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The dietary antioxidant resveratrol affects redox changes of PPARα activity

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Abstract *Background and aims:* Gene–environment interaction is behind the pathogenesis of most widespread diseases, and nutrition is among the environmental factors with the highest impact on human health. The mechanisms involved in the interaction between nutritional factors and the genetic background of individuals are still unclear. The aim of this study was to investigate whether resveratrol (RES), an antioxidant polyphenol of red wine, can influence the activity of PPARα in the rat hepatoma cell line McArdle-RH7777. PPARα is a transcriptional factor that regulates gene expression when activated by endogenous or exogenous long-chain fatty acids. Its activation results in significant protection from cardiovascular diseases in humans.
Methods and results: By means of the electromobility shift assay (EMSA), we observed that PPARα is redox-sensitive as it displays reduced DNA-binding activity following in vivo treatment of the cells with 1 mmol/L diethylmaleate (DEM), a glutathione-depleting agent. This finding could be relevant considering the important role of redox balance in pathological and physiological processes. We also observed a dual effect of 100 μmol/L RES on PPARα activity: it was able to prevent, to a large extent, the DEM-induced reduction of DNA-binding activity at earlier time points, when the effect of DEM was stronger, but it depressed PPARα activity at later time points, when the effect of DEM was greatly reduced.

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Conclusion: A nutritional substance, such as RES, is able to influence the activity of gene-regulating factors, but the net effect is difficult to predict when the compound involved has multiple biological properties. Caution is therefore warranted before drawing conclusions about the potential benefits of RES for human health.

Introduction

Although aerobic organisms exploit the selective advantage of oxygen-based metabolism, they are subject to a certain degree of oxidative stress. Oxidative stress is associated with an excessive formation of free radicals; this results in loss of cell integrity, enzyme function and genome stability, effects caused by damage to lipids in cell membranes, modification of protein structure, and damage to DNA [1,2]. This molecular damage is the basis of pathological processes of paramount importance, such as accelerated senescence, atherosclerosis, and cancer. However, the potential toxicity of oxygen is kept under control by a highly regulated set of antioxidant defenses [3].

In contrast, controlled amounts of free radicals can act as signaling molecules: superoxide, for example, has a role both in the induction of gene expression and of stress response factors [4,5]. Moreover, hydrogen peroxide, which is not an oxygen radical by itself but which is capable of generating the highly toxic hydroxyl radicals if redox-active transition metal ions are present, can act as a signal transduction factor in cells [6,7]. The regulation of gene expression by reactive oxygen species (ROS) has become increasingly appreciated, and more than one hundred genes or proteins have been reported to be redox-sensitive [5]. Transcription factors have also been shown to be affected by redox changes, as in the following examples: ROS activate NF-kB [8]; the glucocorticoid receptor is sensitive to redox changes [9]; Fos—Jun heterodimers bind the *AP-1* DNA consensus sequence only if two conserved cysteines are in a reduced state [10,11]; and the p53 tumor suppressor protein has been shown to require reactive sulfhydryls for effective sequence-specific DNA binding [12,13].

Since nutrition is one of the most relevant environmental factors in the development or prevention of chronic degenerative diseases, and the antioxidant potential of some foods has been implicated in the health-protecting power of some dietary patterns, it is possible that food antioxidants could influence the redox sensitivity of transcription factors, thus identifying an important level of gene—nutrient interaction. Indeed, the importance of nutritional and non-nutritional botanicals or functional food components in the transcriptional regulation of gene expression is now beginning to be fully appreciated and has been extensively reviewed recently [14].

PPARα, PPARβ, and PPARγ form a subgroup of the nuclear receptor superfamily and, upon ligand binding, regulate the expression of several genes mainly involved in lipid metabolism, and are thus linked to atherosclerosis and cardiovascular diseases [15]. Important proof for a protective role of PPARα in such conditions was provided by a large prospective trial showing that treatment with gemfibrozil, a PPARα-activating fibrate, produced a 22% reduction in cardiovascular events or deaths [16]. Several mechanisms can be claimed to explain this finding: for instance, in humans, PPARα activation results in substantial plasma triglyceride lowering and modest high-density lipoprotein cholesterol (HDL-C) raising [15]. Plasma triglycerides are lowered because activated PPARα induces the uptake of fatty acids from plasma lipoproteins by suppressing hepatic apo-CIII and stimulating lipoprotein lipase gene expression. Additionally, PPARα promotes fatty acid metabolism by inducing the expression of genes involved in the transport of fatty acids within the cell and the mitochondria, as well as those coding for many enzymes of the β-oxidation pathway. The effect on HDL-C is probably due to upregulation of *apo-A1* gene expression. PPARs, which are activated by long-chain polyunsaturated fatty acids, are also one of the few examples of nutrient-regulated transcription factors. Hence, it has been suggested that these receptors play a central role in sensing nutrient levels and in modulating their metabolism. In addition, PPARs contain zinc-finger motifs in their DNA-binding domain and, consequently, are good candidates for being influenced by redox perturbations [17].

Resveratrol is a polyphenol that accumulates especially in grape skin and is therefore present in red wine [18]. It has been hypothesized that the antioxidant properties of RES are responsible for the protective effect of a moderate intake of red wine on cardiovascular diseases. This theory provides the basis for the so-called French paradox [19], the observation that the incidence of cardiovascular diseases in France is lower than expected,