Biochimica et Biophysica Acta 1852 (2015) 1195–1201

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Neuroprotective action of resveratrol ☆

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ARTICLE INFO

Article history:
Received 24 July 2014
Received in revised form 9 September 2014
Accepted 16 September 2014
Available online 2 October 2014

Keywords:
Polyphenol
Alzheimer's disease
Amyloid
Ischemia
SIRT-1
Kinase

ABSTRACT

Low-to-moderate red wine consumption appeared to reduce age-related neurological disorders including macular degeneration, stroke, and cognitive deficits with or without dementia. Resveratrol has been considered as one of the key ingredients responsible for the preventive action of red wine since the stilbene displays a neuroprotective action in various models of toxicity. Besides its well documented free radical scavenging and anti-inflammatory properties, resveratrol has been shown to increase the clearance of beta-amyloid, a key feature of Alzheimer's disease, and to modulate intracellular effectors associated with oxidative stress (e.g. heme oxygenase), neuronal energy homeostasis (e.g. AMP kinase), program cell death (i.e. AIF) and longevity (i.e. sirtuins). This article summarizes the most recent findings on mechanisms of action involved in the protective effects of this multi target polyphenol, and discusses its possible roles in the prevention of various age-related neurological disorders. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. Introduction

It is well known that a healthy diet may delay the occurrence of age-related neurological disorders such as Alzheimer's and Parkinson's diseases and stroke [1,2]. Hence, it has been reported that regular consumption of fruits, vegetables and fish lowered the risk of cognitive decline related or not to dementia in the elderly population [1]. Moreover, older adults who consume red wine (up to three glasses per day) on a regular basis reduced (up to 50%) the risk of developing dementia, such as Alzheimer's disease (AD) and vascular dementia, as well as macular degeneration [1,3,4]. This is of particular interest since the number of people that will be at-risk or affected by age-related neurological disorders will rise, resulting in an increase in economic burden of care and treatment of patients.

Scientists have intensively investigated the mechanisms of action by which protective diet, and particularly red wine, prevents age-related neurodegenerative diseases. Although there are numerous polyphenols present in red wine that may be responsible for its beneficial effect, resveratrol has drawn particular attention because it is considered as a red wine-derived polyphenol with cardioprotective effects [5,6]. Numerous studies ranging from cell cultures to animal studies have demonstrated that resveratrol exhibits anti-inflammatory and antioxidant properties, inhibits beta-amyloid (Aβ) protein aggregation and modulates intracellular effectors involved in neuronal cell survival/death. More recently, resveratrol has been proposed to exert neuroprotective effects through activation of SIRT1, an enzyme that deacetylates proteins associated with cellular regulation [7]. Here, we review possible mechanisms underlying the purported neuroprotective action of resveratrol *in vitro* as well as rodent models of diseases. See Table 1 and Fig. 1 for details.

2. Reactive oxygen species

Higher levels of reactive oxygen species (ROS) in aging were shown to be associated with cognitive deficits related or not to AD

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; AIF, Apoptosis Inducing Factor; AMPK, AMP-activated protein kinase; AP-1, activator protein-1; BBB, blood-brain barrier; COX, cyclooxygenase; APP, amyloid precursor protein; ERK1/2, extracellular signal-regulated kinase-1 and -2; GF 109203X, dihydrochloride3-(1-[3-(dimethylamino) propyl]-1H-indol-3yl)-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione; GSK3β, glycogen synthase kinase 3β; HO1, heme oxygenase 1; i.p., intraperitoneal; LKB1, liver kinase B1; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MPP+, 1-methyl-4-phenylpyridinium ion; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor-kappaB; NO, nitric oxide; 6-OHDA, 6-hydroxydopamine; OGD, oxygen–glucose deprivation; PD, Parkinson's disease; PCD, programmed cell death; PI3-k, phosphoinositide3-kinase; PKC, protein kinase C; QR2, quinone reductase 2; ROS, reactive oxygen species; TNFα, tumor necrosis factor α

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http://dx.doi.org/10.1016/j.bbadis.2014.09.011
0925-4439/

Table 1
Summary of the protective effects of resveratrol.

Effects	Proposed underlying mechanisms	References
Increases cerebral blood flow (250 and 500 mg) during cognitive task performance in health adults	Vasodilatory activities	[97]
Protects and rescues (5–25 μM) hippocampal neuronal cells against toxicity induced by nitric oxide	Free radical and ion metal scavenging activities	[11]
Protects (25 μM) primary neuronal cells against excitotoxicity	Increase in HO 1 protein levels	[16]
Protects (10–60 μM) mitochondria against oxidative stress	Phosphorylation of GSK3β	[19]
Protects (10–40 mg/kg/day for 10 weeks) dopaminergic neuronal cells exposed to 6-hydroxydopamine (6-OHDA)	Reduction of the expression of COX-2 protein and tumor necrosis factor α (TNFα) in the substantia nigra	[21]
Inhibits (up to 50 μM) the activation of microglia exposed to lipopolysaccharide (LPS)	Reduction of the production/expression of prostaglandins, NO, TNFα, COX-1 and NF-κB	[23–26]
Protects (15–60 μM) against LPS-induced dopaminergic neuronal death	Attenuation of the activation of MAPK and NF-κB in microglia	[27]
Protects (15–40 μM) hippocampal cells exposed to Aβ peptides	– Induction of the phosphorylation of PKCδ isoform. – Inhibition and destabilization of $A\beta_{1-42}$ fibril formation	[38,42,51]
Protects (10–20 μM) HT22 hippocampal cells against Aβ-induced toxicity	Inhibition of the $A\beta_{1-42}$-induced activation of GSK3β and AMPK activity	[41]
Reduces (diet supplemented with 3.5 g/l of resveratrol for 2 weeks) in brain Aβ levels and amyloid deposition in mice	– Activation of the degradation of Aβ via a mechanism that involves proteasome – Activation of the AMPK signaling pathway	[56]
Reduces (75 and 100 μM) neuronal death in CA1 region of the hippocampus exposed to ischemia	Activation of SIRT1	[62]
Protects (7.5 μM) neuroblastoma cell line exposed to 6-OHDA	Activation of SIRT1	[60]

[8]. Resveratrol displays potent antioxidant activity because of its ability to scavenge free radicals and metals (i.e. copper) and to up-regulate endogenous antioxidant enzymes including glutathione peroxidase [9,10]. We have shown that resveratrol is able to protect and even rescue hippocampal neurons that were exposed to nitric oxide (NO), an effect that could be explained, at least in part, by its purported antioxidant activities, as well as its ROS scavenging properties [11].

Resveratrol may also play a beneficial role in the cellular response by modulating enzymes involved in stress response, such as quinone reductase 2 (QR2), a cytosolic enzyme which enhances the production of damaging activated quinone and ROS [12]. Our group demonstrated that QR2 is overexpressed in the hippocampus – a brain area involved in learning and memory and severally affected in AD – in rat models of learning deficits, suggesting that the overexpression of this enzyme triggers memory impairments [13]. This hypothesis is supported by the fact that selective inhibitors of QR2 were able to block hippocampal neuronal cell death induced by menadione, a QR2 substrate [13]. Interestingly, resveratrol inhibits QR2 at low micromolar concentration (IC50 of 2.9 μM) [14], an effect that may lead to an increase in cellular resistance against oxidative stress-induced neuronal death [15]. Besides its inhibitory action on QR2, resveratrol has been shown to induce heme oxygenase 1 (HO1), an endogenous enzyme that provides resistance against oxidative stress-related neuronal damage [16]. The authors first showed that resveratrol (25 μM) increased HO1 protein levels in primary neuronal cells exposed to glutamate, an effect that was due to an increase in HO1 protein synthesis. Moreover, a pre-treatment with resveratrol (20 mg/kg) significantly attenuated infarct size in wild-type but not HO1 knockout mice exposed to ischemia, suggesting that the polyphenol also interacts *in vivo* with the enzyme [16]. Using neuronal cell lines, Dasgupta and Milbrandt [17] showed that resveratrol is a potent activator of AMP-activated protein kinase (AMPK), a key regulator of cell survival in response to oxidative stress insults [18]. Moreover, resveratrol was shown to protect mitochondria against oxidative stress induced by a mixture of arachidonic acid and iron, through a mechanism that involves AMPK-dependent phosphorylation of glycogen synthase kinase-3beta (GSK3β) [19]. These authors also reported that the neuroprotective action of resveratrol depends on the presence of liver kinase B1 (LKB1), an upstream kinase of AMPK [19]. Furthermore, this LKB1-dependent mitochondrial protection resulted from resveratrol's poly(ADP-ribose)polymerase activation, but not SIRT1 activation [19].

3. Neuroinflammation

Microglial activation may contribute to neuronal death during brain damage by releasing neurotoxic pro-inflammatory molecules [20]. It has been reported that resveratrol inhibits the pro-inflammatory molecules known as cyclooxygenases, particularly cyclooxygenase-1 (COX1) (for review see [10]), an enzyme involved in the production of pro-inflammatory molecules known as cytokines. Moreover, Jin et al. [21] showed that resveratrol exerted an *in vivo* neuroprotective action against toxicity induced by 6-hydroxydopamine (6-OHDA), and this effect was associated with its ability to reduce expression of COX-2 and tumor necrosis factor α (TNFα) in the substantia nigra. Resveratrol is also able to reduce the release of pro-inflammatory factors through the inhibition of cellular cascade signaling pathways involving nuclear factor-kappaB (NF-κB) and activator protein-1 (AP-1) [22]. Using rat primary microglia cultures exposed to lipopolysaccharide (LPS), it has been reported that resveratrol (up to 50 μM) reduced the production of prostaglandins (e.g. PGE2), NO, and TNFα, as well as the expression of COX-1 and activation of NF-κB [23–26]. Finally, it has been shown that resveratrol (15–60 μM) protected against dopaminergic neuronal death induced by LPS by attenuating the activation of mitogen-activated protein kinases (MAPKs) and NF-κB signaling pathways, supporting the hypothesis that neuroprotection triggered by resveratrol involved inhibition of microglia-mediated neuroinflammation [27].

Astrocytes, a type of glial cells, actively regulate brain energy metabolism, neurotransmitter release, ionic homeostasis and defense against oxidative stress [28,29]. Using a model of astrocytes exposed to H_2O_2, Quincozes-Santos et al. [30] have reported that resveratrol (100 μM) decreased nitrite and nitrogen species levels, whose overproduction likely plays a role in Alzheimer's and Parkinson's diseases [31]. Moreover, resveratrol enhanced per se HO1 expression and reduced ROS production possibly through its HO1 in these cells [30]. HO1 can also reduce NF-κB activation (for review, see [32]). Finally, it has been recently shown by the same group that resveratrol stimulated antioxidant defenses by increasing glutathione levels and decreased cytokines in rat hippocampal cultured astrocytes [33], a process that may explain its protective action against toxicity associated with neuroinflammation and be relevant to neurodegenerative diseases [34].

4. Amyloidogenesis

There is accumulative evidence suggesting that progressive accumulation of Aβ plaques plays a crucial role in neuronal death occurring in