SHORT COMMUNICATION

IgE Receptor-Mediated Mast-Cell Renin Release

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Renin is a newly discovered constituent of mast cells. Given that mast cells play a major role in IgE-mediated allergic hypersensitivity, we investigated whether activation of the high-affinity IgE receptor FcεRI elicits release of mast-cell renin. Cross-linking of FcεRI on the surface of mature bone marrow—derived mast cells elicited release of enzymatically active renin protein. The angiotensin I—forming activity of the renin protein was completely blocked by the selective renin inhibitor BILA 2157, which excludes formation of angiotensin I by proteases other than renin. FcεRI-mediated mast-cell renin release was inhibited by dexamethasone and potentiated by the proinflammatory mediator PGE$_2$. Furthermore, cross-linking of mast-cell FcεRI in *ex vivo* murine hearts passively sensitized with monoclonal anti-DNP IgE also resulted in mast-cell degranulation and overflow of renin. Our findings indicate that IgE-mediated allergic hypersensitivity provokes release of renin from both cultured and resident cardiac mast cells, a process likely to be exacerbated in a chronic inflammatory background. Given the widespread distribution of mast cells, and the presence of angiotensinogen and angiotensin-converting enzyme in many tissues, renin release in immediate hypersensitivity reactions could result in local angiotensin II generation and multiorgan dysfunctions. *(Am J Pathol 2014, 184: 376—381; http://dx.doi.org/10.1016/j.ajpath.2013.10.016)*

Mast cells (MCs) express and secrete active renin.[1–3] MCs are known to play a major role in IgE-mediated allergic reactions.[4,5] Whether immediate hypersensitivity can elicit MC renin release is a question of major basic and translational importance, given the ubiquitous presence of MCs[3,6,7] and the multiplicity of angiotensin-induced organ dysfunctions.[8] To address this question, we used murine bone marrow—derived MCs (BMMCs) and MCs in *ex vivo* murine hearts. Here, we report the novel finding that specific cross-linking of the high-affinity FcεRI receptor on the surface of BMMCs and heart MCs elicits the release of enzymatically active renin protein. This process is inhibited by glucocorticoids and is enhanced by PGE$_2$. Similarly, cross-linking of MC FcεRI in *ex vivo* murine hearts resulted in MC degranulation and overflow of renin.

Materials and Methods

Isolation of Murine BMMCs

BMMCs were cultured as described previously.[9] In brief, bone marrow was obtained from femurs and tibias of C57BL/6J mice euthanized by cervical dislocation under light CO$_2$ anesthesia as approved by the Weill Cornell Medical College Institutional Animal Care and Use Committee. Bone marrow cells were cultured in RPMI 1640 medium (Life Technologies, Carlsbad, CA) containing 10 U/mL antibiotics (penicillin—streptomycin), 10% heat-inactivated fetal calf serum, 55 μmol/L 2-mercaptoethanol, and 20 ng/mL each recombinant murine IL-3 and stem cell factor (SCF) (PeproTech, Rocky Hill, NJ). Bone marrow cells were counted and placed in culture at a cell density of 0.5×10^6 cells/mL. Cell medium was changed every 3 to 4 days, and nonadherent cells were transferred to a new flask. Mature BMMCs obtained after 4 weeks of culture stained positive for Toluidine Blue; moreover, >90% of cells expressed both c-Kit and FcεRI. All experiments were performed with BMMCs cultured for 4 to 7 weeks. Cells were plated on coverslips and incubated in 0.05% Toluidine Blue (Sigma-Aldrich, St. Louis, MO) for 10 minutes at 37°C. Cells were then fixed with 4% paraformaldehyde for 15 minutes at room temperature. Coverslips

were mounted on glass slides using VectaMount medium (Vector Laboratories, Burlingame, CA) and were examined under an Eclipse 80i microscope (Nikon Instruments, Melville, NY).

Flow Cytometry

To assess the expression of c-Kit and FcεRI on BMMC cell surface, aliquots of cells cultured for 5 weeks were centrifuged and incubated for 10 minutes with PBS (Sigma-Aldrich) containing 0.1% bovine serum albumin and purified rat anti-mouse CD16/CD32 (Fc Block; BD Biosciences, San Jose, CA) on ice. At the end of the incubation, fluorescein isothiocyanate−conjugated monoclonal anti-mouse FcεRI (eBioscience, San Diego, CA) and phycoerythrin-conjugated monoclonal anti-mouse CD117 (c-Kit; BD Biosciences) were added to the cells for 30 minutes on ice. After a PBS washing, labeled cells were analyzed with a BD LSR II flow cytometer (BD Biosciences).

Western Blotting

BMMCs were lysed using radioimmunoprecipitation assay buffer (Sigma-Aldrich). KNRK rat kidney cell lysate was purchased from Santa Cruz Biotechnology (Santa Cruz, CA). BMMC and KNRK samples for electrophoresis (50 μg/lane) and Western blotting were prepared as described previously.[10] Polyvinylidene difluoride membranes were probed with anti-mouse renin (Santa Cruz) at a dilution of 1:500. Anti-goat IgG horseradish peroxidase (HRP)−linked secondary antibody (EMD Millipore, Billerica, MA) was used at a 1:5000 dilution. Anti−β-actin HRP-conjugated antibody (Alpha Diagnostic International, San Antonio, TX) was used at a 1:30,000 dilution. Proteins of interest were detected using Immobilon Western chemiluminescent HRP substrate (EMD Millipore).

FcεRI-Mediated BMMC Degranulation

In brief, after 16 hours of sensitization with 0.125 μg/mL anti-DNP IgE (Sigma-Aldrich), 1×10^5 BMMCs per sample were washed and resuspended in Ringer's buffer (pH 7.4). Equal cell volumes were aliquoted in 96 wells and challenged with 10 ng/mL antigen [dinitrophenylated human serum albumin (DNP-HSA)] for 20 minutes at 37°C in the absence or presence of 1 μmol/L PGE$_2$ (R&D Systems, Minneapolis, MN). Other cells were preincubated with 2 nmol/L dexamethasone (Sigma-Aldrich) for 5 minutes before antigen challenge. When MC activators were used, cells were incubated with 1 μmol/L A23187 calcium ionophore, 300 μg/mL compound 48/80 (c48/80), or 1 mmol/L ATP (all from Sigma-Aldrich) for 20 minutes at 37°C. At the end of the incubation, samples were placed on ice and centrifuged at $300 \times g$ for 5 minutes. Supernatants were collected and used to measure the β-hexosaminidase (β-HEX) release. Cell pellets were lysed with 0.5% Triton X-100, and total lysates were used to determine total β-HEX content. β-HEX release was expressed as the percentage ratio between supernatant and total β-HEX (where total β-HEX is equal to the sum of β-HEX content in supernatant and total lysate).

Measurement of β-HEX

β-HEX was measured as described previously.[11] Samples of BMMC supernatants, total lysates, and coronary overflow (20 μL) were placed in 96-well plates. Substrate solution (50 μL; p-nitrophenyl-N-acetyl-β-D-glucosaminide, 1.3 mg/mL in 0.1 mol/L citrate buffer, pH 4.5) were added to each well and incubated for 90 minutes at 37°C. The reaction was stopped by adding 150 μL of 0.2 mol/L glycine (pH 10.7). Optical density was read at 405 nm on a spectrophotometric plate reader using SoftMax Pro version 4.8 (Molecular Devices, Sunnyvale, CA).

Measurement of Histamine

Histamine released from BMMCs was measured using an enzyme immunoassay kit, according to the manufacturer's
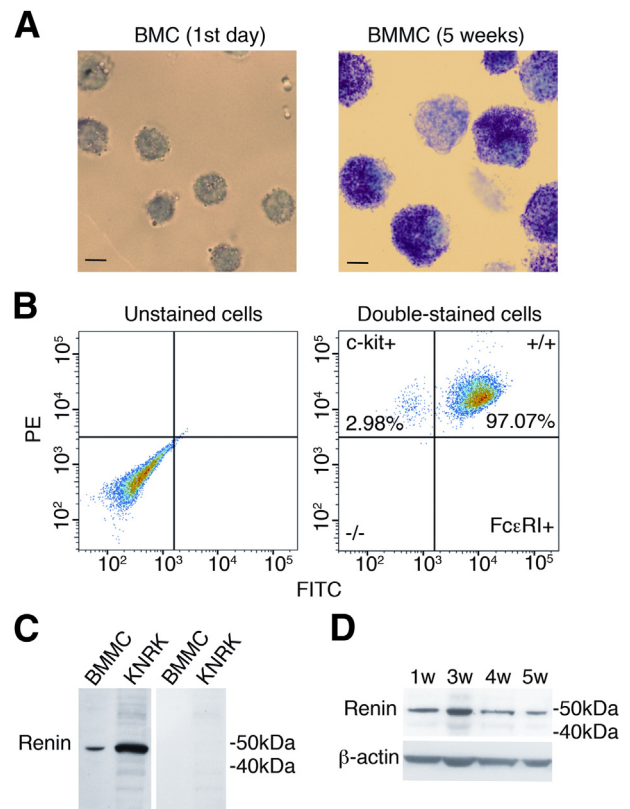

Figure 1 Granular staining and expression of c-Kit, FcεRI, and renin in BMMCs. **A:** Characteristic Toluidine Blue−stained murine bone marrow cells at isolation and differentiated BMMCs after 5 weeks in culture with IL-3 and SCF. **B:** Fluorescence-activated cell-sorting analysis shows c-Kit-PE and FcεRI−fluorescein isothiocyanate coexpression (>90%) on the BMMC surface after 5 weeks in culture. **C:** Representative Western blots with anti-mouse renin antibody show a renin-positive band in total protein lysate (50 μg/lane) of BMMCs (5-week culture) and KNRK rat kidney cells used as positive control (**left lanes**) and lack of immunoreactive bands after direct incubation of total BMMC and KNRK lysates with the secondary antibody (**right lanes**). **D:** Representative Western blots of total lysates isolated from BMMCs at 1, 3, 4, and 5 weeks (w) in culture. Scale bars: 5 μm (**A**). BMC, bone marrow cells; FITC, fluorescein isothiocyanate; PE, phycoerythrin.
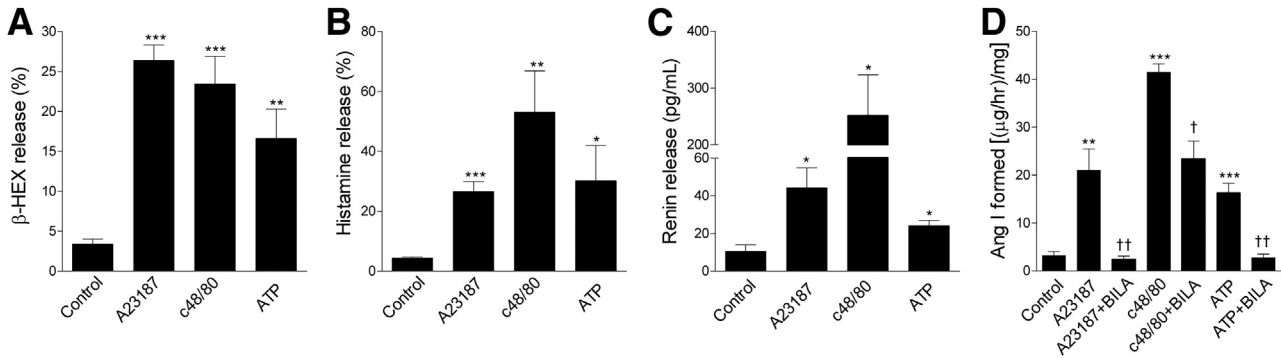
Figure 2   Classical MC activators elicit degranulation and release of histamine and renin from mature BMMCs. BMMCs were incubated for 20 minutes at 37°C with A23187 (1 μmol/L), c48/80 (300 μg/mL), or ATP (1 mmol/L). **A–C:** Release of β-HEX (**A**), histamine (**B**), and renin protein (**C**). Percentages represent the percent ratio between supernatant and total β-HEX or histamine. **D:** Renin activity as affected by the three MC activators in the absence or presence of the renin inhibitor BILA (100 nmol/L) was measured in BMMC supernatant in terms of angiotensin I (Ang I) formation (μg/hour per mg of total protein). Data are expressed as means ± SEM. Number of experiments (left to right): $n = 10, 7, 6$, and 10 (**A**); $n = 7, 14, 5$, and 6 (**B**); $n = 4, 5, 4$, and 7 (**C**); and $n = 6, 5, 8, 4, 3, 13$, and 6 (**D**). $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ versus control. $^{†}P < 0.01$, $^{††}P < 0.001$ versus absence of BILA.

instructions (Beckman Coulter, Brea, CA). In brief, after stimulation, supernatants and total lysates were collected from BMMCs as described above for the β-HEX assay. Absorbance was read in a microplate reader (Molecular Devices, Sunnyvale, CA) at 405 nm, and histamine levels were determined by comparison with a calibration curve. Histamine release was expressed as the percent ratio between supernatant and total histamine.

Measurement of Renin Protein

Mouse renin 1 was measured in BMMC supernatants using an enzyme-linked immunosorbent assay kit (RayBiotech, Norcross, GA) according to the manufacturer's instructions. In brief, 3×10^5 BMMCs were stimulated as described above for the β-HEX assay, and 100 μL from each supernatant was added to wells coated with anti-mouse renin 1 and incubated for 16 hours at 4°C. Absorbance was read in a microplate reader (Molecular Devices, Sunnyvale, CA) at 450 nm, and the renin protein concentration was calculated by comparison with a standard curve.

Measurement of Renin Activity

Renin activity was measured, as described previously,[11] in supernatants from BMMCs (treated as described above) using a radioimmunoassay kit (DiaSorin, Stillwater, MN; Saluggia, Italy), according to the manufacturer's instructions. Porcine angiotensinogen substrate (Sigma-Aldrich) was added to the supernatants. The reaction for angiotensin I production was conducted for 1.5 hours in the presence or absence of 100 nmol/L of the highly selective renin inhibitor BILA 2157 (BILA).[2,12] Total protein concentration was measured using a DC protein assay kit (Bio-Rad Laboratories, Hercules, CA). Results were normalized to total protein.

Perfusion of Mouse Hearts *ex Vivo*

Seven C57BL/6J male mice, 10 to 12 weeks old (Jackson Laboratory, Bar Harbor, ME), were passively sensitized with an intraperitoneal injection of murine anti-DNP IgE (6 μg/200 μL PBS; Sigma-Aldrich). Three other mice (nonsensitized controls) received an intraperitoneal injection of PBS alone.
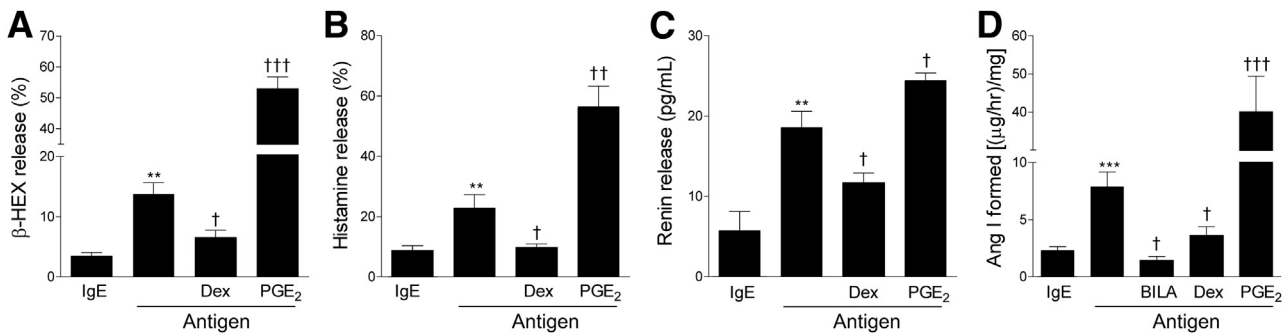

Figure 3   FcεRI aggregation elicits the release of renin from BMMCs, modulated by dexamethasone (Dex) and PGE₂. **A–D:** BMMCs were sensitized for 16 hours with murine anti-DNP IgE and then were challenged with DNP-HSA antigen for 20 minutes at 37°C in the presence or absence of 2 nmol/L dexamethasone (Dex), 1 μmol/L PGE₂. In **D**, in the absence or presence of 100 nmol/L BILA to assess renin-induced angiotensin I formation. For release of β-HEX (**A**) and histamine (**B**), percentages represent the percent ratio between supernatant and total β-HEX or histamine. Renin activity (**D**) was measured in BMMC supernatant with antigen alone or with antigen and BILA, Dex, or PGE₂. Data are expressed as means ± SEM. Number of experiments (left to right): $n = 8, 21, 8$, and 9 (**A**); $n = 8, 21, 18$, and 9 (**B**); $n = 4, 4, 5$, and 4 (**C**); and $n = 16, 12, 3, 6$, and 6 (**D**). $**P < 0.01$; $***P < 0.001$ versus control (IgE). $^{†}P < 0.05$, $^{††}P < 0.01$, and $^{†††}P < 0.001$ versus antigen.

Twenty-four hours later, all mice were intraperitoneally injected with 100 IU heparin, anesthetized with CO_2, and euthanized by cervical dislocation as approved by the Weill Cornell Medical College Institutional Animal Care and Use Committee. The isolated hearts were transferred to a Langendorff apparatus (Radnoti, Monrovia, CA). The aorta was cannulated with a flanged 20-gauge stainless steel needle. The heart was perfused through the aorta in a retrograde mode at a constant pressure of 100 cm H_2O with modified Krebs—Henseleit buffer containing (mmol/L) NaCl, 120; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose, 11; pyruvic acid, 2; and EDTA, 0.5. The perfusion fluid was bubbled with 95% O_2—5% CO_2 at 37°C, to achieve a pH of 7.4. After a 20-minute equilibration period, hearts were challenged with antigen (rapid intra-aortic injection of 200 μg DNP-HSA in 300 μL Krebs—Henseleit buffer). Samples of coronary flow effluent were collected every 2 minutes. The samples were assayed for β-HEX, renin activity, and histamine. For the β-HEX measurements, samples of coronary effluent were concentrated 8- to 10-fold by centrifugal filtration (EMD Millipore).

Statistical Analysis

Unpaired t-test was used throughout the study. $P < 0.05$ was considered statistically significant. Data are expressed as means ± SEM.

Results

Renin Is Expressed in BMMCs

Murine bone marrow cells matured into typical MCs on *in vitro* culture with SCF and IL-3 for 5 weeks, at which point they exhibited the classical Toluidine-Blue granular staining, were double-positive (>90%) for the FcɛRI and c-Kit receptors, and contained renin protein (Figure 1). Notably, renin protein was present in bone marrow cells at the time of their isolation and continued to be present during the differentiation phase (Figure 1).

BMMC Renin Release by Classical Degranulating Agents

Exposure of BMMCs to canonical degranulating agents (1 μmol/L Ca^{2+} ionophore A23187,[13] c48/80,[14] and 1 mmol/L ATP[15]) elicited degranulation (approximately fivefold to eightfold increase in β-HEX release, relative to control), and release of histamine (approximately 7- to 13-fold increase) and renin protein (approximately 2- to 25-fold increase) (Figure 2). Released renin was enzymatically active, because it cleaved angiotensin I from angiotensinogen (approximately 5- to 14-fold increase in angiotensin I formed, relative to control) (Figure 2D). Notably, the formation of angiotensin I in the supernatant of MCs incubated with A23187, c48/80, or ATP or subjected to FcɛRI aggregation was prevented by 100 nmol/L of the highly selective renin inhibitor BILA (Figures 2 and 3),[1,2,12] which demonstrates that proteases other than renin were not involved in the formation of angiotensin I.

BMMC Renin Release by FcɛRI Cross-Linking

After passive sensitization of BMMCs with murine anti-DNP IgE, challenge with DNP-HSA also caused degranulation (approximately fourfold increase in β-HEX release, relative to control), release of histamine (approximately 2.5-fold increase), and release of renin protein (approximately threefold increase), as well as an increase in angiotensin I—forming activity (approximately fourfold increase) (Figure 3).

Given that anti-inflammatory glucocorticoids are known to prevent IgE-mediated MC degranulation,[17] we assessed whether they also modulate MC renin release. When IgE-sensitized MCs were challenged with specific antigen in the presence of 2 nmol/L dexamethasone, β-HEX and histamine release were reduced by approximately 50% to 60%, whereas
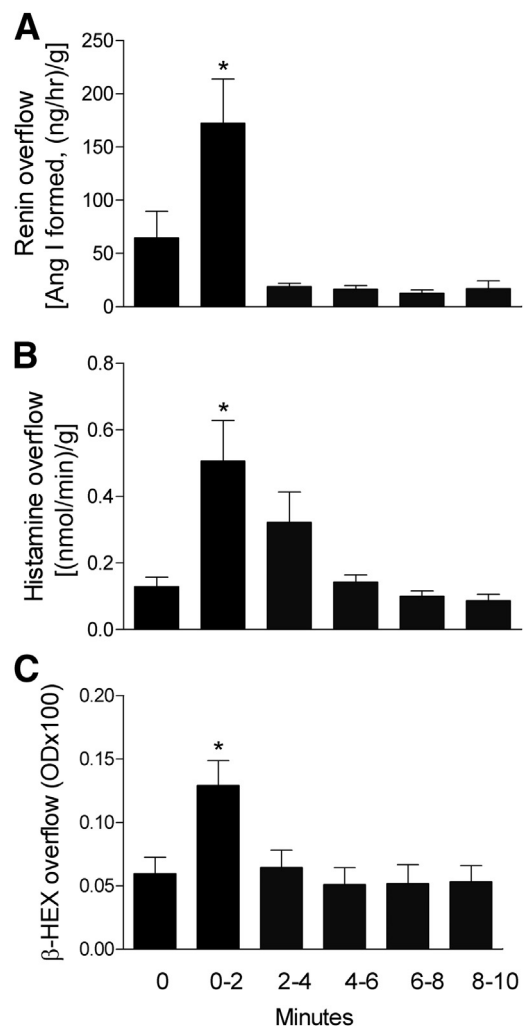

Figure 4 FcɛRI cross-linking on tissue-resident MCs elicits the release of renin from *ex vivo* mouse hearts. Time course of overflow of active renin (indicative of angiotensin I formation) (**A**), histamine (**B**), and β-HEX (marker of MC degranulation) (**C**) from Langendorff-perfused murine hearts. Mice were passively sensitized *in vivo* with 6 μg of murine monoclonal anti-DNP IgE; 24 hours later, hearts were excised and challenged with 200 μg of DNP-HSA. Overflow fractions were collected every 2 minutes after antigen injection. Data are expressed as means ± SEM. $n = 5$ to 7 hearts. *$P < 0.05$ versus coronary effluent preceding antigen, unpaired t-test. OD, optical density at 405 nm.

the release of renin protein and angiotensin I−forming activity decreased by approximately 40% and 60%, respectively (Figure 3).

PGE$_2$ is known to modulate FcεRI-mediated MC activation.[18] We therefore assessed whether this eicosanoid also modulates MC renin release. When IgE-sensitized MCs were challenged with the specific antigen in the presence of 1 μmol/L PGE$_2$, the release of β-HEX, histamine, renin protein, and angiotensin I−forming activity increased approximately fourfold, 2.5-fold, 30%, and fivefold, respectively (Figure 3). This suggests that MC renin release and consequent RAS activation can be magnified in the course of inflammatory responses in which PGE$_2$ is copiously produced.[19]

FcεRI Cross-Linking Induces Renin Release from Resident Tissue MCs

We next asked whether resident tissue MCs also release renin after FcεRI cross-linking. We used Langendorff-perfused hearts excised from mice passively sensitized with monoclonal anti-DNP IgE. Antigen challenge of these hearts resulted in substantial resident MC degranulation, as demonstrated by a marked increase in the coronary overflow of β-HEX, histamine, and renin activity in the first 2 minutes after antigen challenge (two-, four-, and threefold increase, respectively) (Figure 4). Notably, no release of β-HEX or histamine and no renin activity occurred after antigen challenge of hearts from control nonsensitized mice.

Discussion

Here, we report the novel finding that cross-linking of FcεRI-bound IgE antibodies on the surface of BMMCs and tissue-resident MCs elicits the release of enzymatically active renin protein. This process is inhibited by glucocorticoids and is enhanced by the proinflammatory mediator PGE$_2$. To our knowledge, this is the first time that FcεRI aggregation has been shown to elicit MC renin release.

The calcium ionophore A23187[13] was an effective elicitor of renin release from BMMCs, suggesting that activation of Ca^{2+} influx and phospholipase C−dependent mobilization of Ca^{2+} from intracellular stores[20] play a role in MC renin release. Given that an increase in intracellular calcium inhibits renin release from juxtaglomerular cells,[21] different mechanisms must control renin secretion in MCs and in the juxtaglomerular apparatus. The finding that c48/80 induced release of MC renin, together with β-HEX and histamine, suggests the presence of renin in extrudable granular formations, analogous to mastocytoma cells stimulated with c48/80 or substance P.[1,16] Indeed, typical MC degranulation requires the expulsion of membrane-free granules from an intact cell capable of repeated degranulation,[14] as we have previously observed in mastocytoma cells repeatedly stimulated to release renin with c48/80.[1]

Although ATP is known to elicit MC degranulation,[15] the present study is the first to show that ATP promotes the release of active renin from MCs. This novel finding is of particular cardiovascular relevance, because sympathetic purinergic nerve terminals release ATP in close proximity to MCs,[1,22] likely promoting renin release.

Dexamethasone inhibited FcεRI-induced MC degranulation and, most importantly, it also decreased renin release. A dexamethasone-induced decrease in MC degranulation has been attributed to reduced FcεRI expression on the MC surface,[23] and it is reported that dexamethasone diminishes MC degranulation and cytokine production by suppressing FcεRI-induced activation of PI3-kinase.[24] Furthermore, nongenomic mechanisms have been invoked in the rapid glucocorticoid-induced inhibition of IgE-mediated MC degranulation and histamine release in a guinea-pig asthma model *in vivo* and in the RBL-2H3 MC line *in vitro*. These effects were mediated by a suppression of the increase in intracellular Ca^{2+} that characterizes MC degranulation.[25]

The PGE$_2$-induced potentiation suggests that MC renin release and consequent RAS activation can be magnified in the course of inflammatory responses in which PGE$_2$ is copiously produced.[19] Given the pervasiveness of PGE$_2$ production in inflammatory reactions,[26] and also the PGE$_2$-induced potentiation of renin release from BMMCs, PGE$_2$ can be envisioned as a major player in the activation of local RAS in various organs.

In conclusion, we found that FcεRI cross-linking on BMMCs and tissue-resident MCs elicits the release of enzymatically active renin protein. The angiotensin I−forming activity of the renin protein was completely blocked by the highly selective renin inhibitor BILA, a finding that excludes involvement of other proteases in the formation of angiotensin I. The finding that MC renin release was mimicked by canonical degranulators such as calcium ionophore and c48/80 suggests that MC renin may be stored in granules and that its release may depend on an increase in intracellular Ca^{2+}. Our present findings indicate that IgE-mediated allergic hypersensitivity provokes the release of MC renin, which is potentiated by PGE$_2$ and inhibited by dexamethasone. Given the ubiquitous presence of MCs,[3,6,7] and the presence of angiotensinogen and angiotensin-converting enzyme in many tissues,[27] renin release in allergic hypersensitivity reactions could result in local angiotensin II formation and angiotensin II−mediated multiorgan dysfunctions, a process likely exacerbated in an inflammatory background.

Acknowledgments

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