Decreased severity of experimental autoimmune encephalomyelitis during resveratrol administration is associated with increased IL-17+IL-10+ T cells, CD4(-) IFN-gamma+ cells, and decreased macrophage IL-6 expression.

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Abstract

Experimental autoimmune encephalomyelitis (EAE), an animal model of Multiple Sclerosis, is induced after injection of PLP(139-151) myelin peptide in complete Freund's adjuvant into SJL/J mice. During EAE, T cells and macrophages infiltrate the brain, produce cytokines IL-17, IFN-gamma, TNF-alpha, or IL-6, and bring about autoimmune neuroinflammation. However, infiltrating T cells which simultaneously produce IL-17 and IL-10 or infiltrating CD4(-) NKT cells that produce IFN-gamma protect against EAE. Resveratrol, a plant polyphenol, exhibits anti-inflammatory properties. To determine if resveratrol can relieve EAE, SJL/J mice were administered diets enriched in resveratrol at EAE injection. EAE symptoms were significantly less compared with controls in mice fed resveratrol. At day 56 of EAE, splenic T cells from mice fed 0%, 0.04% or 0.08% resveratrol that were restimulated with PLP(139-151) produced similar levels while splenic T cells from mice fed 0.02% resveratrol produced significantly higher levels of IL-17, IFN-gamma, and TNF-alpha. At peak EAE (day 14), mice fed resveratrol had higher numbers of IL-17+ T cells, IL-17+/IL-10+ T cells, and CD4(-)IFN-gamma+ cells in the brain and spleen compared with controls. Adoptive transfer of day 14 EAE encephalogenic T cells into mice fed resveratrol reduced the severity of EAE. In addition, resveratrol directly suppressed expression of IL-6 and IL-12/23 p40 but increased expression of IL-12 p35 and IL-23 p19 from macrophages. Therefore resveratrol protection against EAE is not associated with declines in IL-17+ T cells but is associated with rises in IL-17+/IL-10+ T cells and CD4(-)IFN-gamma+ and with repressed macrophage IL-6 and IL-12/23 p40 expression.

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Abstract

Resveratrol is a phytoalexin structurally related to stilbenes, which is synthesized in considerable amounts in the skin of grapes, raspberries, mulberries, pistachios and peanuts, and by at least 72 medicinal and edible plant species in response to stress conditions. It was isolated in 1940 and did not maintain much interest for around five decades until its role in treatment of cardiovascular diseases was suggested. To date, resveratrol has been identified as an agent that may be useful to treat cancer, pain, inflammation, tissue injury, and other diseases. However, currently the attention is being focused in analyzing its properties against neurodegenerative diseases and as antiaging compound. It has been reported that resveratrol shows effects in in vitro models of epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and nerve injury. However, evidences in vivo as well as in human beings are still lacking. Thus, further investigations on the pharmacological effects of resveratrol in vivo are necessary before any conclusions on its effects on neurodegenerative diseases can be obtained.

PMID: 18684235 [PubMed - indexed for MEDLINE]
Resveratrol (trans-3,5,4'-trihydroxystilbene) ameliorates experimental allergic encephalomyelitis, primarily via induction of apoptosis in T cells involving activation of aryl hydrocarbon receptor and estrogen receptor.

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Abstract

Resveratrol (trans-3,5,4'-trihydroxystilbene), a polyphenolic compound found in plant products, including red grapes, exhibits anticancer, antioxidant, and anti-inflammatory properties. Using an animal model of multiple sclerosis (MS), we investigated the use of resveratrol for the treatment of autoimmune diseases. We observed that resveratrol treatment decreased the clinical symptoms and inflammatory responses in experimental allergic encephalomyelitis (EAE)-induced mice. Furthermore, we observed significant apoptosis in inflammatory cells in spinal cord of EAE-induced mice treated with resveratrol compared with the control mice. Resveratrol administration also led to significant down-regulation of certain cytokines and chemokines in EAE-induced mice including tumor necrosis factor-alpha, interferon-gamma, interleukin (IL)-2, IL-9, IL-12, IL-17, macrophage inflammatory protein-1alpha (MIP-1alpha), monocyte chemoattractant protein-1 (MCP-1), regulated on activation normal T-cell expressed and secreted (RANTES), and Eotaxin. In vitro studies on the mechanism of action revealed that resveratrol triggered high levels of apoptosis in activated T cells and to a lesser extent in unactivated T cells. Moreover, resveratrol-induced apoptosis was mediated through activation of aryl hydrocarbon receptor (AhR) and estrogen receptor (ER) and correlated with up-regulation of AhR, Fas, and FasL expression. In addition, resveratrol-induced apoptosis in primary T cells correlated with cleavage of caspase-8, caspase-9, caspase-3, poly(ADP-ribose) polymerase, and release of cytochrome c. Data from the present study demonstrate, for the first time, the ability of resveratrol to trigger apoptosis in activated T cells and its potential use in the treatment of inflammatory and autoimmune diseases including, MS.

SIRT1 activation confers neuroprotection in experimental optic neuritis.

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Abstract

PURPOSE: Axonal damage and loss of neurons correlate with permanent vision loss and neurologic disability in patients with optic neuritis and multiple sclerosis (MS). Current therapies involve immunomodulation, with limited effects on neuronal damage. The authors examined potential neuroprotective effects in optic neuritis by SRT647 and SRT501, two structurally and mechanistically distinct activators of SIRT1, an enzyme involved in cellular stress resistance and survival. METHODS: Experimental autoimmune encephalomyelitis (EAE), an animal model of MS, was induced by immunization with proteolipid protein peptide in SJL/J mice. Optic neuritis developed in two thirds of eyes with significant retinal ganglion cell (RGC) loss detected 14 days after immunization. RGCs were labeled in a retrograde fashion with fluorogold by injection into superior colliculi. Optic neuritis was detected by inflammatory cell infiltration of the optic nerve. RESULTS: Intravitreal injection of SIRT1 activators 0, 3, 7, and 11 days after immunization significantly attenuated RGC loss in a dose-dependent manner. This neuroprotective effect was blocked by sirtinol, a SIRT1 inhibitor. Treatment with either SIRT1 activator did not prevent EAE or optic nerve inflammation. A single dose of SRT501 on day 11 was sufficient to limit RGC loss and to preserve axon function. CONCLUSIONS: SIRT1 activators provide an important potential therapy to prevent the neuronal damage that leads to permanent neurologic disability in optic neuritis and MS patients. Intravitreal administration of SIRT1 activators does not suppress inflammation in this model, suggesting that their neuroprotective effects will be additive or synergistic with current immunomodulatory therapies.

PMID: 17652729 [PubMed - indexed for MEDLINE]
Pharmacological targeting of IDO-mediated tolerance for treating autoimmune disease.

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Abstract

Cells at the maternal-fetal interface express indoleamine 2,3 dioxygenase (IDO) to consume all local tryptophan for the express purpose of starving adjacent maternal T cells of this most limiting and essential amino acid. This stops local T cell proliferation to ultimately result in the most dramatic example of immune tolerance, acceptance of the fetus. By contrast, inhibition of IDO using 1-methyl-tryptophan causes a sudden catastrophic rejection of the mammalian fetus. Immunomodulatory factors including IFNgamma, TNFalpha, IL-1, and LPS use IDO induction in responsive antigen presenting cells (APCs) also to transmit tolerogenic signals to T cells. Thus it makes sense to consider IDO induction towards tolerance for autoimmune diseases in general. Approaches to cell specific therapeutic IDO induction with NAD precursor supplementation to prevent the collateral non-T cell pathogenesis due to chronic TNFalpha-IDO activated tryptophan depletion in autoimmune diseases are reviewed. Tryptophan is an essential amino acid most immediately because it is the only precursor for the endogenous biosynthesis of nicotinamide adenine dinucleotide (NAD). Both autoimmune disease and the NAD deficiency disease pellagra occur in women at greater than twice the frequency of occurrence in men. The importance of IDO dysregulation manifest as autoimmune pellagric dementia is genetically illustrated for Nasu-Hakola Disease (or PLOSL), which is caused by a mutation in the IDO antagonizing genes TYROBP/DAP12 or TREM2. Loss of function leads to psychotic symptoms rapidly progressing to presenile dementia likely due to unchecked increases in microglial IDO expression, which depletes neurons of tryptophan causing neurodegeneration. Administration of NAD precursors rescued entire mental hospitals of dementia patients literally overnight in the 1930's and NAD precursors should help Nasu-Hakola patients as well. NAD depletion mediated by peroxynitrate PARP1 activation is one of the few established mechanisms of necrosis. Chronic elevation of TNFalpha leading to necrotic events by NAD depletion in autoimmune disease likely occurs via combination of persistent IDO activation and iNOS-peroxynitrate activation of PARP1 both of which deplete NAD. Pharmacological doses of NAD precursors repeatedly provide dramatic therapeutic benefit for rheumatoid arthritis, type 1 diabetes, multiple sclerosis, colitis, other autoimmune diseases, and schizophrenia in either the clinic or animal models. Collectively these observations support the idea that autoimmune disease may in part be considered as localized pellagra manifesting symptoms particular to the inflamed target tissues. Thus pharmacological doses of NAD precursors (nicotinic acid/niacin, nicotinamide/niacinamide, or nicotinamide riboside) should be considered as potentially essential to the therapeutic success of any IDO-inducing regimen for treating autoimmune diseases. Distinct among the NAD precursors, nicotinic acid specifically activates the g-protein coupled receptor (GPCR) GPR109a to produce the IDO-inducing tolerogenic prostaglandins PGE(2) and PGD(2). Next, PGD(2) is converted to the anti-inflammatory prostaglandin, 15d-PGJ(2). These prostaglandins exert potent anti-inflammatory activities through endogenous signaling mechanisms involving the GPCRs EP2, EP4, and DP1 along with PPARgamma respectively. Nicotinamide prevents type 1 diabetes and ameliorates multiple sclerosis in animal models, while nothing is known about the therapeutic potential of nicotinamide riboside. Alternatively the direct targeting of the non-redox NAD-dependent proteins using resveratrol to activate SIRT1 or PJ34 in order to inhibit PARP1 and prevent autoimmune pathogenesis are also
given consideration.

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Emerging potentials for an antioxidant therapy as a new approach to the treatment of systemic sclerosis.

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Erratum in:
• Toxicology 2001 Apr 12;162(1):69. Gabriele, S [corrected to Simonini, G]; Alberto, P [corrected to Pignone, A]; Sergio, G [corrected to Generini, S]; Fernanda, F [corrected to Falcini, F]; Marco, MC [corrected to Cerinic, MM].

Abstract

Oxidative stress, favoring disease progression by a rapid degeneration of endothelial cell function is deeply involved in Systemic Sclerosis (SSc) pathogenesis. Raynaud's phenomenon (RP), present in 90% of patients with SSc, provoking frequent daily episodes of hypoxia-reperfusion injury, produces several episodes of free radicals-mediated endothelial derangement. These events results in a positive feedback effect of luminal narrowing and ischemia and therefore to the birth of a vicious cycle of oxygen free radicals (OFR) generation, leading to endothelial damage, intimal thickening and fibrosis. Thus ischemia and reperfusion are two criticals events that may induce oxidative stress and inactivation of antioxidant enzymes. In RP and SSc, a reduced concentration of ascorbic acid, alpha-tocopherol and beta-carotene as well as low values of Selenium have been reported. This antioxidative potential deficiency increases the propensity to oxidative stress, favoring the development of injury mediated by OFR. We reviewed several antioxidant compounds, aiming at their capacity of reverting endothelial dysfunction and damage, scavenging lipid peroxidation and reducing multiple episodes of hypoxia-reperfusion injury. In order to interrupt SSc vicious cycle, we propose a main strategy for SSc treatment by a supplementation of antioxidants and different kind of drugs with antioxidant property, such as Lazaroids, Resveratrol, Melatonin and Probucol.

PMID: 11154792 [PubMed - indexed for MEDLINE]


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Abstract

BACKGROUND: Digalloyl-resveratrol (di-GA) is a synthetic compound aimed to combine the biological effects of the plant polyhydroxy phenols gallic acid and resveratrol, which are both radical scavengers and cyclooxygenase inhibitors exhibiting anticancer activity. Their broad spectrum of activities may probably be due to adjacent free hydroxyl groups. METHODS: Protein activation and expression were analysed by western blotting, deoxyribonucleoside triphosphate levels by HPLC, ribonucleotide reductase activity by (14)C-cytidine incorporation into nascent DNA and cell-cycle distribution by FACS. Apoptosis was measured by Hoechst 33258/propidium iodide double staining of nuclear chromatin and the formation of gaps into the lymphendothelial barrier in a three-dimensional co-culture model consisting of MCF-7 tumour cell spheroids and human lymphendothelial monolayers. RESULTS: In HL-60 leukaemia cells, di-GA activated caspase 3 and dose-dependently induced apoptosis. It further inhibited cell-cycle progression in the G1 phase by four different mechanisms: rapid downregulation of cyclin D1, induction of Chk2 with simultaneous downregulation of Cdc25A, induction of the Cdk-inhibitor p21(Cip/Waf) and inhibition of ribonucleotide reductase activity resulting in reduced dCTP and dTTP levels. Furthermore, di-GA inhibited the generation of lymphendothelial gaps by cancer cell spheroid-secreted lipoxygenase metabolites. Lymphendothelial gaps, adjacent to tumour bulks, can be considered as gates facilitating metastatic spread. CONCLUSION: These data show that di-GA exhibits three distinct anticancer activities: induction of apoptosis, cell-cycle arrest and disruption of cancer cell-induced lymphendothelial disintegration.

PMID: 20424615 [PubMed - in process]
Suppression of the Inflammatory Cascade is Implicated in Resveratrol Chemoprevention of Experimental Hepatocarcinogenesis.

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Abstract

PURPOSE: Resveratrol, present in grapes and red wine, has been found to prevent diethylnitrosamine (DENA)-initiated rat liver tumorigenesis, though the chemopreventive mechanisms are not completely elucidated. The current study was designed to explore whether the antiinflammatory properties of resveratrol play a role in its antihepatocarcinogenic action.

METHODS: Liver samples were harvested from a 20-week chemopreventive study in which resveratrol (50, 100 and 300 mg/kg) was shown to inhibit DENA-induced hepatocyte nodules in Sprague-Dawley rats in a dose-responsive manner. Hepatic preneoplastic and inflammatory markers, namely heat shock protein (HSP70), cyclooxygenase-2 (COX-2) and nuclear factor-kappaB (NF-kappaB), were studied using immunohistochemical as well as Western blot techniques.

RESULTS: Resveratrol dose-dependently suppressed DENA-induced increased expressions of hepatic HSP70 and COX-2. Resveratrol also attenuated the DENA-mediated translocation of NF-kappaB p65 from the cytosol to the nucleus with stabilization of inhibitory kappaB.

CONCLUSION: The present findings indicate that resveratrol exerts chemoprevention of hepatocarcinogenesis possibly through antiinflammatory effects during DENA-evoked rat liver carcinogenesis by suppressing elevated levels of HSP70, COX-2 as well as NF-kappaB. These beneficial effects combined with an excellent safety profile encourage the development of resveratrol for chemoprevention and intervention of human HCC that remains a devastating disease.

PMID: 20405173 [PubMed - as supplied by publisher]
Resveratrol attenuates the anticancer efficacy of paclitaxel in human breast cancer cells invitro and in vivo.

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Abstract
It was reported recently that resveratrol could sensitise a number of cancer cell lines to the anticancer actions of several other cancer drugs, including paclitaxel. In the present study, we further investigated whether resveratrol could sensitise human breast cancer cells to paclitaxel-induced cell death. Unexpectedly, we found that resveratrol strongly diminished the susceptibility of MDA-MB-435s, MDA-MB-231 and SKBR-3 cells to paclitaxel-induced cell death in culture, although this effect was not observed in MCF-7 cells. Using MDA-MB-435s cells as a representative model, a similar observation was made in athymic nude mice. Mechanistically, the modulating effect of resveratrol was partially attributable to its inhibition of paclitaxel-induced G(2)/M cell cycle arrest, together with an accumulation of cells in the S-phase. In addition, resveratrol could suppress paclitaxel-induced accumulation of reactive oxygen species (ROS) and subsequently the inactivation of anti-apoptotic Bcl-2 family proteins. These observations suggest that the strategy of concomitant use of resveratrol with paclitaxel is detrimental in certain types of human cancers. Given the widespread use of resveratrol among cancer patients, this study calls for more preclinical and clinical testing of the potential benefits and harms of using resveratrol as a dietary adjuvant in cancer patients. Copyright © 2010 Elsevier Ltd. All rights reserved.

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Synergistic effects of combined phytochemicals and skin cancer prevention in SENCAR mice.

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Comment in:

Abstract

The purpose of our study was to determine the inhibitory effect of combined phytochemicals on chemically induced murine skin tumorigenesis. Our hypothesis was that concurrent topical and dietary treatment with selected compounds would lead to more efficient prevention of skin cancer. We tested ellagic acid and calcium D-glucarate as components of diets, while resveratrol was applied topically; grape seed extract was applied topically or in the diet. The 4-week inflammatory-hyperplasia assay based on the 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin carcinogenesis model in SENCAR mice was used. We have found that all the selected combinations caused a marked decrease of epidermal thickness compared with the DMBA-treated group and also with groups treated with a single compound and DMBA. All combinations of resveratrol with other compounds showed a synergistic effect on hyperplasia and Ha-ras mutations. Skin tissue of mice receiving the combinations showed decreased cell proliferation and Bcl2 expression; decreased p21, a regulator of cell cycle; and decreased marker of inflammation cyclooxygenase-2. All the selected combinations diminished the DMBA-induced mRNA expression of the CYP1B1 level, and also caused a marked decrease of proto-oncogenes c-jun and c-fos, components of transcription factor activator protein. In conclusion, all combinations showed either additive or synergistic effects and their joint actions allowed for decreasing the doses of the compounds. Especially, resveratrol combinations with ellagic acid, grape seed extract, and other phytochemicals are very potent inhibitors of skin tumorgenesis, based on the suppression of epidermal hyperplasia as well as on the modulation of intermediate biomarkers of cell proliferation, cell survival, inflammation, oncogene mutation, and apoptosis.

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