Universidade de Lisboa

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Role of Nutrition in Adult Neurogenesis

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Monografia orientada pela Professora Doutora Susana Zeferino Solá da Cruz,
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"**Ever tried**. Ever failed. No matter.
Try again. Fail again. **Fail better**."

- *Samuel Beckett*

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To my parents, for pushing me to take risks and believe in myself. Thank you for encouraging my dreams and showing me that college is just the beginning. Home is wherever our loved ones are, and I love both of you so much.

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I declare to have developed and prepared this work in accordance with the Code of Conduct and Good Practices of the University of Lisbon. More specifically, I affirm that I have not committed any of the varieties of academic fraud, which I hereby declare to be aware of, and that I have complied with the required referencing of sentences, extracts, images and other forms of intellectual work, fully assuming the responsibilities of authorship.

Resumo

A neurogénese adulta é o processo pelo qual novos neurónios são formados no cérebro, sendo essencial para o desenvolvimento saudável e manutenção do sistema nervoso central. Este fenómeno, que antes se pensava ocorrer apenas durante as fases pré-natal e precoce de vida, foi demonstrado ocorrer também durante a vida adulta. Esta descoberta tem facilitado a compreensão de vários componentes patológicos, a plasticidade cerebral e a função cognitiva. É possível estabelecer uma correlação entre a atividade saudável de tecidos neuronais específicos e o efeito de certos elementos dietéticos essenciais. Em termos celulares, há evidências de que a oscilação nos níveis de nutrientes afeta o correto funcionamento de organelas como mitocôndrias, retículo endoplasmático e lisossomas, cruciais para todas as funções cerebrais. Também esclarece novas possibilidades terapêuticas para ajudar nos transtornos de humor, doenças neurodegenerativas e lesões neurais. Intrinsecamente, é fundamental compreender quais os fatores que regulam e influenciam esse processo. Esta monografia pretende, assim, elucidar sobre os efeitos da nutrição na neurogénese adulta, fazendo a correlação com a neuroplasticidade, explorando o impacto das escolhas alimentares no estado de saúde das células neuronais. Vários alimentos têm sido associados à inibição ou à promoção da neurogénese. Em particular, nutrientes como as vitaminas D e C, minerais como o zinco e o lítio, os ácidos gordos ómega-3, e até a ingestão calórica total, têm sido associados a este problema. De facto, a dieta ocidental moderna tem sido associada à diminuição da saúde cerebral e ao aumento de doenças neurológicas, sendo caracterizada pelo elevado consumo de açúcares e gorduras pouco saudáveis, e pelo fraco consumo de nutrientes essenciais. Este conhecimento pode revelar-se crucial não só na melhoria da saúde cognitiva e da longevidade, mas também na melhoria de condições como a depressão, a doença de Parkinson e a doença de Huntington. O controlo das principais vias moleculares geridas pelo consumo de nutrientes específicos pode, em última análise, resultar numa melhoria da qualidade de vida global e na melhoria da esperança de vida.

Palavras-chave: Dieta; Metabolismo; Neurogénese Adulta; Nutrientes

Abstract

Neurogenesis is the process by which new neurons are formed in the brain, essential for healthy development and maintenance of the central nervous system. This phenomenon, once believed to occur during the prenatal and early life phases, has now been confirmed to also exist in adulthood. It also aids in the understanding of several pathologies related to components such as brain plasticity and cognitive function. Curiously, a correlation can be established between the healthy function of specific neuronal tissues and the neuronal tissues and the impact of certain essential dietary components. More specifically, in cellular terms, there is evidence that the oscillation in nutrient levels affects the correct function of diverse organelles, such as the mitochondria, endoplasmic reticulum and lysosomes, crucial for all brain functions. The link between neurogenesis and diet also helps to hypothesize new therapeutic possibilities for mood disorders, neurodegenerative diseases and neural injuries. Intrinsically, it is paramount to understand which factors regulate and influence this process. This work aims to shed some light on the effects of nutrition on adult neurogenesis, correlated with neuroplasticity, exploring the impact of dietary choices on the health status of neuronal cells. Several foods have been linked to either the inhibition or promotion of neurogenesis. Nutrients such as vitamin D and C, minerals like zinc and lithium, omega-3 fatty acids and even total caloric intake have been linked to this problem. In fact, the modern Western diet characterized by high consumption of sugars and unhealthy fats and poor consumption of essential nutrients, has been associated with decreased brain health and an increase in neurological diseases. This knowledge may prove relevant not only for the betterment of cognitive health and longevity but also for the improvement of conditions such as depression, Parkinson's disease and Huntington's disease. The control of key molecular pathways managed by the consumption of specific nutrients might ultimately result in an improvement of overall quality of life and improved lifespan.

Keywords: Adult Neurogenesis; Diet; Metabolism; Nutrients

Abbreviations

1,25(OH)2D3: Calcitriol, the active vitamin D form; 1alpha,25-dihydroxyvitamin D3

25(OH)D: Calcidiol; 25-dihydroxyvitamin D

3-HDT: 3-hydroxytyrosol

abGCs: Adult-born granule cells

ABTS: 2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid);

AD: Alzheimer's disease

ADP-ribose: Adenosine diphosphate ribose

Akt: Ak strain transforming

ALS: Amyotrophic lateral sclerosis

AMPK: 5’ AMP-activated protein kinase

AP1: Activator protein 1

ATP: Adenosine triphosphate

Aβ: Amyloid β-peptide

BACE1: Beta-secretase 1

BAD: BCL2 associated agonist of cell death

BAX: BCL2-associated X protein

BBB: Blood-brain barrier

BChE: Butyrylcholinesterase

Bcl-2: B cell lymphoma 2

BDNF: Brain-derived neurotrophic factor

BrdU: Bromodeoxyuridine

CAT: Catalase

CNS: Central nervous system

COX2: Cyclooxygenase 2

CR: Caloric restriction

CRAC: Calcium release activated channel

CRMs: Caloric restriction mimetics

CSF: Cerebrospinal fluid

DCX: Neuronal migration protein doublecortin

DG: Dentate gyrus

DHA: Docosahexaenoic acid

DHDA: Dehydroascorbic acid

DMPD: N,N-dimethyl-p-phenylenediamine dihydrochloride;

DNA: Deoxyribonucleic acid

DPPH: 1,1-diphenyl-2-picryl-hydrazyl free radical

EGCG: Epigallocatechin-3-gallate

EPA: Eicosapentaenoic acid

ER: Endoplasmic reticulum

ERK: Extracellular signal-regulated kinase

ESCs: Embryonic stem cells

ETC: Electron transport chain

FA: Fatty acid

GABA: Gamma-amino-butyric acid

GCL: Granule cell layer

GL: Glomerular layer

GPx-1: Glutathione peroxidase 1

HD: Huntington's disease

HO-1: Heme oxygenase 1

IF: Intermittent fasting

IFN-γ: Interferon-γ

IGF-1: Insulin-like growth factor 1

IL-1: Interleukin-1

Il-10: Interleukin-10

IL-1β: Interleukin-1β

IL-6: Interleukin-6

iNOS: Inducible nitric oxide synthase

JAK: Janus kinase

JNK: C-jun N-terminal kinase

KO: Knockout

LHb: Lateral habenula

LHPP: Phospholysine phosphohistidine inorganic pyrophosphate phosphatase; histidine phosphatase

LPS: Lipopolysaccharides

LVs: Lateral ventricles

Map5: Microtubule-associated protein 5

MAPK: Mitogen-activated protein kinase

MCI: Mild cognitive impairment

MDA: Malondialdehyde

MGO: Methylglyoxal

mRNA: Messenger RNA

MSNs: Medium spiny neurons

NAD: Nicotinamide adenine dinucleotide

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

NGF: Nerve growth factor

NMDA: N-methyl-D-aspartate

NO: Nitric oxide

NOX2: NADPH oxidase 2

NPCs: Neuronal precursor cells

Nrf2: Nuclear factor erythroid 2-related factor 2

NSCs: Neuronal stem cells

OB: Olfactory bulb

OXPHOS: Oxidative phosphorylation

PD: Parkinson's disease

PI3-K: Phosphoinositide 3-kinase

PPARγ: Proliferator-activated receptor gamma

PSC: Pluripotent stem cells

PUFA: Polyunsaturated fatty acids

RGCs: Radial glial cells

RGL: Radial glia-like

RMS: Rostral migratory stream

RNA: Ribonucleic acid

RNS: Reactive Nitrogen Species

ROS: Reactive oxygen species

SCI: Spinal cord injuries

SGZ: Subgranular zone

SIRT1: Sirtuin 1

SIRTs: Sirtuin

SN: Substantia nigra

SNpc: Substantia nigra pars compacta

SOCE: Store-operated Ca2+ entry

SOD: Superoxide dismutase

Sox1: SRY-box transcription factor 1

Sox2: SRY-box transcription factor 2

Sox9: SRY-box transcription factor 9

STIM1: Stromal interaction molecule 1

SVCT1: Sodium-dependent vitamin C transporter 1

SVCT2: Sodium-dependent vitamin C transporter 2

SVZ: Subventricular zone

TGF-β1: Transforming growth factor-beta 1

TNF-α: Tumour-necrosis factor alpha

Trk: Tropomyosin-related kinase

TUBB3: Tubulin beta 3 class III

TUDCA: Tauroursodeoxycholic acid

UFP: Unproperly folded proteins

VDR: Vitamin D receptor

Wnt: Wingless-related integration site

αSyn: α-synuclein.

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1. Introduction

The process by which new neurons are generated in the adult brain is called adult neurogenesis. Previously, researchers believed this process did not occur after the embryonic and early life stages (1,2). However, over the years, studies have demonstrated that neurogenesis occurs across all stages of life. This constitutes a great possible target in the treatment of neurologic pathologies, such as Parkinson's disease (PD) and Alzheimer's disease (AD), as well as some mood disorders like depression. In fact, studies conducted since the beginning of the century have demonstrated the correlation between several neurogenic facets. Neuroplasticity, for example, has been proven to aid in the neurogenic process, being promoted by antioxidants and anti-inflammatory components (3). Adult neurogenesis is a complex process that encompasses mechanisms such as the proliferation of neuronal stem/precursor cells (NSCs/NPCs), the correct balance between apoptosis and cell survival, neuroblast migration, neuron differentiation and the integration of these cells in the preexisting neuronal network (4,5). This process occurs in specific niches, namely the subgranular zone (SGZ) of the hippocampus, and the subventricular zone (SVZ) of the lateral ventricles. However, recent literature points out new neurogenic niches that have been observed to also sustain the proper conditions to allow for neurogenesis in adults (4,6,7). These include the hypothalamus, the substantia nigra, the striatum, the amygdala, the habenula and the cerebellum (8).

Several factors influence the process of adult neurogenesis. Aging, exercise habits, sleep quality and dietary choices (9). This work will comprise an intelligible list of some diet factors that have been observed to directly influence adult neurogenesis, namely omega-3 Fatty Acids (FAs), vitamins, minerals, polyphenols, caloric intake, tauroursodeoxycholic acid (TUDCA) and the relationship between the gut microbiome and the brain.

The modern diet is characterized by high consumption of red meats, candy, refined grains, fried foods, high-fat dairy and high-fructose products (10). The problem with this diet relies on the fact it only arose in recent decades, replacing the largely unprocessed and nutrient-rich foods previously available (11,12). Nowadays, as a consequence of the Industrial Revolution (13), food is readily available for consumption and its quality has significantly declined to be mass-produced. This food is low on essential nutrients, and high on unhealthy products such as grease and sugar (10). This change occurred rapidly over the past few decades, leaving our bodies little time to adapt. However, our organism still needs the same

crucial nutrients to develop and maintain the necessary mechanisms of life, leading to a growing number of pathologies observed in the Western world, namely neurological diseases (14,15).

To counteract this fact, the supplementation of these essential nutrients might constitute the answer to treat or alleviate some of the notable consequences of this diet. It may even constitute a viable component for the treatment of neurological diseases such as AD, among many others (16,17). Therefore, understanding the mechanisms of adult neurogenesis and the role of nutrients in this process is essential.

2. Neural Stem Cells and Adult Neurogenic Niches

2.1 Neural Stem Cells

During the embryonic and early postnatal periods in mammals, most cells experience a rapid division stage, after which most cell proliferation is confined to long-lived tissue stem cells and their progenies (18). Therefore, these adult stem cells, found in many specific niches (regions where these cells reside after early life development), are subject to various complex signals that guide the cells into remaining in a quiescent state (18,19), a state of reversible cell cycle arrest, normally in the G0 phase of the cell cycle but also G2 - or suffering differentiation.

Neural stem cells (NSCs) give rise to all neurons and almost all glial cells in the brain and spinal cord. In adult mammals, these cells are mainly found in the central nervous system (CNS) in two niches: the SVZ, of the lateral ventricles (LVs), and the SGZ, in the dentate gyrus (DG) of the hippocampus (20–22). Throughout life, NSCs have the ability to contribute to brain plasticity. However, most of these remain inactive unless triggered by certain physiological signals. (18,23,24) (**Figure 1**).

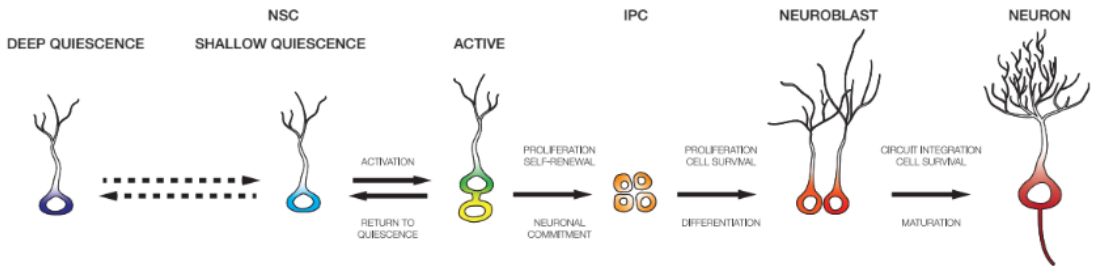

Figure 1. From deep quiescence to mature neuronal cells in the subgranular and subventricular zones. NSCs start by transitioning between a deep quiescence and a shallow

quiescence state. From here, NSCs can suffer activation, converting to an active state. From which they may return to quiescence. Due to internal and external factors, the active cells may start proliferating and self-renewing, suffering differentiation. This process originates intermediate precursor cells, which eventually will develop into neuroblasts. Through the integration of these cells in the preexisting neuronal circuits, some neuroblasts mature and integrate the network, while others suffer apoptosis. *Adapted from: Quiescence of Adult Mammalian Neural Stem Cells: A Highly Regulated Rest (18).*

2.2 Adult Neurogenic Niches

2.2.1 Subgranular Zone of the Hippocampus

The first major neurogenic zone in the adult mammalian brain is the SGZ of the hippocampal dentate gyrus (7,25). This region is responsible for the production, maturation and integration of adult-born granule cells (abGCs) (7,26). These cells have the capacity for self-renewal and multipotency, recognized by their astrocyte-like molecular characteristics and radial glia-like morphology (type 1 cells). During adult neurogenesis, abGCs go through five individual developmental stages: activation of quiescent type 1 cells in the SGZ; amplification of non-radial precursor and intermediate progenitors; creation of neuroblasts through lineage selection; migration of immature neurons; and integration and maturation of abGCs. Type 1 NSCs exist mostly in a dormant state. However, these suffer asymmetrical division after activation, generating type 2 cells - non-RGL (Radial glia-like) progenitor cells. Moreover, type 2 cells can be further differentiated into type 2a and 2b, based on the expression of different proteins (7,26). These cells divide symmetrically and asymmetrically, creating type 3 cells through the second process. Both type 2 and type 3 cells commit in part to the neuronal lineage (7,27,28). Three weeks following this division, most of the aforementioned cells will die through both apoptosis as well as lack of glutamatergic-N-methyl-D-aspartate (NMDA) type input (7,29). The surviving neurons are later integrated into the existing network (7,30,31).

The new abGCs generated are excitatory neurons with the capacity to increase neuroplasticity (7,32). In fact, the newly formed abGCs compete with the pre-existing ones for the available axonal boutons, leading to new synaptic formations. This phenomenon happens once the cell body of the developing neuron is in the granular zone and its dendrites enter the molecular zone (7,33). The process of synaptogenesis occurs following the increase in dendrite length. As the axons move into the CA3 region, the dendrites reach the molecular layer (7,34). The completion of this process has been observed to happen only after 8 weeks,

although studies showed that it may take longer in higher mammals, being thought to take over 6 months in humans (7,35).

2.2.2 Subventricular Zone of the Lateral Ventricles

The SVZ of the LVs is the second of the two major regions involved in the process of adult neurogenesis. The transition from dormant NSCs to immature neurons involves multiple stages, including proliferation, lineage selection, migration, survival, integration, and functional maturation, which are interdependent and often overlap (7).

Resident NSCs are labeled type B cells. They predominantly exist in a quiescent state exhibiting a radial-glial-like morphology and the ability to form vascular connections with blood vessels in this region. Here, NSCs also have an apical end, extended throughout the ependymal layer and reaching the lateral ventricles, contacting with the cerebrospinal fluid (CSF) (7). Type B cells can generate three distinct neural cells – neurons, astrocytes and oligodendrocytes (7,36). In these conditions, the process of neurogenesis starts with type B cells' asymmetric division, originating transit-amplifying type C cells. Type C cells then create neuronal progenitor cells – neuroblasts, type A cells. These newly formed cells then migrate along the rostral migratory stream (RMS) toward the olfactory bulb (OB) (7,37). This relocation takes up to 5 days to complete. There, type A cells differentiate into olfactory granule cells and periglomerular cells. During the migration process, these cells are encased by astrocytes in an organized chain containing 30 to 40 cells, aligned closely together. After reaching the OB, the cells start settling into their final positions, reaching either the granule cell layer (GCL) or the glomerular layer (GL) (7,38).

One of the fundamental aspects of this process is the regulation of newly formed cells' survival. This mechanism is essential to secure a sufficient number of new OB neurons and uses processes such as programmed cell death as a means to maintain adequate migration through the RMS (7,39). Afterward, the remaining neuroblasts differentiate into one of the OB interneuron subtypes. The neurons integrated in the OB are assigned specific functions, being displayed in an organized manner. An example of these specialized cells is hair cells, which reside in the olfactory epithelium and whose axons reach the GL. Each cell has a glomerulus assigned to it, representing an individual scent receptor. The hair cells pickup on stimuli and transmit information to the mitral and tufted cells, whose cell somata resides in the mitral/tufted cell layer, through their interaction with neurotransmitters such as gamma-amino-butyric acid (GABA) or dopamine, secreted by neighbouring periglomerular interneurons (7,40,41). The concluding stage in the integration of new neurons is the synaptic

merging into the already available neuronal network. This process occurs through the principle "use them or lose them", where neurons not well integrated in the neuronal network of the OB perish. In the case of hair cells, an odorant rich biome would positively influence the number of cells integrated (7,42–44) (**Figure 2**).

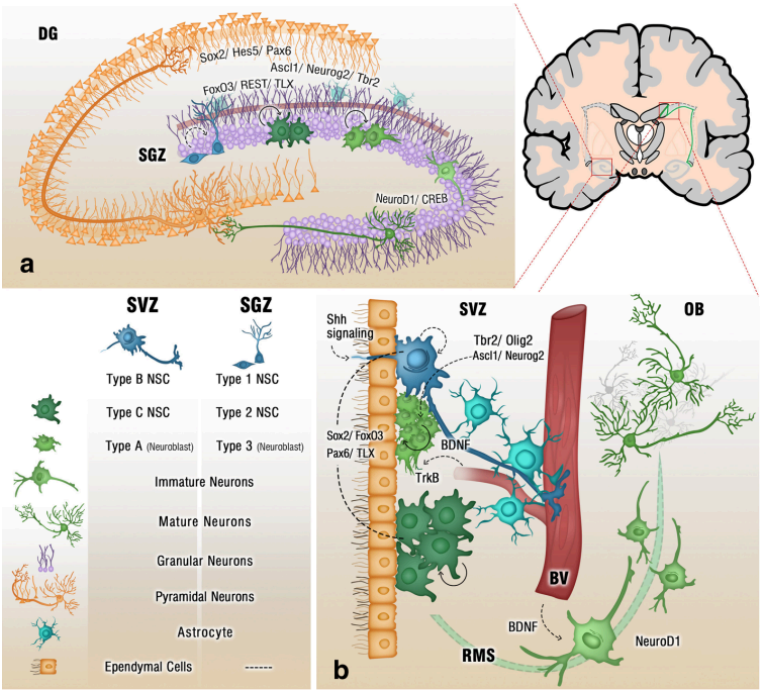

Figure 2. SGZ and SVZ niches. Coronal cross-section of the adult brain shows SGZ and SVZ niches, where the process of neurogenesis occurs. NSCs develop into mature neurons; the schematic shows blood vessels (BV), astrocytes and cilia. SGZ (a) and SVZ (b) are also detailed. In (b) it is also shown the migration of neurons from the SVZ to the OB through the RMS. *Adapted from: Factors that influence adult neurogenesis as potential therapy (9).*

2.2.3 Newly Discovered Neurogenic Niches

While most research on adult neurogenesis suggests that this process occurs almost exclusicely in the SGZ and SVZ, recent studies have indicated that other niches may also have the necessary properties to support it (45). These newly discovered neurogenic niches include the hypothalamus, the substantia nigra, the striatum, the amygdala, the habenula and the cerebellum, although the last two are still controversial and need further research to confirm (46).

2.2.3.1 Hypothalammus

The hypothalamic neurogenic niche is located in the subependymal zone of the third ventricle. Mouse and rat models showed that the hypothalamic niche is distinct from the SGZ

and SVZ, namely because in the first cell proliferation does not occur solely in the cell layers. In fact, the proliferation and generation of new neurons occur throughout the hypothalamic parenchyma (46–48). The precursor cells in the hypothalamus are named “tanycytes” and have been characterized as radial glial cells (RGCs) (46,49). The hypothalamic niche is formed by various cell subsets, located throughout the third ventricle (46,50). Different populations of tanycytes were named α and β, which in turn are also subdivided into α1 and α2, and β1 and β2. The α1 cells are located in the ventromedial nuclei in the third ventricle, while the α2 can be found by the arcuate nuclei. Contrastingly, β1 cells reside in the lateral part of the infundibular recess, while β2 forms in the median eminence, known as the hypothalamic proliferative zone (46,50). The recognition of the hypothalamus as an active neurogenic site occurred when researchers found that hypothalamic cells express markers associated with NSCs and progenitor genes, such as SRY-box transcription factors 9 and 2 (Sox9 and Sox2), Notch 1 and 2, hairy and enhancer-of-split 1 and 5 proteins, cluster differentiation 63, frizzled 5 protein, neurotrophic tropomyosin kinase protein (NTrk-2T1), and thyroid hormone responsive protein (46,51,52). Moreover, studies focusing on the detection of markers of progenitor cells like bromodeoxyuridine (BrdU) and Hu+ turned in positive results (46,50). BrdU and Hu+ are detected by immunostaining of tissue containing specific antibodies anti-BrdU and anti-Hu. These substances get incorporated into newly formed DNA, marking new cell differentiation sites. Furthermore, an experiment conducted on mouse models, with microdoses of insulin-like growth factor 1 (IGF-1) delivered with a cannula implanted into the right lateral cerebral ventricle, demonstrated that local neurogenesis enhanced proliferation, suggesting that the process of neurogenesis in this niche is influenced by IGF-1 (46,53). Immunofluorescence also highlighted that tanycytes express proteins associated with neural precursor cell features, such as the intermediate filament protein nestin (46,54), vimentin, a marker of precursor cells (46,55), and neuronal migration protein doublecortin (DCX), a marker of young neurons (46,56)

2.2.3.2 Substantia Nigra

The substantia nigra (SN) is located in the mesencephalon, and structurally divided into two parts, the pars compacta and the pars reticulata (46,50). It contains a large number of melanized neurons, which give it a darker appearance and justify its name (46). This region has been the subject of many studies throughout the years, which revealed that despite neurogenesis occurring at much lower levels here compared to other well-known neurogenic zones, the generation of new neuronal cells does take place, especially in the substantia nigra

pars compacta (SNpc). The SN is mainly involved in movement control, namely in motor planning and eye movement, and the SNpc is primarily responsible for originating dopamine-producing neurons. This explains the fact that this structure has been observed as one of the most affected in cases of PD. Furthermore, the SN has recently been associated with the regulation of sleep (46)

To confirm the existence of adult neurogenesis in the SN, Zhao et al. administered BrdU and used immunostaining techniques to follow new neurons in the SNpc (46,57). After 2 days of BrdU administration, no immunostaining was observed. However, 10 to 21 days after the administration new neurons were observed, leading the authors to theorize that this later immunostaining happened due to the formation of brand-new cells (46,57). Furthermore, the authors administered a peripheral dose of 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine, a known toxin, to destroy a large number of the nigral dopaminergic cell population. Researchers observed that neurogenesis increased exponentially. It was also theorized that lesions in this structure enhance neurogenesis (46,57).

2.2.3.3 Striatum

The striatum is anatomically divided into the ventral striatum (the nucleus accumbens and olfactory tubercle) and the dorsal striatum (the caudate nucleus and putamen) (46,58). This region receives both GABAergic and glutamatergic inputs and it is responsible for motor behavior and influences the reward system in the brain (46,58). In normal physiological conditions, neurogenesis in the striatum remains dormant, being increased only in response to certain stimuli such as a stroke/ischemia or injury, and pharmacological stimuli, such as some growth factors and neurotrophins (46).

Several studies have highlighted the existence of two distinct cell types capable of neurogenesis in this structure: precursors from the SVZ, whose newly formed neurons migrate to the striatum afterward; and local neuronal precursors in the striatal parenchyma (46,59,60). These latter might encompass a mechanism through which the brain tries to repair itself after considerable trauma. These findings were corroborated through studies carried out on animal models, including adult rats, rabbits, monkeys, and humans (46). In humans, in turn, a technique that retrospectively dates cell birth was used to confirm the existence of neurogenesis in the striatum (46,61). This study used the oscillations in the levels of carbon-14 isotope in the DNA of proliferating cells, followed by accelerator mass spectrometry, leading to the discovery of postnatal cell proliferation in the striatum (46,61).

Moreover, the transcriptome of many human individuals was studied which led to the discovery that DCX was mainly found in the striatum, rather than the hippocampus (46,62).

2.2.3.4 Amygdala

The amygdala integrates the limbic system, being responsible for the processing of emotions, such as fear, and participating in the processes of learning and memory retention (46). Experiences carried out in nine adult squirrel monkeys and four adult cynomolgus monkeys revealed that this structure does possess the capacity to generate new neurons throughout life. Firstly, the subjects were injected intravenously with BrdU twice a day for 3 days and sacrificed at different intervals. Then, a different group of animals was injected in the left lateral ventricle with the dye 1,10-dioctadecyl-3,3,30,30-tetramethylindocarbocyanine, used for molecular imaging and neural cell fate tracing, and later sacrificed after 3 weeks (46,63). After analyzing the results, the authors reported newly differentiated cells at 21 and 28 weeks postinjection. Other studies utilized methods such as the removal of the OB, in 8-week-old male Wistar rats, which showed a decrease in hippocampal neurogenesis but an increase in amygdalar neural cell proliferation (46,64); and the administration of hormones like testosterone, which also revealed an increase in newly generated amygdalar cells, observed through the Tuj1 marker, expressed by these (46,65). This research led to great breakthroughs in the next few years, namely in topics like the effect of social stress or the relationship between hippocampal and amygdalar neurogenesis in the overall regulation of emotions.

2.2.3.5 Habenula

The habenula is a bilateral brain structure responsible for linking several brainstem regions to the forebrain. In mammals, this structure is often divided into three parts, the lateral habenula (LHb), the medial habenula (46,66), and the habenular commissure (46,67). The LHb receives stimuli from various sources, like the basal ganglia, hypothalamus, and limbic regions. These inputs will then travel up ascending projections leading to behavioral modulation (46,68). The presence of neurogenesis in the habenula has been observed in various animal models, from teleost fish (46,69,70) to rodents (46,71,72). For instance, experiments carried out on zebrafish revealed proliferation zones in several structures including the habenula (46,73). In addition, studies focused on the quantification of diverse transcription factors associated with the creation of new neurons took place. These utilized proteins such as prothymosin alpha, an acidic nuclear protein that affects many cellular functions including cell cycle progression, proliferation and survival (46,74). This protein is

expressed in various regions where neurogenesis has been heavily observed, namely the SVZ, the granular cell layer of the DG, and the GCL of the OB. Another molecule is the transcription factor NeuroD1, which is a member of the proneural gene family, playing an important role as a neuronal differentiation factor. This substance has been found in the epithalamus and the dorsal and ventral nuclei of the habenula, in African aquatic frogs (46,75).

In mammals, research showed that neurogenesis in this area can occur if mediated by substances such as antidepressants or brain-derived neurotrophic factor (BDNF) infusions (46,76). Despite these advances, spontaneous adult neurogenesis in mammals is yet to be observed. The fact that the habenula is responsible for the processing of stress responses and learning may suggest that the occurrence of neurogenesis in this region is an adaptive mechanism, only activated in response to trauma stimuli (46,77).

2.2.3.6 Cerebellum

The cerebellum is organized as a trilaminar structure, consisting of a molecular layer, a middle Purkinje cell layer, and an inner granular cell layer, each one with distinct cells like granular cells, Purkinje cells and various interneurons (46,78). In the granular layer exist different cell types such as granule cells and unipolar brush cells, which have excitatory properties (46,79), as well as Golgi and Lugaro cells, which are inhibitory (46,80). In the molecular layer basket and stellate cells can be found, as well as inhibitory interneurons (46,81). Lastly, in the Purkinje layer exist homonymous GABAergic cells, constituting the cerebellar cortex (46,79).

Previously, cerebellar neurogenesis was thought to take place solely in the embryonic and early postnatal stages (46,82). However, emerging research points to the possibility of neurogenic capacity in the cerebellum, under specific circumstances. In fact, studies carried out on transgenic mice models showed that following cerebellar damage the granular layer showed signs of regeneration (46,83). This suggests the cerebellum possesses the capacity to perform injury-induced neurogenesis. Moreover, another experiment involved the transplantation of cerebellar granule neuron precursors from humans into the Harlequin mouse cerebellum, which triggered the proliferation of nestin-positive precursors in the mouse's cerebellum (46,84). Alongside these findings, it was noted that NSCs can create both neurons and glial cells, a process that is controlled by a transcription factor family named Sox genes, in particular SRY-box transcription factor 1 (Sox) Sox1, Sox2, and Sox9. It was observed that the transcription factor Sox2 is involved in Bergmann Glia (Golgi cells)

development during the embryonic, postnatal, and adult neurogenesis phases. Sottile et al. (2006) determined that Sox1 and Sox2-positive Bergmann glia established a distinct pattern when intercalated with calbindin-positive Purkinje cells (46,84,85). This led the authors to conclude that the expression of these three Sox genes results in a different kind of Bergmann glial cell, yet to have been identified. Additionally, studies revealed that the expression of Sox2 was detected in the Purkinje cell layer following physical activity, which might indicate an increased glial population genesis following motor activity (46,86). Finally, research utilizing adult rabbit models revealed that the Purkinje cell layer of these animals incorporated BrdU at 1 to 5 days postinjection, being also detected in some Bergmann glial cells (46,87). A double staining technique for BrdU with polysialic acid neural cell adhesion molecule and Microtubule-associated protein 5 (Map5) showed that in the peripubertal rabbit cerebellar cortex, the newly generated cells expressed these same markers. The authors also observed the presence of DCX+ or Map5+ and BrdU+ cells 15 days after the injections, suggesting that both cell populations originated during the study. The genesis of GABA+ cells immunoreactive for paired box gene two was also reported, leading to the conclusion that the molecular layer of the peripubertal rabbit cerebellum possesses the ability to generate GABAergic interneurons (46,87).

Regarding the experiments described above, it is evident that neurogenic events do occur in the cerebellum, after early mammalian life stages. Nevertheless, these neurogenic events were observed after specific controlled stimuli, which proposed the necessity for further study to focus on the possibilities of naturally occurring neurogenesis.

3. Role of Cellular Organelles in Adult Neurogenesis

3.1 Mitochondria

The mitochondria are well known for their part in energy production, cell signaling and calcium homeostasis. This organelle is continuously subject to remodeling, through mitochondrial dynamics, namely fission and fusion processes (88,89). This last process has been observed to play a role in adult neurogenesis, influencing stem cell renewal and differentiation. This occurs partially via the direct or indirect production of metabolites that regulate maturation pathways. (88,90,91).

Several studies have shown that RGCs in the developing brain present fused mitochondria, while the progenitor cells possess fragmented mitochondria (88,92,93).

Additionally, newly born neurons exhibit mitochondria of even smaller size. This led several investigators to conclude that mitochondria must suffer a higher fission rate while in the neurogenic transition, followed by an increase in size during neuronal maturation (88,92,93). Further studies carried out in mouse models revealed that disrupting genes such as optic atrophy 1 and mitofusin 1 and 2, responsible for mitochondrial fusion, resulted in a decrease of RGCs self-renewal as well as an increased neuronal differentiation. Contrastingly, the disruption of Drp1 (dynamin-related protein 1), which controls fission, precipitates the increase in self-renewal and decreases neurogenesis (88,92,93).

During the cell cycle, mitochondrial fusion spikes in the G1 and S phases, suffering fission during G2 and mitosis (88,94). This dynamic secures the correct distribution of mitochondria between the daughter cells in the division process. Considering its postmitotic nature, researchers aimed to understand how mitochondrial dynamics influence neurogenesis. One study employed a novel in vitro tracking technique to monitor mitochondrial behavior in cortical NSCs/NPCs during self-renewal and neuronal differentiation processes (88,93). While previously stated facts about mitochondrial behavior during cell division were observed, a new observation was made: the daughter cells suffered different fates. In fact, cells that continued as NSCs/NPCs presented enhanced mitochondrial fusion levels, while cells fated to become neurons showed higher levels of mitochondrial fission. This was confirmed through the experimental induction of mitochondrial fusion in cells after mitosis, with either fusion-promoting or fission-inhibiting molecules. In fact, this resulted in the majority of the cells suffering self-renewal instead of differentiating into neurons (88,93).

To assess the relevance of these findings, it is pivotal to establish a comparison between mouse brain development and the human adult brain. In humans, cortical progenitor cells are capable of self-renewing, resulting in an increase in cortical size in humans (88,95). Indeed, researchers used the already mentioned methods to track mitochondria and cell fate in human cortical progenitors, derived from pluripotent stem cells (PSCs). This study concluded the existence of a positive correlation between mitochondrial behavior in neurogenesis in mice and humans (88,93). Strikingly, it was observed that mitochondrial dynamics in human progenitors can influence cell fate for about twice as long when compared to mouse cells (88,93). Nevertheless, further experiments are needed to expand upon this possibility, though this greater period flexibility may be linked to a higher self-renewal capacity in human progenitor cells.

The processes of mitochondrial fission and fusion are closely related to mitochondrial activity, in big part through the maintenance of the mitochondria cristae, in which oxidative phosphorylation (OXPHOS) molecular effectors and the electron transport chain (ETC) are found (88,96). In fact, adenosine triphosphate (ATP) is generated within cells' mitochondria through processes such as glycolysis in the cytosol and OXPHOS. The amount of ATP generated through glycolysis is smaller than that of OXPHOS, but kinetically the first process is much faster overall. This justifies the fact that most highly proliferative cells tend to generate their energy through glycolysis (88,96). Nevertheless, it is also true that mitochondrial respiration through OXPHOS is the most efficient for a cell to generate energy, being a process practiced by cells such as neurons (88,92,97–99). As expected, NSCs/NPCs rely mostly on glycolysis over OXPHOS, while already differentiated neurons operate contrastingly. A particular study revealed that these metabolic changes are likely to drive neuronal differentiation, rather than being a result of it. They have used *Drosophila* models and modulated the genetic disruption of OXPHOS-related genes (88,97) to reduce the size of NSCs/NPCs and promote their transition into their neuronal fate. However, when the disruption of these genes occurred in *Drosophila* neuroblasts, proliferation slowed down significantly, inhibiting the process of cell cycle exit (88,100). Furthermore, research developed in humans accessed the role of OXPHOS in mitochondrial disease modeling, in PSC-derived NSCs. These possessed the pathogenic mutations in the SURF1 gene (responsible for Leigh syndrome), presenting a reduced ability to differentiate into neurons and mature (88,101). Glycolysis was shown to play a role in mouse cortical neurogenesis, namely through the metabolite methylglyoxal (MGO) (88,102). This molecule influences NSC self-renewal, regulating its glycolytic activity. Indeed, increased MGO levels hinder the capacity for NSCs self-renewal, leading to an increase in neurogenesis. This occurs due to the binding of MGO to the key glycolysis enzyme glyceraldehyde-3-phosphate dehydrogenase, which then acts as a ribonucleic acid (RNA)-binding protein (88,103). This affects Notch1 messenger RNA (mRNA), reducing its translation and resulting in a down regulation of the process of cell self-renewal (88,102).

Cellular reactive oxygen species (ROS) are produced by both mitochondrial OXPHOS via ETC activity and Nox enzymes at the plasma membrane (88,104). These have been linked to increased NSCs/NPCs self-renewal and proliferation (88,105), although recent research suggests this effect may be context-dependent (88,106). Interestingly, data collected using adult mouse models highlighted that high levels of ROS may lead to NSCs/NPCs quiescence

while in the embryonic cortex, ROS increases during the conversion from NSCs/NPCs to neurons (88,92). This last process seems to occur due to the upregulation of the BOTCH gene (a gene that expresses a gamma-glutamyl cyclotransferase), a Notch inhibitor, through the nuclear factor erythroid 2-related factor 2 (Nrf2), favoring the transition towards neuronal fate (88,92).

Lastly, another crucial role of OXPHOS activity is the regulation of the reduction-oxidation balance. This process occurs through the pair formed by the oxidized and reduced form of nicotinamide adenine dinucleotide (NAD) (NAD+ and NADH). The ratio between these substances is regulated by the glycolysis-OXPHOS balance and has been observed to influence many aspects of neuronal fate acquisition and differentiation (88,107). This influence stems mainly from the activity of the NAD+-dependent deacetylase sirtuin family, particularly from sirtuin-1 (SIRT1) (88,108–110). SIRT1 is necessary for the determination of NSCs/NPCs fate during embryonic development, interacting with the repressor B cell lymphoma 6 and repressing pathways such as Notch, Wingless-related integration site (Wnt), sonic hedgehog protein and fibroblast growth factor, that keep NSCs/NPCsin the self-renewal phase, thus promoting neuronal differentiation (88,110).

3.2 Endoplasmic reticulum

The endoplasmic reticulum (ER) is one of the largest organelles present in eukaryotic cells. It is constituted by a series of tubules and flattened sacs branching through an enclosed space, the ER lumen. The lumen is envaulted by the ER membrane, a single intracellular lipid bilayer, which regulates the passage of molecules from the cellular cytosol into the ER (111,112). This organelle is crucial for the correct synthesis, folding and structural maturation of most cellular proteins (111,113). When in the ER lumen, these proteins are folded into very specific three-dimensional shapes and experience multiple biochemical modifications such as glycosylation and disulfide bond formation. These processes are facilitated by ER-resident enzymes, namely chaperones, glycosylating enzymes, and oxidoreductases (111,114,115). However, despite ER efforts, only under 20% of these proteins suffer the correct folding to undergo translation and complete their designated functions. Because of this, the ER develops a process designated ER-associated degradation, where unproperly folded proteins (UFP) are removed to the cytosol and later suffer ubiquitylation and degradation by the 26S proteasome (111,116–118). Certain factors may lead to a higher number of UFP, such as genetic mutations, low cellular energy levels and aging. When the ER cannot keep up with the cellular requests, a phenomenon called “ER stress” may occur (111,119). This process tries to

restore homeostasis after the accumulation of UFP since the persistent production of these may increase overall cellular stress and result in death.

Curiously, a study was conducted to assess the relevance of ER stress in cognitive function using adult male mice models (120). The experiment explored the link between spinal cord injuries (SCI) and mechanisms such as adult neurogenesis. Individuals suffering from SCI were reported to present cognitive defects (40 to 60%) (120–123) and depression (25 to 47%) (120,124–128), encompassing issues regarding memory and attention deficits. In this regard, the study separated the mice into different groups ranging in severity levels of SCI – mild, moderate and severe. These groups were then tested on cognitive performance and depressive behavior tasks, independent of motor function. The researchers used tests such as the placement of the animals in a Y-maze (129), object recognition (129,130), and a step-down passive avoidance (129), as well as a sucrose preference test, a tail suspension test and a forced swim test (120). Curiously, the results showed that mice suffering from moderate to severe SCI presented marked cognitive impairments, as well as depression-like behaviors (120). To explain this phenomenon, it has been theorized that an injury in the spinal cord leads to the disruption of neurogenesis in the hippocampus, most noticeably in the dentate gyrus. There is a steep decline in the generation of new neurons as well as an increased level of ER stress in the affected regions (120). This organelle reaction is thought to be one of the reasons for the decrease in neurogenesis, besides neuroinflammation.

3.3 Lysosomes

Studies were performed to establish the relevance of lysosome's role in adult neurogenesis. Specifically, it centered on the assessment of the role of phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP), an enzyme found in the lysosomal membranes of astrocytes (131). This enzyme is responsible for the regulation of lysosomal acidification, facilitated by its relationship with ATPase (131). This is essential for lysosomal degradative activity. An experiment was carried out using mice models, both LHPP knockout (KO) and LHPP wild type. It was observed that the KO group had significant resilience to stress-induced depression-like behaviors, resulting in the increase of certain chemokines (like chemokine ligand 5, CXC motif chemokine ligands 2 and 16) responsible for proliferation and NSC differentiation, leading to greater hippocampal neurogenesis rates. In fact, under stressful conditions, LHPP facilitates the hydrolysis of inorganic pyrophosphate, leading to the acidification of lysosomes. When this process is suppressed, the degradation of proteins such as CCAAT/enhancer binding protein β is compromised,

increasing chemokine release (131). This is why it has been theorized that LHPP may constitute a valuable therapeutic target for stress-related brain pathologies, as its deficiency may protect against stress-induced neurogenesis inhibition. In 2015 a large-scale genome-wide association study was conducted in the Han Chinese population, which revealed that when the single-nucleotide polymorphism associated with the LHPP gene was inactive, the individuals showed a reduced risk of developing depression (131,132).

4. Nutritional Factors and Adult Neurogenesis

4.1 Omega-3 Fatty Acids and Adult Neurogenesis

FAs are carboxylic acids containing a long un-branched aliphatic tail chain, and can be subdivided into saturated, monounsaturated and polyunsaturated (133). Omega-3 polyunsaturated fatty acids (PUFA) are important nutrients present in large quantities in the brain that produce anti-oxidative effects, as well as anti-inflammatory and anti-apoptotic effects (133,134). Three of the most relevant PUFA are α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (133). Given their great involvement in several physiological processes and apparent neuronal protective effects, it is theorized that they may play a large role in the development and progression of various pathologies, namely neurodegenerative diseases.

Unfortunately for animals, it is impossible for them to naturally produce omega-3 FA, having to acquire these through their diet (133,135,136). For the correct apport of these nutrients, the average person should be consuming a ratio of 2:1 to 4:1, with omega-6 to omega-3 (133,137,138). However, thanks to the Western diet, today's ratio is closer to 15 to 20:1. This change is due in part to the decrease in fish consumption, as well as the industrial production of animal feeds, rich in grains containing mostly omega-6 (133,137,138). Indeed, there has been a shift in individuals' diets, with the reduction in the number of products like salmon, mackerel, halibut, sardines, tuna, and herring, as well as flaxseeds, pumpkin seeds, purslane, soybeans, canola oil, and walnuts (133).

Remarkably, these nutrients possess the capacity to impact neurotrophin levels, promoting neuronal survival and development. Beyond just that, the brain is also capable of secreting a molecule, BDNF, which increases upon the consumption of these nutrients, responsible for alterations in neurogenesis and neuronal survival (133,139). Therefore, there is a growing amount of evidence that suggests that the depletion of omega-3 FA may result in

an increase in mood disorders, such as schizophrenia and dementia (140). It is thought that omega-3 PUFA deficiency has been indicated as a risk factor for many pathologies, including cardiovascular, autoimmune, and developmental disorders (133,141).

Focusing, for instance, on AD. The most common form of dementia in the elderly is characterized by the formation of extracellular amyloid β peptide (Aβ) deposits, as well as intracellular neurofibrillary tangles in the brain. This disease is associated with a decrease in omega-3 PUFA levels in both the hippocampus and cortex (133,142,143). Remarkably, it appears as though there is a link between a higher omega-3 PUFA intake and a comparably lower risk of cognitive decline and dementia in old age. In fact, studies showed in animal models that a diet rich in DHA significantly reduces the number of Aβ deposits and plaques (133,144,145). Furthermore, the role of EPA has also been described as protective, limiting the number of plaques formed (133,146,147).

PD it is characterized by the loss of a high number of dopaminergic neurons in the substantia nigra, as well as by the presence of Lewy bodies (protein αSyn inclusions) (133). Although studies have been contradictory when it comes to omega-3 FA's role in PD prevention or treatment, some studies show that these might help reduce bradykinesia associated with the disease (148).

Acute Neuronal Injury is one of the main complications associated with neuroinflammation. There is an exacerbated and prolonged inflammatory response that results in extensive neuronal damage and loss (133). Therefore, studies have been conducted to find modulators of neuroinflammation and discover new therapy pathways. In this way, it has been uncovered that omega-3 PUFA promotes a neuroprotective response following this pathology (133,149). This was expected given that neurodegeneration and acute neurological injury share many pathological mechanisms, such as excitotoxicity, oxidative stress and inflammation.

When it comes to spinal cord injuries, the damage caused is a result of the combination of an initial physical trauma followed by a secondary degenerative process. In this pathology, there is the destruction of ascending and descending axonal tracts (133). These are responsible for motor, sensory and autonomic functions. Depending on the level at which the injury occurred, there can be drastically different, devastating and lifelong consequences for the injured (133,150). In this disease, recovery is complicated since the axons of the CNS have a deficient regeneration capacity. In this matter, the initial injury together with the

subsequent significant inflammatory response will lead to a chronic disease state (133,151). Finally, studies showed that after the SCI, the administration of DHA in a rat model reduced the effect of the injury when administered 30 minutes after the occurrence (133,152).

4.2 Vitamins and Adult Neurogenesis

4.2.1 Vitamin D

Vitamins are critical nutrients necessary to ensure a healthy and balanced human diet. Among these, vitamin D has been shown to play a crucial role in controlling many cell activities, such as autophagy, acting by removing dysfunctional mitochondria and, as well as moderating oxidative stress, calcium signaling, inflammation, DNA disorders such as telomere shortening, among others (153–157). Due to these properties, this vitamin is commonly linked to the aging process and the regulation of its underlying causes.

Vitamin D is a fat-soluble vitamin, synthesized from 7-dehydrocholesterol (provitamin D3) present in the skin, when exposed to ultraviolet-B radiation, namely from sun exposure (153). The exact amount produced by each individual is dependent on many factors such as skin pigmentation, season, and age, as well as personal habits such as exposure to sunlight, time spent outdoors and sunscreen usage (158). When individuals live in geographic locations where sunlight is scarce, or when a skin condition is involved, supplementation must be considered (153,159). Vitamin D deficiency is defined as a concentration of 25-dihydroxyvitamin D [25(OH)D] below 50 nmol/L (153,160).

In animals, the production of vitamin D starts with the conversion of 7-dehydrocholesterol to vitamin D3; contrastingly, in plants, yeast and fungi, it is the conversion of ergosterol that originates vitamin D2 (ergocalciferol) (153). Both vitamin D3 and D2 can be acquired through diet, and both are essential for homeostasis. After acquiring vitamin D3 and D2, these are converted into calcidiol (25(OH)D), in the liver. Subsequently, this molecule is further converted in the kidneys, originating calcitriol (1,25(OH)2D3), the active vitamin D form (153). The vitamin D receptor (VDR), an intracellular transcription factor, interacts with the 1,25(OH)2D3 and binds to DNA sequences, regulating gene transcription involved in various cellular functions(153,161,162).

Several studies state that vitamin D deficiency is intimately linked to accelerated aging. As humans age, the capability of synthesizing 1,25(OH)2D3 suffers a great decline (153,163). In fact, by the time humans reach 70 years old, their capacity to produce the active form of vitamin D is less than 50% when compared to that of 20-year-old individuals

(153,164). The process of aging is largely associated with the loss of neuronal plasticity, resulting in phenomena such as loss of hearing and balance (153,165,166). In fact, studies using mice models have shown that when vitamin D is incapable of binding to the VDR, such as in the case of mice phenotypes incapable of presenting VDR, faster aging occurs. They have also observed many health problems also experienced by humans when aging: muscle atrophy, immune deficiency, and a higher predisposition for cancer formation (153,167–169).

Furthermore, it has been proven that vitamin D also plays a crucial role in cellular differentiation and proliferation, calcium signaling in the brain, and is associated with neurotrophic and neuroprotective actions (153–157). This vitamin is essential for the correct calcium maintenance and reabsorption in the bones (153,170). In individuals with low levels of vitamin D, the blood calcium levels start to rise, leading to excess calcium in the tissues, namely in the brain. This may lead to calcium deposits that pose a threat to normal brain functions (171). Given this fact, it can be inferred that vitamin D deficiency is directly linked to neural degradation, therefore, vitamin D supplementation must be incentivized, especially in the elderly. In fact, recent literature suggests that lower-than-necessary vitamin D levels negatively impact NSCs health. Vitamin D is crucial for maintaining neurogenic activity, particularly through the modulation of the Wnt/ β-caterin pathway. The disruption of this signaling pathway results in disturbances in cognitive activity, since this mechanism influences neurogenesis, preventing NSCs premature differentiation into other cell types, namely astroglia. This leads to reduced activation of NSCs, and increased quiescence levels (**Figure 3**) (153).

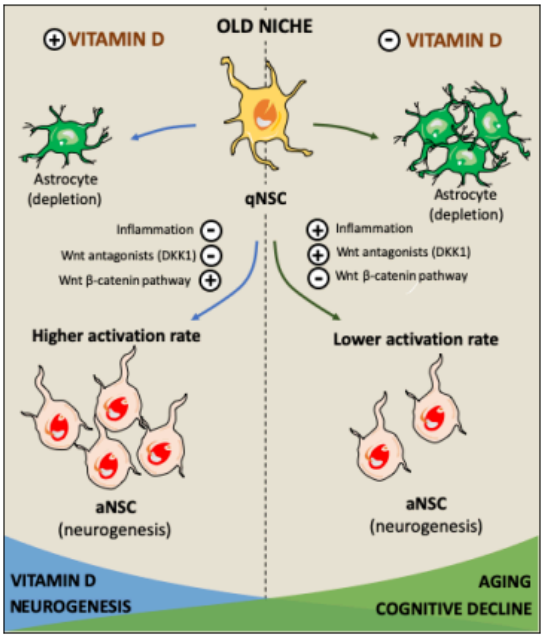

Figure 3. The perceived role of vitamin D in the activation of quiescent NSCs in the adult brain. The decrease in vitamin D may lead to lower NSC activation rates, resulting in decreased neurogenesis levels. This occurs through an increase in inflammation and Wnt antagonists, and a decrease in the Wnt/ β-caterin pathway activity. Meanwhile, an increase in the uptake of vitamin D has the opposite effect, resulting in increased levels of neurogenesis through higher activation rates. This process counteracts the cognitive decline characteristic of aging. *Adapted from: Vitamin D deficiency as a potential risk factor for accelerated aging, impaired hippocampal neurogenesis and cognitive decline: a role for Wnt/β-catenin signaling (153).*

4.2.2 Vitamin C

Another undoubtedly relevant vitamin when it comes to healthy adult neurogenesis is vitamin C. This vitamin, also known as ascorbic acid, is a water-soluble hexose (172) that can be found in many foods such as red peppers, citrus fruits, strawberries, and most leafy greens, to list a few (173). Vitamin C is not only a powerful antioxidant that protects against the accumulation of ROS and reactive nitrogen species (RNS), byproducts of certain cellular metabolic processes, but it also serves as a cofactor in various enzymatic reactions, including the synthesis of catecholamines, carnitine, cholesterol, amino acids, and several peptide hormones (172,176).

Vitamin C presents two isoforms and, naturally, two distinct sodium-dependent vitamin C transporters – SVCT1 and SVCT2 (176,179,180). SVCT1 is mostly confined to the

surface of epithelial cells, assisting in the transportation of vitamin C in the intestine, liver, kidneys, lungs, and other organs (172,180–182); contrastingly, SVCT2 is mostly present in specific tissues, namely the brain, adrenal and pituitary glands, muscles, bones, and lymphoid tissue (176,180). High levels of SCVT2 have also been found in pyramidal neurons, throughout the inner region of the cerebral cortex, in the adult brain (176,183,184). This transporter is also observed in microglia cells, ependymal cells and tanycytes (176,185), and Schwann cells (176,186). Due to the transporters' proximity to the neurogenic niches in the brain, these structures have direct access to vitamin C, present in high concentrations in the brain (172).

For neurogenesis to be successful, the presence of βIII-tubulin is imperative (172,184). This molecule is a microtubule, encoded by the TUBB3 gene, a beta-tubulin gene that endorses the tubulin family of proteins, found almost exclusively in the neuronal tissue (187). In light of these observations, a recent study has demonstrated that vitamin C, when in isolated neurospheres, induced an increase in the differentiation rates related to βIII-tubulin and in SVCT2 expression (172,188). This study used adult rat models, immunofluorescence microscopy and *in situ* hybridization analysis, specifically in proliferating BrdU + C-type cells, isolated from adult rat's SVZ. Contrastingly, after the long incubation period that takes to oxidize ascorbic acid to dehydroascorbic acid (DHDA), a general loss in the formation of neurites was observed (172,189). Susprisingly, it was also observed that astrocytes have the capacity to recycle DHDA, stimulating the maintenance of neurites (172,190). This proves that the recycling of vitamin C *in vitro* aids in the regulation of the morphology of immature neurons, through the differentiation and maturation processes. Moreover, another study illustrated that vitamin C-deficient guinea pigs presented impaired neurogenesis in the SVZ. Indeed, the number of neuroblasts in the SVZ and SVL decreased progressively when being fed a diet deficient in vitamin C for 14 to 21 days. This finding was analyzed through BrdU labeling (172,191).

4.3 Minerals and Adult Neurogenesis

4.3.1 Zinc

Minerals consist of inorganic substances with a defined chemical composition and crystalline structure. They are implicated in most biological functions, being vital for processes of bodily functions such as bone maintenance, oxygen transport in the blood and, of course, CNS homeostasis. In the following sections, we will take a closer look at a few specific minerals. Zinc is an essential catalyst of more than 80 mammalian enzymes (192).

These enzymes include DNA and RNA polymerases, histone deacetylases (193), and DNA ligases (194), crucial for DNA replication and cellular proliferation. Moreover, zinc constitutes an essential component in a family of DNA-binding transcription factors, the zinc-finger proteins (192,195,196). Furthermore, most nuclear receptors in the brain are zinc-finger proteins, namely those that modulate the transcriptional roles of vitamin D, retinoic acid, glucocorticoids, thyroid hormone and estrogen (197). These receptors play indispensable roles in the process of neurogenesis.

The positive effects of zinc consumption on adult neurogenesis have been demonstrated in multiple studies. In fact, it has been shown that zinc intervenes in three distinct phases of neurogenesis: cell proliferation, stem cell survival, and neuronal differentiation. In 2008 a study was carried out on adult rat models. These were provided with a zinc-deficient diet for 3 weeks. This depletion resulted in a 50% decrease in the number of marker Ki67+ cells, in the rat's rat dentate SGZ (198). These rats also showed increased apoptosis in the SGZ of the dentate, and an increase in terminal deoxynucleotidyl transferase-mediated deoxyUTP-biotin nick end labeling cells (198). The apoptotic effect of zinc depletion appears to be related to mitochondria since it induces an increase in ROS generation, the translocation of the pro-apoptotic factor B cell lymphoma 2 (Bcl-2)-associated death promoter (BAD) protein to the mitochondria, the release of cytochrome c into the cytosol, activation of caspase-3, and poly (ADP-ribose) polymerase cleavage (192,198,199).

Further research used weanling mice which were fed a zinc deficient diet for 5 weeks. This trial concluded that this diet decreased the number of BrdU-labeled cells in the dentate (200). When fed this diet for 6 weeks, the number of BrdU-labeled cells decreased even further, as well as marker Ki67+ cells (201). These effects seemed to be reversed once an adequate quantity of zinc was reintroduced to the diet (201). *In vitro* trials also took place to expand the understanding of zinc's action on neurogenesis. This research solidified that zinc deficiency decreased BrdU labeling of human NT-2 cells (198). Finally, zinc deficiency has been associated with the reduction of hippocampal DCX levels (200,201). This decrease might be explained simply by a reduction in the overall number of proliferating cells. Still, lower zinc levels have been linked to a shortening in neuronal branching of DCX+ cells, suggesting that this depletion damages neurogenesis directly (200).

4.3.2 Calcium

Another essential mineral when it comes to the development of the CNS, from neural induction to cellular differentiation, is calcium. Highly selective Orai1 to 3 calcium channels,

present in the plasma membrane, are crucial for the influx of calcium into the cell (202–205). These channels interact with calcium sensors, the stromal interaction molecules, located in the ER (202,206–208). Upon the decrease of calcium levels in the ER, these structures influence the entrance of calcium into the cytoplasm from the extracellular space. This process is named store-operated calcium entry (SOCE) (202). This process has been observed in both non-excitable calls and neurons (209). In fact, recent literature points out SOCE has been crucial in NSC proliferation and neurogenesis (210,211). In NSCs found in embryonic and adult mouse, SOCE is mediated by stromal interaction molecule 1 (STIM1) and Orai1, both calcium release-activated channel (CRAC) proteins (202). Furthermore, the ablation of either of these proteins resulted in a severe decrease of SOCE, hindering the proliferation of NPCs in both *in vitro* and *in vivo* scenarios. This fact points to a role of CRACs in the process of neurogenesis. Moreover, these channels regulate gene expression through the calcineurin/nuclear factor of activated T cell protein pathway, an essential process for cell proliferation (202) (**Figure 4**).

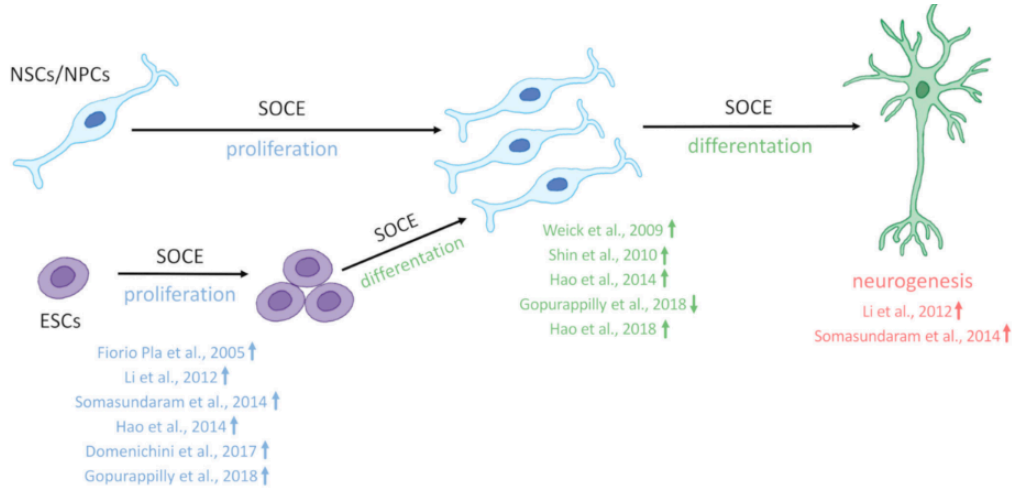

Figure 4. The role of SOCE in the regulation of neurogenesis. SOCE and the molecular components associated promote the differentiation of embryonic stem cells (ESCs) as well as the proliferation of NSCs/NPCs. This fosters neurogenesis both in the embryonic state and in adulthood. *Adapted from: Molecular Components of Store-Operated Calcium Channels in the Regulation of Neural Stem Cell Physiology, Neurogenesis, and the Pathology of Huntington's Disease (HD) (202).*

A study out on human NPCs reinforced that knocking down STIM1 reduced SOCE, inhibiting DNA replication, correct gene expression and neural differentiation (212). In fact, this experiment resulted in smaller and fewer neurospheres, and led to the spontaneous

differentiation of NSCs into a neuronal lineage. Furthermore, transient receptor potential canonical channels were shown to regulate SOCE in NSCs, especially tyrosinase-related protein 1(213). Therefore, the suppression of these channels leads to disturbances in the process of neurogenesis, revealing the importance of calcium signaling in the development of neuronal niches. Finally, calcium is crucial for the correct synaptic processing, namely observed on medium spiny neurons (MSNs) in the striatum (214,215). If the SOCE is occurring abnormally, this will lead to synaptic loss in MSNs (216,217).

4.3.3 Selenium

Another noteworthy mineral is selenium. It is known that exercise increases neurogenesis rates in the hippocampus, and curiously, in 2022, a study reported that this increase is mediated by an elevation in systemic selenium transport (218). Taking this evidence, the study sought to evaluate if dietary selenium supplementation provided similar therapeutic benefits. Firstly, the study used mice models and employed a proteomic screening technique to monitor variations in protein concentration (219). This, in turn, revealed that selenoprotein P suffered the biggest concentration change, reaching more than twice its control levels (218). Subsequent discoveries showed that selenium is, indeed, responsible for NPC proliferation in both *ex vivo* and *in vivo*. The results showed significantly more neurospheres generated in the assays containing selenium, in comparison with the ones where the substance had been removed. This branch of the study also showed great proliferative improvement when using selenium supplementation (218).

Selenium has also been shown to decrease intracellular ROS levels. Earlier studies outlined the change in ROS levels following exercise, and selenoproteins were theorized to pay a role in this process (218,221). To test this theory, the researchers performed an *in vitro* experiment, where primary DG cells were treated with sodium selenite (218). Flow cytometry performed after 16 hours of treatment revealed a significant reduction in DG cells classified as “ROS high” (218). Subsequent tests using live animal models were performed, using mini osmotic pumps to directly infuse selenium into the hippocampus. Three days after this procedure, primary DG cells presented a marked decrease in intracellular ROS levels, corroborating the previous findings (218). Both these studies also showed that most of this decrease was observed in precursor cells. It is also important to note that this reduction occurred in the cytoplasm, not affecting mitochondrial ROS levels (218). Thus, it is hypothesized that exercise does not affect selenium-induced changes in mitochondrial ROS

levels, which confirms the existence of a selective antioxidant role of selenium in neurogenesis homeostasis (219).

4.3.4 Lithium

Another mineral associated with neuronal homeostasis is lithium (222). Lithium is a well-established therapeutic option for both major depression and bipolar disorder (222–224). Throughout the last decade however, studies focusing on the potential usage of this substance in the treatment of AD and PD, as well as other neurodegenerative diseases like amyotrophic lateral sclerosis (ALS), have gained traction (225). These studies have demonstrated that not only does lithium possess great mood-stabilizing properties, but it also acts as a neuroprotective agent in the neuronal biome. This neuroprotective property is based on a few characteristics, namely its capacity to inhibit glycogen synthase kinase-3 β, an enzyme related to tau phosphorylation, which is responsible for maintaining microtubule stability and is implicated in AD (226,227). This mineral is also capable of inhibiting inositol monophosphatase, reducing inositol levels and interfering with the phosphoinositol cycle, supporting neuronal survival through autophagy and intracellular signaling modulating (228). This clears damaged proteins and organelles that could otherwise contribute to an inflammatory response. Additionally, lithium has also been observed to possess a mitochondrial protection capability, preventing neuron energy failure and reducing oxidative stress (229–232). These findings were corroborated through both preclinical and clinical studies. In fact, long-term lithium treatments in bipolar disorder showed an increase in hippocampal volume, as well as higher levels of BDNF, implicated in synaptic plasticity improvement and higher neurogenic rates (222,233). However, its use in AD, PD and ALS treatments is yet to be fully established since studies are still needed to confirm long-term neuroprotective effects.

4.3.5 Magnesium

Finally, another mineral worth discussing is magnesium (234). Being the second most abundant in mammalian cells, it is essential for a vast number of cellular processes, such as ion channel function, DNA and RNA stability, enzymatic reactions and metabolic cycles (235–237). These characteristics make it essential for the correct cellular upkeep of the CNS. It has also been observed to play a crucial role in neuronal development and brain function, being also implicated in neuropathologies such as PD, AD and demyelination (235–239). Studies showed that magnesium deficiency is linked to PD, which is based on a lack of cellular stress response regulation and autophagy, resulting in oxidative stress (240,241),

mitochondrial dysfunction, and protein aggregation (242,243). Magnesium levels are also reduced in AD patients, causing inflammation and resulting in Aβ plaques and tau protein aggregation (244–247). This results in impaired cognitive function and decreased synaptic plasticity. Fortunately, keeping magnesium levels regulated has shown signs of improving the outcome of neurodegenerative diseases, making specialists think supplementation might be part of a possible treatment approach (248–251).

4.4 Polyphenols and Neuroplasticity

Polyphenols are naturally occurring substances present in plant-derived foods and beverages, such as fruits (i.e., berries, grapes, apples), vegetables (i.e., onions), coffee and tea, olive oil and curcumin (252,253). Depending on their chemical composition, polyphenols can be subdivided into different families and subfamilies, namely flavonoids, like flavan-3-ols, anthocyanidins, flavones, flavanones, isoflavones, and chalcones, and "non-flavonoids", such as phenolic acids, stilbenes, tyrosol, curcuminoids, lignans, saponin, and tannins (252,254). In recent years there have been several clinical studies related to the potential neuroprotective properties of polyphenols and their subsequent impact in the treatment of neurodegenerative diseases (**Figure 5**).

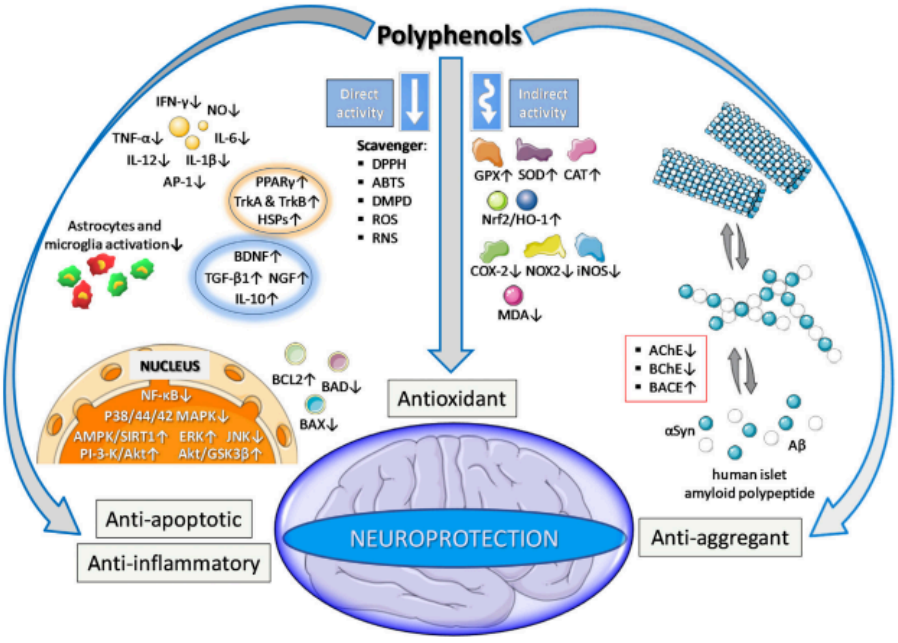

Figure 5. The role of polyphenols in neuroprotection. Phenolic acids provide a combination of benefits such as antioxidant properties, anti-apoptotic and anti-inflammatory effects, and act as an anti-aggregant. This provides crucial neuroprotective qualities to the neuronal tissue. For instance, the consumption of polyphenols results in the decrease in

pro-inflammatory molecules such as IL-6 and IFN-γ, and the increase of substances such as BDNF, NGF and IL-10. These acids also scavenge species like DPPH, ABTS, DMPD, ROS and RNS, and increase molecules such as SOD and CAT. Aβ: amyloid beta; ABTS: 2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid); AChE: acetylcholinesterase; AMPK: 5' AMP-activated protein kinase; AP1: activator protein 1; BACE1: beta-secretase 1; BAD: BCL2 associated agonist of cell death; BAX: BCL2-associated X protein; BChE: butyrylcholinesterase; Bcl-2: B-cell lymphoma 2; BDNF: brain-derived neurotrophic factor; CAT: catalase; COX2: cyclooxygenase 2; DMPD: N,N-dimethyl-p-phenylenediamine dihydrochloride; DPPH: 1,1-diphenyl-2-picryl-hydrazyl free radical; ERK: extracellular signal-regulated kinase; GPx-1: glutathione peroxidase 1; HO-1: heme oxygenase-1; IL-1: interleukin-1; IL-1β: interleukin-1β; Il-6: interleukin-6; Il-10: interleukin-10; iNOS: inducible nitric oxide synthase; IFN-γ: interferon-γ; JAK: Janus kinase; JNK: C-jun N-terminal kinase; MAPK: mitogen-activated protein kinase; MDA: alondialdehyde; NF-κB:nuclear factor kappa-light-chain-enhancer of activated B cells; NGF: nerve growth factor; NOX2: NADPH oxidase 2; Nrf2: nuclear factor erythroid 2–related factor 2; NO: nitric oxide; PI3-K: phosphoinositide 3-kinase; PPARγ: proliferator-activated receptor gamma; RNS: reactive nitrogen species; ROS: reactive oxygen species; SIRT1: sirtuin 1; SOD: superoxide dismutase; TGF-β1: transforming growth factor-beta 1; TNF-α: tumor necrosis factor-alpha; Trk: tropomyosin-related kinase; αSyn: α-synuclein. *Adapted from: Polyphenols and neuroprotection: Therapeutic implications for cognitive decline (252).*

4.4.1 Anthocyanins

Anthocyanins are a class of flavonoids usually found in blue and red fruits, like pomegranates (255). Recent studies have shown that this subfamily might have the capacity to mitigate cognitive decline, after being metabolized into other compounds such as protocatechuic acid (256).

Clinical trials involving adults suffering from age-related diseases like AD have reported memory improvement, increased brain activity, and increased cerebral blood flow following anthocyanin-rich foods (252,257). These neuroprotective finds have been attributed to their antioxidant and anti-inflammatory properties (258). Anthocyanins' structure makes it possible for these substances to cross the blood-brain barrier (BBB) (259), making it possible to inhibit inflammatory mediators such as TNF- α, IL-1β, and COX2, as well as playing a role in the reduction of oxidative stress in the neuronal biome (252,260). These clinical studies confirmed the addition of red and blue fruits, as well as anthocyanin-rich supplementation,

results in a greater neuroprotection factor through neuroimaging techniques such as functional magnetic resonance imaging and positron emission tomography scans (252,257,261). Preclinical studies also showed promising neuroinflammatory reduction and cognitive impairment prevention when using animal models treated with lipopolysaccharides (LPS) or amyloid-β (Aβ). These studies proposed the idea that these substances were responsible for the inhibition of pathways such as the MAPK pathway, directly involved in Aβ formation, linked to AD (252,262).

Emerging research also suggests the possible impact of anthocyanins in the gut-brain axis, mainly through the increased production of kynurenic acid, which is known to have neuroprotective characteristics and may be linked to the regulation of the gut microbiota in aging (263).

4.4.2 Flavanols

Flavanols are a subgroup of flavans, bioactive compounds commonly found in cocoa and green tea, which include molecules like epigallocatechin-3-gallate (EGCG), catechin and proanthocyanidins (252,264). These compounds are recognized as promoting cognitive health through their antioxidant and anti-inflammatory capacities. Clinical studies have shown that the consumption of cocoa flavanols improves memory, cognitive flexibility, and processing speed (265,266). These studies included elderly patients suffering from mild cognitive impairment (MCI) (267). The consumption of cocoa has been associated with increased blood flow and vascular function, and increased secretion of BDNF (268). Similar studies have been conducted on the benefits of green tea flavanol consumption, particularly of EGCG. This consumption resulted in an inhibition of the dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A gene, which has been linked to AD as well as Down-syndrome's cognitive decline (252,269). EGCG was observed to possess the ability to modulate oxidative stress, maintain normal mitochondrial function, and inhibit Aβ aggregation (270,271). However, further investigation is needed to confirm these findings, since other studies have shown disagreeing results, indicating significant improvement upon consumption (272,273). Therefore, it is necessary to consider factors such as dosage and bioavailability.

4.4.3 Flavones

Flavones constitute the most commonly found type of flavonoid, being present in most higher plants (252,274). Quercetin represents the most common flavone found in nature (275). This molecule has been shown to possess both direct antioxidant properties as well as

indirect antioxidant activity - modulation of antioxidant pathways, such as the Nrf2/hemeoxygenase-1 pathway (276,277). In fact, quercetin can act as a scavenger of ROS and RNS (252,278). Furthermore, studies carried out in animal and human models revealed that quercetin can impact gene expression. This may result in an increase of BDNF levels as well as NGF (252,279,280). The neuroprotective properties of this flavone reside in various other mechanisms, such as its ability to modulate autophagy and prevention of Tau phosphorylation. It is also implicated in the downregulation of iNOS, COX2, TNF-α, IL-6, IL-1β, and IFN-γ, in both microglia and macrophages (252,281–283). Additionally, it can influence the activation of SIRT1, which leads to the inhibition of various pro-apoptotic transcription factors (252,284).

Research conducted on the effects of quercetin on neuronal health showed promising results *in vitro* and animal models (285,286). However, further testing is needed to solidify the acknowledgment of these benefits in humans. In this line, a double-blind randomized study was carried out on 100 Japanese participants, half of which suffered from MCI. These individuals were aged 65 to 84 years old and were divided into two groups. One of these was given quercetin in the form of onion powder daily while the other was given a placebo. This trial occurred for 24 weeks, and the impact of quercetin on the participants was evaluated both at week 12 and week 24. The results showed that only the younger participants had improved cognitive abilities (287). Later, the same research group repeated the study on 70 healthy Japanese men and women. These participants, aged 60 to 80 years old, were divided into two groups. One of these was given quercetin in the form of onion powder daily while the other was given a placebo. By the end of the trial, it was revealed that the consumption of quercetin had improved the participants' cognitive function, temporal orientation, and emotional function (288). Since these studies translated contrasting results and given that the understanding of its use in therapeutic plans is still limited, it is necessary to conduct further studies on this subject.

4.4.4 Isoflavones

Isoflavones are polyphenolic non-steroidal molecules found in plants, especially in fava beans, leafy greens and soybeans (252,289). When ingested, isoflavones undergo a transformation prompted by the intestinal microflora, converting its glycosylated form into the aglycone form, increasing its bioactivity (252,290). Isoflavones have been linked to various neuroprotective effects, stemming from mainly two mechanisms: possessing the ability to mimic estrogens at transcriptional and transcription-independent levels; and acting

as antioxidant agents (252,289). The first characteristic results in an increase in both BDNF and NGF mRNAs levels, observed in rat models (291–293). They also influence the up-regulation of antiapoptotic proteins, such as Bcl-2 (294,295), as well as of growth-factor receptors, TrkA and TrkB, in the cortex (291,293). In 2017, Li et al. showed that it also modulates the autophagy pathway, inducing brain-expressed x-linked 2-dependent autophagy. In a study conducted by this team, this resulted in the prevention of atrazine-induced neurotoxicity, in SHSY5Y lineage neural-like cells (296).

4.4.5 Phenolic acids

Most of the studies regarding the role of phenolic acids on cognitive outcomes focused on the effects of hydroxycinnamic acids, namely chlorogenic and caffeic acids (252,297). These substances are most commonly found in coffee and have shown evidence of having neuroprotective and cognition-enhancing properties. These possess the capacity for natural anti-amyloidogenic and anti-aggregant activities, particularly the capacity to inhibit the aggregation of proteins implicated in pathologies such as AD, PD, dementia with Lewy bodies, and multiple system atrophy (252,298–300). Data collected using AD transgenic mouse models revealed that rosmarinic acid was able to inhibit the transition from Aβ monomers to oligomers, and from oligomers to Aβ plaque deposition (252,300). In the cases of PD, dementia with Lewy bodies, and multiple system atrophy, several studies characterize phenolic compounds as potent inhibitors of α-syn aggregation, a key pathogenic event in these neurological disorders. In light of this, Ardah et al. showed how gallic acid leads to the inhibition of α-syn fibrillation and toxicity, as well as the disaggregation of preformed α-syn Aβ fibrils *in vitro* (252,298). These observations were endorsed in various studies. These included a randomly assigned test carried out on thirty-eight healthy participants, aged 50 to 69 years old. The participants were given either a placebo or chlorogenic acid-enriched beverage for 16 weeks daily. By the end of the 16 weeks the chlorogenic acid group exhibited improved cognitive functions such as attention and motor speed when compared to the control group. Moreover, the chlorogenic acid group showed signs of increased blood concentrations of early-stage cognitive decline markers, namely apolipoprotein A1 and transthyretin. These tend to decrease in the CSF in early AD patients (252,301). The same research group also developed an experiment to observe the impact of chlorogenic acid-enriched beverages in patients with MCI. A randomized controlled crossover trial was conducted on thirty-four individuals who were given either a placebo or 553.6 mg/bottle of chlorogenic acid, twice

daily for 12 weeks. Once again, the chlorogenic acid group revealed improved attention maintenance and global attention levels (252,301).

4.4.6 Resveratrol

One of the most studied SIRT1 activators is resveratrol, which is part of a class III histone deacetylase that plays a crucial role in various cellular processes such as apoptotic regulation, stress response management and mitochondrial function (302,303). The neuroprotective and plasticity modulation capacities of resveratrol reside in its ability to induce and activate SIRT1 (252,304). One of the mechanisms integrated in this interaction is the deacetylation of p53 (305), which counteracts DNA damage-induced cell apoptosis. Other relevant mechanisms include substances such as AMPK, PI3-K, Ak strain transforming (Akt), caspase-3/12, apoptotic regulator BAX, and cytochrome c (252,306). Resveratrol has also been observed to possess a potent antioxidant activity, resulting in neuron protection and attenuation of intracellular ROS accumulation, associated with cognitive dysfunction. It can also inhibit NF-Kb activation and p38 MAPK phosphorylation (252,306), which are related to the suppression of astrocytes and microglia activation (252,307). It also inhibits the expression of COX2, iNOS, TNF-α, IL-1β, and IL-6 (308,309). This reduces neuroinflammatory processes. Resveratrol also modulates the estrogen-NMDA-BDNF pathway (310), which results in the improvement of cognitive functions in postmenopausal women (311). It is also capable of enhancing the transcriptional activity of both ER-alpha and ER-beta (252,312). This results in the activation of the MAPK pathways, which in turn lead to an increased endothelial NOS activity and NO bioavailability (252,313). This ultimately results in enhanced cerebral vasodilatation, leading to improved cognitive function (252). Resveratrol also showed potential in the treatment of AD, namely at an *in vivo* level (314). This experiment was carried out using Tg6799 mice models, and revealed a decrease in Aβ plaque formation, inhibition of Aβ-mediated microglial activation in AD model APP/PS1 mice and decrease in the levels of insoluble Aβ in the hippocampus (315), protecting the integrity of the BBB in AD rats (316).

Further testing consisted of a variety of preclinical trials. These included a double-blind placebo-controlled study involving 46 healthy older participants and examined the ramifications of resveratrol supplementation at 26 weeks. The experimental group was given (200 mg plus 320 mg of resveratrol per day. The results showed that the intake of resveratrol improved memory performance and neuroimaging, after analyzing the ameliorated functional connectivity of hippocampus as shown by an MRI (252,317). Another example

resorted to similar conditions, constituting a double-blind placebo-controlled study, conducted in postmenopausal women aged between 45 and 85 years old. The study lasted 14 weeks and by the end the results showed better mood states and global cognitive performance, particularly memory function. Additionally, this substance provoked an effect on cerebral responsiveness both during hypercapnic provocation and neuronal activity, which proposes that it may modulate cerebral blood flow (252,318).

4.4.7 Tyrosol and secoiridoid

Tyrosol is a derivative of phenethyl alcohol found mainly in olive oils, in addition to hydroxytyrosol and glucosides and aglycones, such as oleuropein (a non-toxic secoiridoid) (252,319). These components have been associated with antioxidant and anti-inflammatory effects, promoting better cognitive function. A glucoside derived from tyrosol, salidroside, displays properties regarding neuroprotection, mitochondrial biogenesis, and cognitive improvement. This occurs due to the synergistic activation of SIRT1 and insulin receptor subunit A (252,320). Research states that tyrosol may reduce synaptic impairment and cognitive deficits by preventing the reduction of a post-synaptic scaffold protein named spinophilin (321). This results in the regulation of the cytoarchitecture of dendritic spines.

Another vastly interesting olive oil polyphenol is 3-hydroxytyrosol (3-HDT). This substance has been linked to neuroprotective, antioxidant, and anti-inflammatory effects, having been the subject of both *in vitro* and *ex vivo* studies (252). These properties derive from 3-HDT's ability of reversing dysregulated signalling pathways, such as ERK-MAPK/ ribosomal S6 kinase 2, PI3-kinase/Akt1, JAK 2/signal transducer and activator of transcription 3, and NF-κB (252,322). The consumption of 3-HDT boosts the activity of CAT, resulting in a protective effect in dopaminergic neurons from oxidative stress-induced cell damage (252,323). This polyphenol also provides protection from glutamate-induced toxicity in cortical neurons (323). Researchers also theorized that these neuroprotective properties may also stem from anti-aggregant effects. In fact, Romanucci et al. synthesized new tyrosol-based phosphodiester derivatives which contained a catechol moiety able to inhibit Aβ aggregation and to chelate copper and zinc biometals (252,324). Another study by the same group revealed that 3-HDT is a potent inhibitor of Aβ growth, since it possesses a hydroxyl group crucial in stabilizing its interactions with Aβ. This occurs through the formation of a hydrogen bond network in the proximity of glutamic amino acid 22 residue (252,325).

These findings were corroborated in clinical trials carried out in older individuals using olive oil-derived polyphenols. A study tested the supplementation of 1 liter of

extra-virgin olive oil or the addition of 30 g/day of mixed nuts to a Mediterranean diet versus a low-fat control diet in 285 adults aged 55 to 80 years old. These individuals suffered high cardiovascular risk and were separated into three study groups. The study occurred for 6,5 years, by the end of which participants in the extra-virgin olive oil-rich Mediterranean diet group showed lower risk of developing MCI compared to the control group, as well as better overall cognition specialty regarding memory tasks and fluency (252,326).

4.4.8 Curcumin

Curcumin is characterized as an active compound derived from the rhizome of *Curcuma longa*, which has been linked to properties such as antifungal, antiviral and antibacterial effects, as well as neuroprotective and pro-cognitive activities (252,327,328). These properties stem from its ability to cross the BBB, granting it great therapeutic value in the treatment of pathologies such as AD, PD, and HD (252,328). This substance has also been observed to inhibit AP-1 and NF-κB, chelate metals, induce antioxidant enzymes and enhance neurogenesis. It also reduces the formation of Aβ oligomers and fibrils, binding plaques and supressing Aβ *in vivo* (252,328,329). Importantly, this substance has been linked to the increase of several growth factor levels, namely NGF, BDNF, glial cell derived neurotrophic factor, and platelet-derived growth factor, aiding in the processes of neurogenesis, synaptogenesis and improved cognitive abilities (252,330). Moreover, curcumin is a non-enzymatic phenolic antioxidant vastly stronger than vitamin E in neutralizing ROS – it's a free radical scavenger (331). It is also defined as a chain-breaking antioxidant. It possesses the ability to modulate enzymes with great antioxidant activities such as CAT, SOD, and GPx (252,332). This compound confers strong neuroprotective properties, namely through its anti-inflammatory effect. In fact, it has been noted to downregulate inflammatory biomarkers such lipid peroxidation, ROS, NO and glutathione (252,333–335). It also acts through the JNK pathway and reduces the activation of caspase-3 cleavage, resulting in an anti-inflammatory and anti-apoptotic effect (252,336). Furthermore, it inhibits LPS-dependent activation of microglia, as well as the subsequent increase of iNOS and nicotinamide adenine dinucleotide phosphate oxidase (252,337). Curcumin also inhibits the cytosolic A2 phosphorylation, resulting in a decrease in arachidonic acid production, a precursor for prostaglandins (338). Its neuroprotective effects also stem from the activation of several molecular chaperones such as heat shock proteins 40, 60, 70 and 90. (339).

Several studies have been carried out to assess the impact of curcumin consumption. One of these trials consisted of a double-blind placebo-controlled study

involving 60 healthy adults aged 60 to 85 years old. These individuals were separated into two groups, one of which was given curcumin supplementation. This trial explored the acute as well as chronic (4 weeks) effects of curcumin consumption. Subsequent testing revealed enhanced working attention and memory, improved calmness, contentedness and fatigue (340). Another group developed another double-blind trial to assess the relevance of oral curcumin consumption in the prevention of cognitive decline. In this experiment, 40 healthy individuals aged 50 to 90 years old. These participants were divided into two groups, one of which received a supplement containing 90 mg of curcumin twice a day, for 18 months. By the end of the study, it was revealed that the ingestion of curcumin orally enhanced memory performance and resulted in diminished Aβ and tau protein accumulation in the amygdala and hypothalamus (341).

4.5 Tauroursodeoxycholic Acid and Adult Neurogenesis

TUDCA is the taurine-conjugated form of ursodeoxycholic acid, an endogenous bile acid used in the treatment of cholestatic liver diseases (342–346). The act of conjugating TUDCA enables it to penetrate the CNS, after oral administration (342,347). TUDCA has been observed to help lessen the cognitive impact of neurodegenerative diseases. This bile acid plays a role in mechanisms such as fatty-acid (FA) metabolism in rat hepatocytes. It also helps modulate energy levels, reducing ER stress and improving insulin signaling (348–350). This proved useful in obese and diabetic mice models, reimposing correct glucose levels. Additionally, it is known that TUDCA acts in mitochondrial regulation, resulting in increased neurogenesis and neuroprotection. Recently, its ability to enhance the number of NSC and increase neuronal differentiation was reinforced by Soares et al. (351).

A study was performed to understand the impact of TUDCA on the modulation of NCS proliferation and subsequent relevance in adult neurogenesis (342). The trial was carried out on 6-weeks old male Wistar rats, which were administered an intraventricular infusion of TUDCA (342). This study revealed that TUDCA triggers the downregulation of long-chain acyl-coenzyme A dehydrogenase levels in early differentiating NSCs (342,352,353). This enzyme is responsible for catalyzing FA's beta-oxidation, forming C3 trans-double bond in the FAs. TUDCA also promotes fatty acid oxidation, acting as an antioxidant at the mitochondrial level, reducing the generation of hydrogen peroxide-induced ROS (354,355) (**Figure 6**). Another benefit that aids in NSC proliferation is the metabolic shift from FA degradation to lipid biosynthesis. This occurs via the regulation of proteins like sterol regulatory element-binding protein-1 and acetyl-Coenzyme A carboxylase 1 (342,356). Lipid synthesis

provides crucial components for the formation of new cell membranes in highly proliferating NSCs, being vital for this process. The study also proposes that TUDCA lowers palmitic acid levels, a long-chain fatty acid, that hinders proliferation when elevated, due to toxic effects (342,357,358). Furthermore, TUDCA was shown to increase pyruvate dehydrogenase E1 subunit alpha activity (359). This molecule has been shown to counteract FA and glucose metabolism, providing an energy supply for adult neurogenesis. Finally, the consumption of TUDCA was linked to the promotion of histone acetylation, through the regulation of nuclear pyruvate dehydrogenase complex activity (342,360), promoting cellular differentiation.

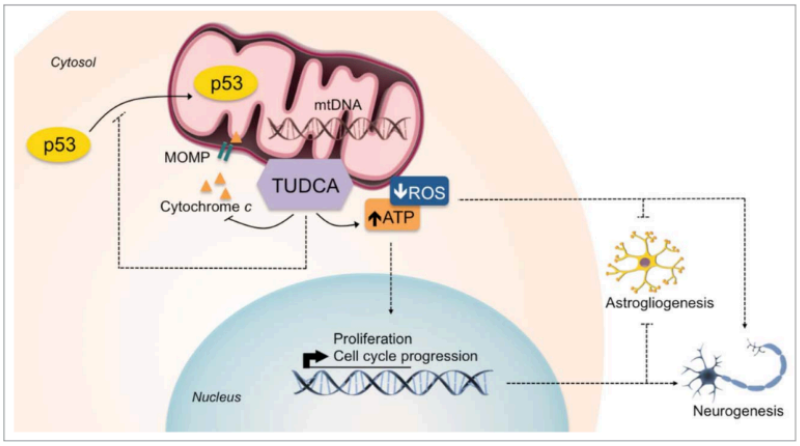

Figure 6. The role of TUDCA in adult neurogenesis. TUDCA interacts with mitochondria-cell cycle retrograde signals, modulating NSC fate. This bile acid inhibits mitochondrial apoptotic events resulting from the differentiation process. This, in turn, decreases astrogliogenesis and increases neurogenesis. TUDCA's effects have been observed to be mitochondrial reactive oxygen species-dependent and rely on stable ATP levels. *Adapted from: Tauroursodeoxycholic acid increases neural stem cell pool and neuronal conversion by regulating mitochondria-cell cycle retrograde signaling (361).*

Considering this study, as well as many others, TUDCA is now a Food and Drug Administration-approved treatment component for liver diseases (342). It is also being considered for the treatment of ALS (362).

4.6 Caloric Intake, Dietary Restrictions and Adult Neurogenesis

Recent literature suggests that caloric restriction (CR) and intermittent fasting (IF) provide beneficial neurotrophic effects in the brain, improving adult neurogenesis (363). These effects have been associated with a switch from glucose to ketone bodies, as an energy source, during a low glucose phase felt after a period of calorie ingestion depletion (364).

This switch causes a metabolic shift, leading to the activation of several signaling pathways related to energy regulation and increasing adult neurogenesis (365–367). The benefits of CR are inherently related to the influence of the hunger hormone ghrelin on glucose homeostasis and the activity of the insulin receptor, influencing neuroprotective and neurogenic pathways (363,368,369). Furthermore, other molecules such as polyphenols, sirtuin (SIRT) activators, and NAD+ precursors are labelled calorie restriction mimetics (CRMs), since these substances can mimic the effects of CR without glucose depletion (363,370–372). Research has suggested the positive impact of CRMs in the regulation of energy metabolism, oxidative stress and inflammation reduction, and as well as in adult neurogenic and cognitive functions (373–376). Although Handschin (2016) (377) raised questions about these studies in terms of overall physiological parameters, there is a consensus in the literature that consuming CRMs offers benefits, including the prevention and treatment of neurodegenerative disorders. In fact, CR, IF and CRMs have been shown to help control epigenetic changes associated with aging, presenting a new window of possible treatments to fight neurodegeneration (363,375,378). However, further clinical trials are needed to confirm this possibility.

Overconsumption and overeating are common habits in our society, stemming from the constant readily available food. According to Mattson (2019) (363,379), nutritional practices that re-establish "adaptive cellular signaling", like IF or CR, have been shown to mitigate the negative effects such as cognitive decline felt in individuals who suffer from food overconsumption. Erbaba et al. (2021) described IF as a "regimen in which there are repeating cycles of *ad libitum* eating and fasting" (363,380). Four forms of IF have been studied, in addition to other religious fasting practices: alternate day fasting, which consists of significantly lowering energy intake every two days; whole day fasting, involving one to two days of food abstinence a week; time-restricted feeding, where food intake is limited to a time window varying from eight to twelve hours, generally; and period fasting, where after five days of *ad libitum* diet there are two days of fasting (381–383). These forms of dieting, including fasting-mimicking diets, have been observed to generate benefits like those of CR, such as improved neurogenesis (384). Fast mimicking diets consist of cycles of reduced caloric and protein intake for a few days to a week, aiming to provide the benefits of fasting without complete abstinence from food (383). Chen J. et al. (2022) (385) provide a bibliometric analysis of IF, while Li et al. (2023) (381) provide a balanced view of IF, relating this diet to the circadian rhythm and discussing potential downsides.

Mattson (2019) states CR requires limiting the daily caloric intake to roughly 1800 to 2200 kcals/day for men and 1600 to 2000 kcals/day for women. This reduction must be maintained over a prolonged period (379). The quantity of nutrients available, indicated by ratios such as adenosine monophosphate over ATP, is responsible for the maintenance of several signaling pathways, relevant for adult neurogenesis (386). CR, in turn, influences many mechanisms that can delay some cognitive effects of aging (387), namely through the reduction of oxidative stress (375,388), promoting the proliferation of new neurons (389,390), and the promotion of the process of autophagy. This diet regime also influences other processes, such as the increase in the production of anti-inflammatory hormones, the decrease of chronic inflammation, as well as the modulation of cell survival, e.g. through apoptosis (372,391).

CRMs are compounds that mimic the benefits of CR, such as improved neuroprotection, synaptic plasticity, and reduction of oxidative stress and neurotoxicity, without the need to significantly reduce caloric intake (392). In this regard, Bonkowski & Sinclair (2016) discussed the increase in the use of NAD+ precursors and SIRT activators in clinical trials, to promote longevity in the context of neurodegenerative disease treatment (393). NAD+ is a key coenzyme in cellular metabolism and energy production, while SIRTs have been explored for their capacity to promote neuronal longevity. These findings would benefit from further research.

4.7 Gut-brain Axis and Adult Neurogenesis

During the last decade, studies have shown evidence of a symbiotic relationship between the gut microbiota and the brain, particularly the hippocampus (394). This research points to the existence of a cause-and-effect relation between these two regions, where a healthy microbiota positively impacts neural well-being, being a potential route in the management of certain illnesses, particularly stress-related psychopathologies such as depression and anxiety. A growing mountain of evidence points to the benefits of probiotic consumption, as these are responsible for maintaining normal and healthy gut microbiota.

Many factors influence the gut microbiome, and therefore its effects on neurogenesis (394,395) (**Figure 7**). Today four direct neuroanatomical routes have been discovered that establish the link between the gut and brain: the vagus nerve, which establishes a direct channel of communication between the gut and the brain (394,396); the hypothalamus-pituitary-adrenal axis, which mediates the stress response (394,397–399); the

neuroactive substance metabolism, since microbiota influence the production of substances such as neurotransmitters (394,400); and inflammatory modulation, since the gut can regulate inflammation, affecting neuronal function (394,401). Moreover, age, physical activity, antibiotics and diet all are responsible for creating changes in the microbiota (394).

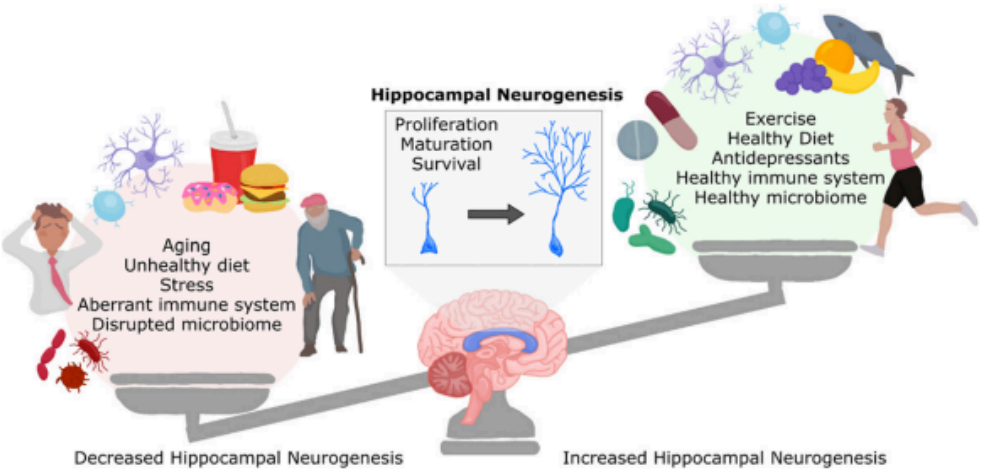

Figure 7. Factors that influence adult hippocampal neurogenesis. A healthy lifestyle consisting of regular physical activity, antidepressant drug consumption, a healthy and complete diet and a subsequent healthy gut microbiome result in increased neurogenic levels in the hippocampus. Meanwhile, factors such as aging, unmanaged stress and an unhealthy diet led to a decrease in hippocampal neurogenesis. *Adapted from: Microbiota-Gut-Brain Axis Regulation of Adult Hippocampal Neurogenesis (394).*

Focusing on the dietary aspect, preclinical studies have shown it plays a crucial role in the regulation and maintenance of adult hippocampal neurogenesis. In fact, diets containing large quantities of fat and sugar trigger a decrease in hippocampal cell proliferation, a reduction in the number of newly born neurons, and a decrease in overall hippocampal function in mice and rats, leading to behavioral changes (402,403). These changes might have been a consequence of neuronal mitochondrial biogenesis (394,402), and/or increased circulating corticosterone (394,404). These nefarious effects are counteracted through long-term running exercises (405). In contrast, dietary patterns like CR and intermittent fasting IF showed signs of leading to improved longevity and memory function (394,406–408), mainly through a mechanism resulting in upregulated brain-derived neurotrophic factors (409).

Prebiotics are compounds such as fermentable fibers and phenolics that get this designation by being selectively used by the gut microbiome. They can be converted into

short-chain fatty acids, such as acetate, butyrate and propionate (394,410,411). Their consumption translates into beneficial effects such as a lesser cognitive decline and mitigation of age-related neuronal complications, namely immune deficits. Certain prebiotic polyphenols have been observed to promote hippocampal neuronal proliferation and survival (412). Recently, oral administration of sodium butyrate has been observed to impact neurogenesis, increasing the number of new neurons and the volume of the hippocampal granular cell layer in pig models (413). It also reduces neuroinflammation and cognitive deficits in stressed or aging rats (414,415). Although these findings point to the beneficial properties of maintaining a balanced gut microbiota, further investigating is required to confirm this hypothesis, evaluating the translation of this information from rodent models to humans, and looking for mechanisms and biomarkers to optimize and standardize supplementation and consumption of probiotics in the context of treatment.

Other foods like fruits and vegetables contain prebiotic polyphenols (416) and have already been shown to improve depressive symptoms and possess antidepressant (417) and antioxidant properties (418–420) in studies with animal models. In addition, diets rich in fish oils and omega-3 FAs, such as the Mediterranean diet, have also been observed to enhance cognitive performance and provide benefits that counteract the mental health problems characteristic of aging individuals (421). For example, studies performed in mice and lobster models showed the positive influence of omega-3s in hippocampal neurogenesis (394,422,423). This ability seems to stem from omega-3s capacity to modulate the gut microbiota.

Soluble dietary fibers such as fructo-oligosaccharides and galacto-oligosaccharides have been shown to regulate BDNF and synaptic protein expression in rodents (394,424,425). However, further investigation is required to fully assess the direct impact of these substances on adult neurogenesis.

Flavonoids have been observed to play a role in the enhancement of learning and memory formation, promoting the proliferation and survival of NSCs. Substances such as quercetin, *Citrus kawachiensis* fruit (3,5,6,7,8,3',4'-Heptamethoxyflavone), spinosyn and oroxylin A contribute to neural homeostasis by increasing BDNF levels and the number of DCX+ cells, preventing hippocampal microglia activation, and improving cognitive performance in mice, respectively (426–429). These properties have been suggested to stem

from their interactions with the gut microbiome, although future studies are needed to confirm this theory and design future therapeutic routes.

5. Conclusion and Future Perspectives

The discovery that neurogenesis continues to take place after the embryonic and early life stages opened new avenues to explore this process in the context of neurological pathology treatment. The progression of adult neurogenesis has been confirmed to occur in specific niches, namely the SGZ of the hippocampus, and the SVZ of the lateral ventricles. The generation of new neurons takes place following the proliferation and differentiation of NSCs/NPCs. These suffer processes such as migration, selective apoptosis, cell survival, and integration in the preexisting network.

Adult neurogenesis is influenced by many external and internal factors, namely aging, exercise regime and dietary habits. This last factor has been revealed to be of extreme importance since the correct amount of nutrients consumed directly impacts the necessary mechanisms to generate new neurons. The decrease in nutrients such as omega-3 FAs, minerals and vitamins, has been shown to negatively impact the process of neurogenesis. This leads to an increased number of neurological pathology cases derived from the depletion of these essential building blocks for the creation of new neuronal connections. These pathologies include diseases such as AD, PD and HD, as well as mood disorders such as depression and bipolar disorder. The hindering of new neuron production worsens the state of preexisting neuronal dysfunction and increases the risk of their development.

To counteract these consequences, studies have sought to understand the benefits of nutrient supplementation in the treatment or reduction of symptoms derived from neurological diseases. Indeed, the research highlighted how increasing the consumption of specific nutrients improved neuronal conditions significantly. However, the impact of nutrition in adult neurogenesis still benefits from further investigation, as the study of the human brain *in vivo* poses several ethical and practical barriers. Therefore, advanced techniques such as neuroimaging, life-cell and tissue experiments, and new animal models might be the way to achieve new findings in this exciting area of research.

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