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Review

Advanced Glycation End Products (AGE) Inhibit Scavenger Receptor Class B type I-Mediated Reverse Cholesterol Transport: a New Crossroad of AGE to Cholesterol Metabolism

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Advanced glycation end products (AGE) -modified proteins behave as active ligands for several receptors belonging to the scavenger receptor family. Scavenger receptor class B type I (SR-BI) was identified as the first high density lipoprotein (HDL) receptor that mediates selective uptake of HDL-cholesteryl esters (HDL-CE). This study investigated whether AGE proteins serve as ligands for SR-BI and affect SR-BI-mediated cholesterol transport using Chinese hamster ovary (CHO) cells overexpressing hamster SR-BI (CHO-SR-BI cells). [^{125}I] AGE-bovine serum albumin (AGE-BSA) underwent active endocytosis and subsequent lysosomal degradation by CHO-SR-BI cells, indicating that SR-BI serves as an AGE receptor. SR-BI-mediated selective uptake of HDL-CE by CHO-SR-BI cells was efficiently inhibited by AGE-BSA although AGE-BSA had no effect on HDL binding to CHO-SR-BI cells. In addition, AGE-BSA significantly inhibited the efflux of [^{3}H] cholesterol from CHO-SR-BI cells to HDL. These findings suggest the possibility that AGE proteins in the circulation interfere with the functions of SR-BI in reverse cholesterol transport by inhibiting the selective uptake of HDL-CE, as well as cholesterol efflux from peripheral cells to HDL, thereby accelerating diabetes-induced atherosclerosis. *J Atheroscler Thromb, 2003; 10: 1-6*.

Key words: HDL, Selective uptake, Cholesterol efflux, Diabetic dyslipidemia

Advanced glycation end products (AGE) and AGE receptors

In the Maillard reaction, proteins react with glucose leading to the formation of Schiff base and Amadori products. These early products are further converted to advanced glycation end products (AGE), which are characterized physicochemically by fluorescence, a brown color, and intra- or inter-molecular cross-linking, and biologically, by specific recognition by AGE receptors (1-4). Immunohistochemical and immunochemical analyses revealed the presence of AGE-modified proteins in human and animal tissues under various pathological conditions related to aging and age-related disorders such as diabetic macro- and microangiopathy (5, 6), atherosclerosis (7), Alzheimer's disease (8, 9) and various types of amyloidosis characterized by the deposition of abnormal amyloid fibril proteins (10). AGE proteins are reported to induce various

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Abbreviations: AGE (s), advanced glycation end products; BSA, bovine serum albumin; CML, N^{ε}-(carboxymethyl) lysine; LDL, low density lipoprotein; HDL, high density lipoprotein; Ox-LDL, oxidized LDL; acetyl-LDL, acetylated LDL; CE, cholesteryl ester; RAGE; Receptor for AGE; SR-A, scavenger receptor class AI/AII; SR-BI, scavenger receptor class B type I; PBS, phosphate-buffered saline; CHO, Chinese hamster ovary.

cellular events in vascular wall cells and other cells. It is possible that the interaction of AGE proteins with AGE receptors modulates the above disease processes.

So far, several AGE receptors have been identified (4, 11-14). The first identified AGE receptor was the receptor for AGE (RAGE) that was originally purified as a 35-kDa protein from bovine lung endothelial cells belonging to the immunoglobulin superfamily (11, 12). Subsequently, two AGE-binding proteins of 60- and 90-kDa (called p60 and p90) were purified from rat liver (13). Further studies identified galectin-3, a lectin-like protein with a high binding affinity for galactose-containing glycoproteins, as a component of p90 (14). We demonstrated that the macrophage scavenger receptor class AI/AII (SR-A), which is the first identified member of the scavenger receptor family (15, 16), serves as an AGE receptor using Chinese hamster ovary (CHO) cells overexpressing bovine SR-A (17). Consistent with this result, peritoneal macrophages obtained from SR-A knockout mice exhibited reduced endocytic uptake of AGE-BSA compared to wild-type littermates (18). Furthermore, we discovered that CD36, a member of the class B scavenger receptor family, also serves as an AGE receptor (19). More recently, lectin-like oxidized low density lipoprotein receptor-1 (LOX-1), another member of the scavenger receptor family, was also identified as a novel endothelial receptor for AGE (20).

SR-BI as a high density lipoprotein (HDL) receptor

Scavenger receptor class B type I (SR-BI) belongs to the growing CD36 family found in various animals such as dictyostelium (21, 22), drosophila (23), mouse (24), and human (25). SR-BI is a glycoprotein with a molecular weight of 82 kDa, which is highly expressed in steroidogenic tissues and the liver (26). SR-BI is also expressed in macrophages (27), astrocytes and vascular smooth muscle cells in the brain (28, 29). Unlike the LDL receptor-mediated delivery of LDL cholesterol to cells, the uptake of HDL-cholesteryl esters (HDL-CE) by steroidogenic tissues or the liver exceeds that of HDL apolipoproteins several-fold (30). This unique cholesterol transfer is currently known as the "selective uptake" of HDL-CE. SR-BI was originally identified as a scavenger receptor that recognized acetylated low density lipoprotein (acetyl-LDL) (31). Subsequently, Acton *et al*. showed that SR-BI also binds to HDL and mediates the selective uptake of HDL-CE (24), the first demonstration of SR-BI as an HDL receptor. Additional studies showed that SR-BI also mediates cholesterol efflux from cells to HDL (32). These studies have shown SR-BI to be an important key player in reverse cholesterol transport from cholesterol efflux from peripheral cells (27) to the selective hepatic uptake of HDL-CE for the excretion of cholesterol as bile acids.

Interaction of AGE with SR-BI

As an extension of our previous studies which demonstrated scavenger receptors such as SR-A and CD36 to be AGE receptors (17-19), we examined whether SR-BI could serve as an AGE receptor by using CHO cells overexpressing hamster SR-BI (CHO-SR-BI cells) (33). We determined the endocytic uptake of [^{125}I] AGE-BSA at 37°C by CHO-SR-BI cells. The cell-association of [^{125}I] AGE-BSA with CHO-SR-BI cells increased in a dose-dependent manner, which was suppressed to the basal level by excess unlabeled AGE-BSA (33), while the endocytic uptake of [^{125}I] AGE-BSA by mock CHO cells was negligible. Binding assays at 4°C exhibited the specific binding of [^{125}I] AGE-BSA to CHO-SR-BI cells with an apparent K_d = 8.3 μg/ml and a maximal binding of 85.7 ng/mg cell protein, indicating that SR-BI recognizes AGE-BSA as a ligand (33).

We next examined the cross-competition between HDL and AGE-BSA, in which modified LDLs such as oxidized LDL (Ox-LDL) and acetyl-LDL were also tested as competitors. The cellular binding of [^{125}I] AGE-BSA to CHO-SR-BI cells was efficiently inhibited by unlabeled AGE-BSA as well as Ox-LDL and acetyl-LDL (> 60%), whereas LDL and HDL had little inhibitory effect (< 20%). The cellular binding of [^{125}I] HDL to these cells was effectively suppressed by unlabeled HDL (> 60%), whereas AGE-BSA had little effect (< 15%). These results suggest that the ligand-binding site on SR-BI for AGE-BSA is different from that for HDL. Moreover, it is likely that AGE-BSA shares a common ligand-binding site on SR-BI with Ox-LDL and acetyl-LDL.

AGE-BSA modulates SR-BI-mediated cholesterol transfer

We next examined the effect of AGE-BSA on the selective uptake of HDL-CE by CHO-SR-BI cells. HDL apolipoproteins and HDL-CE were labeled with [^{125}I] and [^{3}H]cholesteryl oleoyl ether, respectively. Selective HDL-CE uptake was calculated by subtracting [^{125}I] uptake from [^{3}H] uptake, under which it was effectively inhibited by unlabeled HDL by more than 85% (Fig. 1). To our surprise, the selective uptake of HDL-CE was suppressed by AGE-BSA by more than 90%, whereas non-glycated BSA had no effect. It is interesting to note that the inhibitory activity of AGE-BSA (IC_{50} < 10 μg/ml) was much higher than that of unlabeled HDL (IC_{50} = 60 μg/ml) (Fig. 1). Suppression of the selective uptake of HDL-CE by AGE-BSA was also observed in HepG2 cells as a model of human hepatocytes (33), suggesting that plasma AGE proteins could inhibit the selective hepatic uptake of HDL-CE.

Finally, we tested the effect of AGE-BSA on SR-BI-mediated cholesterol efflux from CHO-SR-BI cells to HDL. CHO-SR-BI cells were labeled with [^{3}H] cholesterol and further incubated with 50 μg/ml of HDL in the presence of AGE-BSA. CHO-SR-BI cells showed a 2.5-fold increase in the released [^{3}H] cholesterol from cells to the medium compared with CHO-mock cells (33). The cholesterol

efflux from CHO-SR-BI cells was efficiently inhibited by AGE-BSA whereas AGE-BSA had no effect on that from mock cells, implying that AGE-BSA might inhibit SR-BI-mediated cholesterol efflux from cells (33).

The mechanism for selective uptake of HDL-CE and the role of AGE

The precise mechanism for the selective cellular uptake of HDL-CE mediated by SR-BI is still unclear. Williams and coworkers proposed an interesting model suggesting that SR-BI forms a hydrophobic channel between HDL particles and the cell membrane along which HDL-CE migrates in a CE gradient-dependent manner (34). This model allows speculation that AGE-BSA binding to SR-BI interferes with the formation of this channel rather than inhibiting the HDL binding to SR-BI (Fig. 2). A recent report by Silver *et al*. (35) proposed a novel mechanism of selective HDL-CE uptake; after binding of HDL to SR-BI, HDL particles undergo endocytosis followed by resecretion without lysosomal degradation during which HDL-CE is selectively transferred to cells. In this model, the binding of AGE-BSA to SR-BI could affect this intracellular processing of HDL.

Diversity of AGE proteins and their ligand activities

For a series of experiments (17-20, 33), we used an AGE-BSA sample prepared by incubating 2 g BSA with 1.6 M glucose for 40 weeks at 37°C in 10 ml phosphate-buffered saline. In other laboratories, AGE proteins are prepared under much milder conditions (11-14, 36). We recently found that AGE-BSA samples prepared following the protocols of other laboratories did not show the ligand activity for the scavenger receptors although these protocols could produce N^{ε}-(carboxymethy) lysine (CML), a major immunological epitope of AGE (Horiuchi S. *et al*. unpublished observations). Therefore, it is unlikely that CML serves as a ligand for the scavenger receptors although CML is known as the structure recognized by RAGE (36). Thus, the AGE structure (s) responsible for recognition by the scavenger receptors is still unknown. Our previous observations that the modification of LDL or BSA with glycolaldehyde generates an active ligand for SR-A (37, 38) could be one clue to the identification of such critical AGE structure (s).

Pathophysiological implications and future directions

Our recent findings on SR-BI and AGE (33) may provide some clues to better understanding of the molecular basis for diabetic dyslipidemia and diabetes-induced atherosclerosis. AGE proteins in the circulation might interfere with the functions of SR-BI in reverse cholesterol transport by suppressing the selective uptake of HDL-CE by liver and cholesterol efflux from peripheral cells to HDL (Fig. 3). However, it is currently unclear whether the AGE-protein-induced modulation of SR-BI functions observed *in vitro* is relevant to the pathophysiology of diabetic dyslipidemia *in vivo*. For example, one can argue that if AGE proteins inhibit the selective hepatic uptake of HDL-CE, the plasma levels of HDL cholesterol would be subsequently increased. However, in fact, it is well known that diabetic patients tend to have lower levels of HDL

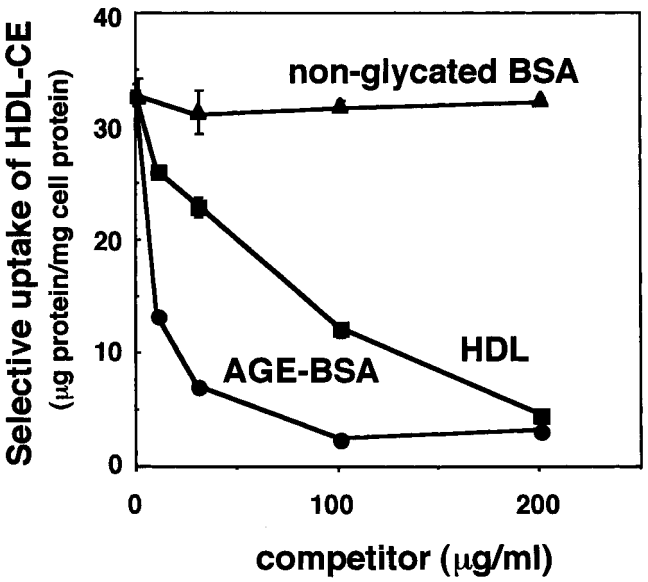

Fig. 1. AGE-BSA suppresses the selective uptake of HDL-CE by CHO-SR-BI cells. CHO-SR-BI cells were incubated at 37°C for 5 h with 10 μg/ml HDL that had been doubly labeled with [^{125}I] and [^{3}H] cholesteryl oleoyl ether in the presence or absence of the increasing concentrations of unlabeled HDL, AGE-BSA, or non-glycated BSA. Selective uptake of HDL-CE was determined by subtracting [^{125}I] uptake from [^{3}H] uptake by CHO-SR-BI cells.

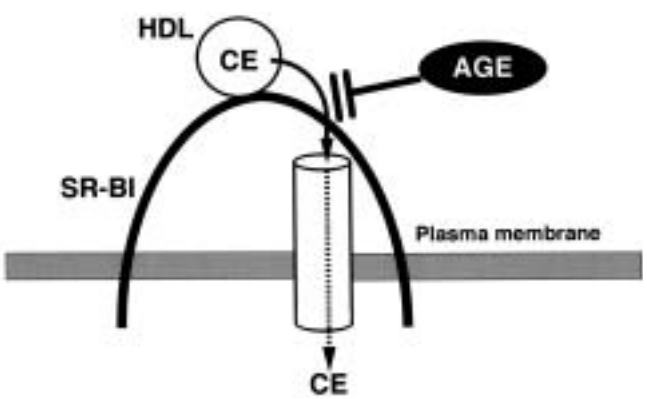

Fig. 2. Hypothetical mechanism for the selective uptake of HDL-CE and the role of AGE. SR-BI may form a hydrophobic lipid channel along which CE is transferred to cells. Binding of AGE-BSA to SR-BI might interfere with the formation of this hydrophobic channel.

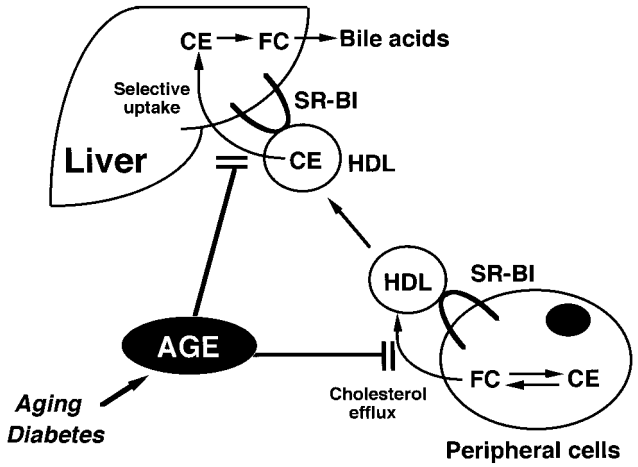

Fig. 3. Possible roles of AGE in reverse cholesterol transport. Our present observations of CHO cells overexpressing SR-BI suggest that AGE proteins bind to SR-BI and inhibit the functions of SR-BI such as cholesterol efflux from peripheral cells to HDL and the selective uptake of HDL-CE by hepatocytes for the excretion of cholesterol as bile acids, thereby suppressing reverse cholesterol transport. FC: free cholesterol, CE: cholesteryl esters.

cholesterol rather than higher levels. In order to clarify the missing link between our *in vitro* findings and the common clinical finding, further studies are needed, particularly using appropriate animal models.

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