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Review article

Does the enriched environment alter memory capacity in malnourished rats by modulating BDNF expression?

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Abstract
Environmental factors interfere in the neural plasticity processes. Among these, malnutrition in the early stages of life stands out as one of the main non-genetic factors that can interfere in the morphofunctional development of the nervous system. Furthermore, sensory stimulation from enriched environments (EE) also interferes with neural development. These two factors can modify areas related to memory and learning as the hippocampus, through mechanisms related to the gene expression of brain-derived neurotrophic factor (BDNF). The BDNF may interfere in synaptic plasticity processes, such as memory. In addition, these changes in early life may affect the functioning of the hippocampus during adulthood through mechanisms mediated by BDNF. Therefore, this study aims to conduct a literature review on the effects of early malnutrition on memory and the relationship between the underlying mechanisms of EE, BDNF gene expression, and memory. In addition, there are studies that demonstrate the effect of EE reversal on exposure to changes in the functioning of hippocampal malnutrition in adult rats that were prematurely malnourished. Thereby, evidence from the scientific literature suggests that the mechanisms of synaptic plasticity in the hippocampus of adult animals are influenced by malnutrition and EE, and these alterations may involve the participation of BDNF as a key regulator in memory processes in the adult animal hippocampus.

Keywords: BDNF; Enriched environment; Hippocampal formation; Malnutrition; Memory, Neural plasticity

Highlights:
- The synaptic plasticity mechanisms in the hippocampus of adult animals are influenced by EE.
- BDNF acts as a regulatory factor in the survival and development of dendritic neuronal precursor cells in the hippocampus of adult animals.
- Exercise-induced cell proliferation can be promoted by increased BDNF expression.

Introduction

The nervous system (NS) can modify its morphofunctional organization in response to internal or external demands, characterizing brain plasticity (Sale et al., 2014). The neural mechanisms that are involved in brain plasticity are responsible for the synaptic facilitation that forms the basis of brain functions associated with the memory process, functionally classified as synaptic plasticity. Studies on this theme include the processes of synaptic sensitization, habituation, long-term potentiation (LTP), and long-term depression (LTD). Specifically, LTP was evidenced in the work of Eric Kandel in the model that used the invertebrate Aplysia (Kandel, 2001). Brain areas of vertebrates, such as the hippocampus, have been investigated since 1973 by Bliss and Lomo, who verified the basis of the mechanisms of memory formation (Bliss and Lomo, 1973).

The hippocampus plays a role in integrating the mechanisms of learning and memory (Ma et al., 1998) and regulates motivational factors, hormonal factors, emotional behaviors, and responses to stress. The subareas involved in these hippocampal functions are segregated topographically along the Spatio-temporal axis, where the dorsal region participates in the learning and memory processes, while the ventral region, behaviors, and emotions are related to anxiety (Bannerman et al., 2004; Moser et al., 1993).

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Exogenous factors can interfere with this synaptic plasticity and modulate memory development and/or maintenance. One of these factors is nutritional malnutrition in the perinatal period. Early malnutrition causes a permanent decrease in the number of granular cells of the hippocampus dentate gyrus (DG). These factors can cause morphofunctional changes in the SN, which may result in a decrease in the number of neurons (Pérez-García et al., 2016) and cells glial generated in the period of neurogenesis and gliogênese, or because of apoptosis due to the insufficient nutritional availability (Sani and Bedi, 2007).

Another exogenous factor is voluntary physical activity that occurs in response to stimulation by enriched environments (EE). Voluntary physical activity can promote changes in motor functions (Risedal et al., 2002), learning, memory (Rossi et al., 2006), and emotional behaviors (Tanti et al., 2012). In this sense, the EE acts as a combination of complex stimuli of inanimate and social objects that influence morphological and functional aspects of NS, increasing sensory, cognitive, motor, and social interaction stimulation (Cutuli et al., 2011). Behavioral studies have shown that exposure to EE increases memory capacity, especially in attempts at spatial learning (Birch et al., 2013; Prusky et al., 2000). The neurogenesis and synaptic density have also been stimulated by EE promoting exploratory activity (Gobbo and O'Mara, 2005), and associated with performance on behavioral tests (Hopkins and Bucci, 2010). The differences found in neural pathways stimulated by EE are related to changes in neurotrophic factors, especially BDNF (Cutuli et al., 2011; Falkenberg et al., 1992; Pietropaolo et al., 2004). This molecular mechanism underlying EE that induces neuroprotection is attributed, in part, to the positive modulation of neurotrophin levels (Rossi et al., 2006).

The term EE as an experimental process emerged in the late 1940 and was created by Donald Hebb (Eckert and Abraham, 2010; Neves et al., 2008). Although there is no consensus on defining suitable EE paradigms, animals are generally kept in larger groups and in cages whose environment is complex and variable (Simpson and Kelly, 2011). The positive effects of EE also include the functioning of the SN. Currently, one of the brain regions most studied to determine the effects of EE on nervous tissue is the hippocampus (Madroñal et al., 2010).

The plasticity in the hippocampus involves changes in the expression of trophic factors, survival promoters, and neuronal differentiation during development (Huang and Reichardt, 2003; Olson et al., 2006). The exposure sequence EE increases the expression of BDNF, GDNF, NGF, neurotrophin-3, and NT-3 levels and many of their corresponding receptors increase in the hippocampus (Olson et al., 2006; Williamson et al., 2012). Therefore, this study aims to conduct a literature review on the effects of early malnutrition on memory and the relationship between the underlying mechanisms of EE, BDNF gene expression, and memory. Furthermore, there are studies on the effect of EE reversal on exposure to changes in the functioning of hippocampus in the adult rats that were malnourished early.

The hippocampus and the formation of memory

The work of Terje Lomo and Timothy Bliss in the late 1960s induced LTP (Bliss and Lomo, 1973). It was found that a few seconds of high-frequency electrical stimulation increases synaptic transmission in the hippocampus for days or even weeks (Neves et al., 2008). However, progress in understanding the LTP mechanism has been strongly based on *in vitro* studies of slices of the hippocampus, as neurons in this region allow for their sectioning so that the circuits remain intact. In these preparations, the cell body of pyramidal neurons is found in a single layer, which is divided into several distinct regions, the main ones being CA1 and CA3 (Izquierdo et al., 1999). The dendrites of the pyramidal cells of the CA1 region form a thick band that receives synapses from the Schaffer collaterals, the axons that originate from the pyramidal cells of the CA3 region (Riedel and Micheau, 2001). Most studies with LTP do so in the synaptic connections between Schaffer collaterals and CA1 pyramidal cells, where the electrical stimulation of Schaffer collaterals generates a postsynaptic excitatory potential (EPSP) in postsynaptic CA1 cells (Martin et al., 2000).

LTP occurs not only in the excitatory synapses of the hippocampus but also in other synapses in a variety of brain regions, including the cortex, the amygdala, and the cerebellum. LTP also exhibits the property of specificity of input: when LTP's are induced by the stimulation of a synapse, the same does not occur in other inactive synapses that are in contact with the same neuron (Zagrebelsky and Korte, 2014). This characteristic of LTP is consistent with its involvement in the formation of memory, since the selective increase in the stimulation of certain sets of inputs is probably necessary to store specific information.

Using the Morris water maze, researchers have shown that blocking NMDA receptors prevents LTP induction *in vivo* and *in vitro* and therefore results in impaired spatial memory (Morris et al., 1990). Genetic manipulation is also used to demonstrate a link between LTP and a specific type of long-term memory (DLM). A study carried out with the modified R1 subunit of the NMDA receptor in the CA1 region of the mouse hippocampus showed a delay in LTP, resulting in damage to spatial memory (McHugh et al., 1996).

Research that studies the role of protein kinases in LTP has advanced since it is known that these proteins influence the induction, expression, and maintenance of this physiological event. Thus, some protein kinases, such as calmodulin-dependent protein kinase (CaMKII), AMPC-dependent protein kinase A (PKA), protein kinase C (PKC), proteins that are tyrosine kinases, and MAPK/ERK, which have been studied because they play a role in the hippocampus plasticity. Other authors point out that ERK plays an important role in different types of LTP, both in NMDA-dependent and non-NMDA-dependent receptors in the CA1 and hippocampal gyrus areas of mammals.

The researchers demonstrated that Morris water maze activates MAPK in neurons CA1 and CA2 of the dorsal hippocampus. However, *in vivo* inhibition of the MAPK/ERK cascade impaired long-term (but not short-lived) spatial memory (Blum et al., 1999). According to the functioning of this protein in neuronal growth and differentiation, this fact suggests that in particular the CA1 and CA2 layers may be sites of intense hippocampal plasticity associated with long-term spatial memory, although studies on this subject still need to be investigated (Adams and Sweatt, 2002; Blum et al., 1999).

The primary circuit of the formation of the hippocampus is based on a series of sequential synapses that transmit information from the entorhinal cortex, granular gyrus cells, CA3 pyramidal cells and CA1area (Neves et al., 2008). These hippocampal pathways – together with the projection of glutamatergic, gabaergic neurons and serotonergic interneurons of the local circuit – represent the basic processing module in the formation of the hippocampus (Morgane et al., 2002) – Fig. 1.

Studies on the molecular mechanisms of memory in sensory neurons of the *Aplysia molluscum* showed that it involves protein kinases, including cAMP-dependent protein kinase, protein kinase C and cAMP-activated protein kinase A (MAPK), which activates protein synthesis in the postsynaptic

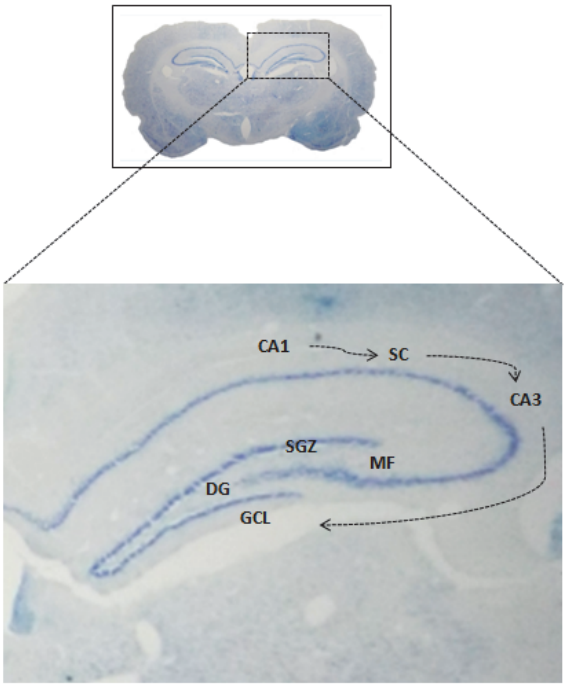

Fig. 1. Photomicrograph of coronal sections in the hippocampus stained with eosin and hematoxylin in 3-month-old control rats illustrating the CA1 region, axonal pathways SC (Shaffer Collaterais), CA3 region, and MF (Mossy Fibers) pathways. DG (Dentate Girus), GCL (cell layers through the granule cell layer), and SGZ (subgranular zone).

neuron. Secondary messengers, such as protein kinase A and MAPK, control the activity of transcription factors, including CREB (cAMP response element-binding protein) (Kandel, 2001). Thus, there is the synthesis of nitric oxide (NO), which is transported retrogradely to the presynaptic neuron, where it will promote the release of more glutamate. Another avenue for facilitation involves the serotonergic interneuron, increasing the excitatory postsynaptic potential between the sensory-motor synaptic connections that induce the LTP facilitation or process (Nikitin, 2007; Olson et al., 2006).

However, memory is a gradual process that, during new information, is consolidated and may or may not be stored in the cerebral cortex. Thus, the memory can be divided into two phases: one independent of RNA synthesis, which lasts from minutes to 1–3 hours (short-term memory, or MCD), and another that depends on RNA synthesis and protein, both occurring in the hippocampus, lasting hours, days, weeks or even longer periods (DLM) (Alonso et al., 2002; Bekinschtein et al., 2008). However, little is known about the molecular mechanisms that allow for greater maintenance of the DLM.

LTP is necessary for the formation of memory, as it favors the memory consolidation process (da Silveira et al., 2013). The other memory processes are acquisition and recovery. The acquisition is known as learning, being the detection of information in the environment by the sensory systems. In the first minutes or hours after contact with the stimulus to be memorized, this information – through processes of protein synthesis and synaptic changes – results in consolidation (Igaz et al., 2006). In 1973, Timothy Bliss and Terje Lomo demonstrated in neurons in the hippocampus of rabbits that high-frequency electrical stimulation in a presynaptic axon for a few seconds produces an increase in the magnitude of the postsynaptic response. This pattern of reinforced and persistent responses was known as LTP (da Silveira et al., 2013). Memory consolidation is the process of forming a memory file in the NS. This occurs in the neurons of the hippocampus, often with the concomitant participation of the entorhinal parietal cortex and the subsequent basolateral nuclear complex of the amygdala (Izquierdo et al., 1999).

BDNF may also induce the hippocampus LTP (Ma et al., 1998). BDNF is a type of neurotrophin that is activated by the CaMKII and plays an important role in synaptic plasticity, as in the mechanisms of learning and memory. BDNF, by binding to the receptor TrkB, regulates synaptic transmission and promotes the enhancement of long-term LTP by modulating the expression of NMDA (N-methyl-D aspartate) (Moriguchi et al., 2018). A study using male Wistar rats verified the performance of BDNF in a late phase of protein synthesis and expression of BDNF in the hippocampus; 12 hours after the formation of the consolidation of DCM, the animals were cannulated. Following this procedure, inhibition of BDNF expression in the hippocampus was performed during DCM processing. Some behavioral tests were carried out, such as inhibitory avoidance tests to observe memory retention (Bekinschtein et al., 2008). For the analysis of the BDNF protein, immunoblotting was performed and a deficit in the persistence of memory was found in the animals, without affecting the formation of DCM, indicating that the synthesis of BDNF during this final phase of protein synthesis is crucial for the persistence memory storage (Bekinschtein et al., 2008; Chen et al., 1999).

Another research group used EE exposure for male mice for 3 weeks and found that there was an increase in BDNF protein expression in the EE group, associated with better performance on the platform hidden in the Morris water maze (Kondo et al., 2012). Previous studies adopting physical exercise models found that there was an increase in BDNF protein expression in the physical exercise group, during which the inhibitory avoidance task increased BDNF mRNA levels during the initial phase of the memory consolidation process (Ma et al., 1998).

Malnutrition and memory

The environment, especially the enriched environment, diet, and physical activity (Morgane et al., 2002), are factors that modify the genomic aspects and metabolic programming. For example, insults during the critical period for the development of the NS can have long-term effects on memory (Chen et al., 1999; Maurage, 2008; Morgane et al., 2002; Patel and Srinivasan, 2010; Pérez-García et al., 2016). There is already a worldwide trend towards an increased risk of developing obesity, not only because of the genotype but also because of the lifestyle of individuals (Maurage, 2008; Naik et al., 2017; Tompkins et al., 2017). Due to the low purchasing power of the population, malnutrition is still a global problem that affects millions of children in the most vulnerable stages of SN development, especially in underdeveloped countries.

The hippocampus is a structure selectively vulnerable to a maternal nutrient restriction, where the duration and magnitude of nutritional disorder are directly related to body development and behavioral changes in adults (Alvarez et al., 2014; Laus et al., 2011). Malnutrition in the early stages of life and maturational events in the NS can result in abnormal behavioral and cognitive disorders, inadequate learning and memory (Duran Fernandez-Feijoo et al., 2017; Morgane et al., 2002). These insults during brain development are long-lasting and lead to permanent deficits in learning and behavior (Georgieff, 2007). The term “malnutrition” indicates that, although all

the nutrients required by the species are available in the diet, the quantities are insufficient (Duran Fernandez-Feijoo et al., 2017; Laus et al., 2011).

Nutritional inadequacy alters the development of the NS, which includes the synthesis of cellular components, such as nucleic acids and proteins, in parallel with neurogenesis and glycogenesis, through cell proliferation, differentiation, migration, and maturation, accompanied by a decrease in cell size (Georgieff, 2007). Also, it can alter the enzymatic activity and interfere in the synthesis of proteins (Berardino et al., 2017). Therefore, the incorporation of lipids in various structures of the brain can lead to changes in the ordered progression of brain development, logic, and memory circuitry (Duran Fernandez-Feijoo et al., 2017) – Fig. 2.

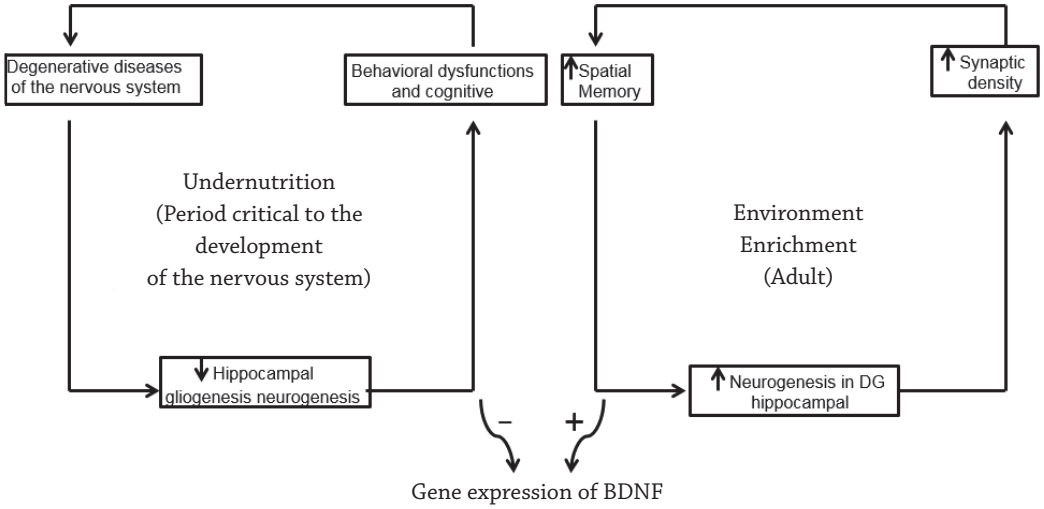

Fig. 2. Schematic representation showing the influences of malnutrition during gestation and lactation and environment enrichment in adults on the memory mechanism and gene expression of BDNF.

Furthermore, an adverse environment can induce epigenetic modification of the genome which can influence an individual's risk of health and disease in the nervous system. Both mechanisms are likely to be responsible for the variation seen in an individual's response to an adverse environment. It is unlikely that these mechanisms are independent, and the relative contributions of each are yet to be determined.

Therefore, nutritional, or environmental factors in these stages of development can lead to permanent changes that possibly reflect cognitive deficit, emotional and behavioral changes, or the later development of degenerative diseases of NS. Currently, epigenetic mechanisms related to stress, malnutrition, and/or environmental chemical agents have been implicated in animals and humans, acting on neuroendocrine behavior and/or function. However, the presence of only epigenetic mechanisms is insufficient to prevent the development of the disease (Barouki et al., 2012).

Factors that can interfere with the epigenetic mechanism, such as environmental or nutritional factors, occur mainly during the critical period of development, as it is the moment when they promote changes due to intense neural plasticity (Hopkins and Bucci, 2010). However, the changes resulting from epigenetic effects are different for each tissue and can extend to early childhood and puberty, such as the nervous and reproductive systems (Arima and Fukuoka, 2020). On the other hand, there is evidence that children of malnourished mothers have reduced expression of neurotrophic factors in the formation of the hippocampus compared to adequately fed control mothers (Sani and Bedi, 2007).

A point to be highlighted in studies on the relationship between caloric restriction, neurogenesis, and synaptic plasticity is the brain's ability to resist aging and restructure function after injury (Gillette-Guyonnet and Vellas, 2008). Thus, researchers carried out a study with 90-day-old Sprague-Dawley rats, where they had 50% food restriction compared to the control group during pregnancy and lactation or only during lactation and observed that the group with food restriction showed a decrease in the survival of the cells in the hippocampus DG, but there was no change in differentiation in the hippocampus of these cells (Hadem and Sharma, 2017).

Furthermore, malnutrition at any stage of life can promote changes in neural systems. A previous study with Sprague Dawley male rats divided into four groups: control, malnourished, status epilepticus and status epilepticus, and malnourished, investigated the relationship between postnatal malnutrition and/or epileptic conditions in the developing brain as causes of damage to the hippocampus (Laus et al., 2011; Rezende et al., 2015). The Morris and Western Blot water labyrinth test was performed and the results showed that in adulthood (80 days of life), both the group with epilepsy and the malnourished group had a spatial learning deficit, loss of hippocampal cells, and a decreased level of CRE B phosphorylation in the CA1 region of the hippocampus (Huang and Reichardt, 2003).

In contrast, another factor, the EE, has effects on the NS, including increased levels of the neurotrophic factor BDNF (Bechara and Kelly, 2013; Kobilo et al., 2011; Williamson et al., 2012), the number of dendritic spines, widening of the synapses, and increasing the number of neurons newly generated in the DG of the hippocampus (Huang et al., 2006; Olson et al., 2006).

The enriched environment, memory, and BDNF

EE is a housing manipulation that increases the physical and social and integrating and modular stimulus of plasticity in the hippocampus and other rodent cortical regions (Hopkins and Bucci, 2010; Lindsey and Tropepe, 2006; Williamson et al.,

2012). The results showed that EE promotes positive responses on learning and memory, and on obtaining acquisition and retention of new tasks (Jankowsky et al., 2005; Madroñal et al., 2010). It also increases the process of neurogenesis, and can facilitate cognition and recovery from interruption, including seizures and ischemia, and models Parkinson's disease (Park et al., 2017; Williamson et al., 2012). One hypothesis is that exposure to EE causes a learning-induced change in synaptic physiology in the hippocampus. For example, by altering baseline synaptic transmission or a change in the induction or persistence of LTP and LTD (Eckert and Abraham, 2010).

Molecular and cellular studies have shown that animal exposure to EE results in anatomopathological changes in the brain compared to those in standard housing conditions (Kobilo et al., 2011; Rezende et al., 2015). These changes include an increase in the total weight of the brain, the amount of protein content, and the thickness of the cerebral cortex of the hippocampus and a region with such changes (Madroñal et al., 2010). It is also noteworthy that the increase in neurogenesis due to exposure to EE occurs in the integration of these new functional circuits of the generated neurons and high number of synapses in the dentate gyrus and CA3-CA1 regions (Madroñal et al., 2010).

Thus, the exposure of adult rats to EE and exercise induces neurogenesis in the GD and is correlated with increased levels of BNDF in the hippocampus (Choi et al., 2009; Meng et al., 2015). A study conducted with male control rats (or those exposed to EE for 6 weeks) looked at the response in the object recognition memory tests, to check short and long-term memories, and the high crossed maze for anxiety, in addition to immunohistochemistry. It was seen that the EE group showed increased cell proliferation in the hippocampus, neurogenesis in the dorsal hippocampus, and a higher percentage of time exploring a new object, proving that there was SCI (Tanti et al., 2012). Another study with adult rats (3–5 months of age) exposed to EE for 3 weeks observed better cognitive performance, increased expression of CREB, and transcription factor LTP in the CA1 region of the hippocampus (Huang et al., 2006).

More recently, EE has been shown to have positive effects on brain function and has been found to increase the survival of newly formed neurons in the DG (Mesa-Gresa et al., 2013) and BDNF levels (Jurgens and Ohnson, 2012; Kobilo et al., 2011; Kondo et al., 2012). A study was conducted on male mice at 90 days of age, divided into two groups: (1) control, EE at 21 days (1 week, 4 weeks, and 8 weeks), and (2) EE at 70 days (4 weeks). An open-field test was carried out and it was found that animals exposed to EE for 4 and 8 weeks showed less locomotion in the open field task. The EE group (4 weeks to 70 days) also showed less locomotion in the open field, however, it was observed that the prolongation of the effect is proportional to the time of exposure to EE (Amaral et al., 2008). Thus, although such data contribute – showing that voluntary physical activity can regulate the levels of BDNF, mRNA, polypeptides encoded in the hippocampus and induce cell proliferation – it is still necessary to understand the functional mechanisms induced by BDNF.

Data suggest that BDNF expression in the adult hippocampus is necessary for the survival of exercise-induced precursor cells, cell proliferation, and dendritic development (Williamson et al., 2012). In this sense, the execution of voluntary exercises can activate NMDA receptors in the hippocampus, increasing the expression of BDNF (Huang et al., 2006).

EE favors other perceptual-cognitive and social aspects, including the greater opportunity for learning and socialization, in addition to physical exercise (Kempermann et al., 2010; Kobilo et al., 2011; Olson et al., 2006). Other researchers have identified that the exposure of rats to EE accelerates the development of the visual cortex, as well as modulating hedonic control, even in animals exposed to EE and stress (Schloesser et al., 2010). The EE can also improve the performance of animals in different aspects of learning and memory tasks involving the operation of the hippocampus (Birch et al., 2013; Huang et al., 2006; Tanti et al., 2012). EE is also related to the restructuring of regions of the NS, including the association between the cortex and the hippocampus. Therefore, EE can promote cell survival through mechanisms that are involved in this cortical reorganization (Olson et al., 2006).

A previous study with male Wistar rats, at 90 days of age, exposed for 3 weeks to EE and weekly exchange of objects, found that among the four experimental groups (sedentary, sedentary with EE, exercise with EE, and exercise), the exercise group with EE showed short-term memory. In the exercise group, there was an increase in the expression of the hippocampal BDNF mRNA and in the open field task there was habituation to the environment in all groups. In addition, immunohistochemistry showed a higher number of cells positive for BrdU with exercise, but not with EA (Bechara and Kelly, 2013).

The increase in locomotor activity in EE is associated with an increase in the volume of cerebral blood due to increased blood flow, increased permeability of the blood-brain barrier, increased angiogenesis, and increased the use of glucose by neurons (Fabel et al., 2009; Olson et al., 2006). Locomotor activity is also accompanied by a substantial increase in hormonal circulation and growth factors. However, in the open field test to assess the distance covered by the animals exposed to EE, studies have identified that there was a reduction in the distance covered, probably due to rapid habituation during the performance of this task (Amaral et al., 2008; Kobilo et al., 2011; Zhu et al., 2009), or this test failed to capture these changes.

Malnutrition, enriched environment, and memory

Nutritional deficiencies resulting from the insufficient intake of macro and/or micronutrients lead to varying degrees of malnutrition. This is recognized as a serious global problem, particularly in underdeveloped countries (Abera et al., 2017). In relation to the central NS, nutritional deficiency at the beginning of life is more severe, because in this phase the growth and development of this system are intense, through the processes of hyperplasia, hypertrophy, and myelination (Santos-Monteiro et al., 2002). Thus, this moment is considered a phase of great vulnerability to various types of aggressions, including nutritional (Morgane et al., 2002). In contrast, EE appears to be an alternative to reshape the effects of early malnutrition in adult memory mechanisms, but few studies have demonstrated such effects.

A study was carried out using Wistar rats during pregnancy and lactation. Their mothers were fed a 25% casein diet (control group) or a 12% casein diet (malnourished group). At 21 days, the animals were removed from their mothers and born in specific cages or exposed to EE for 1 hour a day (5 times a week) for 7 weeks. The open-field test was carried out and the results showed that the animals were malnourished and housed in standard cages with greater locomotion. A test was used to observe the animals' interest in exploring a new environment: a small room (25.5 cm by 23 cm) was built adjacent to the open field and connected by a 12 cm opening. The animals were kept outdoors for 55 minutes. The percentage of

animals in each group that entered the "new space" was counted and the animals that were precociously malnourished remained longer in the EE (Levitsky and Barnes, 1972).

Another study carried out with male Wistar rats divided them randomly into 8 groups: N (nourished); N + EE (nutrient + enriched environment); N + RS (nourished + recurrent crises), N + EE + RS (nourished + enriched environment + recurrent crises); U (malnourished); U + EE (malnourished + enriched environment); U + RS (malnourished + recurrent seizures); U + RS + EE (malnourished + recurrent seizures + enriched environment). As of the second postnatal day, access to the diet was limited, causing malnutrition. The deprivation period was increased by 2 h for 6 consecutive days, from 2 h to 12 h until the seventh day of life. From the 8th to the 15th day the deprivation period remained 12 h/day. After the privation period, the animals were housed with their respective groups. To induce recurrent seizures generated by treatment, flurotil (2,2,2-trifluoroethyl –99%) is a volatile seizure agent that stimulates the CNS quickly. The animals were sacrificed after 51 days of life, and the results demonstrated that the volume of the hippocampus was not affected by malnutrition or seizures. However, exposure to EE increased the volume of the hippocampus of the rats. The results also show that in animals that are malnourished and exposed to EE there is an increase in the thickness of the CA1 region of the hippocampus. These changes in the morphology of the hippocampus associated with EE indicate that the rodent's brain remains plastic in adulthood (Alvarez et al., 2014).

Furthermore, early protein malnutrition in rats alters anxiety and impulsivity, as well as risk assessment behavior in the elevated plus-maze test (EPM). However, it was shown that EE can reverse the damage caused by malnutrition because rats that were submitted to EE showed behaviors similar to those demonstrated by well-nourished rats in EPM. Rats subjected to early protein malnutrition also had high levels of stress (increased cortisol). This result suggests that early malnutrition can alter the activity of the hypothalamic-pituitary-adrenal axis (HPA) (Soares et al., 2013).

Conclusions

Such evidence from the scientific literature suggests that the synaptic plasticity mechanisms in the hippocampus of adult animals are influenced by EE. BDNF acts as a regulatory factor in the survival and development of dendritic neuronal precursor cells in the hippocampus of adult animals and, more importantly, exercise-induced cell proliferation can be promoted by increased BDNF expression. Results suggest that environmental factors may directly influence the memory process. In this way, EE can reverse the effects of malnutrition on the functioning of the hippocampus in adult rats that suffered a process of protein malnutrition in the early stages of life. To our knowledge, there are no studies to date that specifically correlate the effects of reversal of malnutrition by EE on the functioning of the hippocampus, so the explanation of how EE acts preventing or even reversing the deleterious effects of malnutrition is still open to debate.

Molecular and behavioral studies have shown that when these animals are submitted to a "rich" environment in stimuli and/or environmental stimulation sessions during their development, there is an increase in the weight and thickness of cortical and subcortical structures, in the activity of neuronal enzymes in the number and diameter of the cortical capillaries, and a decrease in cell density compared to animals raised in "poor" environments. The increase in the number of synaptic contacts and dendritic ramifications found in these animals also shows increased synaptic plasticity.

Thus, studies at molecular, cellular, and behavioral levels are necessary to investigate whether EE can reverse the effects of malnutrition on the functioning of the adult hippocampus in those who were malnourished early. Therefore, an investigation of the mechanisms by which neuroplasticity can facilitate the recovery of malnourished patients is essential for the treatment of these patients to be properly directed.

The adaptive plasticity processes of the NS provide scientific evidence for the implementation of strategies that facilitate the recovery of small groups that were previously malnourished and, therefore, for their reintegration in richer environments than those in which they are inserted.

The fact that different regions of the SN are susceptible to sensory-motor stimulation will certainly allow specific approaches to obtain better therapeutic results in the future.

Conflict of interests

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 interests.

References

Abera L, Dejene T, Laelago T (2017). Prevalence of malnutrition and associated factors in children aged 6–59 months among rural dwellers of damot gale district, south Ethiopia: community based cross sectional study. Int J Equity Health 16(1): 111. DOI: 10.1186/s12939-017-0608-9.

Adams JP, Sweatt J (2002). Molecular psychology: roles for the ERK MAP kinase cascade in memory. Annu Rev Pharmacol Toxicol 42: 135–163. DOI: 10.1146/annurev.pharmtox.42.082701.145401.

Alonso M, Vianna MRM, Depino AM, Mello e Souza T, Pereira P, Szapiro G, et al. (2002). BDNF-triggered events in the rat hippocampus are required for both short- and long-term memory formation. Hippocampus 12(4): 551–560. DOI: 10.1002/hipo.10035.

Alvarez PS, Simão F, Hemb M, Xavier LL, Nunes ML (2014). Effects of undernourishment, recurrent seizures and enriched environment during early life in hippocampal morphology. Int J Dev Neurosci 33(1): 81–87. DOI: 10.1016/j.ijdevneu.2013.12.004.

Amaral OB, Vargas RS, Hansel G, Izquierdo I, Souza DO (2008). Duration of environmental enrichment influences the magnitude and persistence of its behavioral effects on mice. Physiol Behav 93(1–2): 388–394. DOI: 10.1016/j.physbeh.2007.09.009.

Arima Y, Fukuoka H (2020). Developmental origins of health and disease theory in cardiology. J Cardiol 76(1): 14–17. DOI: 10.1016/j.jjcc.2020.02.003.

Bannerman DM, Rawlins JNP, McHugh SB, Deacon RMJ, Yee BK, Bast T, et al. (2004). Regional dissociations within the hippocampus – memory and anxiety. Neurosci Biobehav Rev 28(3): 273–283. DOI: 10.1016/j.neubiorev.2004.03.004.

Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ (2012). Developmental origins of non-communicable disease: Implications for research and public health. Environ Health 11: 42. DOI: 10.1186/1476-069X-11-42.

Bechara RG, Kelly ÁM (2013). Exercise improves object recognition memory and induces BDNF expression and cell proliferation in cognitively enriched rats. Behav Brain Res 245: 96–100. DOI: 10.1016/j.bbr.2013.02.018.

Bekinschtein P, Cammarota M, Katche C, Slipczuk L, Rossato JI, Goldin A, et al. (2008). BDNF is essential to promote persistence of long-term memory storage. Proc Natl Acad Sci USA 105(7): 2711–2716. DOI: 10.1073/pnas.0711863105.

Belluscio LM, Alberca CD, Pregi N, Cánepa ET (2016). Altered gene expression in hippocampus and depressive-like behavior in young adult female mice by early protein malnutrition. Genes Brain Behav 15(8): 741–749. DOI: 10.1111/gbb.12322.

Berardino BG, Fesser EA, Cánepa ET (2017). Perinatal protein malnutrition alters expression of miRNA biogenesis genes Xpo5 and Ago2 in mice brain. Neurosci Lett 647: 38–44. DOI: 10.1016/j.neulet.2017.03.012.

Birch AM, McGarry NB, Kelly AM (2013). Short-term environmental enrichment, in the absence of exercise, improves memory, and increases NGF concentration, early neuronal survival, and synaptogenesis in the dentate gyrus in a time-dependent manner. Hippocampus 23(6): 437–450. DOI: 10.1002/hipo.22103.

Bliss TV, Lomo T (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetizes rabbit follwing stimulation of the perforant path. J Physiol 232(2): 331–356. DOI: 10.1113/jphysiol.1973.sp010273.

Blum S, Moore AN, Adams F, Dash PK (1999). A mitogen-activated protein kinase cascade in the CA1/CA2 subfield of the dorsal hippocampus is essential for long-term spatial memory. J Neurosci 19(9): 3535–3544. DOI: 10.1523/JNEUROSCI.19-09-03535.1999.

Chen G, Kolbeck R, Barde YA, Bonhoeffer T, Kossel A (1999). Relative contribution of endogenous neurotrophins in hippocampal long-term potentiation. J Neurosci 19(18): 7983–7990. DOI: 10.1523/JNEUROSCI.19-18-07983.1999.

Choi SH, Li Y, Parada LF, Sisodia SS (2009). Regulation of hippocampal progenitor cell survival, proliferation and dendritic development by BDNF. Mol Neurodegener 4(1): 52. DOI: 10.1186/1750-1326-4-52.

Cutuli D, Rossi S, Burello L, Laricchiuta D, De Chiara V, Foti F, et al. (2011). Before or after does it matter? Different protocols of environmental enrichment differently influence motor, synaptic and structural deficits of cerebellar origin. Neurobiol Dis 42(1): 9–20. DOI: 10.1016/j.nbd.2010.12.007.

da Silveira CKB, Furini CRG, Benetti F, da Cruz Monteiro C, Izquierdo I (2013). The role of histamine receptors in the consolidation of object recognition memory. Neurobiol Learn Mem 103: 64–71. DOI: 10.1016/j.nlm.2013.04.001.

Duran Fernandez-Feijoo C, Carrasco Carrasco C, Villalmazo Francisco N, Cebrià Romero J, Fernández Lorenzo J, Jiménez-Chillaron J, Camprubí Camprubí M (2017). Influence of catch up growth on spatial learning and memory in a mouse model of intrauterine growth restriction. PloS One 12(5): e0177468. DOI: 10.1371/journal.pone.0177468.

Eckert MJ, Abraham WC (2010). Physiological effects of enriched environment exposure and LTP induction in the hippocampus *in vivo* do not transfer faithfully to *in vitro* slices. Learn Mem 17(10): 480–484. DOI: 10.1101/lm.1822610.

Fabel K, Wolf SA, Ehninger D, Babu H, Leal-Galicia P, Kempermann G (2009). Additive Effects of Physical Exercise and Environmental Enrichment on Adult Hippocampal Neurogenesis in Mice. Front Neurosci 3: 50. DOI: 10.3389/neuro.22.002.2009.

Falkenberg T, Ernfors P, Persson H, Lindefors N (1992). Cortical transynaptic activation of tyrosine kinase receptor trkB messenger RNA expression in rat hippocampus. Neuroscience 51(4): 883–889. DOI: 10.1016/0306-4522(92)90527-9.

Furini CRG, Myskiw JC, Benetti F, Izquierdo I (2013). New frontiers in the study of memory mechanisms. Braz J Psychiatry 35(2): 173–177. DOI: 10.1590/1516-4446-2012-1046.

Georgieff M (2007). Nutrition and the developing brain: nutrient priorities and measurement. The Am J Clin Nutr 85(2): 614S–620S. DOI: 10.1093/ajcn/85.2.614S.

Gillette-Guyonnet S, Vellas B (2008). Caloric restriction and brain function. Curr Opin Clin Nutr Metab Care 11(6): 686–692. DOI: 10.1097/MCO.0b013e328313968f.

Gobbo OL, O'Mara SM (2005). Combining exercise and cyclooxygenase-2 inhibition does not ameliorate learning deficits after brain insult, despite an increase in BDNF levels. Brain Res 1046(1–2): 224–229. DOI: 10.1016/j.brainres.2005.03.046.

Hadem IKH, Sharma R (2017). Differential Regulation of Hippocampal IGF-1-Associated Signaling Proteins by Dietary Restriction in Aging Mouse. Cell Mol Neurobiol 37(6): 985–993. DOI: 10.1007/s10571-016-0431-7.

Hopkins ME, Bucci DJ (2010). BDNF expression in perirhinal cortex is associated with exercise-induced improvement in object recognition memory. Neurobiol Learn Mem 94(2): 278–284. DOI: 10.1016/j.nlm.2010.06.006.

Huang E, Reichardt L (2003). Trk receptors: roles in neuronal signal transduction. Annu Rev Biochem 72: 609–642. DOI: 10.1146/annurev.biochem.72.121801.161629.

Huang FL, Huang K-P, Wu J, Boucheron C (2006). Environmental enrichment enhances neurogranin expression and hippocampal learning and memory but fails to rescue the impairments of neurogranin null mutant mice. J Neurosci 26(23): 6230–6237. DOI: 10.1523/JNEUROSCI.1182-06.2006.

Igaz LM, Winograd M, Cammarota M, Izquierdo LA, Alonso M, Izquierdo I, Medina JH (2006). Early activation of extracellular signal-regulated kinase signaling pathway in the hippocampus is required for short-term memory formation of a fear-motivated learning. Cell Mol Neurobiol 26(4–6): 989–1002. DOI: 10.1007/s10571-006-9116-y.

Izquierdo I, Medina JH (1997). Memory formation: the sequence of biochemical events in the hippocampus and its connection to activity in other brain structures. Neurobiol Learn Mem 68(3): 285–316. DOI: 10.1006/nlme.1997.3799.

Izquierdo I, Medina JH, Vianna MR, Izquierdo LA, Barros DM (1999). Separate mechanisms for short- and long-term memory. Behav Brain Res 103(1): 1–11. DOI: 10.1016/s0166-4328(99)00036-4.

Jankowsky JL, Melnikova T, Fadale DJ, Xu GM, Slunt HH, Gonzales V, et al. (2005). Environmental enrichment mitigates cognitive deficits in a mouse model of Alzheimer's disease. J Neurosci 25(21): 5217–5224. DOI: 10.1523/JNEUROSCI.5080-04.2005.

Jurgens HA, Ohnson RW (2012). Environmental enrichment attenuates hippocampal neuroinflammation and improves cognitive function during influenza infection. Brain Behav Immun 26(6): 1006–1016. DOI: 10.1016/j.bbi.2012.05.015.

Kandel ER (2001). The molecular biology of memory storage: a dialogue between genes and synapses. Science 294(5544): 1030–1038. DOI: 10.1126/science.1067020.

Kempermann G, Fabel K, Ehninger D, Babu H, Leal-Galicia P, Garthe A, Wolf SA (2010). Why and how physical activity promotes experience-induced brain plasticity. Front Neurosci 4: 189. DOI: 10.3389/fnins.2010.00189.

Kobilo T, Liu Q-R, Gandhi K, Mughal M, Shaham Y, van Praag H (2011). Running is the neurogenic and neurotrophic stimulus in environmental enrichment. Learn Mem 18(9): 605–609. DOI: 10.1101/lm.2283011.

Kondo M, Takei Y, Hirokawa N (2012). Motor Protein KIF1A Is Essential for Hippocampal Synaptogenesis and Learning Enhancement in an Enriched Environment. Neuron 73(4): 743–757. DOI: 10.1016/j.neuron.2011.12.020.

Laus MF, Vales LDMF, Costa TMB, Almeida SS (2011). Early Postnatal Protein-Calorie Malnutrition and Cognition: A Review of Human and Animal Studies. Int J Environ Res Public Health 8(2): 590–612. DOI: 10.3390/ijerph8020590.

Levitsky DA, Barnes RH (1972). Nutritional and environmental interactions in the behavioral development of the rat: long-term effects. Science 176(4030): 68–71. DOI: 10.1126/science.176.4030.68.

Lindsey BW, Tropepe V (2006). A comparative framework for understanding the biological principles of adult neurogenesis. Prog Neurobiol 80(6): 281–307. DOI: 10.1016/j.pneurobio.2006.11.007.

Ma YL, Wang HL, Wu HC, Wei CL, Lee EH (1998). Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats. Neuroscience 82(4): 957–967. DOI: 10.1016/s0306-4522(97)00325-4.

Madroñal N, López-Aracil C, Rangel A, del Río JA, Delgado-García JM, Gruart A (2010). Effects of Enriched Physical and Social Environments on Motor Performance, Associative Learning, and Hippocampal Neurogenesis in Mice. PLoS One 5(6): e11130. DOI: 10.1371/journal.pone.0011130.

Martin SJ, Grimwood PD, Morris RG (2000). Synaptic plasticity and memory: an evaluation of the hypothesis. Ann Rev Neurosci 23: 649–711. DOI: 10.1146/annurev.neuro.23.1.649.

Matos RJB, Orozco-Solís R, Lopes de Souza S, Manhães-de-Castro R, Bolaños-Jiménez F (2011). Nutrient restriction during early life reduces cell proliferation in the hippocampus at adulthood but does not impair the neuronal differentiation process of the new generated cells. Neuroscience 196: 16–24. DOI: 10.1016/j.neuroscience.2011.08.071.

Maurage C (2008). Children's nutrition and health in adulthood. Appetite 51(1): 22–24. DOI: 10.1016/j.appet.2008.02.005.

McHugh TJ, Blum KI, Tsien JZ, Tonegawa S, Wilson MA (1996). Impaired Hippocampal Representation of Space in CA1-Specific NMDAR1 Knockout Mice. Cell 87(7): 1339–1349. DOI: 10.1016/s0092-8674(00)81828-0.

Meng F-T, Zhao J, Ni R-J, Fang H, Zhang L-F, Zhang Z, Liu Y-J (2015). Beneficial effects of enriched environment on behaviors were correlated with decreased estrogen and increased BDNF in the hippocampus of male mice. Neuro Endocrinol Lett 36(5): 490–497.

Mesa-Gresa P, Pérez-Martinez A, Redolat R (2013). Environmental enrichment improves novel object recognition and enhances agonistic behavior in male mice. Aggress Behav 39(4): 269–279. DOI: 10.1002/ab.21481.

Morgane PJ, Mokler DJ, Galler JR (2002). Effects of prenatal protein malnutrition on the hippocampal formation. Neurosci Biobehav Rev 26(4): 471–483. DOI: 10.1016/s0149-7634(02)00012-x.

Moriguchi S, Kita S, Yabuki Y, Inagaki R, Izumi H, Sasaki Y, et al. (2018). Reduced CaM Kinase II and CaM Kinase IV Activities Underlie Cognitive Deficits in NCKX2 Heterozygous Mice. Mol Neurobiol 55(5): 3889–3900. DOI: 10.1007/s12035-017-0596-1.

Morris RG, Davis S, Butcher SP (1990). Hippocampal synaptic plasticity and NMDA receptors: a role in information storage? Philos Trans R Soc Lond B Biol Sci 329(1253): 187–204. DOI: 10.1098/rstb.1990.0164.

Moser E, Moser MB, Andersen P (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. J Neurosci 13(9): 3916–3925. DOI: 10.1523/JNEUROSCI.13-09-03916.1993.

Naik AA, Patro N, Seth P, Patro IK (2017). Intra-generational protein malnutrition impairs temporal astrogenesis in rat brain. Biol Open 6(7): 931–942. DOI: 10.1242/bio.023432.

Neves G, Cooke SF, Bliss TVP (2008). Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. Nat Rev Neurosci 9(1): 65–75. DOI: 10.1038/nrn2303.

Nikitin VP (2007). A new mechanism of synapse-specific neuronal plasticity. Neurosci Behav Physiol 37(6): 559–570. DOI: 10.1007/s11055-007-0053-0.

Olson AK, Eadie BD, Ernst C, Christie BR (2006). Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. Hippocampus 16(3): 250–260. DOI: 10.1002/hipo.20157.

Park J-M, Seong H-H, Jin H-B, Kim Y-J (2017). The Effect of Long-Term Environmental Enrichment in Chronic Cerebral Hypoperfusion-Induced Memory Impairment in Rats. Biol Res Nurs 19(3): 278–286. DOI: 10.1177/1099800416686179.

Patel MS, Srinivasan M (2010). Metabolic programming due to alterations in nutrition in the immediate postnatal period. J Nutr 140(3): 658–661. DOI: 10.3945/jn.109.110155.

Pérez-García G, Guzmán-Quevedo O, da Silva Aragão R, Bolaños-Jiménez F (2016). Early malnutrition results in long-lasting impairments in pattern-separation for overlapping novel object and novel location memories and reduced hippocampal neurogenesis. Sci Rep 6: 21275. DOI: 10.1038/srep21275.

Pietropaolo S, Branchi I, Cirulli F, Chiarotti F, Aloe L, Alleva E (2004). Long-term effects of the periadolescent environment on exploratory activity and aggressive behaviour in mice: social versus physical enrichment. Physiol Behav 81(3): 443–453. DOI: 10.1016/j.physbeh.2004.02.022.

Prusky GT, Reidel C, Douglas RM (2000). Environmental enrichment from birth enhances visual acuity but not place learning in mice. Behav Brain Res 114(1–2): 11–15. DOI: 10.1016/s0166-4328(00)00186-8.

Rezende GH, Guidine PA, Medeiros Dde C, Moraes-Santos T, Mello LE, Moraes MF (2015). Protein-caloric dietary restriction inhibits mossy fiber sprouting in the pilocarpine model of TLE without significantly altering seizure phenotype. Epilepsy Res 117: 85–89. DOI: 10.1016/j.eplepsyres.2015.08.011.

Riedel G, Micheau J (2001). Function of the hippocampus in memory formation: desperately seeking resolution. Prog Neuropsychopharmacol Biol Psychiatry 25(4): 835–853. DOI: 10.1016/s0278-5846(01)00153-1.

Risedal A, Mattsson B, Dahlqvist P, Nordborg C, Olsson T, Johansson BB (2002). Environmental influences on functional outcome after a cortical infarct in the rat. Brain Res Bull 58(3): 315–321. DOI: 10.1016/s0361-9230(02)00796-7.

Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, Babbini F, et al. (2006). Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. Eur J Neurosci 24(7): 1850–1856. DOI: 10.1111/j.1460-9568.2006.05059.x.

Sale A, Berardi N, Maffei L (2014). Environment and brain plasticity: towards an endogenous pharmacotherapy. Physiol Rev 94(1): 189–234. DOI: 10.1152/physrev.00036.2012.

Sani J, Bedi KS (2007). Undernutrition during early life increases the level of apoptosis in the dentate gyrus but not in the CA2 + CA3 region of the hippocampal formation. Brain Res 1143: 60–69. DOI: 10.1016/j.brainres.2007.01.109.

Santos-Monteiro J, de Araújo Guedes RC, de Castro RM, Cabral Filho JE (2002). Estimulação psicossocial e plasticidade cerebral em desnutridos. Rev Bras de Saúde Matern Infant 2(1): 15–22. DOI: 10.1590/s1519-38292002000100003.

Schloesser RJ, Lehmann M, Martinowich K, Manji HK, Herkenham M (2010). Environmental enrichment requires adult neurogenesis to facilitate the recovery from psychosocial stress. Mol Psychiatry 15(12): 1152–1163. DOI: 10.1038/mp.2010.34.

Simpson J, Kelly JP (2011). The impact of environmental enrichment in laboratory rats – behavioural and neurochemical aspects. Behav Brain Res 222(1): 246–264. DOI: 10.1016/j.bbr.2011.04.002.

Soares RP, Oliveira LM, Marchini JS, Antunes-Rodrigues J, Elias LLK, Almeida SS (2013). Effects of early protein malnutrition and environmental stimulation on behavioral and biochemical parameters in rats submitted to the elevated plus-maze test. Nutr Neurosci 16(3): 104–112. DOI: 10.1179/1476830512Y.0000000036.

Tanti A, Rainer Q, Minier F, Surget A, Belzung C (2012). Differential environmental regulation of neurogenesis along the septo-temporal axis of the hippocampus. Neuropharmacology 63(3): 374–384. DOI: 10.1016/j.neuropharm.2012.04.022.

Tompkins CL, Laurent J, Brock DW (2017). Food Addiction: A Barrier for Effective Weight Management for Obese Adolescents. Childhood Obes 13(6): 462–469. DOI: 10.1089/chi.2017.0003.

Williamson LL, Chao A, Bilbo SD (2012). Environmental enrichment alters glial antigen expression and neuroimmune function in the adult rat hippocampus. Brain Behav Immun 26(3): 500–510. DOI: 10.1016/j.bbi.2012.01.003.

Zagrebelsky M, Korte M (2014). Form follows function: BDNF and its involvement in sculpting the function and structure of synapses. Neuropharmacology 76 Pt C: 628–638. DOI: 10.1016/j.neuropharm.2013.05.029.

Zhu S-W, Codita A, Bogdanovic N, Hjerling-Leffler J, Ernfors P, Winblad B, et al. (2009). Influence of environmental manipulation on exploratory behaviour in male BDNF knockout mice. Behav Brain Res 197(2): 339–346. DOI: 10.1016/j.bbr.2008.09.032.