PERSPECTIVE

Resveratrol effects on neural connectivity during aging

Aging has been considered a natural process of any living being. The rate of aging depends on many factors, including genetic and environmental factors. For this reason, many researchers in this field suggest that aging is an epigenetic process.

Nowadays, the age groups have undergone a change. The older age group of 60 years and older has increased its percentage (7.4%), while the age group under 18 years has been reduced in percentage. The World Health Organization (WHO) estimates that in the year 2000, there were 600 million people aged 60 years and that there will be 1.2 billion by 2025 and two billion by 2050. With the increase of the general population age, the percentage of patients with aging diseases is growing. Therefore, the aging population requires more spending for health services. In addition, several reports suggest that 20% of the age group of 80 years and older have some types of dementia. At this age, the most common cause of dementia is Alzheimer's disease (AD), which occurs in 70% of dementia cases, followed by vascular dementia (VD) with 20% of dementia cases (for review see Flores et al., 2016). This does not include other characteristic disorders of this age group such as hypertension, diabetes mellitus, *etc.* In this sense, there is a health problem that seriously affects the aging population stage, which causes economic problems, because the cost of health services will increase dramatically in the future. Therefore, it is necessary to propose new pharmacological alternatives that contribute to slowing the evolution of aging that affects brain function and as a consequence causes cognitive impairment. All of these approaches aim to improve the quality of life and reduce costs in health services.

Currently, there are several natural products, which have been proven to be of benefit in cognitive impairment during the aging processes, such as resveratrol, which belongs to the polyphenols compounds. The present report discusses the most relevant data from our group on the consequences of the aging on neuronal connectivity and the effects of resveratrol on synaptic intercommunication between neurons in animal aging models and their effect on aging in humans.

Prefrontal cortex and hippocampus are involved in cognitive impairment deficit by aging: The prefrontal cortex (PFC) and hippocampus are two major cortical regions involved in the control of memory and learning processes, and are the most affected regions of the brain by aging (for review see Flores et al., 2016). Both structures are interconnected by glutamatergic projections and are disrupted in neurodegenerative disorders (for review see Flores et al., 2016). In addition, both cortical regions undergo changes in local connectivity due to aging (Flores et al., 2016; Hernández-Hernández et al., 2016), which causes cognitive deficits (for review see Bowman and Dennis, 2015). In the older brain, several reports have shown a loss of cortical neurons, with progressive regression of the dendritic arborization and spinogenesis (Pannese, 2011; Flores et al., 2016; Hernández-Hernández et al., 2016). At the cortical level, together with the reduced number of synapses, glucose metabolism is reduced and the lateral ventricles are enlarged (for review see Flores et al., 2016). All these brain changes alter cognitive function, which is expressed by a deterioration in learning and memory processes. In addition, concomitant cerebral vascular diseases due to aging exacerbates the cognitive deficits, because they lead to hypoperfusion and brain ischemia (for review see Flores et al., 2016).

Several neuroimaging studies showed that with aging the thickness of the PFC (for review see Yuan and Raz, 2014) and the hippocampus is reduced (for reviews see Fotuhi et al., 2012). Therefore, the reduced volume of these regions by aging is correlated with cognitive deficits in learning and memory processes (Fotuhi et al., 2012; Yuan and Raz, 2014).

Resveratrol effect on brain aging: In recent years, it has been shown that the consumption of a diet rich in vegetables, fruit and spices brings health benefits, helps prevent diseases and delays aging. These diets are constituted by various phytochemicals with antioxidant properties, such as ascorbic acid or vitamin C, tocopherols like vitamin E, carotenoids and polyphenolic compounds that in pharmacologic doses constitute an alternative for the treatment of various chronic diseases (Diaz-Gerevini et al., 2016).

Polyphenols are abundant micronutrients in our diet; fruits, vegetables and beverages like tea and red wine are rich sources of these types of compounds. Polyphenolic compounds can be classified into different groups according to their base structure and the number of aromatic rings and elements attached to them. Among the main polyphenolic groups are the polyphenolic acids, flavonoids, ligands and stilbenes.

Resveratrol (3,5,4′-trihidroxiestilbeno) is a phytoalexin produced by more than 70 species of plants in response to infections and stressful situations, like mechanical damage, low temperatures, UV radiation and pollutants such as pesticides. Resveratrol is a polyphenol present in nuts like walnuts and peanuts and in wild fruits like berries, grapes and wine, mainly red wine. It was isolated for the first time in 1940. It has various properties which were described and demonstrated 18 years ago, such as inhibiting growth and proliferation of cancer cells. Resveratrol is found in nature as cis and trans isomers. The trans isomer is most abundant and has more biological activity (Chachay et al., 2011).

Resveratrol pharmacokinetics studies reveal that its absorption is rapid and about 95% of absorption is by transepithelial intestinal broadcasting way. It is possible to detect resveratrol concentrations in plasma after 10 minutes of administration, reaching the peak of plasma concentrations in 60 minutes. However, when resveratrol was administered together with a high fat diet, its absorption diminished considerably. Resveratrol binds to plasmatic proteins for transport, mainly albumin, because it has low solubility in water. It has a distribution volume of 1.8 L/Kg, and this polyphenol is able to be distributed

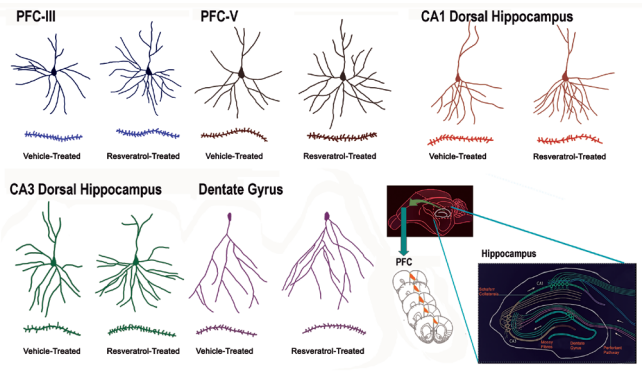

Figure 1 The schematic diagrams show how chronic resveratrol treatment leads to changes in the number of dendritic spines and the length of dendrites in prefrontal cortex (PFC), dentate gyrus and CA1 and CA3 regions of the dorsal hippocampus of aging rats. In addition, the connections between PFC and hippocampus are presented.

and stored in tissues. Studies conducted in different animal models demonstrate that resveratrol after oral administration can be found in tissues, and higher concentrations can be found in liver and kidney tissues and lower concentrations are found in skin, intestine and brain. Its metabolism is mainly associated with conjugation reactions. *In vitro* studies have shown that this polyphenol causes metabolism products mainly conjugated 3 and 4′ glucuronide and 3′ sulfate. In oral administration, resveratrol suffered phase II reactions by the UDP-glucoroniltransferase and sulfotransferase enzymes, obtained as products of hepatic metabolism mainly, transresveratrol-3-O-glucuronide for the human and two metabolic products in the rats, trans-resveratrol-3-O-glucuronide and trans-resceratrol-3-sulfate. Resveratrol has a half-life of 2 hours, and the renal system is responsible for its elimination. The bioavailability of resveratrol is relatively low, approximately 38%, it is proposed that this varies depending upon the hours of its administration. Some reports indicate that bioavailability is greater when resveratrol is administered in the mornings, when due to the circadian cycle, enzyme activity and enterohepatic circulation are most efficient (La porte et al., 2010).

It is suggested that continuous resveratrol treatment could help to reduce obesity and delay aging. Its action mechanism is not yet clear, some studies indicate that resveratrol increases the expression of deacetylase Sir2/SIRT1, an enzyme that resists stress and aging, and PI3K. The resveratrol ability to increase the SIRT1 activity is linked to PGC-1 deacetylation, a factor involved in mitochondrial biogenesis. PGC-1α SIRT1 dependent deacetylation promotes PPAR activation (peroxisome proliferator-activated receptor), which has the ability to protect against mitochondrial damage through Bcl-2 regulation and antiapoptotic proteins (Lopez et al., 2015). The ability of resveratrol to increase SIRT1 and related enzyme activity can lead to changes in the neuronal transcription and an improvement in anti-apoptotic activity. In the same way, resveratrol activates AMPK and the NRF2, which are involved in cell survival, and induces the expression of enzymes, antioxidants like superoxide dismutase (SOD), catalase and hemoxygenase. Other studies suggest that resveratrol also inhibits NFKB expression and cyclooxygenase-2 (COX-2). These two molecules are involved in cancer processes, arterogenesis, neurogenesis and mitochondrial dysfunction. In addition to promoting PPAR expression, which acts as a free radical trap, resveratrol inhibits the oxidase-C cytochrome and caspase-3 and also increases the expression of HIF-1a and BCL2 in order to inhibit apoptosis. Likewise, other reports indicate that resveratrol decreases IL-6, TNF-α and reactive gliosis, which induces LPS (Reuter et al., 2010).

Our working group proposes the use of resveratrol to delay aging, particularly in the brain. Studies in old rats suggest that resveratrol chronic treatment improves memory performance and prevents cognitive impairment. In animal models of Alzheimer's disease, resveratrol has been shown to prevent amyloid-β toxicity, as well as hippocampal neuronal degeneration. In addition, it promotes neurogenesis and neuronal survival, mediates neurotrophin expressions such as brain-derived neurotrophic factor (BDNF). Hernández-Hernández et al. (2016) has demonstrated that at 18 months of age rats (elderly animals) administered with resveratrol for 2 months have no improvement in motor activity related to animal control (**Figure 1**). Regarding neuronal morphology, resveratrol treatment showed an increase in the number of dendritic spines and the length of dendrites in the brain regions, such as the PFC and CA3 and the CA1 regions of the dorsal hippocampus compared to elderly animals without treatment. The resveratrol antioxidant effect protects the structure and function of neurons that can be damaged by oxidative stress during aging. This effect also prevents a reduction of the number of dendritic spines in the limbic regions in elderly animals treated with resveratrol. In addition, as we mentioned before, resveratrol increases the levels of BDNF and it is well known that BDNF may increase the dendritic spines (for review see Flores et al., 2016).

In summary, resveratrol exerts a potent and specific effect on the neuronal plasticity in the brains of elderly rats. Therefore, the changes observed due to continuous treatment that induces resveratrol in older animals could explain the effect of this photochemical in aging or Alzheimer's disease.

Funding for this study was provided by grant from CONACYT (No. 252808) to GF.

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***doi:** 10.4103/1673-5374.187029*
***How to cite this article:** Flores G, Vázquez-Roque RA, Diaz A (2016) Resveratrol effects on neural connectivity during aging. Neural Regen Res 11(7):1067-1068.*

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