Beneficial action of resveratrol: How and why?

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PII: S0899-9007(15)00379-2
DOI: 10.1016/j.nut.2015.08.017
Reference: NUT 9598

To appear in: *Nutrition*

Received Date: 6 April 2015
Revised Date: 6 August 2015
Accepted Date: 19 August 2015

Please cite this article as: Diaz-Gerevini GT, Repossi G, Dain A, Tarres MC, Das UN, Eynard AR, Beneficial action of resveratrol: How and why?, *Nutrition* (2015), doi: 10.1016/j.nut.2015.08.017.

Review

Beneficial action of resveratrol: How and why?

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Abstract

Flavonoid resveratrol modulates transcription factor NF-κB, cytochrome P450 isoenzyme CYP1A1, expression and activity of cyclooxygenase (COX) enzymes, Fas/Fas ligand mediated apoptosis, p53, mTOR and cyclins and various phosphodiesterases, which increases cytosolic cAMP that activates Epac1/CaMKKβ/AMPK/SIRT1/PGC-1α pathway that, in turn, facilitates increased oxidation of fatty acids, mitochondrial biogenesis, mitochondrial respiration, and gluconeogenesis. Resveratrol triggers apoptosis of activated T cells and suppresses tumor necrosis factor-α (TNF-α), interluekin-17 (IL-17) and other pro-inflammatory molecules and thus, is of benefit in autoimmune diseases. In addition, resveratrol inhibits expressions of (hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) explaining its effective action against cancer.

Brain-derived neurotrophic factor (BDNF) that is involved in the pathogenesis of obesity, type2 diabetes mellitus and metabolic syndrome is also altered in depression, schizophrenia, bipolar disorder, and autism. We noted that BDNF protects against cytotoxic actions of alloxan, streptozotocin and benzo(a)pyrene (BP). Resveratrol prevents bisphenol A (BSA)-induced autism, type 2 diabetes mellitus and metabolic syndrome suggesting that it may augment BDNF synthesis and action. We also observed that BDNF levels are low in type 2 diabetes mellitus (47) and BDNF enhances production of anti-inflammatory lipid: lipoxin A4, whose levels are low in diabetes mellitus. Thus, resveratrol may augment production of lipoxin A4. Resveratrol alters gut microbiota and influences stem cell proliferation and differentiation. These pleiotropic actions of resveratrol may explain the multitude of its actions and benefits.

Keywords: Resveratrol, flavonoids, type 2 diabetes mellitus, obesity, Alzheimer's disease, microbiota.

Introduction

The hypothesis that certain flavonoids such as resveratrol protect against dementia seen in elderly diabetic patients is interesting. The epidemic of obesity and type 2 diabetes mellitus that is sweeping both the developed and developing countries could be one reason for the increasing incidence of senile dementia. Consumption of high fat/high calorie diet, refined carbohydrates, and trans-fats and lack of adequate exercise is considered to be responsible for this epidemic of obesity and metabolic syndrome and consequent increase in the risk of coronary and cerebrovascular diseases, certain types of cancers, hypertension, and non-alcoholic fatty liver disease (NAFLD) and Alzheimer's disease (1-3). It has been suggested that an increase in the consumption of dietary fibre, flavonoids, anti-oxidant micronutrients and ω-3 polyunsaturated fatty acids (PUFAs) is beneficial. An imbalance in the modern dietary habit(s) as outlined above can lead to an increase in oxidative stress and endoplasmic reticulum (ER) stress that initiates the development of insulin resistance and onset of type 2 diabetes mellitus and Alzheimer's disease. Yorimitsu et al (4) showed that endomembranes progressively store misfolded proteins which causes ER stress, since unfolded proteins could trigger expression of chaperones resulting in autophagic cell death, included those of neuronal cells (5). Autophagic activity dysregulation is related to obesity and type 2 diabetes mellitus (6). ER stress and low-grade systemic inflammation seen in obesity leads to impairment of insulin sensitivity pathway, peripheral insulin resistance and subsequent development of type 2 diabetes mellitus. This is supported by the work of Yin et al (7), who showed that adipocytes pre-loaded with the saturated fatty acid palmitate leads to endoplasmic reticulum stress and autophagy via protein kinase C-mediated signaling pathway independent of mammalian target of rapamycin (mTOR) (8).

Resveratrol has anti-oxidant actions and increases oxidation of fatty acids, mitochondrial biogenesis, mitochondrial respiration, and gluconeogenesis

One of the best ways to stem the epidemic of obesity, type 2 diabetes mellitus and Alzheimer's disease is to restrict calorie intake and do regular exercise that would lead to a decrease in endoplasmic reticulum stress. In this context, it is interesting to note that some of the beneficial actions of resveratrol seem to mimic several of the biochemical effects of calorie restriction. Resveratrol activates Sirtuin 1 (SIRT1) (9) and peroxisome proliferator-activated receptor-γ coactivator1α (PGC-1α) and improves the functioning of the mitochondria (10, 11). Recent studies have revealed that resveratrol binds to tyrosyl transfer-RNA (tRNA) synthetase (TyrRS) to potentiate a poly(ADP-ribose) polymerase 1) (PARP1)/NAD+ driven signaling cascade to activate p53 and AMPK by inhibiting SIRT1 (12). Cells treated with resveratrol showed a fourteen-fold increase in the action of superoxide dismutase (SOD) that removes superoxide anion, a potent free radical (13). SOD by reducing superoxide restores mitochondrial dysfunction to normal. Resveratrol by activating SIRT1 causes migration of FOXO transcription factors to the nucleus (14), which stimulates FOXO3a transcriptional activity (15) and was shown to enhance the sirtuin-catalyzed deacetylation (activity) of FOXO3a. SOD is a target of FOXO3a, and MnSOD expression is strongly induced in cells overexpressing FOXO3a (16). It is known that high expression of SOD but mild changes in catalse (CAT) and glutathione peroxidase (GPX) expression in cancer cells results in the mitochondrial accumulation of H_2O_2, which in turn induces cancer cell apoptosis (17). It appears that both exercise and resveratrol induce disproportional up-regulation of SOD, CAT and GPX to bring about their beneficial actions in cancer.

In addition, resveratrol modulates the transcription factor NF-κB, inhibits the cytochrome P450 isoenzyme CYP1A1 and suppresses the expression and activity of cyclooxygenase (COX) enzymes, and modulates Fas/Fas ligand mediated apoptosis, p53, mTOR and cyclins A, B1, and cyclin-dependent kinases cdk 1 and 2 that may also account for its benefits (18-21). These actions of resveratrol (9-21) may be responsible for its benefit in Alzheimer's disease (22). Resveratrol competitively inhibits various phosphodiesterases and thus, increases cytosolic cAMP, which acts as a second messenger for the activation of the pathway Epac1/CaMKKβ/AMPK/SIRT1/PGC-1α that facilitates an increase in oxidation of fatty acids, mitochondrial biogenesis, mitochondrial respiration, and gluconeogenesis (23, 24, see Figure 1).

Resveratrol has anti-inflammatory actions

On exposure to different immune stimuli, naïve T cells are activated, undergo proliferation and are made to undergo differentiation into three distinct functional subsets: T_H1 cells produce IFN-γ and mediate protection against intracellular pathogens; whereas T_H2 cells produce IL-4, IL-13 and IL-25 and are concerned with the clearance of extracellular pathogens; the third subset of T_H17 cells produce IL-17 and are needed to clear extracellular pathogens not effectively handled by either T_H1 or T_H2 cells. T_H17 cells defend the body against Gram-positive *Propionibacterium acnes*, the Gram-negative *Citrobacter rodentium*, *Klebsiella pneumoniae*, *Bacteroides spp.* and *Borrelia spp.*, the acid-fast *Mycobacterium tuberculosis*, and fungi such as *Candida albicans*. This wide spread response to a variety of organisms suggests that T_H17 cells act as an early responsive immunocytes to a number of pathogens that are not handled appropriately by T_H1-or T_H2-type immunity (25). Thus, T_H17 cells bridge the gap between innate and adaptive immunity. IL-17 producing T cells have profound pro-inflammatory effects and induce tissue damage. IL-17-deficient mice develop attenuated collagen-induced arthritis and experimental autoimmune encephalomyelitis (EAE); increased levels of IL-17 have been observed in patients with rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and psoriasis-evidences that strongly support the contention that IL-17 and T_H17 cells play a significant role in autoimmune disorders (25-30). It is noteworthy that the ability of resveratrol to trigger apoptosis in activated T cells and downregulates tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin (IL)-2, IL-9, IL-12, IL-17, macrophage inflammatory protein-1alpha (MIP-1alpha), and monocyte chemoattractant protein-1 (MCP-1) may explain its potential in the treatment of inflammatory and autoimmune diseases (31-35).

Both hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) are overexpressed in many human tumors and their metastases, and are closely associated with a more aggressive tumor phenotype. Resveratrol inhibited the expressions of HIF-1α and VEGF implying that it could be an effective anticancer therapy for the prevention of cancer and metastasis (36-38).

Resveratrol is cytoprotective in nature

Increasing incidence of obesity and metabolic syndrome all over the world has been attributed not only to high-fat diet and lack of exercise but also to certain environmental factors such bisphenol-A (BPA), an endocrine disruptor present in plastic. A cross-sectional study performed in 76 out of 139 environmentally exposed adult males, unselected Caucasian subjects, enrolled by routine health survey at the "Federico II" University of Naples outpatient facilities, revealed that BPA and pro-inflammatory cytokine levels were significantly higher in subjects with visceral adiposity. BPA correlated with visceral obesity, triglycerides, glucose homeostasis and inflammatory markers. At the multivariate analysis WC and IL-6 remained the main predictors of BPA. These results supports that BPA and other environmental factors may play a role in visceral obesity-related low grade chronic inflammation (39). Similar association between BSA and autism has also been described (40).

In utero BPA exposure as a model environmental exposure has been shown to disrupt neurodevelopment and thus, cause autism. Studies suggested that prenatal BPA induced lasting DNA methylation changes in the transcriptionally relevant region of the *BDNF* gene in the hippocampus and blood of BALB/c mice. Similar BDNF methylation changes were also reported in the cord blood of humans exposed to high maternal BPA levels in utero (41). It is noteworthy that BDNF expression and DNA methylation are altered in several psychiatric disorders that are associated with early-life adversity, including depression, schizophrenia, bipolar disorder, and autism. BDNF is also involved in the pathogenesis of obesity, type 2 diabetes mellitus and metabolic syndrome (42) indicating that environmental agents could alter the expression and actions of BDNF that may lead to the development of several diseases. In this context, it is interesting to note that BDNF could function as a cytoprotective molecule preventing the cytotoxic actions of alloxan streptozotocin, benzo(a)pyrene (BP), an common environmental pollutant, and anti-cancer drug doxorubicin (Das UN, unpublished data). The protective action of BDNF against BP is especially interesting since it is a common mutagen and carcinogen found in coal tar, automobile exhaust fumes, cigarette smoke, cooked meat products, fried chicken, overcooked charcoal barbecued beef and hamburgers. Since, resveratrol is able to prevent BSA-induced autism, type 2 diabetes mellitus and metabolic syndrome (43-45); it is likely that it (resveratrol) may have the ability to augment BDNF synthesis and action since BDNF also has similar beneficial actions in these diseases (42, 46). In a recent study, we noted that BDNF levels are low in subjects with type 2 diabetes mellitus (47) and that it interacts and enhances the production of an anti-inflammatory bioactive lipid namely, lipoxin A4, whose levels are also low in diabetes mellitus (47-49). Lipoxin A4 is a potent suppressor of pro-inflammatory prostaglandin E2 synthesis (50). This rises the interesting possibility that resveratrol may augment the production of lipoxin A4 and block that of prostaglandin E2 and thus, is able to bring about its beneficial actions in several diseases including autism, obesity, diabetes mellitus, metabolic syndrome, depression, schizophrenia and cancer (22, 24, 43-51).

There are two other potential mechanims by which resveratrol acts: (i) by altering gut microbiota that have a role in several diseases and (ii) influencing stem cell proliferation and differentiation (52-55).

Conclusions

Despite many beneficial actions of resveratrol, one major concern is its poor solubility and absorption when given orally. Poor bioavailability of resveratrol is attributed to its extensive hepatic gluconuridation and sulfation. A recent study (56) revealed that in ApcMin mice (a model of colorectal carcinogenesis) that received a high-fat diet, the low resveratrol dose suppressed intestinal adenoma development more potently than did the higher dose. It was noted that the efficacy of resveratrol correlated with activation of AMPK and increased expression of the senescence marker p21. The nonlinear dose responses observed for AMPK and mechanistic target of rapamycin (mTOR) signaling in mouse adenoma cells correlated with the autophagy and senescence observed. Surprisingly, the effectiveness of low dose of resveratrol in protecting against colon cancer both in the mouse colon cancer cells and human colorectal tissues was found to be due to enhanced AMPK phosphorylation and autophagy and expression of the cytoprotective NAD(P)H dehydrogenase. These observations suggest that sometimes lower dose of diet-derived agents are more effective than higher doses to prevent cancer. These results emphasize the need to perform a dose response studies and develop better methods to deliver diet-derived chemopreventive molecules such as resveratrol reach the target tissues by using modern technologies such as microencapsulation or nanoparticles (57, 58) to derive their beneficial actions.

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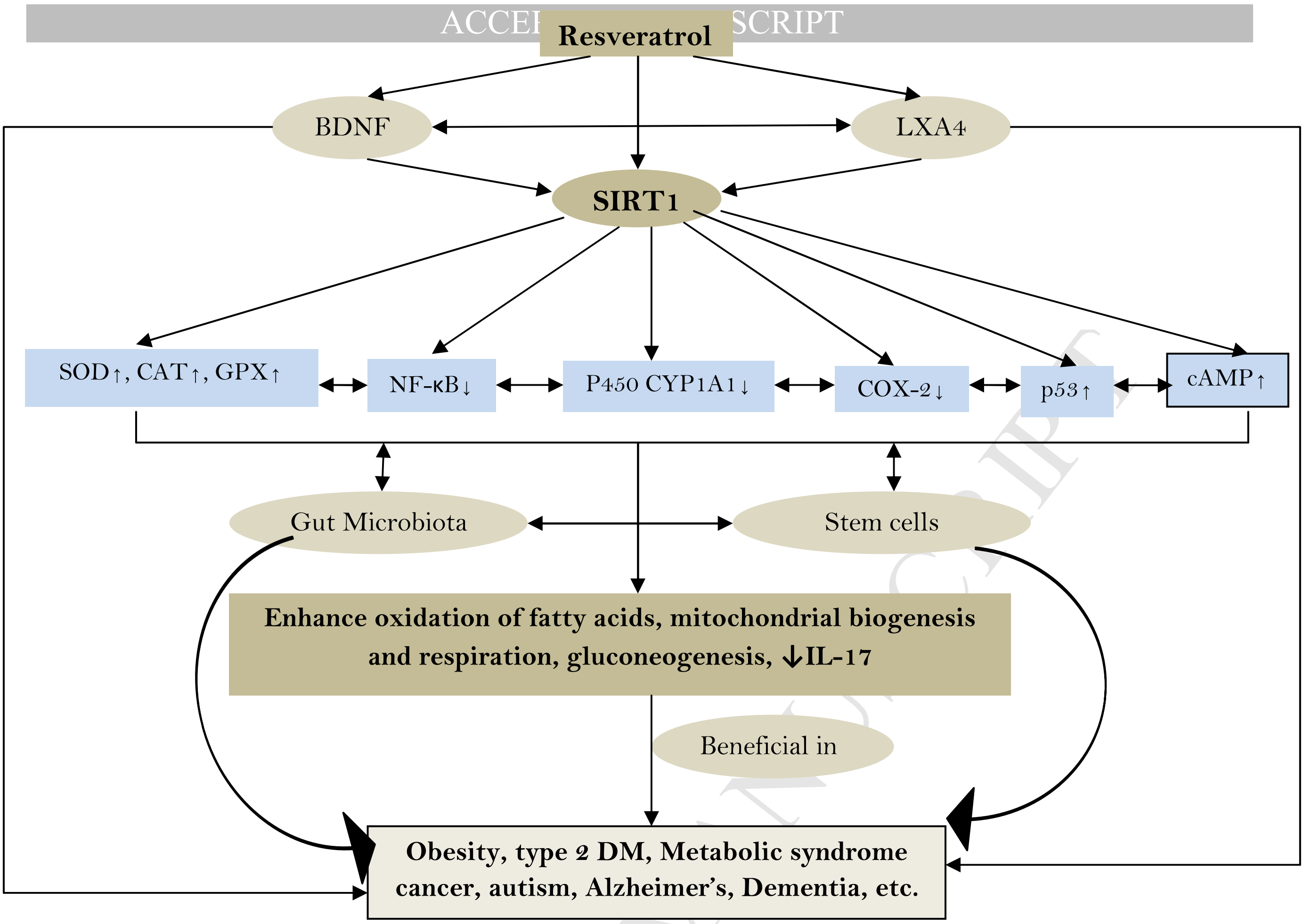

Figure 1. Scheme showing various important actions of resveratrol that form the basis of its benefit in various diseases

Legends to Figure 1:

Resveratrol activates Sirtuin 1 (SIRT1) and peroxisome proliferator-activated receptor-γ coactivator1α (PGC-1α) and improves the functioning of the mitochondria. Resveratrol binds to tyrosyl transfer-RNA (tRNA) synthetase (TyrRS) to potentiate a poly(ADP-ribose) polymerase 1) (PARP1)/NAD+ driven signaling cascade to activate p53 and AMPK by inhibiting SIRT1. Resveratrol induces mitochondrial accumulation of H_2O_2, which in turn induces cancer cell apoptosis. Resveratrol inhibits the production of pro-inflammatory IL-6, TNF-α and suppresses the activity of T_H17 cells and thus, is of benefit in several inflammatory conditions. It also inhibits the expressions of HIF-1α and VEGF that may explain its ability to suppresss cancer. Bisphenol has pro-inflammatory actions and may play a role in metabolic syndrome and autism that may be related to its ability to suppresss BDNF and lipoxin A4 synthesis and action. The beneficial actions of resveratrol and lipoxin A4 in the amelioration of inflammation, suppression of prostaglanin E2 synthesis and in the prevention of autism and metabolic syndrome implies that resveratrol may enhance the synthesis of lipoxin A4 that needs to be confirmed.

- We review the action of resveratrol on multiple enzymes, transcription factors and metabolic pathways.
- Resveratrol effects include facilitation of increased oxidation of fatty acids, mitochondrial biogenesis, mitochondrial respiration, and gluconeogenesis.
- Resveratrol inhibits expressions of HIF-1α and VEGF explaining its effective action against cancer.
- Resveratrol triggers apoptosis of activated T cells and suppresses pro-inflammatory molecules and thus, is of benefit in autoimmune diseases.
- Resveratrol alters gut microbiota and influences stem cell proliferation and differentiation.