endo-cannabinoid receptor CB1 antagonist) posses anti-inflammatory actions that, may add to its beneficial metabolic effects in the prevention of atherosclerosis.
Objectives: We have assessed whether treatment with rimonabant regulates peripheral blood monocyte FcgRs expression.
Methods: The surface expression of the human FcgRs, FcgRI, FcgRIIa, FcgRIIb, and FcgRIII was determined by FACS analysis with specific monoclonal antibodies in peripheral blood monocytes (PBM) obtained from patients treated with rimonabant during at least 6 months.
Results: Treatment with rimonabant (20 mg/day) enhanced the surface expression of PBM-FcgRIIb by 39 ± 3% ($P < 0{\cdot}001$). The expression of both, PBM-FcgRIII and PBM-FcgRIII was significantly decreased by treatment with rimonabant ($P < 0{\cdot}01$). Decreased expression of PBM-FcgRIIb was associated with increased plasmatic levels of adiponectin ($r = 0{\cdot}871$, $P < 0{\cdot}001$), and with decreased plasmatic levels of C reactive protein ($r = 0{\cdot}779$, $P = 0{\cdot}037$).
Conclusions: Treatment with rimonabant decreases peripheral blood monocyte FcgRs expression. This anti-inflammatory action of rimonabant may contribute to its known metabolic effects in the prevention of atherosclerosis.

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Treatment with rimonabant regulates human granulocyte Fc-gamma receptor expression

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Background: Granulocyte (G) Fc-gamma receptors (FcγR) are important in host defence against infection and in the pathophysiology of inflammation. Treatment with the endocannabinoid receptor CB1 antagonist, rimonabant, decreases inflammatory mediators of atherosclerosis.
Objectives: We have assessed whether treatment with rimonabant regulates G-FcγR expression.
Methods: The surface expression of the human FcγRs, FcγRI, FcγRIIa, FcγRIIb, and FcγRIII was determined by FACS analysis with specific monoclonal antibodies in G obtained from patients treated with rimonabant during at least 6 months.
Results: Treatment with rimonabant (20 mg/day) significantly enhanced the surface expression of G-FcγRIIb by 27 ± 2%. The expression of G-FcγRIII was significantly decreased by treatment with rimonabant. Decreased expression of G-FcγRIIb was associated with increased plasmatic levels of adiponectin ($r = 0{\cdot}775$, $P < 0{\cdot}005$), and with decreased plasmatic levels of C reactive protein.
Conclusions: Treatment with rimonabant regulates human granulocyte FcγR expression. This anti-inflammatory action of rimonabant may contribute to their benefit preventing the metabolic syndrome and atherosclerosis.

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Membrane translocation of P-Rex1 is regulated by PI3K and heterotrimeric G proteins

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Background: P-Rex1 regulates GPCR-dependent Rac2 activation and ROS formation in neutrophils and neutrophil recruitment to inflammatory sites. P-Rex1 is directly and synergistically activated by the $\beta\gamma$ subunits of heterotrimeric G proteins and by the PI3K-generated second messenger PIP_3. The subcellular localisation of P-Rexl is cytosolic. We have investigated here the localisation P-Rex1 upon cell stimulation.
Methods: Experiments were performed in Sf9 insect cells, as these can produce several ectopic proteins concomitantly without compromising expression levels. We infected Sf9 cells with viruses to produce epitope-tagged P-Rex1, p110/p101 PI3K, and / or Gβ1γ2 subunits. After protein production, cells were serum-starved, sonicated and fractionated by differential centrifugation. Total lysates, post-nuclear supernatants (10,000xg), cytosol (100,000xg supernatant) and plasma-membrane (100,000xg pellet) were collected and Western blotted for P-Rex1, PI3K, and G$\beta\gamma$ subunits.
Results: In unstimulated cells, 95% of P-Rex1 was cytosolic. Coexpression of P-Rex1 with either PI3K or G$\beta\gamma$ subunits resulted in a small increase in P-Rex1 membrane localisation. In contrast, concomitant expression of P-Rex1 with both PI3K and G$\beta\gamma$ subunits resulted in strongly synergistic P-Rex1 membrane localisation. Use of a panel of P-Rex1 mutants showed that the DH and PH domains of P-Rex1 are sufficient for membrane localisation, but the other domains of P-Rex1 are required to keep membrane localisation low in unstimulated cells. We are currently investigating any correlation between P-Rex1's subcellular localisation and its catalytic activity.
Conclusions: The two stimuli of P-Rex1's GEF activity, G$\beta\gamma$ subunits and PIP_3, are produced at the plasma membrane, but P-Rex1 localisation in basal cells is cytosolic. The work presented here shows that G$\beta\gamma$ subunits and PIP_3 synergistically confer membrane translocation of P-Rex1.

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Ligation of leukotriene B4 receptor BLT1 in human endothelial cells generates a signal via the MAP kinase pathway leading to gradually increases of adhesive events and of release of MCP-1, IL-8 and nitric oxide

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Leukotriene B4 (LTB_4), a powerful chemotactic and immune modulating lipid, signals via distinct G-protein-coupled surface receptors, denoted BLT. Recently, we reported that BLT1 is the predominating BLT expressed on human umbilical vein endothelial cells (HUVEC). Here, we found that LTB_4 stimulation of HUVEC causes adhesion of neutrophils, up-regulation of E-selectin, ICAM-1 and VCAM-1, release of the granule-stored proteins MCP-1 and IL-8, and of nitrite. As L-NAME inhibited the nitrite release, this is suggested to reflect NO production. Adhesion of neutrophils and release of MCP-1, IL-8 and NO required only 15 min to be expressed, but robust increases, similar in magnitude to what lipopolysaccharide conferred, were observed also after 3–7 h, whereas up-regulation and the adhesion molecules peaked at 4–6 h. Using BLT_1 and $_{-2}$ specific blockers we found that these responses were mediated by BLT1. Moreover, they were mediated by the MAP kinase/Erk pathway, whereas no activation of NKκB p65, c-jun or Elk signaling was observed. As IL-8 and MCP-1 plays a role in neutrophil and monocytes recruitment our findings may have functional consequences in the early vascular responses to inflammation. Moreover, the results point to BLT receptors as potential targets for pharmacological intervention in vasculitides of various causes.

