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Resolvin E1 Selectively Interacts with Leukotriene B_4 Receptor BLT1 and ChemR23 to Regulate Inflammation[1]

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Resolvin E1 (RvE1) is a potent anti-inflammatory and proresolving mediator derived from omega-3 eicosapentaenoic acid generated during the resolution phase of inflammation. RvE1 possesses a unique structure and counterregulatory actions that stop human polymorphonuclear leukocyte (PMN) transendothelial migration and PMN infiltration in several murine inflammatory models. To examine the mechanism(s) underlying anti-inflammatory actions on PMNs, we prepared [^{3}H]RvE1 and characterized its interactions with human PMN. Results with membrane fractions of human PMN demonstrated specific binding with a K_d of 48.3 nM. [^{3}H]RvE1 specific binding to human PMN was displaced by leukotriene B_4 (LTB_4) and LTB_4 receptor 1 (BLT1) antagonist U-75302, but not by chemerin peptide, a ligand specific for another RvE1 receptor ChemR23. Recombinant human BLT1 gave specific binding with [^{3}H]RvE1 with a K_d of 45 nM. RvE1 selectively inhibited adenylate cyclase with BLT1, but not with BLT2. In human PBMC, RvE1 partially induced calcium mobilization, and blocked subsequent stimulation by LTB_4. RvE1 also attenuated LTB_4-induced NF-κB activation in BLT1-transfected cells. In vivo anti-inflammatory actions of RvE1 were sharply reduced in BLT1 knockout mice when given at low doses (100 ng i.v.) in peritonitis. In contrast, RvE1 at higher doses (1.0 μg i.v.) significantly reduced PMN infiltration in a BLT1-independent manner. These results indicate that RvE1 binds to BLT1 as a partial agonist, potentially serving as a local damper of BLT1 signals on leukocytes along with other receptors (e.g., ChemR23-mediated counterregulatory actions) to mediate the resolution of inflammation. ***The Journal of Immunology,* 2007, 178: 3912–3917.**

Inflammation and resolution are major mechanisms involved in many human diseases, including cardiovascular disease, arthritis, diabetes, asthma, Alzheimer's disease, and periodontitis (1). Most inflammatory challenges are self-limited in healthy subjects, implicating the existence of endogenous circuits for anti-inflammation and proresolution mediators that are operative during the temporal events of host defense and inflammation (2). Resolution of inflammation is an active process governed by timely and spatially regulated formation and actions of local mediators so that tissues can return to homeostasis (3–5).

Resolvins (Rv)[4] and protectins are local mediators derived from omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid that are generated during the spontaneous resolution phase and act locally at sites of inflammation. These recently uncovered pathways and mediators counterregulate polymorphonuclear leukocyte (PMN) infiltration and promote resolution (2, 3). They are generated during multicellular responses such as inflammation and microbial infections, a unique pathway that involves cell-cell interactions and transcellular biosynthetic routes. When aspirin is present, resolvin E1 (RvE1) is formed from EPA via cell-cell interactions involving cells bearing cyclooxygenase-2 that has been acetylated by aspirin treatment and cells that possess 5-lipoxygenase (5-LO) (5, 6). RvE1 biosynthesis can also be initiated by microbial cytochrome P450 monooxygenase in an aspirin-independent manner (7), which can contribute to its production in vivo. These newly produced resolvins may be responsible for some of the beneficial effects of taking omega-3 EPA that are enhanced with aspirin therapy (8, 9).

PMNs are one of the main cellular targets of RvE1's anti-inflammatory actions. For example, RvE1 reduces PMN transendothelial migration and release of superoxide generation in the nanomolar concentration range (5, 10). These actions are also demonstrable in vivo, where RvE1 blocks PMN infiltration both in peritonitis (6) and in inflamed colon tissue during colitis (8). RvE1 also attenuates APC functions targeting dendritic cell migration and reducing IL-12 production via ChemR23 (6). ChemR23 was identified from a panel of G-protein-coupled receptors (GPCRs) using a counterregulatory screening system. We reasoned that proresolving ligand activation of GPCR would block proinflammatory signals such as TNF-α-driven NF-κB activation. From our GPCR panel described in Ref. 6, only RvE1 selectively bound and activated ChemR23 to block TNF-α signaling in a stereoselective fashion.

In this study, we report that RvE1 specifically binds the leukotriene B_4 (LTB_4) receptor BLT1 on human PMN. RvE1 interacts with BLT1 as a partial agonist serving as a local damper of LTB_4-BLT1

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[4] Abbreviations used in this paper: Rv, resolvin; EPA, eicosapentaenoic acid; PMN, polymorphonuclear leukocyte; RvE1, resolvin E1; 5-LO, 5-lipoxygenase; GPCR, G protein-coupled receptors; LTB_4, leukotriene B_4; PTX, pertussis toxin; WT, wild type; CHO, Chinese hamster ovary; BLT1, LTB_4 receptor 1; BLT2, LTB_4 receptor type 2; DC, dendritic cell; ALX, LXA_4 receptor.

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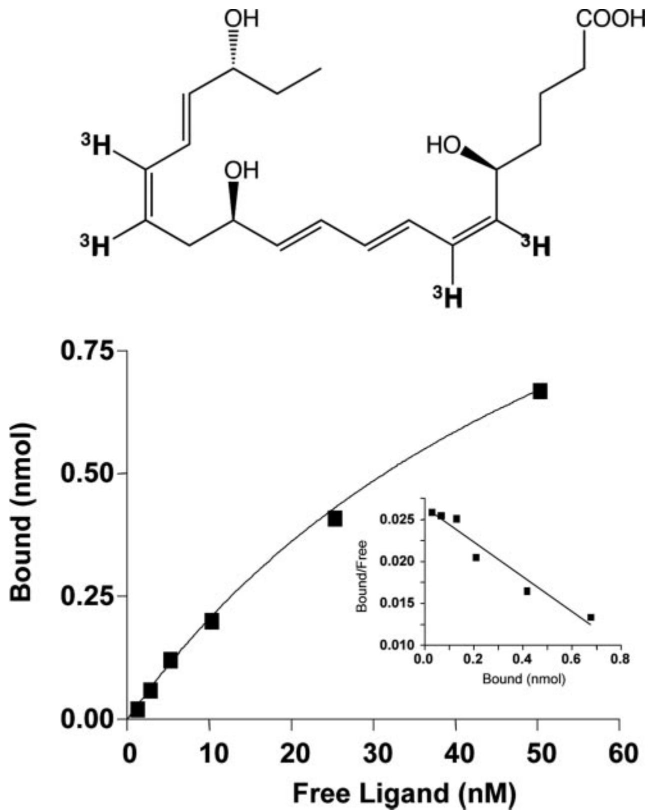

FIGURE 1. [^{3}H]RvE1-specific binding to human PMN. Isolated membrane preparations from human PMN were incubated with the indicated concentrations of [^{3}H]RvE1 in the presence or absence of 10 μM unlabeled RvE1. Saturation curve and Scatchard plot (*inset*) are representative of $n = 3$.

signals on PMN. These RvE1-BLT1 interactions join RvE1-ChemR23-mediated counterregulatory actions to promote the resolution of acute inflammation.

Materials and Methods

Materials

RvE1 (5*S*,12*R*,18*R*-trihydroxy-eicosa-6*Z*,8*E*,10*E*,14*Z*,16*E*-pentaenoic acid) was prepared by total organic synthesis as described in Ref. 6. LTB_4 and U-75302 (6-(6-(3*R*-hydroxy-1*E*,5*Z*-undecadien-1-yl)-2-pyridinyl)-1,5*S*-hexanediol) was obtained from Cayman Chemical. Forskolin, Ro-20-1724, and pertussis toxin (PTX) were purchased from Sigma-Aldrich. Fura 2-AM was obtained from Invitrogen Life Technologies. The expression vectors pcDNA3-hBLT1, hBLT2, and hChemR23 were constructed as described in a recent publication (6).

Mice

BLT1-deficient mice were described earlier (11). C57BL/6 strain from Charles River Laboratories was used as the wild-type (WT) control strain. Female 8- to 10-wk-old mice were used. All procedures were reviewed and approved by the Harvard Medical School Standing Committee on Animals (protocol 02570).

Human peripheral blood leukocytes

Human PMN and PBMC were freshly isolated from venous blood of healthy volunteers (that declined taking medication for 2 wk before donation; Brigham & Women's Hospital protocol 88-02642) by Ficoll gradient as described in Ref. 5.

Cell culture

Chinese hamster ovary (CHO), HEK293, and HeLa cells were cultured in Ham's F-12 and DMEM, respectively, supplemented with 10% FBS. HEK293 cells stably expressing human BLT1 or BLT2 were established by transfecting pcDNA3-hBLT1 or pcDNA3-hBLT2, selected and maintained with 500 μg/ml G418. CHO cells stably expressing human ChemR23 (CHO-hChemR23) were prepared (6) and maintained in the presence of 500 μg/ml G418.

Specific binding with RvE1

Binding studies were conducted with tritiated RvE1 (6,7,14,15-[^{3}H]RvE1; 100 Ci/mmol) synthesized as described in Ref. 6 using custom tritiation (American Radiolabeled Chemicals) of acetylenic RvE1 followed by HPLC isolation. The binding mixture (100 μl) contained isolated membrane fractions (10 μg protein) and indicated concentrations of [^{3}H]RvE1 with or without unlabeled competitors in binding buffer (50 mM HEPES, 1 mM $CaCl_2$, and 5 mM $MgCl_2$) for 1 h at 4°C. For CHO-hChemR23, cells (1×10^6) were incubated in Dulbecco's PBS with $CaCl_2$ and $MgCl_2$ for 1 h at 4°C. For determination of nonspecific binding, at least 1,000 × concentration of unlabeled RvE1 was used. The bound and unbound radioligands were separated by filtration through Whatman GF/C glass microfiber filters and radioactivity was determined. Scatchard plot was obtained and the K_d value was calculated using Prism (GraphPad).

Measurement of cAMP

Cells were seeded on 24-well plates (7.5×10^5 cells/well) and cultured for another 48 h. The medium was replaced with 400 μl of DMEM containing 5 μM forskolin, 100 μM Ro-20-1724 (4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone), and test compounds, and after 15 min of incubation, the reaction was terminated by replacing media with 100 μl of 0.1 N HCl. The cAMP contents in 20 μl of the lysates were determined using the cAMP enzyme immunoassay kit (Cayman Chemical).

Calcium mobilization

Mobilization of calcium was measured in fura 2-AM-loaded cells. Human PBMC (1.0×10^7 cells/ml) were incubated in HBSS with fura 2-AM (5 μM; $<$0.05% v/v DMSO) for 30 min at 37°C. Cells were washed twice and suspended (12.5–15 $\times 10^6$ cells/ml) in HBSS supplemented with Ca^{2+} (1.6 mM). The cell suspension was maintained in a stirred thermostatted cuvette and fluorescence was monitored using 335-nm excitation and 505-nm emission in a spectrofluorometer (PerkinElmer; LS-3B). RvE1 and LTB_4 were added in a volume of 20–40 μl to cuvettes to give the indicated concentrations.

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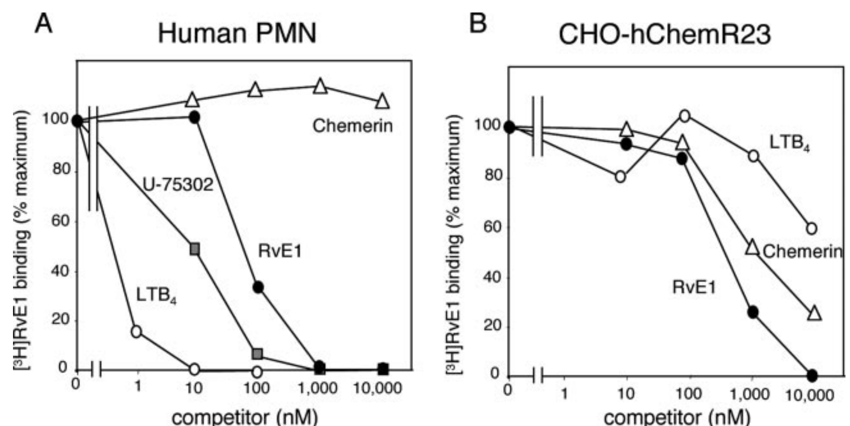

FIGURE 2. Competition for specific [^{3}H]RvE1 binding. *A*, Competition for [^{3}H]RvE1 (5 nM)-specific binding to isolated human PMN with increasing concentrations of RvE1 (●), LTB_4 (○), the specific BLT1 receptor antagonist U-75302 (■), or the specific ChemR23 receptor agonist chemerin peptide (△). *B*, Competition for [^{3}H]RvE1 (10 nM)-specific binding to CHO cells stably expressing recombinant human ChemR23 with increasing concentrations of RvE1 (●), LTB_4 (○), or chemerin (△). Results are representative of $n = 3$ with duplicates in each experiment.

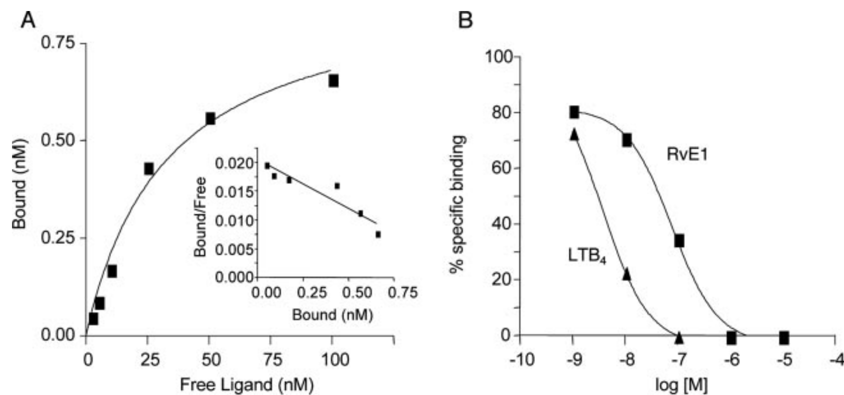

FIGURE 3. [^{3}H]RvE1-specific binding to recombinant human BLT1. *A*, Isolated membrane fractions of human BLT1-transfected HEK293 cells were incubated with indicated concentrations of [^{3}H]RvE1 in the presence or absence of 10 μM of unlabeled RvE1. *B*, Competition for [^{3}H]RvE1 (5 nM)-specific binding to HEK293 cell membranes expressing hBLT1 with increasing concentrations of RvE1 or LTB_4. Results are representative of n = 3.

Luciferase reporter system

HeLa cells were maintained in DMEM supplemented with 10% heat-inactivated FBS. Cells (5×10^5 cells/well) in 24-well plates were transfected with 100 ng of pNF-κB luciferase (Stratagene), 800 ng of either pcDNA3 or pcDNA3-BLT1, and the internal standard pRL-TK (Promega) using Superfect transfection reagent (Qiagen). After 24 h, cells were exposed to test compounds for 6 h in serum-free DMEM. Luciferase activity was measured by the Dual-Luciferase reporter system (Promega).

Zymosan-induced peritonitis

Murine peritonitis was conducted as described in Ref. 4, and 100 ng or 1 μg/mouse RvE1 was injected into the tail vein and followed by 1 ml of zymosan A (1 mg/ml) into the peritoneum. Peritoneal lavages were collected at 2 h and cells were enumerated. For differential leukocyte counts, 100 μl of the lavaged cells was added to 100 μl of 30% BSA and centrifuged onto microscope slides at 2200 rpm for 4 min using a Cytofuge (StatSpin). The slides were air dried, and cells were visualized using Wright-Giemsa stain and light microscopy.

Results

Specific binding of [^{3}H]RvE1

[^{3}H]RvE1 specifically binds to the isolated membrane fraction of human PMN (Fig. 1). At 4°C, RvE1 binding to human PMN membrane fraction was specific with a K_d of 48.3 nM. We next examined the competition of [^{3}H]RvE1 binding with several related eicosanoids. Among the compounds tested, [^{3}H]RvE1-specific binding to human PMN was displaced by the homoligand RvE1 (K_i = 34.3 nM), LTB_4 (K_i = 0.08 nM), and LTB_4 receptor 1 (BLT1) selective antagonist U-75302 (K_i = 1.5 nM) (12), but not by the chemerin peptide (13); a ligand specific for another RvE1 receptor denoted ChemR23 (Fig. 2*A*). For direct comparison, [^{3}H]RvE1 to human ChemR23 was competed with RvE1 (K_i = 330 nM) or chemerin peptide (K_i = 429 nM), but not with LTB_4 (Fig. 2*B*). These results demonstrate that the RvE1 binding site on human PMN is pharmacologically distinct from ChemR23.

We next determined whether RvE1 binds to recombinant BLT1. HEK293 cells stably expressing human BLT1 (HEK-hBLT1) were prepared to determine RvE1-specific binding. As shown in Fig. 3*A*, RvE1 specifically bound to HEK-hBLT1 with a K_d of ~45 nM. RvE1-specific binding was competed with LTB_4 (K_i = 3 nM) or RvE1 (K_i = 70 nM) (Fig. 3*B*). Recombinant human LTB_4 receptor type 2 (BLT2) did not display specific binding for [^{3}H]RvE1 at concentrations up to 10 nM (data not shown). These results clearly demonstrated that RvE1 binds to BLT1 on human PMN.

RvE1 selectively interacts with BLT1 to transmit intracellular signaling

To examine whether the binding of RvE1 to BLT1 transduces functional responses, such as intracellular signaling, we determined adenylyl cyclase activity by measuring the cAMP accumulation. As shown in Fig. 4*A*, LTB_4 inhibited 5 μM forskolin-activated adenylate cyclase activities in HEK-hBLT1 cells with EC_{50} of 0.015 nM, a value consistent with that reported previously (14). In these experiments, RvE1 inhibited adenylate cyclase activities with EC_{50} of 3.2 nM. On the other hand, RvE1 gave no response with HEK-hBLT2 cells where LTB_4 gave signals (EC_{50} = 11.5 nM), a value consistent with the previous report (12) (Fig. 4*B*). These results indicate that RvE1 selectively binds and activates BLT1 to transmit intracellular signals.

RvE1 attenuates LTB_4-BLT1-induced intracellular signals

Fig. 5 reports the increase in intracellular calcium mobilization stimulated by LTB_4 or RvE1 in human PBMC. RvE1 at 100 nM increased intracellular calcium, but the maximum intensity of signal was only about one-third that of LTB_4 (Fig. 5, *A* and *B*). Importantly, prior exposure to RvE1 completely blocked LTB_4-induced calcium response in a concentration-dependent manner

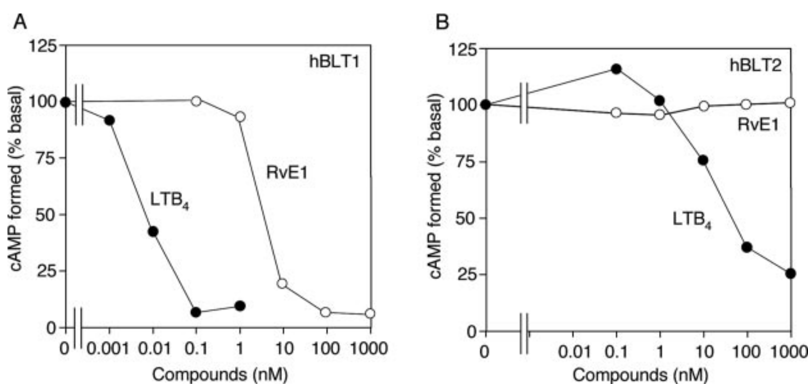

FIGURE 4. RvE1-selectively activates BLT1. Cyclic AMP accumulation in forskolin (50 μM)-treated HEK-hBLT1 (*A*) and HEK-hBLT2 (*B*) cells were monitored in the presence of RvE1 or LTB_4. Results are representative of n = 3.

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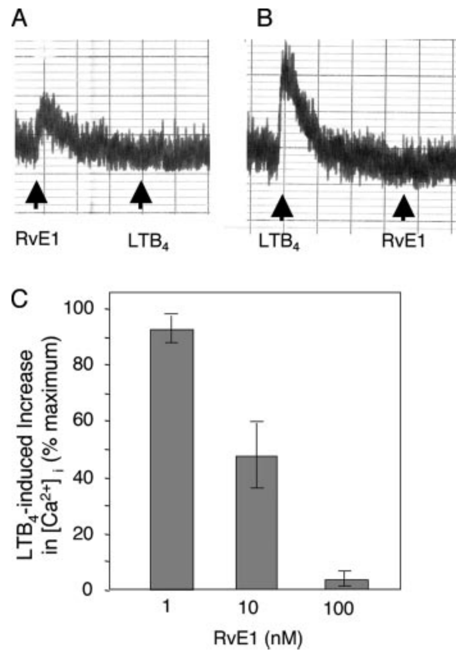

FIGURE 5. RvE1 blocks LTB_4-induced calcium mobilization in human PBMC. *A*, Human PBMC were loaded with fura 2 and then stimulated with LTB_4 or RvE1 at 100 nM. Desensitization of LTB_4-induced calcium flux by RvE1 was measured by sequentially stimulating the cells with both compounds and vice versa (*A* and *B*). Increased concentrations of RvE1 block LTB_4-induced calcium mobilization (*C*). Results are expressed as mean ± SEM ($n = 3$).

(Fig. 5*C*). These results indicate that RvE1 is a partial agonist to attenuate LTB_4-induced calcium responses in leukocytes.

Because LTB_4 induces proinflammatory cytokine and chemokine expression by activating NF-κB (15), we next determined whether RvE1 could modulate LTB_4-BLT1-induced NF-κB activation by using a luciferase reporter gene system. LTB_4 induced NF-κB activation in HeLa cells transfected with human BLT1 with EC_{50} of 0.36 nM (Fig. 6*A*). This induction was almost completely abolished by 100 ng/ml PTX, suggesting that BLT1 coupled to PTX-sensitive G proteins such as Gi/o to activate NF-κB transcription factor (Fig. 6*A*, *inset*). RvE1 concentrations above 100 nM gave partial activations of NF-κB that were in a range comparable to that of the BLT1 antagonist U-75302. Importantly, LTB_4-dependent NF-κB activation was blocked by ~40–50% with RvE1 as low as 1 nM, which is an ~10-fold molar excess of LTB_4 (Fig. 6*B*). These results clearly demonstrated that RvE1 binds to BLT1 and attenuates LTB_4-induced proinflammatory signals as a nonphlogistic ligand.

RvE1 actions in BLT1-deficient mice are dose dependent

We examined the role of BLT1 in the in vivo actions of RvE1 in regulating leukocyte infiltration in zymosan A-induced peritonitis. In this model, zymosan activates resident macrophages and/or early accumulating neutrophils to produce LTB_4 from arachidonic acid, resulting in PMN influx in an autocrine loop of PMN accumulation during acute inflammation (11). Intravenous administration of RvE1 at 100 ng dramatically blocked PMN infiltration by 38% at 2 h after zymosan injection in WT mice (Fig. 7*A*). In contrast, RvE1 at 100 ng did not give statistically significant reduction in mice with targeted disruption of BLT1 ($BLT1^{-/-}$) (Fig. 7*A*). The early reduction of PMN influx in $BLT1^{-/-}$ mice, which represents BLT1-dependent PMN infiltrations, was noted as reported previously (11). RvE1 reduced the numbers of infiltrating PMN in WT mice to the levels of that obtained in $BLT1^{-/-}$ mice (Fig. 7*A*), indicating that i.v. administration of RvE1 at 100 ng blocked PMN migration by dampening BLT1 functions in vivo. Of interest, RvE1 at higher doses (1.0 μg i.v.) retained most of its antimigratory actions in $BLT1^{-/-}$ mice, giving around 35% inhibition of PMN infiltration in both WT and $BLT1^{-/-}$ mice (Fig. 7*B*). Together, these results demonstrate that i.v.-administered RvE1 acts via BLT1, potentially serving as a local damper of BLT1 signals on leukocytes in addition to BLT1-independent mechanisms involving additional receptor(s) in vivo.

Discussion

The omega-3 EPA-derived RvE1 is an endogenous mediator that protects tissues from leukocyte-mediated injuries (5–7; for recent review see Ref. 2). In the present study, we characterized RvE1 binding to human PMNs and identified these sites as the LTB_4 receptor BLT1. RvE1 selectively interacts with BLT1, but not with its closely related receptor, termed BLT2. BLT2 is structurally similar to BLT1 with ~45% identity in deduced amino acid sequence (12). RvE1 effectively blocked LTB_4-induced calcium mobilization in human leukocytes, and also attenuated LTB_4-induced NF-κB activation in BLT1-transfected cells. In vivo anti-inflammatory action of RvE1 was sharply reduced in BLT1 knockout mice when given at low doses in zymosan-induced peritonitis, but RvE1 at high doses gave significant inhibition of PMN infiltration in a BLT1-independent manner. Therefore, RvE1 functions as a local damper of LTB_4-BLT1 signals on leukocytes in addition to other receptor(s)-mediated actions.

LTB_4 is an arachidonic acid-derived mediator produced mainly by activated leukocytes. LTB_4 is a potent chemoattractant for

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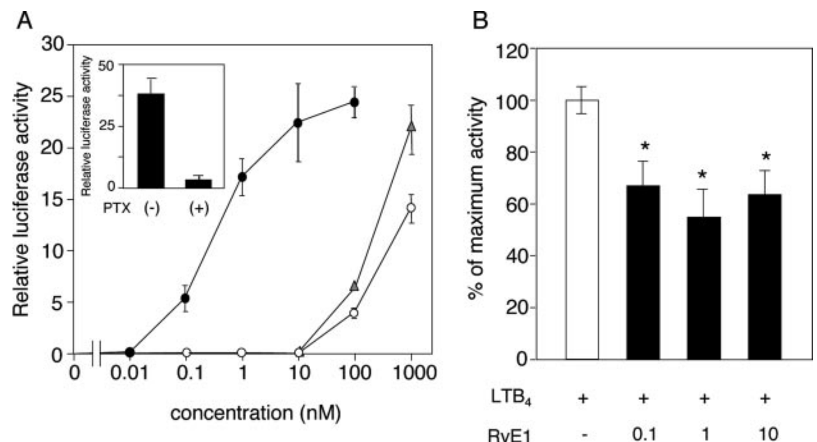

FIGURE 6. RvE1 is a partial agonist to attenuate LTB_4-BLT1-induced NF-κB activation. *A*, Concentration-dependent induction of κB-directed luciferase activity. HeLa cells cotransfected with pcDNA3-hBLT1 and pNF-κB-luciferase were exposed to increasing concentrations of RvE1 (○) or LTB_4 (●). Luciferase activities were measured 6 h after agonist stimulation and expressed as relative luciferase activity compared with vehicle control. *B*, Cells were preincubated with RvE1 for 30 min, then activated with LTB_4 (0.1 nM) for 6 h. Results are expressed as a mean ± SEM ($n = 3$) (*, $p < 0.01$).

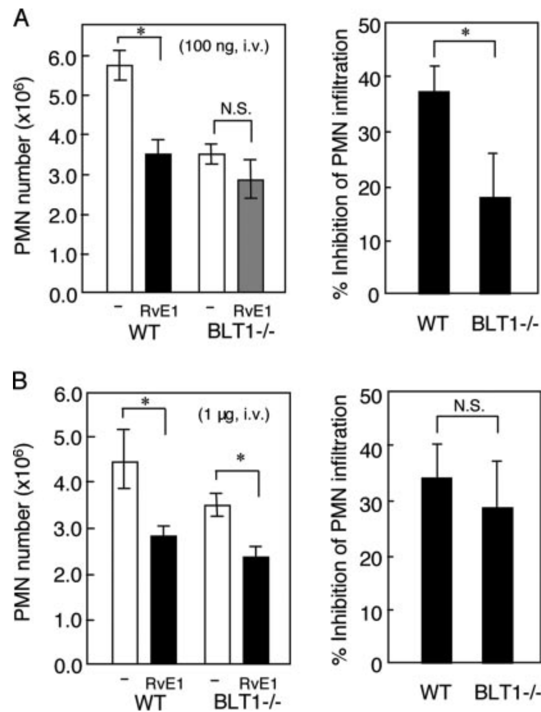

FIGURE 7. RvE1 dose-dependent reduction of PMN infiltration in BLT1-deficient and WT mice. Mice were injected i.v. with RvE1 (100 ng (*A*) or 1.0 μg (*B*)), and peritonitis was induced by i.p. administration of 1 mg of zymosan A. The peritoneum was lavaged at 2 h, and peritoneal exudates cells were enumerated. Values are mean ± SEM; $n = 3–7$ (*, $p < 0.05$). N.S., Not significant.

PMNs, eosinophils, and macrophages and also activates the respiratory burst and granule release from PMNs (16, 17). BLT1 is a high-affinity LTB_4 receptor responsible for the chemotactic actions of LTB_4 (14). In zymosan peritonitis, zymosan activates resident macrophages and/or early accumulating neutrophils that produce LTB_4 from arachidonic acid, resulting in BLT1-dependent PMN influx and PMN accumulation during acute inflammation (11). Along these lines, when we monitored exudate eicosanoids in zymosan-initiated peritonitis during a 72 h time course after zymosan injection, the maximal levels of LTB_4 were at 2 h, and subsequently subsided during the first 24 h (see Ref. 4). LTB_4 is also a strong chemoattractant for T cells, creating a functional link between innate and adaptive immune responses (18). RvE1 within a low nanomolar range was shown to block PMN transendothelial migration initiated by LTB_4 or fMLP (5), and in this study we report that RvE1 directly interacts with BLT1 attenuating the propagation of proinflammatory signals by LTB_4 with similar potencies to the BLT1 antagonist U-75302. This site of action may be particularly important in self-limiting PMN diapedesis, since RvE1 is locally generated from omega-3 EPA when activated PMN interacts with vascular endothelial cells (5, 6). ChemR23 was identified as an RvE1 receptor displaying specific binding with a K_d value of 11.3 nM, phosphorylation signals, G protein activation, and attenuation of TNF-α activated NF-κB (6). ChemR23 is abundantly expressed in macrophages and dendritic cells (DC), but apparently not as much in PMN (13). RvE1 attenuates APC functions targeting DC migration and reducing IL-12 production, and down-regulation of ChemR23 expression by small interference RNA abolished the effect of RvE1 on DCs (6). Taken together, the potent anti-inflammatory and/or proresolution actions of RvE1 in vivo could be mediated by two different sites of actions, namely attenuating LTB_4-BLT1 signals to stop leukocyte infiltration and activation as well as stimulating ChemR23 to regulate migration and cytokine production of macrophages and/or DC. These multiple sites of action are also the case with lipoxin $(LX)A_4$, serving as a local damper of both vascular LTD_4 receptor (CysLT1) signals as well as LXA_4 receptor (ALX)-regulated PMN traffic (19). LXA_4 was as potent as RvE1 in terms of magnitude of inhibition (40–50%) and effective concentration ranges (10–100 ng/mouse) in zymosan peritonitis (20). LXA_4 shares the same receptor denoted ALX with anti-inflammatory peptide annexin 1 (21), and annexin 1 gives the same magnitude of reduction of PMN migration (40–50%) in zymosan peritonitis at higher concentration ranges (10–100 μg) (22). Also, overexpression of human ALX in mouse leukocytes dramatically reduced acute PMN infiltration in ALX transgenic mice (20), suggesting ALX as a counterregulatory receptor whose ligands work as agonists of endogenous anti-inflammation.

Results from studies using mouse models and antagonists of LTB_4 suggested a role for BLT1 in chronic diseases such as rheumatoid arthritis, asthma, and cardiovascular disease (18, 23–25). Increased expression of the genes of the leukotriene pathway such as 5-LO, 5-LO-activating protein, and LTA_4 hydrolase in atherosclerotic plaques are observed and draw particular attentions (26). Results of genetic studies revealed variants of the 5-LO gene promoter, 5-LO-activating protein, and LTA_4 hydrolase genes as risk factors in human atherosclerosis and myocardial infarction (27–29). LTB_4 is produced in human atherosclerotic lesion (26), activates NF-κB transcription factor through BLT1, and induces atherogenic chemokine MCP-1 in human monocytes (15), smooth muscle cells (30), and endothelial cells (31). Of special interest, omega-3 polyunsaturated fatty acids such as EPA and docosahexaenoic acid are widely thought to be cardioprotective (9, 32, 33). The present results demonstrated that RvE1 derived from omega-3 EPA-attenuated LTB_4 induced NF-κB activation via BLT1, suggesting the therapeutic potential of RvE1 in inflammatory diseases where LTB_4 plays a major role in disease progression, including cardiovascular diseases. Moreover, the present findings could explain, at least in part, the molecular mechanism that can underlie the beneficial actions of omega-3 EPA observed in many clinical disorders where LTB_4 is believed to be a proinflammatory signal. Therefore, we reasoned that RvE1 acts as a proresolving ligand and would block proinflammatory signals.

In summation, RvE1 specifically interacts with the LTB_4 receptor BLT1 in addition to ChemR23. BLT1 is expressed abundantly in PMNs, and RvE1-BLT1 interactions regulate migration of leukocytes in acute inflammation. ChemR23 does not appear to be highly expressed in PMNs, but present in APCs such as macrophages and DCs, where it plays a regulatory role to control migration and cytokine production. Also, RvE1 attenuates LTB_4-dependent proinflammatory signals such as mobilization of intracellular calcium and NF-κB activation. These results provide a molecular basis not only for the involvement of omega-3 EPA-derived lipid mediators in controlling inflammatory responses, but also for a potential therapeutic utility of RvE1 and its mimetics for a wide range of inflammatory disorders wherein specifically regulating PMNs may be beneficial.

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Disclosures

C. N. Serhan is the inventor of several U.S. patents on the structural elucidation of resolvins and their use in controlling inflammatory diseases. Brigham and Women's Hospital is the assignee for these patents, and they have been licensed by Resolvyx Pharmaceuticals, with whom Dr. Serhan is a consultant.

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