Molecular mechanisms of niacin-induced flushing

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Nicotinic acid
(niacin, B_3 vitamin, antipellagra vitamin)

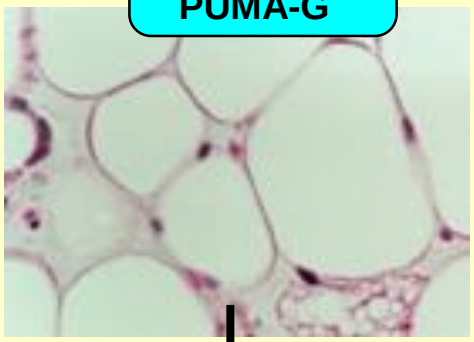
- **Physiological function:** Vitamin (precursor for NAD^+ and $NADP^+$)
- Required dose: >15–20 mg/day in the diet
- Required plasma level: 100–400 nM
- Nicotinamide is equivalent to nicotinic acid as a vitamin
- No side effects

- **Pharmacological effects:** Antidyslipidemic drug (LDL–C↓, TAG↓, HDL–C↑)
- Required dose: 500–2000 mg/day
- Required plasma level: 4–16 μM (peak concentrations: 50–300 μM)
- Nicotinamide does not show the same pharmacological effects as nicotinic acid
- Side effects: flush-reaction, gastrointestinal symptoms

Mediation of the pharmacological effects of nicotinic acid

Nicotinic acid

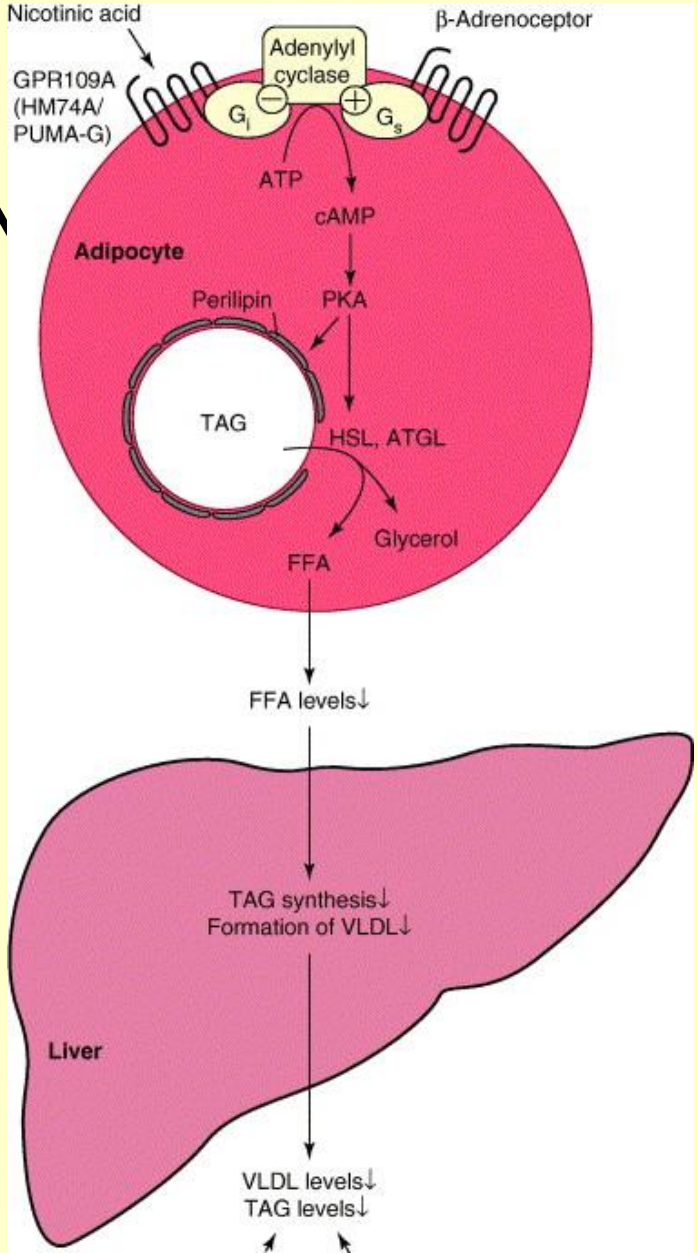
HM 74A / PUMA-G



antilipolytic effect, triglyceride levels ↓

anti-dyslipidemic effect

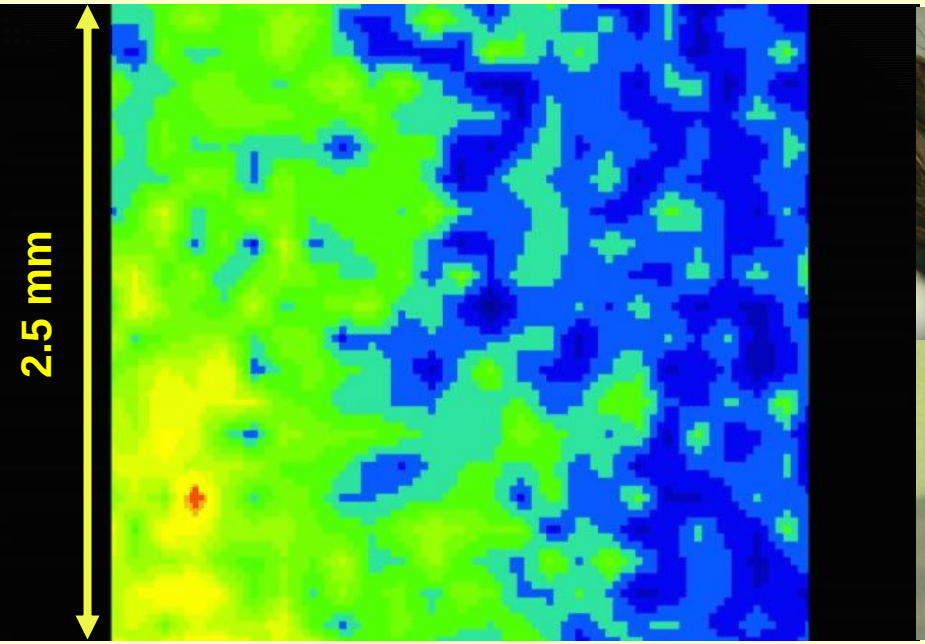
Tunaru et al. Nat Med. 9:352-355, 2003



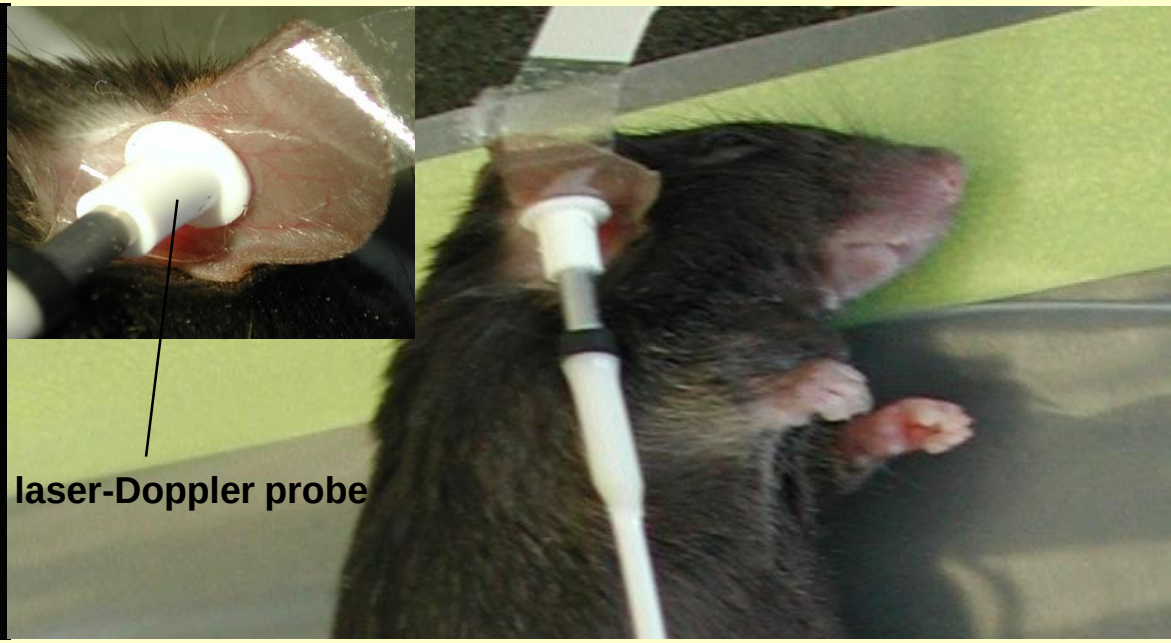
The flush-reaction

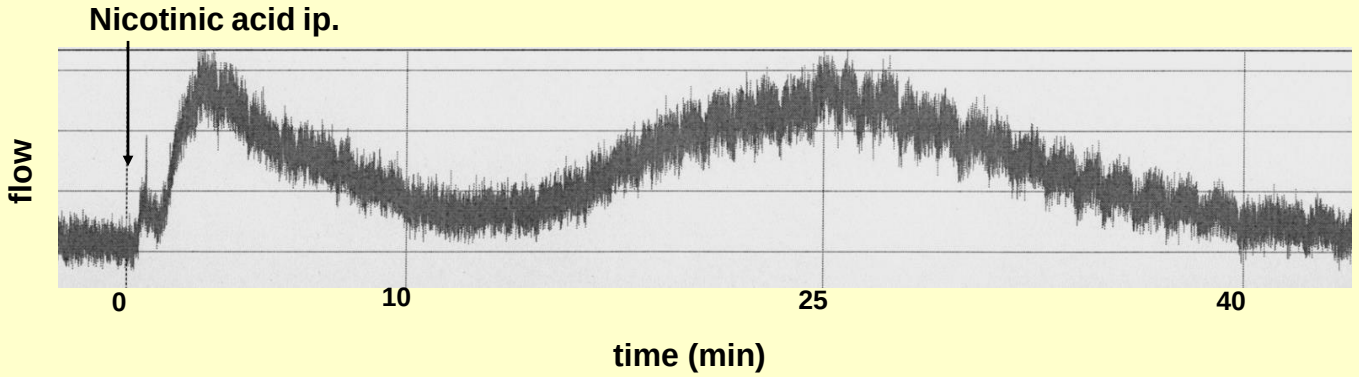
Measurement of nicotinic acid induced flushing in the mouse ear

Laser-Doppler scanner

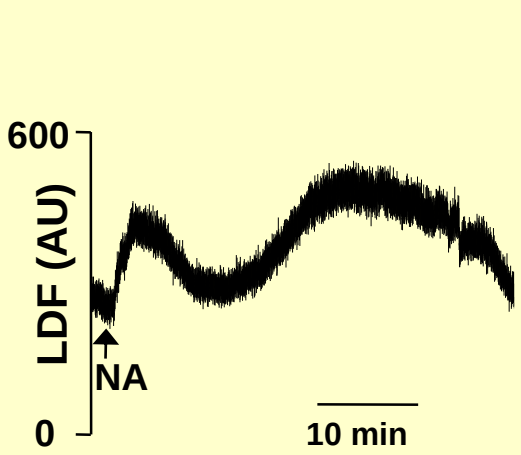


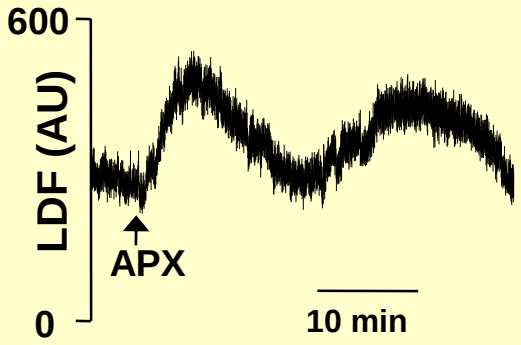
Laser-Doppler monitor

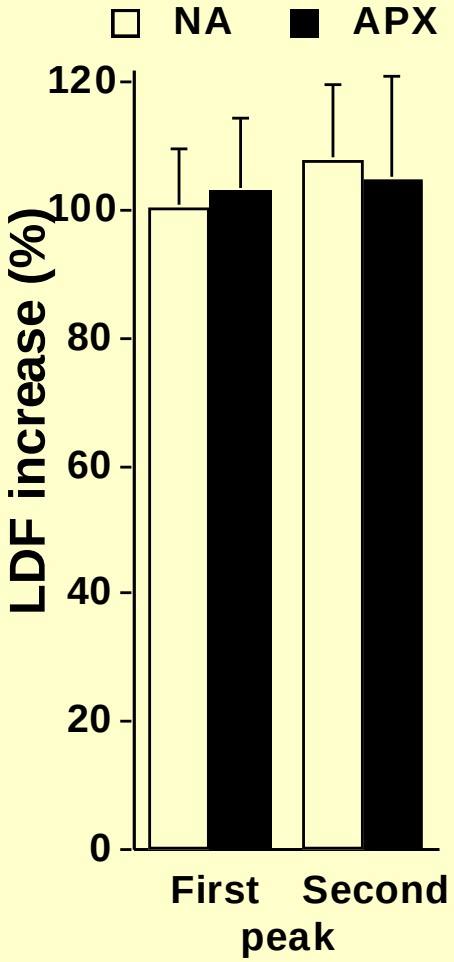




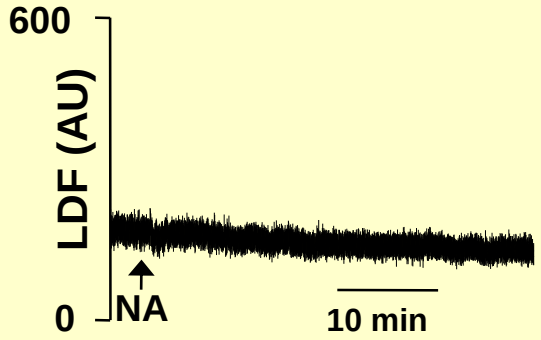
Nicotinic acid- and acipimox-induced flushing response in the mouse ear and its desensitization

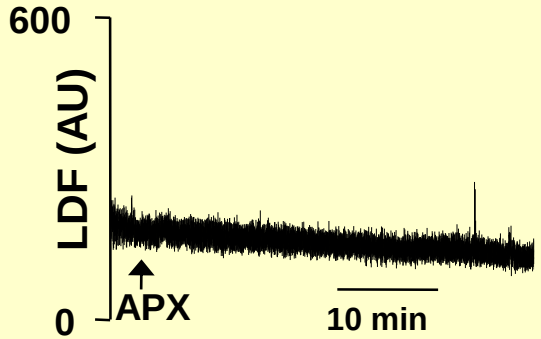






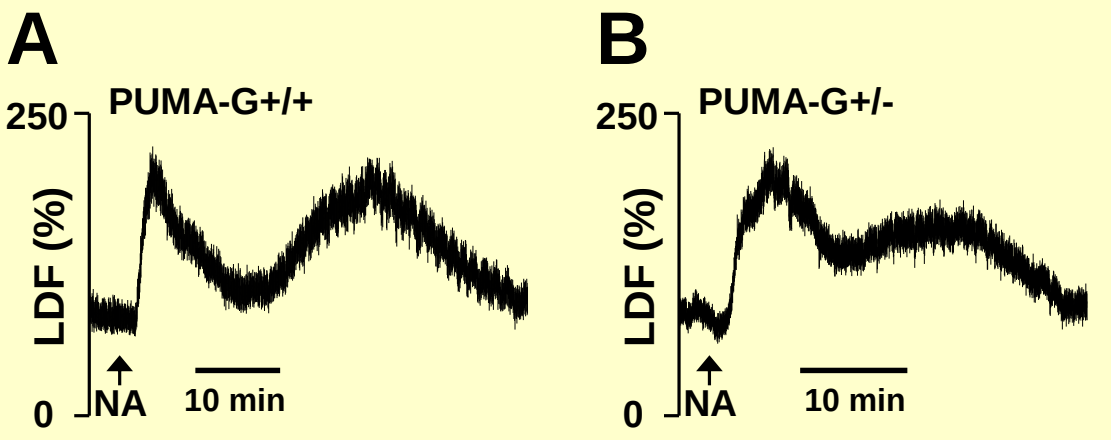
After pretreatment with NA

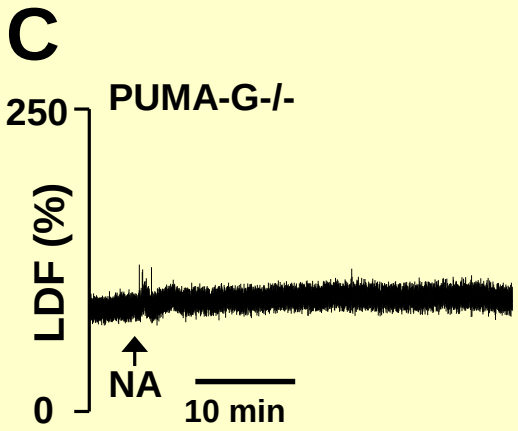


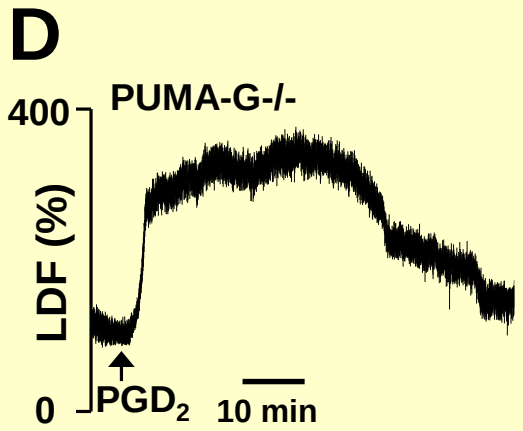


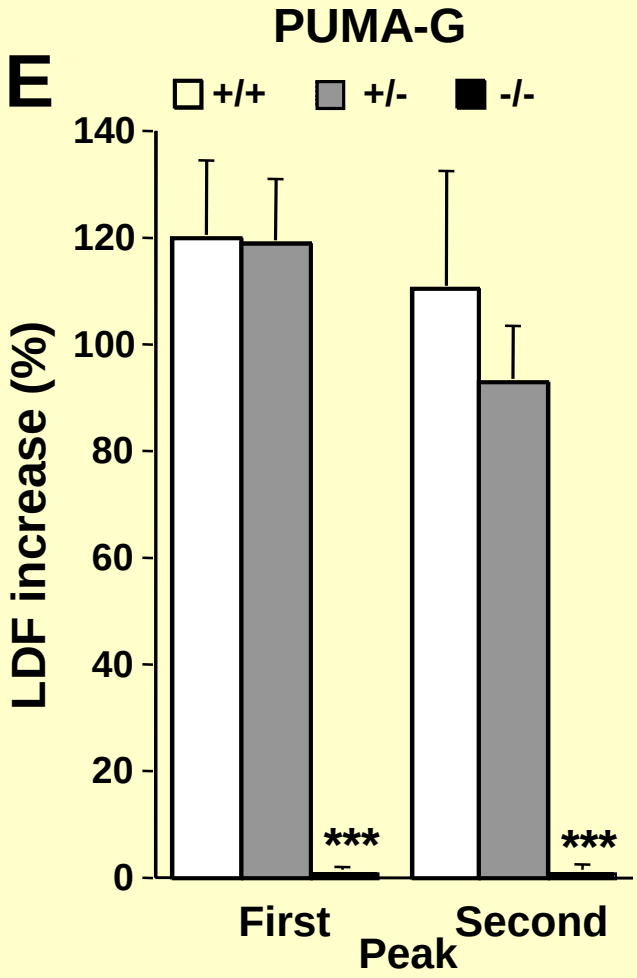
NA = nicotinic acid, APX = acipimox, both 200 mg/kg ip.

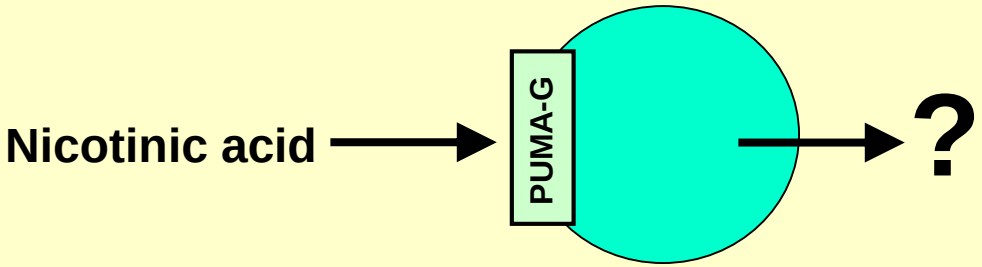
PUMA-G receptor deficiency abolishes the flushing response to nicotinic acid but not to prostaglandin D_2



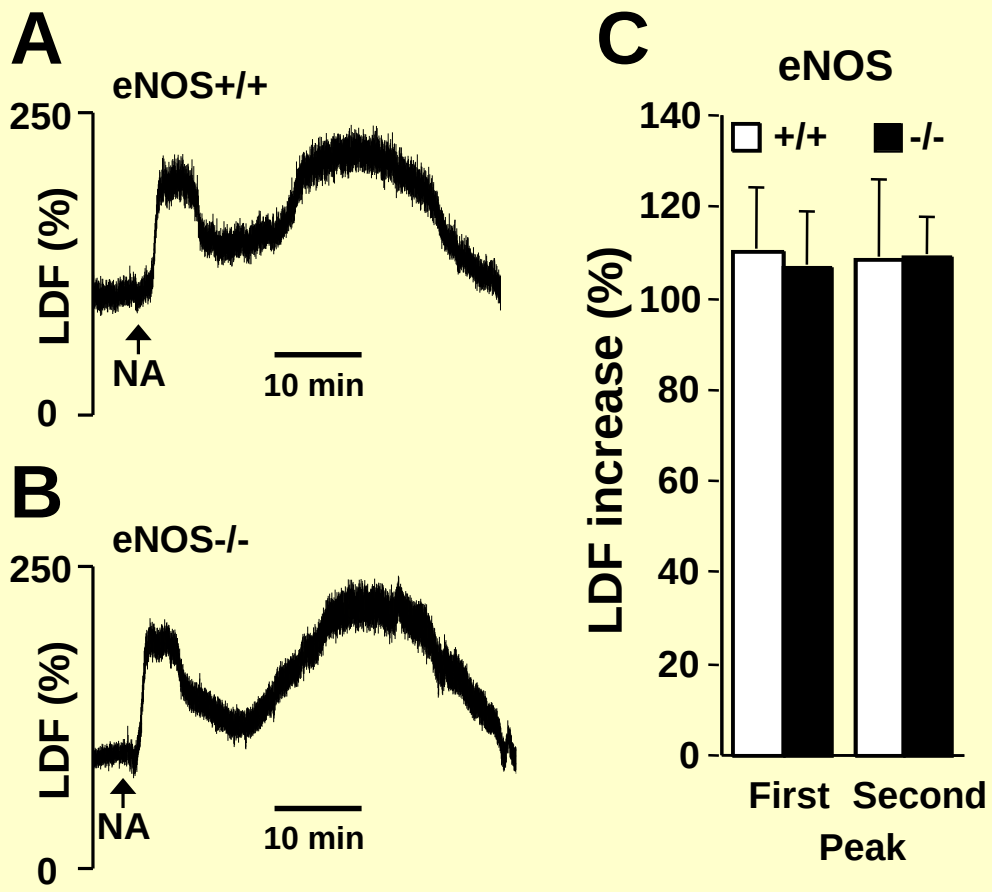




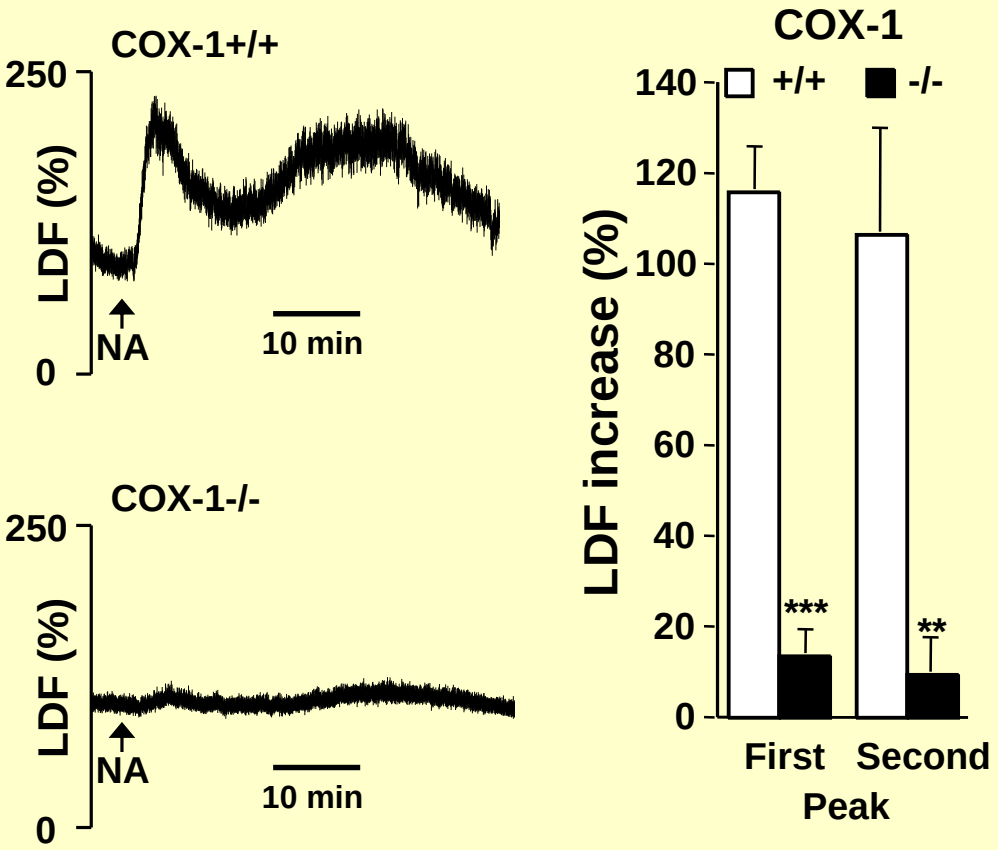


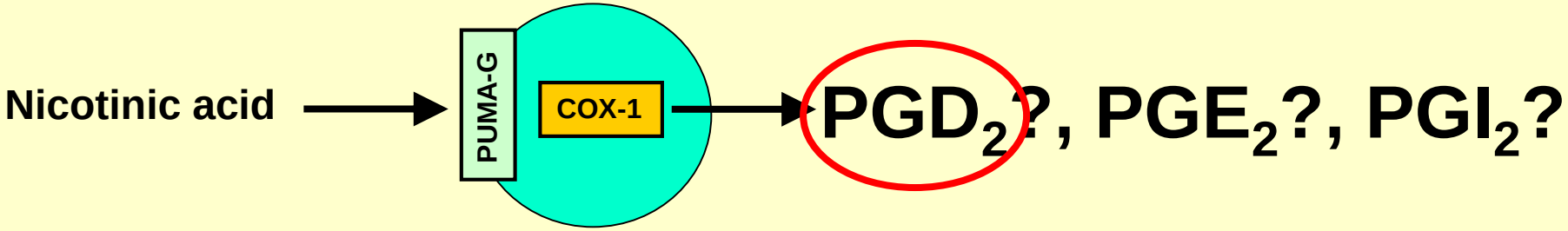


Unchanged flushing response to nicotinic acid in endothelial NO synthase deficient mice

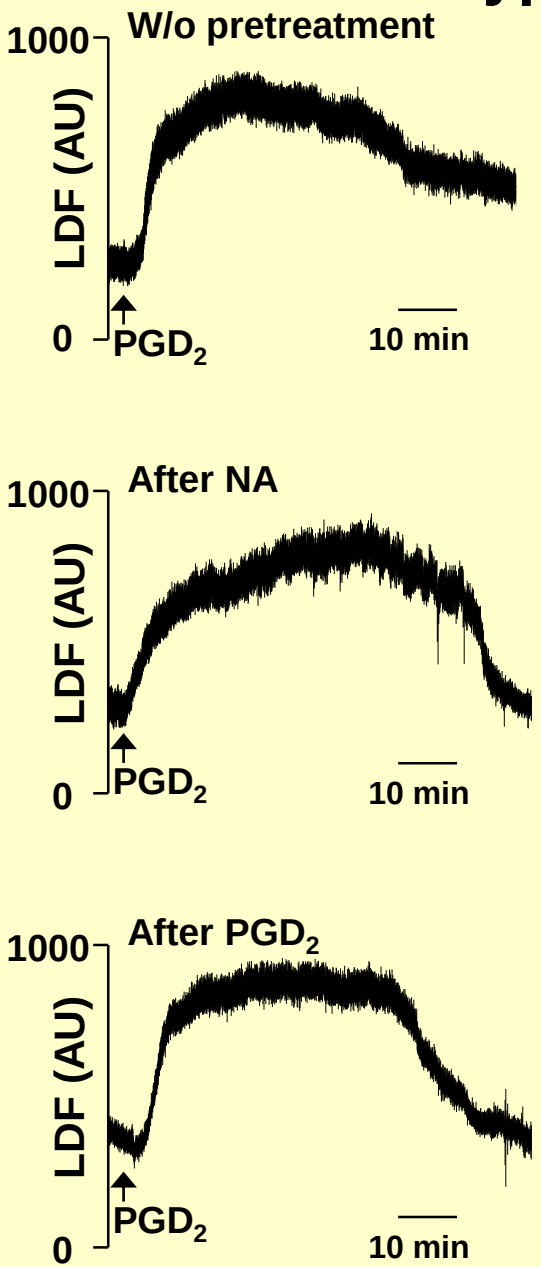


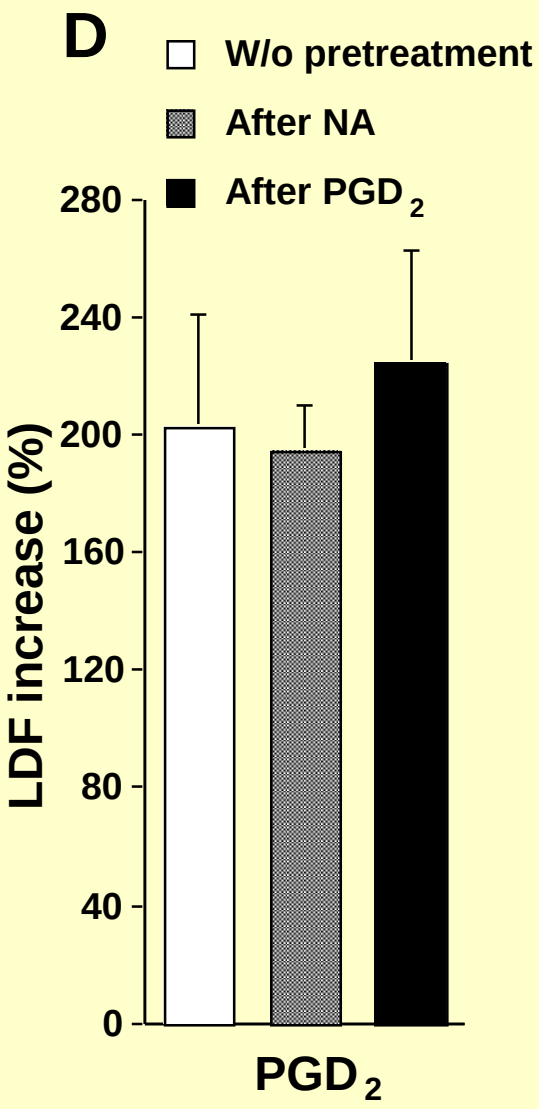
Diminished flushing response to nicotinic acid in cyclooxygenase-1 deficient mice



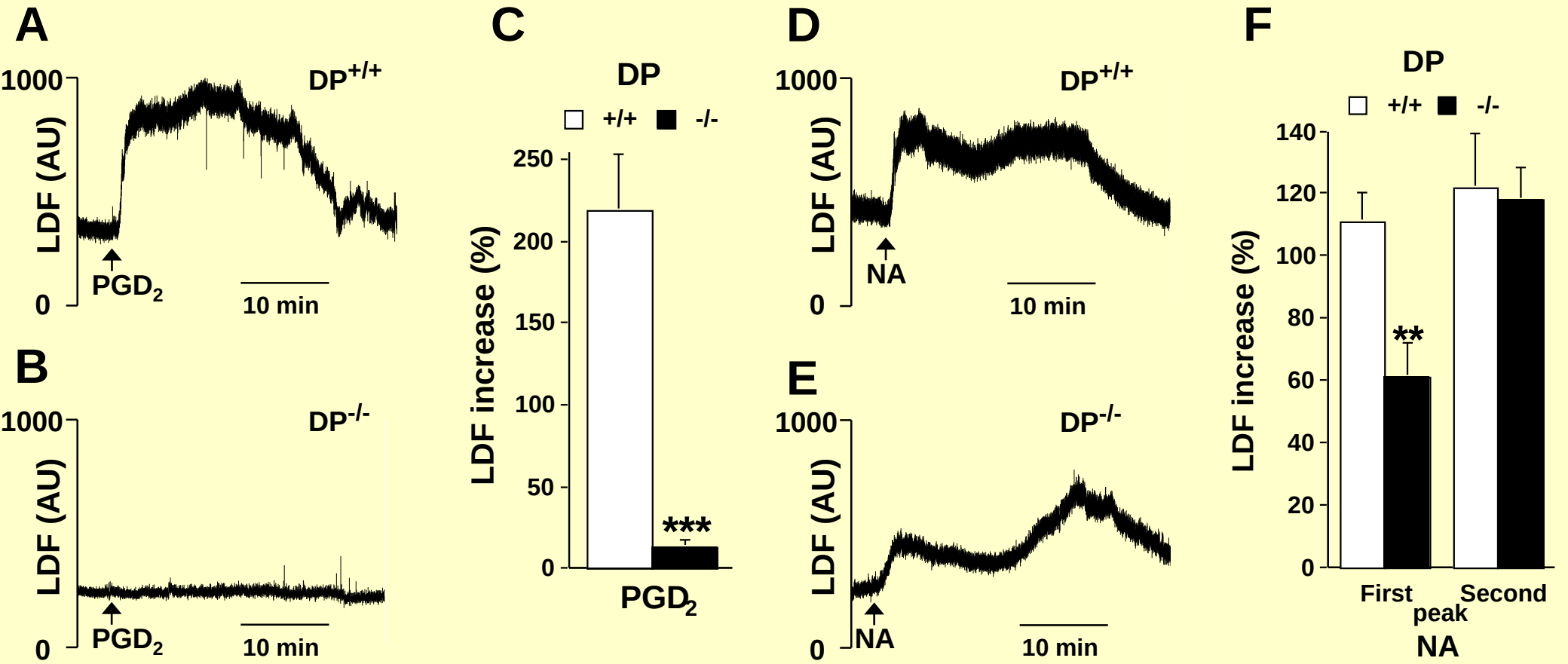


Prostaglandin D_2 induces flushing without development of tachyphylaxia

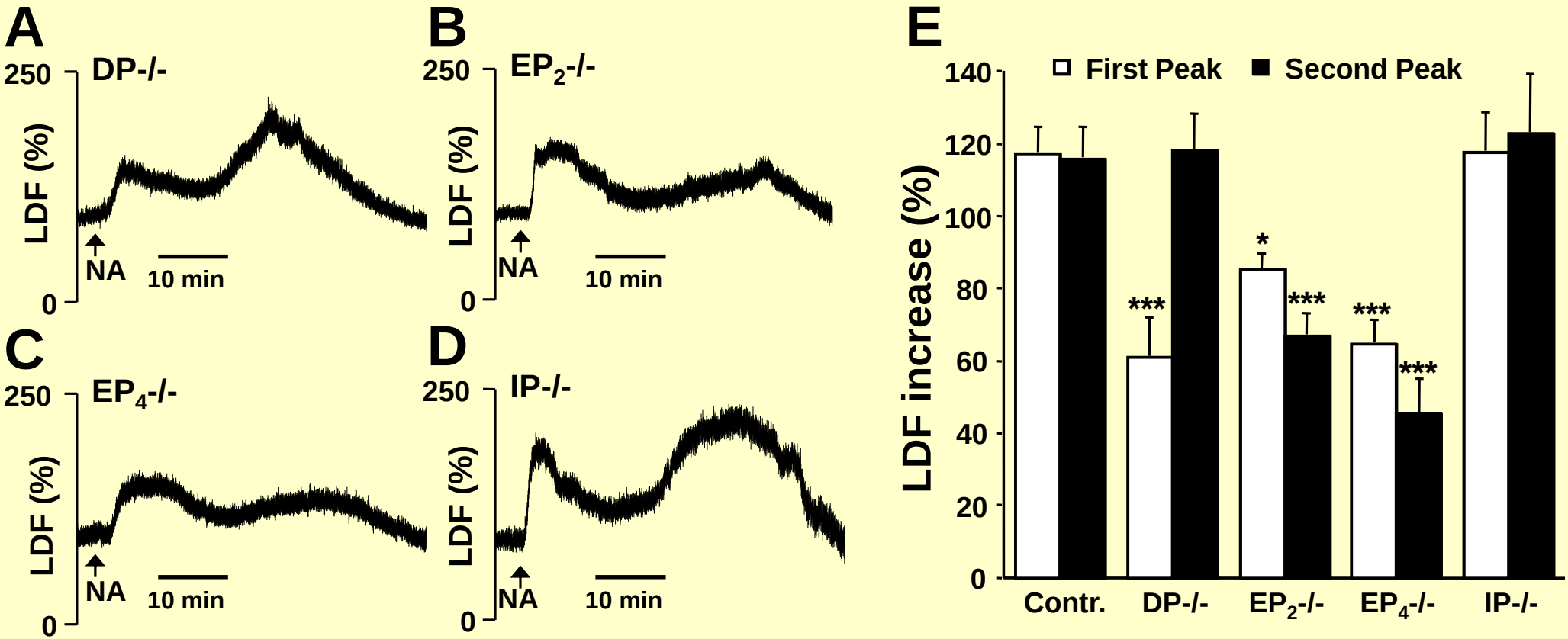


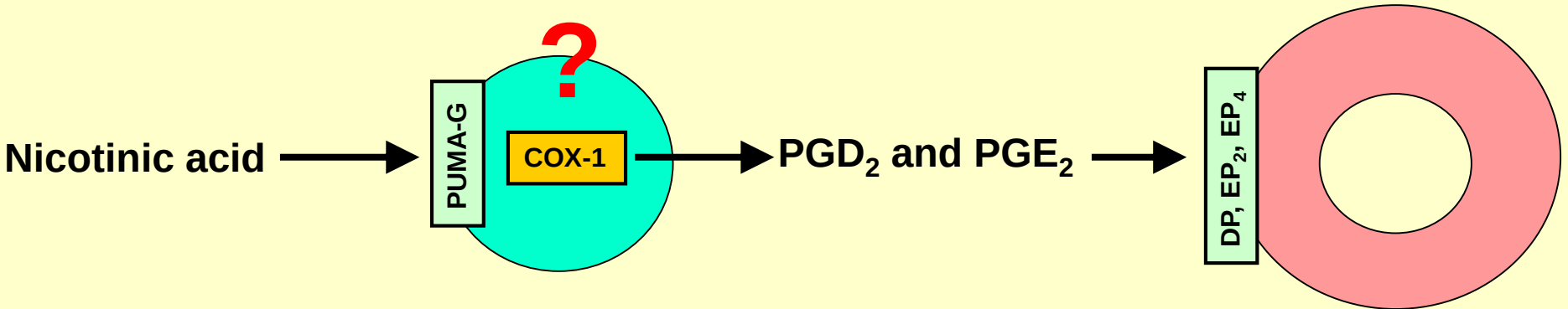


DP receptor deficiency abolishes the flushing response to PGD_2 but only partially reduces the effect of NA

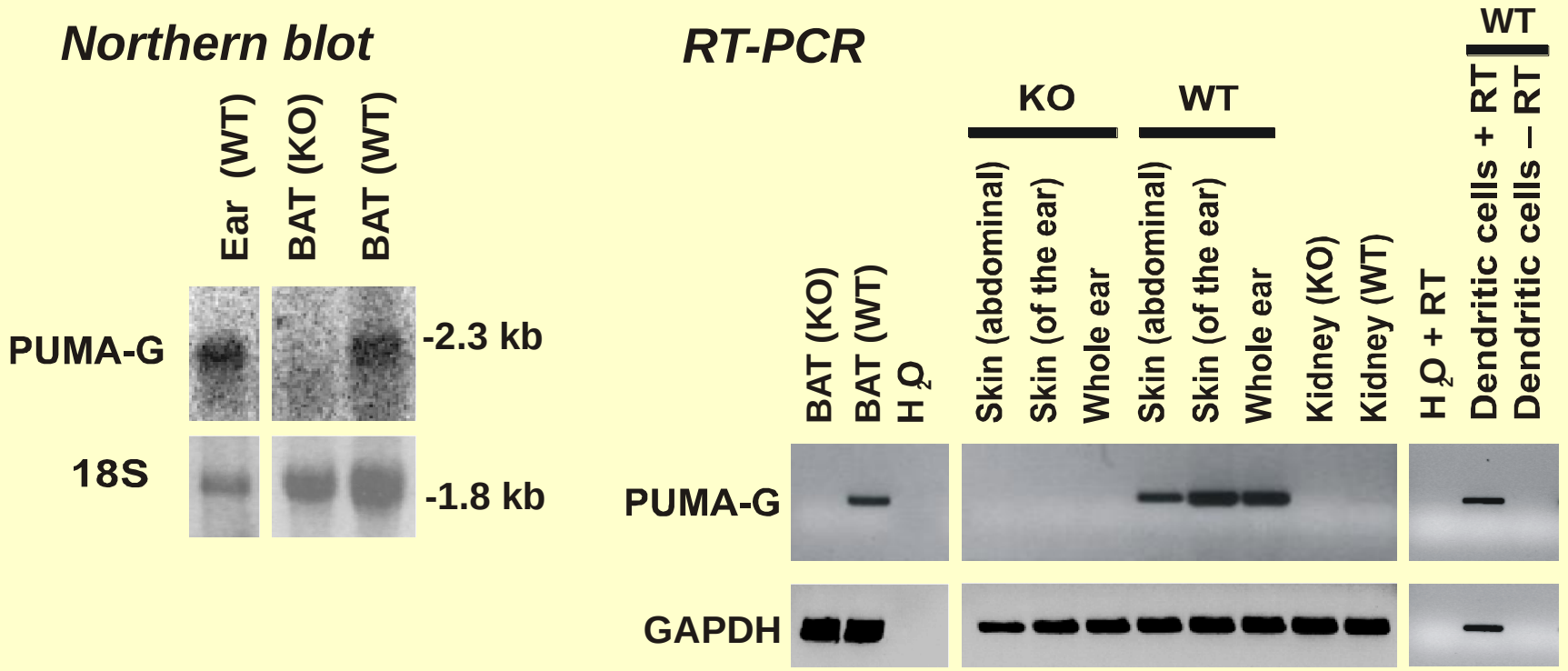


The flush-reaction is mediated by DP, EP_2 and EP_4 receptors



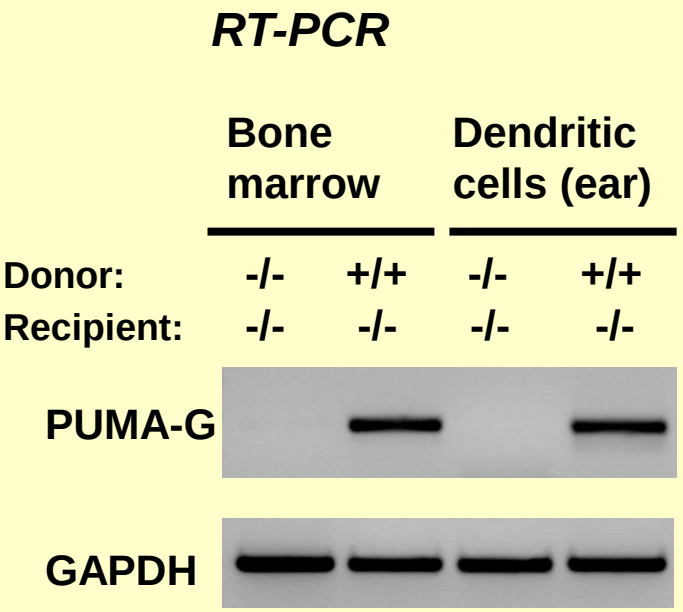


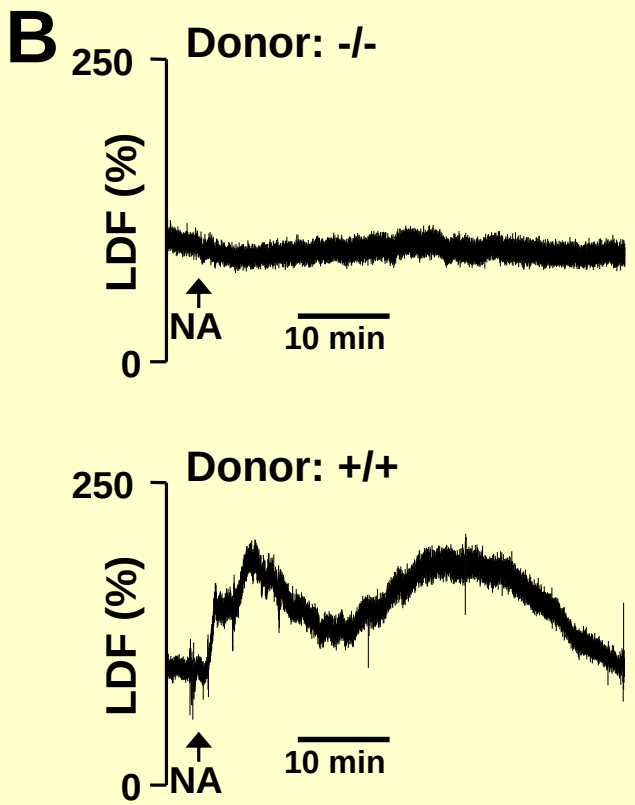
PUMA-G receptor is expressed in immune cells of the skin

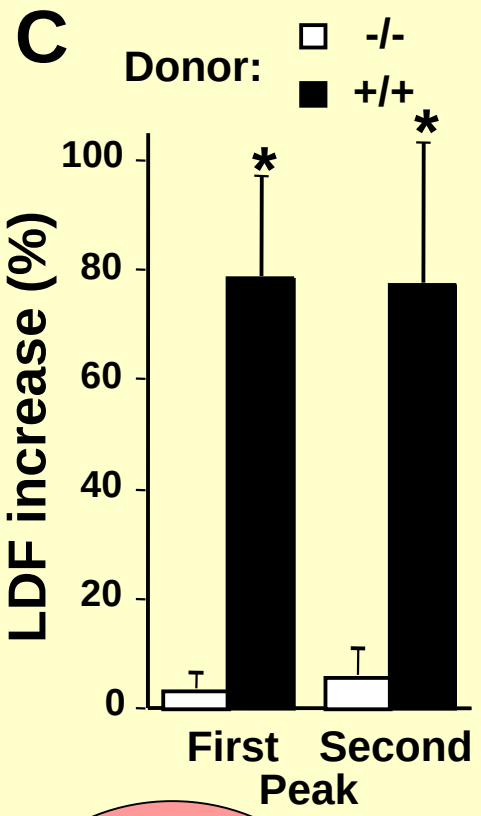


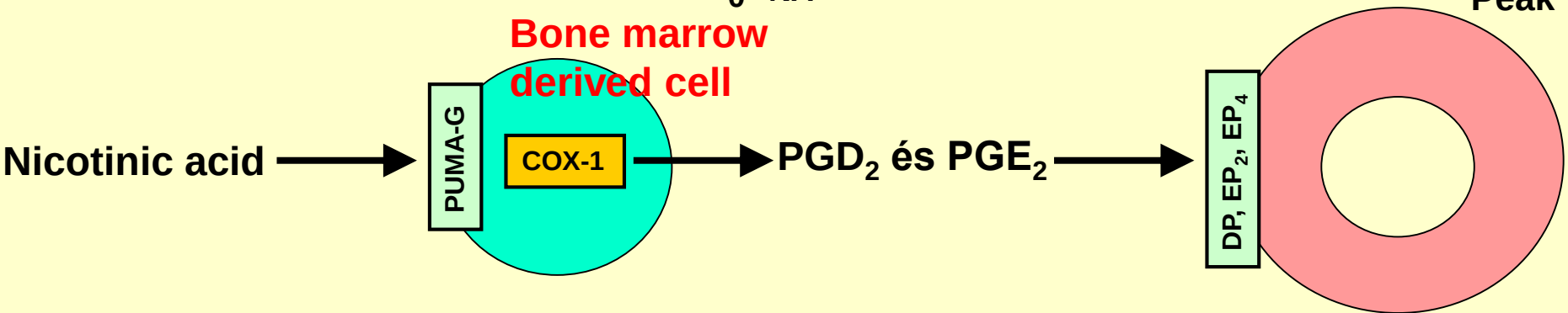
BAT = brown adipose tissue; WT = PUMA-G$^{+/+}$; KO = PUMA-G$^{-/-}$

Transplantation of wild-type bone marrow to PUMA-G$^{-/-}$ recipients restores the flushing response to nicotinic acid



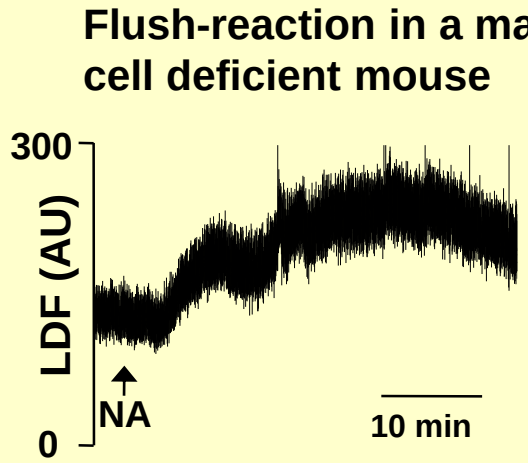






Identification of the immune-cell(s) mediating the flush reaction

Mast cells

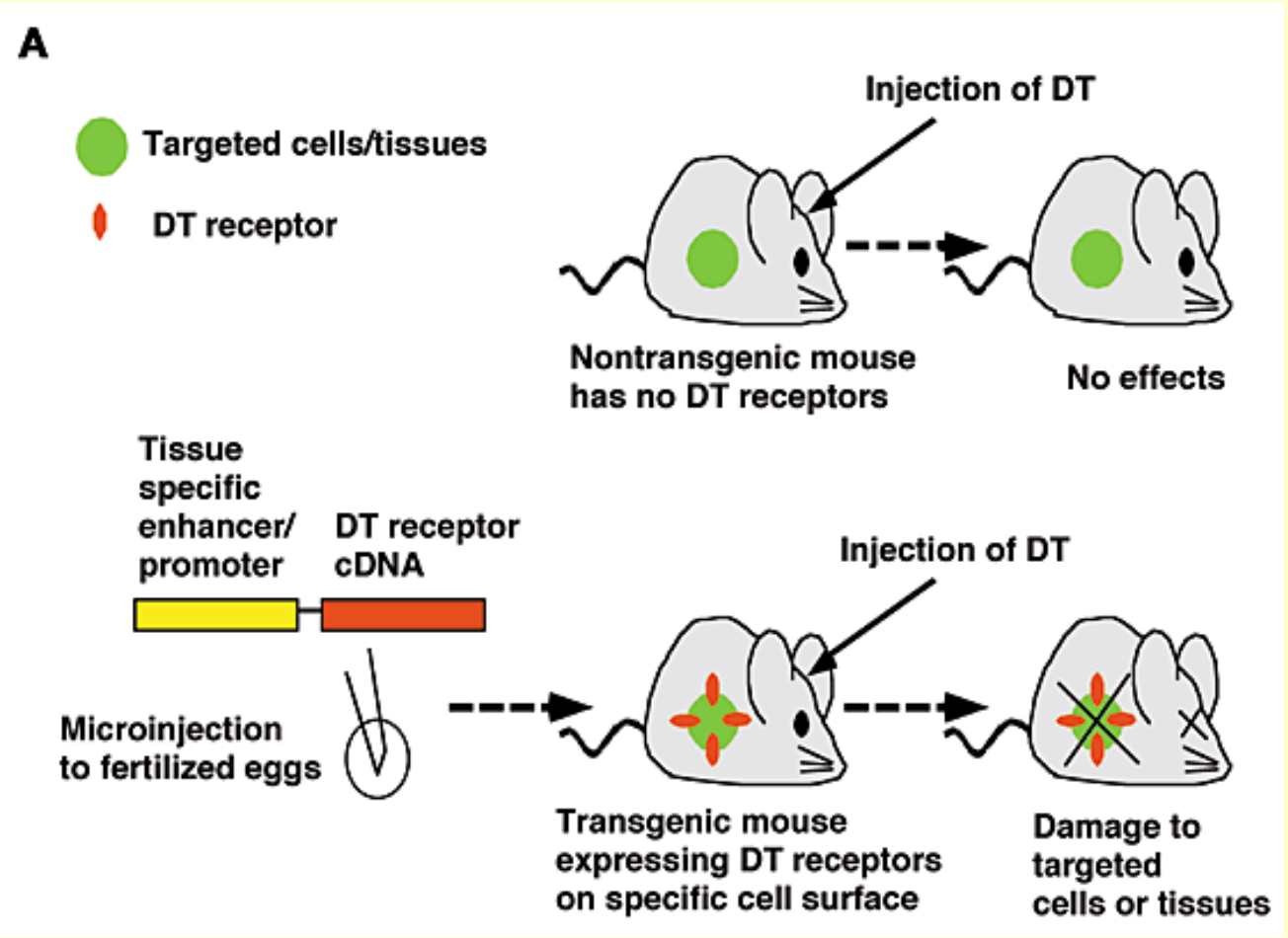


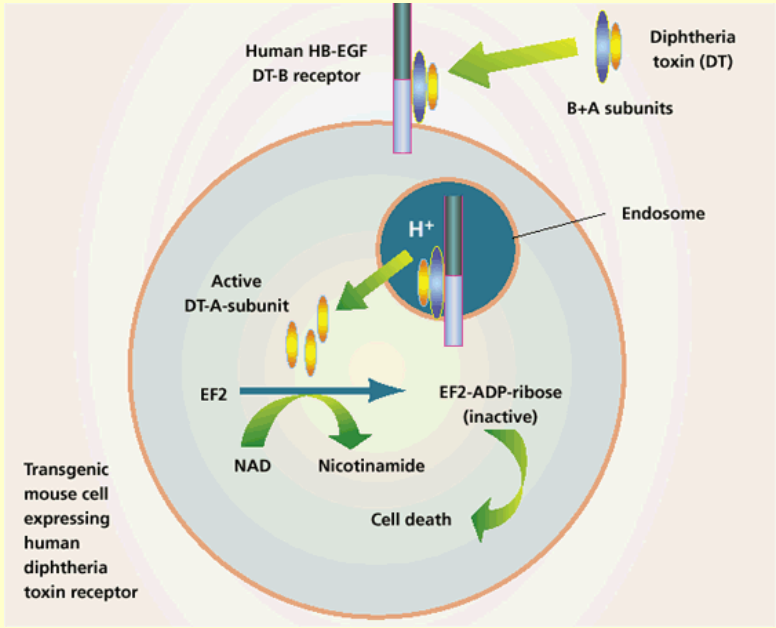
Antigen presenting cells in the skin

- Macrophage
- Dendritic cell
- Langerhans cell

Toxin receptor-mediated conditional cell knockout (TRECK)

Conditional cell ablation using the human diphtheria toxin (DT) / DT receptor (DTR) system



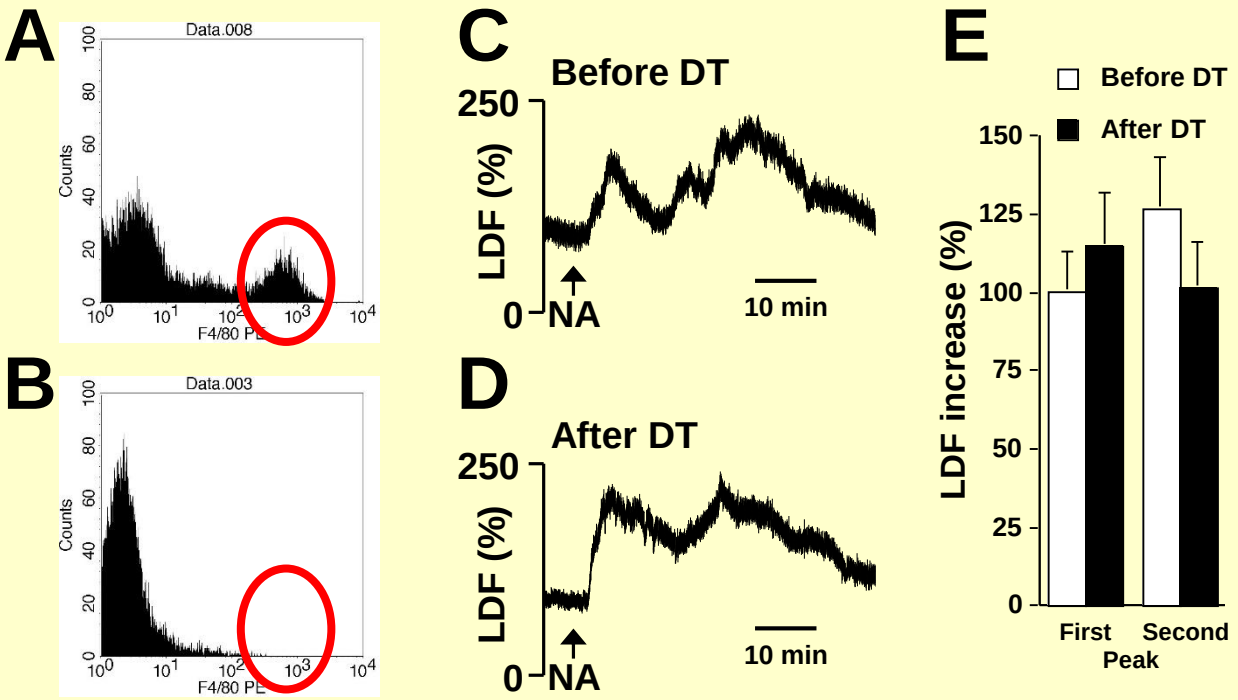


DT = diphtheria toxin

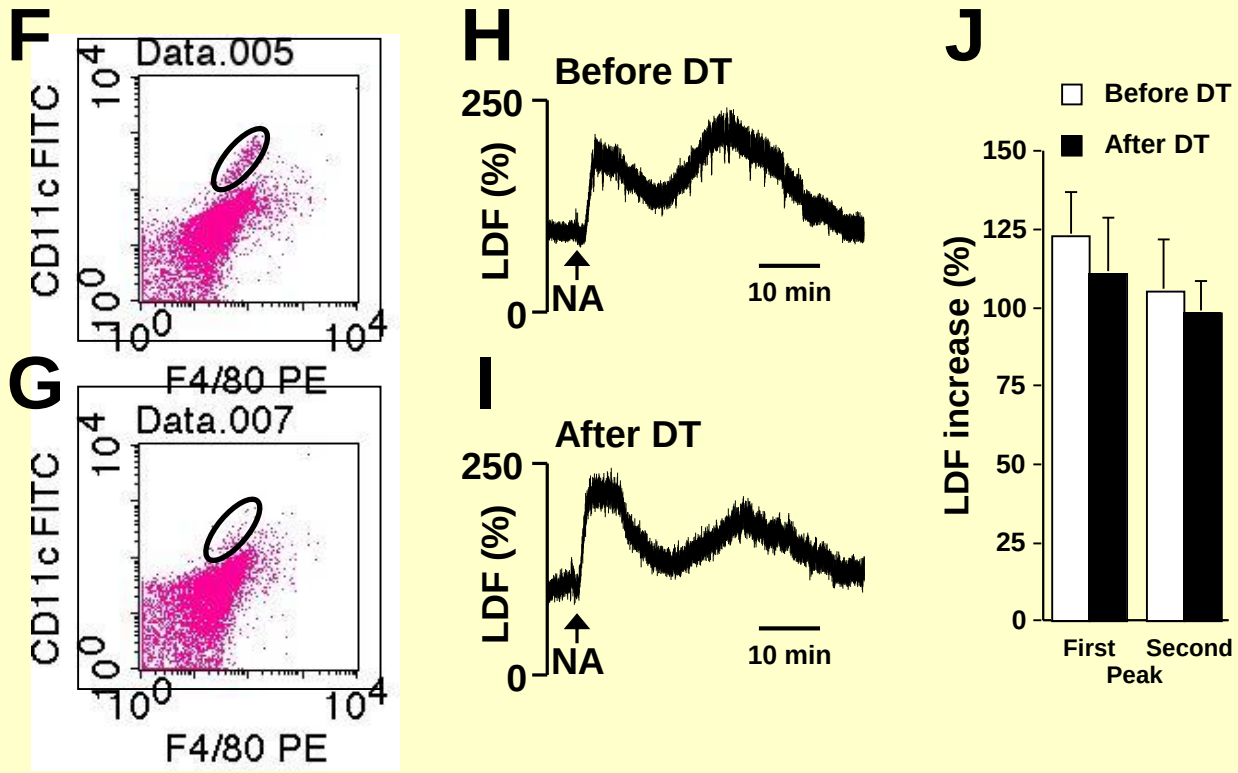
HB-EGF = heparin-binding epidermal growth factor (human DT-B receptor)

EF-2 = elongation factor 2

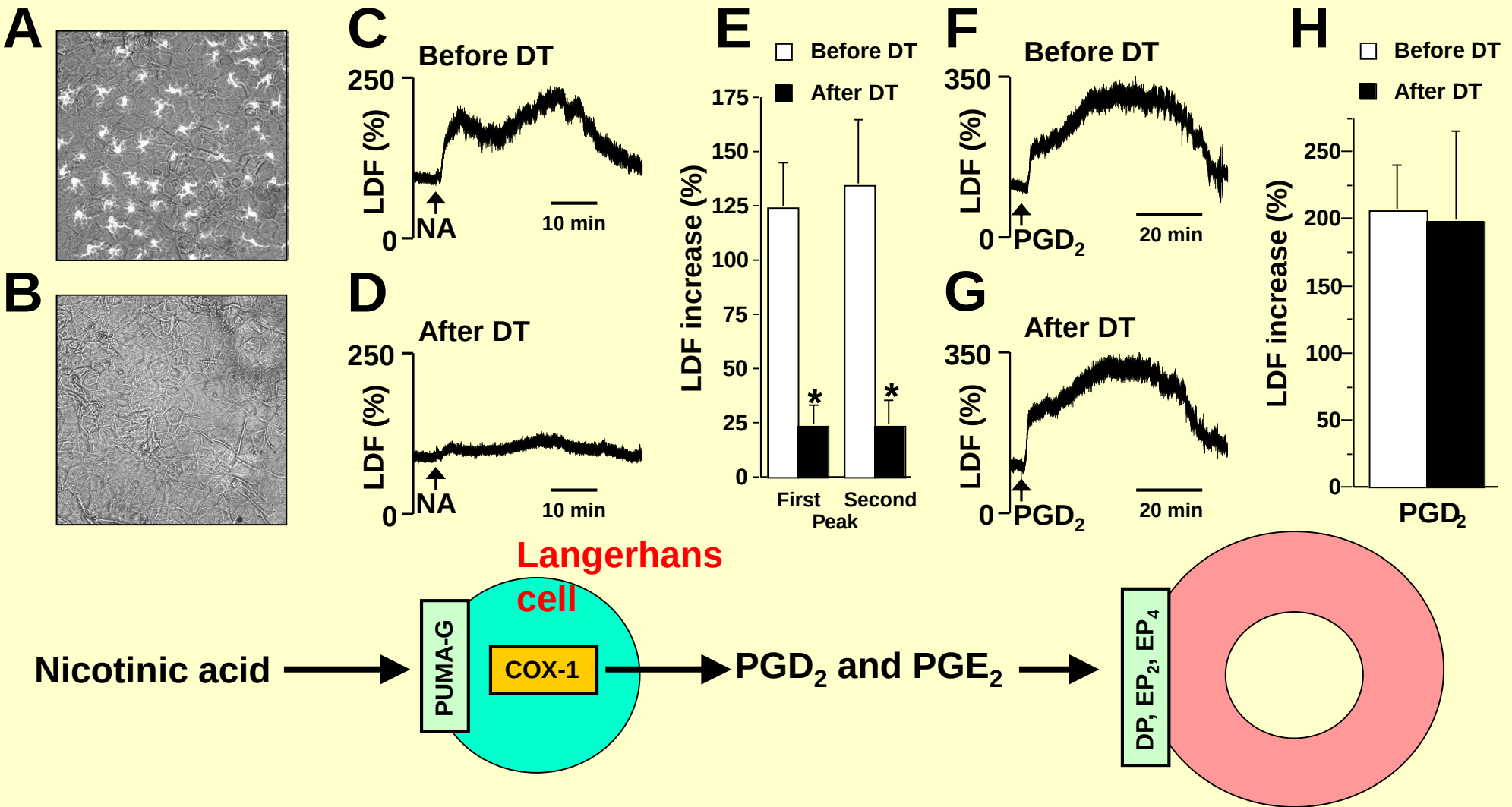
Depletion of CD-11b^{+} macrophages does not influence the flush reaction



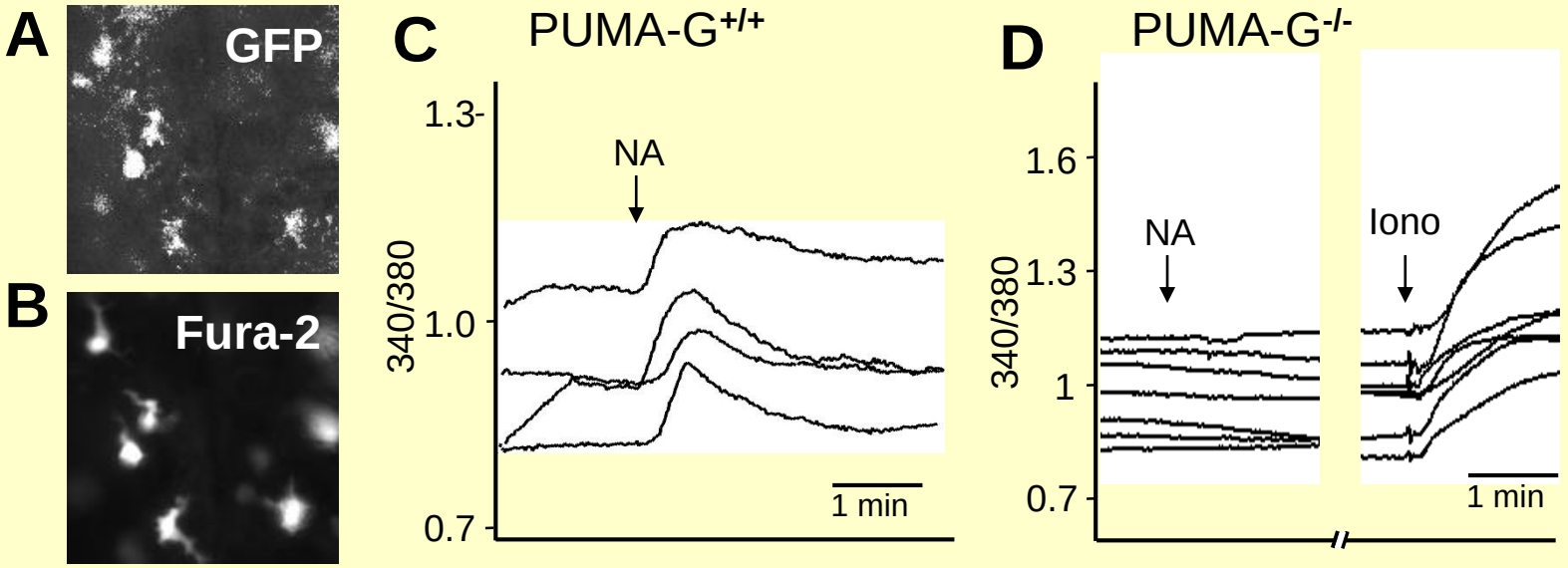
Depletion of CD-11c^{+} dendritic cells does not influence the flush reaction



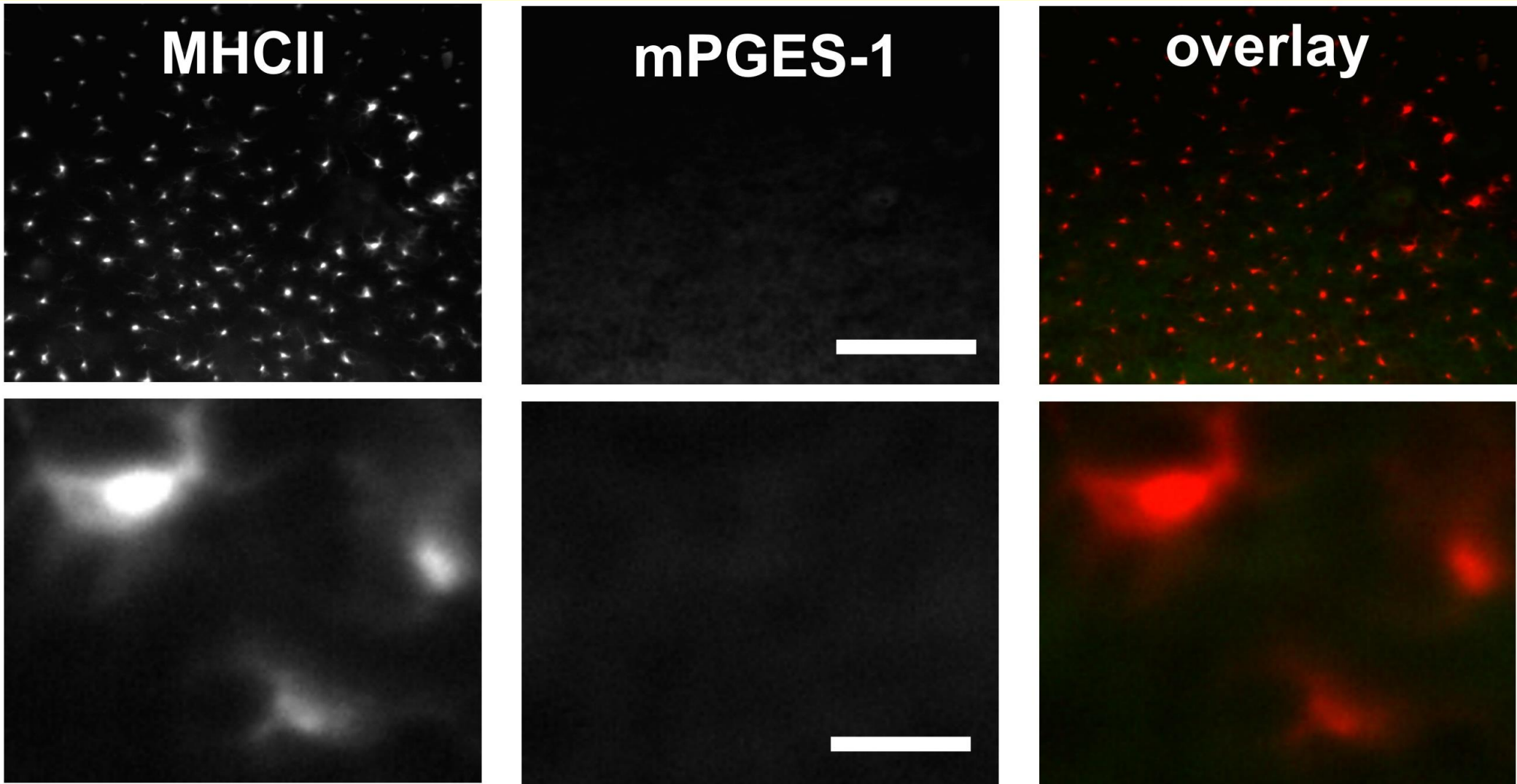
Diminished flushing response after depletion of langerin$^+$ epidermal Langerhans cells



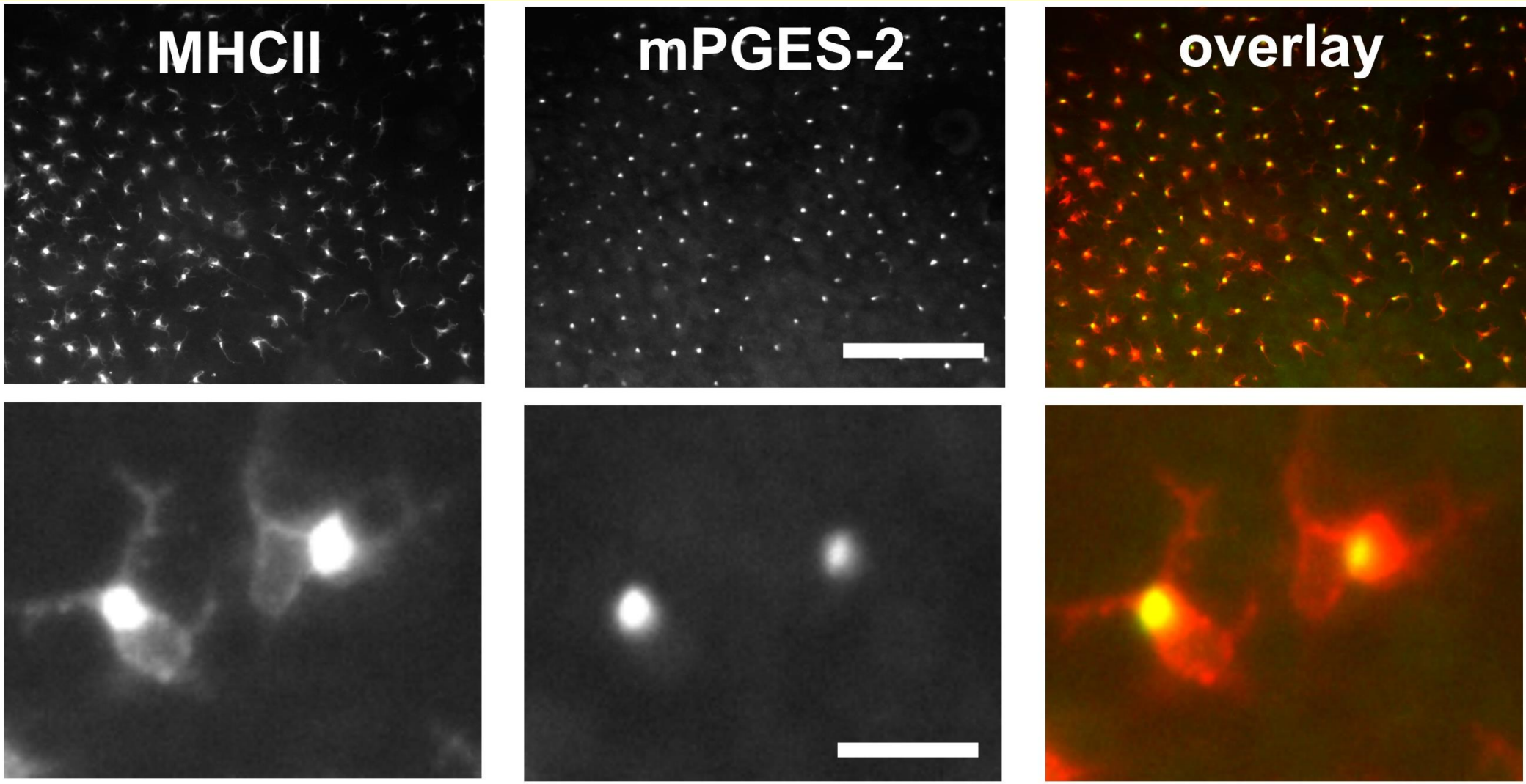
Nicotinic acid induced, PUMA-G receptor mediated $[Ca^{2+}]_i$-increase in epidermal Langerhans cells



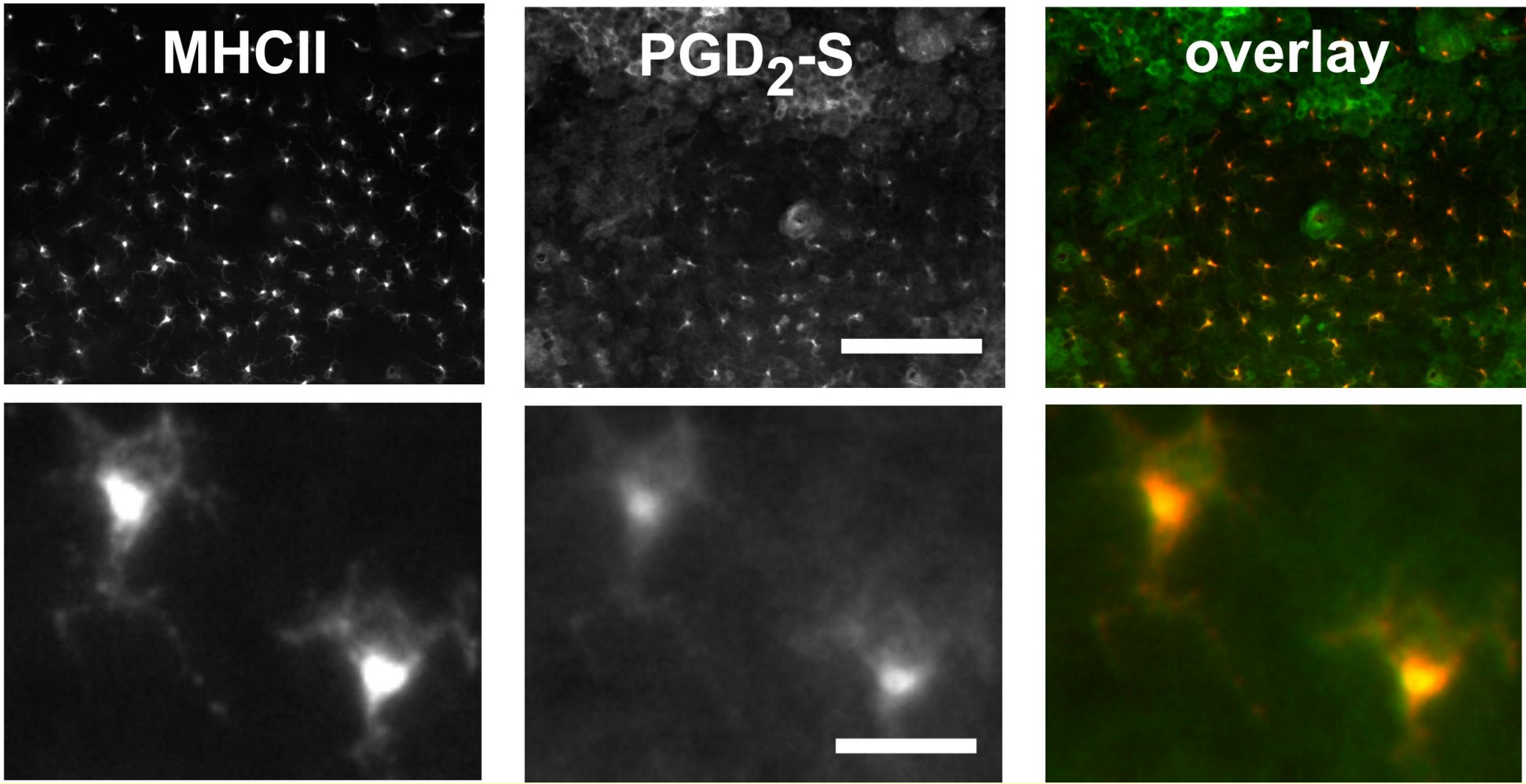
PGE_2-synthase-1 is not expressed in epidermal Langerhans cells



PGE_2-synthase-2 is expressed in epidermal Langerhans cells

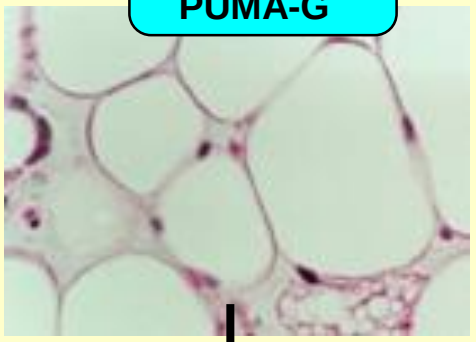


PGD_2-synthase is expressed in epidermal Langerhans cells



Summary: mediation of the pharmacological effects of nicotinic acid

HM 74A / PUMA-G



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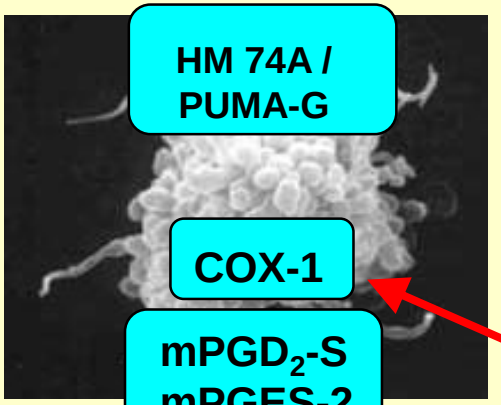


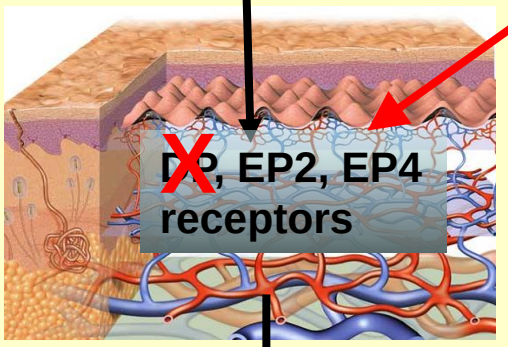
COX-1

$mPGD_2$-S
mPGES-2

Epidermal Langerhans cells

Potential drug targets for the prevention of the flushing

PGD_2 and PGE_2



flush

Cheng et al.: Antagonism of the prostaglandin D_2 receptor 1 suppresses nicotinic acid-induced vasodilation in mice and humans. PNAS 103: 6682; 2006

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Benyó et al. Mol. Pharmacol. 70:1844-1849, 2006

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Thanks for your attention!