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Review Article

How Brain Changes as We Learn

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Abstract

Neuroplasticity is the capacity of the Nervous System to modify its structural organization and function in response to the experience and to several external and internal factors; structural modifications occur at the cellular and molecular level, creating new synaptic connections that modifies the neurotransmitter release, receptors, intracellular messengers, and signal transduction mechanisms. There is neural plasticity during development of the Nervous System, associated with the learning and memory processes, during aging, through the rehabilitation process after injury, on neurodegenerative diseases and even on neuropsychiatric disorders. The purpose of this study is to review the molecular basis of adult hippocampal neurogenesis and the factors that affects the neuroplasticity and neurogenesis in the adult mammalian hippocampus contributing to understand and to improve the fundamental concepts of Cognitive Neuroscience.

Adult Hippocampal Neurogenesis

The structural plasticity of the brain during the learning process involves neurogenesis, gliogenesis and morphological and structural changes such as formation of new synapses and dendrites on the pre- existing neurons [1,2]. Neuroplasticity allows the adult brain to adapt to the external environment based on the establishment of new neuronal connections, strengthening the synapses and enhancing the neuronal transmission; gliogenesis generates new glial cells to support the myelination and the regulation of homeostatic functions of the neurons; there are several findings that show how the glial cells support the neural plasticity of the brain, the ependymal cells are involved on neuronal proliferation [3]; it has been observed an increase in oligodendrocytes and de novo myelination in the some cortical areas associated with the limbic system and also in the CA1 area of the hippocampus, quantified by the administration of thymidine analog 5-ethynyl-20 -deoxyuridine (EdU) throughout the training period using a water maze learning model in mice, suggesting that de novo of myelination is a type of non-neural plasticity that remodels the connections between cortical areas and the hippocampus during the learning process for memory consolidation [4].

Hippocampal neurogenesis occurs during the development of the Central Nervous System and continues during early and late stages of life, adult hippocampal neurogenesis takes place in the Dentate Gyrus, where new granule cells are generated from progenitor cells from the sub granular zone (SGZ), where neurogenic activity is maintained throughout life [5]; considering the hippocampus a fascinated subcortical structure involved in higher cognitive functions such as the learning process and the acquisition of memory and also related with the limbic system; it is important to consider the factors that affects adult hippocampal neurogenesis since the higher cognitive functions such as learning and the acquisition of memory in the adult mammalian brain implies the modulation of synaptic connections and incorporation of new neurons in the preexisting neuronal circuits of the hippocampus [6,7].

The major neurogenic sites in the brain are the Sub granular zone (SGZ) and the Subventricular zone (SVZ), where the capacity to generate proliferating cells is maintained during the complete lifespan. The sub granular zone (SGZ) in the hippocampus is an example of neurogenesis that provides new granular cells in the Dentate Gyrus (DG) of the Hippocampus [8]. Postnatal hippocampal neurogenesis was discovered by Altman and Das [9] and adult

Hippocampal neurogenesis occurs throughout life [10] with a decline in adult hippocampal neurogenesis during aging in the mammalian species [11,12].

Mikkonen et al. [13] assessed adult hippocampal neurogenesis using a PSA-NCAM immunohistochemistry analysis; the polysialylated neuronal cell adhesion molecule (PSA-NCAM) which is considered a marker of adult hippocampal neurogenesis, the expression of PSA-NCAM is associated with the induction of synaptic plasticity, neurite outgrowth and neuronal migration, the analysis was performed on postmortem tissues from the hippocampus and the entorhinal cortex removed from patients with drug-refractory temporal lobe epilepsy, the results suggested a significant number of PSA-NCAM+ cells in the SGZ of the adult human hippocampus, with a decrease in epileptic patients with severe neuronal damage with respect to the analysis performed from the autopsy from a control group. A postmortem study from adult cancer patients identified newly generated neurons in the adult human hippocampus assessed with BrdU-labeled nuclei with NeuN+, calbindin+, and neuron specific enolase+ cell bodies [14]. Spalding et al. [15] used a non-invasive technique to study Human Adult Hippocampal neurogenesis by measuring the concentration of nuclear bomb test-derived 14C in genomic DNA, the results suggested that in adult humans 700 new neurons are added to the hippocampus every day, with a high rate of turnover throughout life, the higher extent of turnover of neurons occurs in the Dentate Gyrus, increasing new pools of neurons susceptible to a decline during aging.

The adult hippocampal neurogenesis is a complex process that includes the proliferation, differentiation, survival, and incorporation in the neuronal hippocampal circuits, adult hippocampal neurogenesis is under the influence of several intrinsic and extrinsic factors; the intrinsic factors more relevant are: neurotrophic factors, signaling pathways mediated by specific proteins, mRNAs transcriptional factors, cell-cycle regulators, inflammatory cytokines, neurotransmitters, hormones, opioids, glucocorticoids and epigenetic factors [16]; among the neurotrophic factors involved in neurogenesis are the nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), glial derived nerve factor (GDNF), insulin like growth factor (ILGF-1,). There are several external factors that increases adult hippocampal neurogenesis like antidepressants, physical activity, a balance diet, and the social interaction is considered another external factor [16-19] however there are some external factors associated with a reduced neurogenesis like stress [20].

In addition to all the intrinsic factors mentioned above, there are several signaling pathways mediated by specific proteins involved in early and late stages of hippocampal neurogenesis such as the Notch, Sonic hedgehog (Shh) and Wnt pathway; the participation of these signaling pathways explains the complexity of the adult hippocampal neurogenesis. The Notch signaling pathway is required for the maintenance of stem cell self-renewal, proliferation and regulation of the cell fate and differentiation into neurons or glial cells [21], the genetic Notch1 manipulation modulates survival and dendritic morphology of newborn granule cells [22]; the Sonic Hedgehog (Shh) is a secreted protein that controls the pattern of neural progenitor cells during development, also involved in the formation and plasticity of neuronal circuits in the hippocampus [23], this protein regulates the migration of the neural progenitor cells generated in the ventral hippocampus to the dorsal hippocampus during the late stage of embryonic development [24], the Shh signaling is involved in the expansion and establishment of postnatal hippocampal progenitors [25]. The pathway of the Wnt protein is involved in early and late stages of brain development, regulation of the cytoskeleton and integrity of the neurons, the Wnt proteins and their receptors are expressed in adult hippocampal progenitors, the suppression of Wnt signaling reduced adult hippocampal neurogenesis [26], the Wnt signaling pathway is also related with the differentiation of neurons in the cerebellum, a subcortical structure involved in motor learning [27].

The explicit memory or the declarative memory is referred as the conscious recall of facts and events, depends on the integrity of the hippocampus and some other subcortical and cortical structures such as the Subiculum and Entorhinal cortex in the temporal lobe while the implicit memory refers to the nonconscious recall of tasks or motor skills, habits, simple conditioning; this type of memory improves with the practice and experience and depends on the integrity of the circuits of the basal ganglia and the cerebellum, which are considered subcortical structures involved in motor learning but certainly these two types of memories depend on the strengthen of the synapses within the circuits generated by each one of these structures [28,29]. The integrity of the hippocampus and the hippocampal circuits are important for the acquisition of memory, the consolidation of long-term memory compromises the activation of the connections between the CA1 area of the hippocampus within the neurons in the frontal cortex, indicating that the hippocampus is important to recall recent memory while the cerebral cortex is important to recall long term memory and the integrity of the connections between these structures is needed for the acquisition and consolidation of memory during the learning process [30].

The extent of the lesion of the temporal cortex and the hippocampus determines the level of the memory impairment produced during aging, trauma or a neurodegenerative disease such as the Alzheimer disease [31].

The Dentate gyrus (DG) of the adult hippocampal formation generates neurons throughout life to support the tri-synaptic circuit of the hippocampus. There are two types of Neural progenitor cells: the Type 1 neural progenitor cells with a radial process on the granule cell layer and the non-radial type 2 cells that differentiate into glutamatergic dentate granule cells (DGCs). The dendrites of the surviving cells of the SGZ project to the molecular layer of DG (they receive inputs from the Entorhinal cortex) while the axonal projections reach the CA3 area of the hippocampus to innervate interneurons, mossy cells and the CA3 pyramidal cells supporting the circuit of the hippocampus [32].

The Hippocampus

The hippocampal region is composed of several subregions, including Dentate Gyrus (DG), the CA3, CA2, CA1 regions and the subcubiculum which is considered a transitional area between the

Hippocampus and the Entorhinal Area, which is part of the Para hippocampal gyrus. The dentated gyrus is composed of granule cells while the pyramidal neurons are in the CA3, CA2 and CA1 areas of the hippocampus. The layers of the Hippocampus from the ventricular surface to the Dentate Gyrus are the external plexiform layer, stratum oriens layer, pyramidal cell layer, stratum radiatum layer, stratum lacunosum-moleculare layer. The external plexiform layer contains the axons of the pyramidal neurons axons and the hippocampal afferent fibers from the entorhinal cortex, the stratum oriens layer contains the basal dendrites and basket cells, the pyramidal cell layer contains pyramidal cells of the hippocampus which are arranged in a C pattern; the stratum radiatum layer and stratum lacunosum-moleculare layer contain the perforant pathway composed of the apical dendrites of pyramidal cells and hippocampal afferent fibers coming from the entorhinal cortex [33].

In the rat brain, there are about 1,000,000 excitatory granule neurons in the Dentate Gyrus, and a considerable amount of excitatory pyramidal neurons in the CA3, CA2 and CA1 area with some inhibitory GABAergic neurons; the excitatory and inhibitory neurons constitute the hippocampal circuit connected with the Entorhinal cortical area and some other association cortical areas of the brain, the Hippocampal formation has been described as a three-dimensional cortical region that process information related to memory storage and spatial representation [34]. The Information flows into and through the hippocampus by three principal pathways: The perforant pathway from the Entorhinal cortex to granule cells of the Dentate Gyrus; The mossy fiber pathway from the granule cell of the Dentate Gyrus to the pyramidal cells of the CA3 region of the Hippocampus and the Schaffer collateral pathway from the CA3 region of the hippocampus to the CA1 region of the Hippocampus; the CA1 pyramidal neurons also receive a direct glutamatergic projection from the pyramidal neurons from the Entorhinal cortex, the neurons in the CA2 area receive an stronger excitatory input from the Entorhinal cortex (from the layer II) with respect of the excitatory input from the granular neurons in the Dentate Gyrus, the neurons in the CA2 area establish synaptic contact with the neurons in the CA1 and this circuit is considered a powerful Hippocampal circuit [35].

The updated circuit of the Hippocampus consist of multiple synaptic connections between the pyramidal neurons of the lateral and medial Entorhinal cortex, the granular neurons of the Dentate gyrus and the pyramidal neurons in the CA3, CA2 and CA1 of the Hippocampus; in addition of the excitatory connections from the pyramidal neurons of the Entorhinal cortex to the pyramidal neurons of the CA3 to the pyramidal neuron in the CA1 area (Entorhinal cortex → CA3 pyramidal neurons→ CA1 pyramidal neurons); inhibitory interneurons in the CA1 area receives input from the excitatory pyramidal neurons from the Medial Entorhinal cortex that provides feedforward inhibition onto the CA1 pyramidal neurons while the pyramidal neurons in the CA2 area receives direct excitatory input from the Entorhinal cortex [36]. The neurons in the CA1 area constitute the major output from the hippocampus; these neurons integrate synaptic information relevant for the arrangement of hippocampal circuits based on the temporal events that encode sequential episodic events, the apical CA1 neurons in the stratum radiatum and in the stratum lacunosum receive different level of excitatory drive input from the parallel pathways from the perforant pathway and from the Schaffer collateral pathway; a powerful excitatory input from the CA2 area and inhibitory connections from the interneurons in the CA1 that are activated by the medial entorhinal cortex [36,37]. The major output from the hippocampus projects to the mammillary nuclei and thalamic nuclei via the post commissural fornix; efferent fibers from the hippocampus to the perirhinal cortex, to the amygdala but also a loop has been described between the neurons in the CA1 area to entorhinal cortex and back to the CA1 area besides the direct connections between the CA1 area to the medial and orbital prefrontal cortex [38].

According with the principle of Donald Hebb [39] "Cells that fire together, wire together" and, "any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated,' so that activity in one facilitates activity in the other". This principle explains how the learning process modifies and strengths the synapses established between the presynaptic and postsynaptic neurons; several studies have revealed structural changes at the synapses and changes in the electrical parameters of the neurons such as the amplitude of Potentials and the firing rate of the neurons.

Long Term Potentiation

Long-term potentiation (LTP) has been described as the long-lasting enhancement of synaptic transmission that can be induced by brief repetitive stimulation of excitatory pathways in the hippocampus [40]. The repetitive stimulation of the perforant pathway with an electrode inserted in the dorsal area of the Dentate Gyrus from adult rabbits with trains of stimuli lasting 10 seconds at frequencies of 10 Hz to 20 Hz produced a long-lasting increase in the efficiency of the transmission described by the rise in the amplitude of excitatory post-synaptic potentials, an increase in the amplitude and a reduction in the latency of the population of spikes, the long-lasting change recorded is due to the strengthen of the synaptic transmission that results for the increase in the efficiency of synaptic transmission in the perforant pathway leading to an increase in the excitability of the granule cell neurons of the hippocampus [41].

Considering the learning process as the acquisition of new information while the memory as the retention process of the new information, there are several molecular, structural and functional changes in the brain that takes place as we learn new tasks; the formation of memories involves the activation of molecular events on the neurons that induces long-lasting changes in synaptic structures at the pre synaptic and postsynaptic levels; the molecular events and the functional changes on the hippocampal circuits activated by long-term potentiation (LTP) of excitatory synapses are considered the molecular and structural basis of proliferation and survival of adult-generated neurons involved in learning and memory consolidation [42,41].

During the adult hippocampal neurogenesis, the new formed cells of the Dentate Gyrus exhibited an increased in the amplitude and a decreased in the threshold generated by Long

Term Potentiation with respect to the older cells [17] showing functional contributions to the learning and memory processes in the hippocampus. Some studies using rodent animals have shown that irradiation or genetic modifications that altered adult neurogenesis produced an impairment on performance in spatial-navigation learning test and long-term spatial memory retention [43]; while some other genetic manipulations and deep brain stimulation boost neurogenesis facilitating learning and memory functions and adaptation under stressful situations [44,45]. Several studies have been conducted to explain the enhancement of the synaptic transmission and the presynaptic and postsynaptic changes within the synapses. Bosch et al. [46] described structural modifications such as the consolidation of the expansions of the dendritic spines exerted by changes on the reorganization of the actin cytoskeleton and the interaction of cofilin with F-actinin during Long Term Potentiation (LTP). Long term potentiation (LTP) increases the quantum release of neurotransmitters of the pyramidal neurons of the CA3 using slices of the rat hippocampus in vitro [47]. It was observed an enhancement of the presynaptic function during long-term potentiation (LTP) induced chemically (with tetraethylammonium) and by high-frequency (200-Hz) electrical stimulation involved the activation of L-type voltage-gated calcium channels and NMDA receptors in the postsynaptic CA1 neuron, using a fluorescent marker of presynaptic activity (FM 1-43) to directly image changes at presynaptic boutons of CA3-CA1 excitatory synapses in hippocampal slices, suggesting that the long-lasting increase in the efficacy of synaptic transmission depends on enhanced transmitter release from the presynaptic neuron [48,49]. These experiments also suggested that the enhancement of synaptic transmission by the neurons in the CA1 region of the hippocampus implies an increase in the release of glutamate that activates both NMDA and non-NMDA receptors on pyramidal cells, resulting in an excitatory postsynaptic potential (EPSP) with two distinct components with the selective increase in the non-NMDA component of the EPSP during LTP [48,49]. Long-term potentiation was inhibited in animal models using knock-down Notch mutant mice, demonstrating that the reduction in the Notch levels impairs long-term potentiation (LTP) at the CA1 hippocampal synapses and the addition of the Notch ligand, Jag-1 enhances LTP in normal mice and corrects the inhibitory effect in LTP in Notch antisense transgenic mice, this findings described the participation of the Notch signaling pathway in the synaptic plasticity related with the learning and memory processes [50].

The molecular mechanism of LTP is considered the most widely proposed mechanism of memory storage in the hippocampus and neocortex of synaptic plasticity, explains how LTP produces structural and functional changes in the presynaptic and postsynaptic neurons in the hippocampus increasing the release of the neurotransmitter and the number of dendritic spines and synapses on the postsynaptic neurons enhancing the neurotransmission; it implies the release of glutamate from presynaptic neurons and the interaction with Glutamatergic postsynaptic NMDA and AMPA-type glutamate receptors (NMDARs, AMPARs); the activation of these two ionotropic glutamate receptors leads to a strong influx of Na+ and a small efflux of K+, leading to the depolarization of the postsynaptic neuron; the NMDA receptors are also permeable to Ca++ when Mg++ is expelled by the depolarization of the neuron; the increase in the Ca++ current in the dendrites activates calcium/calmodulin-dependent kinase II (CaMKII), leading to the phosphorylation of several proteins including AMPARs, increasing the conductance through the AMPAR channel, all these sequential events activates the AMPA receptors in the postsynaptic neurons considered as one of the early events of LTP [51-54].

Another early event that contributes to LTP is the retrograde signals that comes from the activation of CaMKII and protein kinase C (PKC), tyrosine kinase on the postsynaptic neuron producing two retrograde messenger that reach the pre-synaptic terminal which are considered nitric oxide (NO) and endocannabinoids (EC) that probably enhance the release of Glutamate from the presynaptic neuron. The second messengers triggered by LTP on the postsynaptic neurons are calcium/calmodulin-dependent kinase II (CaMKII), cAMP-dependent protein kinase (PKA), protein kinase C (PKC), mitogen-activated protein kinases, and tyrosine kinases that leads to gene expression, protein synthesis, kinase expression and synthesis of growth factors like BDNF in the postsynaptic neurons contributing to the long-term expression of synaptic plasticity that strengthen the connections between the presynaptic and postsynaptic neurons [55].

The brain-derived neurotrophic factor (BDNF) facilitates long-term potentiation (LTP) in the hippocampus, which is considered the cellular mechanism of memory formation [56], this factor belongs to the neurotrophin family of the growth factors, it is essential for the development of the nervous system. The BDNF is synthesized as a precursor, pre-proBDNF protein, which is sequentially cleaved by proteolytic enzymes to yield BDNF; it is found in the spines of the dendrites but also present in the pre- and postsynaptic compartments [56,57]. The molecular mechanism of BDNF involved in the long term potentiation implies the interaction of BDNF with its TRrKB receptor leading to the activation of second messengers pathways like the phospholipase Cγ (PLCγ), phosphatidylinositol 3-kinase (PI3K), extracellular signal-regulated kinases (ERK) which is a mitogen-activated protein kinase (MAPK); PLCγ phosphorylates a nonselective cation TRPC3 channel, also the interaction of BDNF with the TRKB receptor regulates the opening of the Na+ channel Nav1.9, the voltage-gated potassium channel Kv1.3 and of the G protein-gated potassium channel Kir3 and Ca++ channels, another cellular effect is the regulation of Arc/Arg3.1 complex associated with the expression of surface AMPA receptors at excitatory synapses; BDNF regulates the NMDA (phosphorylation, via Fyn-dependent and Fyn-independent mechanisms) and upregulates the expression of the AMPA receptor; thus the extracellular signal-regulated kinases (ERK) are involved in the regulation of NMDA and AMPA receptors enhancing the glutamatergic neurotransmission, the resulting depolarization contributes to the facilitation of the induction of LTP [58-61]. BDNF integrates neural activity with the functional activity of the neuronal circuits by specific cellular mechanism such as up regulation of its own transcription via a CREB signaling mechanism, upregulation the TrkB receptor and increasing its own release [62,63]. The Sonic hedgehog protein can protect hippocampal neurons against Aβ toxicity by inducing

BDNF production [64]. The activation of the CREB signal by BDNF increases adult neurogenesis proliferation survival and dendritic maturation during adult neurogenesis [65] but the hippocampal expression and signaling mechanism of BDNF and CREB signals declines with age [66]. Brain-derived neurotrophic factor (BDNF) has anti-inflammatory and anti-apoptotic effects in vitro and in vivo and facilitate neurogenesis [67].

The learning and memory processes brings about structural changes in the synapses like the arborization of the dendrites of the neurons, increase in the release of neurotransmitters, activation of receptors on postsynaptic neurons [41]; all these events subsequently modify the functional electrical properties of the circuits that brings about the strengthen of the synaptic circuits increasing the brain reserves and cognitive reserves of the brain that depends on the efficiency, integrity and the strengthen of the neuronal circuits; in humans the development of the cognitive reserves increases when we are exposed or committed with cognitive experiences such as learning, teaching, reading a book, learning a new language also social interaction, emotional involvement in the relationships, physical activity and even a balanced diet (Maldonesi et al., 2017).

The mammalian brain is continuously learning and during this process there are structural changes in the rearrangement of synapses. Cognitive neuroscience is the discipline that study the cellular and molecular changes during the learning process. Several non-invasive studies have been conducted in humans like the determination of the electrical cerebral activity or some other techniques based on Magnetic resonance imaging (MRI) or functional Magnetic resonance (fMRI) to measure the activity of several cortical and subcortical areas while the volunteers are performing intellectual tasks such as an educational game or performing a new motor task. Using the diffusion tensor imaging (DTI) technique, an MRI-based framework, allowed the identification of some microstructural changes (as reflected by DTI measures) in some limbic structures (hippocampus and Para-hippocampal area) after only 2 hr. of training session performing a spatial learning memory tasks; these observations identified cellular rearrangement on neural tissue detected by DTI, confirming that some neuroplasticity occurs over short timescales as an evidence of rapid structural plasticity detected in humans even after just 2 hours of playing a video game [68].

The quantification of the electrical cerebral activity of the brain provides some information related to the changes on the electrical cerebral activity and also on the electrical parameters of the neurons like the firing rate pattern during the learning process; Fernandez et al. [69] observed different patterns of EEG activation in humans performing mental calculations measured by power spectral analysis, showing significant differences between tasks in the delta and beta bands in the frontal lobe; significant differences were obtained as well in delta and theta bands in right posterior area and in the beta band in frontal area; the EEG differences observed during different components of mental calculations suggested the participation of different networks [69]. Changes in the alpha-frequency (8–12 Hz) and theta-frequency (4–8 Hz) band powers related to mental and intellectual activities have been assessed in some other studies [70]. Another approach performed evaluating evoked potentials on humans showed that the rapid and repetitive presentation of visual and auditory sensory stimuli to a group of volunteers leads to a long-lasting increase in the amplitude in some components of sensory-evoked potentials registered on the scalp; these observations established a human model to study synaptic plasticity and long-term potentiation [71]. Fu and Zou [72] using rodents as an animal model to study neural plasticity have shown structural synaptic changes on cortical neurons during various sensorimotor learning experiences using photon microscopy in combination with fluorescence labeling, the stabilized synaptic structures are associated with long lasting memories for the task, these finding indicates a circuit plasticity mechanism during the learning and memory process. Whitlock et al. [73] demonstrated that inhibitory avoidance training task induces LTP in CA1, their experiments showed that one-trial inhibitory avoidance learning task in rats produced the same changes in hippocampal glutamate receptors as the induction of LTP with high frequency stimulation causing an increase in the amplitude of evoked synaptic transmission in CA1 in vivo. Bruel-Jungerman et al. [42] revealed that electrically induced LTP in the Dentate Gyrus in vivo provides a cellular and molecular environment that favors proliferation of progenitor cells in the Dentate Gyrus and survival of adult-generated neurons inducing the expression of the plasticity-related transcriptional factors.

The aging process has a deleterious effect on neurogenesis, reducing the number of precursor and proliferative cells affecting the cognitive functions [74,75,76], aging and cognitive decline is associated with oxidative stress, mitochondrial dysfunction, microglial activation and production of inflammatory cytokines, changes in the blood supply to the brain, deficit in glucose availability [77]. Bassani et al. [78] showed that injections of low doses of Streptozotocin as in Wistar rats caused a neuroinflammatory response, characterized by a marked reduction of the proliferation of neural stem cells in the Dentate Gyrus of the Hippocampus and Subventricular Zone; the impairment in the short-term and long-term spatial memory observed resulted from the reduced survival, differentiation, and maturation of newborn neurons.

External Factors That Affect Adult Hippocampal Neurogenesis

As it was previously stated, several external and internal factors regulate neurogenesis, the lifestyle has a direct impact on several neurotrophic factors enhancing their expression and maintaining the homeostasis and survival of the neurogenic niche which represents the specialized microenvironment that has a major role in maintaining and regulating NSCs proliferation; regularly exercise, adequate intake of nutrients, diet restrictions and keeping engaged in cognitive activities prevent or ameliorate neurogenesis during aging and probably in neurodegenerative diseases like the Alzheimer disease considering the fact that adult hippocampal neurogenesis is severely affected by aging and by the Alzheimer disease associated with a decline in cognitive functions.

Several reports have demonstrated that an adequate enrichment environment [78], physical exercise (Van Praag et al.,

1999), and specific hippocampal-dependent learning tasks [79] can facilitate the neurogenic activity in the Dentate Gyrus. Enrichment environment affects hippocampal LTP and improve learning [80,81] and learning itself induces LTP-like mechanisms [29]. The continuous exposure to a favorable enrichment environment during the development of the brain showed an increased in the levels of proBDNF and BDNF in the hippocampus, also associated with an increase on memory performance; a decrease in lipid peroxidation (LP) in plasma and on the hippocampus; these factors are associated with the prevention of oxidative stress in animal models [82].

One of the external factors studied extensively is the impact on daily intense and moderate exercise on neurogenesis; regular daily exercises is accompanied by an increase in neurogenesis, associated with a rise in the synthesis and secretion of BDNF and its receptor tyrosine kinase trkB [83]. Van Praag et al. [80] demonstrated that daily exercises exerts a positive effect an adult hippocampal neurogenesis, increasing the number of neurons in the Dentate Gyrus, exercise slows down the effects of cognitive decline associated with aging and neurodegenerative diseases like the Alzheimer disease, regular exercise boots mood, improves memory and sleep besides the benefits provided in the cardiovascular system increasing the blood flow, bone formation and mineralization, decreases the risk of diabetes and the metabolic syndrome, helps to lower the levels of cholesterol and controls the weight [84].

Chronic endurance exercise for 3 months induced a decrease of the phospho-tau protein levels in the CA3 subregion of the hippocampus determined by immunohistochemical analysis, this findings were obtained using a transgenic mouse model of tauopathies, Tg-NSE/htau23, which expresses human tau23 protein in the brain, among other interesting finding is the increase in the expression of Cu/Zn-superoxide dismutase (SOD) and catalase which are antioxidant enzymes involved in the reduction of oxidative stress and inflammation [85]. Similar results were obtained by Ohia-Nwoko et al. [86] showing that 7-month old P301S tau transgenic mice subjected to 12-weeks of forced treadmill exercise had a significant reduction in full-length and hyperphosphorylated tau protein in the spinal cord and hippocampus but exercise did not attenuate significant neuronal loss in the hippocampus or cortex; while Azimi et al. [87] revealed that moderate treadmill exercise ameliorated the Aβ1−42-induced spatial learning and memory deficit produced by the intra-hippocampal injection of Aβ1−42 , restoring the levels of AMPK activity and PGC-1α/FNDC5/BDNF levels. Nakajima et al. [88] showed that chronic restraint in rats increases oxidative stress, leading to the accumulation of reactive oxygen species (RAS) and lipid peroxide are associated with impairment in the cognitive function and the decrease in hippocampal neurogenesis but the daily voluntary exercise on the same group of rats subjected to chronic restraint can restored hippocampal cell proliferation of newborn cells besides the increase in glutathione s-transferases (GST) with antioxidant activity in the brain. Sleiman et al. [89] have shown that mice that were allowed to use a running wheel for 30 days had a significant increase in BDNF trophic factor associated with cognitive improvement. Similar results were obtained in mice allowed to exercise and run on a wheel exhibiting an increase in neurogenesis in the dentate gyrus, demonstrated by the significant proliferation of the progenitor cells in the sub granular zone and an increase in the survival rate [91] demonstrated that mice allowed to exercise in a wheel running had an increase in BDNF mRNA levels in the dentate gyrus after few days of exercise and remain elevated for several weeks as long as they exercise. Kodaly et al., [92] indicated that Running exercise (RE) improves cognition, formation of anterograde memories, and mood, alongside enhancing hippocampal neurogenesis on a study performed using 6-week-old male Sprague Dawley rats.

Erickson et al. [14] demonstrated that exercises increases adult hippocampal neurogenesis in humans; they conducted an interesting study where older adults without dementia were randomly assigned to receive moderate-intensity aerobic exercise 3 days a week, observing that aerobic exercise increase the volume of the left and right hippocampus by 2.12% and 1.97%, respectively, these findings were determined by Magnetic resonance images (MRI) showing that aerobic exercise selectively increases the volume of the Dentate Gyrus on the anterior hippocampus, where cell proliferation occurs, as well as in subiculum and CA1 area, with minimal effect on the volume of the posterior hippocampus; these findings were associated with the increase in BDNF obtained in plasma from the volunteers, correlating that greater changes in serum BDNF were associated with greater increases in volume of the left and right hippocampus, the cells in the anterior hippocampus mediate acquisition of spatial memory and it is more susceptible to age-related atrophy compared with the tail of the hippocampus [93].

Depression and stressful situations induce atrophy and loss of hippocampal neurons and impairs adult hippocampal neurogenesis, patients with depressive disorders or post-traumatic stress disorders have reduced hippocampal volume, this findings may be involved in the pathophysiology of depression [94], however there is extensive evidence that indicates that antidepressants have a positive impact on adult hippocampal neurogenesis [95-97]; antidepressants increase the number of adult-born neurons [94,98]. Several authors agreed that long term treatment with antidepressants increase adult hippocampal neurogenesis [99,95]. Chronic antidepressant treatments significantly activate ERK-MAPK signaling and CaM kinase IV cascades and at the same time induce CREB phosphorylation [100]. Antidepressant therapy is linked to the increase in BDNF expression and its receptor TrKBr also referred as the neurotrophic receptor tyrosine kinase 2 [99,101]. Furthermore, chronic administration of antidepressant drugs completely blocked the downregulation of BDNF mRNA in the CA3 and CA1 area of the hippocampus and the piriform cortex in response to restraint stress in rats, these results indicate the induction and expression of BDNF mRNA by antidepressants that promote neuronal survival and protect neurons from the damaging effects of stress [102].

Several drugs of abuse like morphine reduces adult hippocampal neurogenesis; Famitafresi et al. [103] showed that Hippocampal neurogenesis was significantly reduced in a model of induced addiction in rats with morphine, demonstrated by the significantly

decrease in the number of cells assessed by immunohistochemistry with BrdU in the dentate gyrus of the hippocampus; the addicted rats with morphine also showed a marked reduced performance in working memory assessed in the Morris water maze.

Isquemic insults affect adult hippocampal neurogenesis, the stroke stimulates neurogenesis in the dentate gyrus leading to an impairment where the newborn neurons generated after the stroke may fail to correctly integrate into pre-existing networks circuits giving rise to aberrant connections producing a memory decline that contributes to a significant decrease in the elderly people's cognitive function [104].

The diet intake is another external factor that influences adult hippocampal neurogenesis, several considerations about the quality and quantity of the diet must be considered to maintain the homeostasis of the neurogenic niche; high levels of saturated fats caused an impairment in neurogenesis, very low performance in learning and memory task evaluated in rodents associated as well with low levels of the expression BDNF [105]. Studies conducted using the transgenic model of fat-1 mouse, rich in endogenous n-3 fatty acids, particularly Docosahexaenoic acid (DHA) indicated that the increased DHA significantly enhances hippocampal neurogenesis showing an increased in the density of dendritic spines of CA1 pyramidal neurons in the hippocampus correlated with better spatial learning performance in the Morris water maze [106]. Polyphenols have been proposed to have anti-inflammatory effect and antioxidant activity, polyphenols inhibit molecular signaling pathways which are activated by oxidative stress and the reactive oxygen species (ROS) [53]. Polyphenols also activate the extracellular signal-regulated kinase (ERK1/2) and the protein kinase B (PKB/Akt) signaling pathways, leading to the activation of the cAMP response element-binding protein (CREB), a transcription factor in the expression of neurotrophins involved in adult hippocampal neurogenesis [107]. Resveratrol is a phenolic compound abundant in berries, grapes, red wine and peanuts have a neuroprotective mechanism against oxidative stress, inhibits pro-inflammatory enzyme expression and reduces nuclear factor-κB activation and cytokine release [108].

Oxidative stress and higher levels of reactive oxygen species (ROS) are related to aging and the formation of senile plaques observed in neurodegenerative disorders [109]. Resveratrol has potent antioxidant activity preventing neurodegeneration in Alzheimer's disease [110] and dietary restriction have shown to decrease oxidative damage decreasing the levels of reactive oxygen species (ROS) and increasing the levels of the antioxidant glutathione [111]. Dietary restriction for 4 weeks in rodents resulted in an increased in neurogenesis in the hippocampus determined by BrdU- and NeuN-positive cells in the dentate gyrus [112], the increase in proliferation and neuronal differentiation in the dentate gyrus was associated with the increase in the expression of BDNF [65]. Wu A. et al. [114] demonstrated the effect of the dietary supplementation of the curcumin derivative for 2 weeks on rats previously exposed to fluid percussion injury (FPI) as a model to study traumatic stress, showing that curcumin derivative treatment after the FPI counteracted the reductions of BDNF and its downstream effectors on synaptic plasticity increasing the neuronal signaling synapsin I, CREB, CaMKII, and Akt in the spinal cord and the hippocampus but also normalized levels of protein carbonyls known as oxidative marker.

We do not all grow older in the same way, some people have a cognitive decline earlier and faster than others, this could be explained based on the concept of the "neuronal reserve" which is considered the Inter-individual variability on the efficiency, capacity and flexibility in the brain networks, people whose networks have strengthen connections are more capable of coping with aging and neurodegenerative disorders [115] but the individual lifestyle such as a balanced diet, physical exercise, social interaction and a cognitively stimulating activities are all external factors that could retard the decline in neurogenesis associated with aging exerting a positive effect on sensory, motor and cognitive functions; enhancing the molecular and cellular mechanisms that contribute to strengthen the synaptic connections of the structures associated with cognitive functions [116-127].

Conclusions

During the learning process there are several molecular, structural and functional changes in the synapses of the neurons that constitute the hippocampal circuit to ensure the acquisition and the retention of new information; the formation of memories involves the activation of molecular events on the neurons that induces long-lasting changes in synaptic structures at the presynaptic and postsynaptic levels activated by long-term potentiation (LTP) of excitatory synapses considered the molecular and structural basis of proliferation and survival of adult hippocampal neurogenesis involved in learning and memory consolidation. There are several internal and external factors that affect adult hippocampal neurogenesis; the intrinsic factors more relevant are neurotrophic factors (BDNF, NGF, GDNF, ILGF-1), signaling pathways mediated by specific proteins, mRNAs transcriptional factors, cell-cycle regulators, inflammatory cytokines, neurotransmitters, hormones, opioids, glucocorticoids and epigenetic factors. Special consideration must be taken with the external factors that increases adult hippocampal neurogenesis like antidepressants, physical activity, a balance diet, cognitively stimulating activities, social interaction while stress reduces adult hippocampal neurogenesis in order to maintain the "neuronal reserves" to cope with aging. The increased in adult hippocampal neurogenesis exerted by several external factors is associated with the increase in the expression of the Brain derived neurotrophic factor (BDNF) which has a facilitatory effect on long-term potentiation (LTP) in the hippocampus, which is considered the cellular mechanism of memory formation.

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Conflict of Interest

No conflict of interest.

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