Neuroscience and Biobehavioral Reviews 90 (2018) 456–470

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

# Dietary polyphenols and neurogenesis: Molecular interactions and implication for brain ageing and cognition

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ARTICLE INFO

*Keywords:*
Polyphenols
Adult neurogenesis
Aging
SIRT1
Inflammation
Oxidative stress
Cognition

ABSTRACT

The increased number of elderly people worldwide poses a major medical and socio-economic challenge: the search of strategies to combat the consequences of the aging process. Oxidative stress and inflammation have been pointed out as the leading causes of brain aging, which in turn alters the functionality of brain. In this context, decline in adult neurogenesis (AN), due to modifications in the neural progenitor stem cells (NSCs) and their microenvironment, is among the aging alterations contributing to cognitive decline. Therefore, the consumption or administration of antioxidant and anti-inflammatory molecules, such as dietary polyphenols, is under study as a potential beneficial strategy for preventing brain aging alterations including AN decline. Polyphenols, through their antioxidant and anti-inflammatory properties, modulate several cascades and effectors involved in the regulation of AN (e.g., SIRT1, Wnt, NF-κB and Nrf2, among others). This work summarizes the latest discoveries regarding the mechanisms whereby polyphenols preserve AN and counteract the cognitive decline present in aging.

## 1. Introduction

In the last years stem cells have been matter of intense research, fuelled by the hope of exploiting their regenerative potential for the treatment of different kinds of biological impairments and diseases, including those associated with functional decline during aging. Nowadays, due to the increased elderly population worldwide, one of the leading health issues is the treatment of cognitive decline and neurodegenerative diseases associated to brain ageing (Wimo et al., 2013).

Brain aging is characterized, among other aspects (Bondolfi et al., 2004), by a progressive metabolic imbalance, brain vasculature alterations, and a decline in adult neurogenesis (AN), which reduces the number and function of neural stem cells (NSCs) and neural progenitor cells (NPCs) (Park and Lee, 2011). All these alterations contribute to cognitive decline, loss of working and episodic memory, impaired learning capacity and motor coordination, not only in the context of human neurodegenerative disorders (Mattson, 2000), but also during normal aging (Sarubbo et al., 2015, 2016).

Although not all the molecular mechanisms underlying brain aging are well known, oxidative stress (Harman, 1956) and neuroinflammation (Salminen et al., 2008a,b) have been identified as the leading causes. Therefore, treatments that oppose these processes could prevent biological imbalances, favouring the correct functionality of brain. In this regard, polyphenols, natural molecules present in plants and a mainstay of healthy diets, such as the Mediterranean diet (Scalbert et al., 2005; Spencer et al., 2008), could become key tools for the forestall of brain aging. Polyphenols are in fact endowed of antioxidant

*Abbreviations:* AN, adult neurogenesis; AHR, aryl hydrocarbon receptor; APC, adenomatous polyposis coli; ARE, antioxidant responsive element; Axin, tumor suppressors Axin; aNSCs, adult neural stem cells; BMSCs, bone marrow-derived mesenchymal stem cells; BMPs, bone morphogenic protein; CREB, cAMP response element-binding protein; DG, dentate gyrus of hippocampus; ESCs, mouse embryonic stem cells; FGF4, fibroblast growth factor 4; FZD, frizzled receptors; GDNF, glial cell line-derived neurotrophic factor; GSH, glutathione enzyme; GSK-3β, glycogen synthase kinase3 beta; HO-1, heme oxygenase-1; hUC-MSCs, cell derived from mesenchimal stem cells; IGF2, insulin-like growth factor 2; iPSCs, induced pluripotent stem cell; NANOG, transcription factor of embryonic stem cells; Notch, transmembrane protein of Notch family; NSCs, neural progenitor stem cells; NF-κB, nuclear factor-kappa B; NPCs, neural progenitor cells; NQO1, NAD(P)H-quinone oxidoreductase 1; Nrf2, nuclear erythroid 2-related factor; LEF/TCF, lymphoid enhancer transcription factor/T-cell factor; LGR5/6, low-density-lipoprotein-related protein5/6; Rac1, Ras-related C3 botulinum toxin substrate 1 protein; RMS, rostral migratory stream; ROS, reactive oxygen species; RNF43, ring finger protein 43; SGZ, subgranular zone of the hippocampus; SIRT1, sirtuin 1; SFRP2, secreted frizzled related protein 2; SVZ, subventricular zone of the lateral ventricles; TACs, transit amplifying cells; TIPs, transient intermediate progenitors; TLE1, transducin-like Enhancer of Split-1; TLX, the orphan nuclear receptor; WISP1, WNT1 inducible signaling pathway protein 1; ZNRF3, zinc and ring finger protein 3

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https://doi.org/10.1016/j.neubiorev.2018.05.011
Received 29 August 2017; Received in revised form 5 April 2018; Accepted 7 May 2018

(Halliwell et al., 1997; Khurana et al., 2013) and anti-inflammatory properties (Elumalai and Lakshmi, 2016; Rahman et al., 2006), that include the inhibition of pro-inflammatory enzymes and signaling pathways (i.e. the nuclear factor-kappa B (NF-κB) cascade), the modulation of several cell survival/cell-cycle genes (Kim et al., 2004; Rice-Evans et al., 2004, Spencer et al., 2008; Stangl et al., 2007; Williams et al., 2004; Yoon and Baek, 2005), the activation of antiaging enzymes like sirtuin 1 (SIRT1) (Chung et al., 2010; Sarubbo, 2016) (more explanations in Section 4.3), and the regulation of developmental pathways (like Wnt/β-catenin) involved in the process of AN (Qu et al., 2010). The activation of defense systems and the modulation of the signaling pathways cited above are part of a multi-dimensional network program known to affect AN in mammalians in the stages of adulthood and especially in aging (Anacker and Hen, 2017; Gonçalves et al., 2016). Central to this article is the idea that dietary polyphenols promote AN, and by extension cognition and resilience to brain ageing, by acting on this multi-dimensional network (Dias et al., 2012). We will therefore review the latest progresses regarding the protective effects of polyphenols on AN in brain aging, addressing some of the molecular mechanisms involved and their implications in cognition.

## 2. Concept of adult neurogenesis (AN), regulation and implications in ageing

### 2.1. Concept of AN

AN denotes the process whereby NSC mature, migrate, and functionally integrate into the pre-existing neuronal network of an adult brain. It occurs throughout life in two specific neurogenic regions or "niches" of the mammalian brain, i.e. micro-environments that anatomically house NSCs and functionally control their development in vivo (Alvarez-Buylla and Lim, 2004; Riquelme et al., 2008); these niches are: 1) the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus, where new dentate granule cells are generated. In this location they participate in vital brain functions including memory, learning, and damage repair (Gage, 2000); 2) the subventricular zone (SVZ) of the lateral ventricles, from which newborn neurons migrate through the rostral migratory stream (RMS) to the olfactory bulb to become interneurons (Gage, 2000). Despite the high level of similarity between these two niches, a major difference reside in the fact that SGZ of hippocampus is enriched with different nerve terminals such as the noradrenergic and serotonergic fibers (Mongeau et al., 1997) and subjected to regulation by different neurotransmitters (including noradrenaline, dopamine, serotonin, acetylcholine, glutamate and GABA) (Veena et al., 2011). In contrast, SVZ does not have these nerve terminals and is separate from olfactory bulb where the integration of new neurons takes place. Also, there are far fewer progenitor cells in the SGZ compared with the SVZ in the human brain. Furthermore, in humans there is minimal progenitor proliferation in the SGZ and extensive proliferation in the SVZ (Curtis et al., 2012).

AN in other adult brain regions (e.g. the neocortex, striatum, amygdala and *substantia nigra*) is limited under normal physiological conditions, but could be induced after injury (Mirescu and Gould, 2006). In fact, AN in these areas has been difficult to replicate consistently other than in the damaged brain due to variations in the sensitivity of the methods used to detect new neurons (Gould, 2007). However, using carbon-14 dating approaches it has been shown that in adult humans new neurons presumably formed in the adjacent lateral ventricle wall integrate in the striatum (Ernst et al., 2014).

#### 2.1.1. Methods for studying AN

Altman and Das in 1965 were pioneers in studying AN in the postnatal rat hippocampus, and their findings established the first step of an extensive research on this topic. Subsequently, other scientists found functional integration of new neurons in neuronal circuitries, under both normal and disease states in rats (Deng et al., 2010). However, although AN was found to occur in humans (Eriksson et al., 1998; Reynolds and Weiss, 1992; Richards et al., 1992), very limited results have been obtained till now, mainly due to technical limitations afflicting human studies. The most frequent methodologies used for AN study are BrdU (Kuhn et al., 1996) and retroviral (van Praag et al., 1999) methodologies for birth-dating, genetic marking, and phenotypic characterization (the latter by immunohistology, electrophysiology, and confocal and electron microscopy). As awareness of the importance of AN in the prevention of cognitive decline increases, researchers are trying to develop more reliable endogenous markers for the characterization of neural precursors of AN in rodents and in post-mortem human tissues (Wang et al., 2011), as much as new high resolution imaging methods for human AN, including optogenetics (Zhang et al., 2010a), transneuronal tracers (Callaway, 2008), and in vivo imaging (Manganas et al., 2007).

### 2.2. Characteristics of AN

AN may contribute to the normal function of the adult brain, being also induced for self-repair in response to cerebral diseases. However, in an aged brain this ability declines respect to a young brain, possibly as a direct consequence of the aging process (Apple et al., 2017b). Although the specific causes and mechanisms responsible for this decline in AN during aging are still incompletely understood, several theories pointed out to either the intrinsic state of NSCs or their local environment.

Intrinsic characteristics of NSC (and of stem cells in general) are: 1) *self-renewing capacity* through cell division, and 2) *differentiation capacity* for generating specialized cell types (Gage, 2000). In vitro studies have demonstrated self-renewal and differentiation into neurons and glia from NSCs derived from adult rodent brains (Reynolds and Weiss, 1992; Richards et al., 1992; Palmer et al., 1999) and adult humans (Roy et al., 2000; Palmer et al., 1995). These capacities are limited by the exposure to growth factors (e.g. insulin-like growth factor-I (IGF-I)) as shown in NSCs derived from adult humans (Bath et al., 2008) and adult rats (Nieto-Estévez et al., 2016; Schänzer et al., 2004), as well as in rodent models in vivo. (Popken et al., 2004).

Specific characteristics of AN have also been identified: 1) In AN the tempo of maturation into neurons is slower compared to embryonic development (Ge et al., 2008; Overstreet-Wadiche, 2006; Zhao et al., 2006); 2) The cellular types originated in SGZ and SVZ can be vascular (endothelial cells), glial (ependymal cells, astrocytes, or microglia), neural, i.e. mature progeny of adult neural precursors; 3) It has been demonstrated that at the SVZ (Jablonska et al., 2010) and at the SGZ (Jessberger et al., 2008) new neurons derived from NPCs have a high degree of synaptic plasticity; 4) In both SGZ and SVZ the following similar stages exist during AN: the intermediate progenitor, the neuroblast stage (Platel et al., 2010) and the immature neuron integration stage (Mouret et al., 2008; Tashiro et al., 2006). Stem cells in both the SGZ and SVZ divide with a low rate to self-renew, giving rise to transit amplifying progenitors. 5) Differences exist between the two niches in the signalling pathways that regulate developmental stages of AN (Johnson et al., 2009) (see below, Section 2.4.1, Intracellular transducers). 6) After NSCs become activated, they divide and produce transit amplifying cells (TACs) in the SVZ and transient intermediate progenitors (TIPs) in the SGZ. The TACs and TIPs are rapidly dividing cells with the potential to differentiate into neurons with limited ability for self-renewal. After a limited number of cell divisions, the TACs and TIPs give rise to the neuroblasts. The proliferating neuroblasts then exit the cell cycle, and differentiates into newborn neurons that will then be integrated into the neuronal network in the brain (Hsieh, 2012; Vishwakarma et al., 2014; Zaidi et al., 2009). The balance between self-renewal and differentiation of adult NSCs is vital for the maintenance of the adult NSC reservoir and the continuous supply of new neurons, but how this balance is fine tuned in the adult brain and how it could be exogenously modulated is not completely understood.