EDITORIAL (SEE URIBARRI ET AL., P. 2579)

Macronutrients, Advanced Glycation End Products, and Vascular Reactivity

Ischemia-induced flow-mediated vasodilatation (FMD) of the brachial artery has emerged as the standard test for endothelial function in humans in vivo (1). It has been established that the reestablishment and the increase in flow following a period of ischemia is due to the release of nitric oxide (NO) from the endothelium, which leads to vascular smooth muscle relaxation through the activation of guanylate cyclase and the release of cyclic monophosphate in the vascular smooth muscle cell (2,3). Since FMD is dependent on NO, any factor that may influence the bioavailability of NO from the endothelium is likely to affect FMD. One major factor that affects NO bioavailability is the superoxide (O_2) radical, which combines with NO to form the toxic peroxynitrite and thus reduces NO bioavailability (4). Thus, any biological or clinical situation that leads to an increase in O-2 radical and the resultant oxidative stress is likely to reduce any vasodilatory process including FMD. In addition, inflammation may also reduce NO release because inflammatory cytokines like tumor necrosis factor-α have been shown to reduce the expression of endothelial NO synthase (eNOS) (5). Indeed, some studies show that the concentration of some of the indexes of inflammation is inversely proportional to FMD (6). There is also evidence that under inflammatory and ischemic conditions, NOS may behave like NADPH oxidase and generate the O_2 radical (7).

A reduction in FMD has been associated with an increase in cardiovascular risk. Type 1 and type 2 diabetes, obesity, hypertension, smoking, menopause, hyperlipidemia, African-American ethnicity, and established macrovascular disease have been shown to be associated with significant reductions in FMD (1,8,9). All of these conditions are associated with increased oxidative and inflammatory stress. FMD is still being used as a research technique to evaluate endothelial function, and its ability to predict cardiovascular events is still not fully validated to a level where we could use it as a part of an algorithm to coronary angiography in patients at risk.

Over the past decade, dietary intake has been shown to be associated with alterations in FMD. A key study by Vogel et al. (10) demonstrated that the intake of a high-fat, high-carbohydrate, fast food meal led to a predictable reduction in FMD and that this could be prevented by pretreatment with antioxidants (11). It has since been demonstrated that both the intake of the fast food meal and fat taken as cream lead to an increase in the generation of O_2 and associated oxidative stress and inflammation at the cellular and molecular level (12).

In contrast to the effect of cream which mainly contains saturated fat, fish oil has different effects. Fish oil is rich in two n-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, which have distinct biological properties. Six weeks of treatment with a combination of these two fatty acids resulted in an increase in postischemic hyperemia in the forearm in patients with coronary heart disease or cardiac failure and in children with hypercholesterolemia (13,14). Consistent with an increase in vasodilatory reserve, the intake of these acids also exerted an antihypertensive effect in older and hypertensive subjects and in patients with posttransplant hypertension (15,16). This effect is also associated with a reduction in systemic arterial compliance. The administration of these fatty acids concomitantly results in a reduction in the plasma concentrations of inflammatory mediators like proinflammatory cytokines and adhesion molecules (17). The plasma concentration of asymmetrical dimethyl-arginine, which is an endogenous inhibitor of endothelial NO synthase, is also reduced (18). On the other hand, the addition of olive oil to a high-fat diet has been shown to reduce FMD both in normal subjects and in hypercholesterolemic patients (19). This raises the question whether olive oil or other elements of the Mediterranean diet are responsible for the protective effect of this diet in relation to cardiovascular events.

Whereas intake of glucose and other macronutrients leads to oxidative and inflammatory stress, there is now ample evidence that advanced glycation end products (AGEs) also induce oxidative stress, since glycated molecules are more susceptible to oxidative damage (20). In addition, AGEs bind to the receptors for AGEs and trigger proinflammatory signal transduction in inflammatory and possibly other cells to lead to an increase in proinflammatory mediators and O_2 generation (20). Previous investigations examining the effects of AGEs were not able to separate the specific effects of AGEs from those of the dietary products with which the investigations were conducted. These dietary products had substantial caloric values, and thus the role of AGEs could not be convincingly separated from that of the diet itself. We now have evidence from the study by Uribarri et al. (21) showing that an AGE-rich product prepared from Coca-Cola Light induced a consistent fall in FMD parallel with an increase in the plasma concentrations of AGEs; thiobarbituric acid reactive substances, an index of oxidative damage to fats; and plasminogen activator inhibitor-1 without a concomitant increase in glucose concentrations. It is clear that AGEs alter FMD acutely, and it is possible that a diet rich in AGEs may, over a prolonged period of time, result in more permanent changes in vascular reactivity. Consistent with the concept that AGEs intake impairs FMD, the same group of investigators published another key study last year showing that treatment with benfotiamine, a thiamine derivative that blocks AGE formation and reduces proinflammatory changes and oxidative stress, prevents the decline of FMD following the intake of an AGE-rich meal (22). Since their current investigation demonstrates the direct effect of pure AGE intake, the action of benfotiamine in their previous experiment was probably the result of its effects on oxidative and inflammatory stress rather than on AGE formation.

Clearly, dietary intake, an important component of our lifestyle, is a modulator of vascular behavior. From the work presented by Uribarri et al., it is clear that the

mode of preparation of our food also determines postprandial vascular reactivity, oxidative stress, and inflammation and that AGEs are important mediators of these effects. The area of macronutrient-induced postprandial changes is set to evolve rapidly such that it will impact our eating and cooking habits and the choice of foods that we eat.

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