CD36-mediated endocytic uptake of advanced glycation end products (AGE) in mouse 3T3-L1 and human subcutaneous adipocytes

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Abstract Interaction of advanced glycation end products (AGE) with AGE receptors induces several cellular phenomena potentially relating to diabetic complications. We here show that AGE-modified bovine serum albumin (BSA) is endocytosed by adipocytes via CD36. Upon differentiation, 3T3-L1 and human subcutaneous adipose cells showed marked increases in endocytic uptake and subsequent degradation of [^{125}I]AGE-BSA, which were inhibited effectively by the anti-CD36 antibody. Ligand specificity of CD36 for modified BSAs was compared with that of LOX-1 and scavenger receptor class A. Effect of fucoidan on [^{125}I]AGE-BSA binding showed a sharp contrast to that on [^{125}I]-oxidized low density lipoprotein. These results implicate that CD36-mediated interaction of AGE-modified proteins with adipocytes might play a pathological role in obesity or insulin-resistance.

Key words: Adipocytes; Advanced glycation end product; CD36; Receptor for advanced glycation end product

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]. During AGE formation, several aldehydes such as 3-deoxyglucosone [2], glycolaldehyde (GA) [3], glyoxal (GO) [3] and methylglyoxal (MG) [2] are generated as intermediates and react mainly with lysine and arginine residues of proteins. Through modification of these basic amino acids, proteins decrease positive charges and increase their net negative charges [3]. AGE proteins are characterized physicochemically by fluorescence, browning, molecular cross-linking [1].

Accumulation of AGE in human tissues is thought to increase with aging and age-related disorders such as diabetic complications and atherosclerosis [4–7]. Cellular interactions with AGE proteins are known to induce several biological responses, not only endocytic uptake and degradation, but also induction of cytokines and growth factors, which linked to the development of diabetic vascular complications [8]. These responses are thought to be mediated by AGE receptors such as the receptor for AGE [9], a complex of OST-48/80K-H/galectin-3 [10,11], class A scavenger receptor (SR-A) [12,13], class B scavenger receptor (CD36 [14] and SR-BI [15]), and LOX-1 [16].

Recent studies revealed that adipose tissues are biologically active and dynamic, and play important endocrine and possibly immunological functions in vivo [17–22]. Our recent study using 3T3-L1-derived adipocytes demonstrated that oxidized low density lipoprotein (OxLDL) is endocytosed by these cells via CD36 [23]. Our previous study using Chinese hamster ovary (CHO) cells overexpressing human CD36 also suggests that CD36 serves as an AGE receptor [14]. Combined these results together, it seems reasonable to expect that AGE proteins are recognized and underwent endocytic degradation by adipocytes via CD36.

The present study using mouse 3T3-L1 and human subcutaneous adipocytes has demonstrated that this is the case, suggesting a potential role of AGE proteins in vivo in regulation of adipocyte functions via CD36.

2. Materials and methods

2.1. Materials

Na[^{125}I] (3.7 GBq/ml) was purchased from Amersham Pharmacia Biotech (Buckinghamshire, UK). Mouse anti-murine CD36 monoclonal antibody (clone 63) and anti-human CD36 antibody (FA6.152) were purchased from Cascade Bioscience (Winchester, MA, USA) and Immunotech (Luminy, France), respectively. Mouse IgA κ (TEPC 15) and IgG (MOPC21) were obtained from Sigma (St. Louis, MO, USA). All other chemicals were of the analytical grade commercially available.

2.2. Cell culture

Mouse 3T3-L1 cells (Health Science Research Resources Bank, Osaka, Japan) were plated and grown in a basal medium (Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum (FCS), 20 U/ml penicillin, and 20 μg/ml streptomycin). Cells were then differentiated by changing to a basal medium plus 10 μg/ml insulin, 0.25 μM dexamethasone (DEX), and 0.5 mM isobutylmethylxanthine (IBMX). After 48 h, the medium was replaced with basal medium containing 5 μg/ml insulin, and cells were maintained in this medium until use.

Human subcutaneous preadipocytes (Toyobo, Tokyo, Japan) were differentiated to adipocytes by changing to a DMEM/Ham's F12 medium containing 1% FCS, 5 μg/ml insulin, 10 μg/ml transferrin,

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Abbreviations: AGE, advanced glycation end product; AGE-BSA, advanced glycation end product-modified bovine serum albumin; LDL, low density lipoprotein; OxLDL, oxidized LDL; SR-A, scavenger receptor class A

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1 nM triiodo-L-thyronine, 0.25 μM DEX, and 0.5 mM IBMX, and the adipocytes used for the cellular assays were at 10 days after differentiation.

2.3. Preparation of AGE-bovine serum albumin (AGE-BSA), aldehyde-modified proteins and lipoproteins

AGE-BSA was prepared as described previously [24]. 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. The extent of lysine modification in AGE-BSA was 75.7% of total lysine residues. MG-, GA-, and GO-modified BSA were prepared as described previously [3]. AGE-BSA was labeled with [^{125}I] using Iodogen (Pierce Chemical Co.) to give a specific radioactivity of 450 cpm/ng [14]. LDL (d = 1.019–1.063 g/ml), OxLDL, and acetylated LDL (AcLDL) were prepared as described previously [25].

2.4. Cellular assays

Binding, cell-association and degradation of [^{125}I]AGE-BSA were performed as described previously [14]. For the binding assay, cells were incubated with 1.0–10 μg/ml [^{125}I]AGE-BSA at 4°C in 1.0 ml of DMEM containing 3% BSA for 1.5 h. Non-specific binding was measured in the presence of a 20-fold excess of AGE-BSA and subtracted from the data. For cell-association and degradation assays, cells were incubated with 5 μg/ml [^{125}I]AGE-BSA at 37°C in DMEM containing 3% BSA for 16 h. For inhibition assays, cells were incubated with or without various compounds (100 μg/ml) or antibodies (0.1–10 μg/ml of anti-CD36 antibody clone 63 or control IgA for 3T3-L1 cells and 10 μg/ml of FA6.152 or control IgG for human adipocytes). Results are represented as the means ± S.D. (n = 3).

3. Results

3.1. Interaction of preadipocytes and adipocytes with [^{125}I]AGE-BSA

We first examined the interaction of 3T3-L1 cells with [^{125}I]AGE-BSA at 37°C. The specific cell-association markedly increased after differentiation to adipocytes at day 5 (Fig. 1A,B). The specific cell-association of the adipocytes exhibited a dose-dependent saturation pattern with a plateau at 1.6 μg/mg of cell protein and apparent K_d of 2.3 μg/ml (Fig. 1B). The cell-association was followed by subsequent endocytic degradation. The specific degradation of [^{125}I]AGE-BSA by adipocytes was similarly increased to reach a plateau at 300 ng/mg of cell protein and apparent K_d of 1.5 μg/ml (Fig. 1D). These results indicate that adipocytes have the ability to endocytose and degrade AGE proteins.

We next examined the cellular binding of [^{125}I]AGE-BSA to adipocytes at 4°C. The total binding of [^{125}I]AGE-BSA was effectively inhibited by excess amount of unlabeled AGE-BSA. The specific binding was saturable (Fig. 2) and Scatch-

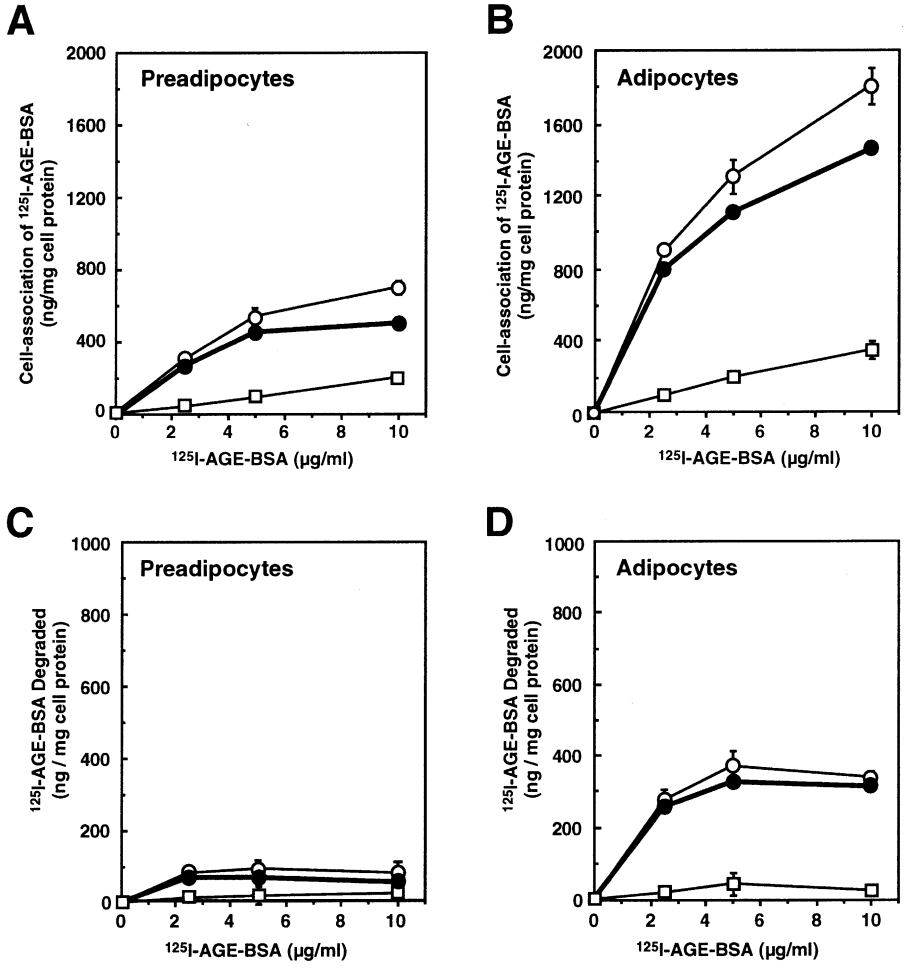

Fig. 1. Endocytic uptake and degradation of [^{125}I]AGE-BSA by 3T3-L1 adipocytes. 3T3-L1 cells of preadipocytes (day 0, panels A and C) and adipocytes (day 5, panels B and D) were incubated at 37°C for 16 h with various concentrations of [^{125}I]AGE-BSA in the presence (open square) or absence (open circle) of an excess of unlabeled AGE. Amounts of cell-associated [^{125}I]AGE-BSA (A,B) and those of degraded (C,D) were determined as described in Section 2. Specific cell-association and degradation (filled circle) were plotted after correcting for non-specific cell-association and degradation. Values are means ± S.D. (n = 3).

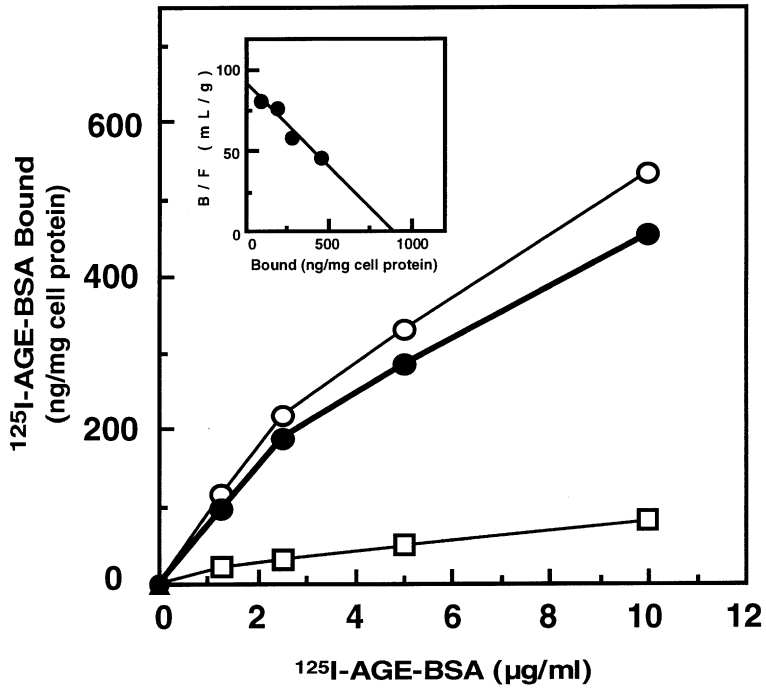

Fig. 2. Cellular binding of [^{125}I]AGE-BSA to 3T3-L1 adipocytes. 3T3-L1 adipocytes (day 5) were incubated at 4°C for 90 min with various concentrations of [^{125}I]AGE-BSA in the presence (open square) or absence (open circle) of excess unlabeled AGE-BSA. Specific binding (filled circle) was determined by subtracting non-specific binding from total binding. Inset: Scatchard analysis of the specific binding curve. *B*/*F* is bound/free.

ard analysis (Fig. 2, inset) revealed a single binding site with an apparent K_d of 7.3 μg/ml and maximal surface binding of 893 ng/mg of cell protein, indicating that differentiated 3T3-L1 adipocytes possess a high affinity binding site for [^{125}I]AGE-BSA. This K_d value of these adipocytes is the same order of magnitude with that of CD36-CHO cells (5.6 μg/ml) [14].

3.2. Anti-murine CD36 monoclonal antibody inhibits endocytic uptake of [^{125}I]AGE-BSA by adipocytes

To assess the relative contribution of CD36 to cellular binding and endocytic degradation of [^{125}I]AGE-BSA by 3T3-L1 adipocytes, we examined the effects of the anti-CD36 antibody on these phenomena. The cellular binding of [^{125}I]AGE-BSA was inhibited by the antibody in a dose-dependent manner and the inhibition level reached 80% of controls (Fig. 3A). Endocytic degradation was almost completely inhibited by the antibody (Fig. 3B), whereas non-immune IgA used as a control had no effect on the cellular binding and endocytic degradation. These results indicate that CD36 plays a major role in both cellular binding of AGE-BSA to and subsequent endocytic degradation by 3T3-L1 adipocytes.

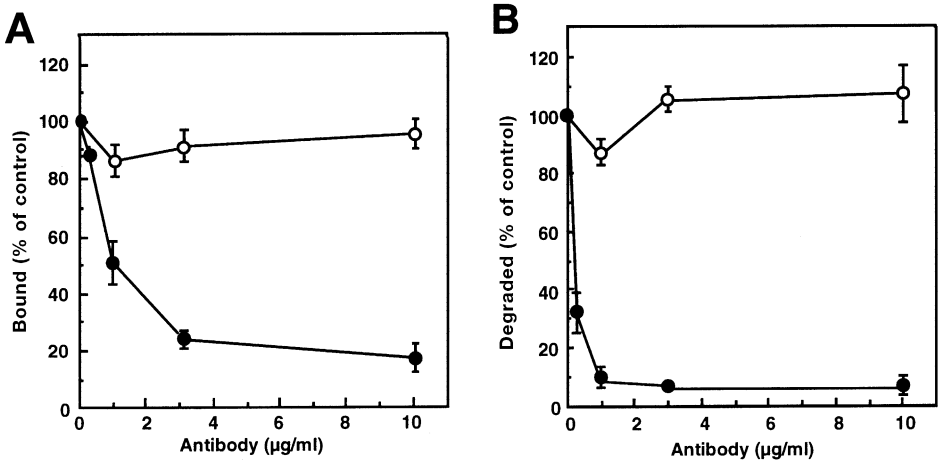

Fig. 3. Effects of anti-CD36 antibody on cellular binding of [^{125}I]AGE-BSA to and endocytic degradation by 3T3-L1 cells. 3T3-L1 adipocytes (day 8) were incubated with [^{125}I]AGE-BSA (5 μg/ml) at 4°C for 90 min (for binding experiments) or 37°C for 16 h (for degradation experiments) in the absence or presence of increased concentrations of the antibody (filled circle) or control IgA (open circle). The amounts of cell-bound [^{125}I]AGE-BSA (A) and those degraded by these cells (B) were determined. The values for specific 100% binding and degradation were 203 and 408 ng/mg of cell protein, respectively.

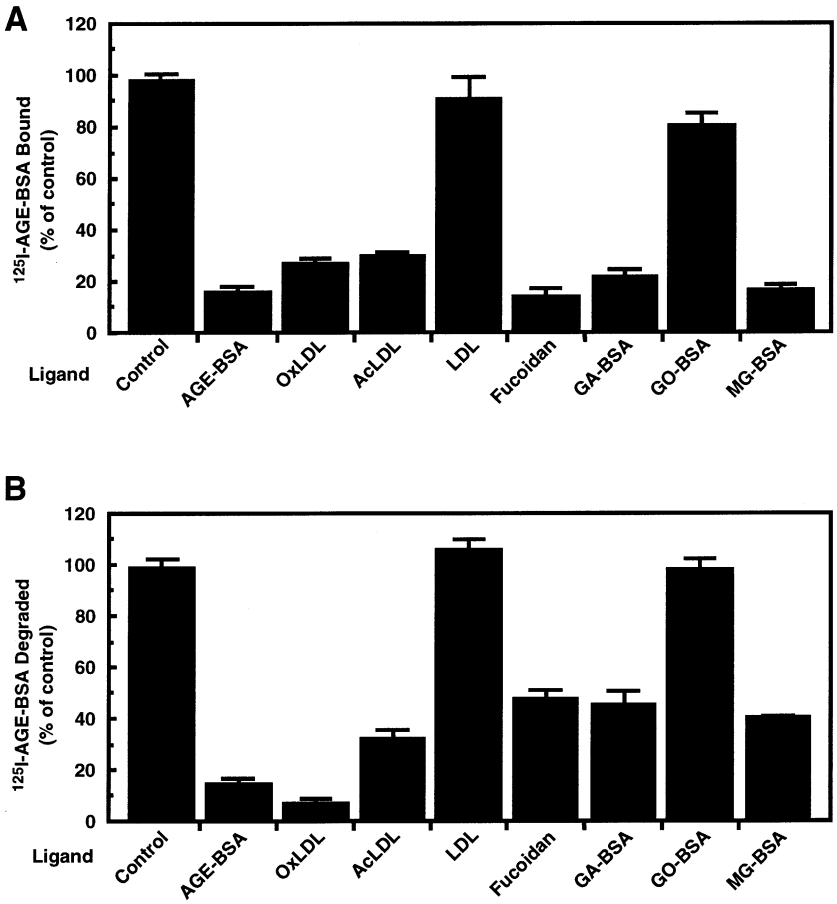

Fig. 4. Effects of several ligands on binding of [^{125}I]AGE-BSA to and endocytic degradation by 3T3-L1 adipocytes. 3T3-L1 adipocytes (day 8) were incubated at 4°C for 90 min or 37°C for 16 h with [^{125}I]AGE-BSA (5 μg/ml) in the presence or absence of 100 μg/ml test compounds, and the amounts of cell-bound [^{125}I]AGE-BSA (A), and those degraded by the cells (B) were determined. The values for 100% binding and degradation were 220 and 430 ng/mg of cell protein, respectively. Values are means ± S.D. ($n = 3$).

3.3. *Effects of AGE ligands and modified LDLs on the cell-association with and endocytic degradation of [^{125}I]AGE-BSA by 3T3-L1 adipocytes*

To determine the ligand specificity of a receptor recognizing AGE-BSA in differentiated 3T3-L1 cells, several compounds were examined for their effects on the binding and endocytic degradation of [^{125}I]AGE-BSA by the adipocytes. The binding of [^{125}I]AGE-BSA was effectively (> 70%) inhibited by OxLDL, AcLDL, and unlabeled AGE-BSA (Fig. 4A). These ligands also inhibited effectively the degradation of [^{125}I]AGE-BSA by adipocytes (Fig. 4B). By contrast, LDL had no effect on the binding and degradation (Fig. 4A,B). Fucoidan, a polyanionic inhibitor for SR-A [26] inhibited the cellular binding and endocytic degradation of [^{125}I]AGE-BSA (85% and 50%, respectively). This finding is in contrast with our previous result that polyanionic compounds had no inhibitory effect on the endocytic uptake of OxLDL by differentiated 3T3-L1 cells [23].

Since it is generally accepted that several aldehydes such as 3-deoxyglucosone, GA, GO and MG [2,3] are generated as intermediates during the Maillard reaction and contribute to formation of AGE structures, we also examined whether BSA modified by aldehydes could serve as ligands for adipocytes. GA-BSA and MG-BSA inhibited the [^{125}I]AGE-BSA binding to adipocytes by 70%, whereas GO-BSA had no inhibitory effect on it (Fig. 4A). Although the extent of inhibition was somewhat weaker, inhibition patterns of these ligands for endocytic degradation of [^{125}I]AGE-BSA were similar to those of binding (Fig. 4B).

3.4. *Human subcutaneous adipocytes recognize and degrade [^{125}I]AGE-BSA via CD36*

We also examined the cellular interaction and response of human subcutaneous adipocytes with [^{125}I]AGE-BSA. The specific cell-association and degradation markedly increased after differentiation to adipocytes (Fig. 5A,B). In addition, binding and endocytic degradation were almost completely inhibited by excess of AGE-BSA and GA-BSA. OxLDL inhibited the binding and endocytic degradation, while LDL had no effects. Anti-human CD36 antibody FA6.152 completely inhibited these activities (Fig. 5C,D). These results clearly indicate that CD36 plays a major role in both cellular binding of AGE-BSA to and subsequent endocytic degradation by human adipocytes as well.

4. Discussion

The present study has clarified that AGE proteins are recognized by 3T3-L1 and human subcutaneous primary adipocytes, and undergo effectively endocytic degradation by these cells. The anti-CD36 antibody inhibited > 80% of the specific binding and > 95% of the specific degradation of AGE-BSA

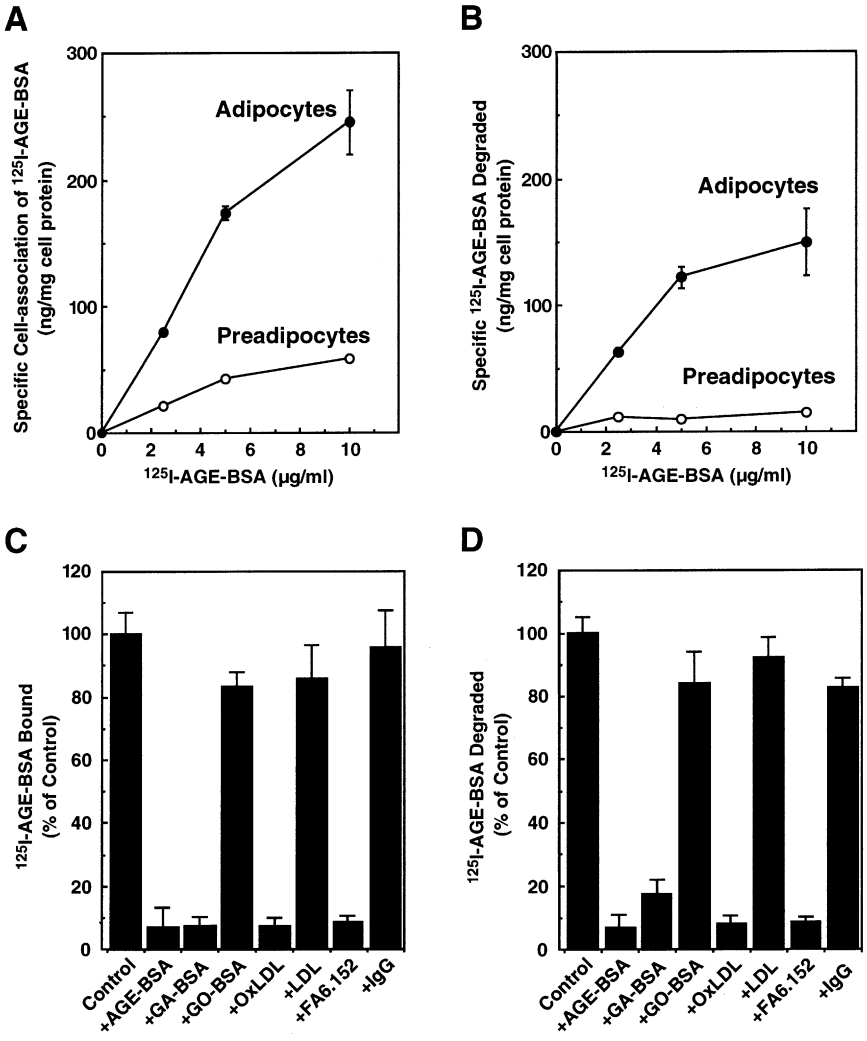

Fig. 5. Endocytic uptake and degradation of [^{125}I]AGE-BSA by human subcutaneous adipocytes. Human subcutaneous preadipocytes (open circle) and adipocytes (filled circle) were incubated at 37°C for 16 h with various concentrations of [^{125}I]AGE-BSA in the presence or absence of excess amount of unlabeled AGE. Specific amounts of cell-associated [^{125}I]AGE-BSA (A) and those of the degraded (B) were plotted after subtracting non-specific cell-association and degradation. Adipocytes were incubated at 4°C for 90 min or 37°C for 16 h with [^{125}I]AGE-BSA (5 μg/ml) in the presence or absence of 100 μg/ml test compounds and 10 μg/ml antibodies, and then the amounts of cell-bound [^{125}I]AGE-BSA (C), and those degraded by the cells (D) were determined. The values for specific 100% binding and degradation were 170 and 180 ng/mg of cell protein, respectively. Values are means ± S.D. ($n = 3$).

by these cells. It is highly likely, therefore, that CD36 plays a major role in interaction of AGE-ligands with adipocytes.

Our previously study using CD36-overexpressed CHO cells clarified that CD36 serves as an AGE receptor [14]. The present study provides a novel information that adipocytes also take up and degrade AGE ligands via CD36. MG-BSA and GA-BSA but not GO-BSA exhibited ligands as effective as AGE-BSA did. This ligand specificity is similar to that of LOX-1 [16], but different from that of SR-A [3]. N^{ε}-(carboxymethyl) lysine (CML) contents were high in GO-BSA, but low in glucose-derived, GA-, and MG-BSA [3]. It is likely that the CML structure does not serve as a signal for the CD36 receptor recognition. Cellular uptake and degradation of [^{125}I]AGE-BSA were inhibited by OxLDL. Polyanionic compound fucoidan inhibited effectively the cellular binding of AGE-BSA to 3T3-L1 adipocytes (Fig. 4A). The latter finding, however, is a sharp contrast to our previous observation that the fucoidan had no effect on [^{125}I]OxLDL binding to 3T3-L1 adipocytes [23]. These results suggest that the binding domain of CD36 for AGE ligands shares with that for OxLDL, but the two binding domains are not identical with the respect of fucoidan binding site. If substantial amount of AGE-BSA and OxLDL coexist in vivo, these results suggest that the potential competition of both ligands may inhibit their clearance by endocytic uptake and degradation in adipocyte to increase the severity and risk of AGE-induced diabetic complications and/or atherogenesis, as discussed later.

Adipose tissues are currently thought to be a biologically active and dynamic tissue playing a major endocrine and possibly immunological role [17–22]. In the present study, we showed that adipocytes endocytosed and lysosomally degraded AGE-BSA. This phenomenon could be potentially related to pathophysiological functions of adipocytes.

In vivo significance of AGE has mainly been examined from the AGE structure(s) expressed in vivo and AGE receptors, through which AGE proteins are believed to elicit several biological phenomena in monocytes/macrophages [27,28], endothelial cells [29] and mesangial cells [30]. In macrophages,

AGE proteins stimulate the production of cytokines such as tumor necrosis factor (TNF)-α [28], and up-regulate the expression of scavenger receptors through activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) [31]. Adipocytes secrete various cytokines, including TNF-α [19], resistin [20] and plasminogen activator inhibitor-1 [21], which are closely associated with occurrence of insulin-resistance and/or atherosclerosis. PPAR-γ also regulates the metabolism of lipid and glucose [32]. Therefore, it would be an interesting issue to determine whether AGE ligands could stimulate the cytokine production and lipid accumulation in adipocytes in vitro, and elucidate the correlation between the plasma level of AGE proteins and adipocyte-derived cytokines in vivo.

Although paradoxical, the opposite way of interpretation of the present results could be that the endocytic activity of adipocytes for AGE-proteins and OxLDL [23] may relate to the clearance of these oxidative stress-induced denatured proteins from the circulation. There is accumulating evidence that plasma levels of AGE proteins positively correlate with the severity of diabetic complications and cardiovascular diseases [8]. Hepatic sinusoidal cells such as endothelial cells and Kupffer cells have been shown to serve as one of the major clearance sites for plasma AGE-BSA [33] and OxLDL [34]. It is possible therefore that CD36-mediated phagocytosis of AGE-BSA by adipocytes could be a physiological mechanism for reducing the severity and risk of AGE-induced diabetic complications and/or atherogenesis.

In summary, the present study demonstrated that CD36 is a key player in active endocytic uptakes by 3T3-L1 and human subcutaneous adipocytes of AGE ligands such as AGE proteins and proteins modified by GA and MG. There has been no report on a functional link between AGE accumulation in adipocytes and the pathogenesis of diabetes or diabetic complications. Our present study may provide insights into a potential role of AGE proteins in regulation of adipocyte functions via CD36. Further studies are required to determine what amount of AGE proteins taken up by adipocytes through CD36 could contribute to AGE-induced pathological states such as diabetic complications and atherosclerosis.

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