Lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) serves as an endothelial receptor for advanced glycation end products (AGE)

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Abstract Advanced glycation end products (AGE) are known to serve as ligands for the scavenger receptors such as SR-A, CD36 and SR-BI. In the current study, we examined whether AGE is recognized by lectin-like oxidized low density lipoprotein receptor-1 (LOX-1). Cellular binding experiments revealed that AGE-bovine serum albumin (AGE-BSA) showed the specific binding to CHO cells overexpressing bovine LOX-1 (BLOX-1), which was effectively suppressed by an anti-BLOX-1 antibody. Cultured bovine aortic endothelial cells also showed the specific binding for AGE-BSA, which was suppressed by 67% by the anti-BLOX-1 antibody. Thus, LOX-1 is identified as a novel endothelial receptor for AGE.

Key words: Advanced glycation end product; Receptor for advanced glycation end product; Lectin-like oxidized low density lipoprotein receptor-1; Endothelial cell

1. Introduction

In the Maillard reaction, incubation of proteins with glucose leads, through the formation of early products such as Schiff base and Amadori products, to formation of advanced glycation end products (AGE) [1,2]. During AGE formation, several aldehydes such as 3-deoxyglucosone [3], glycolaldehyde [4], glyoxal [4] and methylglyoxal (MG) [3] are generated as intermediates and react mainly with lysine and arginine residues of proteins. Through modification of these basic amino acids, proteins lose positive charges and increase their net negative charges [4]. AGE proteins are characterized physicochemically by fluorescence, browning, molecular cross-linking [1,2] and biologically by ligands specifically recognized by AGE receptors [5–13]. Accumulation of AGE in human tissues is thought to increase with aging and age-related disorders such as diabetic complications and atherosclerosis [14–19]. AGE receptors so far identified are the receptor for AGE (RAGE) [5], a complex of OST-48/80K-H/galectin-3 [6,7,10], class A scavenger receptor (SR-A) [8,9], CD36 [12] and SR-BI (a class B scavenger receptor) [13]. AGE ligands bound to SR-A [8], CD36 [12] and SR-BI [13] are known to undergo endocytic uptake and subsequent lysosomal degradation [8]. It is also known that the binding of AGE ligands to RAGE generates intracellular signals that lead to induction of several genes such as vascular cell adhesion molecule-1 [20] and tissue factor [21].

Lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) is identified as a novel scavenger receptor for oxidized low density lipoprotein (Ox-LDL) which is highly expressed on endothelial cells [22]. LOX-1 mediates endocytic uptake and subsequent lysosomal degradation of Ox-LDL. In addition to Ox-LDL, LOX-1 recognizes aged/apoptotic cells [23], activated platelets [24] and bacteria [25] as ligands. Binding of Ox-LDL to LOX-1 induces several cellular events in endothelial cells such as activation of NF-κB [26], up-regulation of monocyte chemoattractant protein-1 [27], and reduction in intracellular nitric oxide [28], which may play as a trigger for onset of cardiovascular events or an accelerator in the development of atherosclerosis.

Since the binding of various ligands to LOX-1 is sensitively inhibited by polyanionic compounds like polyinocinic acid [23,29], negative charge of a ligand is likely to be an essential factor for its binding to LOX-1. AGE proteins are also negatively charged and their binding to mouse macrophage-derived Raw 264.7 cells [4] and rabbit smooth muscle cells [11] is effectively inhibited by polyanionic compounds. Moreover, LOX-1 is a member of the scavenger receptor family to which the AGE receptors such as SR-A [8,9], CD36 [12] and SR-BI [13] belong. Thus, we speculated that AGE-modified proteins might behave as ligands for LOX-1 as well as Ox-LDL. To test this hypothesis, we examined the interaction of AGE proteins with LOX-1. The results showed that AGE behaves as a novel ligand for LOX-1.

2. Materials and methods

2.1. Preparation of AGE-BSA and aldehyde-modified proteins

AGE-bovine serum albumin (AGE-BSA) was prepared as described previously [30]. Briefly, 2.0 g of BSA was incubated with 3.0 g of D-glucose in 10 ml of 0.5 M sodium phosphate buffer (pH 7.4) for 40 weeks at 37°C, and dialyzed against phosphate-buffered saline (PBS). The extent of lysine modification in AGE-BSA was 75.7% of total lysine residues when determined by amino acid analysis after acid hydrolysis [4]. BSA (2 mg/ml) was incubated for 14 days at 37°C with 33 mM MG (Sigma, St. Louis, MO, USA), glycolaldehyde (Sigma) or 3-deoxyglucosone prepared as described previously [31] in 100 mM sodium phosphate buffer (pH 7.4), followed by dialysis against

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Abbreviations: AGE, advanced glycation end product; RAGE, receptor for advanced glycation end product; LOX-1, lectin-like oxidized low density lipoprotein receptor-1

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PBS [4]. AGE-BSA was labeled with ^{125}I by using Iodogen (Pierce Chemical Co.) to a specific radioactivity of 850 cpm/ng.

2.2. Lipoprotein preparation

LDL ($d = 1.019$–1.063 g/ml) was isolated by sequential ultracentrifugation of fresh plasma from normolipidemic subjects after overnight fasting [32]. Ox-LDL was prepared by incubating LDL (0.1 mg/ml) for 16 h at 37°C with 5 μM $CuSO_4$, followed by addition of 1 mM EDTA and cooling [32]. Ox-LDL was labeled with ^{125}I by the method of McFarlane [33] to a specific radioactivity of 510 cpm/ng.

2.3. Cell culture

CHO cells overexpressing bovine LOX-1 (BLOX-1-CHO) were selected after stable transfection of CHO cells with BLOX-1 as described previously [22]. Cells were maintained with Ham's F-12 medium (Gibco) supplemented with 10 μg/ml of blasticidin S (Funakoshi, Tokyo, Japan) and 10% fetal calf serum (FCS) in a humidified air with 5% CO_2 [22]. Bovine aortic endothelial cells (BAEC) were isolated by scraping the inner surface of bovine aorta and cultured with Dulbecco's modified Eagle's medium (DMEM) containing 10% FCS [22]. BLOX-1-CHO cells (4×10^4/well) or BAEC (8×10^4/well) were seeded to 24-well plates (15 mm in diameter) and further grown with each medium for 2 days and subjected to cellular assays as described below.

2.4. Cellular assays

For endocytic degradation assays, BLOX-1-CHO cells grown in 24-well plates were incubated for 6 h at 37°C in 1.0 ml of DMEM containing 3% BSA (medium A) with various concentrations of [^{125}I]AGE-BSA or [^{125}I]Ox-LDL in the presence or absence of excess amounts of unlabeled ligands. An aliquot (0.75 ml) of the culture medium was mixed with 0.3 ml of 40% trichloroacetic acid (TCA). To this solution was added 0.2 ml of 0.7 M $AgNO_3$, followed by centrifugation at $2500\times g$ for 10 min. TCA-soluble radioactivity in the supernatant (0.5 ml) was measured for determination of endocytic degradation [8]. The remaining cells were washed twice with 1 ml of PBS containing l% BSA and then twice with 1 ml of PBS. The cells were solubilized with 0.5 ml of 0.1 N NaOH and the cell-associated radioactivity and cell proteins were determined [8,34]. For binding assays, BLOX-1-CHO cells or BAEC in 1.0 ml of medium A were incubated for 90 min at 4°C with various concentrations of [^{125}I]AGE-BSA or [^{125}I]Ox-LDL in the presence or absence of excess amounts of unlabeled ligands or in the indicated amount of the anti-BLOX-1 antibody [22] or control IgG. Each well was washed twice with ice-cold PBS containing 1% BSA and then twice with ice-cold PBS, followed by determination of cell-bound radioactivity as described previously [11]. The anti-BLOX-1 antibody was prepared in mice as described previously [22].

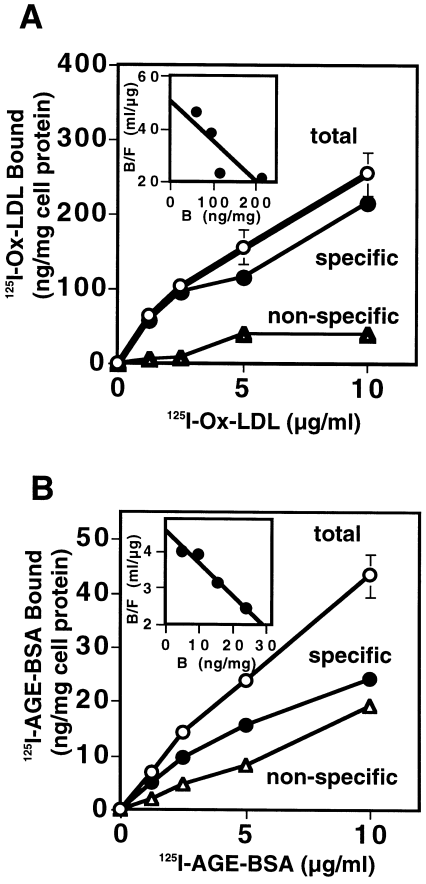

Fig. 1. Cellular binding of [^{125}I]Ox-LDL (A) and [^{125}I]AGE-BSA (B) to BLOX-1-CHO cells. BLOX-1-CHO cells were incubated for 90 min at 4°C with the indicated concentrations of [^{125}I]Ox-LDL (A) or [^{125}I]AGE-BSA (B) in the absence (open circle) or presence (open triangle) of 0.5 mg/ml unlabeled Ox-LDL (A) or AGE-BSA (B), followed by determination of the cell-bound radioactivity. Specific binding (close circle) was determined by subtracting non-specific binding (open triangle) from total binding (open circle). Insets, Scatchard analyses of the specific binding curves. Data are representatives of three separate experiments with duplicate wells.

3. Results

3.1. Interaction of AGE with BLOX-1-CHO cells

Binding assays at 4°C showed specific and saturable binding of [^{125}I]Ox-LDL to BLOX-1-CHO cells with an apparent K_d of 6.6 μg/ml and maximal binding of 339 ng/mg cell protein (Fig. 1A), indicating expression of a significant amount of BLOX-1 by these cells. [^{125}I]AGE-BSA binds to these BLOX-1-CHO cells in a specific and saturable manner and the Scatchard analysis revealed a single binding site for AGE-BSA with an apparent K_d of 9.8 μg/ml and maximal binding of 47.5 ng/mg cell protein (Fig. 1B), indicating that AGE-BSA serves as a ligand for LOX-1. Upon incubation at 37°C, cell-association of [^{125}I]AGE-BSA with BLOX-1-CHO cells increased in a dose-dependent manner, whereas the mock-transfected CHO cells did not show any significant cell-association (Fig. 2A). In contrast to Ox-LDL, however, subsequent endocytic degradation of [^{125}I]AGE-BSA by BLOX-1-CHO cells did not occur at an appreciable level (Fig. 2B), suggesting that AGE-BSA binds to LOX-1 but fails to undergo endocytic degradation in BLOX-1-CHO cells.

3.2. Cross-competition between AGE-BSA and Ox-LDL

Competitive binding assays were performed to further characterize the binding of AGE ligands to LOX-1. Cellular binding of [^{125}I]AGE-BSA was effectively (more than 80%) competed for by unlabeled AGE-BSA and Ox-LDL. In addition to AGE-BSA, we examined whether BSA modified by MG, glycolaldehyde or 3-deoxyglucosone, intermediate aldehydes generated during the Maillard reaction [3,4], could serve as AGE ligands. Effects of MG-modified BSA (MG-BSA) and glycolaldehyde-modified BSA (GA-BSA) on the cellular binding of AGE-BSA to BLOX-1-CHO cells were as inhibitory as unlabeled AGE-BSA and Ox-LDL, whereas 3-deoxyglucosone-modified BSA had no such an inhibitory effect (Fig. 3A). Under the parallel conditions, the binding of [^{125}I]Ox-LDL to these cells was significantly inhibited by unlabeled Ox-LDL, but inhibitory effects of other ligands tested were partial (Fig. 3B). Under these binding conditions, the cellular binding of AGE-BSA and Ox-LDL was significantly inhibited by the anti-BLOX-1 antibody (60 and 70%, respectively), whereas non-immune IgG had no effect at all (Fig. 3A,B).

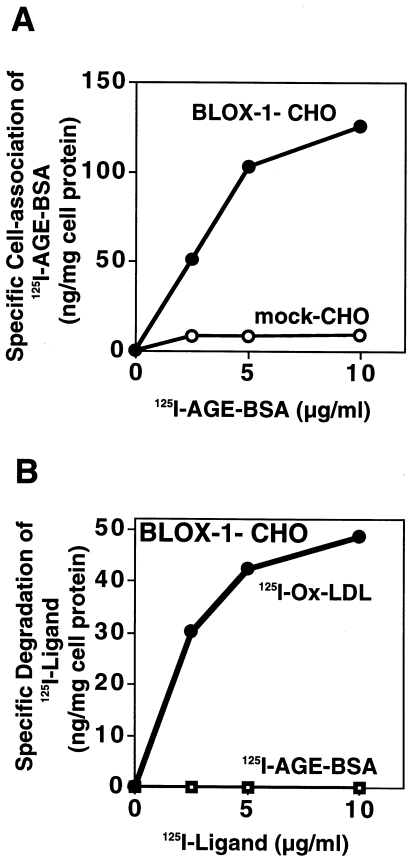

Fig. 2. Endocytic uptake of [^{125}I]AGE-BSA or [^{125}I]Ox-LDL by BLOX-1-CHO cells. A: BLOX-1-CHO cells or mock-CHO cells were incubated for 6 h at 37°C with the indicated concentrations of [^{125}I]AGE-BSA in the absence or presence of 0.5 mg/ml unlabeled AGE-BSA, followed by determination of the cell-associated [^{125}I]-AGE-BSA. Specific cell-association was determined by subtracting non-specific cell-association from total cell-association. B: BLOX-1-CHO cells were incubated for 6 h at 37°C with the indicated concentrations of [^{125}I]AGE-BSA or [^{125}I]Ox-LDL in the absence or presence of 0.5 mg/ml of unlabeled AGE-BSA or Ox-LDL, respectively. TCA-soluble radioactivity in the supernatant was measured for determination of endocytic degradation of each ligand. Specific degradation was determined by subtracting non-specific degradation from total degradation. Data are representatives of three separate experiments with duplicate wells.

3.3. LOX-1 as an endothelial AGE receptor

Since LOX-1 was reported to be highly expressed by endothelial cells, we determine whether LOX-1 could also serve as the AGE receptor on endothelial cells. The binding of [^{125}I]AGE-BSA to cultured BAEC was competitively inhibited by 75% by unlabeled AGE-BSA (Fig. 4) and by 50% by the anti-BLOX-1 antibody (corresponding to two-thirds of the specific binding), whereas non-immune IgG had no effect, indicating that a substantial part of the specific binding of [^{125}I]AGE-BSA to these endothelial cells is mediated by LOX-1.

4. Discussion

We previously demonstrated that AGE-modified proteins serve as ligands for the scavenger receptors such as SR-A [8,9], CD36 [12] and SR-BI [13]. As an extension of these studies, we examined whether AGE ligands could serve as ligands for LOX-1, another scavenger receptor for Ox-LDL [22]. The results clearly showed high affinity binding of AGE-BSA to BLOX-1-CHO cells (Fig. 1B), which was effectively suppressed by the anti-BLOX-1 antibody (Fig. 3A), indicating that AGE ligands are recognized as ligands by LOX-1.

Among ligands tested, MG-BSA and GA-BSA behaved as effective ligands as AGE-BSA (Fig. 3A). MG-BSA is known to undergo receptor-mediated endocytosis by murine P388D$_1$ macrophages [35]. Since LOX-1 is expressed in mouse exudate peritoneal macrophages [36], LOX-1 might be a receptor in P388D$_1$ macrophages responsible for endocytosis of MG-BSA. Similarly, GA-BSA but not MG-BSA, is recognized by SR-A as an active ligand [4]. Although protein modification by MG or glycolaldehyde is known to generate several structures such as N$^{\varepsilon}$-(carboxyethyl)lysine [37], imidazolone [38] and some other AGE-structures, the key structure critical for the interaction with LOX-1 has to be determined by future

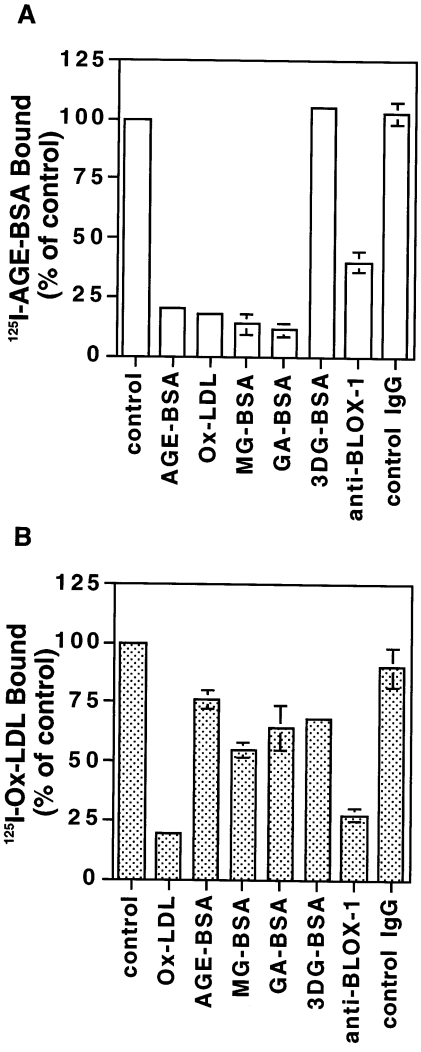

Fig. 3. Cross-competition between Ox-LDL and AGE-BSA. BLOX-1-CHO cells were incubated for 90 min at 4°C with 5 μg/ml of [^{125}I]AGE-BSA (A) or [^{125}I]Ox-LDL (B) in the absence or presence of 0.25 mg/ml of unlabeled ligands, 30 μg/ml of anti-BLOX-1 antibody, or 30 μg/ml of non-immune IgG. After the incubation, the cell-bound radioactivity was determined. Data are representatives of three separate experiments with duplicate wells.

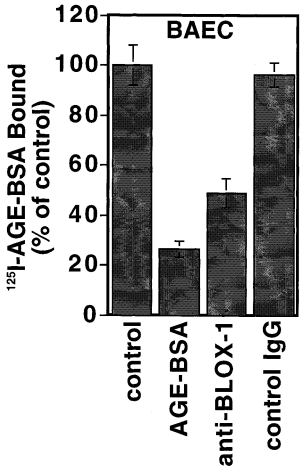

Fig. 4. Effects of anti-BLOX-1 antibody on binding of AGE-BSA to BAEC. BAEC were incubated for 90 min at 4°C with 5 μg/ml of [^{125}I]AGE-BSA in the absence or presence of 0.25 mg/ml of unlabeled AGE-BSA, 30 μg/ml of the anti-BLOX-1 antibody, or 30 μg/ml of non-immune IgG, followed by determination of cell-bound radioactivity. Data are representatives of three separate experiments with duplicate wells.

studies. In this connection, N^{ε}-(carboxymethyl)lysine was reported to serve as a ligand for RAGE [39].

The binding of Ox-LDL and AGE-BSA to BLOX-1-CHO cells is characterized by non-reciprocal cross-competition (Fig. 3) as previously reported in SR-A [40]. Recently, SR-BI, a receptor that binds to high density lipoproteins (HDL) and mediates selective uptake of HDL cholesteryl ester [41], was also demonstrated to serve as the AGE receptor [13]. Cross-competition experiments between AGE-BSA and HDL showed that binding of AGE-BSA or that of HDL to CHO cells overexpressing SR-BI (CHO-SR-BI) was not affected by the other ligand. One possible explanation for such non-reciprocal cross-competition is the presence of multiple ligand binding sites on SR-BI and LOX-1. To test this notion, site-directed mutagenesis of each scavenger receptor will be useful. It is also interesting that fates of Ox-LDL and AGE-BSA after binding to LOX-1 are distinct to each other; endocytic degradation occurs to Ox-LDL but not to AGE-BSA (Fig. 2B). Differential processing of the ligands was also observed in CHO-SR-BI cells; AGE-BSA but not HDL undergoes endocytic degradation after binding to SR-BI [13]. Further studies are needed to elucidate the possible relationship between the specific ligand binding sites on the scavenger receptors and differential intracellular sorting of the ligands.

The most important physiological implication of this study is that a substantial part of the specific binding of AGE-BSA to BAEC is mediated by LOX-1 (Fig. 4), indicating that LOX-1 might contribute to a major AGE receptor expressed on primary endothelial cells. It is generally accepted that RAGE is a representative AGE receptor in endothelial cells [5,20]. Intraperitoneal administration of a soluble form of RAGE (sRAGE) significantly suppressed atherosclerotic lesions accelerated under streptozotocin-induced diabetic conditions in apolipoprotein E-knockout mice [42]. The unique anti-atherogenic effect of sRAGE was explained by trapping plasma or tissue AGE ligands by sRAGE, thus inhibiting the interaction between AGE and RAGE. In this connection, the present study clearly showed that LOX-1 serves as another endothelial receptor for AGE ligands. It seems reasonable to assume that by forming a complex with AGE ligands, sRAGE could block AGE–LOX-1 interaction in addition to AGE–RAGE interaction. Therefore, the anti-atherogenic effect of sRAGE could be due, in part, to blockade of LOX-1 function. To get further insight into this issue, it is important to know whether the interaction of AGE ligands with LOX-1 could induce the cellular events that were reported to occur with the interaction of Ox-LDL with LOX-1 [26–28].

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