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ORIGINAL RESEARCH

Approaches from Resveratrol Activities on Central Nervous System Inflammation

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ABSTRACT
Neuroinflammation is a common protective mechanism in homeostasis breakdown processes on the central nervous system. The prolongation of this process is responsible for the primary immune response of many neurodegenerative diseases. Understand these mechanisms has brought more effective alternatives to the scientific literature, on development of more effective pharmacological interventions. However, allopathic means of intervention to inflammation are sometimes insufficient to promote a good prognosis and reversal of the inflammatory process. Resveratrol is a polyphenol from the stilbene class, that has shown anti-inflammatory characteristics in several disease study methods, mainly in the ability to generate neuroprotection in neuroinflammatory damage models, reducing the production of pro-inflammatory cytokines and allowing survival, as well. Neuronal regeneration activity also as saw mainly through neurotrophin modulation and antioxidant activity. Resveratrol has shown promise in reversing neuronal death, an important activity in the face of the special needs for new drugs, capable enough to promoting better survival for patients with neurodegenerative diseases. In this review, it's possible saw that Resveratrol has significant characteristics for future use in the treatment of neurodegenerative diseases.

KEY WORDS: *Resveratrol, neuroprotection, neuroinflammation*

INTRODUCTION

The Central Nervous System (CNS) at the cellular level is generally composed of neurons, and Glia cells, being one of the organ systems of the human body that has the highest cell diversity (Gomes et al. 2013). Neurons are post-mitotic, bipolar cells, susceptible to toxic protein aggregates (Hajieva 2017). CNS cells are considered vulnerable to oxidative damage due to the high concentration of readily oxidisable substrates (Łuczaj et al. 2014). The accumulation of strongly oxidized and aggregation-prone neuronal proteins play an important role in the development of neurodegenerative diseases, such as Parkison's disease and Alzheimer's disease (Hajieva 2017). Alzheimer's is the most common neurodegenerative disease caused by brain atrophy through the formation of senile plaques, amyloidal fibril deposits and TAU

protein accumulation that causes neuronal loss and consequently glial activation (Sereniki et al. 2008), and inflammation (Association 2013). The second major neurodegenerative disorder is Parkinson's disease, caused due to degeneration of dopaminergic cells through mitochondrial dysfunction (Dantasa et al. 2008), and mainly oxidative stress (Segura-aguilar 2017). Another important CNS disease that causes neurodegeneration is Multiple Sclerosis, an autoimmune disease in which T lymphocytes that cross the blood-brain barrier, together with microglia, a specialized phagocytic CNS cell, act against the myelin sheath, generating an inflammatory response, which leads to demyelination, injuring axons (Marín et al. 2014). Due to their unknown ethnology and pathogenesis, neurodegenerative diseases make the development of effective therapies a great challenge for modern medicine (Stanzione and Tropepi 2010). Natural plant extracts are promising candidates in the treatment and prevention of neurodegenerative diseases. Studies suggest that many of these products may attenuate brain injury by exhibiting protective effects against brain damage (Sairazi et al. 2015, Abdou and Wahby 2016). Research in the drug field has focused on the neuroprotective action of natural compounds present in plants, and many of these components, are- resveratrol and quercetin, have shown neuroprotection against cerebral ischemic injury in experimental studies (Wu et al. 2010). Among the various natural compounds proposed to reduce neurodegeneration, polyphenols and flavonoids that have antioxidant action among many biological activities are among the most important in combating neuronal damage (Ansari and Khodagholi 2013, Mutoh et al. 2016).

There is ample evidence that polyphenol-rich foods or beverages increase antioxidant levels in the bloodstream and thus contribute to the prevention of oxidative stress-induced cell damage (Hajieva 2017). Resveratrol (RSV) 3,5,4 0-trihydroxystilbene is a polyphenol which has two spatial conformations, one CIS and the other TRANS is naturally synthesized in various plant species that can be found in a variety of foods and beverages including red grapes, peanuts, and red wine (Koronowski et al. 2015, Sato et al. 2013). The highest levels are found in grapes and red wine, about 0.16 to 3.54 µg/g and 0.1 to 14.3 mg/L. (Hajieva 2017, Bonsack et al. 2017). RSV is a secondary metabolite belonging to the class of “stilbenes”, which are polyphenolic compounds produced by plants in response to a variety of factors: exposure to biotic or abiotic stress, such as physical injury and fungal/bacterial infection and radiation (Ansari and Khodagholi 2013, Kennedy et al. 2010). Considered a bioactive agent with a potential health benefit, RSV is reported to have a large number of pharmacological properties, including anticancer, antioxidant, cardioprotective and anti-inflammatory action, among others (Khalatbary 2014). RSV ingestion has shown protective effects in animals and humans (Wightman et al. 2014). The therapeutic potential of RSV has been widely investigated in many pathological conditions (Koronowski et al. 2015); animal research has shown improvements in the protection of cognitive function and reversal of cognitive deficits explained by the positive and regulatory effect of cerebral blood flow exerted by resveratrol (Wightman et al. 2014). Some pharmacological studies have found the action of RSV on antiplatelet aggregation; its antioxidant action allows the inhibition of arachidonic acid and the formation of metabolites, thus playing an important role in tumor chemoprevention (Guo et al. 2018).

The mechanisms of neuroprotection of RSV are not fully understood, further studies are needed to influence a greater understanding. These paper aims are mediate through the findings of this work for the academic and scientific community the importance of natural products in covering neuronal protection for the importance of treating neurodegenerative diseases (DNG) and addressing the immunological importance of Resveratrol in neuroprotection.

FINAL CONSIDERATIONS

This study aimed to demonstrate the neuroprotective efficacy of resveratrol from experimental scientific studies. Given the results obtained, resveratrol has high neuroprotection power, promoting neuronal viability in several ways. This polyphenol acts in different ways, and its power is evidenced through anti-apoptotic, anti-inflammatory and antioxidant action, ensuring the neuronal survival.

The authors were unanimous in their considerations, stating resveratrol neuroprotection. Considering damage/inflammatory situations on brain and spinal cord, which originate a large number of reactive species, neuronal death, and many others inflammatory processes, culminating in increased production of cells that are involved in the release of inflammatory substances. Resveratrol is a great ally, modulating responses that promote neuroprotection, because is able to reverse this process to a homeostasis centre on these tissues.

Physiopathology of Neuroinflammation

The brain tissue has some peculiar characteristics, that differs mainly the immune response from other tissues, these ones qualify it as an organ with "immunological privilege", due to vascularization with closed junctions and the blood-brain barrier (BBB) that prevents peripheral immune cells from penetrating CNS, as well (Lima et al. 2007). This privilege is not permanent and may fall apart in acute or degenerative lesions that occur for some reason in the CNS. Astrocyte-mediated cytokine release with reactive morphology, as well as activated microglia also responsible for mediating pro-inflammatory functions lead to BBB deformation, which ultimately allows the recruitment of leukocytes and other peripheral immune cells to consume

neuroinflammation (Silva 2014) (Figure 1). The mechanisms that trigger neuroinflammation are diverse and complex and will be explained further in the body of this article.

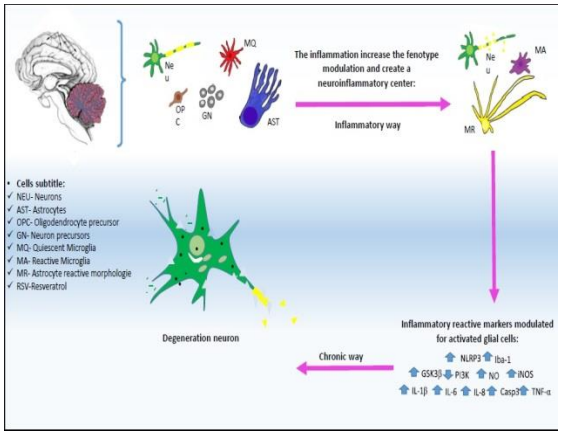

Figure 1: Neuroinflammation mechanisms and their influence on central nervous system cells.

Neuroinflammation is mediated by inflammatory induction culminating in glial phenotypic alteration, as well as the production of inflammatory inducers, which results in neuronal inflammation and/or neurodegeneration. The inflammatory flow (indicated by the pink arrows) sequentially follows cellular alteration, production of inflammatory inducers and consequent neuronal degeneration (Silva 2014, Lent 2010, Bi et al. 2013). Astrocytes (AST) and microglia (MG) are immunomodulatory cells of the CNS, AST under physiological conditions, have a branched morphology, and are responsible for monitoring neuronal communication, synaptic function and biochemical pathways (Lent 2004).

In case of damage, it may undergo changes in its morphology and biochemical function, leading neurons in degenerative process to a programmed death, with the objective to promote homeostasis (Doty 2015) like as observed by Fangfang et al. the secretion of Icn2 molecule (mediated by reactive morphology astrocytes) is capable to activating autophagy processes in degenerating neurons (Doty 2015). Microglia are multifunctional cells and when activated by modulatory stimuli, they release cytokines and other inflammation-inducing molecules and, together with astrocytes, mediate the CNS inflammatory response, (Han and Mook-Jung 2014) during the inflammatory process it assumes a profile called M1, responsible for the production of pro-inflammatory cytokines and interleukins (IL-1β, TNF-α, and INF-γ), this phenotype being the main responsible for the high production of nitric oxide (NO) which plays the leading role of oxidative neuronal degeneration (Orihuela et al. 2016).

Another Microglia profile known as M2 is the most commonly observed in homeostasis and characterizes a “non-inflammatory” process, mainly through the transcription of anti-inflammatory cytokines, like: Interleukin 10 (IL-10) (da Silva et al. 2017), and Arginase (Becher et al. 2017). Peripheral blood cells (Neutrophils, Monocytes, and T-Lymphocytes) are mainly mediated by microglia, responsible for modulating alpha integrins 4 (α4) and selectins such as vascular cell adhesion protein (VCAM) that enable the diapedesis of these peripheral cells to the CNS (Yshii et al. 2015), triggering a stronger inflammatory response.

In Multiple Sclerosis, two cells recruited for the CNS that are important for the inflammatory process to be established are CD8 T lymphocyte and B lymphocyte, which together with microglia mediate damage to myelin and axons respectively (Kleinberger et al. 2014).

Studies show that genetic mutations may also contribute to the process of neuronal degeneration, an example, the mutation from an encoding gene, of TREM2 protein, that is found on the microglial plasma membrane and, which regulates the removal of cellular debris (Selvaraj et al. 2018). Researchers believe that, the mutation of this protein is the key for recover the neuronal inflammation, because it is only expressed on the neuronal membrane surface during the inflammation, thus causing a significant decrease in the removal of cellular debris, which will accumulate in the brain initiating an inflammatory process (Selvaraj et al. 2018).

Another example would be a mutation in the C9ORF72 gene, that can turn into a non-conformed protein and can cause stress to cells, which will produce more toxic substances, could eventually lead to neuronal death (Zhang et al. 2017). Finally, what characterizes a degeneration is a process called glial scarring, where the inflammatory neuron recruits microglia to phagocyte the cell body (Han and Mook-Jung 2014). During the process of phagocytosis the tumour necrosis factor (TNF) attracts astrocytes to the phagocytosis region by chemotaxis, and after this process, the astrocytes start the production of collagen fibers at the damage site, and the glial scar is completed, come finally to degeneration ends, but unfortunately rendering a region infertile to new neurons (Silva 2014).

Stop/change the way to this final process can be essential to recover neurons and, progenitors on the brain, however, find one player capable to play this game, it is an arduous inquiry.

Resveratrol against neuroinflammation

The therapeutic potential of RSV has been widely investigated in many pathological conditions, (Koronowski et al. 2015) this polyphenol exhibit cytoprotective characteristics in many animal models lines of damage CNS manifestations like: seizure, traumatic brain injury, spinal cord ischemia (Wu et al. 2010) and, other patterns of symptomatology

corresponding to neurodegenerative diseases such as Alzheimer's (Khalatbary 2014) and, Parkinson's (Bi et al. 2013) also observed in experimental animal models. Studies have shown that resveratrol's mechanism of neuroprotective action can be assigned to the antioxidant, anti-inflammatory and anti-apoptotic properties (Khalatbary 2014).

In experiments where neurons were exposed to inflammatory damage induced by beta-amyloid proteins, RSV was capable to promoted anti-apoptotic activity by activation of Phosphatidyl-inositol-3-phosphate kinase (PI3-K) signaling pathway, which generates protein stimulation kinase B (AKT), resulting in neuroprotection to neurons via kinase pathways (Han et al. 2004). However, this activity is exerted by others allopathic drugs, that are used in the treatment of neurodegenerative diseases (Han et al. 2004).

Resveratrol also acted on the same signalling pathway, PI3-K. In a study using cell culture submitted to underwent glucose and oxygen deprivation, thereby generating an in vitro model of cerebral ischemia, resveratrol in different concentrations, was competent on reducing cell death, besides activating the PI3-K pathway, also activating the mitogen-activated protein kinase (MAPK or ERK) pathway, both able to promoting cell survival (Ibrahim et al. 2013). Considering the experimental studies carried out in mice, they all, showing the neuroprotective action of resveratrol, that were observed in different segments, that confirm RSV on promoting neuronal viability drug list.

Resveratrol versus Degenerative nervous system disease animal models

In an experimental model of spinal cord injury in rats, resveratrol shown an antioxidant activity, promoting additional neuroprotection over lipid peroxidation generated by the injury model (Ates et al. 2006). The Polyphenol demonstrate, neuroprotective effects acting on decreasing production of inflammatory cytokines such as interleukin 6 (IL-6), interleukin 12 (IL-12) and interleukin 23 (IL-23), both of them, produced by microglia and dendritic cells that are also, associated to Multiple Sclerosis (MS) physiopathology (Imler and Petro 2009). Still on rats MS models, resveratrol was effective in reducing the inflammatory process by Sirtuin 1 (SIRT 1) activation (Fonseca-Kelly et al. 2012), a pathway common in increase the presence of non-inflammatory cell profiles on brain and periphery tissue (Fonseca-Kelly et al. 2012). According to Lin et al. 2014, RSV was efficient to reduce rotenone-induced dopaminergic neurotoxicity by modulating heme oxidase-1.

Koronowski 2015 and collaborators shown in their experiments that resveratrol has a neuroprotective action, mainly on reducing of ischemic brain injury damage ways; when administered before the stroke, RSV develop your neuroprotective effect through the stimulation of SIRT1, presenting primary damage protection. Resveratrol also attenuated a brain injury following subarachnoid hemorrhage by inhibiting the inflammasome pathway of the domain 3 pyrine family (NLRP3) (Zhang et al. 2017). In another study, RSV promoted protection on dopamine neurons by microglial activation inhibiting and, reactive oxygen species (ROX) reduction (Zhang et al. 2010), chiefly suppressing microglia activation and neutrophil infiltration, reducing apoptosis, edema and consequently neurological impairment (Bi et al. 2013).

Resveratrol on inflammatory and non-inflammatory pathways

Passing by on the topics above, were shown that RSV can activate many signalling pathways related to cytoprotection, anti-inflammatory, and antioxidant activity. However given the complexity of these molecular pathways, it is required understanding the exact mechanisms of each pathway, and how RSV can interact with each one of them. This is a major challenge for modern pharmacology research, and now we will try explain some of them.

Resveratrol mediating kinase pathway activities are the most reported molecular activity, for example on the PI3-k and MAPK pathway. The PI3-k pathway is form by two subunits: p85 (regulatory) and p110 (catalytic), the in-link of the two subunits creates the activated form, responsible for regulating various cellular processes such as proliferation, growth, and apoptosis (Zamin 2006). Resveratrol also acts on activation of the MAPK pathway, which covers different types of signalling proteins, it leads to phosphorylation and activation of ERK1/2 (extracellular-regulated kinase) protein, that can promote anti-apoptotic effects and neural survival after ischemia (Zamin 2006).

Studies have shown the RSV interact on the reduction of positive iba-1 cells (structural microglia marker) related to the suppression of TNF-α, interleukin 1 (IL-1), IL-6 and IL-23 production, common cytokines produced by microglia in pro-inflammatory processes (Imler and Petro 2009, Zhang et al. 2010). Resveratrol was able to decrease the production of reactive oxygen species producing by NADPH reductase enzyme, which in large quantities may cause oxidative damage, the neuroprotection performed in this response is related to protein kinase C (PKC) stimulation (Wu et al. 2010, Cosentino-Gomes et al. 2012) a negative regulator of NADPH reductase (Das et al. 2016). Autophagy is an intracellular mechanism responsible for the degradation and recycling of damaged proteins, acts against apoptosis, degrading mitochondria damaged by mitochondrial complex 1, that prevents the release of apoptotic molecules (Lin et al. 2014). Any dysfunction in this process can lead to neuronal degeneration (Lin et al. 2014). Resveratrol acts by abolishing an autophagic inhibitor, promoting the expression of heme oxidase 1 (HO-1) which exerts effects on cell survival and consequently increases autophagy flow (Lin et al. 2014).

Resveratrol is able to modulate SIRT 1, which acts on histones and non-histones by regulating many biological processes, playing neuroprotective properties in pathological situations, RSV was able to generate low modulation of proliferator hypoxia induction factor 1 (HIF-1) peroxisome alfa-1 (PGC1alfa) and NK receptor (p58), key modulators of the CNS microglial and inflammatory response (Koronowski et al. 2015), also being able to negatively modulate the production of pro-apoptotic factors such as Tumor Suppression Factor (p53), B2 Cell Lymphoma Factor (BCL-2) and, Carbonic Anhydrase 1 (CA1) (Singh et al. 2013, Kizmazoglu et al. 2015), factors that are closely related to mitochondrial dysregulation failure and, caspase-3 and caspase-8 production, important transcription factors of inflammatory cytokines such as Interleukin 1 beta (IL-1β) and formation, of the protein inflammasome factor NLRP3 (Gurung and Kanneganti 2015, Krajewska et al. 2011).

Thus it can be concluded that Resveratrol's anti-inflammatory and neuroprotective activity is mainly restricted to the ability to reverse apoptotic processes. The modulation and negative production of factors such as caspase-3 and 8 and consequently NLRP-3 suggest that RSV may be capable to regulate the inflammasome pathway, which has been responsible for the regulation of most inflammatory processes that can be affecting the mammalian organism (Haneklaus and O'Neill 2015) and, which has been presented as the main route of acute and chronic inflammatory processes in neurodegenerative diseases (Song et al. 2017).

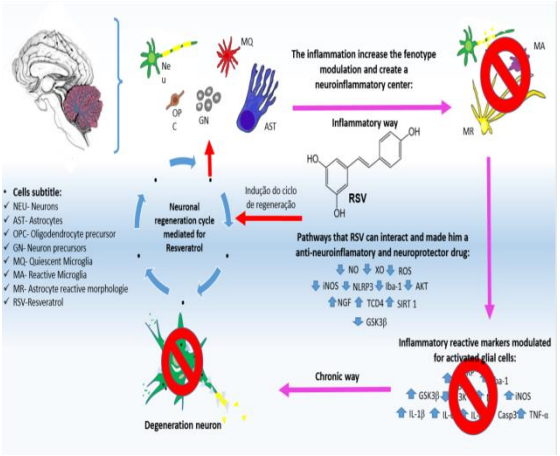

Figure 2: Resveratrol neuroprotective and anti-inflammatory mechanisms that culminate in its activation activity of the neuronal regeneration cycle. Neuroregeneration and decreased inflammatory markers characterize resveratrol as an activator of the neuronal regeneration cycle that can results in homeostasis (represented by the red arrow).

For this reason, a hypothesis of neuronal and astrocytic protection generated by Resveratrol in DNG models is restricted to this characteristic of intervening in the NLRP3 inflammasome pathway, culminating in a lower production of pro-inflammatory cytokines, a circumstance observed by many authors in the last 5 years (Lin et al. 2014, Misawa et al. 2015, Wu et al. 2010).

We can infer that RSV has a promising ability to create a neuronal regeneration cycle (Figure 2), given to the CNS affected by inflammation the possibility of homeostasis.

MATERIALS AND METHODS

This work was prepared from a literature review in the Medline and Science Direct databases, between March and June 2018. The keywords used were “Resveratrol” and “neuroprotection”. Exclusion criteria were: published articles that also referred to reviews of the relationship between the drug and neuroprotection, but their references served as a sieve method for searching for articles targeting the selected keywords. Adding all the databases, we found 105 articles. After reading the titles of the articles, it was noted that some of them were repeated in different bases and others did not meet the criteria of this study. We selected 83 articles to read the abstract and excluded those that did not concern the purpose of this study. After reading the abstracts, 55 articles were selected that met the initially proposed criteria and were read in full. In the final selection, literature review articles were excluded. In the results in which reference is made to the objects studied.

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