

# Resveratrol and Brain Mitochondria: a Review

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Received: 12 December 2016 / Accepted: 7 February 2017  
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**Abstract** Resveratrol (3,4',5-trihydroxystilbene; C<sub>14</sub>H<sub>12</sub>O<sub>3</sub>) is a polyphenolic phytoalexin found in grapes, berries, peanuts, and wines. Resveratrol has been viewed as an antioxidant, anti-inflammatory, anti-apoptotic, and anticancer agent. Moreover, it has been reported that resveratrol modulates mitochondrial function, redox biology, and dynamics in both in vitro and in vivo experimental models. Resveratrol also attenuates mitochondrial impairment induced by certain stressors. Resveratrol upregulates, for example, mitochondria-located antioxidant enzymes, decreasing the production of reactive species by these organelles. Resveratrol also triggers mitochondrial biogenesis, ameliorating the mitochondria-related bioenergetics status in mammalian cells. In the present work, we discuss about the effects of resveratrol on brain mitochondria. Brain cells (both neuronal and glial) are susceptible to mitochondrial dysfunction due to their high demand for adenosine triphosphate (ATP). Additionally, brain cells consume oxygen (O<sub>2</sub>) at very high rates, leading to a proportionally high mitochondrial production of reactive species. Therefore, strategies focusing on the maintenance of mitochondrial function in these cell types are of pharmacological interest in the case of neurodegenerative diseases, which involve mitochondrial impairment and increased generation of reactive species, leading to neuroinflammation and cell death. The mechanism by which resveratrol

protects mitochondrial function and dynamics is not completely understood, and further research would be necessary in order to investigate exactly how resveratrol affects mitochondria-related parameters. Furthermore, it is particularly important because resveratrol is able to induce cytotoxicity depending on its dosage.

**Keywords** Resveratrol · Brain · Mitochondria · Redox biology · Mitochondrial biogenesis · Mitochondrial dynamics

## Introduction

Resveratrol (3,4',5-trihydroxystilbene; C<sub>14</sub>H<sub>12</sub>O<sub>3</sub>), a polyphenolic phytoalexin found in grapes, berries, peanuts, and wines, exhibits antioxidant, anti-inflammatory, anti-apoptotic, and anticancer capacities [1–6]. Resveratrol plays a central role in the “French paradox,” the inverse correlation between the intake of red wine and the incidence of cardiovascular disease [7, 8]. In addition to elicit beneficial effects in the cardiovascular system, resveratrol has been viewed as a neuroprotective agent. Resveratrol is effective in preventing redox impairment in brain cells in several in vitro and in vivo experimental models [9–13]. Additionally, resveratrol exerts anti-apoptotic actions in brain cells challenged with different types of stressors [14–18]. This polyphenol also modulates central nervous system function, as assessed in studies aiming to analyze the impacts of resveratrol on learning and memory abilities [19–23]. Resveratrol-induced antidepressive effects were also described experimentally [24–28]. Thus, resveratrol is able to cross the blood–brain barrier, exerting beneficial effects in both neuronal and glial cells [29]. Brain cells are very sensitive to energetic stress due to the high demand for adenosine triphosphate (ATP) in order to maintain neurotransmission, neuronal plasticity, synthesis of protein, cellular osmolarity,

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and cell division (depending on the cell type and the brain area), among other biological processes that consume ATP [30, 31]. Natural compounds that would be able to modulate bioenergetics in brain cells present potential to be used as neuroprotective agents [32]. In that context, resveratrol has been reported to be able to modulate mitochondrial function, redox biology, and dynamics in different cell types [12, 33–35].

Mitochondria are the major organelles involved in the synthesis of ATP in mammalian cells due to the presence of the components responsible for the maintenance of oxidative phosphorylation [36–38]. The electron flux between the complexes of the respiratory chain generates an electrochemical potential across the inner mitochondrial membrane that is further utilized by complex V (the so-called ATP synthase/ATPase) to produce ATP. Oxygen ( $O_2$ ) is the final acceptor of electrons and, in a reaction mediated by complex IV (also called cytochrome c oxidase), is reduced completely generating water [36]. The maintenance of the mitochondrial function is crucial to maintain the bioenergetic requirements of each cell type containing mitochondria. Perturbations in the mitochondrial function lead to several negative consequences, including impaired synthesis of biomolecules (lipids, proteins, nucleic acids, among others), disruption in the maintenance of cellular osmolarity, and cell death, to cite some examples [39, 40]. Actually, mitochondrial dysfunction has been associated with human diseases, such as neurodegeneration and cardiovascular diseases [41–48]. In that context, strategies aiming to prevent or to treat mitochondrial impairment attracted the attention of researchers mainly in the field of neurobiology, since the loss of neurons is irreversible in the majority of the brain areas [49, 50]. Additionally, mitochondria play a role in neuronal plasticity, which is a complex phenomenon necessary to maintain some central functions, such as learning and memory, among others [51, 52].

Several works have been published showing that dietary components may modulate mitochondrial function and dynamics, causing cytoprotection in different *in vitro* and *in vivo* experimental models involving animals and humans [12, 53–64]. In spite of this, there is a lack for information regarding the exact mechanism by which dietary factors alter mitochondria-related parameters causing benefits. Mitochondrial function may vary according to alterations in the redox environment and these organelles also contribute to change redox-related aspects in mammalian cells [65]. Number of mitochondria may be altered by the triggering of mitochondrial biogenesis (i.e., the synthesis of new mitochondria) or mitophagy (i.e., the degradation of mitochondria during autophagy) [66]. Additionally, mitochondrial fusion and fission alter mitochondrial number, size, and morphology [67]. Furthermore, mitochondria take a key role in mediating cell death through the intrinsic apoptotic pathway [68]. These mitochondria-related phenomena have been investigated in a research field that is

called “mitochondrial medicine,” in which dietary factors are a major focus of interest [69].

Therefore, the aim of this work is to discuss how resveratrol would induce cytoprotective effects by modulating mitochondrial function, redox biology, and dynamics in several cell types. We focused on publications demonstrating the mechanisms by which resveratrol affects such parameters in mammalian cells. We also suggest here several experiments that would be useful to better understand how exposure to resveratrol impacts these organelles.

## Mitochondrial Redox Biology: an Overview

The mitochondrial respiratory chain is a major site of reactive species production due to electron leakage [70]. The major sites of reactive species generation include complex I and complex III [71]. Superoxide anion radical ( $O_2^{\cdot-}$ ) and hydrogen peroxide ( $H_2O_2$ ) may be originated from alterations in the function of the respiratory chain due to variations in the energetic demand cells require [72]. Furthermore, changes in the  $O_2$  concentrations affect the respiratory chain activity and favor  $O_2^{\cdot-}$  production due to partial  $O_2$  reduction [70]. Several toxicants also cause mitochondrial dysfunction and increase the production of reactive species by the mitochondria [73, 74]. Mitochondria exhibit antioxidant defenses, such as the enzymatic and nonenzymatic. Among the enzymatic antioxidant defenses, Mn-superoxide dismutase (Mn-SOD) takes a crucial role in the conversion of  $O_2^{\cdot-}$  into  $H_2O_2$ , which reacts with glutathione peroxidase (GPx) or catalase (CAT) generating water [75–78].

The main nonenzymatic antioxidant defense is reduced glutathione (GSH) [75]. GSH is produced in the cytosol and its transport into mitochondria is necessary in order to attenuate redox impairment that may result from increased  $H_2O_2$  production through the reactions of Mn-SOD [76] and/or from mitochondrial complexes [70]. Moreover, mitochondria-located monoamine oxidase (MAO) enzyme generates  $H_2O_2$  during the reactions of neurotransmitter degradation [79].  $H_2O_2$  is a diffusible molecule that readily crosses biomembranes and may be viewed as both a manner to widespread oxidative stress and a signaling agent [80]. An imbalance in the activity of brain superoxide dismutases and CAT, for example, may render excessive  $H_2O_2$  production and impaired redox homeostasis [81, 82]. Therefore, caution is needed when aiming to interfere with mitochondria-located SOD to avoid deregulation in the  $H_2O_2$  concentrations in neuronal and glial cells, since the central nervous system (CNS) is rich in lipids and also presents high concentrations of iron and copper ions, as well as presents extremely high levels of reactive neurotransmitters [83]. The reaction of  $H_2O_2$  with either iron or copper ions leads to the formation of hydroxyl ( $\cdot OH$ ), which is involved in

neurodegenerative processes [84]. The reaction of  $\text{H}_2\text{O}_2$  with  $\text{O}_2^{\cdot-}$  also generates  $\cdot\text{OH}$  in such situations [83].

Mitochondria also contain an isoform of nitric oxide synthase (mtNOS), which produces nitric oxide ( $\text{NO}^{\cdot}$ ), a free radical and signaling molecule [85, 86].  $\text{NO}^{\cdot}$  may react with  $\text{O}_2^{\cdot-}$  from the respiratory chain yielding peroxynitrite ( $\text{ONOO}^-$ ), a reactive specie that reacts with tyrosine residues in proteins, leading to nitrosative stress [87, 88]. Moreover, peroxynitrous acid ( $\text{ONOOH}$ , which originated from  $\text{ONOO}^-$ ) generates nitryl cation ( $\text{NO}_2^+$ ), nitrogen dioxide radical ( $\cdot\text{NO}_2$ ), and hydroxyl radical ( $\cdot\text{OH}$ ) by homolytic fission [89, 90]. Nitrosative stress has been reported to affect mitochondrial function due to the damage  $\text{ONOO}^-$  may cause in proteins present in the mitochondrial membranes [91, 92]. Additionally, nitrosative stress has been associated with several neurodegenerative diseases, such as Alzheimer's disease [93], Parkinson's disease [94–96], and Huntington's disease [97, 98], among others [99–102].

The levels of antioxidant defenses in mitochondria are modulated by transcription factors, mainly nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor- $\kappa\text{B}$  (NF- $\kappa\text{B}$ ) [103, 104]. Nrf2 has been viewed as a major redox modulator in mammalian cells [104]. Furthermore, Nrf2 participates in the regulation of mitochondria-related bioenergetics processes in different cell types [105–107]. Nrf2 is maintained in an inactive form in the cytosol through binding to Kelch-like ECH-associated protein 1 (Keap1) [108]. During exposure to pro-oxidant or electrophile agents, Nrf2 is released from Keap1 and translocates to the cell nucleus in order to modulate the expression of several antioxidant and detoxifying proteins [109]. The link between Nrf2 activation and maintenance of mitochondrial function has been examined as an important pharmacological target in cases of neurodegeneration, since mitochondrial impairment takes a crucial role in the pathophysiology of these conditions [104, 110]. The activation of NF- $\kappa\text{B}$ , a major immunomodulatory agent in mammalian cells, is regulated by the interaction with the inhibitor  $\kappa\text{B}$  ( $\text{I}\kappa\text{B}$ ) proteins and has been linked to the maintenance of mitochondrial redox status, because NF- $\kappa\text{B}$  is involved in the control of Mn-SOD expression [103]. Additionally, it has been demonstrated that NF- $\kappa\text{B}$  upregulates the synthesis of glutathione-S-transferase (GST), which participates in phase II detoxification in several cell types [111]. GST increases the solubility of toxicants, favoring its excretion after conjugation with GSH [112]. Redox-active toxicants targeting mitochondria, for example, may be excreted more rapidly from cells, decreasing its effects on the organelles [111]. Both Nrf2 and NF- $\kappa\text{B}$  are modulated upstream by protein kinases, including the phosphoinositide-3-kinase (PI3K)/protein kinase B (PKB, also called Akt) signaling pathway, protein kinase C (PKC)-dependent signaling, and

mitogen-activated protein kinases (MAPK), such as extracellular signal-regulated kinase (Erk), p38, and c-Jun N-terminal kinase (JNK), among others, as recently published in excellent reviews [105, 107, 113, 114].

Therefore, mitochondria are sources of reactive species and the maintenance of the function of these organelles is crucial to avoid redox impairment and cell death. Several works have been published demonstrating possible strategies to protect brain mitochondria by the modulation of antioxidant defenses located in the organelles [12, 53–62]. In spite of this, the exact mechanism underlying the chemically induced mitochondrial protection is not clear yet. Thereby, we have made several suggestions in this work that may be useful in further research involving modulation of mitochondrial redox biology in brain cells.

### Mitochondrial Biogenesis: an Overview

Mitochondrial biogenesis (*mitogenesis*) is a complex process responsible for the synthesis of new mitochondria in mammalian cells [115–117]. Both nuclear and mitochondrial genomes are necessary to modulate mitochondrial biogenesis, which is an event needed to alter number of mitochondria according to the requirements of the cells [115]. Peroxisome proliferator-activated receptor gamma coactivator 1- $\alpha$  (PGC-1 $\alpha$ ) is the major regulator in mitochondrial biogenesis by acting with the nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) [118]. PGC-1 $\alpha$  upregulates NRF-1 and NRF-2, as well as the estrogen-related receptor  $\alpha$  (ERR $\alpha$ ) [119–121], leading to the expression of mitochondrial proteins encoded by nuclear DNA [122].

Among these proteins, upregulation of the mitochondrial transcription factor A (TFAM) and mitochondrial transcription factors B1 and B2 (TFB1M and TFB2M) leads to alterations in the DNA located in mitochondria, causing the synthesis of mitochondrial RNA [123]. TFAM is involved with both transcription and replication of mitochondrial DNA (mtDNA) [124, 125]. Additionally, TFAM has been viewed as an important modulator of mtDNA homeostasis and repair [125–127]. The regulation of PGC-1 $\alpha$  involves lysine acetylation by the  $\text{NAD}^+$ -dependent deacetylase sirtuin 1 (SIRT1) [128, 129]. SIRT1, in turn, is modulated by AMP-activated protein kinase (AMPK), which regulates  $\text{NAD}^+$  levels, causing SIRT1 activation and upregulation of PGC-1 $\alpha$  by a SIRT1-mediated deacetylation [130]. The AMPK/SIRT1/PGC-1 $\alpha$  axis is a major signaling pathway orchestrating mitochondrial function and dynamics in mammalian cells. Mitochondrial biogenesis impairments have been reported to take a crucial role in several diseases [131–133] and may be a pharmacological target to prevent or to treat such disturbances [33, 35, 54–62, 134].

## Resveratrol-Induced Mitochondria-Related Effects: Focus on Brain Cells

Resveratrol is an antioxidant, anti-inflammatory, and anticancer agent, as reported by several research groups [135–140]. Additionally, the effects of resveratrol regarding mitochondrial function and dynamics are focus of research due to the role these organelles present in both physiological and pathological conditions [12]. The impact of resveratrol exposure includes alterations in mitochondrial function, redox state, dynamics, and synthesis of new mitochondria. In the present review, we describe, discuss, and compare (whenever possible due to availability of reported data) the effects of resveratrol focusing on brain mitochondria. Mitochondrial dysfunction in neuronal and glial cells has been viewed as an important component of neurodegeneration [141], and modulation of mitochondria-related factors by dietary agents represents a very interesting strategy to prevent or to treat neurodegenerative disorders.

### Redox Effects of Resveratrol on Mitochondria of Brain Cells

Resveratrol modulates mitochondria-related redox aspects by an indirect way through the induction of the expression of mitochondria-located antioxidant enzymes, as will be discussed in this section. It is noteworthy that some of the concentrations of resveratrol utilized in *in vitro* studies are considered high when analyzing the levels resveratrol reaches after *in vivo* administration, as observed in works aiming to obtain data regarding resveratrol bioavailability [142–144]. Furthermore, resveratrol cytotoxicity has been studied *in vitro*, indicating that increased delivery of resveratrol to normal cells may be risky to mitochondrial function [145]. Thus, caution is needed when considering resveratrol to

improve mitochondrial function and/or dynamics therapeutically.

### *In Vitro* Experimental Models

Resveratrol may exert both antioxidant and pro-oxidant effects in mammalian cells depending on its concentration. The pro-oxidant actions elicited by resveratrol have been utilized to induce, for example, apoptosis in cancer cells related to brain tissue [146]. In spite of this, we focused here only on the mitochondria-related antioxidant effects elicited by resveratrol due to the potential this polyphenol presents as a neuroprotective agent in cases of neurodegenerative disorders in which mitochondrial impairment takes a central role (Table 1).

Kairisalo et al. [147] evidenced that resveratrol may modulate the mitochondria-related redox biology by a mechanism associated with the upregulation of Mn-SOD. Resveratrol (50  $\mu$ M for 24 h) upregulated the expression of Mn-SOD and thioredoxin-2 (Trx2), as well as increased the content of X-linked inhibitor of apoptosis protein (XIAP), an anti-apoptotic protein, in neuron-like PC6-3 cells (a pheochromocytoma cell line). The authors also found that resveratrol increased the levels of NF- $\kappa$ B in that experimental model, a transcription factor that is modulated, at least in part, by XIAP and is involved in the regulation of the expression of both Mn-SOD and Trx2 [163]. Therefore, it is very likely that resveratrol ameliorated mitochondrial redox parameters through a XIAP/NF- $\kappa$ B signaling pathway in neuron-like PC6-3 cells. The utilization of specific inhibitors would be useful to understand exactly how resveratrol enhanced the levels of antioxidant proteins located in mitochondria. Thus, further studies are needed focusing in the mechanism by which resveratrol elicited such effects. Additionally, it would be interesting to investigate the effects of resveratrol on the transcription factor NF- $\kappa$ B in brain cells in different experimental models. Actually, Jang and Surh [164] reported that

**Table 1** Summary of the mechanisms involved in the resveratrol-induced mitochondria-related redox effects in brain cells in *in vitro* experimental models

Experimental model	Biological sample	Main findings	Reference
Resveratrol at 50 $\mu$ M for 24 h	Rat pheochromocytoma cell line (PC6.3)	$\uparrow$ the levels of Mn-SOD, Trx2, and XIAP; $\uparrow$ NF- $\kappa$ B levels	[147]
Resveratrol at 20 $\mu$ M for 48 h prior exposure to acrolein	Human adult retinal pigment epithelial (ARPE) cells	Restored Mn-SOD levels; $\uparrow$ respiratory capacity; $\uparrow$ rates of oxidative phosphorylation	[148]
Resveratrol at 5–10 $\mu$ M for 48 h in the presence of MPP <sup>+</sup>	Mouse dopaminergic cell line (SN4741)	$\uparrow$ levels of SIRT1, PGC-1 $\alpha$ , Trx2, and SOD2	[149]
Resveratrol at 25 $\mu$ M for 2 h (resveratrol preconditioning)	Astrocytes obtained from wild-type and Nrf2 <sup>-/-</sup> mice	$\uparrow$ levels of UCP2; $\uparrow$ the production of H <sub>2</sub> O <sub>2</sub> by complexes I and III	[150]
Resveratrol at 100 $\mu$ M for 1 h before exposure to azide	Primary hippocampal astrocytes obtained from rat	Prevented $\downarrow$ MMP; prevented $\downarrow$ of cytochrome c oxidase expression; $\uparrow$ Mn-SOD activity; $\downarrow$ mitochondrial production of reactive species; inhibition of HO-1 abrogated the effects elicited by resveratrol	[151]

Please see the text for more detailed information

resveratrol co-treatment at lower concentrations (25  $\mu\text{M}$  for 36 h) protected PC12 pheochromocytoma cells against amyloid- $\beta$  peptide cytotoxicity by inhibiting NF- $\kappa\text{B}$  and suppressing mitochondria-mediated cell death. Therefore, this is an important point to be addressed in future research.

Sheu et al. [148] reported that resveratrol protected human adult retinal pigment epithelial (ARPE) cells against acrolein-induced oxidative stress and cell death by a mechanism involving mitochondrial protection. Resveratrol (20  $\mu\text{M}$  for 48 h prior chemical challenge) abrogated the acrolein-induced upregulation in Mn-SOD immunoccontent without altering the levels of Cu/Zn-SOD in ARPE cells. Resveratrol also ameliorated the respiratory capacity and the rates of oxidative phosphorylation in the cells exposed to acrolein. Interestingly, resveratrol did not induce mitochondrial biogenesis in that experimental model. Thus, resveratrol probably protected mitochondrial function by an indirect antioxidant effect without involving the synthesis of new organelles. The exact mechanism underlying the resveratrol-elicited Mn-SOD upregulation deserves attention because several transcription factors are involved in the modulation of Mn-SOD expression, as reviewed elsewhere [165]. Additionally, the PGC-1 $\alpha$ -dependent signaling pathway, which is a specific target of resveratrol in mammalian cells, also coordinates the expression of antioxidant enzymes [166, 167]. In this view, mechanistic studies are welcome in order to reveal how resveratrol modulated Mn-SOD expression causing mitochondrial protection. Furthermore, some research groups have demonstrated that resveratrol suppressed the loss of mitochondrial membrane potential (MMP) induced by different challenges in several experimental models [168, 169]. Disruption of MMP leads to increased production of reactive species due to the leakage of electrons from the respiratory chain [170]. In addition, loss of MMP affects ATP production, causing bioenergetics deficits and, in some cases, cell death [68]. Thus, rescuing of MMP in cases of deleterious events potentially affecting mitochondria causes benefits regarding mitochondrial function and cell fate.

Resveratrol (5–10  $\mu\text{M}$  for 48 h) co-treatment elicited mitochondria-related antioxidant effects by a mechanism potentially involving the activation of SIRT1/PGC-1 $\alpha$  signaling pathway in mouse dopaminergic cell line SN4741 exposed to 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>; an *in vitro* experimental model of Parkinson's disease), as reported by Mudò et al. [149]. Resveratrol upregulated the levels of SIRT1, PGC-1 $\alpha$ , Trx2, and Mn-SOD, without affecting the expression of CAT, NRF1, heme oxygenase-1 (HO-1), and XIAP. Consequently, resveratrol decreased reactive species generation and abrogated the loss of viability in MPP<sup>+</sup>-treated SN4741 cells. Similar data regarding Mn-SOD enzyme were obtained in an *in vivo* experimental model performed by the authors using resveratrol at 20 mg/kg (i.p.) 30 min before and 3 days after MPP<sup>+</sup> administration. It would be important to

confirm these effects of resveratrol in clinical trials, for example, using blood cells as the sample.

Narayanan et al. [150] have shown that resveratrol (25  $\mu\text{M}$  for 2 h in an experimental model of resveratrol preconditioning) upregulated the levels of uncoupling protein 2 (UCP2) in astrocytes obtained from both wild-type and Nrf2<sup>-/-</sup> mice. Resveratrol also enhanced the mitochondrial production of H<sub>2</sub>O<sub>2</sub> by complexes I and III. However, resveratrol failed to alter Mn-SOD levels in both wild-type and Nrf2<sup>-/-</sup> astrocytes. Increased UCP2 levels may lead to enhanced mitochondrial uncoupling-dependent reactive species production, causing cytoprotection by mild redox impairment. Nonetheless, Della-Morte et al. [171] previously reported that resveratrol preconditioning (10 mg/kg) decreased UCP2 levels in the mitochondria of CA1 region of rat hippocampus and enhanced the ADP/O ratio (an index of mitochondrial efficiency) by a SIRT1-dependent manner. Those discrepancies may be due to different experimental models utilized by those research groups, and further research is needed in order to better examine the mechanisms induced by resveratrol.

Bellaver et al. [151] recently demonstrated that resveratrol (100  $\mu\text{M}$ ) pretreatment (for 1 h) protected primary hippocampal astrocyte cultures against azide, a mitochondrial toxicant. The authors found that resveratrol prevented downregulation of cytochrome c oxidase (complex IV) expression, as well as suppressed loss of MMP and mitochondrial generation of reactive species in azide-treated cells. Additionally, resveratrol upregulated Mn-SOD activity in that experimental model. Inhibition of HO-1 abrogated the mitochondrial effects induced by resveratrol, clearly indicating a link between HO-1 modulation and mitochondrial protection. Actually, it has been reported that HO-1, which is also an enzyme presenting anti-inflammatory actions [172, 173], may take a role in the maintenance of mitochondrial function and dynamics [60, 174, 175]. Even though the authors did not investigate whether resveratrol would be able to activate Nrf2 (the major regulator of HO-1 expression during exposure to xenobiotics and/or pro-oxidant conditions), it is very likely that this transcription factor is involved with the regulation of both redox environment and mitochondrial function [104, 176].

Overall, *in vitro* studies demonstrate that resveratrol presents a promising role as a mitochondria-targeting agent. Nevertheless, it is necessary to investigate the involvement of other signaling pathways in mediating the mitochondrial protection elicited by resveratrol, as well as other factors that may take a role in the mechanism underlying such resveratrol-induced effects, as suggested above.

#### *In Vivo Experimental Models*

The resveratrol-induced mitochondria-related redox effects were also tested in *in vivo* experimental models. The benefits natural compounds elicit on mitochondria of brain

cells in vivo may take a role in the maintenance of cognitive functions, since mitochondria play a crucial role not only in the production of ATP in these cells but also modulate cell fate according to several intrinsic and extrinsic factors (Table 2).

Robb et al. [152] reported that resveratrol (200 mg/kg day<sup>-1</sup> for 4 weeks) added to high fat diet strongly enhanced the immunocontents and activity of Mn-SOD in mice brain. Resveratrol intake also induced a slight increase in citrate synthase activity, an index of mitochondria abundance. Thus, the increase in Mn-SOD content and activity is very likely to be due to specific regulation of resveratrol regarding gene expression of Mn-SOD and not a consequence, at least in part, of mitochondrial biogenesis. Interestingly, subcutaneous administration of resveratrol (100 mg/kg day<sup>-1</sup>) by using a mini-pump did not modulate Mn-SOD levels in mice brain, showing that the way by which resveratrol is delivered to the organism takes an important role in the regulation of gene expression. It would be also necessary to examine whether resveratrol would be able to modulate the expression of other mitochondria-located antioxidant enzymes, such as catalase and glutathione peroxidase. The specific modulation of mitochondrial antioxidant enzymes by natural compounds would lead to decreased levels of oxidative and nitrosative stress markers in the organelles, as previously demonstrated by some research groups using other natural compounds [61, 177–179]. Resveratrol (30 mg/kg day<sup>-1</sup> for 7 days prior induction of lesion) induced antioxidant and mitochondria-related anti-apoptotic effects in an animal model of cerebral ischemia using rats. However, the redox state of mitochondrial components, such as mitochondrial proteins and mitochondrial membranes, was not analyzed by the authors.

Interestingly, Zhao et al. [153] have shown that resveratrol at 20 mg/kg (for 12 weeks, intragastric administration), but no higher doses of resveratrol (40–80 mg/kg for the same period), increased Mn-SOD enzyme activity in the hippocampus of ovariectomized rats exposed to D-galactose, causing structural and cognitive ameliorations. The mechanism underlying the effect of resveratrol in hippocampal mitochondria was not addressed by the authors, needing further research mainly by a possible link this effect may present with hippocampal-related cognition.

## Effects of Resveratrol on Signaling Pathways Modulating Mitochondrial Fusion and Fission and Mitochondrial Biogenesis in Brain Cells

There is evidence that resveratrol triggers mitochondrial biogenesis in different cell types [12]. Additionally, resveratrol regulates mitochondrial fusion and fission in mammalian cells [158]. Mitochondrial fusion and fission are important to maintain mitochondrial function and morphology and have been implicated also in the maintenance of cell viability and in the complex regulation of cell death, as previously reviewed [180, 181]. Due to limited data reporting the effects of resveratrol on mitochondrial fusion and fission, we decided not to detail these events in the present work. The induction of mitochondrial biogenesis by natural or pharmacological agents attracted the attention of researchers due to the impact this strategy would present in human diseases in which mitochondrial dysfunction takes a role [33]. In this section, we describe, discuss, and compare (whenever possible) the effects induced by resveratrol regarding the synthesis of new mitochondria and/or mitochondrial dynamics in brain cells. We have focused on specific works that described the mechanisms underlying the mitochondrial biogenesis- and/or mitochondrial dynamics-related actions of resveratrol in brain cells (Table 3).

### Alzheimer's Disease

Manczak et al. [154] compared resveratrol with SS31 and MitoQ (two molecules designed to target mitochondria) regarding several parameters, including mitochondrial fusion and fission and mitochondrial biogenesis. The authors found that resveratrol (5 μM) pretreatment (for 48 h) protected mitochondria of N2a cells against exposure to amyloid-β (an experimental model mimicking Alzheimer's disease). Resveratrol prevented amyloid-β-induced disruption of mitochondrial fusion and fission by maintaining the expression of genes such as mitofusin 2 (Mfn2), optic atrophy 1 (Opa1), dynamin-related protein 1 (Drp1), and mitochondrial fission 1 protein (Fis1). Resveratrol alone did not alter PGC-1α protein levels and failed to decrease the amyloid-β-elicited increase in the production of H<sub>2</sub>O<sub>2</sub> by mitochondria. In that context, resveratrol did not trigger mitochondrial biogenesis. Interestingly, resveratrol alone inhibited cytochrome c oxidase enzyme activity in that experimental model. In spite of this, resveratrol prevented

**Table 2** Summary of the mechanisms involved in the resveratrol-induced mitochondria-related redox effects in brain cells in vivo experimental models

Experimental model	Biological sample	Main findings	Reference
Resveratrol at 200 mg/kg day <sup>-1</sup> for 4 weeks added to high fat diet	Mice brain	↑ the levels and activity of Mn-SOD	[152]
Resveratrol at 20 mg/kg for 12 weeks through intragastric administration	Rat hippocampus	↑ activity of Mn-SOD	[153]

Please see the text for more detailed information

**Table 3** Summary of the mechanisms triggered by resveratrol regarding mitochondrial biogenesis and mitochondrial fusion and fission

Experimental model	Biological sample	Main findings	Reference
Resveratrol at 5 $\mu$ M for 48 h prior exposure to amyloid- $\beta$	Mouse neuroblastoma cell line (Neuro-2a)	Maintained the expression of Mfn2, Opa1, Drp1, and Fis1; did not alter PGC-1 $\alpha$ levels; SS31 and MitoQ exhibited better effects than resveratrol	[154]
Resveratrol at 20 $\mu$ M for 1 h	Rat primary visual cortical neurons	Prevented $\downarrow$ of phospho-AMPK and phospho-ACC levels; prevented $\downarrow$ of PGC-1 $\alpha$ and NRF-1 expression	[155]
Resveratrol at 40 $\mu$ M for 12–24 h during serum deprivation	Rat retinal ganglion cell line (RGC-5)	$\uparrow$ SIRT1, NRF1, and TFAM levels; did not affect PGC-1 $\alpha$ levels; $\uparrow$ nuclear translocation of PGC-1 $\alpha$	[156]
Resveratrol at 100 $\mu$ M for 24 h	Human neuroblastoma cell line (SH-SY5Y)	$\uparrow$ phospho-AMPK; $\uparrow$ PGC-1 $\alpha$ , complex I, and complex III expression	[157]
Resveratrol at 60 $\mu$ M for 24 h prior rotenone	Rat pheochromocytoma cell line (PC12)	$\uparrow$ mtDNA; prevented $\downarrow$ of Drp1, Fis1, OPA1, and MFN2 levels; $\uparrow$ PGC-1 $\alpha$ and mtTFA levels; $\uparrow$ ATP content	[158]
Resveratrol at 10 $\mu$ M for 24 h	Ts65Dn neural progenitor cells	$\uparrow$ complex I and complex V levels and activities; $\uparrow$ ATP production; $\uparrow$ PGC-1 $\alpha$ , NRF-1, and TFAM levels; $\uparrow$ SIRT1 activity; $\uparrow$ mtDNA	[159]
Resveratrol at 1–5 $\mu$ M for 96 h	Striatal and cortical neurons obtained from YAC128 transgenic mice embryos	Restored MMP; did not alter SIRT1 activity (effects vary according to the cell type. Please see the text for detailed information)	[160]
Resveratrol at 20 mg/kg body weight i.p. 1 day prior monocular deprivation	Rat visual cortex	$\uparrow$ phospho-AMPK, PGC-1 $\alpha$ , and NRF-1 levels; $\uparrow$ number of mitochondria; $\uparrow$ ATP levels	[155]
Resveratrol at 100 mg/kg day <sup>-1</sup> orally administered during gestation	Rat offspring hippocampus	$\uparrow$ phospho-AMPK, PGC-1 $\alpha$ , and mitochondrial complexes (I, III, IV, and V) levels; $\uparrow$ mtDNA	[157]
Resveratrol-enriched diet for 4 weeks (leading to an ingestion of 160 mg/kg resveratrol)	Ventral part of the lumbar spinal cord in SOD1 <sup>G93A</sup> mice	$\uparrow$ complex I–V levels; $\uparrow$ Fis1 expression; did not alter Mfn2 expression; $\uparrow$ phospho-AMPK levels; $\downarrow$ LC3II and Beclin1 levels	[161]
Resveratrol at 1 mg/kg day <sup>-1</sup> administrated subcutaneously through a mini-pump for 28 days	YAC128 mice striatum and cerebral cortex	$\uparrow$ MT-ND5 and MT-CO1 expression; $\uparrow$ SIRT1 levels (effects vary according to the brain region. Please see the text for detailed information)	[160]
Resveratrol-enriched diet for 8 weeks (leading to an ingestion of 160 mg/kg resveratrol)	SAMP8 mice Hippocampus	$\uparrow$ Opa1 and Mfn2 levels; $\uparrow$ mitochondrial size; $\uparrow$ complex I–V levels; $\uparrow$ phospho-AMPK levels; did not alter SIRT1 or PGC-1 $\alpha$ levels	[162]

Please see the text for more detailed information

loss of MPP and inhibited swelling and fragmentation of mitochondria in amyloid- $\beta$ -treated cells. On the other hand, comparisons made by the authors revealed that molecules specifically targeting mitochondria exhibited better effects than resveratrol. Therefore, it is very likely that strategies aiming to increase the delivery of resveratrol to mitochondria would exert more pronounced effects regarding the function and dynamics of these organelles. It would be especially useful *in vivo*, since amyloid- $\beta$  peptides have been linked to mitochondrial dysfunction in experimental models using animals [40, 44].

#### Monocular Deprivation

Yu and Yang [155] have demonstrated that resveratrol (20  $\mu$ M for 1 h) stimulated AMPK and acetyl-CoA carboxylase (ACC) phosphorylation in rat primary visual cortical neurons. Resveratrol also upregulated PGC-1 $\alpha$  and NRF-1 expression by a dose-dependent manner. The authors also tested the effects of resveratrol on mitochondrial biogenesis-related signaling in the visual cortex of animals subjected to an *in vivo* experimental model of monocular deprivation (MD). Resveratrol (injected

*i.p.* at 20 mg/kg body weight 1 day prior MD) prevented the MD-induced downregulation in the levels of phospho-AMPK, PGC-1 $\alpha$ , and NRF-1 in the rat visual cortex. Importantly, the authors also analyzed whether resveratrol would be able to alter the number of mitochondria *in vivo*. Resveratrol enhanced the number of mitochondria per cell in the visual cortex of animals submitted to MD. Furthermore, resveratrol increased the levels of ATP in that brain area. In that context, resveratrol upregulated the signaling pathway associated with the control of mitochondrial biogenesis (AMPK-PGC-1 $\alpha$ -NRF-1) and increased the number of mitochondria, resulting in the enhancement of mitochondrial quality and function. The authors also observed that resveratrol mimicked the effects of neuronal activity, which was induced by potassium chloride (KCl) experimentally. Further studies are necessary in order to better analyze the complete signaling pathway regulated by resveratrol and involved in the control of this biological event. The use of specific inhibitors and/or gene silencing/overexpression would be interesting strategies in order to reveal the exact mechanism by which resveratrol modulated the synthesis of new mitochondria. Additionally, it is recommended to investigate this issue in

other brain areas due to the important role mitochondrial biogenesis would present in neurodegenerative processes in which mitochondrial dysfunction is involved.

### *Glaucomatous Neurodegeneration*

Chen et al. [156] recently reported that resveratrol (40  $\mu\text{M}$  for 12–24 h) co-treatment inhibited apoptosis in retinal ganglion cell line RGC-5 exposed to serum deprivation. Resveratrol suppressed the serum deprivation-induced loss of MMP and cytochrome c release, consequently blocking caspase-3 activation in RGC-5 cells by a mechanism dependent on SIRT1, since nicotinamide (a SIRT1 inhibitor) blocked the effects elicited by resveratrol. Resveratrol also maintained the normal mtDNA copy number and the number of mitochondria in serum-deprived cells by the same mechanism. Importantly, resveratrol rescued mitochondrial architecture by inhibiting serum deprivation-induced swelling of the organelles. The authors demonstrated that resveratrol enhanced SIRT1, NRF1, and TFAM levels in a time-dependent manner, affecting PGC-1 $\alpha$  with little impact. Nonetheless, resveratrol favored PGC-1 $\alpha$  entry into the cell nucleus, probably assisting with the translocation of this regulator to the nucleus, where it exerts its effect on modulating mitochondrial biogenesis. This is an important point to be addressed in further research: the exact role of resveratrol in mediating PGC-1 $\alpha$  into the nucleus. The proteins translocase of the inner membrane (TIM) and translocase of the outer membrane (TOM) play a crucial role in the transport of proteins from the cytosol to the mitochondria, and whether resveratrol would modulate the mitochondrial transport remains to be investigated. Indirect evidence that resveratrol would modulate mitochondria-located SIRT have been reported by Morris-Blanco et al. [182]. This research group found that resveratrol (25  $\mu\text{M}$  for 48 h) upregulated nicotinamide phosphoribosyltransferase (Nampt) in neuronal–glial cortical cultured cells. Nampt participates in the generation of NAD<sup>+</sup>, which regulates mitochondrial SIRTs, poly(ADP-ribose) polymerase (PARP), and the tricarboxylic acid (TCA) cycle. Resveratrol enhanced Nampt levels by a mechanism dependent on the activation of PKC $\epsilon$ . Therefore, in addition to exhibiting the ability to modulate the cytoplasmic isoforms of SIRTs, resveratrol is very likely to upregulate mitochondria-located SIRT by a PKC $\epsilon$ -Nampt axis. This modulation involving cytoplasmic–nucleus communication also deserves attention due to the impact alterations in the NAD<sup>+</sup>/NADH ratio would cause in mammalian cells, including regulation of bioenergetics parameters and cell fate.

### *Prenatal Stress*

Cao et al. [157] have explored the effects of resveratrol on mitochondrial biogenesis in vitro and in a prenatal restraint stress (PRS) animal model. The authors have shown that

resveratrol (100  $\mu\text{M}$  for 24 h) stimulated the phosphorylation of AMPK and upregulated the expression of PGC-1 $\alpha$ , complex I, and complex III in SH-SY5Y cells. Inhibition of AMPK by compound C revealed that the resveratrol-induced upregulation of complex I and complex III expression occurred by an AMPK-dependent manner. Compound C also blocked the in vitro effects elicited by resveratrol on Nrf2 and HO-1 expression. Interestingly, resveratrol (100 mg/kg day<sup>-1</sup> during gestation, orally administrated) suppressed the PRS-induced downregulation in the levels of phospho-AMPK, PGC-1 $\alpha$ , and mitochondrial complexes (I, III, IV, and V) in the rat hippocampus of both male and female offspring. Resveratrol also restored mtDNA in that experimental model. Redox effects elicited by resveratrol involved upregulation of Nrf2, NAD(P)H:quinone dehydrogenase 1 (NQO1), HO-1, and of the regulatory (GCLm) and catalytic (GCLc) subunits of glutamate-cysteine ligase in the hippocampus of the PRS offspring. Moreover, resveratrol decreased carbonyl and oxidized glutathione (GSSG) levels in that rat brain region. Cognitive dysfunction (deficits in exploration and success rate of exploration in T maze and escape latency in Morris water maze) was also ameliorated by resveratrol in the PRS group. Data obtained by the authors clearly demonstrate that resveratrol upregulated mitochondrial dynamics-related parameters in both in vitro and in vivo experimental models. However, redox aspects were not analyzed directly on mitochondria. Furthermore, it would be interesting to investigate whether the mitochondrial biogenesis-associated effects elicited by resveratrol would be related to the behavioral effects observed in that experimental model. Even though the authors have demonstrated that resveratrol enhanced the levels of neurotrophic factors in the hippocampus of the PRS group, it would be interesting to examine whether there is a causal link between upregulation of mitochondrial biogenesis and neuronal plasticity, for example. In another work, resveratrol (10  $\mu\text{M}$  for 24 h) upregulated PGC-1 $\alpha$  by an AMPK-dependent manner in an experimental model of insulin resistance using SH-SY5Y cells exposed to high glucose concentration [183]. Nonetheless, resveratrol enhanced the levels of complex I by an AMPK-independent mechanism in that work, contrasting with the data published by Cao et al. [157]. However, it is noteworthy that these research groups utilized very different experimental models to study the effects of resveratrol on mitochondria. Thus, data obtained by the authors have shown the complexity involved in the triggering of signaling pathways by resveratrol in mammalian cells. This should be considered when using this molecule pharmacologically.

### *Parkinson's Disease*

Pen et al. [158] have reported that resveratrol modulated mitochondrial biogenesis in PC12 cells exposed to rotenone (an experimental model mimicking Parkinson's disease).

Resveratrol (60  $\mu\text{M}$ ) pretreatment (24 h) enhanced mitochondrial mass (mtDNA) and prevented the rotenone-induced downregulation of proteins involved in the control of mitochondrial fusion and fission, such as Drp1, Fis1, OPA1, and MFN2. Resveratrol triggered mitochondrial biogenesis through a PGC-1 $\alpha$ /mtTFA-dependent signaling pathway in rotenone-treated PC12 cells, resulting in increased levels of ATP. Resveratrol also elicited antioxidant effects by decreasing the formation of reactive species in that cell line. Data obtained by the authors were also confirmed in the brain of rats that were injected (i.p.) with resveratrol (50 mg/kg day<sup>-1</sup> for 30 days) before administration of rotenone. Dysfunctional mitochondrial dynamics has been linked to neurodegeneration, such as Parkinson's disease [12]. In that context, the use of resveratrol as a preventive agent in the case of impaired mitochondrial dynamics is of pharmacological interest.

#### *Down Syndrome*

Recently, Valenti et al. [159] have studied the effects of resveratrol (10  $\mu\text{M}$  for 24 h) in neural progenitor cells (NPCs) obtained from the hippocampus of the Ts65Dn mouse, which has been utilized as an experimental model of Down syndrome. Ts65Dn NPCs exhibit mitochondria-related bioenergetics deficits, such as reduced activity of complexes I and V, as well as decreased ATP synthesis. Resveratrol increased complex I and complex V enzyme activities, consequently enhancing ATP production. Resveratrol also upregulated the immunocentents of PGC-1 $\alpha$ , NRF-1, and TFAM in Ts65Dn NPCs. The content of mtDNA and the levels of complex I and complex V were augmented by resveratrol, strongly suggesting that this natural compound induced mitochondrial biogenesis. Resveratrol did not alter the levels of SIRT1 but increased its activity, since the amounts of acetylated histone 3 (a major target of SIRT1) were decreased by resveratrol treatment. Resveratrol also upregulated the levels of phospho-AMPK, which seems to be involved in the increments induced by resveratrol regarding the mitochondrial production of ATP in Ts65Dn NPCs, since the inhibition of AMPK abrogated the beneficial effects of resveratrol on mitochondrial function. Therefore, it is very likely that resveratrol activated mitochondrial biogenesis through the triggering of the AMPK-SIRT1-PGC-1 $\alpha$  signaling pathway in Ts65Dn NPCs. The findings obtained by that research group are very interesting because it may be useful in the treatment of patients affected by Down syndrome, which present mitochondrial abnormalities, as previously reported [184, 185].

#### *Amyotrophic Lateral Sclerosis*

Interesting data demonstrating the in vivo ability of resveratrol in triggering mitochondrial biogenesis during energetic stress was published by Mancuso et al. [161]. Resveratrol-enriched

diet (leading to a daily ingestion of 160 mg/kg resveratrol for 4 weeks) suppressed the increase in the levels of complexes I–V observed in the ventral part of the lumbar spinal cord in SOD1<sup>G93A</sup> mice, an experimental model of amyotrophic lateral sclerosis. Resveratrol also upregulated Fis-1 expression without affecting the levels of Mfn2, indicating that this polyphenol triggered mitochondrial fission but not mitochondrial fusion in SOD1<sup>G93A</sup> mice. The levels of phospho-AMPK were enhanced by resveratrol in those animals, indicating mitochondrial biogenesis. Resveratrol also normalized the autophagic flux in SOD1<sup>G93A</sup> mice by restoring the levels of LC3II and Beclin 1. Mitochondrial dysfunction has been associated with the neurodegeneration observed in amyotrophic lateral sclerosis [186–189], and the use of mitochondriotropic agents would be an interesting strategy in order to restore mitochondrial function and dynamics, leading to ameliorations in the redox and bioenergetic aspects altered in the cells of patients suffering from this disease.

#### *Huntington's Disease*

Naia et al. [160] have revealed that resveratrol ameliorated mitochondrial function in in vitro (striatal and cortical neurons obtained from YAC128 transgenic mice embryos) and in vivo experimental models mimicking Huntington's disease. Resveratrol was tested at the concentrations of 1 and 5  $\mu\text{M}$  for 96 h, and the effects have varied according to the cell type studied. For example, only resveratrol at 5  $\mu\text{M}$  restored MMP in YAC128 cortical neurons, whereas resveratrol at 1 or 5  $\mu\text{M}$  ameliorated MMP in YAC128 striatal neurons. Resveratrol did not activate SIRT1 in vitro. Moreover, resveratrol (1 mg/kg day<sup>-1</sup> administrated subcutaneously through a mini-pump for 28 days) upregulated the mRNA levels of MT-ND5 (complex I subunit NADH dehydrogenase 5) and MT-CO1 (complex IV subunit cytochrome c oxidase I), which are encoded by mitochondria and take a role in the respiratory chain, in the YAC128 mice cortex. Interestingly, resveratrol did not affect the expression of cytochrome c (CYTC, which is encoded by the cell nucleus) in that mice brain region. Resveratrol upregulated SIRT1 in the striatum of both wild-type and YAC128 mice, whereas it did not affect SIRT1 in the cortex of YAC128 mice. Therefore, differential effects were elicited by resveratrol according to the mice brain region, among other factors. Further studies would be useful in order to reveal whether resveratrol would be able to increase the number of mitochondria in such brain regions.

#### *Aging*

Similarly, Palomera-Avalos et al. [162] have shown that resveratrol administration (through diet at 1 g/kg w/w for 8 weeks, rendering 160 mg/kg day<sup>-1</sup> to each animal) improved cognition and mitochondria-related parameters in senescence-

accelerated prone mouse (SAMP8) subjected to high-fat diet (HFD). Resveratrol induced an increase in the size of hippocampal mitochondria (mitochondrial fusion) through a mechanism involving upregulation of OPA1 and MFN2 proteins. Moreover, resveratrol ingestion caused an increase in the levels of the components of the respiratory chain (complexes I–IV) and of complex V (ATP synthase/ATPase). The authors also found that resveratrol increased the levels of phospho-AMPK without altering SIRT1 or PGC-1 $\alpha$ . SAMP8 mice present spontaneously reduced learning and memory capacities and have been utilized in studies focusing aging [190]. The SAMP8 animals exhibit mitochondrial impairment regarding both bioenergetics and redox-related aspects [190–192]. In that context, resveratrol would be an interesting pharmacological agent presenting cytoprotective effects during aging. More studies are necessary in order to evaluate whether resveratrol would be able to modulate mitochondrial activity (through measuring the activity of complexes, for example). Moreover, we recommend testing the effects of resveratrol on SAMP8-mitochondrial susceptibility, i.e., the ability of mitochondria to resist against chemical challenges in *ex vivo* experiments after *in vivo* administration of the polyphenol.

### Effects of Resveratrol on Autophagy in Brain Cells: Is There a Link with Mitochondria and the Maintenance of Mitochondrial Function and Dynamics?

Resveratrol is able to induce autophagy in brain cells depending on its concentration, among other factors (e.g., duration of the exposure, nutritional state of the cells) [16, 193, 194]. However, it is not still clear whether there is a link between the mitochondria-related effects elicited by resveratrol and the triggering of autophagy. Since autophagy is utilized by cells as an adaptive strategy during several forms of stress, and mitochondrial also play a role during stress response, it would be interesting to examine exactly how autophagy and mitochondrial biogenesis and dynamics interact in these conditions in the presence of resveratrol.

Wu et al. [195] reported that resveratrol (50  $\mu$ M for 24–72 h) induced autophagy in rotenone-treated human neuroblastoma SH-SY5Y cells by a mechanism associated with the AMPK/SIRT1 signaling pathway. The activation of autophagy by resveratrol inhibited the rotenone-induced cell death in SH-SY5Y cells. Additionally, the authors have found that resveratrol increased  $\alpha$ -synuclein clearance in PC12 cells expressing wild-type  $\alpha$ -synuclein, A30P, or A53T  $\alpha$ -synuclein mutants.  $\alpha$ -Synuclein accumulation has been viewed in dopaminergic neurons obtained from patients suffering from Parkinson's disease [196, 197]. Autophagy is involved in the clearance of several proteins, including  $\alpha$ -synuclein, in neuronal cells, avoiding protein accumulation and widespread damage [198, 199]. The authors did not

investigate mitochondria-related parameters in that work. However, autophagy is linked to mitochondrial function due to its role in controlling the levels of damage organelles and proteins [51]. In this view, autophagy is necessary to maintain mitochondrial function. Additionally, accumulation of  $\alpha$ -synuclein may occur in cytosol and mitochondria, limiting mitochondrial function and increasing the production of reactive species [200–204].

A direct link between resveratrol-induced autophagy and the mitochondria-related apoptosis was reported by Jeong et al. [205], who demonstrated that resveratrol (2  $\mu$ M, pretreatment for 12 h) blocked the effects of prion protein on MMP, Bax translocation to mitochondria, and cytochrome c release from the organelles by an autophagy-dependent manner, since the autophagy inhibitor 3-methyladenine (3-MA) abrogated the effects of cytoprotective effects of resveratrol in prion protein-treated SH-SY5Y cells. It is important to note that very low concentrations of resveratrol efficiently protected SH-SY5Y cells in that experimental model. This is a very interesting finding, since several studies demonstrate that the bioavailability of resveratrol is limited.

The relationship between resveratrol and autophagy has been also studied by Lin et al. [206] using the dopaminergic cell line SH-SY5Y exposed to rotenone. The authors found a link between resveratrol-dependent HO-1 expression and autophagy and cell death in experimental model. Resveratrol (20  $\mu$ M) pretreatment (for 24 h) protected SH-SY5Y cells from the toxicity induced by rotenone through a mechanism associated with HO-1, which activated the autophagy-related signaling pathway and inhibited the mitochondria-associated intrinsic apoptotic pathway. In fact, HO-1 has been studied regarding its role in modulating autophagy and cell death in several experimental models [207–209]. However, it remains to be fully understood how HO-1 interacts with mitochondria during autophagy causing cytoprotection in mammalian cells by inhibiting mitochondria-related apoptosis.

The mitochondria–autophagy link needs more studies in order to be fully understood. This research area is complex because the response to stress, for example, may vary according to the cell type analyzed. Additionally, the effects elicited *in vitro* may be different from those observed *in vivo* due to resveratrol bioavailability. This is particularly important in the case of investigating strategies to induce apoptosis in cancer cells, which initiate autophagy as a response to chemical stressors, for example, decreasing the efficacy of the treatment in some cases [210, 211].

### Conclusion

Resveratrol modulates mitochondrial function and dynamics by diverse mechanisms, causing cytoprotective effects in both *in vitro* and *in vivo* experimental models involving brain cells.

It would be important to investigate whether resveratrol would cause mitochondria-related cytotoxic effects in brain cells in order to avoid triggering of cell death in healthy cells by the intrinsic apoptotic pathway, which is dependent on the release of pro-apoptotic factors by mitochondria, or by necrosis due to energetic collapse. Additionally, studying how the resveratrol-induced effects on mitochondria would be associated with neuronal plasticity would be useful in the treatment or prevention of several neurodegenerative diseases. Based on the fact that the resveratrol concentrations utilized in in vitro studies to induce mitochondrial effects may be considered high due to decreased bioavailability of this polyphenol in vivo, it may be recommended also to investigate the impact of nanotechnology-related strategies to improve the delivery of resveratrol to mammalian cells according to the particularities of each tissue, causing better effects in mitochondria. Overall, the mitochondria-resveratrol field is gradually expanding in research areas associated with neurobiology, pharmacology, nutrition, and biotechnology. Therefore, it is expected that the number of publications in this area will be increased, improving our knowledge about the use of resveratrol as a modulator of mitochondrial function, redox biology, and dynamics.

3-MA, 3-methyladenine; ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; CAT, catalase; CNS, central nervous system; Drp1, dynamin-related protein 1; Erk, extracellular signal-regulated kinase; ERR $\alpha$ , estrogen-related receptor  $\alpha$ ; Fis1, mitochondrial fission 1 protein; GCLc, catalytic subunit of glutamate-cysteine ligase; GCLm, regulatory subunit of glutamate-cysteine ligase; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; GST, glutathione-S-transferase; HFD, high fat diet; HO-1, heme oxygenase-1; I $\kappa$ B, inhibitor  $\kappa$ B; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinases; MD, monocular deprivation; Mfn2, mitofusin 2; MMP, mitochondrial membrane potential; Mn-SOD, Mn-superoxide dismutase; MPP<sup>+</sup>, 1-methyl-4-phenylpyridinium ion; MT-CO1, complex IV subunit cytochrome c oxidase I; MT-ND5, complex I subunit NADH dehydrogenase 5; mtDNA, mitochondrial DNA; mtNOS, mitochondrial nitric oxide synthase; Nampt, nicotinamide phosphoribosyltransferase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NPCs, neural progenitor cells; NQO1, NAD(P)H:quinone dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; NRF-1, nuclear respiratory factor 1; NRF-2, nuclear respiratory factor 2; Opa1, optic atrophy 1; PARP, poly(ADP-ribose) polymerase; PI3K, phosphoinositide-3-kinase; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor gamma coactivator 1- $\alpha$ ; PKB, protein kinase B; PKC, protein kinase C; PRS, prenatal restraint stress; SIRT1, NAD<sup>+</sup>-dependent deacetylase sirtuin 1; TCA, tricarboxylic acid; TFAM, mitochondrial transcription factor A; TFB1M, mitochondrial transcription factor B1; TFB2M, mitochondrial transcription factor B2; TIM, translocase of the inner membrane; TOM,

translocase of the outer membrane; Trx2, thioredoxin-2; UCP2, uncoupling protein 2; XIAP, X-linked inhibitor of apoptosis protein.

**Acknowledgements** None to declare.

**Compliance with Ethical Standards**

**Conflict of Interest** The authors declare that they have no competing interests.

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