Universidade de Lisboa

Faculdade de Farmácia

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Monografia orientada pela Professora Doutora Susana Zeferino Solá da Cruz, Categoria Professora Auxiliar.

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Abstract

Adult neurogenesis consists in the synthesis of new neurons in specific areas of the adult brain. Neural stem cells, present in both the developing and adult central nervous system, are classified as multipotent cells and act as a starting point for neurogenesis. Newly synthesized neurons in the adult brain appear to have such important functions as olfaction, tissue repair, memory, learning, and mood regulation. Interestingly, factors as age, stress, high-fat diet, exercise, calorie restriction, environmental enrichment and social interaction/support were shown to deeply influence adult neurogenesis process. Mood disorders are a group of psychiatric illnesses, of which major depressive disorder stands out. In fact, major depressive disorder affects a significant number of individuals worldwide, some of whom do not respond to current antidepressant treatments. Furthermore, it is associated with high morbidity. There are several hypotheses that try to explain the pathophysiology of major depressive disorder, namely the monoaminergic, inflammatory and neurotrophic hypothesis. In recent years, the neurogenic hypothesis has emerged, in which depression may result from a reduction in adult neurogenesis. Indeed, *post-mortem* studies revealed the existence of reduced cell proliferation, one of the stages of adult neurogenesis, in the hippocampus of depressed patients. Additionally, it has been found that factors that affect adult neurogenesis, i.e., stress, high-fat diet, physical exercise, calorie restriction, environmental enrichment and social interaction, similarly impact major depressive disorder. The discovery that chronic antidepressant treatment stimulates adult hippocampal neurogenesis and that this is required for part of the behavioral improvements of antidepressants strengthens the neurogenic hypothesis of depression, allowing a link to be established between adult neurogenesis and major depressive disorder. However, the mechanisms underlying the adult neurogenesis-depression relationship are not clear. In this monograph, it will be addressed and discussed the role of signaling pathways, namely the Wnt, JNK and CREB signaling pathways in mediating adult neurogenesis in major depressive disorder. The future understanding of these molecular mechanisms will be an important step in this area of science, contributing to the identification of innovative and effective therapeutic targets for the treatment of major depressive disorder.

Resumo

A neurogénese adulta consiste na síntese de novos neurónios em zonas específicas do cérebro adulto. As células estaminais neuronais, presentes quer no sistema nervoso central em desenvolvimento, quer no adulto, são classificadas como células multipotentes e atuam como ponto de partida para a neurogénese. Os neurónios recém-sintetizados no cérebro adulto parecem atuar em funções importantes, como o olfato, a reparação tecidular, a memória, a aprendizagem e a regulação do humor. Curiosamente, fatores como a idade, o stress, a dieta rica em gorduras, o exercício físico, a restrição calórica, o enriquecimento ambiental e a interação/suporte social influenciam fortemente o processo de neurogénese adulta. As doenças de humor são um grupo de doenças psiquiátricas, das quais se destaca a depressão *major*. De facto, a depressão *major* afeta mundialmente um número significativo de indivíduos, sendo que parte deles não responde aos tratamentos atuais. Além disso, esta doença encontra-se associada a uma morbilidade elevada. São várias as hipóteses que pretendem explicar a fisiopatologia da depressão *major*, nomeadamente a hipótese monoaminérgica, inflamatória e neurotrófica. Nos últimos anos a hipótese neurogénica tem emergido, na qual a depressão pode resultar da redução do processo de neurogénese adulta. Efetivamente, estudos *post-mortem* revelaram a existência de menor proliferação celular, que constitui uma das etapas da neurogénese adulta, no hipocampo de doentes deprimidos. Adicionalmente, tem-se verificado que os fatores que afetam a neurogénese adulta, como o stress, os hábitos alimentares, o exercício físico, a restrição calórica, o enriquecimento ambiental e a interação social, impactam de forma semelhante a depressão. A descoberta de que terapêutica antidepressiva crónica estimula a neurogénese hipocampal adulta e que esta é requerida para parte das melhorias comportamentais dos antidepressivos fortalece a hipótese neurogénica da depressão, permitindo estabelecer uma ligação entre a neurogénese adulta e a depressão *major*. No entanto, os mecanismos subjacentes à relação neurogénese adulta-depressão não estão ainda esclarecidos. Nesta monografia irei abordar o papel de vias de sinalização, nomeadamente a via de sinalização Wnt, JNK e CREB na regulação da neurogénese adulta durante a depressão *major*. O esclarecimento futuro destes mecanismos moleculares será um passo importante nesta área da ciência, permitindo a identificação de alvos terapêuticos inovadores e mais eficazes para o tratamento da depressão *major*.

Palavras-chave: células estaminais neuronais; depressão *major*; hipocampo; neurogénese adulta.

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To my parents, for always encouraging and supporting me to follow my dreams. For being my haven, in good and bad times. I owe you everything and that's why I dedicate this monograph to you.

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Last but not least, to my persistence and critical spirit.

List of abbreviations

5-HT – Serotonin

AHN – Adult hippocampal neurogenesis

AMPK – AMP-activated protein kinase

BBB – Blood brain barrier

BDNF – Brain-derived neurotrophic factor

BHB - β-hydroxybutyrate

BrdU – Bromodeoxyuridine

cAMP – Cyclic adenosine monophosphate

CM – Childhood maltreatment

CNS – Central nervous system

COVID-19 – Coronavirus disease 2019

CR – Calorie restriction

CREB - cAMP response-element binding protein

CREM – cAMP response-element modulator

CSF – Cerebrospinal fluid

CUMS – Chronic unpredictable mild stress

DBI – Diazepam binding inhibitor

DCX – Doublecortin

DG – Dentate gyrus

DKK – Dickkoff

ECT – Electroconvulsive therapy

EE – Environment enrichment

Egr-1 – Early growth response 1

ERK – Extracellular signal-regulated kinase

FST – Forced swim test

GABA – Gamma-aminobutyric acid

Gadd45b - Growth arrest and DNA-damage-inducible protein 45 β

GCL – Granular cell layer

GFAP – Glial-fibrillary acidic protein

GR – Glucocorticoid receptor

GSK – Glycogen synthase kinase

HFD – High-fat diet

HPA – Hypothalamus-pituitary-adrenal

IGF-1 – Insulin-like growth factor 1

IL – Interleukin

JNK – c-Jun N-terminal kinase

Kyn – Kynurine

LHT- Learned helplessness test

LPS – Lipopolysaccharide

LV – Lateral ventricle

MAPK – Mitogen-activated protein kinase

MDA – Malondialdehyde

MDD - Major depressive disorder

miRNA – microRNA

mRNA – messenger RNA

mTORC1 - Mechanistic target of rapamycin complex 1

NF – Nuclear factor

NPC – Neural progenitor cell

NSC – Neural stem cell

OB – Olfactory bulb

pCREB – Phosphorylated CREB

PEx – Physical exercise

PGC – Proxisome proliferator-activated receptor-γ coactivator

PK – Protein kinase

PPAR - Peroxisome proliferator-activated receptor

PSA-NCAM – Polysialylated-neural cell adhesion molecule

RMS – Rostral migratory system

sFRP - Secreted frizzled-related proteins

SGZ – Subgranular zone

Sox2 – SRY-box2

SS – Social support

SVZ – Subventricular zone

TNF – Tumor necrosis factor

Trk – Tropomyosin receptor kinase

TRPC – Transient receptor potential-canonical

TST – Tail suspension test

VEGF – Vascular endothelial growth factor

VH – Ventral hippocampus

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1 Introduction

Mood disorders are a group of psychiatric illnesses, in which the two most prominent examples are major depressive disorder (MDD) and bipolar disorder (1). These disorders have a complex clinical presentation and are highly comorbid with anxiety, substance misuse and other behavioral changes, such as impulsivity and aggression. Furthermore, once mood disorders develop, they tend to have a chronic and refractory course (2).

In 2017, more than 163 million people were affected with MDD, while there were about 46 million people with bipolar disorder. Noteworthy, since 1990 the number of all age years lived with disability attributed to depressive disorders increased, converting into the third leading cause of disability in 2007 so far (3); for 2030, it is predicted that depressive disorders will become the first cause of global disease burden worldwide (4). Moreover, a study published in 2018 revealed that the lifetime prevalence of MDD in United States adults was 20.6% (5). Considering these data, among the mood disorders, in this monograph it will be essentially addressed MDD.

The median age of onset for MDD is 32 years (1), however, it can also occur in other age groups, such as in childhood and adolescence (6). Despite the non-pharmacological and pharmacological measures for the treatment of MDD, the disease is highly characterized by relapses and recurrences. Only 20% of patients recover and remain continuously well, while the other 80% have at least one recurrence during their lifetime (7). In addition, about 30-40% of depressed patients are thought to not show clinical improvement with therapies currently available (8).

The coronavirus disease 2019 (COVID-19) pandemic has created an emergency state globally, causing a range of psychological and mental disorders. In a recent meta-analysis assessing the impact of the COVID-19 pandemic on mental health, the prevalence of depression with a sample of 44,531 individuals was 33.7% (9). Therefore, more than ever, MDD should be seen as a public health problem, associated with a decrease in the quality of life and productivity, as well as an increase in morbidity, suicide, and in direct and indirect health costs (10).

Post-mortem studies have shown changes in the brain of depressed subjects, namely decreased dentate gyrus (DG) size and granule cell number. Nevertheless, when

patients were taking antidepressants at time of death, the DG size and the number of neurons were found to be increased. Interestingly, chronic antidepressant treatments, either by pharmacological or electroconvulsive therapy (ECT) treatments, enhance adult hippocampal neurogenesis (AHN). Of note, AHN appears to be necessary for antidepressants efficacy, as its removal prevents drug-induced behavioral improvement (11).

In this sense, AHN is emerging as having an important role in MDD. Indeed, the study of AHN in this context will allow a better understanding of the pathophysiology of depression and also to identify novel therapeutic targets. This monograph will review findings that support the correlation of adult neurogenesis and MDD. Although the underlying mechanisms of this fascinating relationship between neurogenesis and depression are not fully elucidated, certain signaling pathways that seem to be involved will be identified and discussed.

2 Adult neurogenesis

Adult neurogenesis is the process in which new and functionally integrated neurons are generated in the adult brain (12,13). A few years ago, it was believed that neurogenesis was restricted to embryonic life and, therefore, new neurons could not be produced after birth. In 1965, Altman and Das were the firsts to suggest that neurogenesis also occurs beyond development in the adult mammalian brain (14). This suggestion was received by the scientific community with skepticism and controversy, but it allowed a great evolution in this research area. Indeed, since then several studies have identified the genesis of new neurons in the adult brain of rats, mice, guinea-pigs, rabbits, cats, dogs, cows, sheep, non-human primates (15), and even in humans (16–19).

Neurogenesis begins with cell division, i.e., proliferation of neural stem cells (NSCs). Newly synthesized cells, known as neural progenitor cells (NPCs), divide rapidly and differentiate into migrating neuroblasts, that, in turn, give rise to immature neurons. After that, the maturation process takes place, in which neurons acquire the final morphology and physiology, and integrate into neuronal circuits in the brain (20–22). Of note, adult NSCs can shuttle between quiescent and active states by exiting and entering cell cycle, respectively (23). The balance between stem cell quiescence and activity determines the rate of neurogenesis, and provides a reserve pool of NSCs available for tissue regeneration and cell replacement throughout life (24,25).

The term "neural stem cell" describes cells that can generate neural tissue; have some capacity for self-renewal; and can give rise to other cells by asymmetric cell division (26). Therefore, NSCs are characterized as multipotent cells that reside in both developing and adult central nervous system (CNS) (27). Moreover, NSCs can be classified as tri-potent cells, once, through differentiation, they generate neurons, astrocytes, and oligodendrocytes (27,28). NSCs are not only the starting point for the production of new cells in the CNS, but also, they might indirectly regulate neurogenesis. For instance, insulin-like growth factor 1 (IGF-1) and microRNA (miR)-124 have already been identified in NSC-derived secretome (29,30). IGF-1 induces NPC proliferation in culture, and increases proliferation and neurogenesis in adult rat hippocampus (31). Interestingly, one mechanism by which IGF-1 leads to increased neurogenesis involves the Ras like without CAAX 1 (RIT1)/Akt/ SRY-box2 (Sox2)

signal transduction cascade (32). On the other hand, miR-124 regulate adult NSC lineages *in vivo* (33). In fact, miR-124 promotes proliferation and differentiation of NSCs by targeting delta like canonical notch ligand 4, through suppressing the Notch pathway (34).

The continued neurogenesis, in which NSCs are responsible, plays a role in the maintenance of neuroplasticity– defined as the ability of the nervous system to change its activity in response to stimuli by reorganizing its structure, functions, or connections (35) - and hippocampus dependent learning, memory and mood function (36).

2.1 Neurogenic niches

Neurogenic niches are brain regions where NSCs are retained after embryonic development, and, therefore, allow and support neurogenesis (37). The niche provides physical support to host or anchor stem cells, and also supplies factors to maintain and regulate them (38). Besides the NSC-neuron lineage, these niches contain glial cells (astrocytes, microglia, and ependymal cells) and vascular cells, such as endothelial cells and pericytes, which play crucial roles in modulating NSC fate and behavior (21,39).

Nowadays it is well accepted that adult mammalian neurogenesis occurs mainly in subventricular zone (SVZ) of lateral ventricles (LVs) and in the subgranular zone (SGZ) in the DG of hippocampus (12,39,40). The behavioral phenotypes that are observed after the inhibition of adult neurogenesis in these regions, as well as the fact that adult neurogenesis is described in many different species of mammals, indicate that this process is functionally important and evolutionarily conserved (40). Interestingly, in addition to the SVZ and the SGZ, adult neurogenesis might occur in substancia nigra, striatum, amygdala, neocortex, piriform cortex, and hypothalamus (41,42).

2.1.1 The subventricular zone niche

The SVZ niche is the largest source of NSCs in the adult mammalian brain (43). It is located along the ependymal cell layer, that separates the ventricular space from the SVZ (44). The niche is surrounded by an ependymal surface lining the cerebrospinal

fluid (CSF)-filled ventricles and, on the other side, by a complex arrangement of blood vessels (21).

In adult rodents, this brain neurogenic region is composed of quiescent radial glia-like cells, also known as B cells, that constitute the NSCs (Figure 1). They exhibit astroglial properties, expressing glial-fibrillary acidic protein (GFAP), and characteristics of immature progenitors (S100β^+, Nestin$^+$, Sox2$^+$) (44,45). B cells display a formation of vascular end feet with the blood vessels and some of these NSCs also have an apical process that extends through the ependymal cell layer, contacting with the CSF in the LVs. Therefore, B cells sense information from both the blood and the CSF (46). After becoming active, radial glial-like cells give rise to transient amplifying Type C cells (NPCs), which lose GFAP immunoreactivity and acquire the expression of the distal-less homeobox (Dlx)-2. In turn, C cells generate neuroblasts (A cells) that express the polysialylated-neural cell adhesion molecule (PSA-NCAM) and the early neuronal marker doublecortin (DCX) (44,45,47). Neuroblasts migrate toward the olfactory bulb (OB) along the rostral migratory stream (RMS) (46). Indeed, neuroblasts form a migrating chain that are unsheathed by glial cells with astrocytic characteristics. These glial cells not only enhance migration, but also support the survival and/or provide directional information to the A cells (48). Once neuroblasts reach OB, they separate from the chain and terminally differentiate into subpopulations of gamma-aminobutyric acid (GABA)ergic interneurons: the majority become granule neurons, which are located deep in the OB, and the minority become periglomerular neurons, which populate the superficial olfactory layers (47,49). As a result, newborn neurons maintenance OB circuitry, being able to replace dying interneurons, and contribute to the local plasticity (50).

Despite conflicting results in studies that attempt to link neurogenesis with olfaction, when adult bulbar neurogenesis is challenged, perceptual learning and olfactory memory are clearly impaired. Adult-born neurons are required for olfactory fear-conditioning, olfactory perceptual learning and long-term memory of associative olfactory learning (50). OB adult neurogenesis also appear to play a role in discrimination of highly similar odorants, allowing to improve performance in a challenging olfactory task (51). Moreover, some studies suggest that SVZ neurogenesis contributes to social behavior, such as paternal recognition of offspring (52), maternal behavior (53,54), and mate recognition (55).

Interestingly, after a brain injury, some of the neuroblasts in the SVZ are able to migrate to the lesion sites and differentiate into functional cells (43,56). In fact, SVZ-derived neuroblasts migrate into the striatum along the blood vessels, after ischemic injury (57). Further, experimental autoimmune encephalomyelitis triggers neuroblasts mobilization in the periventricular lesioned white matter, where they give rise to astrocytes and oligodendrocytes (58). Thus, in the presence of a brain lesion, SVZ-derived cells can modify their traditional migratory route to reach the damage, through the regulation of chemokines and cytokines released by damaged tissues (43). This process does not provide enough new cells for adequate restoration, but neuroblasts can provide the endogenous regeneration of neuronal circuitry to a limited extend (56).
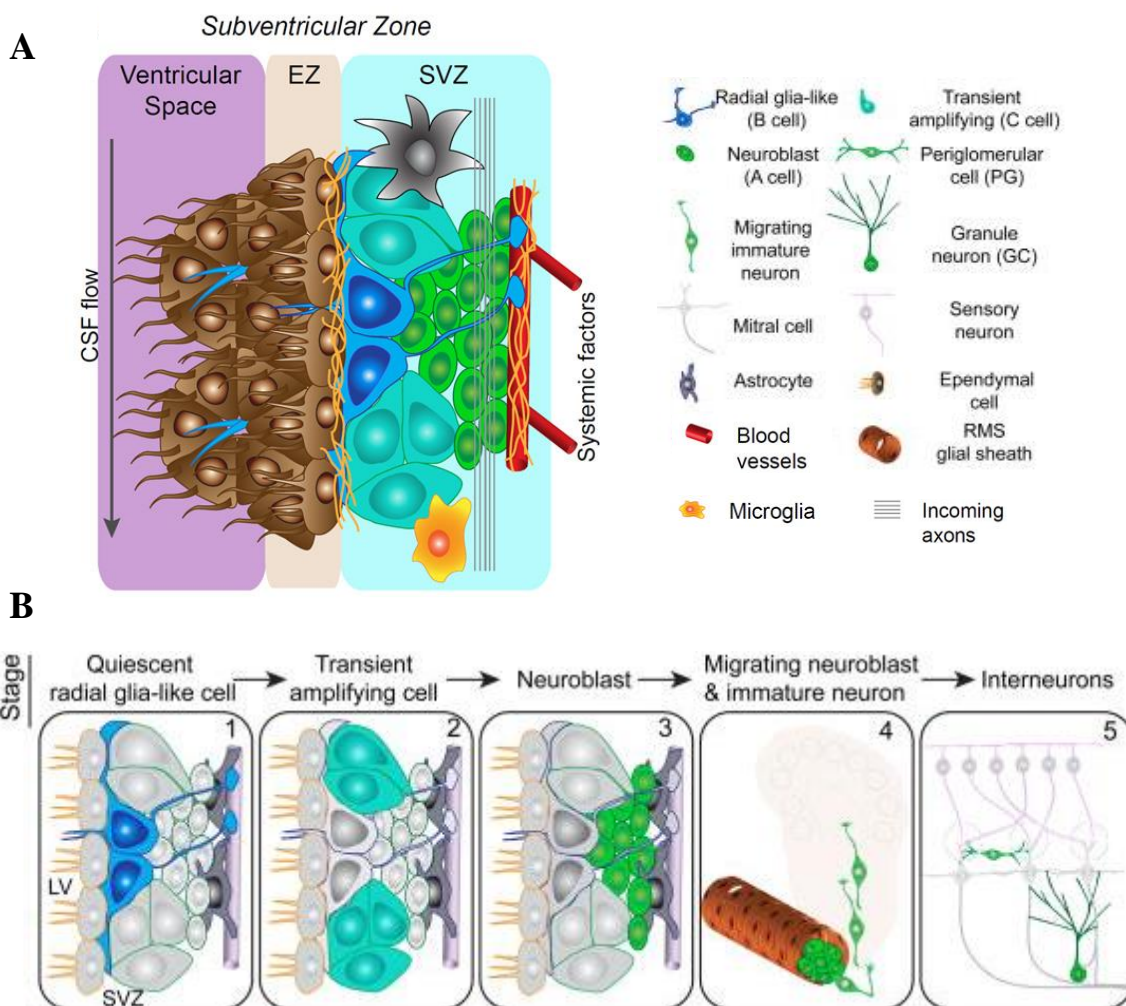

Figure 1 - Schematic representation of the neurogenic niche in the subventricular zone of adult rodents. **(A)** The neural stem cell (NSC)-neuron lineage derived from the subventricular zone (SVZ) is composed by type B quiescent cells (NSCs), type C cells, type A neuroblasts, immature neurons and mature interneurons. **(B)** Summary of stages during adult SVZ

neurogenesis: (i) activation of radial glia-like cells in the SVZ in the lateral ventricle; (ii) proliferation of transient amplifying cells; (iii) generation of neuroblasts; (iv) chain migration of neuroblasts within the rostral migratory stream (RMS) and radial migration of immature neurons in the olfactory bulb; (v) Synaptic integration and maturation of granule cells and periglomerular neurons in the olfactory bulb. CSF, cerebrospinal fluid; EZ, ependymal zone **(23,47)**.

Although most of the research in this area is performed in rodents, in the adult human SVZ the presence of astrocyte-like NSCs was also identified (59). However, after approximately 2 years, SVZ neurogenesis is almost no detectable, and SVZ acquires an organization that differs from the classical cytoarchitecture described for adult rodents, since it organizes into four layers (60,61). The Layer I contains ependymal cells in contact with the ventricular lumen. Next, there is an almost acellular layer (Layer II), also known as gap layer, that appears postnatally because of neuroblast depletion. This is followed by a dense cellular ribbon of proliferative astrocytes (B cells) (Layer III). Finally, Layer IV consists of a transitional region with few cells, similar to the brain parenchyma. Despite astrocytes of the adult human SVZ proliferate, very few cells with the morphology and marker expression of neuroblasts has been observed (60–62).

The existence of an adult human RMS and the integration of newborn neurons in adult human OB remain controversial. Curtis et al. suggested that the human RMS is organized around a tubular extension of the LV that extends from the SVZ to the OB. Further, they revealed the existence of progenitor cells with migratory morphology at all levels of the RMS, and that neuroblasts become neurons in the OB (63). In addition, other study provided evidence for the possible presence of the RMS-like pathway in adult human brain, which neuroblasts appear singly or in pairs without forming chains. However, no neuroblasts were found in OB (64). On the other hand, Sanai et al., found that the human RMS contain an extensive corridor of migrating immature neurons before 18 months of age, but is nearly extinct by adulthood (65). A recent study, using single-cell RNA-sequencing and immunohistochemistry, allowed to identify the presence of neurogenic progenitors and nascent neurons in olfactory neuroepithelium of adult humans (66). Therefore, human SVZ neurogenesis may play a role in olfaction, but it is uncertain.

As in rodents, human SVZ neurogenesis appears to participate in tissue regeneration, once there are a strong upregulation of proliferation and an increase number of NPCs in SVZ in brains with ischemic lesions (67,68). Moreover, in multiple sclerosis SVZ, the density of GFAP$^+$ astrocytes and PSA-NCAM$^+$ progenitors are increased. Also, PSA-NCAM$^+$ progenitors are highly prevalence in lesions proximal to the SVZ, which suggest that some of them migrate into the damaged tissue and, consequently, could contribute to oligodendrocyte renewal (69). Therefore, SVZ-derived NSCs in adult human brain originate migratory cells that could respond to brain tissue damage (43).

2.1.2 The subgranular zone niche

The SGZ niche is located at the interface between the hilus and the granular cell layer (GCL) of the hippocampus (70). It is estimated that about 9,000 new cells are generated per day in the DG of young adult rats (71), whereas in adult humans 700 new neurons are added in hippocampus each day, corresponding to an annual turnover of 1.75% of the renewing neuronal population (72).

In rodents, the NSCs of this region are radial glia-like cells, also referred as type 1 cells (Figure 2). They express nestin, GFAP and Sox2, and possess a defining radial branch that extends through the GCL (73,74). These NSCs are slowly dividing or quiescent. Once they proliferate, type 1 cells divide asymmetrically to generate transit-amplifying non-radial progenitors (type 2 cells), that transition between type 2a cells and neuronal committed type 2b cells, a late stage of transit-amplifying progenitors. Type 2b cells, through differentiation, originate neuroblasts or type 3 cells (DCX$^+$, PSA-NCAM$^+$) (74,75). In turn, neuroblasts migrate tangentially along SGZ and develop into immature neurons, which migrate radially into the GCL to differentiate into mature dentate granule neurons, that become integrated in the hippocampal circuitry (23,74). Newborn neurons are identified through the expression of calretinin and neuronal nuclear protein (NeuN) (75); also, within days, they extend a well-developed dendritic arbor towards the molecular layer (ML) and project axons through the mossy fiber pathway to contact CA3 (47,70). According to Boldrini et al., in adult human SGZ there are also quiescent radial glia-like cells with apical processes crossing the GCL into the ML, amplifying intermediate neural progenitors, neuroblasts,

immature and mature granule neurons, that send their processes to the CA3 region of the hippocampus (17).

To access the functional role of AHN, Shors et al. showed that reduction in the number of newly generated neurons in the adult rat impaired hippocampal-dependent forms of associative memory formation; the recovery of cell production was associated with the ability to acquire trace memories (76). Other study, using focal X irradiation of the hippocampus or genetic ablation of GFAP-positive NPCs, demonstrated a specific impairment in contextual fear conditioning and a loss of long-term potentiation, an important process in the context of synaptic plasticity (77), in DG of adult mice. However, the authors do not found deficit in spatial learning or memory (78). In Nestin-thymidine kinase transgenic mice treated with ganciclovir, the reduction of adult-born immature dentate granule neurons led to a defective long-term retention of spatial memory in Morris water maze, and impaired extinction of both spatial preference and conditioned contextual fear (79). Moreover, the inhibition of hippocampal neurogenesis provoked by different methods was able to compromise long-term social recognition memory (80). Interestingly, the artificial increase of hippocampal neurogenesis was sufficient to promotes forgetting of established memories, even in adult mice (81). In fact, the elevated levels of neurogenesis weakened old memories and, consequently, facilitated the encoding of new conflicting information, a process that can be characterized as a reduction of proactive interference (82). Therefore, although some results seem opposite, AHN plays significant roles in hippocampus-dependent cognitive functions, such as learning, memory and cognitive flexibility (83).

In addition, several studies suggest that AHN function in pattern separation, a process by which similar patterns of neuronal inputs are transformed into distinct neuronal representations, allowing the discrimination of highly similar stimuli in hippocampus-dependent tasks (84). Moreover, a recent meta-analysis supports the general conclusion that adult SGZ neurogenesis is important for behavioral pattern separation (85). Indeed, ablating hippocampal neurogenesis impairs the ability to discriminate highly similar contexts (86). Adult mice with this specific ablation showed impairments in spatial discrimination, i.e., spatial pattern separation (87), and in separating efficiently contextual representation (88). Manipulations to increase neurogenesis have the opposite effect, improving the ability to distinguish nearby

locations on a touchscreen task, similar fear conditioning contexts (89) or overlapping contextual representations (90).
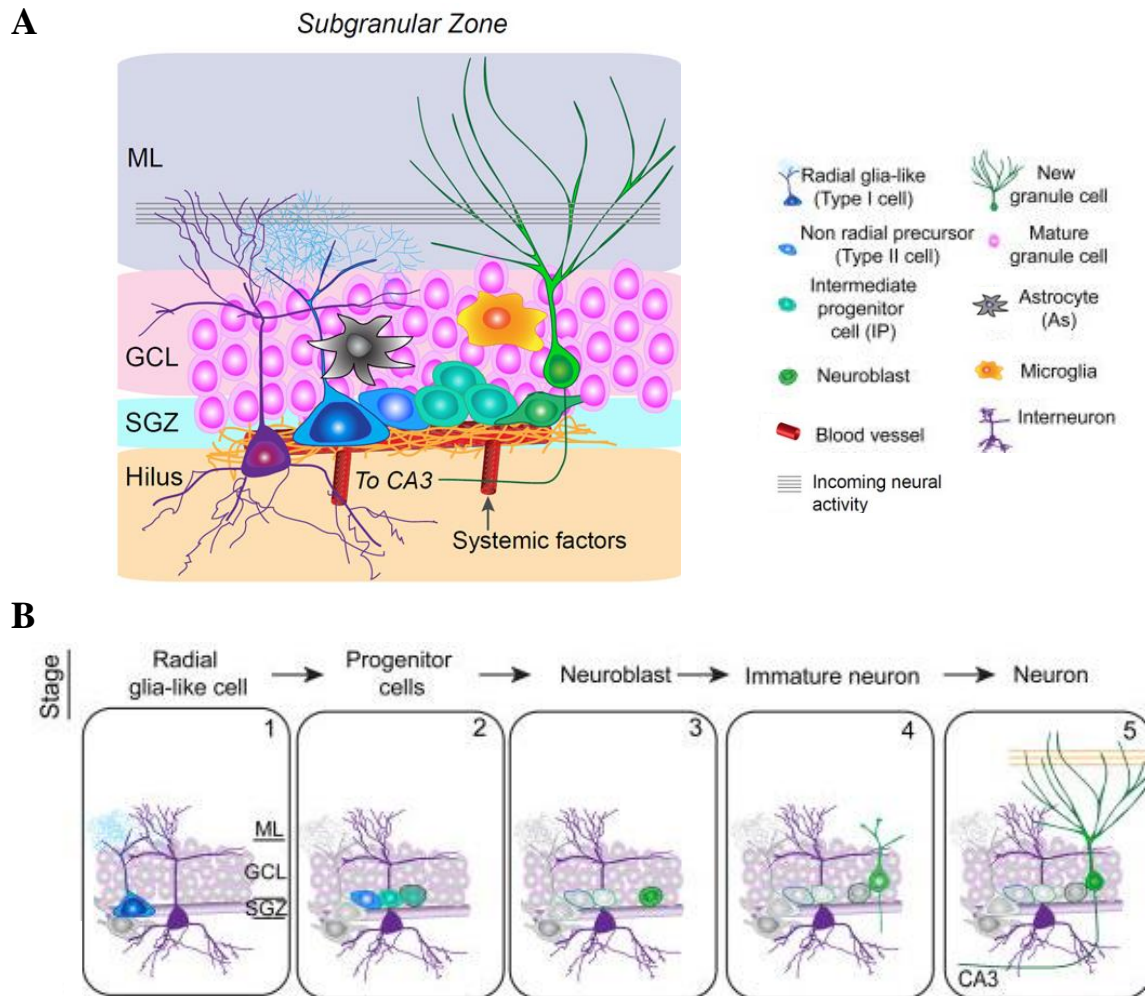
Figure 2 - Schematic representation of the neurogenic niche in the subgranular zone of adult rodents. (A) The neural stem cell (NSC)-neuron lineage derived from the subgranular zone (SGZ) is composed by type 1 cells (NSCs), type 2a/b cells, type 3 neuroblasts, immature neurons and mature dentate granule neurons. **(B)** Summary of stages during adult hippocampal neurogenesis: (i) activation of quiescent radial glia-like cell in the SGZ; (ii) proliferation of non-radial precursor and intermediate progenitors; (iii) generation of neuroblasts; (iv) integration of immature neurons; (v) maturation of adult-born dentate granule cells. GCL, granular cell layer; ML, molecular layer; SGZ, subgranular zone **(23,47)**.

Adult-generated neurons may also participate in other hippocampal functions such as anxiety and stress regulation (91). The dominant view of the hippocampus organization is that the dorsal (or posterior) hippocampus is critical for learning and

memory performance, while the ventral (or anterior) hippocampus (VH) is implicated in anxiety-related behaviors (92,93). Because new neurons are generated throughout the dorsoventral extent of the DG, the possibility that they might participate in more hippocampal function seems high (91). Selectively impaired AHN led to an increase of anxiety-related behaviors, such as avoidance of novel and potentially threatening environments. Thus, decreased neurogenesis likely increased the negative impact of the potential threat associated with new unprotected environments (94). The increase of AHN, in turn, promoted resilience to chronic stress (95,96); further, it appeared to be sufficient to reduce anxiety and depression-related behaviors in mice treated chronically with cortisone (96). Curiously, Lagace et al. showed that, through the artificial manipulation of neurogenesis, AHN is required for stress-induced social avoidance (97).

2.2   Environmental and biological factors in adult neurogenesis

Many extrinsic and intrinsic factors have been found to regulate adult neurogenesis at various developmental stages, including morphogens/growth factors and their receptors, hormones, neurotransmitters, cell adhesion molecules, cytoplasmic factors, transcriptional factors, and epigenetic modifiers. Besides, adult neurogenesis is highly regulated by environmental and biological factors, such as aging (83). In the next topics, it will be address factors that downregulate – stress, high-fat diet (HFD), and aging – and upregulate – physical exercise (PEx), calorie restriction (CR), environmental enrichment (EE), and social interaction and support – the adult neurogenesis. Whenever possible, it will be explained mechanistically how these factors influence neurogenesis.

2.2.1   Stress

Stress is one of the most potent environmental parameters known to suppress AHN. Both psychosocial and physical stressors inhibit one or more phases of the neurogenesis process, such as proliferation, differentiation, and neuronal survival. Of note, stress-induced reductions in proliferation could result from cell cycle arrest, from apoptosis

of NSCs/NPCs (98,99), or even from autophagic cell death of NSCs (100). Further, the duration of stress does not seem to be a relevant factor, since acute and chronic stress exposure negatively impact adult neurogenesis. Curiously, stress may also shift NSCs away from neuronal differentiation and redirect them toward the generation of oligodendrocytes (98,99).

Stress is accompanied by hypothalamus–pituitary–adrenal (HPA) activity, which results in the release of glucocorticoids into the blood (101). Glucocorticoids can cross the blood brain barrier (BBB) to bind to their receptors – mineralocorticoid receptor and glucocorticoid receptor (GR) (102). Some data suggest that GR is the main mediator of direct stress-suppressive effects on neurogenesis (103). Accordingly, quiescent NSCs, amplifying progenitors, neuroblasts and mature neurons express GRs (104). High concentrations of glucocorticoids downregulated transforming growth factor β (TGFβ)-SMAD2/3 and Hedgehog signaling, both in human hippocampal progenitor cells, and in adult rat hippocampus. Increased TGFβ signaling promotes neurogenesis (105), namely stimulating neuronal differentiation/survival (106). In turn, Hedgehog signaling is essential in the maintenance and self-renewal of NPCs (107), and also promotes neuronal differentiation (105). Interestingly, changes produced by glucocorticoids in cell proliferation in DG may also occur indirectly, through N-methyl-D-aspartate (NMDA) receptors-mediated excitatory pathway (108,109).

Moreover, external stress causes an activation of various inflammation-related pathways in the CNS and increased expression of pro-inflammatory cytokines, such as interleukin (IL)-1β (110). IL-1β is consider a critical mediator of the anti-neurogenic effects caused by acute and chronic stress, once the activation of IL-1 receptor I in hippocampal NPCs decrease cell proliferation, via the nuclear factor (NF)-κB signaling pathway (111). The inhibition of NF-κB block the antiproliferative effects of IL-1β in NPCs, and, therefore, block the stress-induced downregulation of neurogenesis (112). Additionally, IL-1 can stimulate glucocorticoid release by the adrenal gland (113), further contributing to the stress-induced inhibition of adult neurogenesis.

The deleterious modifications produced in the hippocampus by stress may also involve a decrease in neurotrophins, in particular in brain-derived neurotrophic factor (BDNF) (99,100). Indeed, in rodents, repetitive restrain stress, social deprivation stress, repeated footshock, and elevated platform stress paradigm reduced hippocampal BDNF levels (114–117). It is well known that mitogen-activated protein kinase (MAPK)/

extracellular signal-regulated kinases (ERK) pathway is one of the signaling pathways stimulated after activation of tropomyosin receptor kinase (Trk) B by BDNF (118). This pathway promotes neuronal proliferation, differentiation and survival through suppression of the pro-apoptotic protein Bcl-2 antagonist of cell death (BAD) and activation of the transcription factor cAMP response-element binding protein (CREB) (119). Thus, decreasing BDNF can negatively impact AHN.

2.2.2   High-fat diet

HFD contribute to obesity, metabolic disturbances, and has been implicated in cognitive impairment, and hippocampal insults (120,121). Further, HFD has a negative influence on AHN, affecting the proliferation of NSCs, differentiation, and the number of newly-born neurons of the dorsal and ventral DG (122–124).

Several studies revealed that HFD decreases hippocampal BDNF levels (125–127), a well-known pro-neurogenesis factor, which may partly explain the impairments in AHN found in animals submitted to this type of diet. Besides reducing BDNF expression, Park et al. showed that HFD increased the level of malondialdehyde (MDA) in mice hippocampus. MDA is a marker of lipid peroxidation and is able to reduce the proliferation of NPCs (121). MDA can result from lipid peroxidation in the mitochondrial membrane, which impairs mitochondrial membrane fluidity. The impaired mitochondrial membrane lead to dysregulated ionic balance and excessive intracellular calcium influx, resulting in neuronal death (128). Also, lipid peroxidation products phosphorylate CREB without a parallel CREB-dependent gene expression and phosphorylate c-Jun N-terminal kinase (JNK) and c-jun, leading to induction of c-jun-dependent promoters. Therefore, these products induce the pro-apoptotic pathway involving c-jun (129). Taken together, these findings suggest that HFD may reduce AHN due to oxidative stress induced by lipid peroxidation.

HFD has been shown to increase inflammation, causing neural alterations (130). Indeed, the HFD-fed rodents hippocampus experiences an increase in the levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, IL-6 and IL-1β (120,126,131,132), which is in line with the M1-type microglia activation observed in these animals (120,133). These cytokines are able to negatively impact all the stages of AHN (128). In terms of mechanisms, TNF-α downregulates the proliferation of NPCs

acting through the TNF-receptor 1 (134). IL-6 decreases AHN in mouse via activation of cyclin-dependent kinase inhibitor 1A (p21), and by reducing soluble factors, such as the protein sonic hedgehog, which is known to promote neuronal differentiation (135).

Interestingly, HFD can also increases serum corticosterone levels, that, in turn, decreases neurogenesis (131,136).

2.2.3 Aging

Although neurogenesis is detectable in older mammals, a dramatic decrease of neurogenesis has been observed across all species (Figure 3) (137,138). Aging functions as a negative regulator of neurogenesis in both SVZ and SGZ niches (139,140), resulting in reduced proliferation of NSC/NPCs and neuron production (141). Noteworthy, decreases in neurogenesis in elderly rats is due to the loss of precursor cells, rather than slowing of the cell cycle (142).
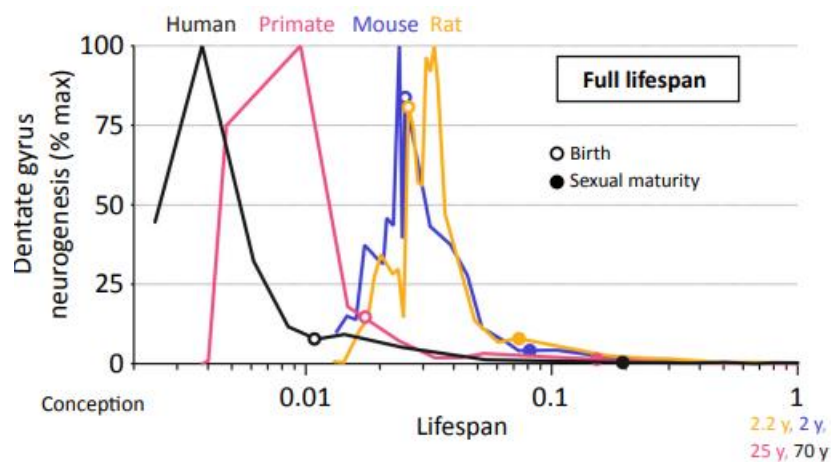
Figure 3 - Comparation of neurogenesis levels in dentate gyrus across the full lifespan of humans, primates, mice, and rats. The general pattern of neurogenesis is similar across all species. Early in life, neurogenesis rapidly rises and falls, and then remains at lower, but detectable, levels throughout the aging process. The x-axis time scale was normalized, using the logarithmic function, to the post-conception age **(137)**.

Increasing evidence suggests that changes in the local microenvironment and in the systemic milieu with age are the main responsible for the increased levels of inhibitory molecules or for decreased levels of neurogenesis-promoting factors (138).

Studies using heterochronic parabiosis allowed to identify pro-aging blood-borne factors, such as C-C motif chemokine ligand 11 (CCL11), and β2-microglobulin, that promote age-dependent decline in neurogenesis (140,143,144). Moreover, glucocorticoid levels increase in older age and are related to decreased neurogenesis in older animals (145,146). In contrast, the brain expression of BDNF, IGF-1, fibroblast growth factor-2 (FGF-2), and vascular endothelial growth factor (VEGF) are downregulated in the aging process (147,148), indicating a sharp loss of the pro-neurogenic effects of these factors.

Wnt signaling is widely accepted as a regulator of multiples aspects of AHN (74). For example, overexpression of Wnt3 is sufficient to increase neurogenesis *in vitro* and *in vivo*, stimulating differentiation into neurons, neuroblast proliferation and neuronal fate, through the activation of Wnt/β-catenin pathway (149). With age there is a reduction in Wnt3 levels that, in turn, affects the regulation of target genes, such as NeuroD1 and retrotransposon L1 (150). On the other hand, Wnt inhibitor Dickkopf (DKK) 1 increases in elderly rodents (147,151). Further, p38, a key factor in the proliferation of NPCs, necessary for preventing the antagonism of canonical Wnt signaling, is downregulated during aging (152). Therefore, the decline in Wnt signaling that occurs in aging is related with reduced neurogenesis.

As in stress and HFD, inflammation is one contributing factor to the reduction in neurogenesis observed with age (141). Elderly rodents show increased inflammation in neurogenic niches, highlighted by the increase in activated microglia (153,154), which become overproducers of pro-inflammatory cytokines (148,155). In addition, aged rats have decreased hippocampal levels of CX3CL1, a chemokine with anti-inflammatory proprieties. The disruption in CX3CL1-CX3C chemokine receptor 1 (CX3CR1) signaling reduces the survival and proliferation of NPCs through IL-1β (156). Thus, age inhibits the neuroprotective role of CX3CL1-CX3CR1 signaling, leading to the decline of neuronal CX3CL1, which may contribute to increase microglia activation and, ultimately, reduce hippocampal neurogenesis (157).

2.2.4 Physical exercise

In 1999, van Praag et al. demonstrated that PEx, namely voluntary running, induced cell proliferation, survival and neuronal differentiation in the hippocampus of

adult mice (158). This group revealed that running not only enhanced neurogenesis in DG, but also improved spatial learning and long-term potentiation (159). Since then, several studies have confirmed the effect of voluntary PEx on the neurogenesis of young and elderly rodents (160–162). Moreover, running can prevent the decline of short-term and spatial memories associated with age (162) and it is able to rescue injury-induced learning deficit (163), both by enhancing hippocampal neurogenesis. Of note, the beneficial effects of PEx in AHN occurs mainly if the exercise is aerobic and sustained (164). PEx induces neurogenesis also in other brain regions, such as SVZ (165), ependymal lining of the third ventricle, and hypothalamus (166).

After aerobic and anaerobic exercise, it was observed an increase in serum/plasma BDNF in humans (167). Also, voluntary exercise significantly increases hippocampal and cerebral cortex levels of BDNF in rodents (168). The rise of BDNF expression in the hippocampus of adult rats was accompanied by an increase of TrkB (169), suggesting their involvement in PEx-enhanced neurogenesis. Interestingly, it was reported that PEx increase the levels of phosphorylated CREB (pCREB) in the hippocampus of aging rats (170).

In addition, PEx-induced neurogenesis may be a result of increased IGF-1, since blocking IGF-1 prevented this effect (171,172). Zhang et al. demonstrated that the elevation of IGF-1 led to activation of the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, which in turn increased the transcription factor Brain-4, thereby promoting NSCs differentiation along neuronal pathways (173). Recently, it was discovered a new cascade of signal transduction in human NPCs, RIT1-Atkt-Sox2, that is associated with an increase in neurogenesis caused by IGF-1 (32). Moreover, PEx showed to promote neurogenesis through the activation of proteasome. This can be explained by the fact that PEx induces IGF-1 elevation, which in turn triggers nuclear translocation of nuclear factor erythroid 2-related factor (Nrf2) to promote the expression of the proteasome subunit beta type-5; this subunit is needed to enhance adult neurogenesis (174).

Curiously, besides BDNF and IGF-1, others neurotrophic/growth factors, such as VEGF and bone morphogenetic protein (BMP) seems to be involved in regulation of adult neurogenesis after PEx (160,175).

Adiponectin, a peptide secreted by adipocytes, may also play a role in mediating effects of PEx on AHN. Indeed, its deficiency abolished running-promoted hippocampal cell proliferation. The mechanism underlying the involvement of adiponectin on neurogenesis is possibly through the activation of the adiponectin receptor 1/AMP-activated protein kinase (AMPK) signaling pathway (176).

2.2.5   Calorie restriction

CR is defined as a reduction between 10% and 40% in the daily caloric intake, without malnutrition and without affecting the consumption of essential nutrients (177). CR enhances neurogenesis by increasing newly generated neural cells in DG, possibly due to increased cell survival (178,179). Further, in SVZ, the age-related decline in neurogenesis was prevented by this dietary restriction, when it started in early adulthood (180).

Ghrelin is an orexigenic hormone produced in stomach able to cross BBB, that has been linked to increased adult neurogenesis (181). Interestingly, CR rises ghrelin levels both in the stomach and hippocampus. Kim et al. demonstrated that ghrelin is necessary for CR-promoted AHN, since CR failed to increase the number of bromodeoxyuridine (BrdU)$^+$ cells in ghrelin knockout mice (182). Moreover, the beneficial effects of CR on AHN are dependent of ghrelin receptor, the growth hormone secretagogue receptor (GHSR). Elevating peripheral ghrelin due to CR induces expression of early growth response 1 (Egr-1) in DG (183). Egr-1, in turn, is involved in survival of newborn DG cells, controlling their neurochemical and morphologic maturation (184). These data suggest that ghrelin may enhances neurogenesis through an NSC-extrinsic mechanism, possibly mediated by activation of Egr-1 dependent genes in DG neurons (185).

Many papers have reported an upregulation of BDNF hippocampal expression as result of CR (178,179,185–187). BDNF plays an important role in regulating AHN in response to CR, promoting the survival of newly generated neurons in hippocampus of adult mice (188). Once CR also increases the ratio of full-length TrkB (functional receptor) to truncated TrkB in the hippocampus, BDNF is expected to affect neurogenesis through TrkB signaling (179). Surprisingly, BDNF-mediated increase in AHN under CR conditions may require ghrelin, because enhanced expression of the

neurotrophin in ghrelin knockout mice failed to increase the number of BrdU-labeled cells (182).

CR exerts a potent anti-inflammatory effect (189). Indeed, this dietary restriction decreases inflammatory markers in healthy non-obese adults (190); also, it is able to mitigate the age-related activation of microglia and the subsequent increase in pro-inflammatory cytokines (180). Interestingly, increased ghrelin production appears to be one of the mechanisms responsible for CR-mediated anti-inflammatory effects (189,191–193). Furthermore, NLRP3 inflammasome has an essential role in the innate immune system, mediating caspase-1 activation, and the consequent secretion of pro-inflammatory cytokines, such as IL-1β and IL-18 (194,195). Macrophages derived from CR mice showed reduced expression of the active forms of caspase-1 and IL-1β. CR attenuates activation of the NLRP3 inflammasome (196), which contributes to reduction of pro-inflammatory environment.

2.2.6   Environmental enrichment

EE is a laboratory paradigm, in which genetically identical animals are exposed to a larger cage, with more animals and a selection of toys and structures to climb and hide (Figure 4) (197). EE enhances AHN, namely rises the number of BrdU[+]-labeled cells and immature neurons, increasing the survival of newborn neurons (198–201). The positive effects were observed in both young and aged animals (198,202), and appear to be more prominent in dorsal DG (203). Curiously, this enrichment is also involved in promotion of post-stroke neurogenesis, in SVZ (204–206).

Exposure to an EE stimulates the production of specific neurotrophic factors. BDNF is one of them (207–209). In heterozygous knockout mice BDNF^{+/-}, EE failed to enhance the number of newly generated neurons, which means that BDNF is necessary for the EE induction of neurogenesis (209). Interestingly, Kuzumaki et al. suggested that EE increases BDNF expression though epigenetic mechanisms, since it induced significant modification of histones in BDNF promoters of hippocampus mice (210). Moreover, growth arrest and DNA-damage-inducible protein 45 β (Gadd45b) is required for DNA demethylation of specific promoter regions and expression of corresponding genes critical for adult neurogenesis, such as *Bdnf* (211,212). It has been shown that the expression of Gadd45b increases in both neurogenic niches after EE

(206,213). Therefore, Tan et al. reported that Gadd45b, via BDNF, mediates EE-induced neurogenesis in SVZ of rats following stroke (206). In turn, hippocampal expression of VEGF is also increased by EE; this upregulation results in improved neurogenesis. Indeed, VEGF is not only an angiogenic factor, but it can act via kinase insert domain protein receptor mediating the effect of EE on AHN (214,215).
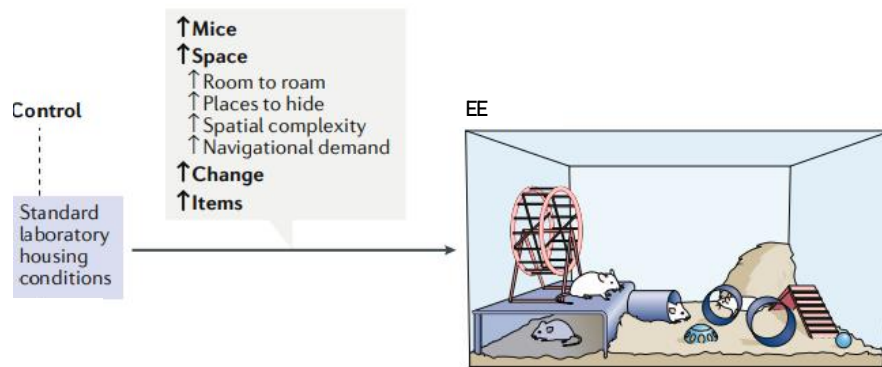

Figure 4 - Environmental enrichment conditions. The precise paradigm of environmental enrichment (EE) varies between studies. However, the key elements are physical activity, social interaction and mental or cognitive stimulation. Of note, the contribution of each component cannot be determined *per se*, and, therefore, EE must be seen as a mixture of effects **(197,216)**.

Recent findings indicate that the transient receptor potential-canonical (TRPC)-1 plays an important role in the EE-induced neurogenesis (217). In fact, these membrane channels are widely expressed in the hippocampus and can modulate neuronal functions (218). EE raised the levels of TRPC1, which, in turn, elevated the proliferation and survival of the newborn cells in DG. Once TRPC1 knockout suppressed the EE-induced ERK1/2 and CREB activation, and over-expression of TRPC1 rescued these effects, TRPC1 may facilitate neurogenesis though activating ERK-CREB pathway (217).

In addition, GABA signaling influences adult neurogenesis (219–221). Diazepam binding inhibitor (DBI) is a negative modulator of $GABA_A$ receptor due to its ability to bind to the benzodiazepine binding site. Importantly, DBI inhibits GABA currents in stem cells, promoting their proliferation. Of note, DBI knockdown prevented not only the increase of DCX^{+} cells, but also the increase of Ki67^{+} cells in adult DG verified under EE conditions. In this sense, the pro-neurogenic effects of EE seem to be dependent of DBI action (222).

2.2.7 Social interaction and support

Adult neurogenesis can be regulated by various social manipulations. Social isolation, for example, results in a decrease in cell proliferation and in the number of newborn neurons in DG. However, social interaction, such as rats placed in groups of 5 per cage, reversed these effects (223). Moreno-Jiménez et al. found that social enrichment increased the number and morphological maturation of DCX$^+$ cells in DG of adult female mice (224). Therefore, social environments can positively modify neurogenesis without any additional stimuli.

"Social buffering" refers to the ability to show a better recovery from negative distress experiences in the presence of specific social partners (225,226). Indeed, social support (SS) can counteract adverse effects of stress, such as stress-decreased neurogenesis. The presence of familiar and unfamiliar conspecifics or their odors reversed the stress-induced reduction of BrdU/DCX-labeled cells in mouse DG. This reversal is independent of corticosterone (227). A later study showed that hippocampal levels of nerve growth factor (NGF) and BDNF reduced by stress are involved in stressor-decrease DG neurogenesis. Noteworthy, the presence of companions was able to restore the levels of neurotrophins; it is possibly due to this mechanism that social interaction has restored the negative effects caused by stress in AHN (228). Although these studies demonstrate the importance of social interaction and support, socially-mediated alterations in neurogenesis are often specific to species and/or sex (229). As an example, when experiencing stress, middle-aged female C57BL/6N mice are more likely to benefit from social interaction, compared to middle-aged males (230).

A study of female prairie vole suggests that oxytocin in the paraventricular nucleus mediates the effects of social buffering on behavioral responses to stress (231). Moreover, oxytocin, which is released centrally and peripherally after social interaction, promotes cell proliferation and dendritic maturation of new neurons in DG (232). Interestingly, airborne oxytocin, probably acting on the oxytocin receptor in the nasal epithelium, prevented the stress-induced decreases in the number of newly proliferated cells and neuroblasts in hippocampus of Balb/C mice. Oxytocin receptors are highly expressed along the olfactory pathways, and signaling through these receptors modulates the processing of social olfactory stimuli (233). In this sense,

oxytocin appears to play a role in reversing stress-decreased neurogenesis mediated by social environment.

Additionally, in a model of Alzheimer disease, double transgenic APP/PS1 mice, cohousing potentiates the rise of protein and messenger RNA (mRNA) levels of BDNF, which, in turn, results in increased hippocampal BrdU/NeuN-labeled cells (234). Thus, social contact can be also valuable in enhancing AHN in disease models.

3 Mood disorders, focus on major depressive disorder

According to the ICD-10 Classification of Mental and Behavioral Disorders, mood disorders are categorized into maniac episode, bipolar affective disorder, depressive episode, recurrent depressive disorder, persistent mood disorders, other mood disorders, such as mixed affective episode and recurrent brief depressive disorder, and unspecified mood disorder (235).

MDD is the most prevalent mood disorder and the most common disabling psychiatric disease across the globe (236). The disease occurs about twice as often in women than in men and contains a significant genetic contribution, approximately 35%. However, social and environmental factors, for example, low socioeconomic status, lack of social support, natural disasters, and stressful life events, are associated with the risk and the outcome of MDD (237). For the diagnostic of MDD five or more symptoms (see Attachment A1) must be present for at least two weeks and represent a change in normal functioning; one of the symptoms necessarily must be depressed mood or loss of interest or pleasure. In addition, the symptoms must have a significant negative impact on the patient's daily life and not be attributable to the use of substances or other pathologies (238).

Several theories have been proposed to explain the pathophysiology of MDD. The monoamine, inflammatory, and neurotrophic hypothesis will be discussed below.

The most common and oldest is the monoamine hypothesis, which proposes that main symptoms of depression are due to an absolute or relative deficiency of the brain monoamines, such as norepinephrine (NE), serotonin (5-HT), and dopamine (DA) (239,240). The emergence of the monoamine hypothesis occurred in the 1950s, when patients treated for several months with reserpine, an anti-hypertensive drug that causes presynaptic depletion of NE, 5-HT and DA, developed depression (240–242). One of the biggest driving forces of this theory is the fact that antidepressant drugs, namely monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine and serotonin reuptake inhibitors (SNRIs), act at the level of brain monoamines, allowing to increase their concentrations in the synaptic cleft. However, in order to prove the reduced

monoamine availability, several studies that measured neurotransmitters and/or their metabolites in *post-mortem* brain tissues and body fluids had inconsistent results (240). Further, it takes more than two weeks to achieve a significant improvement in the depressive symptomatology, even though the blockade of the reuptake of biogenic amines by antidepressants is almost immediate (243). Therefore, despite being a cornerstone in pathophysiology of MDD, there is a need to develop and explore monoamine-alternate hypothesis.

The inflammatory hypothesis results from a large body of evidence that suggests an important role of inflammation in the pathogenesis of MDD. Depressed patients suffer a dysregulation in innate and adaptative immune system; they exhibit elevation in pro-inflammatory cytokines in peripheral blood and CSF, as well as elevation in peripheral blood concentrations of acute phase proteins, such as C-reactive protein, chemokines, adhesion molecules and prostaglandins (244,245). Interestingly, clinical trials have indicated antidepressant effects for anti-inflammatory agents, both as add-on treatment and as monotherapy (246). Nonsteroidal anti-inflammatory drugs, in particular celecoxib (247), and cytokine-inhibitors have shown antidepressant effects compared to placebo (246). On the other hand, the administration of inflammatory cytokines, for example interferon-α, to non-depressed individuals causes symptoms of depression (248). Thus, cytokines appear to be implicated in pathogenesis of MDD (249). Once cytokine signals reach the brain, they enhance CNS inflammation, leading to dysregulation of mood-relevant neurotransmitter metabolism, including 5-HT, DA, and glutamate. In addition, cytokines are able to impair neuronal growth and survival, decrease neurogenesis, dysregulate HPA axis functioning, and alter neural activity in mood-relevant brain regions (245,250). Nevertheless, only about one third of MDD patients have inflammatory values higher than the majority of nondepressed comparison individuals (251). Indeed, inflammation seems not to have the same impact on every MDD subtype (252), being essentially associated with atypical symptoms of depression and with suicidal MDD (244). In this sense, inflammation is neither necessary nor sufficient to induce or sustain MDD, but it is an actor in the pathophysiology of the disease (250).

The neurotrophic hypothesis proposes that MDD results from reduced BDNF levels, which, in turn, contribute to atrophy and cell loss in the hippocampus and pre-frontal cortex (253). In fact, it has been reported that depressed patients have reduced

levels of BDNF and TrkB in hippocampus and in serum, as well as decreased hippocampal volume (254). The rationale behind this theory derives from observations that antidepressant treatments, such as MAOIs, TCAs, SSRIs, SNRIs, ketamine, and ECT, increase BDNF expression and activate TrkB signaling (255,256), thereby reverse neuronal atrophy and cell loss (257). Moreover, direct infusion of BDNF into midbrain areas or hippocampus mimics the behavioral effects of antidepressants (258). Since BDNF plays a central role in neuronal plasticity, decreased BDNF leads to dysfunction of synaptic plasticity, reduction of excitatory neurons and glutamate, that eventually lead to depression (259). However, there are some evidence that contradicts this hypothesis. For instance, genetic disruption of the pathways involving BDNF and TrkB does not produce depression-like symptoms. Also, BDNF levels in the nucleus accumbens were increased in animal depression models. Thus, BDNF is a target of antidepressants, but not the only mediator of MDD (253,256,258,259).

In short, there is no perfect theory to explain the pathophysiology of MDD, which emphasizes the complexity of the disease and the need for further studies in this area of neuroscience.

3.1 The impact of environmental factors on major depressive disorder

As mentioned before, MDD is highly affected by environmental factors, which are able to change the risk of onset of depression or even the evolution of the disease. Stress and HFD are seen as negative experiences in the context of depression, while PEx, CR, EE and SS positively influence MDD. In this sense, adjusts in environmental factors and/or lifestyle can be considered as a window of opportunity for the prevention, treatment and prognosis of MDD.

3.1.1 Stress

Stress is the most important causal agent of MDD (260). In fact, stressful life events, including past or recent experiences, are associated with an augmented risk for developing a depressive episode (261), and commonly they precede first episodes of

MDD (262). The main events occur most often in adulthood, however, adverse experiences during childhood, such as abuse, neglect or loss, increase four-fold the risk to develop depression (263).

Stressful life events could induce several psychological and physiological changes like the activation of HPA axis, leading to its hyperactivity (264). Although inconsistent results, studies suggest that hypercortisolemia is a common finding in patients with MDD (261,264–266). About 70% of depressed individuals manifest dysfunction of HPA axis (264). Specifically, it is described GR resistance at the limbic-hippocampal level due to decreased receptor expression and sensitivity. In such circumstances, cortisol does not exert receptor-mediated negative feedback on the HPA axis (265), which, in turn, increase the release of corticotropin-releasing hormone (CRH) from hypothalamus (261,267). Of note, traumatic stress- or chronic stress-induced abnormalities of the HPA axis have been speculated to play a critical role in development of depressive symptoms, persistence of symptoms, and recurrence of depression (268).

Growing evidence suggests that epigenetic changes are a key mechanism through which stress leads to the development of depressive symptoms. Indeed, stressors can interact with the genome to produce stable changes in DNA structure and expression (Figure 5). Among genes that undergo changes associated with stress and depression, *NR3C1* and *SLC6A4* stand out. In particular, DNA methylation at CpG sites in these genes are associated with depressive symptoms and partially mediated the association between stress and depression (269). Of note, DNA methylation is the most studied epigenetic modification, being involved in gene silencing (270). The *NR3C1* gene, which encodes the human GR, suffer epigenetic modifications in response to childhood maltreatment (CM) that alter the function of the HPA axis (271). Radtke et al. identified a positive correlation between methylation of cg17860381, a specific CpG site located in the promoter of the *NR3C1* gene, and CM. Methylation of cg17860381 was also positively correlated to depression symptoms (272). Therefore, *NR3C1* is epigenetically modified in individuals with a history of CM and depression (269). On the other hand, *SLC6A4* encodes a sodium-dependent 5-HT transporter protein that are responsible for 5-HT reuptake (273). Stressors, namely the lower socioeconomic status during adolescence is associated with an increase in methylation of the proximal promoter of *SLC6A4*, which predicts increased threat-related amygdala reactivity.

Interestingly, the greater amygdala reactivity is implicated in the increase of depressive symptoms among adolescents with a positive family history of depression (274). It could be hypothesized that stress increases *SLC6A4* methylation, which reduces 5-HT transporter expression and thereby dysregulated 5-HT system function (269).
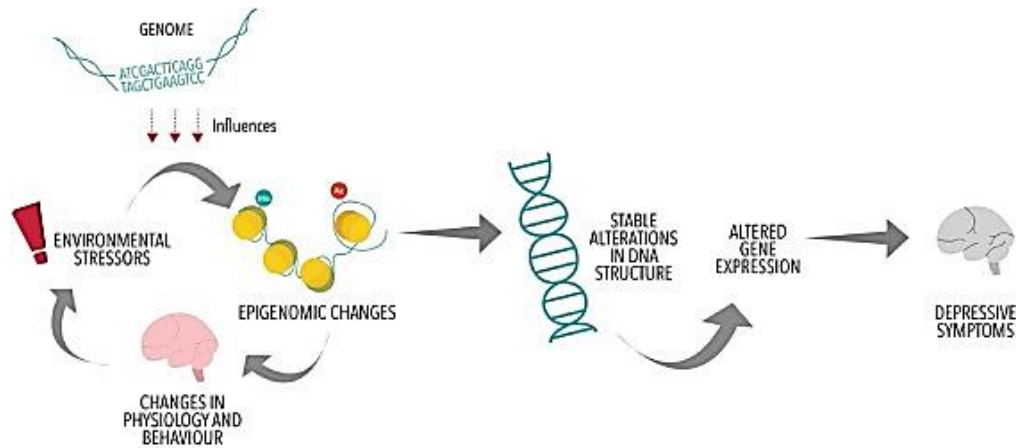
Figure 5 – Stress and major depressive disorder. Stress produces long-lasting epigenetic changes in stress-related genes, which alter gene expression patterns and thereby precipitate symptoms of depression **(269)**.

However, it is important to note that not all people exposed to stress develop depression. For example, individuals with a functional polymorphism in the promoter region of the *SLC6A4* gene (5-HTTLPR polymorphism), namely with one or two copies of the short allele of the 5-HT transporter promoter, exhibit more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele (275). Also, Val66Met polymorphism in *Bdnf* gene moderates the effect of childhood adversity on adult depressive symptoms (276). Thus, preexisting factors known to modulate the organism's ability to compensate in response to stressor challenge might interfere with successful adaptation and convey vulnerability to develop depression (263).

3.1.2   High-fat diet

Several observational studies have been showing a positive relationship between HFDs, such as Western diet and fast-food consumption, and the risk of

depression (277–280). In accordance, HFD-fed mice develop a depression-like phenotype (281).

Diets rich in total or saturated fats can increase free radical production and promote pro-inflammatory states (279). For example, palmitic acid and other saturated fatty acids present in HFD, through the binding to Toll-like receptor (TLR)-4, activate human dendritic cells accompanied by IL-1β secretion; also, palmitic acid induces macrophages secretion of IL-6 (282). Noteworthy, HFD triggers transcriptomic and epigenomic reprogramming of myeloid progenitor cells, that increase proliferation and enhance innate immune responses. These responses are maintained for prolonged periods after the reversal of the diet (283). HFD not only induces the hypothalamic expression of pro-inflammatory cytokines and inflammatory responsive proteins (284), but also is able to impairs BBB integrity (285). In this sense, inflammatory mediators that reach the brain or are produced in the CNS can lead to the activation of intracellular pathways, such as JNK and NFκB, which potentiate chronic inflammation and, consequently, contribute to the pathogenesis of MDD.

Studies demonstrate that protein kinase (PK) A signaling mediate antidepressant effects of many molecules (286–288). One possible mechanism by which HFD promotes depression-like behavior in mice is through the hypothalamic suppression of PKA signaling. Indeed, HFD-induced accumulation of dietary fatty acids in the hypothalamus leads to increased expression levels and activity of phosphodiesterase-4A5, an enzyme that degrades cyclic adenosine monophosphate (cAMP). Therefore, there is a suppression of cAMP/PKA signaling pathway, that results in the development of depression phenotype (289). On the other hand, prolonged HFD exposure decreases plasma or brain levels of 5-HT in rodents (290). As mentioned before, the reduction in 5-HT levels is one of the hypotheses of MDD pathophysiology since this neurotransmitter is essential in mood regulation. 5-HT may mediate mood improvement through the phosphorylation of glycogen synthase kinase (GSK)-3β. Curiously, HFD abolishes the 5-HT-activation of Akt/GSK3β cascade in the DG; also, it inhibits Akt and GSK3β phosphorylation induced by leptin and insulin, which promotes depressive-like symptoms in rodents (291).

The gut-brain axis is defined as a bidirectional message transformation pathway between brain and gut; its dysfunction is emerging as a possible mechanism that leads to the onset of depression. Therefore, through this axis, the brain function and mood

can be influenced by the gut microbiota (292). MDD patients have a significantly different gut microbiotic compositions in comparation to healthy individuals (293–296). HFD, in turn, is determinant for gut microbiota, changing its composition and relative abundance (293,297). Curiously, the caecal microbiota of HFD-treated mice shared several features with those found in the stools of patients with depression (281). HFD raises plasma lipopolysaccharide (LPS) levels in mice, leading to "metabolic endotoxemia". In humans it happens in a similar way, with a 50% increase in plasma LPS concentration after a single high-fat meal (298). The explanation of these findings could be due to the fact that HFD increases intestinal permeability by reducing the expression of genes encoding for tight junctions proteins (299). Then, the bacterial LPS originating from the gut microbiota reaches the bloodstream. Grigoleit at al. demonstrated that injection of LPS in healthy volunteers caused increases in plasma pro-inflammatory cytokines, cortisol and norepinephrine, as well as negative mood (300). Thus, LPS-derived from the gut microbiota may mediate the effects of HFD on depressive behavior (298).

3.1.3 Physical exercise

High levels of physical activity showed a protective effect against the emergence of depression in youths, adults, and elderly persons (301). Moreover, Hallgren et al. reported that PEx improved depressive symptoms more effectively, in patients diagnosed with mild to moderate depression, than usual treatment (302). In another study, the authors found no differences between PEx intervention and antidepressant treatment, meaning that PEx is not less effective than traditional treatments commonly used (303). Exercise, therefore, can be an useful addition to pharmacotherapy and psychotherapy of MDD (304,305). Interestingly, negative changes in physical activity during COVID-19 pandemic were associated with higher depression symptoms (306), which demonstrate the importance of physical activity in preventing/reducing these symptoms.

PEx potentiates an anti-inflammatory state, both in the periphery and in the brain. It has been postulated that exercise, especially of moderate intensity, reduces depressive symptoms by decreasing inflammation (307). There are many mechanisms by which PEx exerts its anti-inflammatory effect: transient release of IL-6 by

contracting muscles during exercise, and a subsequent elevation in circulating levels of anti-inflammatory IL-10 and IL-1 receptor antagonist; reduction of the TLR expression on monocytes; mobilization of regulatory T cells, the main source of IL-10; protection against oxidative stress, due to increased production of antioxidant enzymes and enzymes that repair reactive oxygen species (ROS) damage; and reduction of adipose tissue along with change of macrophage phenotype from M1 to M2, which determines a lower release of pro-inflammatory cytokines, as well as an increase in the release of anti-inflammatory molecules from this tissue (304,308). Curiously, although confirmation is still needed, recent evidence suggests that the effect of PEx in the treatment of depression may be mediated by circulating extracellular vesicles, associated with reduced systemic inflammation (309).

Accumulation of kynurenine (Kyn) in the brain has been related with depression. However, this accumulation can be suppressed due to the activation of Kyn clearance in exercised skeletal muscle (310). PEx induces kynurenine aminotransferase (KAT) expression, through the activation of peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α1/ peroxisome proliferator-activated receptor (PPAR)α/δ in skeletal muscle. KAT enhance the conversion of Kyn into kynurenic acid (311), which does not cross the BBB, preventing neurotoxic effects of Kyn metabolism in the brain (Figure 6) (312). Importantly, the muscle expression of PGC-1α1 induced by exercise protects from depressive behavior (311). Moreover, the increase in PGC-1α in skeletal muscle is associated with the reduction of oxidative stress and pro-inflammatory cytokines, that in turn lower the activity of indoleamine 2,3 dioxygenase, contributing to increase availability of 5-HT and decrease neuroinflammation (312).

Additionally, PEx increases the levels of circulating neurotrophic factors and their expression in the hippocampus (303–305,313). In particular, exercise-induced hippocampal expression of BDNF can be due the activation of PGC-1α/fibronectin type III domain-containing protein 5 (FNDC5) pathway. Exercise not only up-regulates PGC-1α on the skeletal muscle, but also leads to increase *Pgc1a* expression in hippocampus. Therefore, PGC-1α form a transcriptional complex with Errα, that activates *Fndc5* gene expression, culminating in an increase in BDNF levels (314). BDNF, in turn, binds to TrkB and is able to activate mechanistic target of rapamycin complex 1 (mTORC1) (315). Interestingly, PEx exerts an antidepressant effect by stimulating mTORC1 signaling (316). These findings suggest that PEx-increased

BDNF is, at least in part, responsible for beneficial impact of exercise in MDD, through the modulation of mTORC1 signaling pathway.
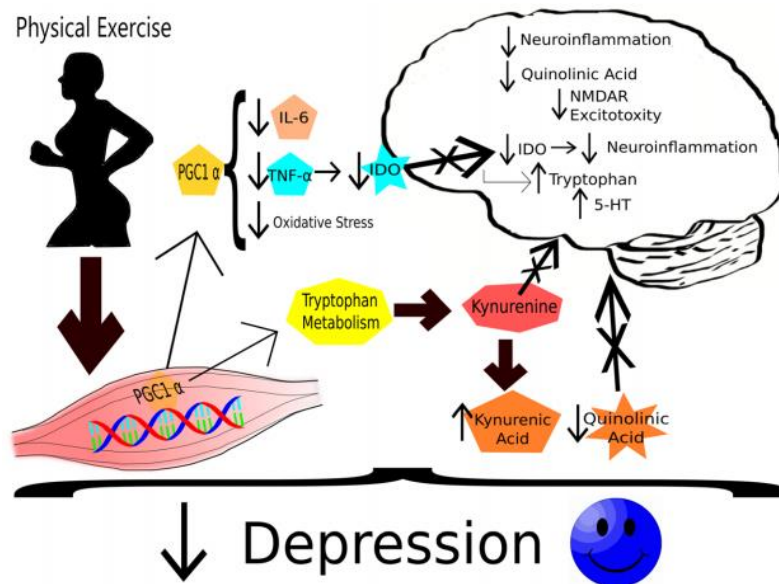

Figure 6 - The interaction between physical exercise, kynurenine pathway and depression. Peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α is overexpressed in exercised skeletal muscles. On the one hand, PGC-1α lead to reduction of oxidative stress and pro-inflammatory cytokines, which ultimately contributes to decreased inflammation, as well as increased availability of tryptophan and serotonin (5-HT) in the brain. On the other hand, PGC-1α enhance the conversion from kynurenine to kynurenic acid **(312)**. Therefore, kynurenine metabolites, such as quinolinic acid, are prevented from exerting neurotoxicity mediated by N-methyl-D-aspartate (NMDA) receptors **(312,317,318)**. Through these mechanisms, exercise counteracts depressive behaviors. IDO, indoleamine 2,3 dioxygenase; IL, interleukin; TNF, tumor necrosis factor. **(312)**

3.1.4   Calorie restriction

CR has been shown to be a powerful tool to reverse/ameliorate depressive symptoms in both animal models and humans (319,320). Despite the concerns about negative effects of this dietary restriction, the CALORIE 2 randomized clinical trial proved that 2 years of CR significantly improved mood, and, importantly, contributed to better depression scores compared with the *ad libitum* group (321).

Orexin signaling is advanced as a mechanism underlying the CR's antidepressant actions (322,323). Intracerebroventricular administration of orexin produces antidepressant-like behavior in mice (324). Ji et al. demonstrated that

hypothalamic orexinergic neurons project directly in ventral pallidum (VP). Consequently, through orexin receptor 1 and 2, orexin depolarizes GABAergic VP neurons and prevents depression by promoting resilience to stress (325). Of note, CR improved the forced swim test (FST) and completely reversed the social interaction deficits induced by social defeat, which means that it exerted antidepressant-like effects in wild-type mice; however, the same did not happen in orexin null mice. CR was also able to enhance the activation of orexin cells after social defeat, inducing antidepressant responses (326).

CR, due to reduced carbohydrate intake, downregulates glucose metabolic pathway, but upregulates ketone bodies metabolism (327,328). β-hydroxybutyrate (BHB), a ketone body elevated in CR conditions, promotes ramification of murine microglia, with the consequent change in microglia profile to M2 polarization. In models of neuroinflammation-induced depression, BHB treatment reverses the depressive-like behaviors; this is dependent of Akt, as Akt inhibition prevents the behaviors improvement. In this sense, the functional microglia ramification induced by BHB reduces neuroinflammation, which helps mice against depressive behavior (329).

As mentioned before, one of the hypotheses of MDD assumes that the disease results from BDNF dysfunction. CR increases levels of BDNF (330). This rise can be explained, at least in part, due to BHB-induced BDNF expression in neurons. Indeed, BHB may induce *Bdnf* gene transcription by inhibiting histone deacetylases (331). Moreover, BHB, by increasing mitochondrial respiration, leads to the generation of ROS, which in turn promotes nuclear translocation of NF-κB. At this level, there is an interaction between histone acetyltransferase p300 and NF-κB, allowing increased expression of the *Bdnf* gene in cortical neurons (332). On the other hand, CREB is another transcription factor that, when activated, promotes *Bdnf* transcription (322). Curiously, CR increases brain CREB phosphorylation (333). Li et al. provided evidence that the increased pCREB/CREB ratio in frontal cortex and hippocampus was responsible for the antidepressant-like effects of acute dietary restriction (334).

3.1.5 Environmental enrichment

EE has been shown to improve several aspects of health, in particular depression (335). Recent reports reveal that EE minimizes depressive-like behavior in animal

models of depression (336–338). Despite the translation problem to humans, EE is associated with positive emotions and well-being, therefore it may have therapeutic potential in MDD (335).

Chronic immobilization stress induces behavioral depression in Wistar rats, and reduces BDNF, VEGF, GFAP and GR expression in hippocampus and frontal cortex. Importantly, EE reverses these effects. Thus, the antidepressant-like properties of EE may be due to the upregulation of BDNF, VEGF, GFAP and GR proteins (339). In mice lacking BDNF expression through promoter IV, EE also reversed depressive behavior, enhancing BDNF mRNA and protein due to other intact promoters in the *Bdnf* gene. The efficacy of EE in these animals was greater when the treatment was in early development, with the persistence of beneficial effects after the decontamination of EE (340,341).

p11 is able to regulate depression-like behaviors and/or responses to antidepressants (342). Interestingly, BDNF increases p11 expression through TrkB and via the MAPK signaling pathway. Moreover, the antidepressant-like effects of BDNF require p11 (343). Seo et al. revealed that exposure to EE early in life avoided depression behavior induced by chronic unpredictable mild stress (CUMS); the underlying mechanism may involve EE-prevented decrease in p11 mRNA, due to epigenetic modifications of the hippocampal p11 gene promoter (344).

Sirtuin 1 (SIRT1) is a NAD^+-dependent deacetylase. Studies correlate SIRT1 not only to MDD, but also to the positive effects of EE in depression (345). Indeed, EE reverted CUMS-induced depression by activating the SIRT1/miRNA-134 pathway, which is responsible for the regulation of BDNF, postsynaptic density protein 95 and synaptophysin, dendritic remodeling and ultrastructural changes in synapses in the hippocampus (346).

3.1.6 Social support

In a general and simplistic way, SS consists of any process whereby social relationships promote health and well-being (347), so it is inversely related to depression (348). Positive and greater SS not only facilitates recovery from a MDD episode, but also is a protective factor against the onset of depression (347). Hallgren et al. showed that depressed adults with access to supportive social relationships had

better treatment response and improvements in MDD, compared to those with low availability of relationships (349). Interestingly, the sources of SS vary across the life periods. Parents, teachers and family are the most protective sources of SS in children and adolescents, while in adults and older people the most salient source is spousal support (350). In turn, the lack of SS is associated with longer duration of the current depressive episode, worse prognosis, relapse of depression, and increases the risk of its onset (347,351–353).

Importantly, narrative interviews with people who had experienced depression reveal that the SS is seen as an essential factor to getting better and staying well (354). Despite the positive influence of SS, it can also negatively affect depressed individuals. The different outcome has to do with the way social relationships are perceived. When perceived as fulfilling basic psychological need, SS reduces depression. In contrast, social relationships perceived as thwarting basic needs decrease well-being, increasing depression (347). Thus, the perceived SS is more important than that received SS (355).

Therefore, since the quality of social relationships predicts depression and the way the disease progresses, social interventions in individuals with lack or low quality of SS can be considered (352).

4 The link between adult hippocampal neurogenesis and major depressive disorder

As one of the neurogenic niches is located in the hippocampus, newborn adult neurons in this region are involved in memory, but also in mood control (356). Importantly, it has been reported the presence of smaller hippocampal volume in MDD patients. *Post-mortem* studies have identified lower levels of cell proliferation in the hippocampus of depressed individuals (357). In addition, Boldrini et al. described an association of untreated MDD with fewer mature granule neurons in anterior DG, as well as smaller DG and GCL volume (358). Thus, the reduction in hippocampal volume could result from a decreased level of adult neurogenesis (356,359).

The neurogenic hypothesis of depression proposes that antidepressants may confer their mood-improving effects through upregulation of adult neurogenesis. Therefore, the decreased production of new neurons in the hippocampus seems to contribute to the pathogenesis of MDD (356,357). Curiously, factors influencing adult neurogenesis affect MDD to the same extent. Stress and HFD are considered negative experiences, which inhibit adult neurogenesis and increase the vulnerability to depression, while PEx, CR, EE and SS have beneficial effects on both neurogenesis and MDD. Chronic antidepressant treatment with ECT, tranylcypromine, reboxetine, and fluoxetine raised the number of BrdU-labeled cells in adult rodent DG, meaning an increased in cell proliferation (360). Additionally to rodents findings, *post-mortem* studies also revealed an increase in neurogenesis in MDD patients taking antidepressants (361). Indeed, antidepressants may regulate AHN at level of cell proliferation, maturation, survival, but they do not affect cell differentiation (Figure 7) (359). A possible explanation for antidepressant-induced neurogenesis is associated with monoamine neurotransmitters. Since monoamines influence neurogenesis in adult brains, common antidepressant drugs and ECT may enhance neurogenesis in part by increasing synaptic levels of 5-HT and other monoaminergic neurotransmitters (362,363). Of note, the neurogenesis increased has been only reported after chronic, but not acute, administration of antidepressants (360). This fact is consistent with the knowledge that it takes 2-3 weeks for granule cells in DG to become functionally integrated in existing brain circuitry. Further, there is a typical delay of at least 2 weeks between antidepressant

administration and clinical efficacy of the medications (364). The similarity of these time courses supports the neurogenic hypothesis of MDD.
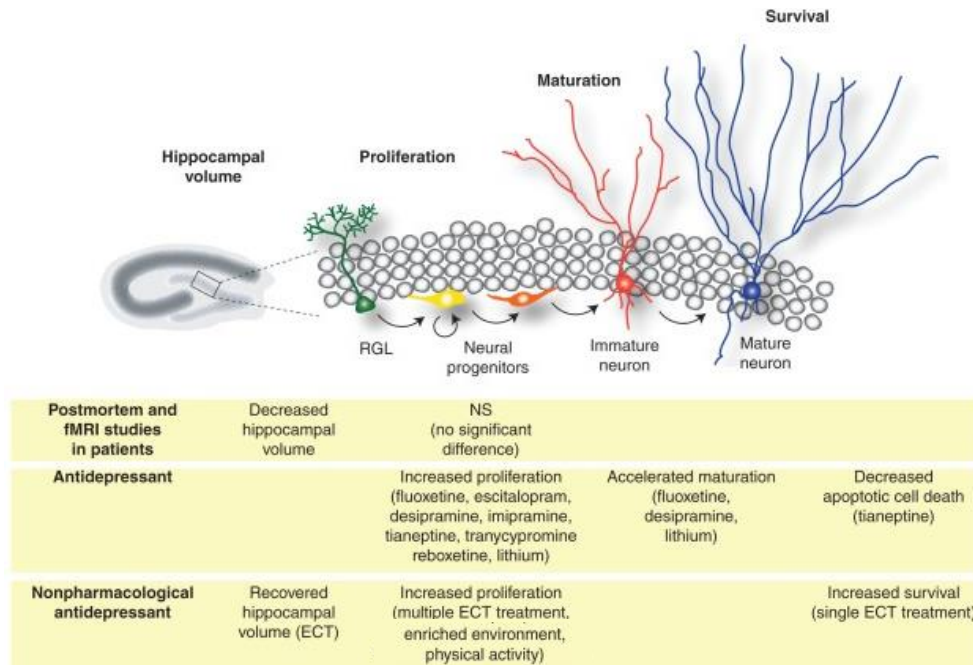

Figure 7 – The relation between adult hippocampal neurogenesis and major depressive disorder. It has been reported that depressed patients experience changes in hippocampal volume. Importantly, many classes of antidepressant drugs, as well as electroconvulsive therapy (ECT) and environmental interventions can upregulate adult hippocampal neurogenesis; the stages commonly affected are neural cell proliferation, maturation and survival. fMRI, functional magnetic resonance imaging **(357)**.

Ablation of AHN, either by genetic or radiological methods, prevented the behavioral improvements in mice being treated with fluoxetine or imipramine (365). Furthermore, continuous neurogenesis is necessary for spontaneous and pharmacological remission of depressive-like behaviors, with arrest of neurogenesis compromising long-term recovery from depression (366). These findings suggest that antidepressants require adult neurogenesis to exert their behavioral effects and that increased neurogenesis may be an essential mechanism for their therapeutic benefits (361).

Hill et al. used a transgenic adult mouse model, in which gene *Bax* was removed from NSCs and their progeny, to increase AHN. They found that increased adult neurogenesis was sufficient to reduce anxiety and depression-related behaviors in

animals chronically treated with corticosterone. So, under stress, the promotion of AHN is sufficient to mimic the antidepressant effects, regardless of the HPA axis (96). In fact, newborn neurons can affect depressive behavior, buffering the effects of prior stress (367).

Despite some reports that animals lacking neurogenesis exhibit increased anxiety/depression-like behaviors (367), there are studies that failed to find similar results. For example, inhibition of neurogenesis by factors other than stress, such as irradiation, does not cause a depressive phenotype. Moreover, enhancing AHN under basal conditions does not produce antidepressant-like effects *per se* (357,359,361). Noteworthy, preclinical findings suggest that volumetric changes in MDD brains are result from decreased dendritic complexity and not from ablation/reduction of AHN (368). On the other hand, it has been observed antidepressants actions dependent and independent of neurogenesis. Hodes et al., in a mice model of depression, abolished AHN by X-irradiation. The efficacy of fluoxetine to reverse the depressive-like state was blocked in novelty suppressed feed test (NSF), but not in all behavioral paradigms (369). In this sense, AHN may not be a major contributor to the development of depression but it may be required for some of the behavioral effects of antidepressants (368).

At the present, the studies suggest a link between AHN and MDD. The loss of neurogenesis in the hippocampus disables throughput in brain circuits essential for the formation of new cognitions and memories. Therefore, patients cannot "escape" the psychological impact of the initial precipitating events and remain mired in a chronic depressive state. Decreased neurogenesis in DG may also be directly involved in mediating the depressive mood due to the anatomical connections between DG and other limbic structures, such as the amygdala (363). Althought there is currently no direct evidence for causative role of the relationship between adult neurogenesis and MDD, the next sections will address signaling pathways that might be possibly involved.

4.1 Wnt signaling

Wnt signaling starts with the biding of Wnt proteins to Frizzled receptors and co-receptors to trigger the canonical Wnt/β-catenin pathway, or the non-canonical Wnt/Ca^{2+} and Wnt/planar cell polarity pathways. Importantly, there are endogenous Wnt inhibitors, such as secreted frizzled-related proteins (sFRPs) and DKK proteins, that prevent the interaction between Wnt ligand and receptors/co-receptors (74,370).

Nowadays it is well accepted that Wnt signaling, in particular the canonical pathway, plays a role in the regulation of AHN. In this pathway, GSK3β phosphorylates β-catenin, which undergoes degradation in the absence of the Wnt ligand. When the Wnt ligand is present, β-catenin is stabilized and translocates to the nucleus, promoting transcription of Wnt target genes (Figure 8) (371). Of note, some steps of AHN are related with Wnt/β-catenin target genes. For instance, cyclinD1 is implicated in the Wnt-mediated proliferation of NPCs, while NeuroD1 is associated in the induction of neuronal differentiation. Therefore, in AHN the canonical Wnt signaling regulates proliferation and fate commitment (Figure 9) (74).
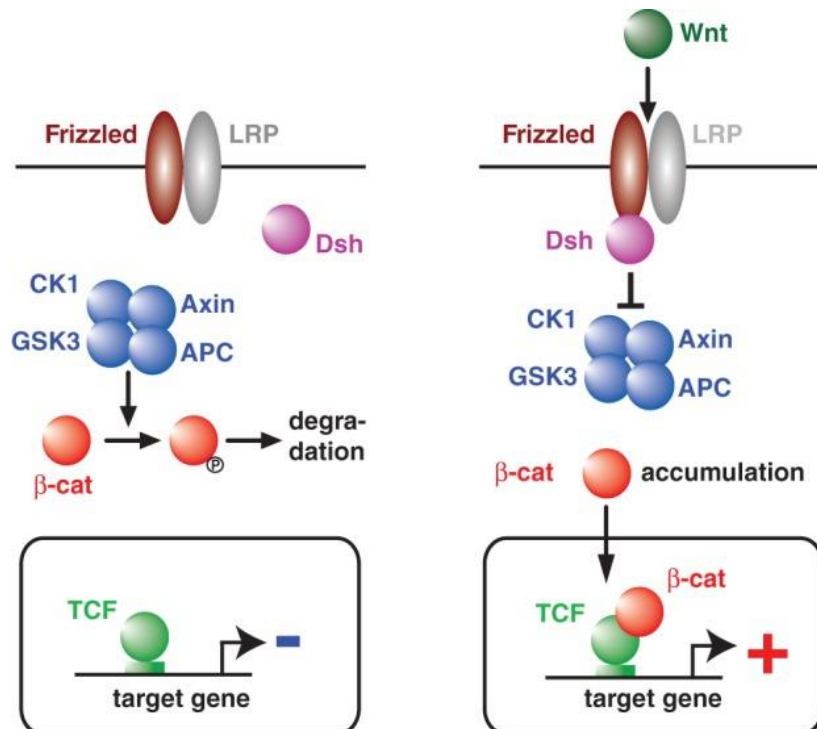

Figure 8 – The canonical Wnt/β-catenin pathway. The key transcriptional effectors of this pathway are transcription factors of the T-cell factor (TCF) family and the transcriptional coactivator β-catenin (β-cat). APC, adenomatous polyposis coli; CK1, casein kinase 1; Dsh,

Dishevelled; GSK3, glycogen synthase kinase 3; LRP, lipoprotein receptor-related protein **(372)**.

Additionally, emerging evidence indicates that Wnt/β-catenin pathway participates in psychiatric disorders, such as MDD (371). Indeed, *post-mortem* and pharmacological studies revealed that the components of the canonical Wnt signaling undergo changes in response to antidepressant treatments, as well as the regulation of these elements can lead to antidepressant-like responses.
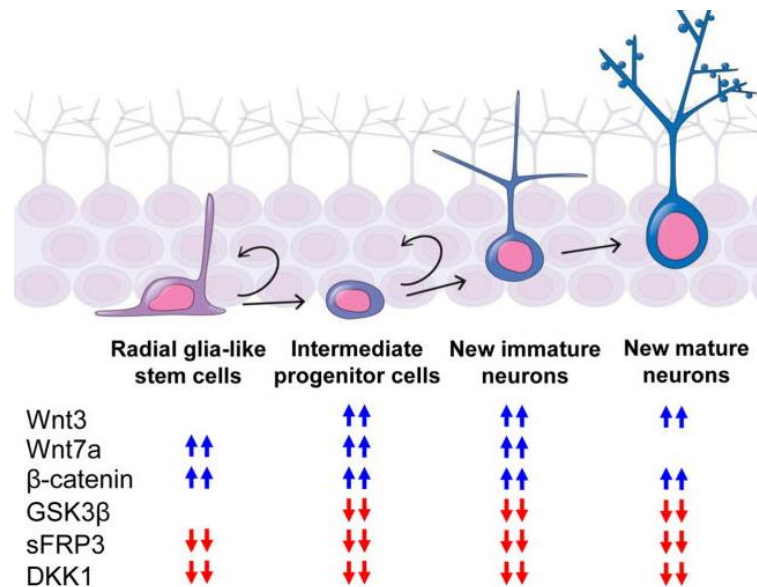
Figure 9 – Members of the canonical Wnt/β-catenin pathway regulate the adult hippocampal neurogenesis. Wnt3, Wnt7a and β-catenin influence positively, whereas glycogen synthase kinase-3β (GSK3β), secreted frizzled related protein 3 (sFRP3) and Dickkopf 1 (DKK1) impact negatively several steps of the adult hippocampal neurogenesis **(371)**.

Increased levels of GSK3β mRNA were found in the hippocampus of MDD patients (371). Further, antidepressant treatments, including ketamine, potentiate the phosphorylation of GSK3β, causing its inactivation (373,374). Curiously, GSK3 knockin mice exhibited defects in hippocampal neurogenesis. Co-administration of lithium and fluoxetine was able to increase NPC proliferation in wild-type animals, whereas it had no effect in GSK3 knockin mice (375). These findings allow to connect

adult neurogenesis and depression treatments with Wnt signaling, suggesting that antidepressant induced-NPC proliferation is dependent of inhibitory control of GSK3.

Contrary to what happens with GSK3β, *post-mortem* brains from depressed patients revealed low levels of β-catenin (376). β-catenin inactivation enhanced depressive-like responses. The animals with this inactivation also had reduced number of BrdU$^+$, Ki-67$^+$ and DCX$^+$ cells in SGZ. In turn, β-catenin stabilization induced an increase in Ki-67$^+$ cells and tended to improve depressive-related behaviors, conferring resilience to some depressive manifestations when mice were subjected to chronic corticosterone administration. Therefore, β-catenin signaling in SGZ modulates proliferation in the adult brain, that appears to be contributing to the antidepressive-like behavior (377).

Curiously, in mice the downregulation of sFRP3 was sufficient to induce antidepressant-like behaviors. In parallel to this experiment, the authors conduced a clinical cohort study, revealing that polymorphisms in *FRZB*, the human sFRP3 gene, were associated with antidepressant response, namely with latency to drug response (378). On the other hand, deletion of DKK1 increased Wnt activity in NPCs, which enhanced the self-renewal and generation of immature neurons in mice SGZ. The same animals, with increased neurogenesis, presented lower immobility in tail suspension test (TST) and higher sucrose preference (151). In this way, increased Wnt activity by loss of its natural inhibitors counteracts depression behaviors and contributes to antidepressant response, possibly due to Wnt-enhanced AHN.

Okamoto et al. demonstrated that different chronic antidepressant approaches, such as citalopram, fluoxetine, atomoxetine, venlafaxine, and electroconvulsive seizures, an animal model for ECT, upregulated Wnt2 in hippocampus. Further, elevated Wnt2 expression was sufficient to produce antidepressant-like behaviors, accessed by learned helplessness test (LHT), NSF, and sucrose preference test (373). Consistent with these results, fluoxetine treatment increased Wnt2 and Wnt3 levels in the VH. Knocking down Wnt2 or Wnt3 eliminated the protective effect of fluoxetine, leading to depression-like behavior. Interestingly, the knockdown disrupted Wnt/β-catenin signaling; it also decreased the number of surviving newborn neurons and reduced cell proliferation in adult VH. On the other hand, the overexpression of Wnt2 or Wnt3 reversed depression-like behaviors, enhanced Wnt/β-catenin signaling, and neurogenesis is DG. Therefore, the depression behavior may result from impairment in

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the canonical Wnt pathway or in AHN (379). Since Wnt/β-catenin signaling regulates AHN, its disruption can lead to neurogenesis deficits, which, in turn, may precipitate the depression-like conduct. In this sense, fluoxetine may possibly counteract depression through Wnt2- or Wnt3-enhanced AHN. Other study showed that fluoxetine increased NPC mitosis and Wnt3a expression in adult DG. However, high levels of Wnt3a may be necessary but not sufficient for the stimulating action of fluoxetine on NPC proliferation (380).

Baicalin is flavonoid compound derived from the roots of *Scutellaria baicalensis*, a plant commonly used in Chinese traditional medicine. Recent evidence indicates that, among other pharmacological functions, baicalin have neuroprotective and antidepressant-like properties (381). Noteworthy, the baicalin treatment was able to upregulate components of Wnt/β-catenin signaling, such as Wnt3a and β-catenin; in addition, there was a rise in the phosphorylation rate of GSK3β and β-catenin nuclear translocation, as well as higher levels of the β-catenin target genes cyclinD1, c-myc, NeuroD1, and Neurogenin-2. Moreover, mice submitted to this treatment showed an increase in Ki-67$^+$ and DCX$^+$ cells in hippocampus, which indicates the restoration of CUMS-induced suppression neurogenesis. This suggests that baicalin regulates canonical Wnt pathway, leading to expression of target genes to promote neurogenesis. Once the authors also reported an improvement in CUMS-induced depression-like behaviors in baicalin treated animals, it is hypothesized that baicalin may play an antidepressant role by regulating neurogenesis through Wnt/β-catenin signaling (382).

All together these data suggest that canonical Wnt signaling may be a link between adult neurogenesis and MDD, although it is not yet established.

4.2 JNK signaling

JNKs are members of the MAPK family. In the mammalian brain, three genes are expressed, *Jnk1*, *Jnk2* and *Jnk3*, which results in more than ten isoforms. JNKs act as sensors of stress, once they can be activated by cellular stressors (383,384). In addition to stress response, JNK pathway is involved in the maintenance of tissue homeostasis, regulating apoptosis, growth, proliferation, differentiation, migration and invasion (Figure 10) (385).
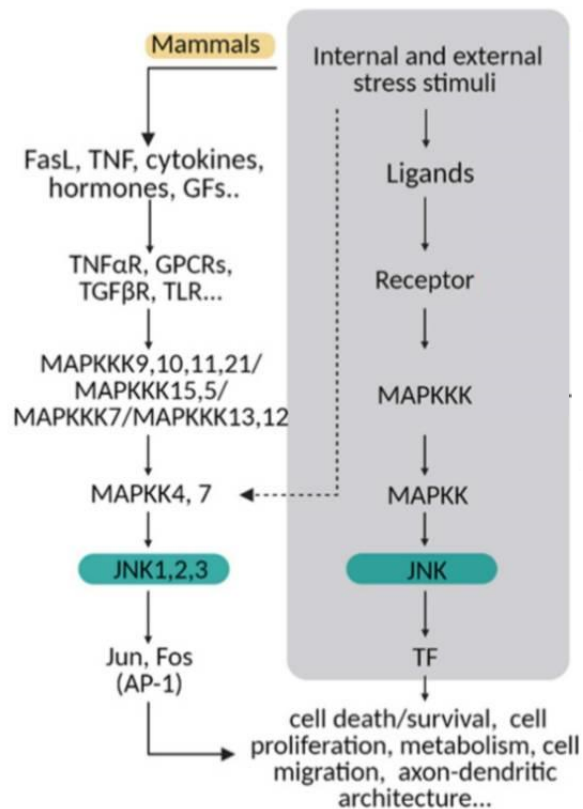
Figure 10 - The JNK signaling pathway. Upon internal and external stress stimuli, ligands (ex. tumor necrosis factor, TNF) activate transmembrane receptors (ex. TNFαR) and initiate a cellular response based on a mitogen-activated protein kinase (MAPK) cascade phosphorylation The cellular response converges in c-Jun N-terminal kinase (JNK) phosphorylation, which triggers the expression of transcription factors as Jun and Fos known as an AP-1 complex. Finally, AP1 modulates the transcriptional program of genes involved in a variety of biological activities **(385)**.

Genetic deletion of *Jnk1* or JNK1 inhibitor infusion into the ventricles leads to an increased in AHN, characterized by improved cell proliferation and survival, and increased maturation of newborn neurons in mice VH (386). In other study, JNK1-knockout mice showed a higher number of immature neurons in DG, while no changes were detected in the lack of JNK2 and JNK3 isoforms (387). Thus, JNK isoforms are involved in adult neurogenesis control in a different way. JNK1 appears to be the dominate isoform in neurogenesis regulation, both in the developing and adult brain (383).

In the prefrontal cortex of MDD patients, an elevation of activated forms of JNK has been reported (388). Importantly, in a model of neuroinflammation-induced

depression, JNK activation was increased. Blocking JNK improved depressive-like behaviors, which may be due to reduced pro-inflammatory cytokines and GR phosphorylation in habenula, amygdala and medial prefrontal cortex (389). Galeotti et Ghelardini demonstrated that JNK inhibitor II reduced immobility in both forced swim test (FST) and TST; the intensity of these antidepressant effects were comparable to that produced by amitriptyline (390). Similarly, the lack of JNK1 reduces depressive-like behaviors in adult mice (386). The finding that JNK1 loss enhances all stages of AHN may contribute to explain why animals with lack/inhibition of JNK1 showed a low depressive phenotype. However, JNK inhibition only in immature granule cells was sufficient to improve anxiety and depressive mood in mice without having any effect on cell number, meaning that neurogenesis was not necessary for the behavioral change (386,391). Thus, although it requires further confirmation, the authors raise the possibility that JNK controls the properties of immature granule cells, leading to increased excitatory output in VH, which in turn evoke negative mood (391).

In this sense, JNK may be involved in the pathophysiology of depression, but further studies are needed to elucidate its role in the disease and how its influence on AHN can affect depressed subjects.

4.3 CREB signaling

CREB is a transcription factor that binds to cAMP response element (CRE) of its target gene promoters, regulating neuronal processes involved in metabolism and survival, and the expression of different transcription and growth factors. To be activated, CREB needs to undergo phosphorylation on Ser133; this process can be mediated by many canonical signaling pathways, such as PI3K/Akt/GSK3β, and cAMP/PKA pathways (Figure 11) (392).

pCREB appears to be expressed after NSC stage, becoming stable with the expression of DCX in both neurogenic niches. Neuronal cells show transient pCREB when they lose immature proteins, DCX and NeuroD, and begin to express neuronal markers (393–395). Curiously, factors, such as treatment with corticosterone, that reduce NSC/NPC proliferation also correlate with decrease in CREB phosphorylation (393). Studies with rolipram, which activates the cAMP cascade and causes pCREB stimulation, reported that cAMP-CREB cascade was involved in neuronal proliferation,

differentiation, survival, and maturation of newborn neurons in adult hippocampus (396). Moreover, loss of CREB function led to impair in dendritic development, and decreased NeuroD and DCX proteins expression, compromising morphological maturation and survival of DG newly generated neurons (395). Thus, the intact CREB signaling is essential for multiple aspects of AHN.
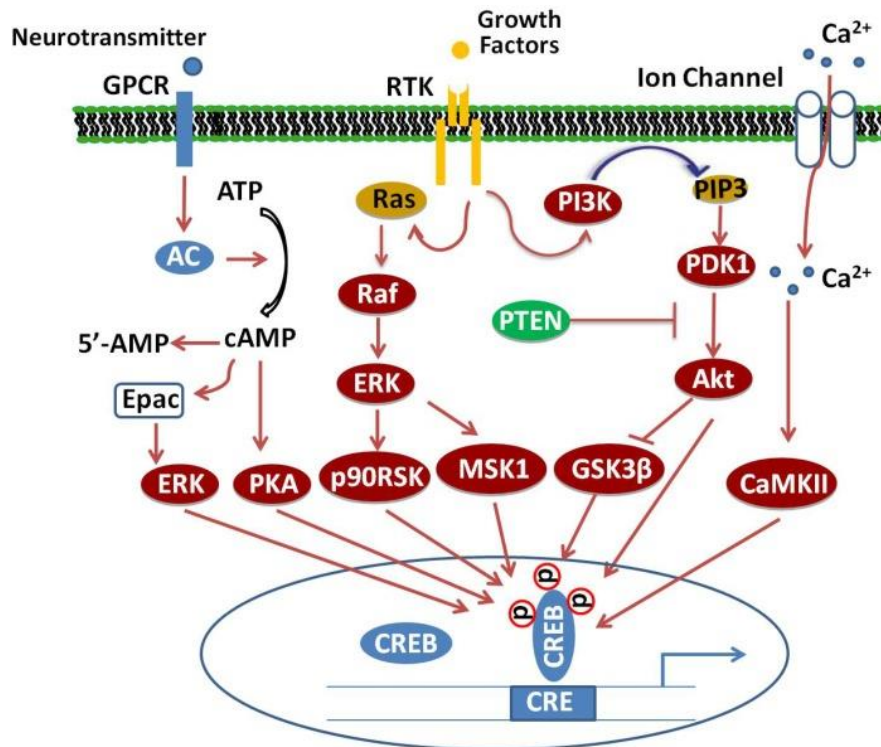
Figure 11 – The CREB signaling pathway. Adenylate cyclase (AC) activated upon stimulation of cellular G-protein-coupled receptors (GPCR) by neurotransmitters increases cyclic adenosine monophosphate (cAMP) levels, which, in turn, activate protein kinase A (PKA). The catalytic subunits of PKA translocate into the nucleus and phosphorylate cAMP-response element binding protein (CREB). Binding of growth factors to receptor tyrosine kinases (RTK) stimulate the activation of PI3K/Akt/GSK3β, Ras/Raf/MEK/ERK/p90/RSK and ERK/MSK1 signaling pathways, which subsequently enhance the phosphorylation of CREB at different sites. Additionally, activation of excitatory N-methyl-D-aspartate (NMDA) receptors will increase the phosphorylation of CREB through Ca^{2+}/Ca^{2+} calmodulin-dependent protein kinase (CaMK)-dependent pathways **(392)**.

Chronic treatment with various classes of antidepressant drugs increased CREB mRNA levels in rat hippocampus, as well as expression and function of CREB protein (397). *Post-mortem* studies indicate that CREB levels were elevated in patients taking

antidepressants at the time of death. Importantly, in rodent models of depression, increasing CREB levels results in antidepressant-like behaviors. For instance, overexpression of CREB in DG of rat reduced immobility time in the FST and decreased the number of escape failures in the LHT (398). However, activation of CREB in the nucleus accumbens produced pro-depression-like-symptoms (392), suggesting that the resulting behaviors will depend on the brain region where CREB is active.

Pharmacological experiments have demonstrated a coincidence of enhanced CREB expression and phosphorylation with increased neurogenesis (399). Intranasal administration of lixisenatide, an analog of incretin glucagon-like peptide-1, in mouse depression model ameliorated depressive symptoms. This effect was accompanied by an increase of AHN and pCREB levels in hippocampus. The inhibition of DG neurogenesis compromised the behavioral improvement. Moreover, antagonize CREB activation decreased DCX$^+$ cells and blocked the positive behavioral effects. Therefore, CREB mediates the antidepressant effects of lixisenatide through the control of AHN (400). The 5-aminoimidazole-4-carboxamide-1-β-d-ribonucleotide (AICAR) is an AMPK activator that, when administrated to an animal model of depression, exerted antidepressant effects, increased the levels of phosphorylated AMPK, PKCζ, NF-κB, CREB, and BDNF, and promoted hippocampal neurogenesis. Blocking AMPK/PKCζ/NF-κB/BDNF/TrkB/CREB pathway, either through the PKCζ inhibitor or the TrkB antagonist, attenuated AICAR-induced antidepressant effects and neurogenesis. In this regard, the authors hypothesized that antidepressant-like behaviors induced by AMPK activation were mediated by hippocampal neurogenesis potentially via PKCζ/NF-κB/BDNF/TrkB/CREB signaling in neurons. Of note, AMPK/PKCζ/NF-κB pathway may promote the secretion of BDNF, activating the TrkB/CREB signaling pathway (401). Although BDNF activates CREB through TrkB receptors, *Bdnf* is also a target gene for the CREB transcription factor (402). As mentioned before, BDNF is able to enhance adult neurogenesis and is elevated in response to antidepressant drugs treatment. Thus, stimulation of BDNF/TrkB/CREB signaling appears to improve depression-like symptoms due to regulation of hippocampal neurogenesis.

Surprisingly, CREB$^{\alpha\Delta}$ mutant mice demonstrated an antidepressant phenotype in the TST and FST. In addition, the mutant animals exhibited increased hippocampal cell proliferation and neurogenesis (403). This can be explained by upregulation of the

CREB-family protein cAMP response-element modulator (CREM). After CREB deletion, hippocampal CREM levels were higher, which compensates for CREB. Overexpression of CREM led to an increase in AHN and reduced latency to consume in the novel environment, as observed in CREB$^{\alpha\Delta}$ mice (404).

Despite some apparently contradictory findings, CREB signaling appears to mediate antidepressant responses/behaviors by enhancing AHN. However, more research must be carried out, in particular to elucidate the role of the other CREB-family protein, CREM. In the future, both CREB and CREM may emerge as potential therapeutic target for MDD.

Conclusion

An important landmark in the history of neuroscience was the recognition that neurogenesis, which is defined as generation of new neurons, occurs in specific areas of the adult brain. Although there are conflicting results, the adult neurogenesis was already identified in mammalians, and, importantly, in humans. The most characterized neurogenic niches are in SVZ of LVs and in the SGZ in the DG of hippocampus. Therefore, newborn adult neurons appear to be involved in functions such as olfaction, damage repair, learning, memory, and mood regulation.

Across lifespan of mammalians, there are a sharp decline in neurogenesis process. In addition, environmental factors, namely the exposure to stress and HFD contribute to the reduction of neurogenesis. Contrary, PEx, CR, EE and SS can enhance neurogenesis. These factors, except for age, are modifiable with lifestyle interventions. Thus, making the necessary changes, such as reducing the intake of fat in the diet, practicing aerobic exercise regularly, will possibly have beneficial effects on neurogenesis. In this sense, it is also expected that the functions that seem to be associated with newborn neurons will improve with these interventions.

Considering that currently there are no therapies approved by the regulatory agencies, either the European Medicines Agency or the Food and Drug Administration, that allow a complete cure for mood disorders, interventions that enable positive regulation of mood should be seen as a window of opportunity for the treatment and prevention of these diseases. In this regard, this is how we should look at adult neurogenesis.

MDD, in particular, does not have a high mortality rate, however it strongly affects the quality of life of patients. The course of the disease is characterized by relapses and recurrences. Further, due to the particularities of the disease, it may be associated with other comorbidities, as anxiety. To make matters worse, there are also depressed patients who do not respond to current antidepressant therapies.

Environmental factors, such as stress, HFD, PEx, CR, EE and SS, influence MDD. At this point, lifestyle changes also appear to play an important role in the prevention, treatment, and prognosis of MDD. The finding that factors affecting neurogenesis influence MDD to the same extent is fascinating and highlights the link between adult

neurogenesis and MDD. Moreover, the decrease in AHN, i.e., reduced production of new neurons in hippocampus appears to contribute to the development of depression. Chronic pharmacological treatment with antidepressants or even ECT are able to stimulate AHN. Indeed, it takes approximately 2 weeks for individuals to experience improvement with the use of antidepressants. Furthermore, new neurons generated in the adult brain require about 2-3 weeks for their maturation and complete integration. Thus, it is very possible that behavioral improvements induced by antidepressant therapies may be due to increased adult neurogenesis.

In this way, despite some contradictory studies and although the underlying mechanisms are not yet known, scientific evidence suggests the existence of a relationship between adult neurogenesis and MDD. The Wnt, JNK and CREB signaling pathways might explain the relationship between adult neurogenesis and depression. Overexpression of stimulant members of Wnt/β-catenin pathway potentiate AHN and reverse depressive-related behaviors. Therefore, activation of the canonical Wnt signaling may plays a role in improvement of depression phenotype induced by increased adult neurogenesis. On the other hand, the absence of JNK not only enhances certain AHN steps, but also ameliorates depressive-like behaviors. CREB leads to the transcription of genes that upregulates adult neurogenesis. Moreover, the increase of CREB in DG reduces depression behaviors in paradigms such as FST and LHT. Importantly, one of CREB's target genes is *Bdnf*. BDNF is a well-known neurotrophic factor with pro-neurogenesis properties; in addition, it appears to be involved in the pathophysiology of depression (neurotrophic hypothesis of MDD). Finally, CREM, the other CREB-family protein, may also mediate the increase in AHN and the antidepressant phenotype.

In the future, more studies should be performed to further clarify the impact of adult neurogenesis in MDD, and what mechanisms are effectively involved. Once these underlying mechanisms are identified, a new hope will certainly emerge for the development of better therapeutic approaches to this public health problem. Not least, more studies should also be carried out to determine the link between adult neurogenesis and other mood disorders, as bipolar disorder.

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Attachments

A1.   Diagnostic criteria for major depressive disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   Note: Do not include symptoms that are clearly attributable to another medical condition.

   1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note**: In children and adolescents, can be irritable mood.)

   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)

   4. Insomnia or hypersomnia nearly every day.

   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

   6. Fatigue or loss of energy nearly every day.

   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A–C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition (238).