Editorial Comment

Reversal of Hypercholesterolemia-Induced Endothelial Dysfunction by L-Arginine

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Hypercholesterolemia impairs endothelial function (manifested as an attenuation of endothelium-dependent relaxation) prior to the formation of atherosclerotic lesions. Endothelial dysfunction in return can evoke abnormal interactions between the vascular wall and blood cells (neutrophils, monocytes, and platelets) and promote expression of mitogens, which contribute to the development of atherosclerosis.1 Thus, early “treatment” of endothelial dysfunction may prevent the later consequences of this abnormality, including atherosclerosis. In a paper published in this issue of Circulation, Cooke et al2 report that infusion of l-arginine (the proposed precursor of endothelium-derived relaxing factor [EDRF]) to hypercholesterolemic rabbits normalizes endothelium-dependent relaxation. This finding suggests that increasing the synthesis of EDRF may be of benefit in the reversal of endothelial dysfunction caused by hypercholesterolemia, and could be a novel approach to prevent the development of atherosclerotic lesions.

L-Arginine is the Precursor of EDRF (NO)

After the cornerstone observation of Furchgott and Zawadsky3 that the presence of endothelium is obligatory for acetylcholine-induced vasorelaxation, bioassay studies demonstrated that a very labile nonprostanoid substance(s) (called endothelium-derived relaxing factor, or EDRF) mediates endothelium-dependent vasorelaxation.4-5 Based on the discovery that the effect of EDRF, like that of nitric oxide (NO), is mediated by an increase in smooth muscle cyclic GMP content,6 and that hemoglobin7 and superoxide anion8,9 inactivate both NO and EDRF, it was proposed that EDRF and NO are the same substance.10,11 The demonstration of NO production by endothelial cells12 provided more direct evidence for this hypothesis. Although it is still uncertain whether EDRF is free NO or a labile nitroso compound from which NO is liberated,13,14 it is widely accepted that L-arginine is the substrate required for formation of NO and EDRF.15-17

Impairment of Endothelium-Dependent Vasodilation in Atherosclerosis and Hypercholesterolemia

Chronic feeding of cholesterol-enriched diets to certain animals leads to atherosclerotic lesions like those observed in the human disease. Diet-induced experimental atherosclerosis impairs endothelium-dependent vasorelaxation in vitro and in vivo,18,19 but generally leaves endothelium-independent relaxations intact. Atherosclerotic human coronary arteries (both in vitro and in vivo) also show impaired endothelium-dependent dilation to intracoronary infusion of acetylcholine, but not to nitroglycerin.20,21 Hypercholesterolemia was found to be one of the most important factors predicting endothelial dysfunction in human coronary arteries.22 Acute exposure of isolated blood vessels in vitro to low density lipoprotein (LDL) (but not to high density lipoprotein) inhibits endothelium-dependent vasorelaxation in response to a variety of agonists.23-25 Oxidatively modified LDL but not native LDL impaired endothelium-dependent relaxations to acetylcholine in rabbit aorta.26 Several studies demonstrated impaired endothelium-dependent relaxation in resistance arterioles (which do not develop atherosclerotic lesions) of hypercholesterolemic animals.27,28 It was also found that endothelial dysfunction can be observed in large arteries very soon after the onset of high-cholesterol feeding, when no or only minimal morphologic abnormalities of vascular intima exist.29

Possible Mechanisms of Impaired Endothelium-Dependent Relaxation in Hypercholesterolemia

It is thus well established that hypercholesterolemia, in the absence of gross morphological signs of atherosclerosis, impairs endothelium-dependent vasorelaxation. Several possible mechanisms were proposed, including 1) reduced synthesis of EDRF(s),30 2) altered membrane receptor coupling mechanisms affecting synthesis of EDRF(s),31-33 and 3) impaired diffusion or augmented destruction of EDRF(s) in the intima.34 Alternatively, endothelium-dependent relaxation can be reduced by the concomitant augmented synthesis and release or action of endothelium-de-
rived contracting factor(s) (EDCF).35,36 Thus, there are a variety of mechanisms (probably acting in concert in a complex manner in the different animal models and in the human disease) that can contribute to impaired endothelium-dependent vasodilation.

Reversal of Hypercholesterolemia-Induced Impaired Endothelium-Dependent Vasodilation

Although the exact mechanism of impaired endothelium-dependent vasodilation in hypercholesterolemic animals has not been determined yet, there are reports showing that it can be reversed. The successful treatments used so far included 1) reducing serum cholesterol levels either by returning to normal diet or treating the animals with lovastatin, an inhibitor of HMG-CoA reductase, and 2) altering the lipid composition by feeding the animals with cod-liver oil.

In their study, Cooke et al2 report that infusion of L-arginine, the precursor of EDRF, restores normal endothelium-dependent relaxation in hypercholesterolemic rabbits. Stimulation of EDRF synthesis thus appears to be a novel alternative treatment strategy for endothelial abnormalities induced by hypercholesterolemia. It is suggested, based on this interesting finding, that in the given animal model of hypercholesterolemia, substrate (L-arginine) deficiency and/or impairment of EDRF production from L-arginine appears to be a critical factor that leads to depression of endothelium-dependent vasorelaxation. It is possible that hypercholesterolemia leads to reduced L-arginine levels in endothelial cells either by suppression of L-arginine uptake or by its accelerated degradation in endothelial cells. Alternatively, impairment of L-arginine metabolism may develop (e.g., by generation of an endogenous inhibitor of the enzyme[s] involved) without significant change in endothelial L-arginine levels. In either case, availability of L-arginine becomes a rate-limiting factor in the production of EDRF, and infusion of exogenous L-arginine may indeed enhance the synthesis and release of EDRF. However, it remains to be determined whether this is the case, because in their report Cooke et al have not used a bioassay system to demonstrate that the increased endothelium-dependent relaxation is due to enhanced production and release of EDRF.

It is also possible that the observed phenomenon is due to alterations in muscarinic receptors and/or post–receptor coupling mechanisms. Indeed, altered endothelial receptor function and impaired G protein coupling processes were reported in atherosclerosis.30–32 The observed parallel shift to the right of the acetylcholine dose–response curve suggests that such a mechanism may occur. Impairment of synthesis of EDRF can be proven only if non–receptor-mediated endothelium-dependent relaxations (e.g., as evoked by the calcium ionophore A23187) are also suppressed.

Endothelial cells exposed to high levels of LDL may generate free radicals, especially superoxide anions (O$_2^-$), that inactivate EDRF.8,9 Thus, production of EDRF may be normal, but destruction of EDRF is augmented in hypercholesterolemia. L-Arginine can improve endothelium-dependent relaxation by increasing the levels of available (not destroyed) EDRF. High plasma L-arginine level may also restore normal endothelium-dependent relaxation by acting on cell types other than endothelial. It has been reported that monocytes and polymorphonuclear neutrophils have the ability to produce NO.40,41 All these cells are intimately involved in the atheromatous process of the vessel wall, and substances produced by these cells (e.g., O$_2^-$ and vasoconstrictor substances) can suppress endothelium-dependent relaxation. Enhanced NO production by these cells may neutralize O$_2^-$, thereby protecting EDRF.43 Enhanced production of NO by these various cell types and by endothelial cells may also be of benefit by inhibiting platelet aggregation and by preventing oxidative modification of LDL.

Regardless of the exact mechanism(s), the findings of Cooke et al2 suggest a novel possibility for reversal of endothelial dysfunction in the early stages of atheromatous disease. Although much remains to be done, the use of L-arginine and other potential strategies to improve endothelial function, especially endothelium-dependent vasodilation, should be considered as important novel approaches for the treatment of vessel wall dysfunction in hypercholesterolemia and atherosclerosis.

References

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