EXPERIMENTAL STUDIES

Expression of Lectin-Like Oxidized Low-Density Lipoprotein Receptors During Ischemia-Reperfusion and its Role in Determination of Apoptosis and Left Ventricular Dysfunction

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OBJECTIVES	The goal of this study was to determine the role of lectin-like oxidized low-density lipoprotein receptors (LOX-1), a recently identified oxidized low-density lipoprotein (ox-LDL) receptor, in ischemia-reperfusion injury to the heart.
BACKGROUND	Reactive oxygen species (ROS) released during ischemia-reperfusion oxidize low-density lipoproteins; LOX-1 is upregulated by ox-LDL and ROS, and is involved in cell injury.
METHODS	Anesthetized rats were subjected to left coronary artery ligation for 60 min (n = 10, ischemia group), or ischemia followed by 60 min of reperfusion (n = 30, ischemia-reperfusion group). Rats in the latter group were treated with saline, the LOX-1 blocking antibody JXT21 (10 mg/kg), or nonspecific anti-goat immunoglobulin G (IgG) (10 mg/kg). Ten other rats underwent thoracotomy without coronary ligation (sham control).
RESULTS	Ischemia-reperfusion was associated with an increase in LOX-1 expression, lipid peroxidation and apoptosis, a large infarct area, and a decrease in left ventricular function (all, p < 0.01 vs. sham control and ischemia alone groups). Treatment of rats with LOX-1 antibody prevented ischemia-reperfusion–induced upregulation of LOX-1. Importantly, the LOX-1 antibody reduced apoptosis by 48%, lipid peroxidation by 39%, and myocardial infarct size by 45%, and improved left ventricular function (first derivative of pressure measured over time: −47% to −18%, p < 0.01). Nonspecific IgG had no effect.
CONCLUSIONS	Lectin-like oxidized low-density lipoprotein receptors are upregulated during myocardial ischemia-reperfusion, and appear to be associated with apoptosis, necrosis, and left ventricular functional deterioration. (J Am Coll Cardiol 2003;41:1048–55) © 2003 by the American College of Cardiology Foundation

Myocardial ischemia-reperfusion represents a clinically relevant problem associated with thrombolysis, percutaneous coronary interventions, and coronary bypass surgery. Injury to myocardium during ischemia-reperfusion includes cardiac contractile dysfunction (1), arrhythmias (2), and irreversible myocyte damage (3). Reperfusion injury is thought to be associated with generation of reactive oxygen species (ROS) (4), which overwhelm the scavenging capacities of antioxidant enzymes and result in oxidation of lipids and oxidative damage to the myocardium. Recent studies suggest that plasma levels of oxidized low-density lipoproteins (ox-LDL) are markedly elevated in patients with acute coronary syndromes, and the ischemic-reperfused tissues contain large amounts of ox-LDL (5,6).

Oxidized low-density lipoproteins and ROS trigger apoptosis that is mediated by the activation of the caspase cascade and results in the cleavage of protein substrates and fragmentation of deoxyribonucleic acid. Apoptosis is recognized as a major mechanism of cell death during ischemia-reperfusion (3,4), although the relative contribution of necrosis and apoptosis to total cardiac cell loss remains controversial. Nonetheless, the extent of myocardial injury during ischemia-reperfusion correlates with the degree of myocardial dysfunction (7,8).

Recent studies show that LOX-1, a newly described lectin-like receptor for ox-LDL, plays an important role in cell injury and phagocytosis of dead cells (9–11); LOX-1 activation also mediates adhesion of inflammatory cells to the activated endothelium by facilitating expression of adhesion molecules (10). Expression of LOX-1 gene is upregulated by ox-LDL, angiotensin II, endothelin, ROS, inflammatory cytokines, and shear stress (12–16). Angiotensin II, endothelin, ROS, and proinflammatory cytokines are considered major mediators of injury during ischemia-reperfusion.

Abbreviations and Acronyms

IgG = immunoglobulin G
LOX-1 = lectin-like oxidized low-density lipoprotein receptors
mRNA = messenger ribonucleic acid
ox-LDL = oxidized low-density lipoprotein
ROS = reactive oxygen species
TTC = triphenyl tetrazolium chloride
TUNEL = terminal dUTP nick end-labeling

The present study was designed to explore the expression of LOX-1 and its role in apoptosis, necrosis, and cardiac dysfunction during myocardial ischemia-reperfusion.

METHODS

Animal model. Male Sprague-Dawley rats (250 to 300 g) were anesthetized with pentobarbital (30 mg/kg, given intraperitoneally), intubated, and ventilated. A left thoracotomy was performed, and the left coronary artery identified and ligated with 6-0 silk suture 4 mm from its origin with a slipknot. Total ischemia was confirmed by myocardial blanching and electrocardiographic evidence of injury. Ischemia was continued for 1 h, when in some animals the ligature was removed and the blood flow allowed to resume (reperfusion) for 1 h. Other rats were subjected to thoracotomy without left coronary artery ligation (sham control group). Rats subjected to ischemia-reperfusion were given saline, the anti-rat LOX-1 blocking antibody (JTX21) or the anti-goat nonspecific immunoglobulin G (IgG) (10 mg/kg) intravenously. Preliminary studies showed that LOX-1 antibody exerted its maximal effects on cardiac protection when 50% of the total dose was given just before ischemia and the remaining 50% during ischemia and reperfusion.

Materials. Anti-rat LOX-1 monoclonal antibody was generated by immunizing Balb/c mice with rat LOX-1-CHO cells stably expressing rat LOX-1. Hybridoma from the splenocytes was prepared by standard procedures, and screened by cell-surface immunobinding to rat LOX-1-CHO cells. The LOX-1 antibody (JTX21) was selected based on its ability to block ox-LDL binding and uptake in rat LOX-1-expressing cells as described previously (17,18). Immunostaining kit was purchased from Santa Cruz Biotechnology (Santa Cruz, California). Caspase-3 fluorescent protease and terminal dUTP nick end-labeling (TUNEL) kits were purchased from Promega (Madison, Michigan). Other reagents were purchased from Sigma (St. Louis, Missouri).

Northern blot assay. Total ribonucleic acid (15 μg) from the core of left coronary artery-supplied myocardium was fractionated on a formaldehyde-denatured 1.2%-agarose gel and transferred to a nylon membrane filter. After prehybridization, the filter was hybridized with the ^{32}P-labelled rat LOX-1 probe (10^6 cpm/ml) in a solution containing 50% formamide at 42°C for 16 h. The membrane was washed twice in 2×SSC (0.3 M sodium citrate and 3 M sodium chloride) containing 0.1% (w/v) SDS (sodium dodecyl sulfate) at room temperature, followed by washes in 0.16×SSC containing 0.1% (w/v) SDS at 50°C for 15 min. The filter was exposed to Kodak film with an intensifying screen at −80°C. The band density was quantified by Gel-Scan-it software (Sigma); LOX-1 expression was standardized with that of housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (12).

Western blot assay. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was performed on 10% separation gels with a 6% stacking gel. Proteins were transferred to nitrocellulose membrane (Bio-Rad, California). Blots were incubated with antibody to LOX-1 with 1:500 dilution at 4°C overnight. Blots were incubated with horseradish peroxidase—conjugated secondary antibody—and signal was detected with enhanced chemiluminescence (Amersham Life Science, New Jersey) (10,12).

Immunostaining. Details of immunostaining have been published earlier (19). In brief, 5 μm-thick sections from myocardial tissues taken from the core of left coronary artery-supplied regions were incubated with primary antibody to LOX-1 overnight at 4°C, rinsed in phosphate-buffered saline, and incubated with anti-mouse IgG conjugated to tetramethylrhodamine.

To localize the expression of LOX-1, myocardial sections were subjected to double immunostaining. EnVision doublestain system was purchased from DAKO Co. (Carpinteria, California). The first stain was anti-rat LOX-1 antibody shown as the dark-brown color. Sections were subsequently incubated with anti-rat desmin (rat cardiac myocytes). The red color reflects the secondary target antigen.

Caspase-3 activity assay. Homogenate of myocardial tissues from the ischemic (or the ischemic-reperfused) areas was prepared. Protein concentration of the homogenate was adjusted to 1 to 2 μg/μl. Myocardial tissue extracts (50 μg) were incubated with 245 μl of reaction buffer containing 80 μl of caspase buffer, 5 μM of Me₂SO, and 10 mM DTT for 30 min at 30°C. Thereafter, the fluorescence substrate Ac-DEVD-AMC was added at a final concentration of 50 μM. The reaction mixtures were incubated for 2 h at 30°C. Cleavage of fluorogenic substrate was quantitated by using a fluorescence spectrophotometer at 400/505 nm (20).

TUNEL staining. The TUNEL staining was performed as described earlier (21) with propidium iodide nuclear counterstaining. Negative controls were cells without terminal deoxynucleotidyl transferase. Positive controls were samples pretreated with DNase I. Nuclei were counted in 8 to 10 microscopic high power fields (×40) in the core of the ischemic region of the heart supplied by the left coronary artery. Virtually all TUNEL-positive nuclei were confined to a well-circumscribed area within the ischemic zone; TUNEL-positive nuclei from this region were randomly counted in 8 to 10 high power fields in each slide.
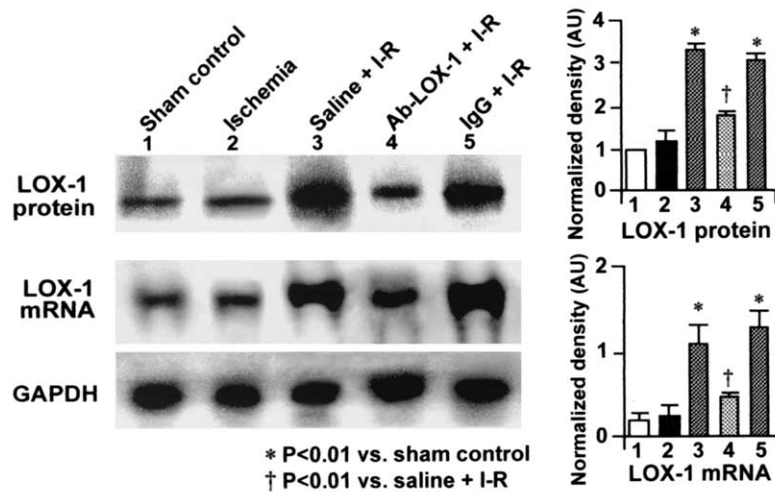
Figure 1. Expression of lectin-like oxidized low-density lipoprotein receptor (LOX-1) messenger ribonucleic acid (mRNA) and protein after ischemia-reperfusion (I-R); LOX-1 protein and mRNA were determined by Western and Northern blots, respectively. The expression of LOX-1 was markedly increased in the saline-treated rats subjected to I-R. Ischemia alone did not increase the expression of LOX-1. Administration of blocking antibody to rat LOX-1 attenuated the expression of LOX-1 despite I-R. In contrast, administration of nonspecific immunoglobulin G (IgG) had no effect. Density of LOX-1 mRNA band was normalized by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) band density. Each band density of LOX-1 protein was normalized with that in the sham control rat heart. **Left panel** shows representative examples; **right panel** is the summary of data (mean ± SD) from eight separate experiments.

Measurement of lipid peroxidation. Myocardial malondialdehyde was measured using the thiobarbituric acid reactive substances assay, as described previously (22).

Determination of infarct size. At the end of ischemia-reperfusion, the heart was quickly removed and mounted on a Langendorff apparatus (Astra-Med, West Warwick, Rhode Island), and flushed with saline for 60 s. The left coronary artery was re-ligated, and Evan's Blue dye was infused into the perfusate to mark the area at risk. The heart was then cut into six transverse slices. The slices were incubated in 1% triphenyl tetrazolium chloride (TTC) in pH 7.4 buffer for 15 min. For each section, the area-at-risk (Evan's blue-negative area) and infarct area (TTC-negative area) were traced and measured by planimetry. Infarct size was calculated as: TTC-positive area divided by the area at risk for that slice. Infarct size in all six slices was then calculated and averaged (23).

Hemodynamic measurements. Left ventricular pressure was monitored using a fluid-filled catheter (PE-50) inserted through the right carotid artery and advanced to the left ventricle. Left ventricular contractility (±dP/dt) and arterial pressure were recorded on a Astra-Med four-channel physical recorder throughout the procedure.

Data analysis. All data represent mean of at least eight independently performed experiments. Data are presented as mean ± SD. Data were analyzed by analysis of variance, followed by a Bonferroni correction. A p value of <0.05 was considered to be statistically significant.

RESULTS

**LOX-1 expression during myocardial ischemia-reperfusion.** The expression of LOX-1 (messenger ribonucleic acid [mRNA] and protein) was markedly increased in the ischemia-reperfusion group compared with that in the sham control group (p < 0.01, n = 8). Ischemia alone did not increase the expression of LOX-1. Administration of the LOX-1 antibody before ischemia attenuated the upregulation of LOX-1 (p < 0.01 vs. ischemia-reperfusion group treated with saline). Administration of nonspecific IgG had no effect on LOX-1 expression (Fig. 1).

The expression of LOX-1 was confirmed by immunostaining, which showed an increase in LOX-1 expression in the core of the ischemic-reperfused area. Positive immunoreactivity for LOX-1 was identified mainly in the endocardium and the subendocardial regions of myocardium. Use of the antibody reduced LOX-1 expression, whereas the nonspecific IgG had no effect. A representative example of LOX-1 expression in each group of rats is shown in Figure 2.

To identify the location of LOX-1 in the myocardial sections, double immunostaining was performed. As shown in Figure 3, LOX upregulation was identified mainly in the cardiac myocytes.

Ischemia-reperfusion and apoptosis. Ischemia alone only slightly increased the number of apoptotic cells. In contrast, apoptotic cells were clearly evident in the ischemic-reperfused regions in saline-treated rats. Administration of LOX-1 antibody reduced the number of apoptotic cells despite ischemia-reperfusion (p < 0.01 vs. saline-treated group). The administration of nonspecific IgG had no effect on the number of apoptotic cells. Figure 4 shows representative examples of the presence of apoptotic cells in the ischemic-reperfused area in each group, as well as a summary of the data on the number of apoptotic cells in each group.

Ischemia-reperfusion–induced apoptosis was confirmed
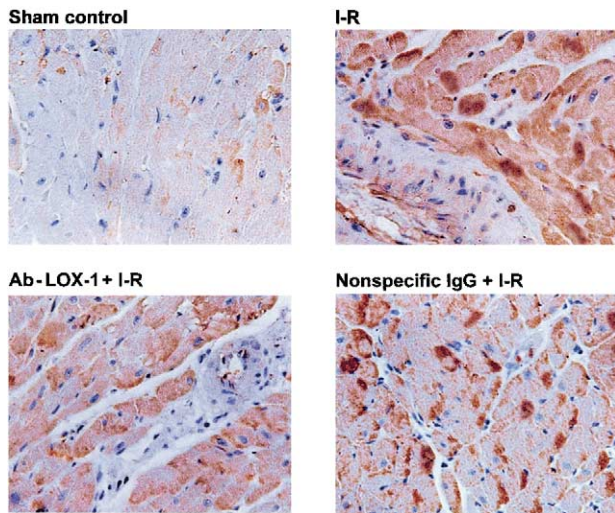
Figure 2. Expression of lectin-like oxidized low-density lipoprotein receptors (LOX-1) in the ischemic-reperfused (I-R) areas was confirmed by immunostaining. Positive immunoreactivity for LOX-1 was identified mainly in the endocardium and the subendocardial areas of the myocardium. Again, the use of LOX-1 antibody (Ab-LOX-1) reduced LOX-1 staining after I-R, while nonspecific immunoglobulin G (IgG) had no effect.

by the measurement of caspase-3 activity, which was consistently increased in the hearts from saline-treated rats subjected to ischemia-reperfusion (p < 0.01 vs. sham control group). Ischemia alone had no effect on caspase-3 activity. Administration of the LOX-1 antibody reduced caspase-3 activity despite ischemia-reperfusion (p < 0.01 vs. saline group), whereas nonspecific IgG had no effect (Fig. 4).

Ischemia-reperfusion and lipid peroxidation. The malondialdehyde levels were markedly increased in the hearts from saline-treated rats subjected to ischemia-reperfusion (p < 0.01 vs. sham control group, n = 10). Ischemia alone did not affect malondialdehyde levels. Administration of the antibody to LOX-1 reduced myocardial malondialdehyde levels (p < 0.01 vs. saline group, n = 10), whereas nonspecific IgG had no effect (Fig. 5).

Ischemia-reperfusion and infarct size. Hearts from sham control group did not show any TTC-positive areas. The area-at-risk in the ischemia alone group and the three ischemia-reperfusion groups was similar. There was extensive TTC positivity in the hearts from the saline-treated ischemia-reperfusion group (33 ± 5% vs. 22 ± 4% at area-at-risk in ischemia alone group, p < 0.01, n = 10). Treatment of rats with the LOX-1 antibody decreased infarct size (18 ± 6% vs. 33 ± 5%, p < 0.01, n = 10). The use of nonspecific IgG had no effect (Fig. 6).

Ischemia-reperfusion and cardiac dysfunction. As shown in Figure 7, dP/dt and mean arterial pressure were significantly decreased during ischemia. Reperfusion caused a further decrease in dP/dt, arterial pressure, and heart rate (p < 0.01 vs. sham control group or ischemia alone group, n = 10). Administration of the LOX-1 antibody significantly improved dP/dt, arterial pressure, and heart rate despite ischemia-reperfusion (all, p < 0.01 vs. saline group, n = 10). The administration of nonspecific IgG had no effect.

DISCUSSION

We show that LOX-1 expression is upregulated in the ischemic-reperfused myocardium. The upregulation of LOX-1 contributes to reperfusion injury as evident from the data on the use of LOX-1 antibody, which decreased infarct size and improved cardiac function. The antibody to LOX-1 also reduced ischemia-reperfusion–mediated apoptosis and lipid peroxidation. Importantly, nonspecific IgG had no protective effect against ischemia-reperfusion injury.

Release of ROS during ischemia-reperfusion and LOX-1 expression. Reactive oxygen species are released during reperfusion and induce peroxidation of lipid bilayer of cell membrane, injure endothelial cells, denature constitutive nitric oxide, and promote migration and accumulation of inflammatory cells in the ischemic-reperfused areas (7,8). Inhibition of ROS has been shown to reduce the phenomenon of reperfusion injury and improve cardiac dysfunction
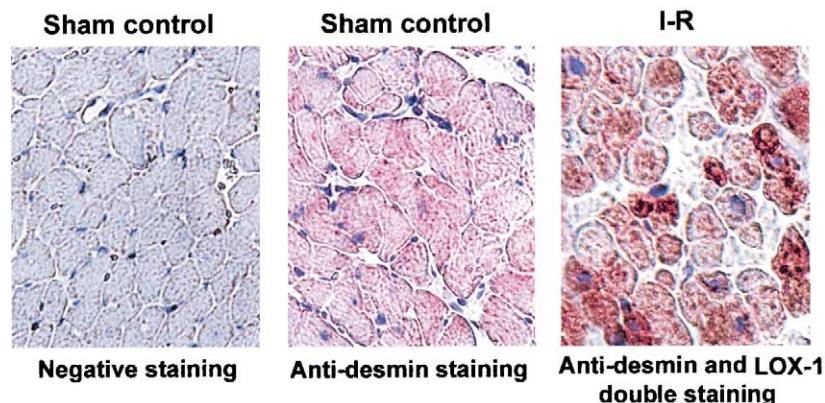
Figure 3. Location of lectin-like oxidized low-density lipoprotein receptor (LOX-1) expression in rat cardiac myocytes was confirmed by double immunostaining (**brown color** = LOX-1; **red color** = anti-desmin for rat cardiac myocytes); LOX-1 expression was primarily within the cardiac myocytes. **Left panel** is a negative control specimen, **middle panel** is myocyte staining in sham control heart, and **right panel** is double staining showing LOX-1 expression in myocytes. I-R = ischemia-reperfusion.
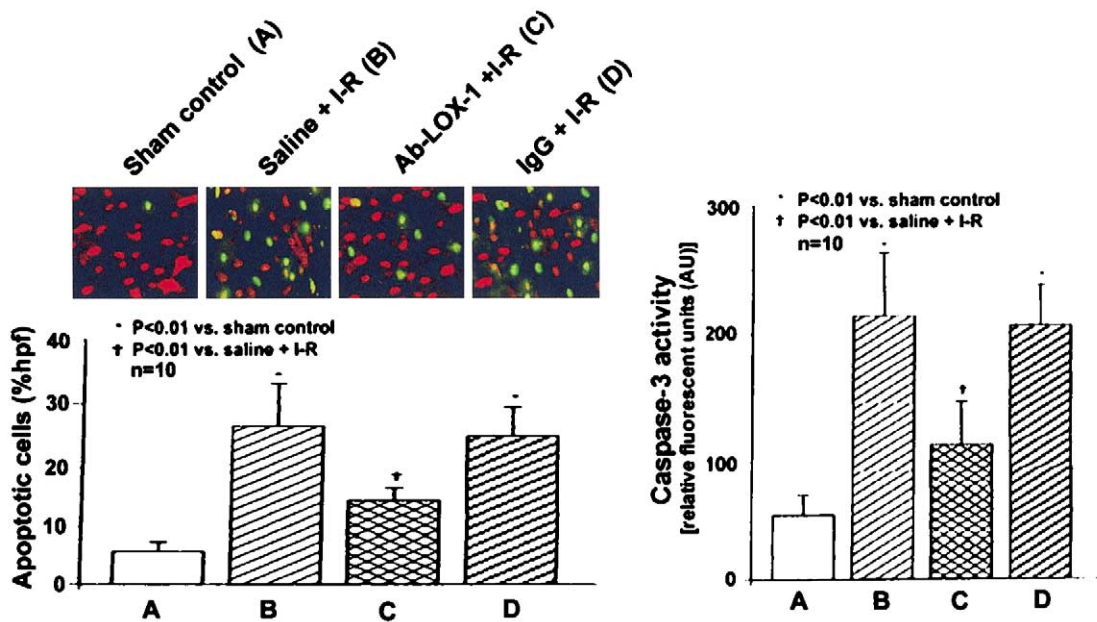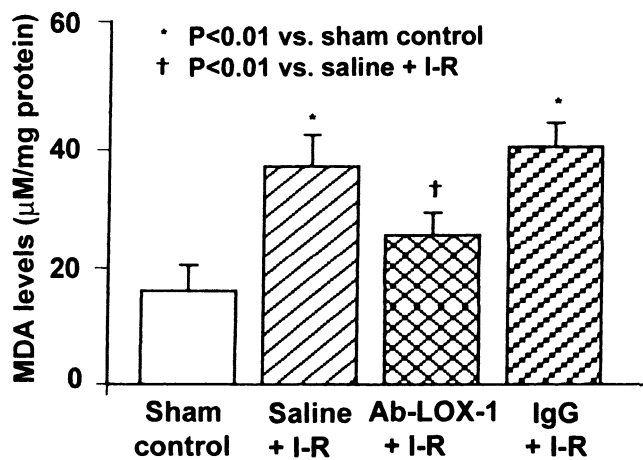
Figure 4. Effect of lectin-like oxidized low-density lipoprotein receptor (LOX-1) antibody (Ab-LOX-1) on apoptosis and caspase-3 expression in response to ischemia-reperfusion (I-R). The number of apoptotic cells was increased in the I-R group (saline-treated rats) compared with the sham control group. Use of the LOX-1 antibody reduced the number of apoptotic cells. Nonspecific anti-goat immunoglobulin G (IgG) had no effect. **Left top panel** shows representative examples of apoptotic cells **(green color)**. **Left bottom panel** is summary of data on the number of apoptotic cells from 10 separate experiments. Caspase-3 activity in the myocardium was also increased in the I-R group (saline-treated rats) compared with the sham control group. Use of the LOX-1 antibody reduced caspase-3 activity. Nonspecific IgG had no effect **(right panel).**

(7,24). Reactive oxygen species oxidize lipids, and result in increased ox-LDL levels. Plasma levels of ox-LDL have been shown to be elevated in patients with acute coronary syndromes (5). Tsutsui et al. (25) have suggested that ox-LDL can be used as a prognostic predictor in patients with chronic congestive heart failure. Another study (6) found that ox-LDL is localized in the myocardium of patients with ischemia; ox-LDL was present in large amounts in the left and right ventricles of these patients.

Positive immunoreactivity for ox-LDL was mainly identified in the endocardium and the subendocardial areas of the left ventricle.

We observed that a brief period of ischemia followed by a brief period of reperfusion, but not ischemia alone, upregulated LOX-1, which suggests that reperfusion is necessary for LOX-1 upregulation. In fact, we observed that malondialdehyde levels were higher in the ischemic-reperfused myocardium compared with those in sham con-

Figure 5. Lectin-like oxidized low-density lipoprotein receptors (LOX-1) expression and lipid peroxidation. Lipid peroxidation was determined by the measurement of malondialdehyde (MDA). Myocardial MDA levels were markedly higher in the saline-treated rats subjected to ischemia-reperfusion (I-R); LOX-1 antibody (Ab-LOX-1) reduced MDA levels, while the nonspecific immunoglobulin G (IgG) had no effect. The data is mean (± SD) of values from 10 separate experiments.
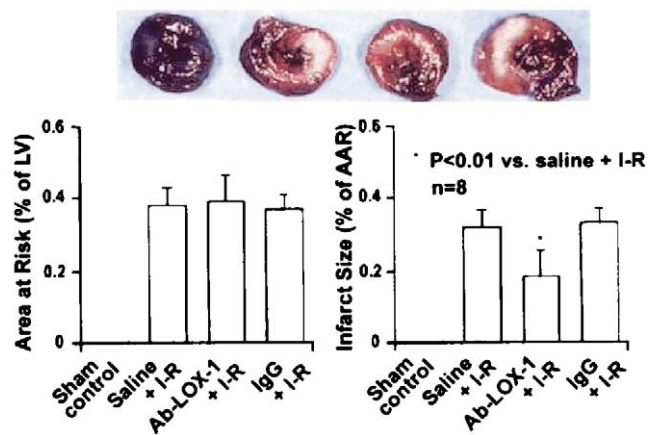
Figure 6. Lectin-like oxidized low-density lipoprotein receptor (LOX-1) expression and infarct size. The sham control group did not show any necrotic area. The risk area in all ischemia-reperfusion (I-R) groups (saline-treated, LOX-1 antibody [Ab-LOX-1]-treated, and nonspecific immunoglobulin G [IgG]-treated) was similar. Infarct size was smaller in the LOX-1 antibody-treated rats compared with that in the saline-treated or the nonspecific IgG-treated rats. The data on infarct size (mean ± SD) is from 10 separate experiments. AAR = area at risk; LV = left ventricle.
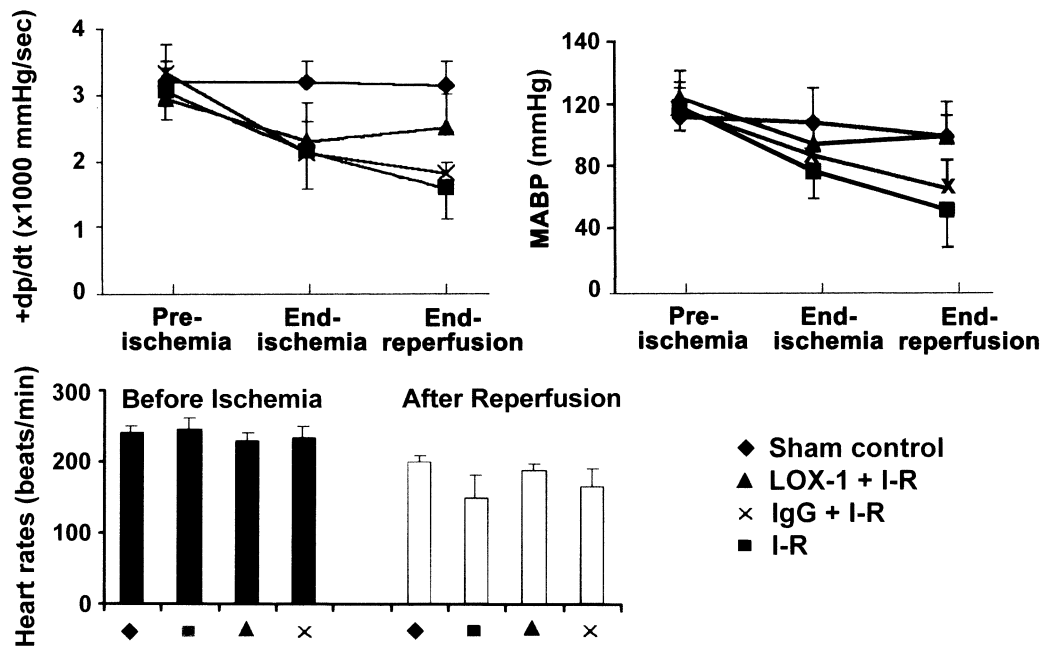
Figure 7. Lectin-like oxidized low-density lipoprotein receptor (LOX-1) expression and cardiac dysfunction during ischemia-reperfusion (I-R) and dP/dt and mean arterial blood pressure (MABP) during ischemia. Reperfusion further reduced dP/dt, MABP, and heart rate. Administration of LOX-1 antibody significantly improved dP/dt, MABP, and heart rate, whereas nonspecific immunoglobulin G (IgG) had no effect.

trol and the ischemia alone groups, indicating that the release of ROS during reperfusion oxidizes lipids. We speculate that ROS and ox-LDL both upregulate the expression of LOX-1 and activate LOX-1 receptors. Activation of LOX-1 would further increase ROS generation and lipid oxidation. This positive feedback amplifies the interaction between ROS and ox-LDL resulting in cell death and cardiac dysfunction. The role of LOX-1 upregulation in this process became clear from experiments in which treatment of rats with a specific LOX-1 blocking antibody decreased LOX-1 expression and, subsequently, the extent of myocardial injury.

LOX-1 expression and apoptosis during ischemia-reperfusion. Apoptosis is a critical cellular event involved in the pathogenesis of myocardial ischemia-reperfusion injury (3,26–31). Expression of a number of genes, such as Fas and Bcl_2, is altered during reperfusion and leads to apoptosis (3,26–31). Caspases are cysteine proteinases that have been shown to be specifically involved in the initiation and execution phases of apoptosis (26–28). Scarabelli et al. (28) found that activation of caspase-9 occurs primarily in endothelial cells, while caspase-8 activation is present in rat cardiomyocytes exposed to ischemia-reperfusion. As evidence for the pathogenic role of caspase-9, addition of a specific caspase-9 inhibitor to the perfusate before ischemia prevented endothelial apoptosis, whereas infusion of a specific caspase-8 inhibitor affected only myocyte apoptosis. Both caspase-8 and caspase-9 activate caspase-3 and then cleave vital cellular proteins. Experimental studies have indeed shown that the activation of caspase-3 is an important process in myocardial reperfusion injury (29). Other

studies show that oxidative stress plays an important role in apoptosis (30,31). For example, Maulik et al. (30) found that apoptotic cells were markedly increased in isolated perfused rat hearts subjected to 15 min of ischemia followed by 60 to 120 min of reperfusion. The number of apoptotic cells in the myocardium was eliminated by preperfusing the hearts in the presence of ebselen, which removed the oxidative stress. Minamino et al. (31) also found that oxidative stress induces apoptosis of cardiac myocytes and that inhibition of oxidative stress inhibits apoptosis.

Oxidized low-density lipoprotein, a potent oxidative stress factor, induces apoptosis in endothelial cells (22), smooth muscle cells (32), and monocytes/macrophages (33). We (21) have recently shown that LOX-1 activation plays a critical role in ox-LDL-induced apoptosis of human coronary artery endothelial cells because inhibition of LOX-1 expression by a specific antisense to LOX-1 mRNA significantly decreased ox-LDL-induced apoptosis. Iwai-Kanai et al. (34) recently observed that overexpression of LOX-1 in cardiac myocytes induces apoptosis through activation of the p38 mitogen-activated protein kinase pathway. In the present study, we show that reperfusion after total ischemia markedly increases the activity of caspase-3 and the number of apoptotic cells in the region supplied by the left coronary artery. Ischemia alone has no significant effect on the degree of apoptosis. We suggest that LOX-1 expression and activation are related, at least in part, to the development of apoptosis because the LOX-1 antibody JXT21 reduced caspase-3 activation and the number of apoptotic myocytes. In contrast with this effect of LOX-1 antibody, the nonspecific IgG antibody had no effect.

Some investigators (35,36) have suggested that oncosis may play a more important role than apoptosis in the ischemia-reperfusion injury to the heart. However, additional data are needed to justify this statement because experimental model and protocol have varied in different studies. In the present study, we cannot exclude oncosis-mediated ischemia-reperfusion injury. We found an increase in apoptosis in the ischemic-reperfused regions, and some of the TUNEL-positive cells may have been undergoing oncosis.

LOX-1, infarct size, and cardiac dysfunction after ischemia-reperfusion. It is generally recognized that reperfusion therapy prolongs survival in patients with acute myocardial infarction. However, reperfusion also enhances myocardial injury beyond that caused by ischemia, perhaps related to the release of cytokines, ROS, calcium overload, and leukocyte recruitment (1–3,7,8,24). Studies in isolated perfused rat heart have demonstrated that ox-LDL induces ultrastructural abnormalities and decreases myocardial contractile function.

Reperfusion injury occurs in the early hours after reperfusion, especially the first hour (1–3,7,8,24). Generation of ROS and ox-LDL and release of certain cytokines during ischemia-reperfusion cause cell injury through different pathways, and induce injury in a synergistic fashion. Our study shows an increase in myocardial lipid peroxidation and LOX-1 expression in the reperfused regions. Evidence for the important role of LOX-1 in reperfused injury came from the use of LOX-1 blocking antibody, which decreased infarct size by about 45%. The salutary effect of LOX-1 antibody may be secondary to blockade of LOX-1 activation and its interaction with other injurious stimuli.

Size of the infarcted tissue is an important determinant of left ventricular function, and therapies that decrease infarct size generally improve cardiac function. Indeed, LOX-1 blocking antibody, when used before the onset of ischemia, significantly reduced cardiac dysfunction. This beneficial effect may relate to the inhibitory effect of LOX-1 antibody on generation of ROS, ox-LDL, and apoptosis.

Conclusions. This study shows that myocardial ischemia-reperfusion increases LOX-1 expression that contributes to reperfusion injury through an increase in apoptosis, lipid peroxidation, infarct size, and cardiac dysfunction. The contribution of LOX-1 in reperfusion injury became evident from experiments in which blockade of LOX-1 activation reduced myocardial ischemia-reperfusion injury. Notably, LOX-1 antibody only reduced, and not abolished, ischemia-reperfusion injury, suggesting that LOX-1 expression is one of many pathways involved in the genesis of reperfusion injury.

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