CYSTEINYL LEUKOTRIENES IN HUMAN ENDOTHELIAL CELLS: SYNTHESIS AND ACTIVITIES

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The cysteinyl leukotrienes represent an important class of inflammatory mediators arising from the oxidative metabolism of arachidonic acid. Although their contribution to the inflammatory response has been clearly established in airway diseases such as asthma, cysteinyl leukotrienes can also affect the cardiovascular system, where endothelial cells play a critical role at the interface between the bloodstream and tissues, regulating the influx of cells and plasma proteins during the inflammatory process. We provide evidence that endothelial cells can synthesize the potent inflammatory mediator leukotriene C_4, through the activity of microsomal glutathione S-transferase II (mGST-II), not affected by compounds inhibiting the leukotriene C_4-synthase. We show that this enzyme is strategically located on the membranes of endothelial transcytotic vescicles. Endothelial cells mainly express the Cysteinyl Leukotriene-2 ($CysLT_2$) receptor subtype, and we show that cysteinyl leukotrienes can raise intracellular Ca^{2+}, cause myosin light-chain kinase activation, stress fiber formation, and endothelial cell contraction through the activity of a PTX-insensitive, G-protein coupled $CysLT_2$ receptor. Administration of the substrate for mGST-II, namely leukotriene A_4, also resulted in myosin light-chain kinase activation and significant changes in endothelial cell monolayers permeability, clearly showing the ability of leukotriene C_4 to act on endothelial cells in an autocrine fashion. The data presented suggest that the $CysLT_2$ receptor expressed by endothelial cells may represent an important target for novel antiinflammatory drugs.

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