Oxidized Lipoproteins Inhibit Endothelium-Dependent Vasodilation

Effects of Pressure and High-Density Lipoprotein

Jan Galle, Markus Öchslen, Peter Schollmeyer, Christoph Wanner

Abstract
Hypertension and atherogenic low-density lipoproteins cause attenuation of endothelium-dependent dilations in vivo. We investigated a potential interference of high transmural pressure with the effects of low-density lipoproteins on endothelium-dependent dilatation in vitro. Furthermore, we determined whether high-density lipoproteins preserve endothelial function. Endothelium-intact rabbit renal arteries were isolated, placed in an organ bath, perfused intraluminally with Tyrode's solution, and exposed to different degrees of transmural pressure and native or oxidized low-density lipoproteins. In preconstricted arteries perfused under low-pressure conditions (30 mm Hg), acetylcholine dose-dependently elicited endothelium-dependent dilations that were not altered by increasing the perfusion pressure to 100 mm Hg for 90 minutes (high-pressure conditions). Incubation of the arteries with native or oxidized low-density lipoproteins (0.2 and 1 mg/mL for 60 minutes, respectively) under low-pressure conditions did not attenuate acetylcholine-induced dilations. However, under high-pressure conditions dilations were dose-dependently attenuated by oxidized but not by native low-density lipoproteins. Endothelium-independent dilations to glyceroenitrate (0.001 to 3 μmol/L) were not affected. Preincubation of the segments with high-density lipoproteins (0.5 mg/mL, 30 minutes) prevented attenuation of dilator responses. The attenuation of endothelium-dependent dilations by oxidized low-density lipoproteins under high-pressure conditions was accompanied by a transmural, dose-dependent infiltration of the vessel wall with lipoprotein, as detected by light microscopy of cryostat sections stained with Sudan III. This infiltration was prevented by high-density lipoprotein. Under low-pressure conditions no lipoprotein infiltration was visible. In segments incubated with native low-density lipoprotein, no lipoprotein infiltration was detectable. We suggest that the inhibitory effect of oxidized low-density lipoprotein on endothelium-dependent dilations is related to the arterial infiltration with lipid, which depends on the transmural pressure and is prevented by high-density lipoprotein. This mechanism may be important in patients with hypercholesterolemia and hypertension. (Hypertension. 1994;23:556-564.)

Key Words
• hypercholesterolemia • lipoproteins, LDL • endothelium-derived relaxing factor

Methods

Drugs
Norepinephrine was purchased from Hoechst; glyceroenitrate from Merck; and indomethacin, L-arginine, and acetylcholine from Sigma Chemical Co. Glyceroenitrate was dissolved in ethanol and indomethacin in ethanol/0.1 mol/L NaHCO3.
vascular smooth muscle was denuded of its endothelium before use. In each experiment two segments obtained from the same animal were studied. In each experiment two segments obtained from the same animal were studied simultaneously. The segments were preconstricted by addition of norepinephrine to the organ bath superfusion until a preconstriction of 450 to 600 \( \mu \text{m} \) Hg was reached (Table). Endothelium-dependent dilations were elicited by addition of cumulative doses of acetylcholine (1 \( \mu \text{mol/L} \) to 1 \( \mu \text{mol/L} \)) to the intraluminal perfusion. A first stimulus-response curve was obtained under low-pressure conditions in both segments. To study the influence of high-pressure conditions on endothelium-dependent dilations, we slowly elevated the outflow tubing pressure of the perfused vessel above the initial perfusion pressure of 100 mm Hg. The outflow tubing of the control segment was kept at the original level. After an equilibration period of 90 minutes, the segments were again preconstricted by addition of norepinephrine to the organ bath superfusion, and the acetylcholine-induced dose-response curve was repeated. Special care was taken to achieve similar levels of preconstriction in the control segment and in the segment incubated under high-pressure conditions, because it is known that the initial stretch influences the effects of EDGF on vascular tone.

To study the influence of the lipoproteins on endothelium-dependent dilations, we incubated another series of preconstricted segments with 0.2 or 1 \( \mu \text{g/mL} \) of N-LDL or Ox-LDL for 60 minutes or their respective buffers as control (added to the intraluminal perfusion) before adding acetylcholine under low- or high-pressure conditions. It is noteworthy that the distension of the preconstricted vessels did not differ between low- and high-pressure conditions (Table). The lipoproteins were then present in the intraluminal perfusion throughout the experiment. Because Ox-LDL has an enhancing effect on norepinephrine-induced vasoconstrictions, the concentration of norepinephrine before addition of Ox-LDL was chosen to induce a vasoconstriction that was approximately 150 to 200 \( \mu \text{m} \) lower than in the control segments. Then when Ox-LDL was added to the intraluminal perfusate, the vessels responded with a further decrease in diameter, resulting finally in an almost identical level of preconstriction compared with the control segments (see the Table).

To determine whether high-pressure conditions in the presence of Ox-LDL (1 \( \mu \text{g/mL} \)) affect the endothelium-independent dilator capacities of the isolated arteries, we used glycero-linitrate (0.001 to 3 \( \mu \text{mol/L} \)) as vasodilator instead of acetylcholine in four additional experiments, performed according to the above-mentioned protocol.

To determine the influence of HDL on endothelium-dependent vasodilations in the absence and presence of Ox-LDL, we preincubated arteries with HDL (0.5 \( \mu \text{g/mL} \) added to the intraluminal perfusion) starting 30 minutes before treatment with Ox-LDL or its buffer and acetylcholine as described above. Intraluminal HDL perfusion was continued throughout the experiment.

To exclude the possibility that acetylcholine induced the release of other endothelial dilating or constricting factors, we performed several experiments in the presence of indomethacin (10 \( \mu \text{mol/L} \)) added to the intraluminal perfusate. The effectiveness of the indomethacin treatment in terms of suppression of prostacyclin formation has been demonstrated in earlier studies by measurement of the stable prostacyclin metabolite 6-keto-prostaglandin F\(_{1\alpha}\). Indomethacin did not significantly alter acetylcholine-induced dilations under low- or high-pressure conditions or in the presence of 1 \( \mu \text{g/mL} \) Ox-LDL (data not shown).

**Lipoprotein Staining of Arterial Slice Preparations**

For detection of arterial wall infiltration with lipoprotein, segments were incubated with N-LDL, Ox-LDL, Ox-LDL plus HDL, or buffer as control under low- and high-pressure conditions as described above (n=3-4 segments in each group). Then the segments were imbedded in OCT (Nieth)
Resting Diameters, Norepinephrine Concentrations, and Preconstriction Values in Isolated Rabbit Renal Arteries Perfused With N-LDL, Ox-LDL, and HDL Under Low- and High-Pressure Conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>N-LDL (0.2 mg/mL)</th>
<th>Control</th>
<th>N-LDL (1 mg/mL)</th>
<th>Control</th>
<th>Ox-LDL (0.2 mg/mL)</th>
<th>Control</th>
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</thead>
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<tr>
<td>High-pressure conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Resting diameter, μm*</td>
<td>2020±33</td>
<td>2100±55</td>
<td>1965±84</td>
<td>1957±85</td>
<td>1970±51</td>
<td>2016±41</td>
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<tr>
<td>Norepinephrine concentration, μmol/L†</td>
<td>0.2±0.07</td>
<td>0.2±0.05</td>
<td>0.1±0.03</td>
<td>0.1±0.03</td>
<td>0.1±0.06</td>
<td>0.2±0.04</td>
</tr>
<tr>
<td>Preconstriction, μm</td>
<td>554±29</td>
<td>519±28</td>
<td>582±42</td>
<td>570±39</td>
<td>686±22</td>
<td>612±38</td>
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<td>11</td>
<td>14</td>
<td>14</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Resting diameter, μm*</td>
<td>. . .</td>
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<td>1832±54</td>
<td>1886±49</td>
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<td>. . .</td>
</tr>
<tr>
<td>Norepinephrine concentration, μmol/L†</td>
<td>. . .</td>
<td>. . .</td>
<td>0.3±0.06</td>
<td>0.3±0.05</td>
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<td>Preconstriction, μm</td>
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<td>. . .</td>
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<td>. . .</td>
<td>10</td>
<td>10</td>
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</tr>
</tbody>
</table>

N-LDL indicates native low-density lipoprotein; Ox-LDL, oxidized low-density lipoprotein; and HDL, high-density lipoprotein. Data are presented as mean±SEM.

*Resting diameter was determined after an equilibration period before norepinephrine stimulation.
†Norepinephrine was added to the organ bath superfusion of lipoprotein-treated arteries in a concentration that elicited preconstriction levels similar to those under control conditions.

and frozen in liquid nitrogen. Cryostat sections (thickness, 5 μm) were prepared by a microtome (Nieth) and stained with Hemalaun and Sudan III (Sigma) for 45 minutes. Sudan III reacts strongly with LDL, forming stable complexes.29 Staining of tissue was visualized by light microscopy (Leitz), where lipoprotein-infiltrated areas appear bright red. Staining of segments under different treatments was compared by the appearance of bright red-stained tissue in relation to unstimulated tissue.

En Face Silver Staining of Endothelial Cell Margins

To investigate the integrity of the endothelial cell layer after treatment of the vessels with Ox-LDL under high-pressure conditions, we cut some segments open longitudinally after incubation with Ox-LDL (1 mg/mL) or buffer for 90 minutes under high-pressure conditions and exposed them to silver nitrate (0.5%, Sigma) for 5 minutes. After development in distilled water by daylight, the tissue was embedded in gelatinized glycerin (Sigma) on glass slides. Endothelial cell margins visualized by microscopy appeared as brown lines.

Statistics

Data are presented as mean±SEM. Dilator responses are expressed as the percentage of the initial steady-state constriction induced by norepinephrine. The EC50 values for norepinephrine were determined with a linear regression computer program. Differences between EC50 values were determined with the use of one-way ANOVA. Dose-effect curves in the plots in Figs 1 through 4 were compared with the use of one-way ANOVA for repeated measurements followed by a point-by-point comparison with the unpaired t test. For multiple comparisons of data, Bonferroni's correction was applied. Differences were considered significant at an error probability of .05.

Results

Influence of Increased Transmural Pressure on Vascular Prestretching and Contractile Responses

Under low-pressure conditions the unstimulated diameter of the rabbit renal arteries averaged 1841±30 μm. Preconstriction elicited by norepinephrine (0.4 μmol/L) averaged 476±40 μm. Raising the transmural pressure from 30 to 100 mm Hg resulted in an increase in unstimulated vascular diameter to 2018±30 μm and in a higher sensitivity of the segments to norepinephrine: the EC50 averaged 0.1 μmol/L under high-pressure conditions versus 0.3 μmol/L under low-pressure conditions. To achieve a comparable level of preconstriction, we preconstricted segments under high-pressure conditions with 0.2 μmol/L norepinephrine (contractile responses of 529±18 μm, n=40).

Effect of Transmural Pressure on Endothelium-Dependent Dilation

Acetylcholine induced concentration-dependent dilations in segments perfused under low-pressure conditions and in time-matched segments perfused under high-pressure conditions (Fig 1). The stimulus-response curves were not significantly different, indicating that raising the transmural pressure from 30 to 100 mm Hg for 90 minutes did not alter endothelium-dependent dilator responses.

Influence of N-LDL and Ox-LDL on Endothelium-Dependent Dilation Under Low- and High-Pressure Conditions

Under low-pressure conditions treatment of the isolated renal arteries with N-LDL or Ox-LDL (both were perfused intraluminally at 1 mg/mL for 60 minutes) had no influence on acetylcholine-induced dilator responses (data not shown). Under high-pressure conditions treatment of the arteries with N-LDL also did not affect dilations to acetylcholine (Fig 2). However, treatment of the arteries with Ox-LDL under high-pressure conditions dose dependently inhibited acetylcholine-induced dilations (Fig 3). Preconstriction levels did not differ between the lipoprotein-treated renal arteries and controls (Table). In preliminary experiments the segments were incubated with 1 mg/mL Ox-LDL at a transmural pressure of 65 mm Hg. At this transmural pressure acetylcholine-induced dilator responses were reduced by Ox-LDL; however, inhibition of dilator responses was less pronounced and less reproducible.
vascular wall. However, under high-pressure conditions, vessel segments were frozen in liquid nitrogen, and cryostat sections were prepared. Light microscopy of Hemalaun- and Sudan III-stained sections showed no fat staining in control arteries (not shown). Similarly, under low-pressure conditions incubation of the segments with N-LDL (not shown) or Ox-LDL (Fig 6, left) revealed no visible lipoprotein infiltration of the vascular wall. However, under high-pressure conditions, marked transmural lipoprotein infiltration of the vascular wall of segments incubated with Ox-LDL under high-pressure conditions was revealed. As shown in Table 1, vessel segments incubated with 1 mg/mL Ox-LDL showed uptake of lipoproteins throughout the vascular wall. Staining of segments incubated with 1 mg/mL Ox-LDL was more pronounced than that in segments incubated with the lower concentration. No lipid staining was visible after treatment of the arteries with N-LDL under high-pressure conditions (not shown).

Table. Continued

<table>
<thead>
<tr>
<th>Ox-LDL (1 mg/mL)</th>
<th>Control</th>
<th>Ox-LDL + HDL (0.5 mg/mL)</th>
<th>Control</th>
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<td>1994±60</td>
<td>1992±63</td>
<td>1975±57</td>
<td>2010±65</td>
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<tr>
<td>0.1±0.03</td>
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<tr>
<td>592±91</td>
<td>605±45</td>
<td>561±57</td>
<td>548±61</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>1795±48</td>
<td>1811±51</td>
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<td>0.2±0.04</td>
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<tr>
<td>467±51</td>
<td>440±45</td>
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<tr>
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<td>9</td>
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</tr>
</tbody>
</table>

compared with the high transmural pressure of 100 mm Hg (data not shown).

**Endothelium-Independent Dilation in Ox-LDL-Treated Segments Under High-Pressure Conditions**

To determine whether the smooth muscle dilator capacity is changed under high-pressure conditions in arteries treated with Ox-LDL (1 mg/mL), we induced endothelium-independent dilator responses by adding glyceroltrinitrate (1 mmol/L to 3 mmol/L) to the intraluminal lining instead of acetylcholine. Glyceroltrinitrate-induced dilations did not differ between the Ox-LDL-treated segments and control vessels (Fig 4).

**Influence of HDL on Ox-LDL-Induced Inhibition of Endothelium-Dependent Vasodilations Under High-Pressure Conditions**

To determine whether HDL prevents the Ox-LDL-induced attenuation of dilator responses to acetylcholine under high-pressure conditions, we preincubated segments with HDL (0.5 mg/mL) starting 30 minutes before treatment with Ox-LDL (1 mg/mL). Acetylcholine-induced dilations were fully preserved when the segments were preincubated with HDL before Ox-LDL treatment (Fig 5). Treatment of segments with HDL in the absence of Ox-LDL had no influence on acetylcholine-induced dilations compared with controls (n=7, Fig 5).

**Arterial Lipoprotein Infiltration After Incubation With N-LDL and Ox-LDL Under Low- and High-Pressure Conditions**

We investigated whether lipoprotein infiltration into the arterial wall of segments incubated with N-LDL (1 mg/mL) and Ox-LDL (0.2 and 1 mg/mL) is related to the transmural pressure. After incubation with lipoproteins or buffer (as control) under low- and high-pressure conditions, vessel segments were frozen in liquid nitrogen, and cryostat sections were prepared. Light microscopy of Hemalaun- and Sudan III-stained sections showed no fat staining in control arteries (not shown).

Similarly, under low-pressure conditions incubation of the segments with N-LDL (not shown) or Ox-LDL (Fig 6, left) revealed no visible lipoprotein infiltration of the vascular wall. However, under high-pressure conditions sections of segments incubated with 0.2 (not shown) and 1 mg/mL Ox-LDL (Fig 6, right) showed uptake of lipoproteins throughout the vascular wall. Staining of segments incubated with 1 mg/mL Ox-LDL was more pronounced than that in segments incubated with the lower concentration. No lipid staining was visible after treatment of the arteries with N-LDL under high-pressure conditions (not shown).

**Lipid Staining After Incubation With Ox-LDL Under High-Pressure Conditions in the Presence of HDL**

When the segments were preincubated for 30 minutes with HDL (0.5 mg/mL) before treatment with Ox-LDL (1 mg/mL) under high-pressure conditions, no lipid staining was visible (not shown).

**En Face Silver Staining of Endothelial Margins**

Fig 7 shows endothelial cell margins of a representative vessel after incubation with Ox-LDL (1 mg/mL, 90 minutes) under high-pressure conditions, stained with silver nitrate and visualized by light microscopy. The typical formation of the cell margins demonstrates that the endothelial cell layer was still intact.

**Discussion**

In this study we investigated the interaction of increased transmural pressure and lipoproteins on endothelium-dependent dilations in isolated perfused rabbit renal arteries. The salient findings were that Ox-LDL but not N-LDL dose dependently attenuated acetylcholine-induced dilations under high-pressure conditions and that this attenuation was prevented by HDL. Conversely, Ox-LDL and N-LDL were without effect under low-pressure conditions. Histological sections revealed a marked transmural lipoprotein infiltration of the vascular wall of segments incubated with Ox-LDL under high-pressure conditions, which also was prevented by HDL. In view of the known ability of Ox-LDL to inactivate EDRF,16,17 we suggest that the infiltration of Ox-LDL into the vessel wall under high-pressure conditions is one factor responsible for inactivation of EDRF and attenuation of endothelium-dependent dilations.
Hypertension is another pathophysiological state in which attenuation of endothelium-dependent dilations occurs. Information on disturbed endothelial function in hypertension has been obtained mainly from chronically hypertensive animals. However, several studies have indicated that an acute increase in transmural pressure also can impair endothelium-dependent dilations. It has been suggested that hypertension induces morphological changes of the endothelium that increase its permeability for macromolecules. One might assume that the access of LDLs to the vascular wall is facilitated under such conditions.

In recent years several investigations have demonstrated inhibition of endothelium-dependent dilations by Ox-LDL in a variety of experimental models. Proposed mechanisms responsible for this observation include the suppression of the formation of EDRF, an accelerated inactivation of this labile compound, and an attenuation of its effector pathway in the smooth muscle cells.

The experimental model used in this study allowed us to differentiate between the effects of transmural pressure and of lipoproteins on endothelium-dependent dilations. It is important to emphasize that the distension of the preconstricted arteries before addition of the lipoproteins did not differ between segments investigated under low- and high-pressure conditions. The lack of effect of lipoproteins under low-pressure conditions and the failure of high pressure alone to impair endothelium-dependent dilations enabled us to investigate the potential interaction of increased pressure and atherogenic lipoproteins. When Ox-LDL was applied under high-pressure conditions, endothelium-dependent dilations were attenuated, whereas endothelium-independent dilations were preserved, indicating an intact smooth muscle function. Attenuation of endothelial function by Ox-LDL and high pressure was accompanied by a marked transmural lipoprotein infiltration of the vessel wall. Furthermore, the degree of lipoprotein infiltration was dependent on the concentration of Ox-LDL, and no infiltration was detected under low-pressure conditions. Thus, attenuation of endothelial function by Ox-LDL and high pressure was accompanied by a marked transmural lipoprotein infiltration of the vessel wall. Furthermore, the degree of lipoprotein infiltration was dependent on the concentration of Ox-LDL, and no infiltration was detected under low-pressure conditions.
Ox-LDL inhibits vasodilation

Function occurred only in the presence of a substantial Ox-LDL infiltration of the vessel wall. This infiltration could provide a mechanism for the inhibition of EDRF-mediated vasodilations. After its release from the endothelium, the labile EDRF, which is likely to be or closely related to nitric oxide, must reach the smooth muscle cell layers by diffusion. We and others previously have shown that Ox-LDL directly inactivates EDRF. Ox-LDL, present in the vascular wall, thus could inactivate EDRF during its transit from the endothelium to the smooth muscle cells. Therefore, we suggest that lipoprotein infiltration of the vessel wall after incubation with Ox-LDL under high-pressure conditions favors inactivation of EDRF.

The possibility that Ox-LDL inhibited formation of EDRF under high-pressure conditions cannot be excluded in our experiments. On the other hand, this possibility seems less likely because endothelium-dependent dilations were not attenuated in lipoprotein-treated arteries under low-pressure conditions. However, discrepancies among the different studies concerning the effect of Ox-LDL on EDRF formation have been found. This may be explained by different Ox-LDL preparations produced with various experimental protocols. LDLs, when highly oxidized at 37°C for 24 hours, contain a significant amount of lysophosphatidylcholine, which is likely to be responsible for part of the effects of Ox-LDL on endothelial func-

Fig. 6. Photomicrographs show representative transmural cryostat sections from rabbit renal arteries stained with Hemalaun and Sudan III to detect lipoprotein infiltration after incubation with oxidized low-density lipoproteins (Ox-LDL, 1 mg/mL, 60 minutes) under low- or high-pressure conditions (magnification x80, bar=80 μm). Above, Section obtained from an artery after incubation with Ox-LDL under low-pressure conditions. No lipid staining is visible. Below, Artery incubated with Ox-LDL under high-pressure conditions. Lipoprotein infiltration (appearing bright red) can be detected throughout the vascular wall.
When LDLs are only moderately oxidized (ie, at 20°C for 15 to 20 hours), lysophosphatidylcholine content of Ox-LDL is relatively low (unpublished observations), and Ox-LDLs inactivate EDRF without attenuation of EDRF formation. Thus, the lack of effect of Ox-LDL under low-pressure conditions in this study could be due to the relatively short exposure of the segments to Ox-LDL and the relatively mild degree of oxidation compared with preparations oxidized to a higher degree.

The idea that lipoprotein infiltration contributes to inactivation of EDRF provides an explanation for differences between this and other investigations using arterial ring or strip preparations. In an earlier study we could demonstrate that arterial ring preparations are more sensitive to Ox-LDL-induced attenuation of endothelium-dependent vasodilations than intact segments. In ring or strip preparations immersed in a lipoprotein-containing solution, the access of Ox-LDL to the vascular wall and the subsequent inactivation of EDRF may be easier than in intact segments, in which the lipoproteins have to first surmount the endothelial barrier to reach the subintimal space.

N-LDLs, which also have the capacity to inactivate EDRF directly, did not affect acetylcholine-induced dilations. However, fat staining of segments incubated with N-LDL revealed no significant infiltration of the vascular wall under low- or high-pressure conditions. We therefore assume that the intact endothelium can act as a barrier against N-LDL and prevent a significant infiltration and thus a direct inactivation of EDRF in the subintimal smooth muscle layers.

The resistance of the intact endothelium against a transendothelial convective transport of N-LDL is in accordance with a recently published study by Fry and coworkers. They reported that the transendothelial transport of LDL is insensitive to pressure as long as the endothelium is intact. However, in arteries with injured endothelium, transendothelial transport increased significantly with increasing pressure. Because Ox-LDLs are potentially cytotoxic for endothelial cells, one can speculate that incubation of the arteries with Ox-LDL can injure the endothelium, thus initiating a greater pressure-dependent transendothelial transport into the subintima and smooth muscle cell layers. Under these conditions lipoproteins might reach the vessel wall via transcellular and paracellular channels, as suggested recently. Binding of LDL to proteoglycans produced by arterial smooth muscle cells might contribute to accumulation of lipoprotein in the vessel wall.

The lipoprotein infiltration and attenuation of endothelial function were prevented by HDL. In a recent study it was shown that HDL can remove lysophosphatidylcholine from Ox-LDL and thereby prevent toxic effects of lysophosphatidylcholine on the endothelium. Such a removal of lysophosphatidylcholine from Ox-LDL thus could provide one mechanism as to how HDL prevented increased permeability and impairment of endothelium-dependent vasodilations under high-pressure conditions in the present study.

Study Limitations

Care must be taken in applying the results of this study directly to the situation of subjects with hypercholesterolemia and hypertension. It is not clear whether Ox-LDL occurs in vivo only in atheromatous lesions or also within the bloodstream. Reasons argue against the presence of Ox-LDL within the circulation. However, lipoproteins that resemble Ox-LDL have been isolated from human plasma. But even if Ox-LDL does not occur within the circulation, a pressure-dependent convective transport component should increase Ox-LDL in deeper layers of the vascular wall, because Ox-LDLs accumulate in the subendothelial, extracellular space. Furthermore, it is difficult to compare the acute alteration of transmural pressure under the constant-flow conditions chosen in this study with acute or chronic hypertension in patients. A luminal pressure of 30 mm Hg is certainly lower than the pressure occurring naturally in conduit arteries, and a mean pressure of 100 mm Hg does not correspond to excessive hypertension. In addition, arteries in vivo are exposed to pulsatile instead of constant pressure changes, and we cannot exclude the possibility that this difference contributed to part of the results. However, in our experimental setup, without fascia and tissue pressure surrounding the vessels,
a pressure of 30 mm Hg was sufficient to prestretch the isolated arteries to a diameter similar to that in situ, and raising the pressure to 100 mm Hg resulted in a significant increase in diameter. Thus, the prestretching of the arteries may reflect the in vivo situation and the effective transmural pressure.

In summary, we suggest that the inhibitory effect of oxidized LDL on endothelium-dependent dilations is related to the infiltration of Ox-LDL into the blood vessel wall, which depends on the transmural pressure. This mechanism may be important in patients with hypercholesterolemia and hypertension.

Acknowledgments

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References


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