Review

Exercising New Neurons to Vanquish Alzheimer Disease

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Abstract. Alzheimer disease (AD) is the most common type of dementia in individuals over 65 years of age. The neuropathological hallmarks of the condition are Tau neurofibrillary tangles and Amyloid-β senile plaques. Moreover, certain susceptible regions of the brain experience a generalized lack of neural plasticity and marked synaptic alterations during the progression of this as yet incurable disease. One of these regions, the hippocampus, is characterized by the continuous addition of new neurons throughout life. This phenomenon, named adult hippocampal neurogenesis (AHN), provides a potentially endless source of new synaptic elements that increase the complexity and plasticity of the hippocampal circuitry. Numerous lines of evidence show that physical activity and environmental enrichment (EE) are among the most potent positive regulators of AHN. Given that neural plasticity is markedly decreased in many neurodegenerative diseases, the therapeutic potential of making certain lifestyle changes, such as increasing physical activity, is being recognised in several non-pharmacologic strategies seeking to slow down or prevent the progression of these diseases. This review article summarizes current evidence supporting the putative therapeutic potential of EE and physical exercise to increase AHN and hippocampal plasticity both under physiological and pathological circumstances, with a special emphasis on neurodegenerative diseases and AD.

Keywords: Adult hippocampal neurogenesis, neural plasticity, Alzheimer disease, neuroprotection, newborn granule neuron, memory

ADULT HIPPOCAMPAL NEUROGENESIS (AHN) AND NEURODEGENERATIVE DISEASES: INTRODUCTORY NOTES

During adulthood, the addition of new neurons under physiological conditions occurs naturally in two regions of the brain, namely the lateral ventricles/rostral migratory stream and the hippocampal dentate gyrus (DG) [1]. Recent decades have witnessed the increasing relevance of the latter structure. This relevance can be explained by the fact that it participates in the acquisition, processing and consolidation of memory [2]. Moreover, there is solid evidence that the rate of AHN is sustained in humans during adulthood [3–5]. Furthermore, the hippocampus and the main afferent of this structure, namely the Entorhinal cortex (EC), are severely affected by neurodegenerative diseases in general, and by Alzheimer disease (AD) in particular, which are among the greatest challenges currently facing modern medicine [6].

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Indeed, growing evidence supports the notion that AD is a synaptopathy characterized by a generalized lack of neural plasticity in the hippocampus and other related structures [7, 8]. Thus, various therapeutic strategies attempt to preserve brain plasticity in order to prevent or slow down the progression of this disease [9, 10]. In this regard, adult hippocampal neurogenesis (AHN) contributes to the unique complexity of the hippocampal circuitry, and the continuous addition of new neurons through this process is believed to confer remarkable plasticity to this structure throughout life [11–18], and to increase the cognitive reserve during aging [19]. Moreover, given that numerous external factors, including lifestyle, exert a rapid and multi-directional regulation of the rate of AHN, this process has been referred to as a sensor of information processing requirements [20–27].

In this regard, environmental enrichment (EE) and physical exercise are among the most potent selective and positive regulators of AHN [25, 28–30]. They also exert numerous beneficial effects on hippocampal-dependent memory and preserve brain plasticity throughout life [29, 31–38]. This review article summarizes current evidence supporting the putative therapeutic potential of EE and physical exercise to increase AHN and hippocampal plasticity both under physiological and pathological circumstances, with a special emphasis on neurodegenerative diseases and AD.

REASONS WHY THE ADDITION OF NEW NEURONS TO THE HIPPOCAMPUS IS IMPORTANT

The hippocampus is a bilateral structure located in the temporal lobes of the brain. It has been considered a "memory gateway" [39, 40]. It plays key roles in the transition from short-term to long-term memory, and it is crucial for spatial memory and navigation [2, 41, 42]. The vast diversity of neuronal cell types located in the different hippocampal subfields, together with the presence of complex, multi-directional, intra- and extra-hippocampal neural circuits [43–45], confer this structure unique information-encoding capacity. Indeed, several parallel pathways orchestrate the information flux into and from the hippocampus to other regions of the brain. The hippocampal formation belongs to the limbic system, and it receives afferents from various brain regions, including the EC, the mammillary bodies (MB), the amygdala and

the hypothalamus [40]. Once the information has been processed in the hippocampus, it is projected back to the EC via the *subiculum*. The DG exerts a sparse encoding of memories [46]. Moreover, both pattern separation and pattern completion capacity have been attributed to the main population of neurons present in this structure, namely granule neurons [11, 47]. Although this topic is not devoid of controversy, the general consensus in the field is that either granule neurons generated during development or those generated as a consequence of adult neurogenesis play differential—sometimes collaborative and other times competitive—roles in information processing [15, 48–50]. In general terms, pattern separation, which consists of producing differentiated outcomes in response to very similar inputs, is facilitated by newborn granule neurons [11, 16, 47, 51–53]. This capacity is conferred by special electrophysiological properties, namely increased intrinsic excitability and a lower activation threshold [54, 55], and by a particular innervation timing [56–61] exhibited by these neurons when they are *young and excitable* [13, 54, 62]. In contrast, fully mature and developmentally generated granule neurons are believed to contribute to more stable memory storage and to pattern completion, a phenomenon based mostly on generalization processes [47]. Within the hippocampal circuitry, the DG itself participates in two major circuits. The first, named *classic trisynaptic hippocampal circuit*, includes a projection from the granule neurons to the *Cornu ammonis* CA3 region [44]. This connection is involved in spatial memory and mood regulation, and it has been extensively explored [63–67]. In addition, Keiko Kohara and Susumu Tonegawa recently described the *alternative trisynaptic circuit*, in which granule neurons project to the CA2 hippocampal subfield [68]. Subsequently, our group showed that maturing newborn granule neurons also project to this structure following a temporal pattern similar to the one they follow to establish connections with the CA3 field [69]. Whether all newborn granule neurons connect to the CA3 or to the CA2 fields or whether they establish connections to both fields is still a matter of debate since technical difficulties currently prevent scientists from answering this challenging question. However, the field has acknowledged that the connection between the DG and the CA2 field is required for context discrimination and social memory [70, 71]. The participation of newborn granule neurons in these tasks remains to be fully elucidated. However, previous evidence supports the contribu-

tion of this cell population to the processing of similar contextual cues [53, 72, 73]. Interestingly, physical exercise selectively increases the number of axonal terminals (named mossy fiber terminals, MFTs) of newborn granule neurons in the CA2 field [69]. This finding may have important consequences for the hippocampal network remodeling that occurs in response to physical exercise and EE [74, 75] and may be related to the selective enhancement of pattern separation capacity exerted by exercise [32, 76].

ENVIRONMENTAL ENRICHMENT AND PHYSICAL EXERCISE INCREASE ADULT HIPPOCAMPAL NEUROGENESIS THROUGH THE ACTIVATION OF CONFLUENT PATHWAYS

Several years ago, three seminal studies were published by Gage´s lab. Gerd Kempermann and Henriette van Praag showed that physical exercise and EE increase the proliferation and survival of new-born granule neurons [25, 30, 77]. Their findings have since been replicated by numerous labs working in AHN, and many valuable pieces of information have been added to shape our current knowledge of the regulation of this phenomenon by physical exercise and EE [24, 28, 78–80]. In addition to increasing proliferation and survival, subsequent technical and methodological refinement has revealed that physical exercise and EE modify almost every single step of AHN [81–84]. These two interventions increase the maturation [30] and the complexity of dendritic arbor morphology of newborn granule neurons [17, 79, 82, 85–89]. This increase in maturation is also reflected by the modification of the electrophysiological properties of these neurons [17, 82]. Moreover, an observation of particular relevance for research on neurodegenerative diseases is that physical exercise and EE increase the synaptic integration of these cells [61, 69, 90–92]. Indeed, retrograde tracing experiments have revealed that these two interventions completely rewire the afferent connections of newborn granule neurons [91–93] in a maturational stage-dependent way [91]. These changes are supported by observation of a marked increase in the number and size of dendritic spines [61, 82, 94] and postsynaptic densities [86], and by the increase in the size of the MFTs in the CA3 and the CA2 regions [69, 95] in these cells after stimulation with either physical exercise or EE.

Whether the neuroprotective effects exerted by physical exercise and EE on newborn granule neuron maturation in wildtype animals can be exploited as a therapeutic strategy to counteract the hippocampal alterations observed in AD models and patients will be further discussed in subsequent sections of this article. In this regard, several aspects of the neuroprotective actions of physical exercise and EE are often neglected in the literature. For instance, gender- [96–99], inter-individual- [100, 101], housing condition- [102], age- [103–106], and regional- [107–110] dependent differences in the effects of EE and physical exercise have been reported. These data should be taken into account when prescribing these interventions as co-adjuvant therapies to patients, since they may limit the success not only of these but also of other therapies prescribed to the same individuals.

Regarding the molecular mechanisms mediating the effects of physical activity or EE on AHN and cognition, these two strategies differ in some aspects [111–116]. In fact, EE encompasses a multi-factor protocol that includes, but is not limited to, voluntary physical activity. In addition to the physical activity component, EE is also characterized by increased social interaction and continuous cognitive stimulation. These additional aspects of EE may account for some of the aforementioned differences and for the broader actions of EE in comparison to those of physical exercise. Indeed, even very short EE interventions can elicit metaplastic events in the hippocampus [36, 117, 118].

Regardless of the variable degree of overlap between the mechanisms of action of EE and physical activity, it is widely accepted that these two stimuli entirely remodel the transcriptome of the hippocampal milieu [119] and thus create a novel, neuroprotective, and enriched scenario in which newborn granule neurons grow and mature. Physical exercise and EE modify the secretion pattern of growth factors [120–125], neurotransmitters [122, 126, 127] and neuromodulators [128]. Moreover, the structure of perineuronal nets and the extracellular matrix is remodeled [71, 129], and blood influx is finely regulated through changes in microvasculature and endothelial cells [130, 131]. In addition, these two interventions exert a complex modulation of neuroinflammation [132–137] and oxidative stress [114, 138] and modify the behavior of two cell populations that tightly regulate the maturation of newborn granule neurons, namely astrocytes and microglial cells [59, 139, 140]. Moreover, EE and physical exercise have

an impact on diverse hippocampal neurotransmission systems [36, 61, 91, 141, 142], including the expression and properties of glutamate receptor subunits [143–147], synaptic adaptor proteins [148–151], and other molecules related to plasticity [152–156].

Thus, through a shift in the environment in which newborn neurons are born [145, 157, 158], physical exercise and EE positively modulate the neurogenic permissiveness of the subgranular zone (SGZ) and facilitate the incorporation of highly plastic, newly generated, maturing granule neurons into the trisynaptic circuit. Consequently, these interventions improve hippocampal-dependent learning [159, 160] and pattern separation ability in mice [32] and humans alike [76, 161]. Therefore, EE and exercise converge at a crossroad: a profound and multi-faceted increase in hippocampal plasticity [36, 74, 75, 142]. Given that many neurodegenerative diseases are characterized by a generalized lack of neural plasticity, the therapeutic potential of making certain lifestyle changes, such as increasing the level of physical activity, has become the cornerstone of several non-pharmacologic strategies aimed to slow down or prevent the progression of these diseases.

MULTIPLE STAGES OF ADULT HIPPOCAMPAL NEUROGENESIS ARE AFFECTED BY NEURODEGENERATIVE DISORDERS

Classical approaches to study neurodegenerative diseases include the use of transgenic animal models that mimic specific pathological aspects of neurodegeneration. In the case of AD, these animals are often engineered to carry mutations in specific genes that encode proteins such as Amyloid-β precursor protein (APP) [162, 163], Tau [164], or Presenilin I and II [165]. These mutations have been described in families that exhibit an increased risk and frequency of AD cases. However, as familial cases of the disease account for a negligible proportion of the total number of AD cases, other animal models have been engineered to mirror the increase in the activity of several molecules involved in the pathogenesis of the condition. Such is the case of glycogen synthase kinase 3β-overexpressing mice (GSK-3β-OE mice) [166, 167]. Other animal models mimic pathological aspects related to inflammation and the propagation of Amyloid-β [168] and Tau [169, 170], or exhibit accelerated aging [171]. Although there is no current evidence that alterations in AHN are the primary cause of AD, most of these models show alterations in this process [9, 172, 173]. In this regard, alterations in the proliferation of progenitor cells, survival of newly generated neurons or exhaustion of the radial glia-like cell pool have been reported in a number of animal models of AD [9, 173], and importantly in patients with this disease [174].

In addition, several years ago our group described that granule neurons in AD patients exhibit a profound morphological alteration, and that this phenotype is identical to that described in a murine model of the disease that overexpresses GSK-3β in these cells, namely GSK-3β-OE mice [86]. Both in wildtype animals and control subjects, the classical morphology of granule neurons is featured by the presence of a single primary apical dendrite emerging from the soma. This dendrite is increasingly branched as the dendritic tree goes through the molecular layer (ML) of the DG, thus forming a "Y" shape [175]. However, in AD patients and in GSK-3β-OE mice, these neurons exhibit a phenotype we named "V-shape", due to the presence of several primary apical dendrites emerging from the soma and that are poorly branched in the ML. [86, 176]. Interestingly, granule neurons exhibit an extremely similar morphological phenotype under a variety of pathological situations, such as seizures [177], stress [178] and inflammation [179, 180], and in other models of neurodegenerative conditions, such as Parkinson´s disease [181]. Further studies are needed to determine whether shared mechanisms trigger the appearance of this morphological phenotype in response to the previously mentioned insults. However, of note, all these circumstances converge in an increase in GSK-3β activity [182–184]. In fact, we demonstrated that the cell-autonomous expression of GSK-3β in newborn granule neurons is sufficient to replicate the morphological phenotype observed in the transgenic animal model and in patients [185, 186]. Given this finding, this kinase emerges as key component in the regulation of the morphology of this cell population.

In addition to the morphological alterations observed in the granule neurons of GSK-3β-OE mice and AD patients, there is a profound impairment in the connectivity of these cells [86, 187]. In this regard, GSK-3β plays key roles in the synaptic compartment [188, 189]. Although the physiological function of this kinase and that of its main downstream target Tau are required for the proper functioning of the glutamatergic synapse, the aberrant phosphorylation of Tau or the overexpression of GSK-3β trigger the endocytosis of glutamate receptors and the dis-

appearance of synapses [86, 190–192]. Whether the aforementioned alterations can be ameliorated by non-pharmacological interventions such as physical exercise or EE will be further discussed in the next sections of this review article.

EFFECTS OF PHYSICAL EXERCISE AND ENVIRONMENTAL ENRICHMENT IN ALZHEIMER DISEASE

Physical activity and EE trigger an AHN-dependent increase in long-term memory [193]. Moreover, these interventions exert a variety of beneficial neurological effects [38, 194, 195], including a reduction in anxiety and depression [98, 196–198], an improvement of pattern separation capacity in healthy subjects [76, 161], and an amelioration of cognitive deficits in patients with mild cognitive impairment [199] and in AD patients [200]. Moreover, physical exercise and EE reduce neuroinflammation [132, 201] and oxidative stress [144, 202, 203]. These and other beneficial effects are observed in a wide variety of physiological and pathological conditions, such as in aging [35, 204–210], traumatic brain injury [132, 211, 212], ischemia [123, 213–219], brain lesions [198, 220, 221], acute and chronic stress [222–225], maternal deprivation [226, 227], cranial irradiation [228, 229], bacterial infection [133, 230], inflammation [231, 232], diabetes and metabolic syndrome [233–235], seizures [236–238], exposure to toxic molecules [239–243], and chemotherapy [244]. In addition, physical exercise and EE improve cognition in other neurological conditions such as schizophrenia [245, 246], autism [247], post-traumatic stress disorder [248], developmental alterations [249, 250], Angelman [251], Rett [252], Fragile X [253] and Down [254–257] syndromes, vascular dementia [258], and Huntington´s disease [259, 260]. Moreover, despite the unknown nature of the etiology of AD, the general consensus in the field points to lifestyle as an important factor able to decrease the risk and/or halt the progression of the disease [38, 158].

In this regard, the *neurotrophic hypothesis* of the mechanisms of action of physical exercise [194, 261–264] postulates that the increase in the levels of neurotrophins and growth factors triggered by this stimulus are responsible for its beneficial effects on brain and cognition [265–267]. In fact, previous reports demonstrate that the effects of physical exercise and EE on cognition are dependent on the circulating levels of the insulin-like growth factor I (IGF-I) [268–270], brain-derived neurotrophic factor (BDNF) [266, 271], and vascular-endothelial growth factor (VEGF) [272]. Importantly, the molecular pathways activated by these and other growth factors converge to inhibit GSK-3β through phosphorylation of Serine9 [273–275]. Thus, the signaling cascades activated by growth factors could potentially ameliorate some of the pathological consequences of AD, namely the over-activation of GSK-3β and the hyperphosphorylation of Tau. Importantly, these two phenomena are among the most potent inhibitors of AHN [180, 274, 276–278], whereas growth factors are potent positive regulators of this process [263, 279]. Thus, when addressing why AHN, despite not being the primary cause of AD, is so dramatically impaired in this disease, it should be taken into account that most neurodegenerative diseases are characterized by a marked decrease in the levels of neurotrophins [280]. It has been proposed that, by increasing the levels of circulating neurotrophic factors, physical exercise can serve as a neuroprotective strategy for neurodegenerative conditions [262].

Despite the clear benefits of physical activity on humans, testing the efficacy of physical exercise and EE to alleviate the pathological features of AD in animal models has rendered complex and sometimes contradictory results [281, 282]. As pointed out by several authors, differences in exercise protocols, gender, housing conditions and mouse strains can account for these discrepancies [113, 283, 284]. With regard to memory impairments and neuropathological features, numerous bodies of evidence point to the neuroprotective or even therapeutic potential of these interventions [171, 225, 285–287], whereas other studies report no improvement in memory tasks after the exposure of certain AD animal models to exercise [281, 288]. In agreement, these interventions do not appear to recover all the aspects of AHN affected by the progression of AD [282, 289], although most of the studies support the neuroprotective potential of exercise and EE to sustain increased levels of AHN in models of this disease [103, 225, 287, 290–294]. Nevertheless, some reports also provide evidence of a slight discrepancy between the effects of physical exercise and EE on AHN and on cognition [282, 293, 295].

Over the last decade we have extensively characterized the dynamics of AHN in GSK-3β-OE mice in response to physical exercise and EE. One of the most outstanding alterations in the newborn neurons of these mice, namely their aberrant morphology, is completely reversed when these animals are exposed

to voluntary running for 2 weeks or to EE for 4 weeks respectively [86, 176, 185]. However, we found that the impaired connectivity of these neurons was not normalized by these non-pharmacological strategies [86, 185]. In addition, a mouse model that lacks Tau [296] exhibits a marked decrease in the number and size of synaptic contacts in the most distal part of the dendritic tree, and these alterations are not reversed by EE [95]. Further studies are needed to address why newborn neurons of these animal models are not responsive to the stimulatory actions of physical exercise and EE. However, it is known that the outer segment of the dendritic tree of granule neurons receives most of the afferent information from the EC under physiological conditions, and Zhao and Gage elegantly demonstrated several years ago that synaptogenesis in this domain of the dendritic tree of newborn granule neurons is selectively regulated by environment in a very particular way. In this regard, spatial cues related to the size of the living environment selectively increase spinogenesis in this region [297]. The incapacity of newborn granule neurons of certain AD animal models to show an increase in synaptogenesis in response to physical exercise or EE can be explained by two alternative mechanisms. On the one hand, this incapacity may reflect a specific synaptic role played by GSK-3β or Tau in encoding the aforementioned type of spatial information, which increases distal synaptogenesis under physiological conditions. On the other hand, the dysregulation of GSK-3β activity or the absence of Tau may alter the plasticity of dendritic microtubules, thereby impeding the correct transport of synaptic proteins to the most distal parts of the dendritic tree. Further studies are needed to determine whether this insensitivity is a particular feature of these animal models or whether it represents a common mechanism that may limit the effectiveness of physical activity to potentiate the synaptic integration of newborn granule neurons in AD models and patients.

A final crucial consideration that affects not only AD but many other neurodegenerative diseases is that the first "invisible" silent alterations occur several decades before the appearance of the first clinical manifestation of the disease [298, 299]. Deciphering the exact time at which preventive strategies would have a greater impact is currently impeded by the lack of full elucidation of the etiology of these conditions. Nevertheless, previous evidence suggests that the rate of AHN is sustained throughout life in humans [3–5]. Thus, it is postulated that the contri-

bution of this phenomenon to the neurogenic reserve [19] is maintained during adulthood. Nevertheless, in the unlikely event that humans experience a decrease in the rate of AHN similar to that observed in rodents, physical exercise would be expected to lead to a robust improvement of AHN at all ages. This notion is supported by previous lines of evidence in mice demonstrating that physical exercise enhances AHN both in healthy and AD mice and that this increase is quantitatively greater than that detected in young mice [206, 300, 301]. Thus, strategies designed to increase AHN in young, aged, healthy or diseased individuals is expected to greatly contribute to boosting neurogenic and cognitive reserves both during physiological and pathological ageing.

CONCLUDING REMARKS AND FURTHER DIRECTIONS

Despite the unknown nature of numerous neurodegenerative diseases, including AD, a common feature of their progression is a generalized lack of neural plasticity in certain susceptible brain regions. The hippocampus and its main afferent structure, namely the EC, are two of the first areas affected by AD progression. In these brain regions, neurons exhibit morphological alterations, as well as a marked decrease in their afferent and efferent connectivity. The continuous addition of new neurons to the trisynaptic circuit serves as an endless source of novel synaptic connections that can be finely tuned in response to changing environments or to changing information processing requirements. In this regard, AHN has emerged as an alternative strategy to preserve neuroplasticity in the hippocampus. The observation that clinically and economically affordable, non-pharmacological interventions, such as increasing the level of physical activity, enhance the rate of AHN and improve memory has put them in the spotlight as strategies to improve brain health and to keep hippocampal plasticity at high levels throughout life. Given that neurodegenerative diseases are multi-faceted pathologies with slow progression and they involve numerous non-cell autonomous effects, such as inflammation and neurovascular alterations, promising therapies often lead to nothing. Moreover, data obtained from animal models of the disease suggest that cell-autonomous effects derived from the deregulation of the activity of certain toxic proteins limit *per se* the beneficial effects of physical exercise and EE on brain health. Further studies

should address whether the combination of these non-pharmacological strategies and targeted drugs against deregulated pathological proteins can effectively prevent, slow down, ameliorate the symptoms or even vanquish these as yet incurable and devastating diseases.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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