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Therapeutic role of sirtuins in neurodegenerative disease and their modulation by polyphenols

Marjan Ajami[a,1], Hamidreza Pazoki-Toroudi[b,1], Hamed Amani[b,1], Seyed Fazel Nabavi[c], Nady Braidy[d,**], Rosa Anna Vacca[e,***], Atanas Georgiev Atanasov[f,g], Andrei Mocan[h], Seyed Mohammad Nabavi[c,*]

[a] National Nutrition and Food Technology Research Institute, Faculty of Nutrition Science and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Physiology Research Center and Department of Physiology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran
[c] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[d] Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Australia
[e] Institute of Biomembranes and Bioenergetics, National Council of Research, Bari, Italy
[f] Department of Pharmacognosy, University of Vienna, 1090 Vienna, Austria
[g] Institute of Genetics and Animal Breeding of the Polish Academy of Sciences, 05-552 Jastrzebiec, Poland
[h] Department of Pharmaceutical Botany, Iuliu Haţieganu University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania

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ABSTRACT

Searching for effective therapeutic agents to prevent neurodegeneration is a challenging task due to the growing list of neurodegenerative disorders associated with a multitude of inter-related pathways. The induction and inhibition of several different signaling pathways has been shown to slow down and/or attenuate neurodegeneration and decline in cognition and locomotor function. Among these signaling pathways, a new class of enzymes known as sirtuins or silent information regulators of gene transcription has been shown to play important regulatory roles in the ageing process. SIRT1, a nuclear sirtuin, has received particular interest due to its role as a deacetylase for several metabolic and signaling proteins involved in stress response, apoptosis, mitochondrial function, self-renewal, and neuroprotection. A new strategy to treat neurodegenerative diseases is targeted therapy. In this paper, we reviewed up-to-date findings regarding the targeting of SIRT1 by polyphenolic compounds, as a new approach in the search for novel, safe and effective treatments for neurodegenerative diseases.

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* Corresponding author at: Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, P O Box 19395-5487, Iran.
** Corresponding author at: Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, Australia.
*** Corresponding author at: Institute of Biomembranes and Bioenergetics, National Council of Research, Via Amendola 165/A, 70126 Bari, Italy.
E-mail addresses: n.braidy@unsw.edu.au (N. Braidy), r.vacca@ibbe.cnr.it (R.A. Vacca), Nabavi208@gmail.com (S.M. Nabavi).
[1] These authors contributed equally to this work.

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1. Introduction

Neurodegenerative disorders represent an ever-growing socio-economic challenge around the world particularly with changes in lifestyle, nutrition, environmental and physiological conditions (Tarailo-Graovac et al., 2016). During pathological conditions, the loss of structure or function of neurons is a consequence of multiple factors leading to neuronal degeneration in the central nervous system or peripheral nervous system, and to the development and progression of neurodegenerative diseases (Carr, 2015). Common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) as well as amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA) and spinal muscular atrophy (SMA).

Recent studies in cells, primary neurons, and mouse models, point to SIRT1, which belongs to the Sirtuin family of NAD-dependent protein deacetylases, for its neuroprotective action and its role as a central player in counteracting neurodegeneration. Sirtuins belong to a family of enzymes that are described as nicotinamide adenine dinucleotide (NAD)-related protein lysine deacetylases that are present in both prokaryotes and eukaryotes (Bheda et al., 2016; Chen et al., 2015). Another enzymatic activity of sirtuins is as mono (ADPribosyl) transferases (Kupis et al., 2016). These enzymes play an important role in several cellular processes such as regulation of transcriptional activity, energy metabolism (Haigis and Li, 2016), and genotoxicstress response by deacetylating substrate proteins in the cytoplasm and nucleus (Bindu et al., 2016; Teng et al., 2015). In addition sirtuins play an important role in the maintenance of genomic stability (Bosch-Presegué and Vaquero, 2015; Jeong and Haigis, 2015) .

So far, seven isoforms (SIRT1 to SIRT7) have been identified, all sharing a common catalytic domain and NAD^+-binding site in mammalian cells (Chen et al., 2015; Winnik et al., 2015). SIRT1, SIRT6, and SIRT7 are present in the nucleus whereas SIRT3, SIRT4, and SIRT5 are located in the mitochondria. It has been found that SIRT2 under certain physiological conditions is located in the cytoplasm but may translocate to the nucleus (George and Ahmad, 2016).

Dietary polyphenolic compounds, natural antioxidants present in daily foods, fruits, seeds, vegetables, and beverages, have been proposed as key players in the protection against neurodegenerative disorders via different signaling pathways (Asthana et al., 2016; Couturier et al., 2016; Ebrahimi and Schluesener, 2012). These compounds represent the largest groups of phytochemicals with favorable biological roles such as the scavenging of reactive oxygen species (ROS) and protection against photosynthetic stress in plants (Zhang et al., 2015). It has even been shown that some polyphenols can act as activators of SIRT1 in different settings whereas other polyphenolic compounds may exert an inhibitory function on SIRT1 (see Table 1). It is known that during AD, down-regulation of the expression level of SIRT1 activates NFκB, which mediates inflammatory pathway and Aβ toxicity (Almeida et al., 2016; Gao et al., 2016a). Activation of SIRT1 by, several flavonoids, such as kaempferol, quercetin, acacetin, apigenin and luteolin reduces neuroinflammation via NFκB repression (Zhang and Tsao, 2016). Also rutin a natural flavonol present in vegetables and fruits, inhibits H_2O_2-induced inflammation by suppressing expression of p-NF-κB, p-ERK, p-p38 MAPK, and p-JNK through SIRT1 activation which remarkably inhibits the release of pro- inflammatory cytokines such as TNF-α, IL-1β and MMP-2/9 (Na et al., 2016). On the other hand resveratrol, the main polyphenol found in the skin of the red grapes, has been shown to inhibit both SIRT1 expression and activity, inducing FOXO3A hyperacetylation and apoptosis in Hodgkin lymphoma cells (Frazzi et al., 2013), and to activate SIRT1/AMPK and promote neurites outgrowth and neural plasticity (Dias et al., 2016). It has been also reported that white tea polyphenols effectively inhibit adipogenesis and stimulate lipolysis-activity through SIRT1 down-regulation (Söhle et al., 2009).

Herein, the role of polyphenolic compounds in neurodegeneration treatment by targeting SIRT1 was reviewed and further discussed.

2. Neurodegeneration, a matter involving multiple factors and pathways

Different molecular signaling pathways are engaged in neurodegeneration that have been discovered in several models for neurodegenerative diseases (Gerdts et al., 2016; Mehrjerdi et al., 2013; Zheng et al., 2016).

The main pathological hallmark common to neurodegenerative diseases is the progressive accumulation of abnormal protein aggregates. For example, AD is characterized by the presence of plaques composed of amyloid beta aggregates, and intracellular neurofibrillary tangles containing hyperphosphorylated tau, a microtubule protein (Lee and Masliah, 2015; Ludtmann and Abramov, 2016; Walsh and Selkoe, 2016). $A\beta_{1-42}$-induced toxicity in AD leads to overexpression of caspase 3/7 and consequently induces apoptosis (Chen et al., 2016b). Endosomal sorting complexes required for transport (ESCRT) are multimolecular assemblies that play a pivotal role in degradation and refolding of protein aggregates and misfolded proteins through an autophagy-dependent mechanism. ESCRT abnormalities mediate apoptotic and necrotic cell death via activation of the JNK pathway (Oshima et al., 2016). The tumor suppressor WW domain-containing oxidoreductase WWOX, or WOX1, is a protein aggregation -control agent in the human brain. This protein binds to tau and tau-hyperphosphorylating enzymes GSK3β, ERK, and JNK1 through different domains. During senescence, the expression level of WWOX is decreased, and this leads to accumulation of protein aggregates in neurons and subsequently neurodegeneration (Sze et al., 2015). Misfolding and aggregation of proteins can directly and indirectly target cellular components that result in neuronal cell death.

Neurodegeneration has been directly associated with cellular senescence (Cho et al., 2015). Repressor element 1 silencing transcription factor (REST) protein is a nuclear factor that leads to neuroprotection against ageing and cell death, and the preservation of cognitive functions during senescence (Nechiporuk et al., 2016). During 'healthy' ageing, exposure to neurotoxic stimuli elevates the expression level of REST and activates Wnt-signaling pathways. REST induction inhibits the expression of several pro- apoptotic genes and reduces the production of highly reactive free radicals, which in turn prevents neurodegeneration (Lu et al., 2014; Tsai and Madabhushi, 2014). REST, however, in another study has been suggested to contribute to neuronal death (Guida et al., 2016). A significant reduction in endogenous antioxidant defenses in the central nervous system is responsible for its higher susceptibility to oxidative stress that may serve as the basis for the onset of neurodegenerative diseases.

Mitochondrial deficiency is at the core of the pathogenesis of neurodegenerative diseases (Chan et al., 2016; Krols et al., 2016; Palomo and Manfredi, 2015). Mitochondrial electron chain impairment results in cell energy deficit, acceleration in free radical production by mitochondria and leakage of pro-apoptotic factors which lead to defective bioenergetics, oxidative stress and neural cell death key events in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and Down syndrome (DS) (Akbar et al., 2016).