Histamine Inhibits Advanced Glycation End Products-Induced Adhesion Molecule Expression on Human Monocytes

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ABSTRACT

Advanced glycation end products (AGEs) are modifications of proteins/lipids that become nonenzymatically glycated after contact with aldose sugars. Among various subtypes of AGEs, glyceraldehyde-derived AGE (AGE-2) and glycolaldehyde-derived AGE (AGE-3) are suggested to play roles in inflammation in diabetic patients. Because of the engagement of intercellular adhesion molecule (ICAM)-1, B7.1, B7.2, and CD40 on monocytes with their ligands on T cells plays roles in cytokine production, we examined the effects of AGE-2 and AGE-3 on the expression of adhesion molecules and cytokine production in human peripheral blood mononuclear cells (PBMC) and their modulation by histamine in the present study. AGE-2 and AGE-3 induced the expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes and the production of interferon-γ in PBMC. Histamine concentration-dependently inhibited the action of AGE-2 and AGE-3. The effects of histamine were antagonized by an H2 receptor antagonist, famotidine, and mimicked by H2/H4 receptor agonists dimaprit and 4-methylhistamine. Histamine induced cAMP production in the presence and absence of AGE-2 and AGE-3. The effects of histamine were reversed by a protein kinase A (PKA) inhibitor, N-[2-(4-bromocinnamylamino)ethyl]-5-isoquinoline (H89), and mimicked by a dibutylryl cAMP and an adenylyl cyclase activator, forskolin. These results as a whole indicated that histamine inhibited the AGE-2- and AGE-3-induced adhesion molecule expression and cytokine production via H2 receptors and the cAMP/PKA pathway.

AGEs are products of the nonenzymatic glycation/oxidation of proteins/lipids that accumulate during natural aging and are also greatly augmented in disorders such as diabetes, renal failure, and Alzheimer’s disease (Schmidt et al., 1994; Brownlee, 1995; Takedo et al., 1996). AGEs are also implicated in the pathogenesis of atherosclerotic vascular disease of diabetic etiology (Takeuchi and Yamagishi, 2004). Direct immunochemical evidence for the existence of four distinct AGE structures, including AGE-2, AGE-3, AGE-4, and AGE-5, was identified, within the AGE-modified proteins and peptides (Takeuchi and Yamagishi, 2004). Among various subtypes of AGE, toxic AGE structures, AGE-2 and AGE-3, are the main structures of AGEs that are detectable in the serum of diabetic patients (Takeuchi and Yamagishi, 2004). AGE-2 is reported to induce diabetic microangiopathy (Takeuchi et al., 2000). AGE-2 and AGE-3 also have diverse biological activities on vascular wall cells, mesangial cells, Schwann cells, malignant melanoma cells, and cortical neurons (Okamoto et al., 2002; Yamagishi and Imaizumi, 2005). AGEs and the receptor for AGEs (RAGE) are detected in atherosclerotic plaque of diabetic patients (Cuccurullo et al., 2006). The stimulation of RAGE induces plaque rupture in diabetic patients. In vitro work has shown the involvement of RAGE, leading to oxidative stress and vascular damage, particularly in atherosclerosis (Vlasisara and Palace, 2002) and in diabetes (Ruderman et al., 1992).

Microinflammation is a common major mechanism in the...
pathogenesis of diabetic vascular complications. It is reported that diabetes has greater infiltration of macrophages and T cells in atherosclerotic plaques (Burke et al., 2004). Activation of monocytes/macrophages and T cells induces the progression of inflammatory atherosclerotic plaques (Stoll and Bendzus, 2006). It has been found that the enhancement of ICAM-1, B7.1, B7.2, and CD40 expression on monocytes results in the activation of T cells (Durie et al., 1994; Ranger et al., 1996; Camacho et al., 2001). Therefore, the blockade of engagement of adhesion molecules by antibodies against ICAM-1, B7.1, B7.2, and CD40 reduced the production of IFN-γ by PBMC (Morichika et al., 2003; Takahashi et al., 2003). In a previous study, we found that AGE-2 and AGE-3 induced the expression of ICAM-1, B7.1, B7.2, and CD40 on monocytes and production of IFN-γ in human PBMC, but AGE-4 and AGE-5 had no effect (Takahashi et al., 2009). The effect of AGE-2 and AGE-3 on the production of IFN-γ was dependent on cell-to-cell interaction via engagement between ICAM-1, B7.1, B7.2, and CD40 on monocytes and their ligands on T cells, and the stimulation of RAGE on monocytes was involved in the actions of AGE-2 and AGE-3 (Takahashi et al., 2009).

Histamine has immunoregulatory properties because it modulates cytotoxic T-cell activity (Khan et al., 1989), natural killer cell activity (Hellingström et al., 1994), and cytokine production in PBMC (Dohlsen et al., 1987; Elenkov et al., 1998; van der Pouw Kraan et al., 1998). Histamine exerts its effects through the stimulation of H1, H2, H3, and H4 receptors (Elenkov et al., 1998; van der Pouw Kraan et al., 1998). In general, immunoregulatory effects of histamine depend on the stimulation of H2 receptors (Elenkov et al., 1998; van der Pouw Kraan et al., 1998; Hough, 2001). H2 receptor stimulation is coupled with the activation of adenylate cyclase and the AMP/PKA pathway in monocytes (Shayo et al., 1997). However, little is known about the effect of histamine on the AGEs-induced activation of monocytes. In the present study, we examined the effect of histamine on the expressions of ICAM-1, B7.1, B7.2, and CD40 and the production of IFN-γ induced by AGE-2 and AGE-3.

Materials and Methods

Reagents and Drugs. Recombinant human IL-18 was purchased from Medical and Biological Laboratories (Nagoya, Japan). Histamine dihydrochloride was purchased from Nacalai Tesque (Kyoto, Japan). Dimaprit dihydrochloride and 4-methylhistamine dihydrochloride (4-MH) were gifts from Drs. W. A. M. Duncan and D. J. Durant (The Research Institute, Smith Kline and French Laboratories, Welwyn Garden City, Hertfordshire, UK). d-Chlorpheniramine maleate, ranitidine, and famotidine were provided by Yoshitomi Pharmaceutical Co. Ltd. (Tokyo, Japan), Glaxo Japan (Tokyo, Japan), and Yamanouchi Pharmaceutical Co. Ltd. (Tokyo, Japan), respectively. Thioperamide hydrochloride was provided by Eisai Co. Ltd. (Tokyo, Japan). AGE-modified bovine serum albumin (BSA) (Sigma-Aldrich, St. Louis, MO) was prepared as described previously (Takeuchi et al., 2000; Takahashi et al., 2009). In brief, each protein was incubated under sterile conditions with glyceraldehyde-3-phosphate (AGE-2) (Sigma-Aldrich) or glycolaldehyde (AGE-3) (Sigma-Aldrich) in 0.2 M phosphate buffer, pH 7.4, at 37°C for 7 days. AGE-BSA was dialyzed for 2 days at 4°C. The endotoxin concentration of AGEs at 100 μg/ml described above was measured at SRL (Okayama, Japan) and was found to be 1.2 pg/ml. AGE-specific fluorescence was measured at 450 nm after excitation at 390 nm with a fluorescence spectrophotometer (Hitachi, Tokyo, Japan). db-cAMP and forskolin were purchased from Wako Pure Chemicals (Tokyo, Japan). H89 was purchased from Sigma-Aldrich. For flow cytometric analysis, fluorescein isothiocyanate (FITC)-conjugated mouse IgG1 monoclonal antibody (mAb) against ICAM-1/CD54 and phycoerythrin-conjugated anti-CD14 mAb were purchased from BD Biosciences (San Diego, CA), and FITC-conjugated IgG1, as an isotype-matched control, was obtained from Sigma-Aldrich.

Fig. 1. Effects of histamine on the AGE-2- and AGE-3-induced expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes and production of IFN-γ in PBMC. PBMC at 1 × 10⁶ cells/ml were incubated with AGE-2 (A) and AGE-3 (B) at 100 μg/ml and histamine at increasing concentrations from 0.1 to 100 μM for 24 h. The expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes were determined by flow cytometry. FITC-conjugated IgG1 was used as an isotype-matched control Ab. IFN-γ concentration in conditioned media was determined by ELISA. Filled circles (●) represent the effect of histamine on the adhesion molecule expression and cytokine production in the presence of AGE-2 and AGE-3. Open circles (○) represent the effect of histamine in the absence of AGE-2 and AGE-3. The results are expressed as the means ± S.E.M. of five donors with triplicate determinations. **, P < 0.01 compared with the value for AGE-2 and AGE-3. ##, P < 0.01 compared with the value for medium alone. When an error bar was within a symbol, the bar was omitted.
Isolation of PBMC and Monocytes. Normal human PBMC were obtained from 10 healthy volunteers after acquiring institutional review board approval (Okayama University Institutional Review Board 106). Twenty to 50 ml of peripheral blood was withdrawn from a forearm vein, and PBMC were prepared from buffy coat as described previously (Takahashi et al., 2003). When monocytes were isolated from PBMC, counterflow centrifugal elutriation was used for separation as described previously (Takahashi et al., 2003). The PBMC and monocytes were then suspended at a final concentration of 1 × 10^6 cells/ml in the medium as described previously (Takahashi et al., 2003).

Flow Cytometric Analysis. Changes in the expression of human leukocyte antigens ICAM-1, B7.1, B7.2, and CD40 on monocytes were examined by multicolor flow cytometry using a combination of anti-CD14 Ab with anti-ICAM-1, anti-B7.1, anti-B7.2, or anti-CD40 Ab. PBMC at 1 × 10^6 cells/ml were incubated for 24 h. Cultured cells at 5 × 10^6 cells/ml were prepared for flow cytometric analysis as described previously (Takahashi et al., 2003) and analyzed with an FACSCalibur flow cytometer (BD Biosciences, San Jose, CA). The data were processed using the CellQuest program (BD Biosciences).

Cytokine Assay. PBMC at 1 × 10^6 cells/ml were used to analyze IFN-γ production. After culturing for 24 h at 37°C in a 5% CO2/air mixture, cell-free supernatant was assayed for IFN-γ protein by enzyme-linked immunosorbent assay (ELISA) using the multiple Abs sandwich principle (R&D Systems, Minneapolis, MN). The detection limit of ELISA for IFN-γ was 10 pg/ml.

Proliferation Assay. PBMC were treated with various conditions. Cultures were incubated for 24 h, during which they were pulsed with [3H]thymidine (3 Ci/well) for the final 16 h. Cells were then divided into 96-well microplates, 200 μl/well, resulting in 1 μCi of [3H]thymidine per well and harvested by the Micro-Mate 196 cell harvester (PerkinElmer Life and Analytical Sciences, Boston, MA). Thymidine incorporation was measured by a beta-counter (Matrix 9600; PerkinElmer Life and Analytical Sciences).

Measurement of cAMP Production in Monocytes. Monocytes at 1 × 10^6 cells/ml were incubated at 37°C in a 5% CO2/air mixture under different conditions. When the effects of histamine receptor antagonists were examined, the antagonists were added to the media 30 min before histamine addition. AGEs and histamine were simultaneously added to the media. After 24 h, cells at 2 × 10^5 cells/200 μl/well were supplemented with trichloroacetic acid to a final concentration of 5% and 3-isobutyl-1-methylxanthine, an inhibitor of phosphodiesterase, at 100 μM and frozen at −80°C. Frozen samples were subsequently sonicated and assayed for cAMP using a cAMP enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions, for which no acetylation procedures were performed. The results are expressed as the means ± S.E.M. of triplicate findings from five donors.

Statistical Examination. Statistical significance was evaluated using analysis of variance followed by Dunnett’s test. A probability value of less than 0.05 was considered to indicate statistical significance. The results are expressed as the means ± S.E.M. of triplicate findings from five donors.

Results

Effects of Histamine on AGE-2- and AGE-3-Induced Expressions of ICAM-1, B7.1, B7.2, and CD40 on Monocytes; Production of IFN-γ; and Lymphocyte Proliferation in PBMC. In a previous study, to evaluate the binding of AGE subtypes to RAGE, we established an in vitro assay by using immobilized AGE subtypes and His-tagged sRAGE protein (Takahashi et al., 2009). AGE-2 and AGE-3 showed relatively high-affinity binding for sRAGE, whereas AGE-4 and AGE-5 showed moderate affinity for sRAGE. The proper incubation time and concentration of AGEs were determined according to Takahashi et al. (2009). AGE-2 and AGE-3 at 100 μg/ml significantly induced the expressions of ICAM-1, B7.1, B7.2, and CD40 and production of IFN-γ at 16 h and thereafter up to 24 and 48 h. As shown in Fig. 1, we observed the effects of histamine at concentrations ranging from 0.1 to 100 μM on the expression of ICAM-1, B7.1, B7.2,
and CD40, the production of IFN-γ in the presence (100 μg/ml) or absence of AGE-2 and AGE-3 at 24 h. Moreover, AGE-2 and AGE-3 significantly induced the lymphocyte proliferation at 16 h and thereafter up to 24, 48, and 72 h (Fig. 2). The effect of histamine on lymphocyte proliferation was determined at 24 h.

Histamine concentration-dependently inhibited the AGE-2- and AGE-3-induced expressions of ICAM-1, B7.1, B7.2, and CD40; production of IFN-γ; and lymphocyte proliferation. The IC₅₀ values for the inhibitory effect of histamine on the expressions of ICAM-1, B7.1, B7.2, and CD40, the production of IFN-γ, and the lymphocyte proliferation in the presence of AGE-2 were 1, 1, 1.5, 2, 0.8, and 0.8 μM, and those in the presence of AGE-3 were 1, 1, 1.7, 1.5, 0.8, and 0.8 μM, respectively. In the absence of AGE-2 and AGE-3, histamine induced the production of IFN-γ but had no effect on adhesion molecule expression and lymphocyte proliferation. The ED₅₀ value for the effect of histamine alone on the production of IFN-γ was 4 μM.

Involvement of H2 Receptor in the Actions of Histamine. To determine the histamine receptor subtypes involved in the effects of histamine on the expressions of ICAM-1, B7.1, B7.2, and CD40 and the production of IFN-γ in the presence of AGE-2 and AGE-3, the effects of an H1 receptor antagonist d-chlorpheniramine; an H2 receptor antagonist, famotidine; and an H3/4 receptor antagonist, thioperamide, at concentrations ranging from 0.1 to 100 μM in the presence or absence of AGE-2 and AGE-3 (A) and AGE-3 (B) at 100 μg/ml. The expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes were determined by flow cytometry. In addition, IFN-γ concentration was determined by ELISA. Filled circles (●) represent the effect of antagonists on histamine-inhibited adhesion molecule expression and cytokine production in the presence of AGE-2 and AGE-3. Open squares (□) represent the effect of antagonists in the presence of AGE-2 and AGE-3 without histamine stimulation. Open circles (○) represent the effect of antagonists on adhesion molecule expression cytokine production in the absence of histamine, AGE-2, and AGE-3. The results are expressed as the means ± S.E.M. of five donors with triplicate determinations. *, P < 0.05; **, P < 0.01 compared with the value for histamine. When an error bar was within a symbol, the bar was omitted.

As shown in Fig. 4, the effects of H2/H4 receptor agonists...
dimaprit and 4-MH (Parsons et al., 1977), at concentrations ranging from 0.1 to 100 μM, were determined in the presence of AGE-2 and AGE-3 at 100 μg/ml. Both dimaprit and 4-MH inhibited the expressions of ICAM-1, B7.1, B7.2, and CD40 and the production of IFN-γ in a concentration-dependent manner. The potency and efficacy of two agonists were quite similar to those of histamine in each response. Moreover, we found that an H1 agonist, 2-(2-pyridyl)ethylamine dihydrochloride (Durant et al., 1975), and an H3 agonist, (R)-α-methylhistamine dihydrochloride (Arrang et al., 1987), had no effect on the adhesion molecule expression and cytokine production induced by AGE-2 and AGE-3 (data not shown).

Effects of Histamine on the Production of cAMP in Monocytes in the Presence or Absence of AGE-2 and AGE-3. The effects of histamine at 100 μM on the production of intracellular cAMP in monocytes isolated from PBMC in the presence (100 μg/ml) or absence of AGE-2 and AGE-3 were determined (Fig. 5). Histamine induced the production of cAMP in monocytes with a peak 30 min after stimulation. The presence of AGE-2 and AGE-3 did not influence the production of cAMP induced by histamine. The H2 receptor antagonist famotidine at 100 μM inhibited the effect of histamine on the production of cAMP (Fig. 5). In addition, the H2/H4 receptor agonist dimaprit at 100 μM induced the production of cAMP at the corresponding value in the presence of histamine. The results are expressed as the means ± S.E.M. of five donors with triplicate determinations. **P < 0.01 compared with the value for AGE-2 or AGE-3 alone. When an error bar was within a symbol, the bar was omitted. ND, not detected.

Involvement of cAMP in the Action of Histamine. To investigate the involvement of the cAMP/PKA pathway in the action of histamine, the effects of a PKA inhibitor, H89, at concentrations ranging from 0.1 to 100 μM, on the action of histamine at 100 μM were determined (Fig. 6). In the absence of histamine, the PKA inhibitor had no effect on adhesion molecule expression and cytokine expression. H89 reversed the inhibitory effect of histamine on the expressions of ICAM-1, B7.1, B7.2, and CD40 and the production of IFN-γ in the presence of AGE-2 or AGE-3. As shown in Fig. 7, the effects of a membrane-permeable cAMP analog, dbcAMP, and an adenylate cyclase activator, forskolin, at concentrations ranging from 0.1 to 100 μM, on the expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes and the production of IFN-γ in PBMC were examined. Both dbcAMP and forskolin inhibited the AGE-2- and AGE-3-induced adhesion molecule expression and cytokine production in a concentration-dependent manner.

Effect of Addition of IL-18 on Modulatory Effects of Histamine on AGE-2- and AGE-3-Induced ICAM-1 Expressions on Monocytes. The addition of increasing concentrations of IL-18 to the culture medium at the start of incubation antagonized the inhibitory effect of histamine at
Discussion

It is reported that the AGE-BSA enhances dendritic cell-induced stimulation of lymphocyte proliferation and cytokine production (Ge et al., 2005). In contrast, histamine inhibits lymphocyte proliferation and cytokine production via H2 receptors (Nakane et al., 2004). However, little is known about the effect of histamine on the actions of AGE-2 and AGE-3 in human PBMC. In the present study, we clearly demonstrated that histamine inhibited the AGE-2- and AGE-3-induced expressions of ICAM-1, B7.1, B7.2, and CD40 on human monocytes; production of IFN-α-γ; and lymphocyte proliferation in PBMC (Figs. 1 and 2). The action of histamine was inhibited by the H2 antagonist famotidine but not the H1 antagonist d-chlorpheniramine and the H3/4 antagonist thioperamide (Fig. 3). The H2/H4 receptor agonists dimaprit and 4-MH mimicked the action of histamine (Fig. 4). Because the IC50 values of histamine and H2/H4 receptor agonists to prevent the up-regulation of adhesion molecule expression and cytokine production were consistent with the affinity of those agonists to typical H2 receptors (Johnson, 1982; Elenkov et al., 1998; Kohka et al., 2000; Takahashi et al., 2002; Morichika et al., 2003), it was concluded that the inhibitory effect of histamine was mediated by the stimulation of H2 receptors but not H1, H3, and H4 receptors.

As shown in Fig. 5, histamine induced the production of cAMP in monocytes via H2 receptor irrespective of the presence of AGE-2 or AGE-3. The findings that the PKA inhibitor H89 inhibited the action of histamine (Fig. 6) and that the cAMP analog dbcAMP and the adenylate cyclase activator forskolin mimicked the effect of histamine (Fig. 7) strongly suggested the involvement of the cAMP/PKA pathway in the action of histamine.

We observed a similar pattern of inhibitory effects of histamine on lipopolysaccharide (LPS)- and IL-18-induced activation of monocytes in human PBMC via H2 receptors (Takahashi et al., 2002; Morichika et al., 2003). IL-18 is reported to induce the expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes (Takahashi et al., 2002, 2003). Although AGE-2 and AGE-3 do not induce production of IL-18 in PBMC (Takahashi et al., 2009), histamine induces production of IL-18 via H2 receptor and the cAMP/PKA pathway in monocytes (Takahashi et al., 2006). Thus, there may be a common pathway triggered by LPS, IL-18, and AGEs that

Fig. 6. Effects of PKA inhibitor on the histamine-induced expressions of ICAM-1, B7.1, B7.2, and CD40 and production of IFN-γ. The effects of a PKA inhibitor, H89, at increasing concentrations from 0.1 to 100 μM, on the 100 μM histamine-induced inhibition of expressions of ICAM-1, B7.1, B7.2, and CD40 and production of IFN-γ in the presence of AGE-2 (A) and AGE-3 (B) at 100 μg/ml were determined. Filled circles (●) represent the effect of H89 on the histamine-induced inhibition of responses in the presence of AGE-2 and AGE-3. Open squares (○) represent those in the presence of AGE-2 and AGE-3 without histamine stimulation. Open circles (▲) represent the effect of H89 on the responses in the absence of both histamine and AGEs. The results are expressed as the means ± S.E.M. of triplicate findings from five donors. **P < 0.01 compared with the value in the presence of histamine and AGEs. When an error bar was within a symbol, the bar was omitted.

Fig. 7. Effects of forskolin and dbcAMP on AGEs-induced expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes and production of IFN-α-γ in PBMC. PBMC at 1 × 10^6/ml were incubated with a cAMP analog, dbcAMP (A), and an adenylate cyclase activator, forskolin (B), at increasing concentrations from 0.1 to 100 μM in the presence of AGE-2 and AGE-3 at 100 μg/ml for 24 h. Filled circles (●) represent the effects of dbcAMP or forskolin on AGE-2-induced responses, and open circles (○) represent the effects of dbcAMP or forskolin on the AGE-3-induced responses. The results are expressed as the means ± S.E.M. of five donors with triplicate determinations. **P < 0.01 compared with the value for AGE-2 or AGE-3 alone. When an error bar was within a symbol, the bar was omitted.
was regulated by the H2 receptors-cAMP/PKA system. Further work is necessary on this issue.

Although AGE-2 and AGE-3 do not induce production of IL-18 in PBMC (Takahashi et al., 2009), histamine induces production of IL-18 via H2 receptor and the cAMP/PKA pathway in monocytes (Takahashi et al., 2006). The amount of IL-18 production induced by histamine at 100 μM was 2.5 ng/ml. IL-18 is reported to induce the expressions of ICAM-1, B7.1, B7.2, and CD40 on monocytes (Takahashi et al., 2002, 2003). As shown in Fig. 8, the requirement of relatively higher concentration of exogenous IL-18 for reversing the inhibitory effect of histamine on AGE-2- and AGE-3-induced action may reflect the IL-18 concentration needed for the functional antagonism of histamine action on ICAM-1 expression. The regulatory mechanisms for ICAM-1 expression in the presence of plural stimuli should be clarified.

In the previous study, we found that AGE-2 and AGE-3 have higher affinity for RAGE than AGE-4 and AGE-5 by using an in vitro binding assay (Takahashi et al., 2009). AGE-2 and AGE-3, but not AGE-4 and AGE-5, induced the up-regulation of their receptor RAGE expression on the cell surface of monocytes. A NF-κB activation inhibitor, SN50, inhibits AGE-2- and AGE-3-induced adhesion molecule expressions and cytokine production (Takahashi et al., 2009), and the interaction of AGE and RAGE enhances the expression of RAGE through activation of NF-κB in monocytes (Li and Schmidt, 1997). However, histamine had no effect on the expression of RAGE in the presence and absence of AGE-2 and AGE-3 (data not shown). Thus, it might be possible that the downstream pathways of NF-κB activation leading to up-regulation of adhesion molecules and RAGE are probably differentially regulated by the cAMP-PKA system.

Histidine decarboxylase (HDC), which produces histamine from L-histidine, is detected in monocytes/macrophages located in the arterial intima in human atherosclerotic lesions (Higuchi et al., 2001). In a rat model of streptozotocin-induced diabetes mellitus, histamine levels are elevated in various tissues, including the aorta (Gill et al., 1990). Moreover, vascular smooth muscle cells express HDC after injury to endothelial cells (Sasaguri et al., 2005). The resultant production of histamine may regulate vascular contraction directly or indirectly via nitric oxide production (Tanimoto et al., 2007). In addition to the control of vascular contraction, the modulatory effects of histamine on microinflammation in atherosclerotic intima through the regulation of monocytes/macrophages are shown in the present study. In fact, AGEs have been demonstrated in atherosclerotic plaque, where macrophages with up-regulated RAGE are present (Cucurullo et al., 2006). Therefore, the regulatory action of histamine through the stimulation of H2 receptors may inhibit the macrophage-mediated events stimulated by AGE-2 and AGE-3, including the production of IFN-γ and adhesion molecule-dependent activation of T cells (Takahashi et al., 2009). Thus, locally produced histamine may exert inhibitory influence on the secretory response of macrophages and T-cell activation, leading to the reduction of atherosclerotic plaque formation. Such a possibility should be evaluated by an in vivo atherosclerotic model. It is reported that atherosclerotic lesions are reduced in HDC-knockout mice, compared with wild-type mice (Tanimoto et al., 2006). However, in HDC-knockout mice, the deficiency of granule formation and proteinases expression in mast cells is also observed (Ohtsu et al., 2002). Therefore, attention should be paid to obtaining a straightforward explanation for the phenotype of knockout mice.

It is reported that an H1 receptor antagonist, diphenhydramine, reduces the formation of intimal hyperplasia in a mouse model with endothelial injury; however, an H2 receptor antagonist, cimetidine, is ineffective (Miyazawa et al., 1998). Cimetidine inhibits neither the proliferation nor migration of mouse vascular smooth muscle cells stimulated by platelet-derived growth factor, whereas diphenhydramine significantly inhibited proliferation but did not inhibit migration (Miyazawa et al., 1998). Therefore, stimulation of H1 receptor may induce the proliferation of vascular smooth muscle cells, whereas H2 receptor stimulation may inhibit the activation of monocytes, leading to the prevention of atherosclerosis. Further study of the role of H1 and H2 receptor stimulation should be continued.

In conclusion, histamine inhibited the AGE-2- and AGE-3-induced expressions of ICAM-1, B7.1, B7.2, and CD40 and production of IFN-γ via H2 receptors and the cAMP/PKA pathway. Through the inhibition of toxic AGE-dependent responses in monocytes, the stimulation of H2 receptors may partially contribute to regulating the development of atherosclerotic plaques in diabetes.

Acknowledgments

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