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Distinct effects of antigen and compound 48/80 in the guinea pig trachea

To the Editor,

Mast cells (MCs) can be activated immunologically by allergen and non-immunologically via the Mas-related G protein-coupled receptor member X2 (MRGPRX2).[1] With the emerging interest of MRGPRX2, we compared the airway smooth muscle (ASM) response and release of mediators in airways exposed to the human MRGPRX2 agonist compound 48/80 (C48/80) and house dust mite (HDM). A guinea pig model was selected for greatest similarity with human airways.[2]

We measured ASM contraction using organ baths. Both C48/80 and HDM induced marked constriction in trachea from sensitized guinea pigs (Figure 1). The effects of HDM were most likely due to specific IgG which, in addition to IgE, has been shown to induce smooth muscle contractions in guinea pig trachea[3] (Figure S1). Antagonizing histamine H_1 receptors inhibited the concentration-response curves and the initial 15 minutes of responses induced by submaximal bolus dose challenges, indicating that the early response of both treatments was mediated by histamine. In contrast, the whole phase responses could only be dampened by inhibition of both histamine and 5-lipoxygenase (5-LOX) pathways, suggesting that both C48/80 and HDM contractions were mediated through histamine and 5-LOX products (Figure 1).

For measuring mediator release induced by C48/80 and HDM, a bolus dose of the strongest concentration of each stimulus was given. Histamine and lipid mediators in the bath fluids were measured by ELISA and a recently developed mass-spectrometry platform with high specificity and sensitivity for detecting lipid mediators.[4] Both C48/80 and HDM released histamine to similar levels (Figure 2). In addition, 29 lipid mediators were changed after 60 minutes stimulation; 15 were elevated by both C48/80 and HDM challenge, and an additional 13 only by C48/80, while LTE_4 was only elevated by HDM (Figure S2 and Table S1).

The prostanoids were the most abundant bioactive lipid mediators detected in the organ baths after challenges. Prostaglandin (PG) D_2, a major lipid mediator from MCs, together with PGD_1 and PGD_3, were elevated in bath fluids challenged by C48/80 and HDM to similar levels. On the other hand, thromboxane (TX) B_2, was to a greater extent released by C48/80 than HDM, and PGE metabolites, $PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$, and TXB_3 were solely increased by C48/80 (Figure 2 and Figure S3).

Both C48/80 and HDM increased LTB_4, whereas only HDM triggered the release of cysteinyl leukotrienes (CysLTs) reflected by the elevation of LTE_4 (LTC_4 0%, LTD_4 1.7%, and LTE_4 98.3% of measured products by an additional analysis). In addition to prostanoids and leukotrienes, low levels of other lipid mediators were primarily increased by C48/80 (Figure 2 and Figure S3).

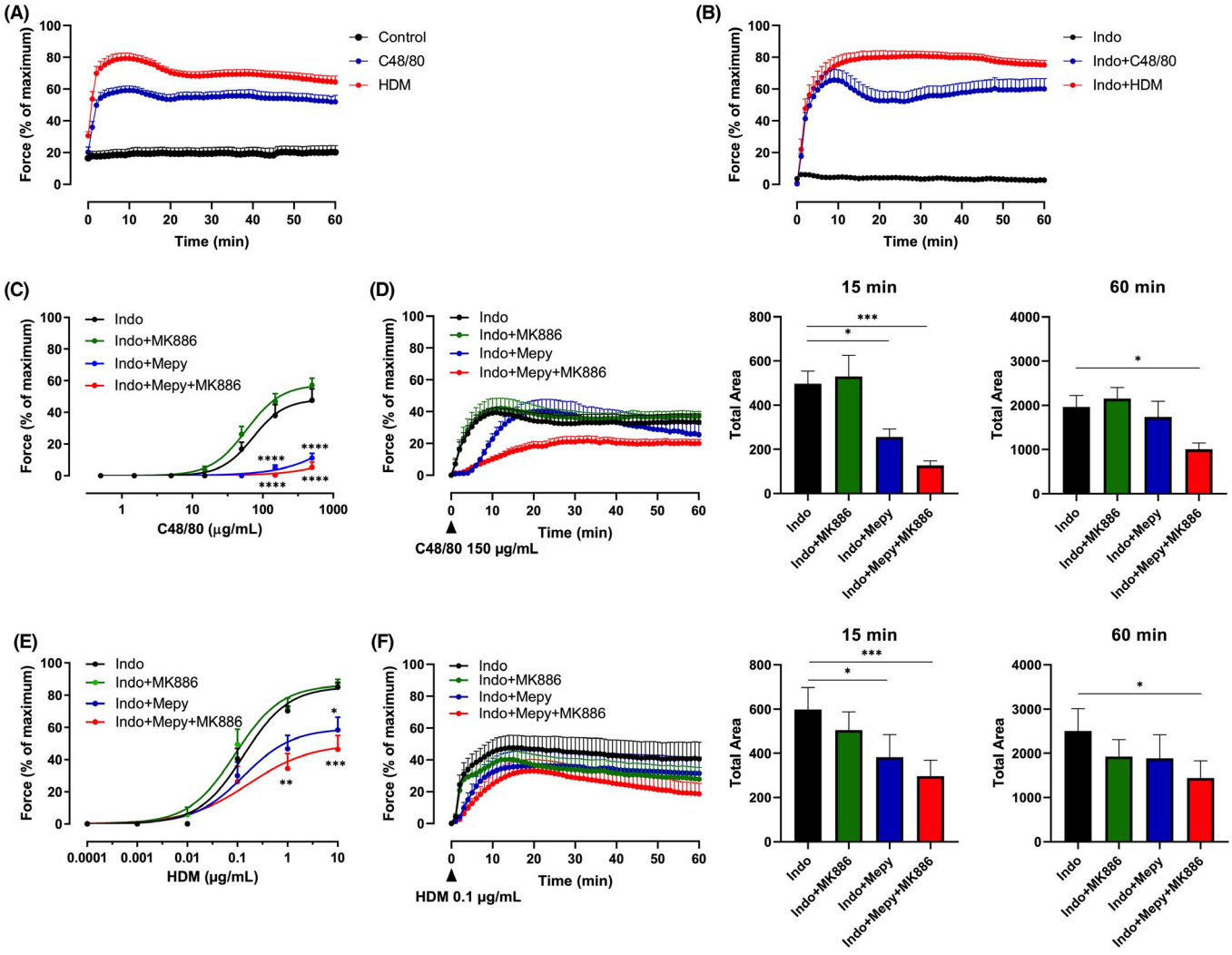

FIGURE 1 Responses to C48/80 or HDM with or without inhibitors/antagonists. Responses to C48/80 (500 µg/mL) and HDM (10 µg/mL) in absence (A) and presence (B) of indomethacin (Indo; 3 µM). Concentration-response curves of (C) C48/80 and (E) HDM. Response to (D) C48/80 (150 µg/mL) and (F) HDM (0.1 µg/mL) with area under curve (AUC). C48/80 challenge in (C) and (D) were done in naïve animals. In C-F indomethacin was used to block the spontaneous tone by PGE_2. Mepyramine (Mepy; 1 µM), MK886 (10 µM). N = 3–4, n = 5–12. N: number of animals; n: number of tracheal segments

The strong histamine release induced by C48/80 and HDM indicated that the main effect of the stimuli is most likely due to direct activation of MCs. The different responses can be due to distinct intracellular signaling pathways for G protein-coupled receptors and Fc-receptors.[5,6] However, since the receptor responsible for C48/80 responses in the guinea pig trachea is not completely defined, we cannot rule out a release from other cells present in the airways. But it is likely that the response is mediated through MRGPRX2 orthologues existing in guinea pigs, as other known MRGPRX2 agonists also induced ASM contractions that were blocked by histamine H_1 receptor antagonist (Figure S4).

In conclusion, C48/80 and HDM demonstrated distinct patterns of MC activation and smooth muscle contraction in guinea pig trachea. Both stimuli induced release of histamine and PGD_2, while only HDM challenge caused biosynthesis of CysLTs, C48/80 produced a greater release of several prostanoids. Thus, these findings support the need to characterize the differential release of MC synthesized lipid mediators and their effects in asthma.

KEYWORDS

asthma, drug allergy, histamine, mast cells, "omics" and systems biology

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CONFLICT OF INTEREST

Dr. Kolmert reports personal fees from Gesynta Pharma AB, outside the submitted work. All the other authors declare that there is no conflict of interest.

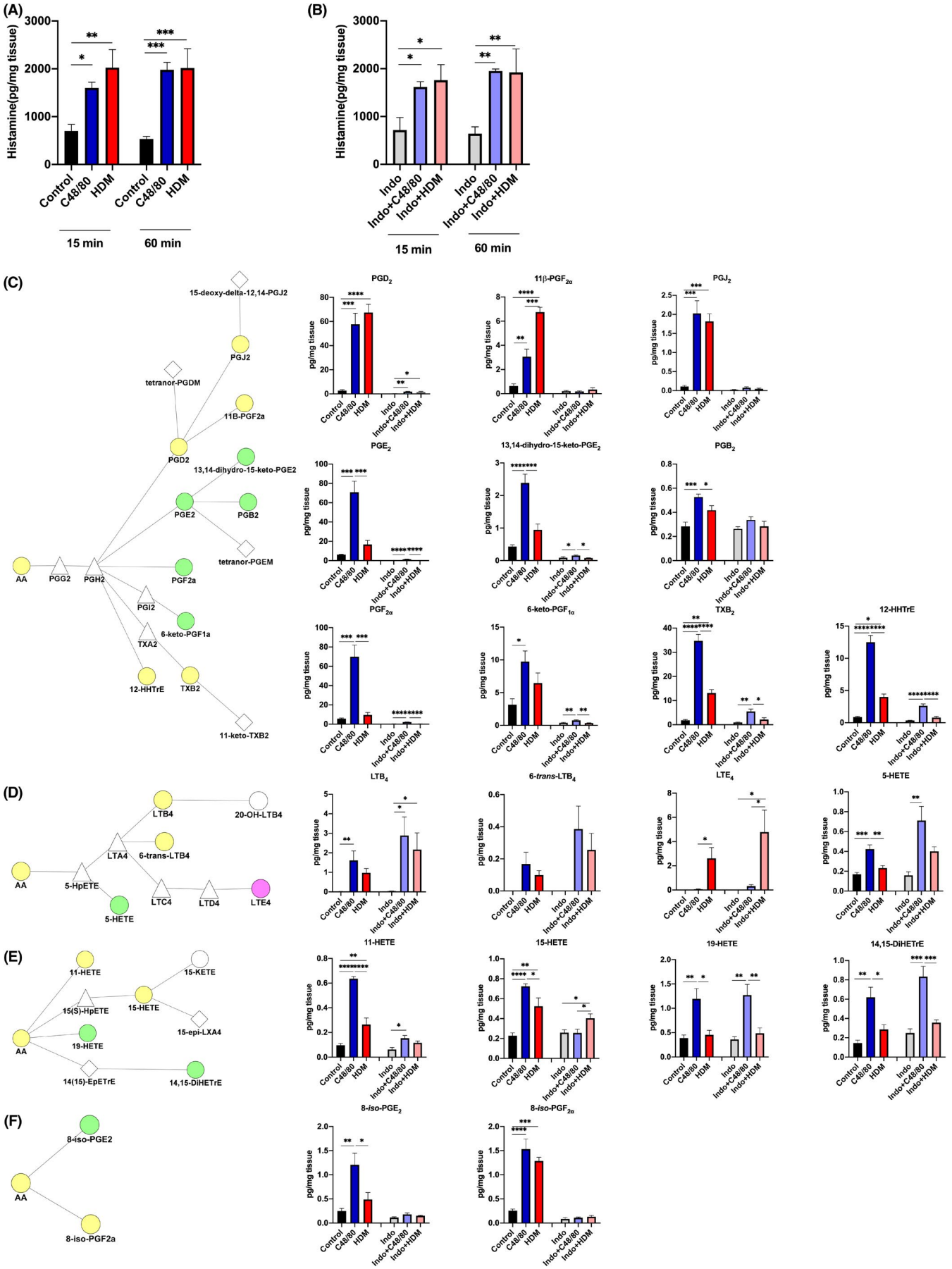
(A)
Histamine(pg/mg tissue)
Control
C48/80
HDM
15 min
60 min
(B)
Indo
Indo+C48/80
Indo+HDM
(C)
15-deoxy-delta-12,14-PGJ2
PGJ2
tetranor-PGDM
11B-PGF2a
PGD2
13,14-dihydro-15-keto-PGE2
PGE2
PGB2
tetranor-PGEM
AA
PGG2
PGH2
PGF2a
PGI2
6-keto-PGF1a
TXA2
12-HHTrE
TXB2
11-keto-TXB2
PGD2
11β-PGF2α
PGJ2
PGE2
13,14-dihydro-15-keto-PGE2
PGB2
PGF2α
6-keto-PGF1α
TXB2
12-HHTrE
LTB4
6-trans-LTB4
LTE4
5-HETE
(D)
LTB4
20-OH-LTB4
LTA4
6-trans-LTB4
AA
5-HpETE
LTC4
LTD4
LTE4
5-HETE
11-HETE
15-HETE
19-HETE
14,15-DiHETrE
(E)
11-HETE
15-KETE
15(S)-HpETE
15-HETE
15-epi-LXA4
AA
19-HETE
14(15)-EpETrE
14,15-DiHETrE
8-iso-PGE2
8-iso-PGF2α
(F)
8-iso-PGE2
AA
8-iso-PGF2a
pg/mg tissue

FIGURE 2 Mediator release after challenge with C48/80 (500 μg/mL) or HDM (10 μg/mL). Histamine release in absence (A) and presence (B) of indomethacin (Indo; 3 μM). Metabolites from arachidonic acid at 60 minutes: (C) Prostaglandins and thromboxanes, (D) FLAP/5-LOX metabolites, (E) HETEs and DiHEtrE metabolites, and (F) Isoprostanes (N = 4, *n* = 5–6). Lipid mediators not monitored are denoted (Δ), below limit of detection (LOD) (◊), detected but not changed (○), significantly changed by both C48/80 and HDM (○) (yellow), changed only by C48/80 (green) and changed only by HDM (pink). N: number of animals; *n*: number of tracheal segments

AUTHOR CONTRIBUTIONS

JL, SED, GN, and MA conceived and designed the studies. JL, JK, AKJ, and JZ carried out the studies. JL and JK acquired and analyzed the data. JL, JK, JS, CEW, SED, GN, and MA interpreted the data. JL, JK, JS, and MA wrote the manuscript draft. All authors reviewed, critically revised, and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Increasing rates of influenza vaccination were associated with lower asthma prevalence in United States children

To the Editor,

Rapidly changing asthma prevalence trends in the United States[1] suggest there are environmental and/or epigenetic factors at play, rather than alterations in population genetics.[2] Respiratory syncytial virus, rhinovirus, and influenza are common viral triggers for asthma induction or exacerbation. There is evidence to suggest that influenza vaccination is protective against asthma exacerbation.[3] We hypothesized that widespread influenza vaccination decreased