Conundrum of the “French Paradox”

To the Editor:

Certain populations, such as the French and the Greeks, have a low incidence of coronary artery disease, despite a diet relatively high in saturated fat. It has been suggested that regular consumption of red wine may explain this phenomenon, which has been dubbed the “French paradox,”1 i.e., the coexistence of a high-fat diet and a low incidence of coronary artery disease.

Although the cardioprotective effects of most alcoholic beverages are probably due to an elevation of high-density lipoprotein, as well as the ability of alcohol to prevent platelet aggregation and to increase fibrinolysis, there is an increased favorable effect of red wine.2 The unique cardioprotective properties of red wine reside in the action of flavonoids, which are absent in white wine (with the exception of champagne) and sparse in beer (with the exception of dark beers). The best research flavonoids are resveratrol and quercetin, which confer antioxidant properties more potent than α-tocopherol.2

As was summarized recently by Hung et al.,3 in purified or synthetic form, resveratrol has been shown to reduce the synthesis of lipids in rat liver, to inhibit the synthesis of eicosanoids in rat leukocytes, to interfere with arachidonate metabolism, to inhibit platelet activation/aggregation, to inhibit the activity of some protein kinases, and to exert a strong inhibitory effect on reactive oxygen species produced by human polymorphonuclear leukocytes. As an antioxidant, resveratrol is more powerful than vitamin E in preventing low-density lipoprotein oxidation.3

Recently, Hung et al.3 showed that preinusion of resveratrol is effective in preventing reperfusion-induced arrhythmias and mortality. This protective effect on arrhythmias and cardiac cell damage by resveratrol may be associated with its antioxidant activity, free radical scavenging activity, and enhanced NO release during the reperfusion period.

Another fascinating new facet of resveratrol was reported by Gehm et al.4 On the basis of the structural similarity of resveratrol (trans-3,4',5-trihydroxystilbene) to the synthetic estrogen diethylstilbestrol (4,4'-dihydroxy-trans-a, β-diethylstilbene), these authors hypothesized that resveratrol might be a phytosteroid. Given the known cardioprotective benefits of estrogens, this speculation seemed particularly appealing.

Now, Blanco-Colio et al.5 offer another potential mechanism to explain the beneficial effects of red wine in the reduction of cardiovascular mortality. They found that red wine intake, but not another form of alcohol beverage intake (vodka), prevented nuclear factor (NF)-κB activation in peripheral blood mononuclear cells elicited in healthy volunteers by postprandial lipemia. Because NF-κB activation is involved in the pathogenesis of atherosclerotic lesions, the inhibitory effect of red wine on NF-κB activation provides a further explanation of the beneficial effects of red wine intake in cardiovasculardisease.

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Response

Epidemiological studies suggest that the consumption of wine, particularly red wine, reduces the incidence of morbidity and mortality from coronary heart disease. As stated by Dr Cheng in his letter, it is conceivable that the unique cardioprotective properties of red wine reside in the multiple actions of flavonoids, among which the antioxidant activity is probably the most relevant. Although we agree that resveratrol, one of the flavonoids most studied, is a strong potential candidate to explain the cardioprotective effect of red wine, it is difficult to determine clearly which antioxidant is responsible for this effect. On the one hand, quercetin and catechin reduce the progression of atherosclerosis in apoE-deficient mice and the susceptibility of LDL to oxidation and aggregation.6 Catechin and vitamin E also prevent the development of fatty streaks in hypercholesterolemic hamsters.7 On the other hand, although resveratrol inhibits platelet activation and has anti-inflammatory properties, paradoxically, it promotes atherosclerosis in hypercholesterolemic rabbits.8 The complexity of the issue is further stressed by the absence of an apparent effect of vitamin E on cardiovascular events in high-risk patients, at least during the years of this study.4

Given the pleiotropic effects of nuclear factor (NF)-κB in regulating cell growth/apoptosis and inflammation, some have suggested that it could be implicated in the pathogenesis of cardiovascular disease. In our article, we demonstrated that red wine, but not another form of alcoholic beverage like vodka, prevented NF-κB activation in peripheral mononuclear cells during postprandial lipemia in healthy volunteers. During in vitro studies, we also noted that 2 antioxidants present in red wine (quercetin and α-tocopherol succinate) attenuated the NF-κB activation caused by VLDL. Although, as mentioned in our article, Wadsworth et al.4 reported that resveratrol did not inhibit lipopolysaccharide-induced NF-κB activation in murine macrophage cell line RAW 264.7, recent reports show that it suppresses the NF-κB activation elicited by tumor necrosis factor-α and inhibits inhibitor KB kinase activation.

It is of paramount importance to unravel which components of red wine are implicated in its beneficial cardiovascular effects. In this regard, red wine contains ~60 antioxidants, and it is possible that there could be a certain synergism among some of them. In addition, we could not discard that possibility that red wine alcohol also participates in the beneficial effect by allowing a better absorption of other wine components.

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