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Regulation of macrophage lipoprotein lipase secretion by the scavenger receptor

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The effects of ligand binding to the scavenger receptor on the secretion of lipoprotein lipase by murine macrophages were examined. Inflammatory macrophages exposed to acetylated low-density lipoprotein (AcLDL) exhibited a dose-dependent, 40–80% increase in lipoprotein lipase secretion. This stimulation appeared to be unrelated to intracellular cholesterol and triacylglycerol levels and to phagocytosis in general. Resident and inflammatory macrophages treated with maleylated bovine serum albumin (Mal-BSA) showed a 3-fold increase in lipoprotein lipase secretion in a dose-dependent and time-dependent fashion. In contrast, dextran sulfate, which is another ligand recognized by the scavenger receptor, caused a dose-dependent decrease in lipoprotein lipase secretion. Casein, a ligand recognized by the Mal-BSA receptor, did not affect lipoprotein lipase secretion nor the ability of Mal-BSA to stimulate the enzyme, while dextran sulfate abolished the stimulatory effects of Mal-BSA. Since ethylamine, an inhibitor of receptor-mediated endocytosis, attenuated the increase in lipoprotein lipase secretion induced by AcLDL and Mal-BSA, but did not affect the inhibition induced by dextran sulfate, it is suggested that receptor-mediated endocytosis of ligands via the scavenger receptor might play a key role in the stimulation of lipoprotein lipase secretion in macrophages. This study reveals another mechanism for regulation of macrophage lipoprotein lipase secretion.

Introduction

The regulation of lipid metabolism in macrophages has recently been the subject of intense research. Macrophages possess receptors for low-density lipoproteins (LDL), but no lipid accumulation is observed in these cells following exposure to LDL because of cellular homeostatic mechanisms [1]. Macrophages also possess scavenger receptors which bind and internalize chemically or biologically altered lipoproteins such as acetylated LDL (AcLDL) and peroxidized lipoproteins [1–4]. Since the uptake of AcLDL through the scavenger receptor is not regulated by cellular cholesterol levels, receptor-mediated endocytosis of these modified lipoproteins results in massive intracellular cholesterol ester accumulation [1]. The scavenger receptor exhibits affinity for other negatively charged molecules including maleylated bovine serum albumin (Mal-BSA), polysulfated glycoproteins such as fucoidan and dextran sulfate, and polynucleotides such as polyinosinic acid (poly(I)) and polyinosinic-polycytidylic acid

Abbreviations: AcLDL, acetylated low-density lipoprotein; VLDL, very-low-density lipoprotein; Mal-BSA, maleylated bovine serum albumin; PBS, phosphate-buffered saline; DMEM, Dulbecco's modified Eagle's medium.

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(poly(IC)) [5]. Mal-BSA has been reported to bind not only to the scavenger receptor, but also to a second receptor in human monocytes that does not recognize altered lipoproteins [6].

Ligands recognized by the scavenger receptor cause a variety of biochemical responses in macrophages. Uptake of Mal-BSA increases neutral proteinase secretion [7] and induces expression of certain proteins involved in endotoxin response [8]. Incubation of macrophages with AcLDL results in a dose-dependent increase in the secretion of various hydrolases [9]. Uptake of AcLDL also increases the secretion of apolipoprotein E, but this is due to increased intracellular cholesterol levels and is not an effect specific for the scavenger receptor [1,10]. In previous studies examining the hormonal and immunological regulation of lipoprotein lipase secretion by macrophages [11,12], we and others [13] observed that inflammation was the most potent stimulus for increasing lipoprotein lipase secretion, while profound decreases occurred in fully activated macrophages. In the present study, we investigated the possibility that binding of ligands to the scavenger receptor and the Mal-BSA receptor might control lipoprotein lipase secretion in macrophages.

Materials and Methods

Materials. Adult, male Swiss-Webster mice were obtained from Simonsen Labs (Gilroy, CA). Thioglycolate medium was from Difco Laboratories (Detroit, MI) and *Corynebacterium parvum* was from Burroughs Wellcome Co. (Research Triangle Park, NC). Culture dishes were from Costar (Cambridge, MA). Fetal calf serum and Dulbecco's modified Eagle's medium were from GIBCO Laboratories (Grand Island, NY). Fatty acid-free bovine serum albumin was from Armour Pharmaceuticals (Kankakee, IL). [9,10(n)-^{3}H]triolein (20 Ci/mmol) was from New England Nuclear (Boston, MA). All other chemicals and organic solvents were obtained from Sigma Chemical Co. (St. Louis, MO) or J.T. Baker Chemical Co. (Phillipsburg, NJ).

Macrophage cell culture. Macrophages were prepared as described previously [12]. In brief, Swiss-Webster mice were left untreated for resident macrophages, injected with 2 ml thioglycolate medium 3 days prior to death for inflammatory macrophages, or with 700 μg of *C. parvum* 7 days prior to death for activated macrophages. Macrophages were collected by peritoneal lavage with 10 ml of phosphate-buffered saline (PBS) and plated in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal calf serum at a concentration of $1 \cdot 10^6$ cells/well (inflammatory cells) or $2 \cdot 10^6$ cells/well (activated and resident cells) in 12-well cell culture trays. Nonadherent cells were removed by extensive washing with DMEM 2 h after plating. Greater than 99% of attached cells were macrophages as determined by light microscopy and phagocytosis of latex beads and antibody-coated red blood cells. The cells were kept in DMEM containing 10% fetal calf serum for 3 days prior to use.

Lipoprotein lipase assay. 3-day old macrophages were incubated overnight in 1 ml DMEM only (control) or in 1 ml DMEM containing various ligands. On the next day, the media was removed, the cells were washed once with DMEM, 0.5% fatty acid-free BSA, and the amount of lipoprotein lipase secreted into 0.5 ml DMEM, 0.5% fatty acid-free BSA over 6 h was assayed as described previously [12]. In order to release the secreted enzyme from the cell membrane, heparin (0.5 U/well) was added 10 min. prior to the end of the incubation time. Then, 100 μl of medium was assayed for enzyme activity by incubation at 37 °C with 150 μl of [^{3}H]triolein emulsion substrate (final concentration 2.5 mM triolein, 2.4% BSA, 0.2 M Tris (pH 8.5), 0.1 M NaCl, 8% heated horse serum in a 250 μl final volume). The reaction was stopped by adding 3.2 ml of heptane/methanol/chloroform (180:250:230, v/v) containing 20 μg/ml oleic acid. 1 ml of 0.1 M sodium borate-carbonate buffer, (pH 10.5) was subsequently added. After the tubes had been vortexed and spun at 3000 rpm for 15 min at 25 °C, the amount of radioactivity in the supernatant was determined in a scintillation counter. Activity was then expressed in pkat/mg cell protein.

Cellular lipid levels. Cells were incubated overnight in DMEM only (control) or in DMEM containing various lipoproteins. On the following day, the cells were washed and the cellular lipids were extracted and assayed as described previously [14].

Isolation of lipoproteins. Blood from normal volunteers was treated with plasma preservative concentrate (final concentrations in blood: EDTA (3 mM), ϵ-amino caproic acid (10 mM), chloramphenicol (60 μM), dithionitrobenzoic acid (1 mM), gentamycin (60 μg/ml) and spun at 1500 × *g* for 10 min at 4°C. Very-low-density lipoproteins (VLDL) and LDL were then isolated by differential ultracentrifugation as described [14], extensively dialyzed against PBS, and sterilized by filtration prior to use. β-migrating VLDL (β-VLDL) from cholesterol-fed rats were isolated as previously described [15].

Chemical modifications of low-density lipoprotein and bovine serum albumin. AcLDL was prepared as described previously [15]. Mal-BSA was prepared according to the method of Butler et al. [16]. In a typical preparation, 0.05 g of fatty acid-free BSA was dissolved in 10 ml of 0.2 M sodium phosphate buffer (pH 9.0) and placed on ice. Over a period of 30 min, maleic anhydride (0.10 g) was added in small aliquots and the pH of the reaction was maintained at 8.5–9.0 by addition of 4 M NaOH. The reaction was considered complete when the pH stabilized at 8.5–9.0 without further addition of base. The Mal-BSA was then extensively dialyzed against PBS prior to use.

Statistical analysis. Analysis of variance was used to test the hypothesis of equality. If the equality hypothesis was rejected, Duncan's multiple range test was used to detect differences among population means. Results are expressed as the mean ± S.E.

Results

Lipoprotein lipase secretion by AcLDL treated macrophages

In order to determine whether binding of ligands to the scavenger receptor regulates lipoprotein lipase secretion, thioglycolate-elicited macrophages were incubated overnight with AcLDL. As shown in Fig. 1, AcLDL induced a dose-dependent increase in lipoprotein lipase secretion by macrophages, with a maximum increase of 80% above control, and the half-maximal increase occurring at an AcLDL protein concentration of approx. 20 μg/ml.

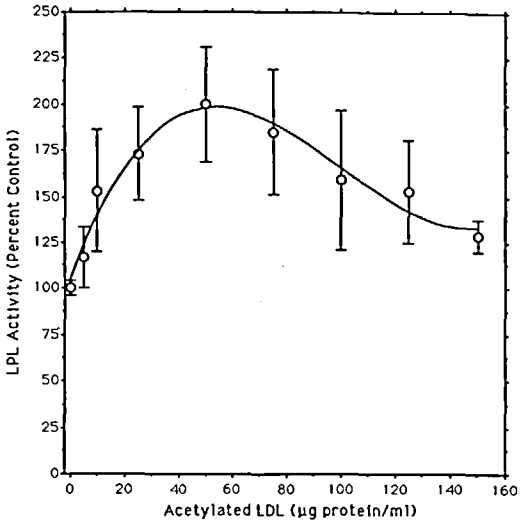

Fig. 1. Effect of AcLDL on lipoprotein lipase (LPL) secretion by inflammatory macrophages. Cells were preincubated overnight in quadruplicate wells with varying concentrations (5–150 μg/ml) of AcLDL in 1 ml of DMEM. On the following day, the media were removed and the cells were incubated for another 6 h at 37°C in 0.5 ml of DMEM containing 0.5% BSA. The amount of lipoprotein lipase secreted into the media was assayed as described in the Materials and Methods and expressed as percent control lipoprotein lipase activity (100% activity, 140 pkat/mg protein). Results are expressed as mean ± S.E.

Effects of intracellular lipid levels and phagocytosis on lipoprotein lipase secretion

Next, the possibility was tested that the increased intracellular levels of cholesterol induced by AcLDL uptake were responsible for the change in lipoprotein lipase secretion, as is the case in the modulation of apolipoprotein E secretion [1,10]. However, when thioglycolate-elicited cells were exposed to β-VLDL, which is taken up by the LDL receptor [15,17], there was no alteration in secretion of the enzyme (Fig. 2) even though marked intracellular cholesterol ester accumulation occurred (Table I). Increased intracellular triacylglycerol levels caused by incubation with VLDL (Table I) also did not affect lipoprotein lipase secretion (Table II). In addition, exposure to unmodified LDL failed to influence lipid accumulation (Table I) or lipoprotein lipase secretion in macrophages (Table II). The role of phagocytosis in modulation of lipoprotein lipase secretion was next examined. Overnight incubation of mac-

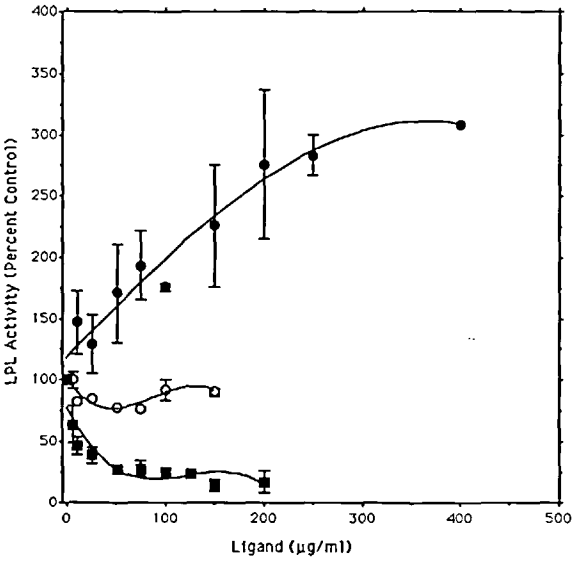

Fig. 2. Effects of maleylated BSA (●), β-VLDL (○) and dextran sulfate (■) on lipoprotein lipase (LPL) secretion by inflammatory macrophages. Cells were incubated overnight in triplicate wells with varying concentrations of Mal-BSA (10–400 μg/ml), β-VLDL (10–150 μg/ml) and dextran sulfate (10–200 μg/ml) in 1 ml of DMEM. On the following day, the media were removed and the cells were further incubated for 6 h in 0.5 ml of DMEM 0.5% BSA. The amount of lipoprotein lipase secreted into the media was assayed as described in the Materials and Methods and expressed as percent control lipoprotein lipase activity (100% activity, 180 pkat/mg protein). Results are expressed as mean ± S.E.

rophages with latex beads did not affect secretion of the enzyme (Table II). Moreover, in contrast to a recent report [18], no stimulation of secretion

TABLE I

CELLULAR LIPID ACCUMULATION IN INFLAMMATORY MACROPHAGES

Cells were incubated overnight in triplicate wells with the indicated amounts of lipoprotein in 1 ml of DMEM. On the following day, cells were washed and the cellular lipids were extracted and assayed as described previously [14]. Results are expressed as mean ± S.E.

Treatment	Cholesterol ester (μg/mg cell protein)	Triacylglycerol (μg/mg cell protein)
No lipoproteins	5.8 ± 0.55	5.8 ± 0.25
AcLDL (30 μg/ml)	29 ± 1.5	4.8 ± 0.80
β-VLDL (80 μg/ml)	21 ± 2.7	17 ± 1.1
LDL (30 μg/ml)	5.0 ± 1.7	4.9 ± 0.10
VLDL (30 μg/ml)	5.2 ± 0.54	52 ± 5.0

TABLE II

EFFECTS OF VARIOUS LIGANDS ON LIPOPROTEIN LIPASE SECRETION BY INFLAMMATORY MACROPHAGES

Cells were incubated overnight in quadruplicate to decuplicate wells in DMEM containing the indicated concentrations of the ligands. Controls were incubated in DMEM alone. The cells were then incubated for 6 h in 0.5 ml DMEM, 0.5% BSA and assayed for lipoprotein lipase as described in the Materials and Methods. Results are expressed as mean ± S.E. with the lipoprotein lipase activity of controls (195 pkat/mg protein) taken as 100% activity.

Ligand	Lipoprotein lipase activity (% control)
VLDL (70 μg/ml)	92.4 ± 4.16
LDL (70 μg/ml)	111 ± 3.74
Poly(I) (100 μg/ml)	99.7 ± 2.29
Poly(I,C) (100 μg/ml)	88.5 ± 4.59
Latex beads (10^{13} beads/ml)	101 ± 0.33

was observed with β-VLDL, LDL or latex beads even when these various ligands were present throughout the entire incubation. Therefore, increased lipoprotein lipase secretion induced by AcLDL is due to the binding of the ligand to the scavenger receptor and is unaffected by intracellular lipid levels and by internalization or phagocytosis of other ligands and particles.

Effects of other ligands of the scavenger receptor on lipoprotein lipase secretion

The roles of other scavenger receptor ligands in the regulation of LPL secretion was then examined. Depending on the ligand, markedly different effects on enzyme secretion were seen. Thioglycolate-elicited macrophages exposed to poly(I) and poly(I,C) did not alter their lipoprotein lipase secretion (Table II), while dextran sulfate caused a dose-dependent decrease in the secretion (Fig. 2). At maximum inhibition, cells secreted only 20% as much lipoprotein lipase as controls; half-maximal inhibition was reached at a concentration between 5–10 μg/ml of dextran sulfate.

Effects of Mal-BSA on lipoprotein lipase secretion

When inflammatory cells were incubated overnight with varying amounts of Mal-BSA, a maxi-

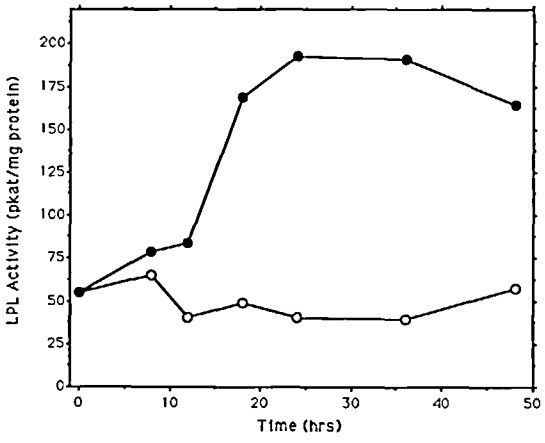

Fig. 3. Time course of lipoprotein lipase (LPL) secretion by macrophages treated with Mal-BSA. Cells were preincubated with 300 μg/ml Mal-BSA in DMEM for 8, 12, 18, 24, 36, and 48 h (●) (controls (○) were treated with DMEM alone). After preincubation, the cells were incubated for an addition 6 h in 0.5 ml DMEM, 0.5% BSA, and lipoprotein lipase was assayed as described in the Materials and Methods. Results are the average of duplicate wells.

mum increase of 3-fold in lipoprotein lipase secretion was observed (Fig. 2). The increase in enzyme secretion was dose dependent with a half-maximal increase observed at a concentration of approx. 520 nM. The effect of Mal-BSA was not due to an immediate burst of lipoprotein lipase secretion following cellular uptake, but was time-dependent (Fig. 3). The enzyme secretion did not rise significantly before 12 h incubation and a maximal effect was observed after 24 h following exposure of cells to Mal-BSA. Addition of cycloheximide (1 μM) during the 24 h preincubation completely blocked the increased lipoprotein lipase secretion induced by Mal-BSA on inflammatory macrophages (control, 220 ± 6; Mal-BSA, 335 ± 18; Mal-BSA + cycloheximide, 82 ± 6 pkat/mg protein), suggesting that Mal-BSA was stimulating new enzyme synthesis. Cycloheximide had no effects on the ability of Mal-BSA to stimulate lipoprotein lipase secretion when present only during 12–15 h or 15–18 h of preincubation. The effect of Mal-BSA on lipoprotein lipase secretion was not limited to inflammatory macrophages; a similar dose-dependent effect was seen in resident macrophages, with a maximum of 2.5-fold increase in lipoprotein lipase secretion (Fig. 4). In contrast to the ability of Mal-BSA to stimulate lipoprotein lipase secretion in resident and inflammatory macrophages, lipoprotein lipase secretion in *C. parvum*-elicited macrophages, which secrete low to undetectable amounts of the enzyme [12], was not affected by Mal-BSA (data not shown).

When inflammatory macrophages were co-incubated with Mal-BSA and another ligand recognized by the scavenger dextran sulfate, the ability of Mal-BSA to stimulate lipoprotein lipase secretion was abolished (Fig. 5). Recently, it was reported that Mal-BSA can bind not only to the scavenger receptor, but also to a functionally distinct Mal-BSA receptor [6]. To determine whether the Mal-BSA receptor also regulates lipoprotein lipase secretion, inflammatory macrophages were incubated with casein, a ligand which competes for the Mal-BSA receptor, but does not bind to the scavenger receptor [6]. Exposure of cells to casein did not cause a significant change in lipoprotein lipase secretion (Fig. 5). In addition, up to a 3-fold molar excess of casein had no effect on the ability of Mal-BSA to stimulate lipoprotein lipase secretion, thereby suggesting that the Mal-BSA receptor does not play a role in the regu-

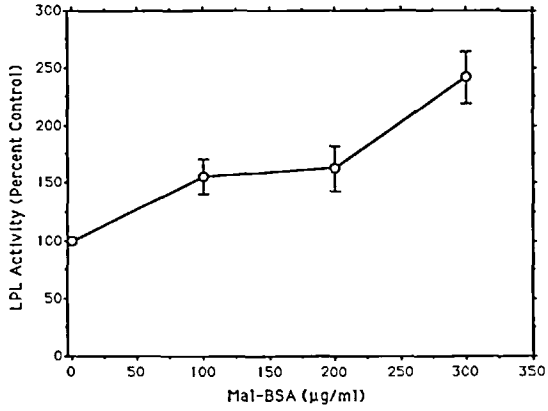

Fig. 4. Effect of Mal-BSA on lipoprotein lipase (LPL) secretion by resident macrophages. Cells were incubated overnight in triplicate wells with varying concentrations of Mal-BSA (100, 200, 300 μg/ml) in 1 ml of DMEM. On the following day, the media was removed and the cells were further incubated for 6 in 0.5 ml of DMEM, 0.5% BSA. The amount of lipoprotein lipase secreted into the media was then assayed as described in the Materials and Methods and expressed as percent control lipoprotein lipase activity (100% activity, 80 pkat/mg protein). Results are expressed as mean ± S.E.

lation of lipoprotein lipase secretion in macrophages.

Effects of inhibition of ligand internalization

It is surprising that ligands recognized by the scavenger receptor (dextran sulfate, AcLDL and Mal-BSA) cause opposite effects on lipoprotein lipase secretion. This could be explained if the ligands, after binding to the scavenger receptor, are metabolized differently; for example, internalization of a receptor-ligand complex might be the key step in control of lipoprotein lipase secretion. To determine whether the internalization of the ligands plays any part in lipoprotein lipase regulation, inflammatory cells were treated concurrently with various ligands and ethylamine, a primary amine that inhibits receptor-mediated endocytosis [19]. As seen in Table III, ethylamine attenuates the ability of Mal-BSA and AcLDL to stimulate lipoprotein lipase secretion without having any significant effect of its own. Compared to the cells treated with Mal-BSA, which increased lipoprotein lipase secretion 3-fold, cells that were exposed simultaneously to Mal-BSA and ethylamine exhibited only a moderate (8% above control) increase in the lipoprotein lipase secretion. However, ethylamine failed to attenuate the decrease in secretion of this enzyme caused by dextran sulfate. Thus, these results are consistent with the hypothesis that endocytosis of ligands through the scavenger receptor might be an essential step in increasing lipoprotein lipase secretion in macrophages.

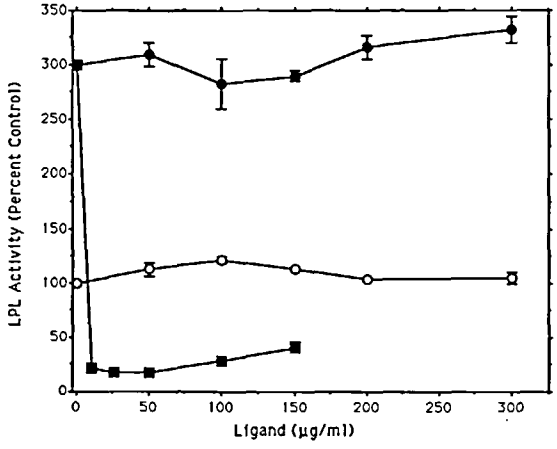

Fig. 5. Effects of casein and dextran sulfate on the increased lipoprotein lipase secretion by Mal-BSA treated inflammatory macrophages. Cells were incubated overnight in triplicate wells in the presence of 50–300 μg/ml of casein (○), or 300 μg/ml Mal-BSA plus 50–300 μg/ml casein (●), or 300 μg/ml Mal-BSA plus 10–150 μg/ml dextran sulfate (■) in 1 ml of DMEM. On the following day, the media were removed and the cells were further incubated for 6 h in 0.5 ml of DMEM, 0.5% BSA. The amount of lipoprotein lipase secreted into the media was assayed as described in the Materials and Methods and are expressed as percent control lipoprotein lipase activity (100% activity, 230 pkat/mg protein). Results are expressed as mean ± S.E.

TABLE III

ABILITY OF ETHYLAMINE TO ATTENUATE THE INCREASED LIPOPROTEIN LIPASE SECRETION IN INFLAMMATORY MACROPHAGES

Cells were incubated overnight in triplicate wells in DMEM containing either 300 μg/ml Mal-BSA, 75 μg/ml AcLDL, 150 μg/ml dextran sulfate, 10 mM ethylamine, 300 μg/ml Mal-BSA plus 10 mM ethylamine, 75 μg/ml AcLDL plus 10 mM ethylamine or 150 μg/ml dextran sulfate plus 10 mM ethylamine. Controls were incubated in DMEM alone. The cells were then incubated for 6 h in 0.5 ml DMEM, 0.5% BSA and assayed for lipoprotein lipase activity as described in the Materials and Methods. Results are expressed as mean ± S.E. with the lipoprotein lipase activity of controls (230 pkat/mg protein) taken as 100% activity.

Treatment	Lipoprotein lipase activity (% control)
Control	100 ±5.50
Mal-BSA	310 ±8.89
AcLDL	142 ±4.55
Dextran sulfate	28.7±1.67
Ethylamine	108 ±7.85
Mal-BSA + ethylamine	149 ±14.1
AcLDL + ethylamine	118 ±8.52
Dextran sulfate + ethylamine	15.2±1.69

Discussion

The present studies indicate that binding of ligands to the scavenger receptor controls lipoprotein lipase secretion by resident and thioglycolate-elicited murine macrophages. Thus, AcLDL, Mal-BSA and dextran sulfate regulated lipoprotein lipase secretion. *C. parvum*-elicited macrophages secreted too little lipoprotein lipase activity to detect any effects. The effects of these ligands on secretion of the enzyme were time-dependent and

their stimulatory effects required new protein synthesis, suggesting that their actions were not due to an immediate effect on an intracellular secretory pool of lipoprotein lipase. This is further supported by the fact that macrophages contain only small quantities of intracellular lipoprotein lipase [11] and by the fact that the changes in secretion of the enzyme were observed during a 6 h period subsequent to the removal of the respective ligands. Unlike apolipoprotein E secretion in macrophages, which is controlled in part by intracellular cholesterol levels [1,10], the AcLDL-induced increase in lipoprotein lipase secretion is unrelated to cellular cholesterol, since β-VLDL, which causes cellular cholesterol accumulation [1], did not affect enzyme secretion. Likewise, intracellular triacylglycerol did not influence lipoprotein lipase secretion. Furthermore, in contrast to apolipoprotein E regulation by several different receptor-mediated pathways [20], lipoprotein lipase secretion was not affected by β-VLDL or LDL uptake via the LDL receptor nor by phagocytosis of latex particles. Thus, macrophage lipoprotein lipase secretion is regulated by mechanisms involving the scavenger receptor that are unrelated to cellular lipid levels and to endocytosis in general. These results are in contrast to a recent report [18] in which the uptake of either triacylglycerol-rich or cholesterol-rich rat lipoprotein was found to stimulate lipoprotein lipase secretion in rat alveolar macrophages. In this previous study, changes in secretion of this enzyme were assessed while lipoproteins were present in the incubation; however, we did not observe increases in lipoprotein lipase secretion even when β-VLDL, VLDL, LDL or latex beads were present in the preincubation or throughout the incubation. The reasons for the discrepancy between the two studies are not entirely clear. Possible explanations might be the differences in the source and type of macrophage or the differences in lipoproteins used.

It is of interest that Mal-BSA and dextran sulfate, which are both competitive inhibitors of AcLDL binding to the scavenger receptor [5], caused opposite effects on lipoprotein lipase secretion, with Mal-BSA stimulating and dextran sulfate suppressing it. Similarly, dichotomous effects of AcLDL and dextran sulfate on apolipoprotein E secretion by macrophages have been observed previously [20]. A mechanism to explain this finding is not readily apparent; however, the fact that primary amines which inhibit endocytosis attenuated the increase in lipoprotein lipase secretion induced by Mal-BSA without influencing the inhibitory effects of dextran sulfate suggest that internalization of scavenger receptors and/or ligands might play a major role in the stimulation of lipoprotein lipase secretion by macrophages. Conversely, it is possible that differences in the size or charge of the particles might be responsible for determining whether this secretion is stimulated or inhibited.

The half-maximal effects of AcLDL and dextran sulfate are observed at concentrations that are consistent with their affinities for the scavenger receptor [5]. In addition, the large increase in lipoprotein lipase secretion induced by Mal-BSA also appears to be due to the interaction of the ligand with the scavenger receptor and not with other receptors that recognize Mal-BSA. This conclusion is based on the fact that casein, a ligand recognized by the Mal-BSA receptor, but not the scavenger receptor [6], did not affect lipoprotein lipase secretion alone, nor was casein able to attenuate the stimulatory effects of Mal-BSA. In addition, the K_m for the stimulation of lipoprotein lipase by Mal-BSA (approx. 520 nM) approximates the K_d reported for Mal-BSA binding to the scavenger receptor (270 nM) in mouse macrophages [21] and is an order of magnitude below the K_d (3.5–5 μM) for Mal-BSA binding to the Mal-BSA receptor in human monocyte macrophages [6,22]. Thus, the increase in lipoprotein lipase secretion caused by incubation with Mal-BSA is probably due to ligand binding to the scavenger receptor. However, because the K_m for the stimulation of lipoprotein lipase by Mal-BSA is higher than the K_d (37 nM) reported for the scavenger receptor in human monocyte macrophages [22], it is possible that some of the effects of Mal-BSA on lipoprotein lipase secretion might be mediated by a Mal-BSA receptor. If Mal-BSA does exert its effects via both the scavenger receptor and the Mal-BSA receptor, this might explain the greatly enhanced secretion of lipoprotein lipase and various hydrolases [7,8] by Mal-BSA when compared to the modest stimulation observed with

AcLDL. Nevertheless, it seems likely that the binding of Mal-BSA to the scavenger receptor, which is involved in lipid metabolism, results in a response which is also implicated in the breakdown of lipid-protein complexes, while the binding of Mal-BSA to the Mal-BSA-specific receptor results in immunological responses such as chemotaxis [22], or possibly increased synthesis of proteins that appear to be involved in biochemical responses of human macrophages to endotoxins [8].

We have previously shown that the secretion of lipoprotein lipase in macrophages can be regulated by their state of activation, with increased secretion in inflammatory and primed cells and diminished secretion in activated cells [12]. The present study reveals yet another level of regulation of lipoprotein lipase secretion in macrophages. Since the monocyte macrophage has been implicated as the precursor of lipid-laden foam cells in atherosclerotic lesions [23,24], the present study suggests that certain glycosaminoglycans, chemically altered proteins or modified lipoproteins generated within the arterial wall can regulate lipoprotein lipase secretion and might thereby influence the atherosclerotic process.

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