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Polyphenols - What's Behind their Antiaging Brain Reputation?

*Sarubbo F, Moranta D, Miralles A and Esteban S**

Department of Biology, University Institute of Research in Health Sciences, Spain

Abstract

The timeline by year of PubMed website shows as more than hundred documents appears under the search of the formula "polyphenols+brain+aging", being the beginnings of the present century the initial period of this eye-catching interest. This fact inevitably poses a question -what's behind the antiaging brain reputation of polyphenols? The alteration of brain functionality, the cognitive and motor decline characteristic of brain aging process are due in part by the increase in oxidative stress and the phenomenon known as inflammaging. For this reason, if there are molecules able to prevent aging these should be able to counteract these processes. This is part of the attractive of polyphenols, who apart from being natural molecules reachable in diet, have also antioxidant and anti-inflammatory properties, among other antiaging properties that become them suitable to prevent brain aging and neurodegenerative diseases, acting on neurons and glia, by crossing the blood brain barrier. This communication is focus on explaining through recent articles why polyphenols have become promising molecules in the fight against the consequences of brain aging and neurodegeneration.

Introduction

Brain aging is mainly characterized by a progressive metabolic imbalance, brain vasculature alterations, and a decline in adult neurogenesis, among other signs [1], leading to a cognitive and motor decline, not only in the context of neurodegenerative diseases [2], but also during normal aging [3-5]. As the current demographic context is marked by an increase in the population over 65, one of the leading health challenges is the treatment of the cognitive decline and neurodegenerative diseases associated to brain ageing [6]. Since the finals of the last century polyphenols have been pointed as possible molecules that can strategically prevent or slow down aging in general, and particularly brain aging. Polyphenols (i.e. resveratrol, silymarin, quercetin and naringenin) are natural compounds present in plants and food commonly consumed in the Mediterranean diet, such as grapes, red fruits, orcitrics, among many other foods [7,8], with ability to cross the blood brain barrier, due to their lipophilic nature [9-12]. Polyphenols have antioxidant [13,14] and anti-inflammatory properties [15,16], includinginhibition of pro-inflammatory enzymes and signaling pathways (i.e. the nuclear factor-kappa B (NF- κ B) [4,5], maintenance of cerebral mass [17]and mitochondrial integrity [18], modulation of several cell survival/cell-cycle genes [8,19-21], activation of antiaging enzymes like sirtuin 1 (SIRT1), among other properties [5,4,22]. On the whole these properties seem to be the key points of the antiaging effects of polyphenols, since oxidative stress [23] and activation of neuro inflammation [24,25] have been identified as the leading causes of brain aging. The aim of this communication is explain in an abbreviated form what is behind the positive effects of polyphenols in brain aging, focusing in the studies [3-5], that have recently demonstrated cognitive and motor improvement after polyphenolic treatments in old rats and in neurodegenerative diseases, both in animal models of these diseases and in humans [26], and have also glimpsed the molecular mechanisms behind these positive effects.

Which Effects Exert Polyphenols on Cognition and Motor Coordination in Aging?

Aging is a physiological process caused by a set of mechanisms [27], influenced mainly by the oxidative stress [23] and neuroinflammation [28], which in turn influence each other affecting the anatomy and physiology of the body, and the correct functionality of the brain, generating a general state that contributes to cognitive impairment [5]. It is worth noting the decline in several cognitive function such as short-term memory, spatial working and episodic memory, learning, and motor coordination demonstrated in several studies in old rats [3-5,29] and in humans [30].In old rats these

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Correspondence:
Esteban S, Department of Biology, University Institute of Research in Health Sciences, Laboratory of Neurophysiology, Ctra. Valldemossa Km 7,5 E-07122 Palma de Mallorca, Spain, Tel: +34 971 173150; Fax: +34 971 173184;
E-mail: susana.esteban@uib.es

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findings have been obtained after testing these animals in behavioral test such as radial maze for the study of spatial working memory, novel object recognition test for examining episodic memory, Barnes maze test for testing spatial learning, and rotarod test for the assessment of motor coordination. These studies have shown as aging affects in a progressive and negative way the correct execution of these cognitive and motor functions, having as a result a marked decline in memory and in the ability to learn in aged rats. The scientific community has always tried to give answer to this apparently inevitably problem that everybody seems condemned to suffer. Many are the molecules studied in an attempt to resolve this challenge, but the polyphenols have attracted attention by many scientists due to their properties as antioxidants, anti-inflammatories, with an elevated neuroprotective potential, and their ability to modulate several cellular mechanism that become them as a worthy candidates to prevent aging symptoms [31]. In this sense, the key question is - can polyphenols prevent or delay the decline in memory, in the ability to learn and in motor coordination due to brain aging process? The answer is affirmative, it has been demonstrated that polyphenols such as resveratrol, silymarin, quercetin and naringenin preserve cognition in aged rats, improving short-term memory, spatial working and episodic memory, learning and motor coordination after chronic treatments (30 days) with these polyphenols in a doses of 20 mg/kg/day [3-5]. The first findings seems promising and open a new way to extrapolate these kind of therapies in humans, where there has been demonstrated that polyphenols exert numerous beneficial properties improving human health [32] and also it was suggested that can act on the physiopathology of the most common brain aged-related diseases such as dementia [33], Alzheimer's disease, Parkinson's disease or depression [26]. However, it remains to know some points as the exact bioefficacy, the specific design and interpretation of the treatments with polyphenols in humans. For this reason is also important to understand some findings about the possible mechanisms behind their effects.

What are the Mechanisms Behind their Effects?

Part of the answers that will give solution to the questions regarding if polyphenols are antiaging brain molecules have relation with the mechanisms behind the effects found after the treatment with polyphenols. The main mechanisms apparently responsible for their effects are the prevention of oxidative stress [34] and the anti inflammaging effect [35], whose result is an increase in monoamine levels, the modulation of antiaging proteins such as SIRT1, and the attenuation of inflammatory signaling pathways involve in inflammation as it is the NF- κ B signaling pathways.

Effects of Polyphenols on Monoamine Levels in Brain Aging

Oxidative damage and inflammaging, two processes with a feedback among themselves, have different effects on brain during aging one is the decline in functionality of enzymes involve in monoamines synthesis Tryptophan Hydroxylase (TPH) and Tyrosine Hydroxylase (TH) enzymes due to their inefficient phosphorylation after Reactive Oxygen Species (ROS)and cytokine injury [36,37]. Altogether brings a marked reduction in monoamines levels such as serotonin (5-HT), Norepinephrine (NA) and Dopamine (DA) [3-5,38,39] which are believed to be partially responsible for impairments in memory and motor coordination [3,40-42], and for the prevalence of neurodegenerative diseases during senescence [37]. Results from recent studies demonstrated that chronic administration (30 days) in doses of 20 mg/kg/day of the polyphenols resveratrol; silymarin, quercetin and naringenin to old rats are enough to restore TPH-1, TPH-2 and TH activity. Besides, after these treatment monoamine levels (NA, DA and 5HT) were also increased, in regions directly involved in cognitive and motor processes such as the hippocampus and the striatum; and also in the pineal gland, involved in the control of circadian rhythms; which also directly affect the cognitive function [3-5]. Besides, polyphenols inhibit (especially the flavonoid quercetin) the enzymes Monoamine Oxidase (MAO), resulting in antidepressant effects that helps to the recovery of brain functions [43].

Effects of Polyphenols on SIRT1 and Inflammation

SIRT1is important for the maintenance of the synaptic plasticity, memory and the attenuation of other ageing-related processes such as inflammaging [44,45]. Aging reduces SIRT1 levels in hippocampus [46], since it seems that oxidative stress reduces SIRT1 mRNA levels inducing inhibition of SIRT1 expression [47]. In addition, cysteine residues from SIRT1 are vulnerable to oxidation affecting both the activity of SIRT1 and its degradation by the proteasome [48,49]. However, polyphenolic chronic treatments (30 days;20 mg/kg/day) with resveratrol, silymarin, quercetin and naringenin can increase SIRT1 levels in aged rats [3,5]. Therefore, these studies suggest that polyphenols due to their antioxidant properties may avoid the consequences of oxidative damage, protecting SIRT1 enzyme and preserving the levels of SIRT1 during aging. Besides, SIRT1 modulation could contribute to modulate the efficiency of the NF- κ B signaling pathway involve inflammaging processes [25,50-52]. SIRT1 interacts with the RelA/p65 subunit of NF- κ B and inhibits transcription of proinflammatory factors by deacetylating the RelA/p65 at lysine 310 [52-55]. Thus, the age-related decrease in SIRT1 activity enhances the NF- κ B signaling, which supports inflammatory responses in brain [56]. The chronic treatments with polyphenols (resveratrol, silymarin, quercetin and naringenin) detected an increase in NF- κ B acetylated levels in hippocampus of old rats without significant changes in total protein levels of NF- κ B [4,5].These results suggest that polyphenolic treatments could lead to a down regulation of the NF- κ B signaling pathway through a SIRT1 mediated mechanism; which would contribute to neuroprotection by reducing the proinflammatory state in the hippocampus of aged rats. Which could be helped also by the fact that polyphenols also reduce the expression of inflammatory cytokines (e.g. TNF- α, IL-1 β, IL18) and chemokines (CCL19, CCL2) in aging, as well as they increase expression of anti-inflammatory cytokines (e.g. IL24, Il4, IL10) with anti-inflammatory or immune-modulating effects in hippocampus [44,57]. Interestingly, the expression of these markers also supports tissue repair and stem cell proliferation [58,59], and enhance the expression of pro neurogenic genes throughout the activation of oxidative stress-and inflammation-responsive pathways, the increased release of growth factors (GDNF and FGF4) and the attenuation Wnt/ β-catenin pathway. Collectively, these actions support proliferation and survival of neural progenitors, and counteract age-dependent neurogenic decline preventing brain aging symptoms [60].

Conclusion

Behind polyphenol antiaging brain reputation are their demonstrated positive effects on working, episodic and spatial memory/learning and motor coordination originated by the attenuation of inflammaging (by modulating NF- κ B levels and cytokines) and oxidative stress, together with the modulation of

hippocampus SIRT1, the conservation of the activity of enzymes involve in monoamine synthesis and the levels of monoamines, and favoring the conservation of adult neurogenesis.

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