, microglia may sense diet-induced changes on peripheral molecular levels providing a response that affects adult neurogenesis. In the following paragraphs, we review some data indicating that diet induces changes in the density of microglial cells and in their secretome that have the potential to influence adult neurogenesis.

The density of microglial cells is influenced by dietary factors like fat content and dietary complements. HFD induces an increase in the density of both microglia and apoptotic cells in the DG,[140] suggesting a detrimental effect on the survival of newly generated cells that has not been directly tested. Furthermore, a dietary complement rich in polyphenols combining blueberry, green tea extract, carnosine, and vitamin D3, known as NT-020, decreases the number of microglial cells expressing the class II major histocompatibility complex (MHC-II), a protein involved in antigen presentation, while at the same time increases adult hippocampal neurogenesis and improves memory in the DG of aged rats.[167] Therefore, diet may influence the surveillance capacity of microglia by changing microglial cell density, which may have an impact on phagocytosis of cells and synaptic pruning in the DG neurogenic niche.

Dietary habits have been also shown to change cytokine levels while modulating cognition. Indeed, HFD increases IL-1β and TNFα production in the brain, while the polyphenol luteolin (relatively abundant in celery, carrots, chamomile tea, and green pepper) reduces the levels of these proinflammatory cytokines and improves memory in the hippocampus.[168] Importantly, mice fed with an omega-3 rich diet showed decreased levels of hippocampal TNFα, increased neurogenesis, and improved learning capacity.[169] All these data reveal that diet induces changes both in microglia and in the adult neurogenic cascade, leaving open the possibility that microglia play a role in the modulation of adult neurogenesis and memory mediated by diet.

COMMON ASPECTS ON THE EFFECTS OF STRESS, EXERCISE, AND DIET ON ADULT NEUROGENESIS

Adult neurogenesis is promoted by a low caloric diet and physical exercise, while it is impaired by chronic stress and HFD (Figure 1). Although the individual effects of running, diet, and environmental stressors on hippocampal neurogenesis and memory function are well described, the interaction between these three factors on neurogenesis has just begun to be unraveled. A recent study described the synergistic effects of diet (complex dietary supplement), exercise (free access to a running wheel), and chronic unpredictable stress on neurogenesis.[170] Stress abolished the increase mediated by exercise on the production of new neurons, while stress-induced anhedonia (an indicator of depression) was partially rescued by the combination of supplemented diet and exercise. However, the stress paradigm used on this paper did not induce an effect on adult neurogenesis,[170] in contrast to other studies that demonstrated reduced neurogenesis[79] and a positive effect of exercise on stressed animals.[106] Thus, further analyses are required to know the relative contribution of each of these life factors, and the net effect of their combined action on adult neurogenesis.

The individual mechanisms activated by stress, exercise, and diet that regulate microglial function present some convergent modes of action. For instance, both stress and exercise activate the sympathetic system inducing an increase in glucocorticoids levels that may affect microglia.[76,117] Similarly, both exercise and HFD affect the release of cytokines from adipose tissue.[115−117,159] Physical exercise promotes the production of anti-inflammatory molecules while HFD induces the release of proinflammatory cytokines.[117,159] Ghrelin, the "hunger hormone" that increases adult neurogenesis, is elevated in human beings following low-intensity exercise and reduced after high-intensity exercise,[171] while it is decreased after 3 weeks of treadmill forced running in rats.[172] Furthermore, leptin (the diet-regulated modulator of neurogenesis) sensitivity is increased by physical exercise in obese rats.[173] Thus, ghrelin and leptin may act as mediators of the interaction between diet and exercise in the modulation of adult neurogenesis. These soluble factors may cross the blood-brain barrier[118,151,156] and exert effects on microglial cells that may lead to effects on adult hippocampal neurogenesis, as reviewed above. These data suggest that stressors, physical exercise, and diet use some common molecular mediators with the potential to modulate adult neurogenesis through their action on microglia (Figure 1). However, a direct effect of microglia on the hippocampal neurogenic cascade under any of these conditions is far from being demonstrated. This fact makes hard to tackle the study of a more naturalistic effect of the synergies of stressors, exercise and

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diet on the modulation of microglial control of hippocampal adult neurogenesis, and its consequences on memory function.

CONCLUSION

The effect of stress, aerobic exercise, and diet in our brains can be understood from an evolutionary perspective. Escaping from (stressful) predators, running while hunting, and food deprivation were probably the most energy-requiring challenges of our ancestors, which had their brains wired to cope with an ever changing environment. Thus, evolutionary pressure shaped our brains to optimally work under a risky life characterized by daily stressors, physical activity, and fasting periods.[174] This environmental scheme confronts with the current lifestyle in developed countries, in which work-related stress problems are a large source of mental diseases, physical exercise is a choice, and highly energetic food is provided ad libitum. Therefore, it is important to consider that stress, exercise, and diet may act synergistically to optimize brain function and energy consumption, preparing the brain for future challenges. Here we propose that microglia, the fast-responding surveyors of the brain, are one of the common players used by these life factors to shape the brain's architecture and function, and increase the cognitive reserve for a healthy aging.

AUTHOR INFORMATION

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