NEURAL REGENERATION RESEARCH
www.nrronline.org

Neurotrophic fragments as therapeutic alternatives to ameliorate brain aging

Itzel Ortiz Flores[1], Samuel Treviño[2], Alfonso Díaz[2,*]

https://doi.org/10.4103/1673-5374.331867

Date of submission: May 18, 2021

Date of decision: June 9, 2021

Date of acceptance: July 5, 2021

Date of web publication: June 6, 2022

From the Contents

Abstract

Aging is a global phenomenon and a complex biological process of all living beings that introduces various changes. During this physiological process, the brain is the most affected organ due to changes in its structural and chemical functions, such as changes in plasticity and decrease in the number, diameter, length, and branching of dendrites and dendritic spines. Likewise, it presents a great reduction in volume resulting from the contraction of the gray matter. Consequently, aging can affect not only cognitive functions, including learning and memory, but also the quality of life of older people. As a result of the phenomena, various molecules with notable neuroprotective capacity have been proposed, which provide a therapeutic alternative for people under conditions of aging or some neurodegenerative diseases. It is important to indicate that in recent years the use of molecules with neurotrophic activity has shown interesting results when evaluated in *in vivo* models. This review aims to describe the neurotrophic potential of molecules such as resveratrol (3,5,4′-trihydroxystilbene), neurotrophins (brain-derived neurotrophic factor), and neurotrophic-type compounds such as the terminal carboxyl domain of the heavy chain of tetanus toxin, cerebrolysin, neuropeptide-12, and rapamycin. Most of these molecules have been evaluated by our research group. Studies suggest that these molecules exert an important therapeutic potential, restoring brain function in aging conditions or models of neurodegenerative diseases. Hence, our interest is in describing the current scientific evidence that supports the therapeutic potential of these molecules with active neurotrophic.

Key Words: Alzheimer's disease; brain; cerebral cortex; cognitive function; dendritic spines; HC-TeTx; hippocampus; neurodegeneration; neuronal survival; neurotrophins

Introduction

Aging is a biological and complex process that is considered a global phenomenon (Jylhävä et al., 2017; Baghel et al., 2019). In 2019, the United Nations established that there were 703 million persons aged 65 years in the global population and projected a doubling of this number to 1.5 billion by 2050 (Estebsari et al., 2020). Therefore, the percentage of patients with aging diseases will increase proportionally (Flores et al., 2016).

Aging usually manifests itself as a decline in functional capacity due to reduced reparative and regenerative potential in tissues and organs (Khan et al., 2017). The importance of aging lies in the fact that it is a risk factor not only for developing chronic diseases, such as cardiovascular disease, cancer, osteoporosis, arthritis, and diabetes, but also for the two main neurodegenerative diseases Alzheimer's disease (AD) and Parkinson's disease (PD) (Kanasi et al., 2016; Jylhävä et al., 2017; Mattson and Arumugam, 2018; Wahl et al., 2019). Neurodegenerative diseases are characterized by accelerated cellular and metabolic processes and are favored during aging (Wahl et al., 2019).

Aging is also characterized by systemic changes such as increased arterial stiffness, intrinsic heart rate reduction, functional loss of respiratory system compliance, renal diffuse glomerulosclerosis, hematopoietic tissue changes by decreased bone marrow mass and replacement with fat, and immunosenescence, which are redundant with the development of neurodegenerative diseases (Khan et al., 2017). Hence, age raises the risk of suffering multi-morbidity (Zhang et al., 2017; Bektas et al., 2018). In this review, emphasis will be placed on brain changes during aging, as well as on recent findings of numerous preclinical and clinical studies that used similar therapeutic alternatives to demonstrate how these molecules might delay or modulate the negative impact of these changes on many cognitive functions during aging and neurodegenerative diseases.

Database Search Strategy

The literature review was performed electronically with the help of the PubMed database. For the initial selection of the articles to be evaluated, the combinations of keywords were used: brain aging, and neurotrophic factors; neurotrophins and neuronal survival; TRK's and neuroplasticity; neurotrophic molecules and neuronal hyperplasia; Neurotrophins and pharmacotherapy, cerebrolysin, Hc-TeTx, neuropeptide-12 and limbic neuronal morphology. Most of the chosen studies (70% of all references) were published between 2009 and 2021. An old publication from 2000 was included in consideration of its relevance to protein-protein interactions and specificity in signal transduction.

Brain Aging

It is well documented that aging itself is not a disease; however, no system is exempt from changes associated with this natural process (Danka Mohammed et al., 2017). The brain particularly undergoes several changes that make it the most affected organ during the aging process (Flores et al., 2020). In addition, brain plasticity presents many modifications over time due to its increased vulnerability to structural, chemical, and functional changes associated with aging (Danka Mohammed et al., 2017; Islam et al., 2017; Baghel et al., 2019). Moreover, other reported changes that might occur during aging include decreases in the number, diameter, length, and branching of dendrites, as well as in the dendritic spine density (Isaev et al., 2019). Several studies have demonstrated an overall reduction in brain volume, with most of the grey matter shrinkage occurring in the prefrontal cortex (PFC) and hippocampus, which are critical areas for various complex cognitive processes, such as learning, memory, and planning (Flores et al., 2016; Danka Mohammed et al., 2017; Isaev et al., 2019; Lima Giacobbo et al., 2019). Moreover, these structures are interconnected by glutamatergic projections and are disrupted in neurodegenerative disorders. Thus, a gradual loss of local connectivity due to aging causes cognitive deficits (Flores et al., 2016). Likewise, morphological changes are associated with low concentrations of neurotransmitters, such as acetylcholine, glutamate, and dopamine, which also participate in cognitive and motor processes (Vazquez-Roque et al., 2021).

Brain metabolism uses approximately 25% of the total oxygen and glucose ingested. Nevertheless, brain metabolism is also affected during aging (Morita et al., 2019; Wahl et al., 2019). Astrocytes sense and mediate nutrient uptake from the systemic circulation because they are ideally positioned between the cerebral vasculature and neuronal synapses. Furthermore, astrocytes possess a robust enzymatic capacity for glycolysis, glycogenesis, and lipid metabolism, managing nutrient support for neuronal consumption. Moreover, glycolysis and glycogenesis processes are regulated by noradrenaline and insulin, but mitochondrial adenosine triphosphate (ATP) production and fatty acid oxidation are responsible for triiodothyronine (Morita et al., 2019). During aging, circulating glucose concentrations generally increase due to impaired glucose transport and low insulin response (Mattson and

[1]Department of Health Sciences, School of Medicine, University of the Americas Puebla, Puebla, Mexico; [2]Faculty of Chemical Sciences, Benemerita Autonomous University of Puebla, Puebla, Mexico

***Correspondence to:** Alfonso Díaz, PhD, alfonso.diaz@correo.buap.mx.
https://orcid.org/0000-0003-4092-6636 (Alfonso Díaz)

How to cite this article: *Flores IO, Treviño S, Díaz A (2023) Neurotrophic fragments as therapeutic alternatives to ameliorate brain aging. Neural Regen Res 18(1):51-56.*

Arumugam, 2018). Consequently, hyperinsulinemia, low insulin sensitivity, and aging-associated insulin resistance (abnormal brain insulin binding) also impair glucose uptake in the precuneus, prefrontal cortex, and other brain regions, playing a central role in the progression of AD, even in the absence of hyperglycemia (Wahl et al., 2019). Studies performed with positron emission tomography (PET) coupled to radiolabelled glucose (fluorodeoxyglucose) have shown a progressive reduction in glucose uptake in the temporal, parietal, and frontal lobes and motor cortex. These changes contribute to a decline in hippocampus-dependent learning and increased gliosis (Mattson and Arumugam, 2018; Morita et al., 2019).

Other hallmarks of brain aging include mitochondrial dysfunction, intracellular accumulation of proteins, nucleic acids, and oxidized lipids, impairment of cellular waste disposal mechanisms, adaptative stress response signaling, DNA repair pathways, neuronal network activity, neuronal Ca^{2+} handling, stem cell exhaustion, and inflammation (Mattson et al., 2018). Additionally, the downregulation of neurotrophins (NTs) in brain regions, including the cortex and hippocampus, diminishes plasticity, neuronal survival, *de novo* synapses, dendritic branching, and modulation of excitatory and inhibitory neurotransmitter profiles (Numakawa et al., 2018; Lima Giacobbo et al., 2019; Vazquez-Roque et al., 2021).

Consequently, these changes at the brain level negatively impact cognitive functions such as attention, perception, speech, language, reasoning, decision-making, executive control, intelligence, and memory, which are crucial for normal human life (Jylhävä et al., 2017; Baghel et al., 2019). Cognitive function is considered an important factor that determines the quality of life in the aging population. Accordingly, in recent years, further consideration has been given to research on the potential of therapeutic alternatives to minimize aging-associated damage at the brain level (Danka Mohammed et al., 2017). Some therapeutic options, shown in **Figure 1**, are resveratrol (RSV), nonsteroidal anti-inflammatory drugs (NSAIDs), rapamycin, and NTs, including brain-derived neurotrophic factor (BDNF), heavy chain of tetanus toxin (HC-TeTx), cerebrolysin (CBL), and neuropeptide-12 (N-PEP-12).

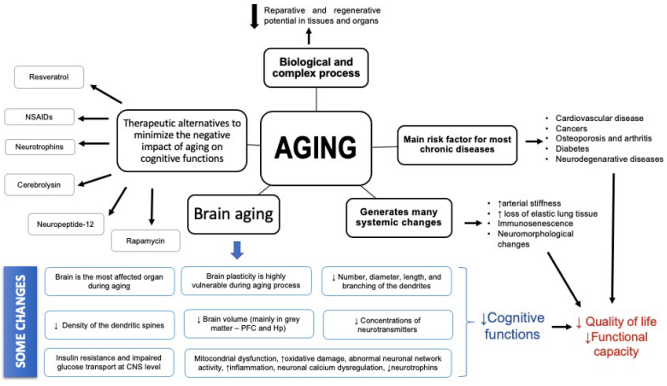

Figure 1 | **Neurotrophic fragment as a therapeutic alternative.**
The Schematic diagram shows the main characteristics of aging and how brain aging participates in the downregulation of cognitive functions, quality of life, and functional capacity. In addition, therapeutic alternatives to ameliorate the negative impact of aging are mentioned. CNS: Central nervous system; Hp: hippocampus; NSAIDs: non-steroidal anti-inflammatory drugs; PFC: prefrontal cortex.

Endogenous Neurotrophins

The neurotrophic factor hypothesis proposes that at the brain level, there is a limited secretion of survival factors, which function to ensure a balance between the size of the organ and the number of innervating neurons (Huang and Reichardt, 2001). This class of cell growth and survival molecules is commonly termed NTs, which are widely known due to their capacity to regulate neural survival, development, function, and plasticity (Molinari et al., 2020). Nevertheless, alterations in neurotrophic factor expression are considered important factors in the development of a variety of central nervous system (CNS) diseases, including neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis), as well as psychiatric disorders such as depression and schizophrenia. In this sense, NTs may be considered potential therapeutic agents (Sangiovanni et al., 2017).

Nerve growth factor (NGF) was the first neurotrophin to be characterized. Subsequently, its ability to enhance the growth of sensory and sympathetic neurons was discovered (Colardo et al., 2021). Eventually, other NTs, such as BDNF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5), were described. Another important characteristic to note regarding NTs is their structural homology (Kozlov et al., 2020).

In addition, there is available evidence demonstrating the outstanding contribution of other protein families, such as the glial cell-derived neurotrophic factor (GDNF) family and neuropoietic cytokines, to the regulation of survival, development, and function in the nervous system (Houlton et al., 2019; Molinari et al., 2020).

As mentioned above, it has been demonstrated that NTs show changes in their expression in response to neural or adjacent cell damage due to their capacity to contribute to neuronal survival and regeneration (Huang and Reichardt, 2001; Barrio et al., 2021). In addition, it has been reported that NTs are expressed by numerous populations of neurons in regions invaded by sensory axons; thus, they might supply trophic support to neurons that have not yet contacted their final targets (Huang and Reichardt, 2001; Yang et al., 2015; Caffino et al., 2020). Furthermore, other studies have reported that BDNF may also act in both autocrine and paracrine manners to support dorsal root ganglion (DRG) sensory neurons. Moreover, other important features of BDNF are its ability to be transported anterogradely and to act transsynaptically. Therefore, it is important to mention that in some circumstances, a neurotrophin provided by one cell is not only effective at supporting neurons with axons in its vicinity but also to provide support to more distant neurons via transcellular transport (Huang and Reichardt, 2001).

With regard to the mechanism of action of NTs, they interact with two types of transmembrane-specific receptors, known as tyrosine-kinase receptors (Trks) and the p75 neurotrophin receptor ($p75^{NTR}$). The Trk family includes the isoforms TrkA, TrkB, and TrkC, which bind to mature forms of NGF, BDNF, and NT-3, respectively (Kozlov et al., 2020; Barrio et al., 2021). The structure of these receptors consists of an extracellular neurotrophin-binding domain composed of two cysteine-rich regions separated by a leucine-rich repeat. Additionally, Trks have two tandem immunoglobulin G (IgG)-like domains that are located in close proximity to the plasma membrane. Moreover, the interaction between NT mature forms and Trks occurs via the second IgG-like domain. Other elements of these receptors are the single-pass transmembrane region and an intracellular domain with intrinsic tyrosine kinase activity (Meldolesi, 2018).

The interaction of NTs with their respective receptors results in Trk receptor homodimer formation and subsequent triggering of tyrosine kinase activity by autophosphorylation (Colardo et al., 2021). Phosphorylated tyrosine residues in Trk receptors may then act as docking sites for adapter proteins containing phosphotyrosine-binding (PTB) or src-homology-2 (SH-2) motifs (Pawson and Nash, 2000; Lo et al., 2005; Jiang et al., 2018). In addition, these adapter proteins are absolutely essential to activate intracellular signaling cascades, such as the Ras/ERK (extracellular signal-regulated kinase) protein kinase pathway, the phosphatidylinositol-3-kinase (PI3K)/Akt kinase pathway, and phospholipase C (PLC-γ1) (Huang and Reichardt, 2001).

Activation of the Ras pathway is crucial for the normal differentiation of neurons and other cell functions, such as survival, cytoskeletal structure, intracellular transport, and gene expression patterns (Zhong, 2016; Colardo et al., 2021). Moreover, in studies using cultured embryonic sensory neurons, it has been demonstrated that activated Ras promotes axon extension and survival in the absence of NGF (Zhong, 2016; Li et al., 2018).

Therefore, for activation of the Ras pathway, NTs must bind to Trk receptors, thus inducing phosphorylation at their Tyr490 residue. This process results in the subsequent recruitment and phosphorylation of Shc (Wills et al., 2017). When this adaptor protein is phosphorylated, it binds to the Grb2-SOS complex, activating the guanine nucleotide exchange factor son of sevenless (SOS). Subsequently, SOS removes GDP from the small GTPase Ras, which is then able to bind to guanosine triphosphate (GTP) and switch to the active form (Huang et al., 2019). Next, Raf kinase is activated by Ras and in turn phosphorylates ERK. Finally, ERK is responsible for the activation of several downstream substrates and mediates different cellular mechanisms, such as proliferation, differentiation, survival, cell growth, and apoptosis (Colardo et al., 2021). It is important to note that NT signaling through Shc/Grb-2/SOS pathways mediates transient, but not prolonged, ERK signaling pathways (Huang and Reichardt, 2001)).

Likewise, PI3K and protein kinase Akt/protein kinase B activation are considered essential for neuronal survival. The PI3K pathway activated by Ras in numerous neurons is the major pathway by which NTs transmit survival-promoting signals (Gite et al., 2019). Conversely, Akt modulates cell survival via BCL2-associated agonist of cell death (BAD) inhibition, thus avoiding apoptosis (Colucci-D'Amato et al., 2020). Another target of Akt is IκB, the phosphorylation of which results in its degradation and subsequent activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). Transcription activated by NFκB has been shown to promote neuronal survival (Shih et al., 2015). Akt also influences the forkhead transcription factors FKHRL1 and caspase-9, which are related to apoptosis processes (Huang and Reichardt, 2001). Moreover, glycogen synthase kinase 3-β (GSK3β) is negatively regulated by Akt, thus avoiding apoptosis and Tau hyperphosphorylation (Hetman et al., 2000). Akt is also involved in cell cycle progression through S6 kinase and essential cyclins. In limbic cerebral regions, insulin and insulin growth factors (IGFs) participate in modulating this signaling pathway (Barrio et al., 2021).

Through these signaling pathways, NTs induce cytoskeletal rearrangements, endocytosis, and membrane sorting. These changes enhance the communication of survival signals from nerve terminals to neuronal cell bodies that require retrograde transport (Huang and Reichardt, 2001). Additionally, NTs have been shown to encourage neurite outgrowth and axon growth when neurons receive adequate trophic support and innervation by sensory neuron fibers. The chemoattractant activities of NGF and BDNF via PI3K can be converted into chemorepellent activities when the cAMP signaling cascade is inhibited (Zhong, 2016). Although it is thought that different Trk receptors function through similar signal transduction pathways,

the chemoattractant activity of NT-3, acting through TrkC, is not affected by agents that affect cAMP-mediated signaling (Hetman et al., 2000). Instead, inhibitors of cGMP signaling convert this chemotrophic response from an attractive to a repulsive response (Huang and Reichardt, 2001). These observations persuasively argue that there are fundamental differences in the signaling mediated by different Trk receptors. However, in adulthood, the presence of processes such as systemic low-grade chronic inflammation and neurodegenerative diseases can promote damage to the CNS through progressive oxidation and nitration patterns and a subsequent reduction of NT levels (Huang and Reichardt, 2001).

Conversely, PLCγ1, through the hydrolysis of phosphatidylinositol 4,5-biphosphate, generates two distinct second messenger systems: diacylglycerol (DAG) and inositol trisphosphate (IP3) (Colardo et al., 2021). DAG activates protein kinase C (PKC), and IP3 binds to its receptors, resulting in the release of Ca^{2+} from endoplasmic reticulum (ER) stores, which subsequently activates Ca^{2+}-calmodulin-dependent protein kinases (Kozlov et al., 2020). In this way, there is ample evidence to show the importance of the PLCγ1 pathway in Trk activation. Moreover, this interaction is crucial for the induction and maintenance of synaptic plasticity (Houlton et al., 2019; Colardo et al., 2021).

Conversely, $p75^{NTR}$ can bind to both pre-processed and mature forms of NTs. Nevertheless, this receptor has a higher affinity for pro-neurotrophins (pro-NTs), which are the pre-processed forms of NTs (Houlton et al., 2019; Barrio et al., 2021). This interaction between $p75^{NTR}$ and pro-NTs activates signaling pathways and promotes apoptotic events (Kozlov et al., 2020; Barrio et al., 2021). Additionally, $p75^{NTR}$ has the ability to interact with Trk receptors and improve their affinity to mature forms of NTs, thus enhancing pro-survival signaling (Barrio et al., 2021).

In some CNS projection neurons, Trk receptors are sequestered in intracellular vesicles (Numakawa et al., 2018; Caffino et al., 2020), and only in the presence of a second signal, such as cAMP or Ca^{2+}, can these receptors be inserted efficiently into the plasmalemma. In these neurons, the expression of Trk receptors may not be sufficient to confer responsiveness to an NT. In this sense, NT responsiveness is controlled by several factors (Huang and Reichardt, 2001). Additionally, the production of mature forms of NTs is a cell tissue-dependent process (Colardo et al., 2021). Nevertheless, the expression of both NTs and their receptors decreases with age. Consequently, they have a trophic ability to combat natural and pathological neurodegeneration (Houlton et al., 2019).

Several preclinical studies are currently examining neurotrophic factor small-molecule mimetics, such as ciliary neurotrophic factor (CNTF) small-molecule peptide mimetics and peptide 021 (P021). CNTF is part of the IL-6 family of cytokines, and its importance is based on its pivotal role in adult hippocampal and subventricular zone neurogenesis and the differentiation of neural stem cells. Thus, its neuroprotective effects are well established. Regarding its location at the CNS level, CNTF is expressed in astrocytes in neurogenic niches, and its receptor, CNTF receptor α (CNTFRα), is expressed predominantly in neural progenitor cells and hippocampal neurons and many other areas of the brain, including the motor cortex and cerebellum. In addition, preclinical studies using AD transgenic mice have reported that recombinant CNTF can alleviate cognitive impairment and stabilize synaptic protein levels (Kazim and Iqbal, 2016). Furthermore, the ability of P021, a neurogenic and neurotrophic molecule, to enhance dentate gyrus neurogenesis and memory processes has been demonstrated. In the above studies, a triple-transgenic mouse model of AD (3xTg-AD) was utilized, and the results of these studies demonstrated a role for P021 through inhibition of the leukemia inhibitory factor (LIF) signaling pathway and an increase in BDNF expression. Moreover, Kazim et al. demonstrated that oral administration of compound P021 could rescue cognitive aging by enhancing neurogenesis via increased BDNF expression and by decreasing tau levels in aged Fisher rats (Kazim and Iqbal, 2016).

Treatments to Positively Modulate Neurotrophins

Neurotrophins and nutrition

Nutrition significantly influences the development and health of brain structure and function. Moreover, nutrition is responsible for providing the proper building blocks for the brain to create and maintain connections that are essential for multiple functions. The consumption of appropriate dietary factors has a broad and positive effect on neuronal function and plasticity. Therefore, brain function is certainly dependent on adequate nutrition, and short-term variations in the amount and composition of nutrient intake in healthy individuals influence measures of cognitive function. Accordingly, there has been a recent growing interest in the possible beneficial effects of polyphenols on brain health (Meeusen, 2014). Polyphenols are considered powerful antioxidants. Moreover, these micronutrients are highly abundant in plant-derived foods. Sources of polyphenols include tea, red wine, cocoa, and coffee. Additionally, polyphenols have been reported to exert their neuroprotective actions through protection against toxin-induced injury and inflammation and by promoting processes such as memory, learning, and cognitive function. Moreover, they contribute to delaying neurosenescence (Cuevas et al., 2009; Meeusen, 2014; Diaz et al., 2019).

Flavonoids, the main group of polyphenols, are subdivided into six dietary groups: flavones, flavanones/flavanonols, isoflavones, flavonols, flavanols, and anthocyanidins. Flavonoids comprise the most common group of polyphenolic compounds in the human diet. Some sources of these compounds are fruits, vegetables, cereals, teas, and wines (Beecher, 2003). Studies indicate that intake of flavonoids is inversely related to cognitive decline during aging (Devore et al., 2012). Although the mechanism of action of these molecules is still a subject of discussion, several flavonoid-binding sites have been reported, such as adenosine receptors, GABA (γ-aminobutyric acid type A receptor), δ-opioid (delta opioid receptor), nicotinic, testosterone, and estrogen receptors (Williams and Spencer, 2012). Xu et al. (2013b) demonstrated that after the addition of calycosin (isoflavone), isorhamnetin (flavonol), and luteolin (flavone), the phosphorylation of estrogen receptors in astrocyte cultures results in high levels of synthesis and secretion (time- and dose-dependent) of NTs such as NGF, GDNF, and BDNF.

The first flavonoid described as a receptor agonist was 7,8-dihydroxyflavone (7,8-DHF). Furthermore, 7,8-DHF has been shown to induce the dimerization and autophosphorylation of TrkB receptors on neurons, thus reducing neuronal death *in vitro* and *in vivo* (Liu et al., 2010). Moreover, studies have demonstrated that the administration of 7,8-DHF and other flavonoids induces the expression of synaptic proteins, synaptotagmin, and post-synaptic density protein-95 in animal models of neurodegenerative and neurological diseases, generating beneficial responses similar to those induced by BDNF (Liu et al., 2010; Devi and Ohno, 2012; Zeng et al., 2012; Xu et al., 2013a; Zhao et al., 2016). Evidence suggests that dietary-derived flavonoids can improve memory and neurocognitive performance by protecting vulnerable neurons, enhancing existing neuronal function, and stimulating neuronal regeneration (Vauzour, 2012). Of particular interest is the ability of flavonoids to activate the PI3K/Akt signaling pathways, leading to cAMP, PKC, protein kinase A, calcium-calmodulin kinase, and MAPK activation that increases NT expression, improving short- and long-term memory (Spencer, 2008).

The non-flavonoid group of polyphenols includes phenolic acids and stilbenes. Caffeic acid is the most abundant phenolic acid in food and can be found predominantly in blueberries, kiwis, plums, and apples (Sova and Saso, 2020). Furthermore, resveratrol (RSV), the main stilbene isolated in 1939 by Takaoka from Veratrum grandiflorum (Shaito et al., 2020), can be found in the cis or trans configurations. Additionally, RSV can be isolated and purified from grapes, apples, raspberries, blueberries, plums, peanuts, and products derived therefrom, such as wine (Vauzour, 2012; Weiskirchen and Weiskirchen, 2016).

The importance of this compound lies in its capacity to induce neuroprotective effects by reducing oxidative damage and chronic inflammation and by improving vascular function and activating longevity genes. Moreover, it also has the ability to promote the activity of neurotrophic factors. In a study conducted by Hernández-Hernández et al., administration of RSV (20 mg/kg orally daily for 60 days) demonstrated a significant increase in dendritic length and spine density in pyramidal neurons of the PFC and regions CA1 and CA3 of the dorsal hippocampus (DH) in all resveratrol-treated rats (Monserrat Hernández-Hernández et al., 2016).

Conversely, RSV can activate sirtuins, enzymes that are well known due to their ability to modulate the properties and functions of proteins such as histones, kinases, and transcription factors by removing acetyl groups that have been post-translationally attached to their lysine residues by acetyltransferases (Jęśko and Strosznajder, 2016; Kupis et al., 2016). Sirtuins (SIRTs) are class III histone deacetylases (HDACs) and possess a conserved catalytic NAD^+-binding domain. Therefore, NAD^+ is required for their activity (Jęśko and Strosznajder, 2016; Wątroba and Szukiewicz, 2016; Tang, 2017). In addition, NAD^+ is considered a strong regulator of metabolism due to its important role in processes such as oxidation-reduction reactions of glycolysis, the tricarboxylic acid (TCA) cycle, the electron transport chain (ETC), and survival/death signaling. Thus, SIRT activity could be crucial in the regulation of cellular metabolic status, inflammation, oxidative stress, and senescence (Covington and Bajpeyi, 2016; Jęśko et al., 2017).

Another important feature of SIRTs is that they participate in the crosstalk of a wide spectrum of transcription factors, such as forkhead box subgroup O (FOXOs), p53, NFκB, and proteins engaged in DNA repair as DNA-dependent protein kinases (DNA-PKs) (Jęśko et al., 2017). Regarding their cellular localization, their presence in the cytoplasm, nucleus, and mitochondria has been demonstrated. Examples of nuclear proteins are sirtuin 1 (SIRT1), SIRT6, and SIRT7. However, SIRT1 can also be found as a mitochondrial SIRT, such as SIRT3, SIRT4, and SIRT5 (Jęśko et al., 2017). SIRT2 is mainly a cytoplasmic protein, but it can also be translocated into the nucleus. All SIRTs are present in the brain in a highly regulated, spatiotemporal pattern and may influence the course of aging and pathological changes (Jęśko et al., 2017).

In addition, other functions of SIRTs are to control and counter stress and macromolecular damage associated with aging. Additionally, they are bidirectionally linked to insulin and insulin-like growth factor-1 (IGF-1) signaling pathways, which are collectively known as IIS (insulin/IGF signaling) (Jęśko et al., 2017). IGF-1 increases SIRT1 expression via JNK1 (c-Jun N-terminal kinase 1) (Ng and Tang, 2013). In turn, SIRT1 restores the activity of the IGF/insulin receptor target Akt. Nevertheless, IGF-1 synthesis declines in old organisms, which probably causes a significant proportion of the observed age-related disturbances in brain function (Belfiore et al., 2009; Ashpole et al., 2015; Pardo et al., 2016). FOXO suppression is observed in aging-associated stress, as well as in oxidative damage or starvation (Jęśko et al., 2017). Moreover, SIRTs might be involved in the longevity-modulating role of IIS, while SIRT1 seems to be involved in neuronal long-term survival through signaling events in specific CNS regions, which are influenced by FOXO (Jęśko et al., 2017).

Low SIRT1 levels or activity in hippocampi have been reported in aged rats and humans that develop AD (Quintas et al., 2012; Braidy et al., 2015; Wiciński et al., 2020). However, RSV administration (30 mg/kg per day for 8 weeks) in animal models has been shown to restore SIRT1 levels and activity (Chao et al., 2017). The importance of SIRT1 lies in the fact that it can promote neurite outgrowth, enhance neural plasticity in the hippocampal region, reduce tau hyperphosphorylation levels, and exert protective properties against neurodegeneration. Moreover, administration of RSV diminishes the expression of ubiquitin ligase midline-1 (MID1) and increases protein phosphatase 2A (PP2A) activity, which promotes tau dephosphorylation by preventing its accumulation (Cicero et al., 2019; Wiciński et al., 2020). The importance of this pathway has also been described in induced neuropathological AD-like pattern rat models. In rodents, RSV has been shown to improve Aβ peptide clearance, reduce fibrillary amyloid deposition and diminish the burden of plaques and tangles (Wahl et al., 2019). Other studies have reported that RSV decreases neuroinflammation, increases synaptic plasticity, and enhances immunity (Wahl et al., 2019). SIRT1 activation after RSV administration attenuates tau hyperphosphorylation induced by intracerebroventricular injection of streptozotocin, confirming the hippocampal neuron protection (Cicero et al., 2019). Additionally, reactive oxygen species (ROS) attenuation and restoration of glutathione (GSH) levels have been reported. In this way, RSV antioxidant activity occurs via MAPK and nuclear factor erythroid 2-related factor 2 (NRF2). This process results in the expression of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and haem oxygenase. Other studies suggest that RSV also inhibits NFkB and cyclooxygenase-2 (COX-2) expression, high levels of which cause neurodegeneration and mitochondrial dysfunction (Flores et al., 2016). In cultures of neurons, glia, and oligodendrocytes, treatment with 25–100 µmol/L RSV for 12–48 hours increased BDNF and GDNF production in a manner dependent on ERK1/2 and cAMP, mainly in astroglia. Therefore, RSV has been shown to be beneficial in the treatment of aging and AD, preventing hippocampal neurodegeneration and cognitive deficits (Wiciński et al., 2020).

Neurotrophins and pharmacotherapy

Rapamycin, also known as sirolimus, is a macrocyclic lactone that is produced by the bacterium Streptomyces hygroscopicus. In 1994, it was demonstrated that rapamycin bound a specific protein known as the target of rapamycin (mTOR), which is a serine/threonine kinase (Richardson et al., 2015; Garza-Lombó and Gonsebatt, 2016). This signaling pathway plays important roles in several physiological functions, such as cell growth, proliferation, protein synthesis, metabolism, and autophagy, and at the brain level, the mTOR pathway regulates synaptic plasticity, neuronal transmission, axon outgrowth, neuronal size, spine morphology, and gliogenesis. In addition, several lines of evidence demonstrate that loss of homeostasis of the mTOR pathway is involved in the pathophysiology of a variety of neurologic diseases, such as tuberous sclerosis complex, genetic and acquired epilepsy, brain tumors, and neurodegenerative diseases such as AD and PD (Yang et al., 2015; Garza-Lombó and Gonsebatt, 2016; Wu et al., 2018). In most of these diseases, the mTOR pathway is excessively activated (Yang et al., 2015). mTOR signals can be triggered by different stimuli, such as changes in the cellular energy state, while at the brain level, mTOR signals are activated by the transduction of neurotransmitters and neurotrophic signals (Garza-Lombó and Gonsebatt, 2016).

As mentioned above, mTOR participates in various functions at the brain level, such as synaptic plasticity and adult neurogenesis, thus contributing to learning and memory mechanisms (Garza-Lombó and Gonsebatt, 2016). In this regard, it is important to mention that mTOR has two distinct multi-protein complexes, known as mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The first complex is sensitive to rapamycin, while mTORC2 is relatively insensitive to rapamycin. However, some studies suggest that long-term rapamycin treatment might also inhibit mTORC2 (Richardson et al., 2015). Other functions of mTORC1 are ribosome biogenesis, mRNA translation, nutrient metabolism, and autophagy inhibition. In this regard, the mechanism by which mTORC1 regulates protein synthesis is through the phosphorylation and inactivation of a repressor of mRNA translation, eukaryotic initiation factor 4E-binding protein (4E-BP1), and through the phosphorylation and activation of S6 kinase (S6K1). Therefore, 4E-BP1 and S6K1 phosphorylation can be used as an *in vivo* readout of mTOR activity. The importance of understanding the activity of mTORC1 lies in the fact that it is an important key downstream molecule in a signaling cascade beginning with the transduction of neurotransmitter and NT signals (Garza-Lombó and Gonsebatt, 2016). Moreover, the activity of mTORC2 includes Akt activation, and some important roles of Akt include the regulation of numerous cellular mechanisms, such as metabolism, survival, proliferation, and pleiotropic cellular ability (Garza-Lombó and Gonsebatt, 2016).

In a study conducted by Andrade-Talavera et al. (2015), wild-type (control group) and Ts1Cje mice (experimental group) were used. The last group is characterized by carrying a 7.6-Mb segmental trisomy from the distal end of chromosome 16 (MMU16) because this chromosome has conserved synteny to a large portion of human chromosome 21 (HSA21). Therefore, these genetic mouse models have features that mimic human Down's syndrome (DS), such as craniofacial abnormalities and deficits in learning and memory. Therefore, Ts1Cje mice are commonly used as DS models (Shimohata et al., 2017).

Andrade-Talavera et al. (2015) reported that mTOR hyperactivation in Ts1Cje mice provokes abnormally augmented synaptic local translation due to increased BDNF/pro-BDNF levels. In this regard, the mTOR signaling pathway is an attractive candidate to study with respect not only to aging and age-related diseases but also DS (Richardson et al., 2015). In addition, this study demonstrated that an mTOR-dependent form of synaptic plasticity is known as CA3–CA1 BDNF-long-term potentiation (BDNF-LTP) is impaired in Ts1Cje mice and that its restauration requires the activation of TrkB receptors (Andrade-Talavera et al., 2015).

In this sense, Andrade-Talavera et al. (2015) administered rapamycin (10 mg/kg per day for 5 days) by intraperitoneal injection and demonstrated that its application restored the basal synaptic transmission deficit and paired-pulse facilitation (PPF), BDNF-dependent plasticity, long-term memory (LTM) persistence in the Barnes maze and local translation rates in Ts1Cje mice. These findings suggest that rapamycin might be a potential therapeutic alternative for improving cognition in DS. Nevertheless, the authors suggested the need for further research.

Aging is considered the major risk factor for neurodegenerative diseases such as AD due to the slow deterioration of cognitive performance, particularly in learning and memory processes. Therefore, several studies in mouse models have demonstrated that rapamycin reduces amyloid-beta levels and abolishes cognitive deficits. Conversely, chronic treatment with rapamycin enhances learning and memory in young mice and can maintain memory in old mice. Moreover, rapamycin can exert anxiolytic and antidepressant-like effects (Kolosova et al., 2013).

Other drugs of interest are NSAIDs, which are commonly used to reduce inflammation by inhibiting the COX pathway, resulting in a decline in pro-inflammatory prostaglandins (Morris et al., 2020). Studies have been conducted to elucidate how NSAIDs contribute to minimizing neurodegenerative diseases. Initially, in the AD brain, there is a "well-intended" activation of microglia and astrocytes that increases chemokines, ROS, and pro-inflammatory cytokines. This response aims to assist in aggregated peptide clearance; nevertheless, this pro-inflammatory environment may have deleterious effects on neural maturity, synapse formation, and neuronal plasticity (Rojas-Gutierrez et al., 2017; Patel et al., 2018). Patel et al. (2018) conducted a study to demonstrate whether acetylsalicylic acid (ASA) might evoke calcium influx in cultured hippocampal neurons. The above results are supported by the finding that aspirin not only has anti-inflammatory properties but also might contribute to evoking calcium influx through α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl D-aspartate (NMDA)-type glutamate receptors *in vitro*, thus regulating numerous essential processes, such as kinase and phosphatase activities, protein trafficking, structural and functional synaptic plasticity, cell growth, cell survival, and apoptosis (Ayyadevara et al., 2017; Veronese et al., 2017; Patel et al., 2018). Moreover, ASA and other NSAIDs can activate the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα) (Patel et al., 2018; Gaspar et al., 2020; Morris et al., 2020). PPARα is present in the hippocampus and spinal cord, upregulates CREB transcription, and improves hippocampal neuronal plasticity, long-term learning, and memory. Patel et al. demonstrated that after ASA treatment, both AMPA and NMDA mediate calcium currents that stimulate the expression of BDNF mRNA in hippocampal neurons (Patel et al., 2018). In the endothelium, ASA has an antithrombotic effect and is also used to treat vascular dementia (Rizwan et al., 2016).

The administration of NTs is another therapeutic option. The regenerative ability of NTs has been shown in preclinical interventions in models of neurodegenerative diseases. Systemic administration of BDNF, NGF, and NT-3 has demonstrated neurite outgrowth, neurogenesis, and functional recovery in rodent stroke models. However, clinical application as a treatment represents a challenge because NTs have a limited capacity to cross the blood-brain barrier (BBB), limited effects on the peripheral nervous system (PNS), and short half-lives due to their rapid enzymatic inactivation (Houlton et al., 2019; Gavrilova and Alvarez, 2021). Therefore, other options with similar advantages and without disadvantages have been investigated. In recent years, HC-TeTx, a nontoxic fragment of tetanus toxin, has been used as a neurotrophic agent to prevent damage in neurodegenerative models such as amyotrophic lateral sclerosis, ischemia, spinal cord injury, and, more recently, in PD (Mendieta et al., 2016; Getachew et al., 2019). HC-TeTx maintains the capacity of membrane binding, internalization, and retrograde transport with preferential localization in motoneurons, as demonstrated by studies *in vitro* and *in vivo*, until it reaches the CNS (Netzahualcoyotzi and Tapia, 2018; Herrando-Grabulosa et al., 2020). Since HC-TeTx shares the same retrograde transport machinery as NT Trk receptors, it exerts a neuroprotective effect by activating signaling pathways related to NTs, including p21ras/MAPK, PI3K/Akt, and PLC/PKC (Mendieta et al., 2016; Sozbilen et al., 2018; Herrando-Grabulosa et al., 2020; Vazquez-Roque et al., 2021). *In vivo*, HC-TeTx administration has demonstrated motor and cognitive improvements, protecting against neuronal death caused by neurotoxins such as 1-methyl-4-phenylpyridinium (MPP^+), 6-hydroxydopamine (6-OHDA), $A\beta_{25-35}$, and methamphetamine (Moreno-Galarza et al., 2018; Vazquez-Roque et al., 2021). In rats, HC-TeTx treatment increases BDNF levels in the hippocampal and frontal cortex 24 hours after a single administration (Getachew et al., 2019). Additionally, HC-TeTx is used to transfer some NTs into the CNS (Moreno-Galarza et al., 2018; Patricio et al., 2019). Thus, HC-TeTx could be a novel treatment to enhance brain aging and reduce cognitive deterioration.

Likewise, cerebrolysin (CBL) is a small peptide that is studied in stroke models and closed head injury due to its proven potential to reduce neuronal cell death and increase neurogenesis and brain functions such as memory (Kang et al., 2020). Commercial CBL is a neuropeptide preparation obtained from

porcine brain tissue and consisting of low-molecular-weight neuropeptides and free amino acids (Zhang et al., 2017; Flores-Páez et al., 2020). Many studies have been conducted on the remarkable ability of CBL to act as a neurotrophic drug because it increases NGF and BDNF levels and regulates intracellular pathways related to neuronal survival, such as PI3K/Akt and NFkB, promoting synaptogenic and neurogenic pathways (Kang et al., 2020; Gavrilova and Alvarez, 2021). CBL treatment decreases inflammatory factors (TNF-α and IL-1β), oxidative stress, and cytotoxic cascades, and it modulates enzymatic activities related to Aβ, Tau, GSK3β, and cyclin-dependent kinase 5 (CDK5). Moreover, CBL modulates the synaptic transmission of GABA and glutamate and displays cholinotrophic activity (Gavrilova and Alvarez, 2021).

N-PEP-12, derived from cerebrolysin, is a peptide preparation produced enzymatically from purified nerve cell proteins that have been demonstrated to have multiple neurochemical and neurophysiological effects, many of which mimic the effects of NGF. N-PEP-12 has two main differences from CBL. First, it can be administered orally, whereas CBL administration is intravenous. Second, N-PEP-12 is less potent than CBL (Hernández-Hernández et al., 2018; Flores et al., 2020; Balea et al., 2021). In experimental studies using aged rats, N-PEP-12 has been shown to exert neuroprotective and pro-cognitive effects, increasing NTs, synapsis, plasticity biomarkers, the density of dendritic spines, and the total dendritic length in neurons of the PFC (layers 3 and 5) and hippocampi (CA1 and CA3). Thus, N-PEP-12 improves recognition memory and promotes neuronal plasticity (Hernández-Hernández et al., 2018; Balea et al., 2021).

Conclusion

In summary, current *in vivo* and *in vitro* studies and clinical trials provide wide evidence that demonstrates how RSV, NTs such as BDNF, and neurotrophic-like compounds, including HC-TeTx, cerebrolysin, N-PEP-12, and rapamycin, are valuable and up-and-coming therapeutic options to modulate or minimize brain aging and the negative impact of neurodegenerative diseases. However, further information is needed to elucidate all the pathways through which they exert their neuroprotective properties because their impact is favorable not only to cognitive functions but also to the quality of life of both patients and their families. Likewise, nutritional intervention is essential to provide macro- and micronutrients, such as flavonoids and polyphenols, which improve cell mechanisms related to NT, anti-inflammatory, and antioxidant pathways. Additionally, the correct use of NSAIDs, rapamycin, and RSV as a complementary strategy to improve the aging environment is a viable therapeutic option. Together, the options discussed in this review are not mutually exclusive in therapeutic interventions to positively impact healthy aging and prevent or treat neurodegenerative diseases.

Author contributions: *IOF and AD performed the literature searches. AD and ST wrote the first draft of the manuscript. All authors approved the final manuscript.*
Conflicts of interest: *Authors have no conflicts of interest to declare.*

References

Andrade-Talavera Y, Benito I, Casañas JJ, Rodríguez-Moreno A, Montesinos ML (2015) Rapamycin restores BDNF-LTP and the persistence of long-term memory in a model of Down's syndrome. Neurobiol Dis 82:516-525.
Ashpole NM, Sanders JE, Hodges EL, Yan H, Sonntag WE (2015) Growth hormone, insulin-like growth factor-1 and the aging brain. Exp Gerontol 68:76-81.
Ayyadevara S, Balasubramaniam M, Kakraba S, Alla R, Mehta JL, Shmookler Reis RJ (2017) Aspirin-mediated acetylation protects against multiple neurodegenerative pathologies by impeding protein aggregation. Antioxid Redox Signal 27:1383-1396.
Baghel MS, Singh P, Srivas S, Thakur MK (2019) Cognitive changes with aging. Proc Natl Acad Sci India Sect B Biol Sci 89:765-773.
Balea M, Birle C, Costin C, Marton J, Muresanu IA, Jemna N, Popa LL, Slavoaca D, Rosu OV, Stan A, Vacaras V, Strilciuc S, Muresanu DF (2021) Effects of N-Pep-12 dietary supplementation on neurorecovery after ischemic stroke. Neurol Sci 42:2031-2037.
Barrio T, Vidal E, Betancor M, Otero A, Martín-Burriel I, Monzón M, Monleón E, Pumarola M, Badiola JJ, Bolea R (2021) Evidence of p75 neurotrophin receptor involvement in the central nervous system pathogenesis of classical scrapie in sheep and a transgenic mouse model. Int J Mol Sci 22:2714.
Beecher GR (2003) Overview of dietary flavonoids: nomenclature, occurrence and intake. J Nutr 133:3248s-3254s.
Bektas A, Schurman SH, Sen R, Ferrucci L (2018) Aging, inflammation and the environment. Exp Gerontol 105:10-18.
Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R (2009) Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev 30:586-623.
Braidy N, Poljak A, Grant R, Jayasena T, Mansour H, Chan-Ling T, Smythe G, Sachdev P, Guillemin GJ (2015) Differential expression of sirtuins in the aging rat brain. Front Cell Neurosci 9:167.
Caffino L, Mottarlini F, Fumagalli F (2020) Born to protect: leveraging BDNF against cognitive deficit in Alzheimer's disease. CNS Drugs 34:281-297.
Chao SC, Chen YJ, Huang KH, Kuo KL, Yang TH, Huang KY, Wang CC, Tang CH, Yang RS, Liu SH (2017) Induction of sirtuin-1 signaling by resveratrol induces human chondrosarcoma cell apoptosis and exhibits antitumor activity. Sci Rep 7:3180.
Cicero AFG, Ruscica M, Banach M (2019) Resveratrol and cognitive decline: a clinician perspective. Arch Med Sci 15:936-943.
Colardo M, Martella N, Pensabene D, Siteni S, Di Bartolomeo S, Pallottini V, Segatto M (2021) Neurotrophins as key regulators of cell metabolism: implications for cholesterol homeostasis. Int J Mol Sci 22:5692.
Colucci-D'Amato L, Speranza L, Volpicelli F (2020) Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. Int J Mol Sci 21:7777.
Covington JD, Bajpeyi S (2016) The sirtuins: markers of metabolic health. Mol Nutr Food Res 60:79-91.
Cuevas E, Limón D, Pérez-Severiano F, Díaz A, Ortega L, Zenteno E, Guevara J (2009) Antioxidant effects of epicatechin on the hippocampal toxicity caused by amyloid-beta 25-35 in rats. Eur J Pharmacol 616:122-127.
Danka Mohammed CP, Park JS, Nam HG, Kim K (2017) MicroRNAs in brain aging. Mech Ageing Dev 168:3-9.
Devi L, Ohno M (2012) 7,8-dihydroxyflavone, a small-molecule TrkB agonist, reverses memory deficits and BACE1 elevation in a mouse model of Alzheimer's disease. Neuropsychopharmacology 37:434-444.
Devore EE, Kang JH, Breteler MM, Grodstein F (2012) Dietary intakes of berries and flavonoids in relation to cognitive decline. Ann Neurol 72:135-143.
Diaz A, Treviño S, Pulido-Fernandez G, Martínez-Muñoz E, Cervantes N, Espinosa B, Rojas K, Pérez-Severiano F, Montes S, Rubio-Osornio M, Jorge G (2019) Epicatechin reduces spatial memory deficit caused by amyloid-β25¯35 toxicity modifying the heat shock proteins in the CA1 region in the hippocampus of rats. Antioxidants (Basel) 8:113.
Estebsari F, Dastoorpoor M, Khalifehkandi ZR, Nouri A, Mostafaei D, Hosseini M, Esmaeili R, Aghababaeian H (2020) The concept of successful aging: a review article. Curr Aging Sci 13:4-10.
Flores G, Vázquez-Roque RA, Diaz A (2016) Resveratrol effects on neural connectivity during aging. Neural Regen Res 11:1067-1068.
Flores G, Flores-Gómez GD, Díaz A, Penagos-Corzo JC, Iannitti T, Morales-Medina JC (2020) Natural products present neurotrophic properties in neurons of the limbic system in aging rodents. Synapse 75:e22185.
Flores-Páez LA, Pacheco-Rosado J, Alva-Sánchez C, Zamudio SR (2020) Cerebrolysin enhances the expression of the synaptogenic protein LRRTM4 in the hippocampus and improves learning and memory in senescent rats. Behav Pharmacol 31:491-499.
Garza-Lombó C, Gonsebatt ME (2016) Mammalian target of rapamycin: its role in early neural development and in adult and aged brain function. Front Cell Neurosci 10:157.
Gaspar JC, Okine BN, Llorente-Berzal A, Roche M, Finn DP (2020) Pharmacological blockade of PPAR isoforms increases conditioned fear responding in the presence of nociceptive tone. Molecules 25:1007.
Gavrilova SI, Alvarez A (2021) Cerebrolysin in the therapy of mild cognitive impairment and dementia due to Alzheimer's disease: 30 years of clinical use. Med Res Rev 41:2775-2803.
Getachew B, Mendieta L, Csoka AB, Aguilera J, Tizabi Y (2019) Antidepressant effects of C-terminal domain of the heavy chain of tetanus toxin in a rat model of depression. Behav Brain Res 370:111968.
Gite S, Ross RP, Kirke D, Guihéneuf F, Aussant J, Stengel DB, Dinan TG, Cryan JF, Stanton C (2019) Nutraceuticals to promote neuronal plasticity in response to corticosterone-induced stress in human neuroblastoma cells. Nutr Neurosci 22:551-568.
Hernández-Hernández EM, Caporal Hernandez K, Vázquez-Roque RA, Díaz A, de la Cruz F, Florán B, Flores G (2018) The neuropeptide-12 improves recognition memory and neuronal plasticity of the limbic system in old rats. Synapse 72:e22036.
Herrando-Grabulosa M, Casas C, Talbot K, Aguilera J (2020) Neurotrophic properties of C-terminal domain of the heavy chain of tetanus toxin on motor neuron disease. Toxins (Basel) 12:666.
Hetman M, Cavanaugh JE, Kimelman D, Xia Z (2000) Role of glycogen synthase kinase-3beta in neuronal apoptosis induced by trophic withdrawal. J Neurosci 20:2567-2574.
Houlton J, Abumaria N, Hinkley SFR, Clarkson AN (2019) Therapeutic potential of neurotrophins for repair after brain injury: a helping hand from biomaterials. Front Neurosci 13:790.
Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24:677-736.
Huang WYC, Alvarez S, Kondo Y, Lee YK, Chung JK, Lam HYM, Biswas KH, Kuriyan J, Groves JT (2019) A molecular assembly phase transition and kinetic proofreading modulate Ras activation by SOS. Science 363:1098-1103.
Isaev NK, Stelmashook EV, Genrikhs EE (2019) Neurogenesis and brain aging. Rev Neurosci 30:573-580.
Islam F, Mulsant BH, Voineskos AN, Rajji TK (2017) Brain-derived neurotrophic factor expression in individuals with schizophrenia and healthy aging: testing the accelerated aging hypothesis of schizophrenia. Curr Psychiatry Rep 19:36.
Jęśko H, Strosznajder RP (2016) Sirtuins and their interactions with transcription factors and poly(ADP-ribose) polymerases. Folia Neuropathol 54:212-233.
Jęśko H, Wencel P, Strosznajder RP, Strosznajder JB (2017) Sirtuins and their roles in brain aging and neurodegenerative disorders. Neurochem Res 42:876-890.

Jiang L, Su H, Keogh JM, Chen Z, Henning E, Wilkinson P, Goodyer I, Farooqi IS, Rui L (2018) Neural deletion of Sh2b1 results in brain growth retardation and reactive aggression. FASEB J 32:1830-1840.
Jylhävä J, Pedersen NL, Hägg S (2017) Biological age predictors. EBioMedicine 21:29-36.
Kanasi E, Ayilavarapu S, Jones J (2016) The aging population: demographics and the biology of aging. Periodontol 2000 72:13-18.
Kang DH, Choi BY, Lee SH, Kho AR, Jeong JH, Hong DK, Kang BS, Park MK, Song HK, Choi HC, Lim MS, Suh SW (2020) Effects of cerebrolysin on hippocampal neuronal death after pilocarpine-induced seizure. Front Neurosci 14:568813.
Kazim SF, Iqbal K (2016) Neurotrophic factor small-molecule mimetics mediated neuroregeneration and synaptic repair: emerging therapeutic modality for Alzheimer's disease. Mol Neurodegener 11:50.
Khan SS, Singer BD, Vaughan DE (2017) Molecular and physiological manifestations and measurement of aging in humans. Aging Cell 16:624-633.
Kolosova NG, Vitovtov AO, Muraleva NA, Akulov AE, Stefanova NA, Blagosklonny MV (2013) Rapamycin suppresses brain aging in senescence-accelerated OXYS rats. Aging (Albany NY) 5:474-484.
Kozlov EM, Grechko AV, Chegodaev YS, Wu WK, Orekhov AN (2020) Contribution of neurotrophins to the immune system regulation and possible connection to alcohol addiction. Biology (Basel) 9:63.
Kupis W, Pałyga J, Tomal E, Niewiadomska E (2016) The role of sirtuins in cellular homeostasis. J Physiol Biochem 72:371-380.
Li WP, Ma K, Jiang XY, Yang R, Lu PH, Nie BM, Lu Y (2018) Molecular mechanism of panaxydol on promoting axonal growth in PC12 cells. Neural Regen Res 13:1927-1936.
Lima Giacobbo B, Doorduin J, Klein HC, Dierckx R, Bromberg E, de Vries EFJ (2019) Brain-derived neurotrophic factor in brain disorders: focus on neuroinflammation. Mol Neurobiol 56:3295-3312.
Liu X, Chan CB, Jang SW, Pradoldej S, Huang J, He K, Phun LH, France S, Xiao G, Jia Y, Luo HR, Ye K (2010) A synthetic 7,8-dihydroxyflavone derivative promotes neurogenesis and exhibits potent antidepressant effect. J Med Chem 53:8274-8286.
Lo KY, Chin WH, Ng YP, Cheng AW, Cheung ZH, Ip NY (2005) SLAM-associated protein as a potential negative regulator in Trk signaling. J Biol Chem 280:41744-41752.
Mattson MP, Arumugam TV (2018) Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab 27:1176-1199.
Meeusen R (2014) Exercise, nutrition and the brain. Sports Med 44 Suppl 1:S47-56.
Meldolesi J (2018) Neurotrophin Trk receptors: new targets for cancer therapy. Rev Physiol Biochem Pharmacol 174:67-79.
Mendieta L, Granado N, Aguilera J, Tizabi Y, Moratalla R (2016) Fragment C domain of tetanus toxin mitigates methamphetamine neurotoxicity and its motor consequences in mice. Int J Neuropsychopharmacol 19:pyw021.
Molinari C, Morsanuto V, Ruga S, Notte F, Farghali M, Galla R, Uberti F (2020) The role of BDNF on aging-modulation markers. Brain Sci 10:285.
Monserrat Hernández-Hernández E, Serrano-García C, Antonio Vázquez-Roque R, Díaz A, Monroy E, Rodríguez-Moreno A, Florán B, Flores G (2016) Chronic administration of resveratrol prevents morphological changes in prefrontal cortex and hippocampus of aged rats. Synapse 70:206-217.
Moreno-Galarza N, Mendieta L, Palafox-Sánchez V, Herrando-Grabulosa M, Gil C, Limón DI, Aguilera J (2018) Peripheral administration of tetanus toxin Hc fragment prevents MPP(+) toxicity in vivo. Neurotox Res 34:47-61.
Morita M, Ikeshima-Kataoka H, Kreft M, Vardjan N, Zorec R, Noda M (2019) Metabolic plasticity of astrocytes and aging of the brain. Int J Mol Sci 20:941.
Morris R, Armbruster K, Silva J, Widell DJ, Cheng F (2020) The association between the usage of non-steroidal anti-inflammatory drugs and cognitive status: analysis of longitudinal and cross-sectional studies from the global alzheimer's association interactive network and transcriptomic data. Brain Sci 10:961.
Netzahualcoyotzi C, Tapia R (2018) Tetanus toxin C-fragment protects against excitotoxic spinal motoneuron degeneration in vivo. Sci Rep 8:16584.
Ng F, Tang BL (2013) When is Sirt1 activity bad for dying neurons? Front Cell Neurosci 7:186.
Numakawa T, Odaka H, Adachi N (2018) Actions of brain-derived neurotrophin factor in the neurogenesis and neuronal function, and its involvement in the pathophysiology of brain diseases. Int J Mol Sci 19:3650.
Pardo J, Uriarte M, Cónsole GM, Reggiani PC, Outeiro TF, Morel GR, Goya RG (2016) Insulin-like growth factor-I gene therapy increases hippocampal neurogenesis, astrocyte branching and improves spatial memory in female aging rats. Eur J Neurosci 44:2120-2128.
Patel D, Roy A, Kundu M, Jana M, Luan CH, Gonzalez FJ, Pahan K (2018) Aspirin binds to PPARα to stimulate hippocampal plasticity and protect memory. Proc Natl Acad Sci U S A 115:E7408-7417.
Patricio F, Parra I, Martínez I, Pérez-Severiano F, Montes S, Aguilera J, Limón ID, Tizabi Y, Mendieta L (2019) Effectiveness of fragment c domain of tetanus toxin and pramipexole in an animal model of Parkinson's disease. Neurotox Res 35:699-710.
Pawson T, Nash P (2000) Protein-protein interactions define specificity in signal transduction. Genes Dev 14:1027-1047.
Quintas A, de Solís AJ, Díez-Guerra FJ, Carrascosa JM, Bogónez E (2012) Age-associated decrease of SIRT1 expression in rat hippocampus: prevention by late onset caloric restriction. Exp Gerontol 47:198-201.
Richardson A, Galvan V, Lin AL, Oddo S (2015) How longevity research can lead to therapies for Alzheimer's disease: The rapamycin story. Exp Gerontol 68:51-58.
Rizwan S, Idrees A, Ashraf M, Ahmed T (2016) Memory-enhancing effect of aspirin is mediated through opioid system modulation in an AlCl(3)-induced neurotoxicity mouse model. Exp Ther Med 11:1961-1970.
Rojas-Gutierrez E, Muñoz-Arenas G, Treviño S, Espinosa B, Chavez R, Rojas K, Flores G, Díaz A, Guevara J (2017) Alzheimer's disease and metabolic syndrome: A link from oxidative stress and inflammation to neurodegeneration. Synapse 71:e21990.
Sangiovanni E, Brivio P, Dell'Agli M, Calabrese F (2017) Botanicals as modulators of neuroplasticity: focus on BDNF. Neural Plast 2017:5965371.
Shaito A, Posadino AM, Younes N, Hasan H, Halabi S, Alhababi D, Al-Mohannadi A, Abdel-Rahman WM, Eid AH, Nasrallah GK, Pintus G (2020) Potential adverse effects of resveratrol: a literature review. Int J Mol Sci 21:2084.
Shih RH, Wang CY, Yang CM (2015) NF-kappaB signaling pathways in neurological inflammation: a mini review. Front Mol Neurosci 8:77.
Shimohata A, Ishihara K, Hattori S, Miyamoto H, Morishita H, Ornthanalai G, Raveau M, Ebrahim AS, Amano K, Yamada K, Sago H, Akiba S, Mataga N, Murphy NP, Miyakawa T, Yamakawa K (2017) Ts1Cje Down syndrome model mice exhibit environmental stimuli-triggered locomotor hyperactivity and sociability concurrent with increased flux through central dopamine and serotonin metabolism. Exp Neurol 293:1-12.
Sova M, Saso L (2020) Natural sources, pharmacokinetics, biological activities and health benefits of hydroxycinnamic acids and their metabolites. Nutrients 12:2190.
Sozbilen MC, Ozturk M, Kaftan G, Dagci T, Ozyalcin H, Armagan G (2018) Neuroprotective effects of C-terminal domain of tetanus toxin on rat brain against motorneuron damages after experimental spinal cord injury. Spine (Phila Pa 1976) 43:E327-333.
Spencer JP (2008) Food for thought: the role of dietary flavonoids in enhancing human memory, learning and neuro-cognitive performance. Proc Nutr Soc 67:238-252.
Tang BL (2017) Sirtuins as modifiers of Parkinson's disease pathology. J Neurosci Res 95:930-942.
Vauzour D (2012) Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. Oxid Med Cell Longev 2012:914273.
Vazquez-Roque R, Pacheco-Flores M, Penagos-Corzo JC, Flores G, Aguilera J, Treviño S, Guevara J, Diaz A, Venegas B (2021) The C-terminal fragment of the heavy chain of the tetanus toxin (Hc-TeTx) improves motor activity and neuronal morphology in the limbic system of aged mice. Synapse 75:e22193.
Veronese N, Stubbs B, Maggi S, Thompson T, Schofield P, Muller C, Tseng PT, Lin PY, Carvalho AF, Solmi M (2017) Low-dose aspirin use and cognitive function in older age: a systematic review and meta-analysis. J Am Geriatr Soc 65:1763-1768.
Wahl D, Solon-Biet SM, Cogger VC, Fontana L, Simpson SJ, Le Couteur DG, Ribeiro RV (2019) Aging, lifestyle and dementia. Neurobiol Dis 130:104481.
Wątroba M, Szukiewicz D (2016) The role of sirtuins in aging and age-related diseases. Adv Med Sci 61:52-62.
Weiskirchen S, Weiskirchen R (2016) Resveratrol: how much wine do you have to drink to stay healthy? Adv Nutr 7:706-718.
Wiciński M, Domanowska A, Wódkiewicz E, Malinowski B (2020) Neuroprotective properties of resveratrol and its derivatives-influence on potential mechanisms leading to the development of Alzheimer's disease. Int J Mol Sci 21:2749.
Williams RJ, Spencer JP (2012) Flavonoids, cognition, and dementia: actions, mechanisms, and potential therapeutic utility for Alzheimer disease. Free Radic Biol Med 52:35-45.
Wills MK, Keyvani Chahi A, Lau HR, Tilak M, Guild BD, New LA, Lu P, Jacquet K, Meakin SO, Bisson N, Jones N (2017) Signaling adaptor ShcD suppresses extracellular signal-regulated kinase (Erk) phosphorylation distal to the Ret and Trk neurotrophic receptors. J Biol Chem 292:5748-5759.
Wu M, Zhang H, Kai J, Zhu F, Dong J, Xu Z, Wong M, Zeng LH (2018) Rapamycin prevents cerebral stroke by modulating apoptosis and autophagy in penumbra in rats. Ann Clin Transl Neurol 5:138-146.
Xu SL, Bi CW, Choi RC, Zhu KY, Miernisha A, Dong TT, Tsim KW (2013a) Flavonoids induce the synthesis and secretion of neurotrophic factors in cultured rat astrocytes: a signaling response mediated by estrogen receptor. Evid Based Complement Alternat Med 2013:127075.
Xu SL, Zhu KY, Bi CW, Choi RC, Miernisha A, Yan AL, Maiwulanjiang M, Men SW, Dong TT, Tsim KW (2013b) Flavonoids induce the expression of synaptic proteins, synaptotagmin, and postsynaptic density protein-95 in cultured rat cortical neuron. Planta Med 79:1710-1714.
Yang X, Hei C, Liu P, Song Y, Thomas T, Tshimanga S, Wang F, Niu J, Sun T, Li PA (2015) Inhibition of mTOR pathway by rapamycin reduces brain damage in rats subjected to transient forebrain ischemia. Int J Biol Sci 11:1424-1435.
Zeng Y, Lv F, Li L, Yu H, Dong M, Fu Q (2012) 7,8-Dihydroxyflavone rescues spatial memory and synaptic plasticity in cognitively impaired aged rats. J Neurochem 122:800-811.
Zhang X, Meng X, Chen Y, Leng SX, Zhang H (2017) The biology of aging and cancer: frailty, inflammation, and immunity. Cancer J 23:201-205.
Zhao S, Gao X, Dong W, Chen J (2016) The role of 7,8-dihydroxyflavone in preventing dendrite degeneration in cortex after moderate traumatic brain injury. Mol Neurobiol 53:1884-1895.
Zhong J (2016) RAS and downstream RAF-MEK and PI3K-AKT signaling in neuronal development, function and dysfunction. Biol Chem 397:215-222.

C-Editor: Zhao M; S-Editor: Li CH; L-Editors: Li CH, Song LP; T-Editor: Jia Y