A glass of red wine to improve mitochondrial biogenesis? Novel mechanisms of resveratrol

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Numerous epidemiological studies demonstrated an association between moderate alcohol consumption and reduced coronary heart disease. Red wine, especially, is shown to be protective against numerous cardiovascular and metabolic diseases. Frankel et al. (5) demonstrated that red wine polyphenols inhibited the oxidation of low-density lipoprotein more than did the established antioxidant a-tocopherol. Resveratrol (3,5,4′-trihydroxystilbene) is known to be a component of some plants of medicinal use like Polygonum cuspidatum, a plant used in traditional medicine. Resveratrol, initially characterized as phytoalexin, attracted much attention in 1992 when it was postulated to explain the cardioprotective role of red wine.

Resveratrol and its analogs have been investigated in numerous trials over a couple of decades reporting in vitro and in vivo beneficial effects of these compounds in a variety of human disease models, such as cardio- and neuroprotection, immune regulation, and cancer chemoprevention. These studies have underscored the high degree of diversity in terms of the signaling networks and cellular effector mechanisms impacted by resveratrol. Among them are cell surface receptors, membrane signaling pathways, intracellular signal transduction machinery, nuclear receptors, gene transcription, and metabolic pathways. The promise shown by resveratrol has prompted heightened interest in studies aimed at translating these observations to the clinical settings.

There is accumulating evidence that resveratrol can exert antioxidant effects in biological systems via multiple direct and indirect mechanisms, including effects on reactive oxygen species (ROS) and nitric oxide (NO) production, lipid peroxidation, and endogenous antioxidant systems, all of which may contribute to the cardiovascular benefits of the compound (2). The multifaceted anti-inflammatory effects of resveratrol are not restricted to the increase of NO bioavailability and anti-oxidative properties. In various inflammatory disease models (such as ischemia-reperfusion, sepsis, etc.), a key step of tissue injury is the increase of leukocyte adherence and vascular transmigration into the injured tissue microcirculation (9). A recent study has demonstrated that intravenous administration of resveratrol attenuates these deleterious effects of ischemia-reperfusion (9). Importantly, resveratrol may also confer vasculoprotection by regulating the expression of proinflammatory and proatherogenic genes in endothelial cells. Local leukocyte recruitment into the vessel wall is controlled by the expression of cell adhesion molecules. It is significant that resveratrol was shown in vitro to decrease endothelial VCAM and ICAM-1 expression and attenuate monocyte adhesiveness to the endothelium (4). Several lines of evidence suggest that inhibition of NF-κB by resveratrol underlies many of the anti-inflammatory effects of resveratrol (6).

It has been proposed that high levels of inflammatory cytokines (in particular TNF-α) play a role in the development of cardiac and vascular dysfunction. Numerous studies demonstrated that increased levels of ROS may activate NF-κB in endothelial, smooth muscle cells, and other cell types, leading to the upregulation of adhesion molecules, inducible NO synthase (iNOS), TNF-α, and other cytokines. Importantly, resveratrol treatment significantly decreases iNOS expression in different cell types (3). A second proinflammatory transcription factor, activator protein 1 (AP-1), may also be inhibited by resveratrol (6). AP-1, similarly to NF-κB, is important in the regulation of many inflammatory genes that are induced by oxidative stress, and its inhibition may contribute to the anti-inflammatory properties of resveratrol.

Recently, resveratrol has been shown to have positive effects on age longevity and lipid levels and a preventative quality against certain cancers and viral infections. Resveratrol induces apoptosis by upregulating the expression of Bax, Bak, PUMA, Noxa, Bim, p53, TRAIL, TRAIL-R1/DR4, and TRAIL-R2/DR5 and simultaneously downregulating the expression of Bcl-2, Bcl-XL, Mcl-1, and survivin. Resveratrol causes growth arrest at the G1 and G1/S phases of cell cycle by inducing the expression of CDK inhibitors p21/WAF1/CIP1 and p27/KIP1. Resveratrol has also been shown to reduce inflammation via inhibition of prostaglandin production, cyclooxygenase-2 activity, and NF-κB activity. Modulation of the cell signaling pathway by resveratrol explains its diverse bioactivities related with human health. Resveratrol also potentiates the apoptotic effects of cytokines, chemotherapeutic agents, and γ-radiation. Pharmacokinetic and pharmacodynamic studies demonstrated that the main target organs of resveratrol are the liver and kidney, and it is metabolized by hydroxylation, glucuronidation, sulfation, and hydrogenation. As a chemoprevention agent, resveratrol has been shown to inhibit tumor initiation, promotion, and progression (8).

Although many possible pathways are already shown to be responsible to the beneficial actions, Csiszar et al. (1) could demonstrate novel mechanisms of resveratrol at the mitochondrial level. They identify resveratrol as a potent activator of mitochondrial biogenesis in coronary arterial endothelial cells (CAECs). An important recent paper published by the same authors in Cell Metabolism (7) raised the therapeutic possibility of resveratrol against both diabetes-induced and age-related vascular pathophysiological alterations. In the current article, the authors provide a very careful evaluation of the signaling cascades activated by resveratrol in endothelial cells, using both in vitro and in vivo (mouse models) approaches. First, they show that in CAECs resveratrol increased mitochondrial mass and mitochondrial DNA content, upregulated expression of electron transport chain constituents, and induced the mitochondrial biogenesis factors proliferator-activated receptor-
coactivator-1α, nuclear respiratory factor-1, and mitochondrial transcription factor A. Second, sirtuin 1 (SIRT1) expression and activity in endothelial cells was induced by resveratrol and knockdown of SIRT1 by small interfering RNA prevented the effects of resveratrol. Third, endothelial NO synthase (eNOS) was upregulated in a SIRT1-dependent manner and inhibition of NO synthesis prevented resveratrol-induced mitochondrial biogenesis. Finally, in aortas of type 2 diabetic db/db mice, impaired mitochondrial biogenesis was normalized by chronic resveratrol treatment. Overall, these results convincingly indicate that resveratrol activates SIRT1 and upregulates eNOS in endothelial cells and that these effects result in increased mitochondrial biogenesis. The study by Csiszar et al. (1) provides important novel information on the mechanisms underlying the vasoprotective action of resveratrol in aging and metabolic diseases.

The present study extends the knowledge and understanding about the beneficial effects of resveratrol. The novel data about the mitochondrial function as a missing puzzle complete the complex picture of the all-in-one nature of this substance. Since intact mitochondrial function is a prerequisite of cellular integrity in any tissue, any drug that improves mitochondrial function under pathological conditions may have large potential in the treatment of a wide variety of diseases. As such, resveratrol may have a significant impact on the treatment of different cardiovascular, metabolic, and inflammatory diseases.

Back to the title of this editorial, the novel mechanisms proposed in the present research article may further underline the epidemiological observations that show not only a lower prevalence of coronary artery disease but lower overall mechanisms in predominantly (red) wine-drinking countries. Under these aspects, the beneficial effects of resveratrol (and, thereby, red wine) cannot be limited to sole antioxidant effects but a more general cytoprotection and favorable influence on cellular metabolism.

REFERENCES