Journal of Chemical Neuroanatomy 101 (2019) 101667

Contents lists available at ScienceDirect

Journal of Chemical Neuroanatomy

journal homepage: www.elsevier.com/locate/jchemneu

Review

Regulation of adult hippocampal neurogenesis exerted by sexual, cognitive and physical activity: An update

P. Leal-Galicia[1,*], H. Romo-Parra[2], L.M. Rodríguez-Serrano[1], M. Buenrostro-Jáuregui[1]

[1] Laboratorio de Neurociencias, Departamento de Psicología, Universidad Iberoamericana Ciudad de México, México
[2] Facultad de Psicología, Universidad Anáhuac, Mexico City, Mexico

ARTICLE INFO

Keywords:
Adult hippocampal neurogenesis
Cognitive activity
Sexual activity
Physical activity
LTP

ABSTRACT

In 1962, Joseph Altman described that the brain generates neurons after the postnatal period, and this continues throughout your life (Altman, 1962). This was a breakthrough in the neuroscience field because before this the accepted paradigm was that the brain only generated neurons during the embryonal development. This discovery has been controversial ever since, especially since one of the areas of the brain with neurogenic properties is the hippocampus, which is the area involved in memory storage and neurodegenerative processes. The adult hippocampal neurogenesis modulates in response to different environmental factors. In this article, we review how exercise and cognitive and sexual activity can regulate the generation of new neurons in the hippocampal in an adult brain and the impact of these new neurons in the brain circuitry.

1. Introduction

The traditional paradigm in neuroscience argued that the adult brain does not have the capacity to generate new neurons after the postnatal period. This was declared by one of the founding fathers of the neuroscience, Santiago Ramón, who argued that nothing in the brain regenerates (Ramon and Cajal, 1928). This is actually true because old neurons do not generate new ones because the generation of new cells is only observed in other cell lineages. In the brain, there are niches of neural precursor cells that have the capacity to generate new neurons throughout the lifespan. This was first described by Lois and Alvarez-Buylla (1993). These areas are located in the sub-ventricular zone (SVZ) and in the hippocampus, between the hilus and the granular cells, known as sub-granular zone (SGZ) (Altman, 1962; Altman and Das, 1965).

The existence of this neuronal niche has been demonstrated in several species and recently in humans. At the beginning of 2018, an article in *Nature* was published, which claimed that neurogenesis in the human hippocampus can diminish and be undetectable (Sorrells et al., 2018). This initiated a debate on the importance of studying adult hippocampal neurogenesis (AHN). Seminal reports on AHN demonstrated that the human adult brain actually generates new cells in the hippocampus. This result is based on studies analyzing post-mortem brains of persons that received 5-Bromo-2′-deoxyuridine (BrdU), an analogue of thymidine injected in order to track the growth of cancer (Eriksson et al., 1998).

Knoth et al. (2010) documented the brain-specific microtubule-associated protein, doublecortin (DCX) found in human brains. This protein has been identified in murine brains during the early period after division and demonstrates a neural commitment. This labelling in the human brain was detected by Knoth et al. (2010) in brains of neonates with individuals up till 100 years, contributing another important piece of evidence, which documents the existence of AHN in human adults. Recently, Boldrini et al. (2018) analyzed the brains of healthy people from 14 to 79 years-old, identifying cells markers of AHN. Lledo et al. (2006) studied neurogenesis in the hippocampus and found that under normal conditions it is confined only to the subgranular zone (SGZ) within the granule cell layer (GCL) of the dentate gyrus (DG). This research documents the presence of ANH in the adult human brain and therefore reinforces the relevance of studying the mechanism of this plasticity phenomena. This research also highlights its functional relevancy and the stimulus that promotes the incorporation of new cells in the hippocampal circuitry. Recently, a study conducted by the group of Dr. María Llorens-Martín was published in Nature Medicine. This report described the developmental stages of AHN in the human adult brain (Moreno-Jiménez et al., 2019). Researchers argue that tissue fixation and pretreatment conditions are crucial for efficient cell marker detection. The supplementary data showed that there is a relationship between the cell markers detection efficiency and the time elapsed after a person dies. The longer time

* Corresponding Authors.
E-mail addresses: p32409@correo.uia.mx (P. Leal-Galicia), mario.buenrostro@ibero.mx (M. Buenrostro-Jáuregui).

https://doi.org/10.1016/j.jchemneu.2019.101667
Received 20 December 2018; Received in revised form 29 July 2019; Accepted 13 August 2019
Available online 14 August 2019

lapses after a person dies the less number of immunoreactive cells are detected. As shown by Moreno-Jiménez et al. (2019) 10 h after time of death is the optimal amount immunofluorescence of DCX, NeuN, Calretinin, Calbindin, PSNA-CAM and Phosphorylated histone 3 (PH3) can be detected in the brain tissue. In addition, fixation times and solutions also influence the cell markers immunodetection. This design and meticulous analysis is proof that AHN exists in the adult human brain. However, many researchers contest this finding and we argue that this is due to their methodological procedures and how their research is framed, and is not a sign of evidential proof.

Due to the importance of the research of AHN in neuroscience, we reviewed the existing literature relating to how exercise and cognitive and sexual activity may influence the generation of new neurons in adult hippocampus brains.

2. The impact of cognitive activity in the generation of new neurons in the dentate gyrus

Kempermann et al. (1997) published the first study which proved that AHN could be up-regulated by being exposed to a novel and complex environment. The work of Prof. Kempermann started a new line of study in the field of AHN and its activity-depending regulation. This has captured the attention of many researchers since. In this 1997 article, mice were exposed to a novel and complex environment in the form of a larger cage with toys and tubes. Usually, laboratory animals are housed under standard laboratory conditions. The animals under our experimental conditions had the chance to achieve social interaction, which is also important for rodents. Results showed that these rodents living in these experimental conditions had an increase in hippocampal neurogenesis.

The enriched environment (EE) conditions comprise of housing rodents in small groups in a large cage, with toys and tubes, which the rodents find novel and complex but have no biological relevance. The animals have the chance to display social interaction, voluntary exercise and exploratory behaviour (Rosenzweig, 1966). This exposure to an enriched environment has produced benefits such as an improvement in learning and memory tasks, as well as an increase in the proliferation, survival, and differentiation in neurons of newly generated cells in the dentate gyrus (Kempermann et al., 1997; Nilsson et al., 1999; Van Praag et al., 1999; Bruel-Jungerman et al., 2005). Interestingly, providing rodents with a complex and novel environment does not necessarily stimulate the animals in the same way because the benefits are related to how the animals interact with the system. Animals that engage in more activity inside the EE cage have a higher number of new cells, compared to those animals that enter the EE cage at the same time but interact less with the novel and complex elements in the cage. This highlights the necessity of engaging in activity inside the EE cage, rather than just being present (Leal-Galicia et al., 2007). The advantages of the EE can be seen by combining the setting. For example, introducing mice in a cage with a running wheel and after the 10 days removing the mice to an EE cage into a EE cage has an accumulative effect as it increases the number of newly generated neurons in the mice (Fabel et al., 2009). This effect is noticeable when comparing rodents only exposed to just the running wheel or just the EE cage, highlighting the importance of combining these two settings.

The duration of the exposure to the EE setting is a contributing factor in the neurogenic effect. An exposure of 7 weeks with the transgenic mouse model of Alzheimer Disease expressing the human mutant β-amyloid (Aβ) precursor protein (APP Sw, Ind) results in cognitive benefits associated to benefits in the population of mature adult newborn neurons, which show an increase in the number, the dendritic length and number of projections to the cornu ammonis (CA) 3 region of the hippocampus (Valero et al., 2011).

The age of the rodent when it is exposed to these conditions plays an important role and has a beneficial effect on EE and AHN. In wild-type rats, lengthy exposure to EE since youth helps maintain the pool of new neurons and has a positive impact on the execution of memory tasks in 18 months-old rats (Leal-Galicia et al., 2008). With the murine model f Alzheimer Disease, the APP23 transgenic mice, exposes animals to an EE starting at 6 or 18 months-old have different effects and show improvement when exposure starts at 6 months-old (Mirochnic et al., 2009). Evidence suggests that the APP23 mice have more newly generated neurons compared with animals just running on the wheel (Mirochnic et al., 2009).

The exposure to EE results in several benefits for the animals, such as improved memory performance. Garthe et al. (2016), show that 6 to 8-week-old female C57BL/6 N mice exposed for 7 weeks to an EE setting, perform better in memory tests, such as the Morris Water Maze. This was shown in how the mice chose more effective search strategies to locate the platform, highlighting an increase in memory performance and novel problem-solving. The researchers employed conditions that required them to move the goal twice. Once on the test day 4–5 and twice on the days 8–9. The animals exposed to an EE setting show increased memory functioning, novel and fluid problem-solving techniques which suggest improved neurogenesis. The mice´s ability to change strategies to find the platform when its location was changed is demonstrative of this. The improved performance introduced by the EE conditions is related to adult hippocampal neurogenesis due to the generation of new neurons as abolished by treatment with Temozolomide, a drug that inhibits neurogenesis (Garthe et al., 2009). The improved problem-solving skills, which included searching for new and novel strategies are not observed in animals who are injected with Temozolomide at 50 mg/kg (i.p., 2.5 mg/ml in 0.9% NaCl), 3 days per week by 4 weeks. Therefore, the researchers conclude that the presence of newly generated neurons is necessary for these mice to display novel and complex problem-solving skills, which can be seen in their flexible and improvised searching strategies for the platform in the experiment.

Another cognitive stimulus that promotes AHN is learning tasks, in particular, spatial learning, which is a hippocampal-dependent task, with high relevance for the animals in terms of survival. The group of Liisa Galea, in Canada, have reported interesting information regarding the effect of Water Maze test in AHN. Epp et al. (2007) demonstrated that spatial training in the Water Maze test increases the number of BrdU positive cells when the BrdU is delivered 6 days before the task. This increase was observed only in animals that displayed poor or below average learning abilities, determined by a median split. Interestingly, the researchers did not find differences in the pool of newly generated cells in animals injected 1–5 or 11–15 days before they performed the test. This suggests that there is a critical period for the cells to be recruited in the hippocampal network. Furthermore, the same group which, was subjected to the same degree of difficulty in the Water maze test, produced new hippocampal neurons. Depending on the number of platforms, if there were hidden or not and the availability of visual cues, the generation of new neuron decayed or increased (Epp et al., 2010) The animal strain also influences the impact of learning in AHN. Sprague-Dawley rats, during the probe trial, showed an increase in the number of new young neurons labelled with doublecortin that exhibit firing patterns, identified with the presence of the early intermediary gene product zif268, whereas Long-Evans rats showed an increase in BrdU cells but not doublecortin which suggest that rat strains have different maturation patterns exerted by learning task (Epp et al., 2011).

Another important group in the field of learning and AHN is the group of Nora Abrous in France. In collaboration with the research team of Alejandro Schinder in Argentina, it was proven that spatial learning has no effect on cell survival, cell death, cell proliferation and dendritic development in mice (Trinchero et al., 2015). Trinchero et al. (2017) research showed that aged mice when exposed to the EE setting result in neuronal development and the integration of the newly generated cells, which is mediated by neurotrophins, which are accelerated by voluntary exercise or environmental enrichment.

3. Sexual behaviour, adult neurogenesis and cognitive performance

Sexual behaviour has a high evolutionary value since copulation is necessary for the survival of many species via the reproduction and genes transmission. However, it is not crucial for individual subsistence. It is well known that sexual behaviour induces a reward state that increases the probability that copulates patterns behaviour will be repeated in the future (Bedos et al., 2018). Sexual motivation is considered a case of incentive motivation and stimuli with sexual meaning must be capable of activating behaviours that induce males to seek and approach the stimulus (Ågmo, 1999). Despite sexual behaviour not being considered a primary motivational behaviour such as eating or drinking, phylogenetically it should be considered at the same level. In line with this argument, sexual behaviour which is important for species survival exists in conjunction with neurobiological mechanisms that allow the adaptation of animals (including humans) to environmental demands and changes that allow them to perform adaptive behaviours which could reach the mating couple. In this section, we will briefly review how sexual behaviour could induce neurogenesis (as neurobiological mechanisms of adaptation), particularly in the hippocampus (and also in the olfactory bulb). The olfactory bulb is an important region for neurogenesis in the adult brain of mammals. However, this review does not focus on this structure. For a more detailed and in-depth review of neurogenesis and sexual behaviour, we recommend reading Bedos et al. (2018) and Trivino-Paredes et al. (2016) to gain a deeper understanding of the hormone's effects on hippocampal structural plasticity.

Hippocampus has been linked to a fundamental function in learning and memory. In natural environmental conditions, it is common for animals (including humans) to have to look for a mating partner in a large, complex, and changing environment. Therefore, it is understandable that evolution favours by natural selection the animals with better memory (visuospatial memory), higher learning capacity and better skills for finding a partner. Another important issue is neurogenesis inhibitors. In this vein, it is known that microglia are abundant in the DG, and it has been suggested that microglia could participate in the negative control of neurogenesis. These glial cells performed as immune cells inside the brain in inflammatory reactions. Gebara et al. (2013) suggests that microglia inhibit the proliferation of neural stem/progenitor cells despite the absence of inflammatory stimulus.

It is known that stress is one of the strongest hippocampal neurogenesis inhibitors (Paizanis et al., 2007). Kim et al. (2013) reported that sexual interactions prevented a reduction in neurogenesis caused by exposure to chronic stress by restricting movement among male mice. Kim et al., 2013 suggest that sexual interaction could protect adult neurogenesis in the hippocampus and memory function against chronic stress suppressive actions. Also, it has been confirmed that a single sexual interaction was sufficient to increase the proliferation of hippocampal cells, and 14 consecutive days of 30-minute sexual interactions caused a significant increase in neurogenesis and stimulated the growth of dendritic spines and dendritic architecture (Leuner et al., 2010). In addition, the same paper reported that a single sexual interaction increased corticosterone levels, but not chronic sexual exposure. Researchers suggest that a rewarding experience in the form of a sexual interaction buffers against the harmful effects of early-elevated glucocorticoids and promotes neuronal growth and reduces anxiety (Leuner et al., 2010). It has been described that sexual interactions with unfamiliar females caused a significant reduction in neurogenesis in the dentate gyrus compared to males that interacted with familiar females and control group. Significantly more ejaculations and intromissions were observed in males in the familiar group compared to the unfamiliar group. The researchers in the study suggest that these results indicate that the intensity and level of sexual activity could be associated with neurogenesis, and interactions with unfamiliar sexual partner reduce adult neurogenesis (Spritzer et al., 2016).

It is known that the brain-derived neurotrophic factor (BDNF) is involved in synaptic plasticity and memory function (Poo, 2001), is required for new hippocampal neurons to grow and survive, (Sairanen et al., 2005), promote cellular differentiation in the hippocampus (Barde, 1994) and the subventricular zone (Bath et al., 2012). In this vein, it was proven that sexual activity increased the expression of BDNF, and also its main receptor tyrosine kinase B (TrkB), and cyclic adenosine monophosphate (cAMP) response element-binding factor (Kim et al., 2013). In females, it has been demonstrated that dominant-male pheromones stimulate neuronal production in both the hippocampus and olfactory bulb in female mice (Mak et al., 2007).

Neurogenesis is important because it improves brain functioning and increases adaptive behaviours that allow animals to adapt to the constant changes in their environment. Cognitive functioning, such as memory, are linked to hippocampal functioning and the incorporation of new neurons in the brain structure. As it is known, age-related decline in neurogenesis could contribute to impaired cognitive functions. As mentioned before, sexual behaviour induces a reward state (Bedos et al., 2018) and promotes neuronal growth (Leuner et al., 2010). Consequently, a possible sexual behaviour's protective function against age-related cognitive impairment is possible. It has been reported that sexual experience increased the neurogenesis in the dentate gyrus with either single or repeated (14 or 28 days) exposure to sexual experience in middle-aged (9–11 months) rats. The repeated long-term (14 or 28 days) access to sexually receptive female also improved the cognitive function. Nevertheless, the improvements in cognitive function were lost in a 14 days withdrawal period and were shown not to disturb neurogenesis. Researchers suggest that repeated sexual experience could promote adult incorporation of new neurons and restore cognitive functioning in the middle-aged as long as the mating behaviour persists (Glasper and Gould, 2013). Also, it has been concluded that mating contributes to improving recognition memory, which was tested in a novel object recognition task (NORT) paradigm that has been associated to hippocampal learning and memory, and moreover sexual exposure protects against chronic stress suppression of neurogenesis (Kim et al., 2013).

There is no data in humans demonstrating that sexual behaviour induces hippocampal neurogenesis and beneficial effects on cognition. However, recently there have been studies in elderly humans (50–83 years) in which sexual activity and cognitive function have been associated, it has been found that at a higher frequency of sexual activity resulted in improved verbal fluency and increased visuospatial skills (Wright et al., 2017; Wright and Jenks, 2016). There is an association between cognitive functioning and one´s own perception of sexuality in older adults (71 ± 8.87 years), concluding that greater cognitive functioning was associated with the way in which older people perceived their current sexuality (Hartmans et al., 2015). Little is known about the association between neurogenesis, cognitive functioning, and sexual behaviour, particularly in normal ageing and dementia. Therefore, it is vital that more research is carried out on the relationship between neurogenesis, sexual behaviour, and cognitive function.

4. Physical exercise-induced adult neurogenesis and enhanced memory

Learning is the process by which we acquire knowledge, whilst memory is the process by which we retain that knowledge over time (Kandel, 1991). Scientists divide memory systems into two broad categories: declarative and non-declarative. The first is the most familiar system of memory: the conscious memory that has memories of facts and events (Reber, 2013). This is also referred to as explicit memory. The non-declarative memory is the unconscious memory and is also known as implicit memory. Non-declarative memory includes simple forms of learning and memory such as habituation, sensitization, and classical conditioning (Leff et al., 2002).

It is well known that exercise can have many benefits for the body.

These benefits can be observed in the cardiovascular system (Myers, 2003), the motor system, the skeletal system and even the nervous system (Hegde, 2018). In the brain, physical activity can increase neurogenesis, synaptic plasticity and accuracy in terms of performance in learning and memory tasks (Patten et al., 2015). Therefore, physical exercise has many benefits on structural and functional plasticity in the hippocampus, the region related to memory and learning. In a recent study, it was demonstrated that blood cells, specifically platelets, were able to modulate adult neural precursor cells and evoke neurogenesis. Blood cells impact neural stem cells by introducing stages of differentiation in the newly generated cells and ultimately changing them into neurons (Leiter et al., 2019).

Synaptic plasticity and memory, independent of the different brain areas where they might occur, share a common feature. This is that during memory formation the activity-dependent synaptic plasticity is induced at specific synapses, which is a prerequisite for information storage that underlies the type of memory mediated in the brain area where neuronal plasticity is observed (Martinez and Derrick, 1996). The main mechanism of synaptic plasticity that reflects the activity of synaptic information storage processes is called long-term potentiation (LTP) (Bliss, 2016; Bliss et al., 1990). LTP refers to a long-lasting increase in the amplitude of an evoked post-synaptic potential or post-synaptic current, in vitro or in vivo (Bliss, 2016). This phenomenon has been demonstrated in many regions of the hippocampus, and the cellular and molecular bases behind the LTP of each region are varied. Along these lines, it is well known that LTP-duration can vary from several minutes to hours or even days (shown in vivo) (Bliss, 2016). LTP has two phases, the first phase, called early LTP, begins immediately after the LTP-inducing stimulus and depends primarily on short-term kinase activity (Malinow et al., 1988). The Late-LTP is dependent on the on-demand protein synthesis, which requires activation of kinases and transcription factors (Lonze and Ginty, 2002). An example would be the calcium/calmodulin-dependent protein kinase II (CaMKII), a kinase that is been referred to as a “memory molecule” by Tosh et al. (2000) and is associated with the enhancement of spatial memory and fear conditioning (Bejar et al., 2002).

Van Praag et al. (1999) made one of the first connections between exercise and LTP in 1999. They found that groups of housed female mice with free access to an exercise wheel showed better learning performance on the Morris water maze, but also greater LTP in the dentate gyrus after 7 days of exercise (Van Praag et al., 1999). Later on, many researchers have shown that animals that exercise have granule cells in the dentate gyrus with longer and more complex dendritic arborisations than control animals who do not exercise (Eadie et al., 2005; Pertwee, 2012; Redila and Christie, 2006; Stranahan et al., 2007). These observations contribute to the enhancement in synaptic connectivity and the subsequent improvement of synaptic plasticity (Williams et al., 2010), or deterioration in synaptic strength as suggested in Alzheimer disease (Lin and Koleske, 2010).

Is known, that N-methyl d-aspartate (NMDA) receptors are important for the maintenance of learning-dependent long-term potentiation in rat hippocampal CA3 area (Brandalise et al., 2016). As shown by Yu et al. (2013), exercise training improved the opening conductance level, time and probability of NMDA receptor channels through the modification, made by the motor activity, on the characteristics of long-term potentiation NMDA-dependent type in the hippocampal CA3 neurons of rats with cerebral infarction (Yu et al., 2013). Is suggested that the time of exercise can contribute directly to the structural and functional changes in hippocampus and results suggest that long-term exercise may increase LTP in vivo in the DG in rats (Patten et al., 2013), therefore improving synaptic plasticity. In another study by Radahmadi et al. (2016), it was shown that a 21-day exercise treatment increased both the cell excitability and LTP in the dentate gyrus of hippocampus; but a 21-day withdrawal period from exercise impaired the beneficial effects of the exercise shown in control rats (Radahmadi et al., 2016). Else, late- LTP was shown to be impaired in sedentary Aβ rats but not in exercised Aβ rats, of a rat model of Alzheimer’s disease, with the respective neuroprotective effect of regular treadmill exercise training on long-term memory (Dao et al., 2016)

However, not everything is related to the Hippocampus. Recently, Zhou, Li, Chen, Luo, and Pan, described the importance of LTP NMDA-dependent, in corticostriatal, pathways as a prominent role in motor learning and habit formation (Zhou et al., 2018). Along this line is known that hyperexcitability of the same pathway induces basal ganglia dysfunction as seen in Parkinson Syndrome, which can be improved by exercise (Chen et al., 2017). Research revealed that whole-cell patch clamp recordings, which enhanced presynaptic glutamate release and downregulated postsynaptic NMDA receptor functioning, also lead to the impaired corticostriatal plasticity in exercise-induced fatigue mice, thus, corticostriatal synaptic plasticity is impaired when the animals reach fatigue levels (Ma et al., 2018). It is important to note that classical conditioning activates NMDA receptors in the amygdala, and facilitates LTP leading to modifications of neuronal circuitry within the hippocampus (Frith and Loprinzi, 2018). Classical conditioning also promotes BDNF action, neural plasticity, augment neurogenesis, and contributes to structural morphologies conducive to memory (Frith and Loprinzi, 2018).

Recently, a rapid reorganization of synaptic inputs and biophysical properties in response to exercise has been reported (He et al., 2018). The authors found, with patch clamp technique, that physical activity depolarized and increased firing rate of arcuate pro-opiomelanocortin which was concomitant with increased excitatory inputs to these neurons; therefore, leading to a reorganization due to leptin receptors (He et al., 2018).

Overall, many questions arose concerning the fact that LTP is so closely related memory (Stevens, 1998). LTP is relevant to encoding, storage, consolidation and retrieval in terms of memory functioning (Martin et al., 2000). There are also many questions about the relationship between exercise and LTP. For example: are the uniformity and the parameterization in experimental protocols employed enough to explain the role of exercise in animal models? Does the free access to the wheel influence the results if the animals are forced to exercise? These research questions are important and require further investigation.

As mentioned before the hippocampus plays a critical role in the consolidation and extinction of memory (Deng et al., 2010; Fan et al., 2018). New hippocampal neurons are believed to contribute to the functioning of the hippocampus and there is evidence that they are recruited in the hippocampal neuronal circuits involved in spatial learning (Kee et al., 2007). It is known that physical activity induces neurogenesis and enhanced synaptic plasticity, and this phenomenon is strictly correlated with a significant increase in hippocampus-dependent learning and memory tasks (Wu et al., 2015). In this vein, running exercises (RE) enhances hippocampal neurogenesis, which allows for the formation of new memories (Cooper et al., 2018), and the promotion of long-term potentiation (Vivar and van Praag, 2017), which is considered a physiological model of certain forms of learning and memory. In particular, RE induces structural and functional plasticity in the hippocampus, including cell proliferation, survival and differentiation in the dentate gyrus (Voss et al., 2013), which may also facilitate the acquisition and retention of memories (Motta-Teixeira et al., 2016). For example, Greenwood et al. (2009) showed that 6 weeks of RE before conditioning improves hippocampus-dependent memory for context, but not extinction (amygdala-dependent), suggesting that voluntary physical activity selectively increased hippocampus-dependent memory.

In line with this argument, Kim and Leem (2016) suggest that regular and prolonged exercise can alleviate chronic stress-induced hippocampal-dependent memory deficits. In addition, this report shows that an increase in BDNF may contribute to hippocampal neurogenesis and enhanced memory induced for RE. In this regard, in the adult brain, BDNF is known to be important in synaptic plasticity (Park and Poo,

2013), learning and neurogenesis (Pinnock and Herbert, 2010), and is considered to be the most important factor to be up-regulated by RE (Vivar et al., 2012). Mature BDNF activates the TrkB, which is followed by the phosphorylation of downstream effectors, including protein kinase B, extracellular signal-regulated kinase, and calcium-calmodulin-dependent kinase (Park and Poo, 2013). Ultimately, the transcription factor cAMP-calcium response element binding protein (CREB) is phosphorylated and activated, which mediates the transcription of genes that are essential for the survival and differentiation of neurons (Phillips et al., 2014). Therefore, BDNF improves various aspects of adult hippocampal neurogenesis such as neural stem cell proliferation, neuronal survival, dendritic arborization and synaptic plasticity (Liu and Nusslock, 2018; Pinnock and Herbert, 2010). This neurotrophin decrease with age in humans and rats, nevertheless RE can increase BDNF hippocampal levels, leading to increasing neurogenesis even in aged animals (Seib and Martin-Villalba, 2015).

It has been shown that RE in rats from 3 to 9 months of age, significantly reduced the age-dependent decline in cell proliferation and leading to a consecutive increase in the number of mature cells (Kronenberg et al., 2006). Recently, Choi et al. (2018) show that RE induces neurogenesis, improved cognition, increase levels of BDNF despite the presence of Aβ. This study shows that promoting neurogenesis in the hippocampus can ameliorate Alzheimer's disease pathology and cognitive deficits but only in the presence of a healthier, improved local brain environment, stimulated by RE. Therefore, the studies prior show that RE benefits brain function and may prevent or delay the onset of neurodegeneration-associated memory loss in humans (Duzel et al., 2016). Ming and Song (2011) suggest that the presence of functional adult neurogenesis throughout the lifetime demonstrates the strikingly plastic nature of the adult mammalian brain. Another study highlights the assumption that RE has beneficial effects in memory process by enhancing neuroplasticity and preventing diseases associated with cognitive decline (Hötting and Röder, 2013). In this regard, Smith et al. (2010) reported in a meta-analysis study that 1 to 12 months of exercise in healthy adults results in behavioural benefits in memory, attention, processing speed and executive function. Another meta-analysis study suggests that humans also experience a dose-response relationship in which each exercise session corresponds to a dose of increased BDNF expression (Szuhany et al., 2015). Therefore, manipulation of adult neurogenesis has currently been a target of a potential treatment for ageing-related cognitive deficits (Yau et al., 2014). For a more detailed and in-depth review of neurogenesis and physical exercise, we recommend reading Trivino-Paredes et al. (2016). In summary, convergent evidence in animal studies suggests that physical exercise facilitates neurogenesis in the hippocampus and consequently could improve memory.

5. Conclusion

AHN is a fascinating plasticity phenomenon. The discovery in animal studies that up-regulation produces beneficial effects in cognitive performance and exposing up-regulation to certain environmental conditions protects the brain modulation used for daily activities, is ground-breaking. So far, nobody has demonstrated in humans that sex induces neurogenesis and benefits cognition, highlighting an interesting possibility in future research. This review on the existing research on hippocampal neurogenesis has revealed several interesting research questions that are certainly worth investigating.

Funding

Authors thank Universidad Iberoamericana for funding this publication. Luis Miguel Rodríguez-Serrano, was supported by CONACyT postdoctoral grand, México.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

The authors thank Sarah Frances Gordon for language revision, proofreading and editing the text.

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