**Neurotrophic fragments as therapeutic alternatives to ameliorate brain aging**

Itzel Ortiz Flores¹, Samuel Treviño², Alfonso Díaz³,⁴  

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

**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 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 estimated 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 (Estebari 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, hemato poetic 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., 2018; Bektah 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 due to 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 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...
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. NGF and its corresponding receptors, TrkA and p75NT-R, are crucial for normal cranial neural crest development and peripheral nerve regeneration (Huang and Reichardt, 2001). NGF is also involved in the axonal branching of sensory neuron fibers. The chemoattractant activities of NGF and BDNF are closely related to their role in neurotrophic signaling (Shih et al., 2015). NGF is also involved in the activation of Ras, a small GTPase that plays a role in cell proliferation and survival (Huang and Reichardt, 2001).

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., 2021). Caffino et al. (2019) demonstrated that BDNF may also act in both autocrine and paracrine manners to support dorsal root ganglion (DRG) sensory neurons. Moreover, NTs may be able to be transported anterogradely and act in an axonotrophic manner (Caffino et al., 2019). Therefore, NTs may have considerable potential in the treatment of conditions such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis (ALS), as well as psychiatric disorders such as depression and schizophrenia. In this sense, NTs may be considered potential therapeutic agents (Mohammed et al., 2017). Some therapeutic options, shown in Figure 1, are resveratrol (RSV), nonsteroidal anti-inflammatory drugs (NSAIDs), rapamycin, and NT-3, which bind to the BDNF receptor (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; NSADs: non-steroidal anti-inflammatory drugs; PFC: prefrontal cortex.
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 neuroinflammation can promote NTs to exert their neuroprotective actions through the activation 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. CNTF is part of the TNF family of cytokines, and its expression is based on its pivotal role in adult hippocampus 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 P2O1, a neurogenic and neurotrophic molecule that catalyzes the synthesis of the pro-NT transforming growth factor beta 1 (TGF-β), 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 P2O1 through inhibition of the leukemia inhibitory factor (LIF) signal transduction. In particular, it has been shown that P2O1 activation and the co-expression of optogenetic Trk receptors can rescue cognitive aging by enhancing neurogenesis via increased BDNF expression and by decreasing tau levels in aged Fisher rats (Kazim and Iqbal, 2016).

Conversely, p53 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 p53 and pro-NTs activates signaling pathways and promotes apoptotic events (Kozlov et al., 2020; Barrio et al., 2021).

Treatments to Positively Modulate Neurotrophins

Neurotrophins and nutrition
Nutritional factors influence 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 animal models can influence neurogenesis 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 from endoplasmic reticulum (ER) stores, which subsequently activates Ca2+-calmodulin-dependent protein kinases (Kozlov et al., 2016). This is ameliorative 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).

The first flavonoid described as a receptor agonist was 7,8-dihydroxyflavone (7,8-DHF). Furthermore, 7,8-DHF also showed neuroprotective 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 RSV can be isolated and purified from grapes, apples, raspberries, blueberries, plums, peanuts, and products derived therefore, 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. It is 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 FPC and regions CA1 and CA3 of the dorsal hippocampus (DH) in all resveratrol-treated rats (Monserrat Hernández-Hernández et al., 2016).

Another important feature of RSV 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-dependent protein kinase proteins (DNA-PKs) (Jęśko et al., 2017). Resveratrol’s cellular localization, their presence in the cytoplasm, nucleus, and mitochondria has been demonstrated. Examples of nuclear proteins are sirtuin 1 (SIRT1), SIRT6, and SIRT7, which can be found in the nucleus and cytoplasm of cells. 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 substrate-level phosphorylation. Moreover, this activity could be associated with the regulation of cellular metabolic status, inflammation, oxidative stress, and senescence (Covington and Bajpeyi, 2016; Ježko 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-dependent protein kinase proteins (DNA-PKs) (Jęśko et al., 2017). Resveratrol’s cellular localization, their presence in the cytoplasm, nucleus, and mitochondria has been demonstrated. Examples of nuclear proteins are sirtuin 1 (SIRT1), SIRT6, and SIRT7, which can be found in the nucleus and cytoplasm of cells. 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 substrate-level phosphorylation. Moreover, this activity could be associated with the regulation of cellular metabolic status, inflammation, oxidative stress, and senescence (Covington and Bajpeyi, 2016; Ježko 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 SIRT expression via JNK1 (c-Jun N-terminal kinase 1) and AMPK. In turn, SIRT1 represses the activity of the IGF/insulin receptor targetAkt. Nevertheless, IGF-1 synthesis declines in old organisms, which probably causes a significant proportion of the observed age-related impairments in cognitive function (Belfiore et al., 2009; Ashpole et al., 2015; Pardo et al., 2016). FOXO suppression-induced aging-associated stress, as well as in oxidative damage or starvation (Ježko et al., 2017). Moreover, SIRTs might be involved in the longevity-modulating role of IIS, as 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).

The first flavonoid described as a receptor agonist was 7,8-dihydroxyflavone (7,8-DHF). Furthermore, 7,8-DHF also showed neuroprotective 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 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. It is 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 FPC and regions CA1 and CA3 of the dorsal hippocampus (DH) in all resveratrol-treated rats (Monserrat Hernández-Hernández et al., 2016).

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-dependent protein kinase proteins (DNA-PKs) (Jęśko et al., 2017). Resveratrol’s cellular localization, their presence in the cytoplasm, nucleus, and mitochondria has been demonstrated. Examples of nuclear proteins are sirtuin 1 (SIRT1), SIRT6, and SIRT7, which can be found in the nucleus and cytoplasm of cells. 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 substrate-level phosphorylation. Moreover, this activity could be associated with the regulation of cellular metabolic status, inflammation, oxidative stress, and senescence (Covington and Bajpeyi, 2016; Ježko 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; Brady et al., 2015; Wicirkshi et al., 2020). However, RSV administration (30 mg/kg per day for 8 weeks) in 6-month-old transgenic mice (known to show reduced levels of AD-related proteins) induced 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; Wicirkshi et al., 2020). This finding has been described in mouse models as a neuroprotective AD-like pattern rat models. In rodents, RSV has been show 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 inflammation and improves synaptic plasticity, and enhances immunity (Wahl et al., 2019). SIRT1 activation after RSV administration attenuates tau hyperphosphorylation induced by intracerebroventricular injection of lipopolysaccharide, confirming the hippocampal neuroprotective effect (Wahl et al., 2019). Additional studies have shown that ROS attenuates and neurodegeneration therapy (NSAIDs) 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 anti-inflammatory 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 mediators (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 pathways regulate cell metabolism, 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 neurological diseases, such as tuberous sclerosis complex, genetic and acquired epilepsy, brain tumors, and, more recently, Alzheimer’s disease (AD). This signaling pathway regulates synaptic plasticity, neuronal transmission, axon outgrowth, 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.
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 neuroprotective drug, and it increases NGF and BDNF levels and regulates intracellular pathways related to neuronal survival, such as PI3K/Akt and NFκB, promoting synaptic and neurogenic pathways (Kang et al., 2020; Gavrilova and Alvarez, 2021). CBL treatment decreases inflammatory factors (TNF-α and IL-1β) in the 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, synaptic 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, cerebruslin, 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 few balancing strategies is 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.

Open access statement: This is an open access journal, and authors have no conflicts of interest to declare. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

References

Andrade-Talaver a Y, Benito I, Casas a J, Rodriguez-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-I and the aging brain. Exp Gerontol 68:76-81.
Ayaydeva S, Balasubramani am M, Kabkara S, All a R, Mehta JS, Shoemaker Rei SJ (2017) Aspirin-mediated acetylation protects against multiple neurodegenerative pathologies by inhibiting protein aggregation. Antioxid Redox Signal 27:1383-1396.
Baghel MS, Singh P, Sivas V, Thakur MK (2019) Cognitive changes with aging. Proc Natl Acad Sci India Sect B 69:765-773.
Balea M, Biricel C, Costic M, Marton J, Muresanu IA, Jem na N, Popa LL, Slovaca D, Rosu OV, Stan A, Vacar a s V, Stilliciu s, Muresanu DF (2021) Effects of N-Pep-12 dietary supplementation on neuro recovery after ischemic stroke. Neuro Sci 42:2031-2037.
Barrio T, Vidal D, Betoret A, Martínez-Burriel I, Monzón M, Monleón E, Pumarola A, Otero A, Barrio T, Vidal E, Betancor M, Otero A, Martín-Burriel I, Monzón M, Monleón E, Pumarola A, Otero A (2020) 11C) 11C) RDP (11C) RDP (11C) RDP (11C) RDP (11C) of the D2 receptor in the striatum and substantia nigra of C57BL/6J mice. J Cereb Blood Flow Metab 30:573-580.
