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s PROMISING ACTION OF 7-CHLORO-4-PHENYLSELANYL QUINOLINE (4-PSQ) FOR DEPRESSION AND ALZHEIMER'S DISEASE

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Abstract: Alzheimer's disease (AD) is the leading and most common cause of senile dementia, accounting for 50-75% of diagnosed cases. In developed countries, AD is the fourth leading cause of death, second only to cardiovascular disease, cancer and stroke. Oxidative stress plays a central role in the initiation and progression of AD due to its high rate of oxygen utilization; high content of polyunsaturated lipids that are susceptible to lipid peroxidation; and poor concentrations of antioxidants. Histologically, the presence of hyperphosphorylated tau protein, amyloid β peptide aggregates, reduction of synaptic density, activation of glial cells and neuronal loss, including nervous cells of the cholinergic system, in which neurotransmission is related to learning processes and consolidation of memory, is evidenced. memory. Studies suggest that amyloid beta plaques cause cognitive damage by interrupting synaptic function leading to an underregulation of these networks and compromising anatomically and functionally interconnected brain areas. Depression is an important comorbidity of AD, being the most frequent neuropsychiatric complication in this disease, affecting approximately 50% of patients. Heterocyclic compounds have shown importance in the construction of new drugs, among which quinoline and its derivatives stand out through different mechanisms of action, such as inhibitors of cell cycle growth and apoptosis. Given the above, the present study aimed to investigate the involvement of cell signaling molecules and the cholinergic and monoaminergic systems in an experimental model of depression and AD using the amnesia method induced by the injection of scopolamine bromide - a non-selective cholinergic antagonist of muscarinic receptors. Therefore, the therapeutic activity of a quinoline derivative, 4-PSQ, was evaluated in oxidative stress parameters such as oxygen levels (ERO); thiobarbituric acid reactive substances (TBARS); activity of catalase enzymes (CAT); superoxide dismutase (SOD) as well as the activity of the enzyme glutathione peroxidase (GPx) in the cerebral cortex and hippocampus. Based on evidence, we conclude that the effects of 4-PSQ may be associated with attenuation of HPA axis activation, attenuation of changes in the monoaminergic system, modulation of oxidative stress, restoration of AChE activity and reduction of neuroinflammation.
Keywords: AD. Depression. Monoaminergic. Quinoline. 4-PSQ.

INTRODUCTION

Alzheimer's disease (AD) is the most common type of neurodegenerative dementia characterized by the presence of senile plaques and neurofibrillary tangles. The main neuropathological characteristics include the extracellular deposit of β-amyloid peptide (βA) plaques in the cerebral cortical regions, accompanied by the presence of intracellular neurofibrillary tangles, composed of hyperphosphorylated tau protein. βA accumulation leads to microglia activation and consequent production and release of cytokines with activation of glial cells producing inflammatory mediators such as nitric oxide, interleukins and nuclear transcription factor kappa B that are related to the neuroinflammatory process (ALZHEIMERS ASSOCIATION. 2021).

Amyloid beta derives from the cleavage of amyloid precursor protein (APP), a transmembrane glycoprotein present in neural membranes, which is believed to play an important role in neuroplasticity and protection of the brain against infections. The cleavage of PPA can be done by two metabolic pathways and the natural process does not generate beta amyloid, being done by the enzyme α-secretase. Its product is later

cleaved by γ-secretase, generating a small and soluble peptide with biological function. This pathway is called non-amyloidogenic. In the amyloidogenic pathway, APP is cleaved by β-secretase and then by γ-secretase, originating a peptide with a sequence of 40 or 42 amino acids, with characteristics of insolubility and predisposition to aggregate, causing dysregulation of activity of kinases and phosphatases, hyperphosphorylating the Tau protein (SMITH, 1999).

It has been shown that in patients with depression/AD, there is a deregulation of the hypothalamic-pituitary-adrenal (HPA) axis, promoting an increase in glucocorticoid levels. Other common neuronal pathways in depression/AD include dysfunction in the monoaminergic system, oxidative stress, neuroinflammatory processes and changes in neuroplasticity (MAES et al. 2011).

Furthermore, dysregulation occurs in glutamate, which acts on excitatory ionotropic receptors of the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type. Hyperactivation of glutamate receptors leads to excessive calcium influx. Generally, calcium levels in the cell are regulated through an intimate collaboration between various cellular components that coordinate the mechanisms of entry, sequestration and removal of Ca2+. Upon prolonged exposure to glutamate, there is an overstimulation of NMDA receptors and continuous opening of the coupled ion channel, due to the displacement of the magnesium responsible for blocking the channel. Consequently, calcium influx exceeds normal levels, saturation of the buffering capacity of the mitochondria occurs and triggers the activation of various subcellular degradation processes harmful to neuronal cells, excitotoxicity and apoptosis. In addition to glutamate, there are changes including gamma-aminobutyric acid decarboxylase (GABA), a significant decrease in the enzyme tyrosine hydroxylase (YAMANOTO, 2022).

Molecules with a quinoline nucleus represent a fundamental class of heterocyclic compounds due to their therapeutic potential. Quinolin-based bioactive compounds are obtained from a variety of natural products and others by chemical synthesis processes or via biotechnology.

Quinolinic acid (QA) is an endogenous metabolite of tryptophan known as 2,3-dicarboxylic acid. The chyrunenin route is the main route of tryptophan metabolism, and occurs in the liver with the main function of nicotinamide adenine dinucleotide (NAD) biosynthesis. The effects of 4-PSQ include its antioxidant action as well as the ability to modulate serotonergic, glutamatergic and cholinergic systems. In addition, this compound has already demonstrated modulation of synaptic plasticity through increased levels of neural cell adhesion molecules in addition to reducing glutamate uptake in the brain of mice (LUCHESE et al., 2020).

Quinoline derivatives boosted the investigation of the potential of this class in the control of several pathological processes in AD, in the modulation of amyloid beta protein aggregation, in the inhibition of the expression and action of presenilins and other proteins involved in the production of Aβ, such as beta secretase, inhibition of NMDA binding to glycine receptors, antagonization of 5-HT receptors, neutralization of toxicity mediated by soluble oligomeric forms of Aβ, as well as inhibition of essential kinases in the process of tau hyperphosphorylation (PALTIAN et al. 2020).

In view of the aforementioned considerations, the present study aimed to investigate the involvement of cell signaling molecules and the cholinergic and monoaminergic systems induced by

acute restraint stress (ARS) in mice in an experimental model of depression and AD. Therefore, the therapeutic activity of a quinoline derivative, 4-PSQ, was evaluated in oxidative stress parameters such as oxygen levels (ERO); thiobarbituric acid reactive substances (TBARS); activity of catalase enzymes (CAT); superoxide dismutase (SOD) as well as the activity of the enzyme glutathione peroxidase (GPx) in the cerebral cortex and hippocampus.

METHODOLOGY

In the present experimental model of depression and AD, amnesia induced by the injection of scopolamine bromide - a non-selective cholinergic antagonist of muscarinic receptors - was used to investigate and analyze the effect of 4-PSQ.

4-PSQ was prepared and characterized at the laboratory of oxidative stress and antioxidants at the ''Universidade Luteran do Brasil" (Ulbra) and at the laboratory of experimental hepatology at the ''Universidade Federal do Rio Grande do Sul" (UFRGS). The ARS protocol was performed for 180 min. After restriction, stressed animals were kept under standard environmental conditions with free access to food and water for 20 minutes. Then, the animals in groups I received 4-PSQ (15 mg/kg), group II received memantine (positive control, 10 mg/kg). After 30 min of treatments, the animals were submitted to behavioral tasks: open field test, tail suspension test and Y-maze task. After evaluating the behavior, the mice were anesthetized before blood collection by cardiac puncture. Then, the animals were euthanized.

Plasma was used to determine corticosterone levels. The prefrontal cortex and hippocampus were removed and immediately homogenized in 50 mM pH 7.3 to determine reactive species (RS) levels, thiobarbituric acid reactive species (TBARS) levels, and superoxide dismutase (SOD) activity.), glutathione peroxidase (GPx) and glutathione reductase (GR).

For the determination of acetylcholinesterase (AChE) activity, mouse brain structures were homogenized in sucrose buffer and centrifuged at 900×g at 4°C for 8 min. Furthermore, the prefrontal cortex and hippocampus were separated for extraction and expression of NF-kB, IL-1β, IL-18, IL-33, PI3K and AKT2. For this, the samples were immediately processed and properly stored (-80 °C) until the expression levels were evaluated.

MAO enzymatic activity was determined with an aliquot of MP from each sample that was incubated at 37°C for 5 min in a medium containing buffer solution and specific inhibitors. Samples were incubated at 37°C for 30 minutes. After incubation, the reaction was stopped by adding 10% trichloroacetic acid (TCA). The fluorescence intensity was detected spectrofluorimetrically with excitation at 315 nm and emission at 380 nm. The concentration of 4-hydroxyquinoline (4-OH quinoline) was estimated from the 4-OH quinoline fluorescence curve. MAO activity was expressed as nmol 4-OH quinoline/mg protein/min.

Samples from the prefrontal cortex and hippocampus were collected to determine RS and TBARS levels. These measurements were performed to evaluate the effect of 4-PSQ on the modulation of cerebral oxidative stress. RS levels were determined using the spectrofluorimetric method (LOETCHUTINAT et al., 2005). Fluorescence intensity was recorded at 520 nm (with 480 nm excitation).

Absorbance was measured at 532 nm in a spectrophotometer. TBARS content was used as a marker of lipid peroxidation. SOD activity was analyzed

spectrophotometrically. This method is based on SOD's ability to inhibit epinephrine autooxidation. GPx activity was evaluated spectrophotometrically which involves monitoring the dismutation of H_2O_2 at 340 nm and the enzymatic reaction was initiated by the addition of H_2O_2.

RESULT AND DISCUSSION

A reduction in acetylcholine levels and choline acetyltransferase (ChAT) activity was shown to significantly alter cholinergic neurotransmission, contributing to cognitive dysfunction. In addition, oxidative stress increases the enzymatic activity of monoamine oxidase isoform B (MAO-B), neuroinflammation, as well as hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, promoting an increase in glucocorticoid levels in patients with depression and DA.

Musafa et al (2021), evaluated the effects of 5-HT depletion on spatial memory and learning in rats treated with desipramine, followed by intraventricular injection of a selective 5-HT neurotoxin, 5,7-hydroxytryptamine (5,7-DHT), which induces 5-HT depletion. The results point to an intense and permanent decrease in 5-HT levels in the hippocampus and in the prefrontal region, which are areas related to spatial memory, short/medium and long term memory. Furthermore, 5-HT binds to serotonergic receptors projecting from the brainstem to all areas of the brain. Thus, the serotonergic pathway acts in the frontal cortex, a region associated with attention, cognition and motor functions and which has innervation with the hippocampus, a fundamental area for memory and learning.

The levels and functions of several neurotransmitters are influenced by the stock of their food precursors, and can influence mood and behavior, with the main example of tryptophan intake and cerebral serotonergic action. L-Tryptophan nanoparticles may be an alternative to increase the bioavailability, transport and incorporation viability of hydrophobic substances by altering the levels of monoamines in the brain. The potentiation of synapses by 5-HT in the CA1 and CA3 areas of the hippocampus are fundamental for cognitive tasks, recognition, spatial memory and consolidation of long-term memory. Furthermore, drug-induced increased 5-HT levels may modulate neuronal plasticity and excitability (CAI 2013; REMONDES, 2004).

Selenium has a protective action against cellular damage mediated by oxidative stress through the mechanisms of action of selenoproteins such as glutathione peroxidase (GSHPx) and selenoprotein, by inhibiting the formation of reactive oxygen and nitrogen species. Organic selenium compounds such as Ebselen (Ebs) and diphenyl diselenide (DPDS) with antioxidant activity. Therefore, analogous molecules to Ebs and DPDS have been produced through the insertion of functional groups in the chemical structure of these compounds in an attempt to produce new drugs. Among the most used functional groups are chlorine and fluorine ions, as well as methyl and ethyl groups. Thus, the insertion of methyl and methoxy functional groups in phenyl linked to selenium increases the ability to mimic Glutathione Peroxidase (GPx) (BRAGA, 2013).

The replacement of hydrogen atoms present in the chemical structure of diaryl diselenides by methoxy groups increased the activity of the GPx enzyme, precisely by increasing the characteristics of the molecules. The insertion of amine and amide groups in the chemical structure of organic selenium compounds enables an increase in GPx activity by promoting a reduction in the interaction between the selenium atom with nitrogen or oxygen (BHABAK & MUGESH, 2012).

Barth et al. (2021) demonstrated that treatment with 4-PSQ restored plasma selenium contributing to the restoration of damage caused by aging. Therefore, it is suggested that 4-PSQ is able to reach the blood stream after its absorption. In this regard, considering that complex disorders, such as depression and memory impairment, are more likely to be attenuated through simultaneous modulation of multiple targets, the versatility of 4-PSQ led us to consider its use as a possible therapeutic strategy for depression comorbidities. and memory impairment. In view of this, the ARS was proposed as an accepted stress-inducing experimental model to investigate behavior as well as its relationship with memory impairment in rodents.

ARS is a validated model for causing hyperactivation of the HPA axis, with a notable increase in plasma corticosterone levels. The action of these glucocorticoids occurs primarily through their binding to their receptors in the brain, the glucocorticoid receptor and the mineralocorticoid receptor to supplementally drive the regular activity of the HPA axis (HARRIS et al. 2013). In this context, ARS caused depressive-like behavior and memory impairment, demonstrated by the reduction of spontaneous alternations in the Y-maze task and reduced exploratory preference for new object (NIKSIYAR et al., 2021).

On the other hand, glucocorticoid receptors are activated after stress is established, thus leading to a reduction in HPA axis activity. It is important to emphasize that our results demonstrated that the treatment with 4-PSQ was able to attenuate the activation of the HPA axis, reducing the plasmatic levels of corticosterone.

Dysregulation of the HPA axis is known to cause cortisol to bind to its glucocorticoid receptors and mineralocorticoid receptors in the limbic system, hippocampus and prefrontal cortex which have a high density of these receptors. Consequently, neural atrophy occurs in these regions, resulting in changes and memory dysfunction, symptoms that are found in patients with depression and AD (COLCIAGO et al. 2015).

Wolf (2008) reported that cortisol responses in humans in the presence of psychosocial stressors triggered impairments on tasks that required participants to remember previously learned information. Thus, our data confirmed that HPA axis hyperactivation contributed to the development of depressive-like behavior and memory impairment observed in rats submitted to ARS.

MAO is the enzyme of the monoaminergic system responsible for regulating the levels of neurotransmitters, such as serotonin (5-HT), norepinephrine, and/or dopamine, through its oxidative deamination, reducing the availability of these monoamines in the synapses. This enzyme exists in two enzyme isoforms, MAO-A and MAO-B, which differ in their substrate and inhibitor specificity and in their tissue distribution. MAO-A isoform selective inhibitors act as potent antidepressants, while MAO-B inhibitors are useful in neurodegenerative disorders such as AD (SAURA et al. 1994).

In the present study, our results demonstrated that ARS increased RS production and favored lipid peroxidation, as evidenced by increased TBARS levels in the prefrontal cortex and hippocampus of mice. Furthermore, we identified an increase in SOD, GPx and GR activities in the brain structures of mice subjected to ARS. The increase in SR levels induced by stress favors the process of lipid peroxidation and changes in antioxidant defenses in limbic regions, causing impairment of the antioxidant status in the brain. Furthermore, SOD, GPx,

and GR are the main antioxidant defenses responsible for redox balance and an increase in these enzymatic activities is an attempt to eliminate the RS generated by ARS in brain structures. Thus, some experimental models of depression/AD demonstrated results similar to those found in our study, in which ARS caused an increase in lipid peroxidation and SOD, GPX and GR activities in the prefrontal cortex and hippocampus of rodents. Therefore, based on evidence, we believe that the effects of stress-induced HPA axis hyperactivation may be related to the process of oxidative stress, contributing to depressive behavior.

Dysregulation of pro-inflammatory cytokines favors oxidative imbalance and consequently causes an increase in RS production, which can synergistically induce tissue injury, neuroinflammation, neurodegeneration, and neuronal apoptosis. In parallel, another key component in these responses is the action of pro-inflammatory cytokines in the hypothalamus, promoting an exacerbated increase in the release of cortisol, and consequently triggering hyperactivity of the HPA axis. In view of these mechanisms, previous reports have shown that the activation of NF-κB, as well as the increase in pro-inflammatory cytokines, is related to the development of depressive behavior with impaired memory in rodents (BAKUNINA et al. 2015; HEPPNER et al. 2015) .

In this context, hyperactivation of the HPA axis and increased oxidative stress were essential for the translocation of the Nuclear Factor Kappa Beta (nuclear NF-κB), promoting the transcription of pro-inflammatory genes and, thus, initiating a neuroinflammatory response. However, an important finding of our study was that 4-PSQ reversed the increase in neuroinflammatory parameters in the prefrontal cortex and upper hippocampus compared to the control group.

The effect of 4-PSQ on modulating neuroinflammation is associated with attenuation of the HPA axis and reduction of oxidative stress in the prefrontal cortex and hippocampus of stressed mice. Thus, 4-PSQ was able to attenuate neuroinflammation and oxidative stress, as well as activation of the HPA axis, reducing symptoms and memory impairment caused by stress.

Notably, to adapt to stressful events, intracellular signal transduction pathways are activated to promote neuronal survival and neuroplasticity (BEGNI et al. 2017).

Among these signaling pathways, PI3K/AKT stands out, which is involved in synaptic plasticity, learning and memory, and can modulate the release of neurotransmitters, cell viability, apoptosis and postsynaptic responses. Thus, the results suggest an involvement of the PI3K/AKT2 signaling pathway in the effect of 4-PSQ, considering that the compound was able to normalize PI3K and AKT in the prefrontal cortex, contributing to the reestablishment of neuroplasticity processes and changes behavioral (LI et al. 2015).

In the present study, 7-chloro-4-(phenylselanyl) quinoline (4-PSQ), a quinoline derivative containing an organoselenium group, increased AChE activity, neurogenesis and neuroplasticity as well as showed antioxidant effect. Thus, we can suggest that one of the possible justifications for the neuroprotective effect of 4-PSQ is its ability to modulate oxidative stress and the regulation of synaptic plasticity in the PI3K/AKT pathway. Our results demonstrated that treatment with 4-PSQ decreased AChE activity in the prefrontal cortex and hippocampus of mice, attenuating ARS-induced memory impairment.

4-PSQ exhibited an antidepressant effect and attenuated ARS-induced memory impairment in mice Based on the evidence, we believe that these effects are associated,

at least in part, with its ability to attenuate HPA axis activation, attenuate changes in in the monoaminergic system, modulate oxidative stress, restore neuroplasticity, modulate the cholinergic system and attenuate neuroinflammation. Therefore, the results of the present study suggest 4-PSQ as a promising alternative for the treatment of the depression/AD dyad.

FINAL CONSIDERATIONS

The activity of the MAO isoform is associated with an imbalance in the monoaminergic system, with a reduction in neurotransmitters; and based on the evidence, we believe this contributed to the depressive-like behavior and memory impairment seen in our study. Thus, dual inhibition of MAO-A and MAO-B may be valuable for the treatment of depression and AD.

Given the etiology of depression and AD, multifunctional molecules with two or more complementary biological activities could represent an important advance in the treatment of depression and AD. Thus, it is concluded that 7-chloro-4-(phenylselanyl) quinoline (4-PSQ) has an effect on AChE activity, neurogenesis, neuroplasticity and antioxidant action. Thus, one of the main advantages of 4-PSQ is the possibility of a single drug for the treatment of depression and AD.

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