DIFFERENTIAL CONTRIBUTION OF CYCLOOOXYGENASE-ISOZYMES TO THE GENERATION OF PROSTACYCLIN AND PROSTAGLANDIN E_2 BY ENDOTHELIAL CELLS IN RESPONSE TO STEADY LAMINAR SHEAR STRESS

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Prostacyclin (PGI_2) and prostaglandin(PG)E_2, the major prostanoids released from endothelial cells, play different roles in cardiovascular(CV) homeostasis. PGI_2 is a general restraint on endogenous stimuli to platelet activation, vascular proliferation and remodeling, hypertension, atherogenesis, and cardiac function. Differently, PGE_2 accelerates atherogenesis and can activate platelets. We explored the contribution of cyclooxygenase (COX)-isozymes and down-stream specific synthases to the generation of PGI_2 and PGE_2 in endothelial cells in response to steady laminar shear stress (LSS, 10 dyne/cm^2) versus interleukin-1β (5 ng/ml). Western blot analysis showed that primary human umbilical vein endothelial cells (HUVECs) cultured in static conditions in the presence of foetal calf serum 5% expressed COX-1, PGI_2 synthase (PGIS), cytosolic PGE_2 synthase (cPGES) and microsomal PGES-2 (mPGES-2) but not COX-2 and mPGES-1. They released 6-keto-$PGF_{1\alpha}$ (the hydrolysis product of PGI_2) and PGE_2 (799±340 and 559±142 pg, respectively). After the loading of laminar shear stress for 6 h, COX-2, mPGES-1 and mPGES-2 were induced. This was associated with a significant ($P<0.01$) increase of 6-keto-$PGF_{1\alpha}$ and PGE_2 generation (2372±414 and 3600±588 pg, respectively). Under static conditions, IL-1β induced the expression of COX-2, mPGES-1 and mPGES-2. This was associated with a significant increase in the generation of 6-keto-$PGF_{1\alpha}$ and PGE_2 generation (11744±6700 and 6376±510 pg, respectively). Using NS-398 (a selective inhibitor of COX-2) we showed that endothelial COX-2 is the dominant isozyme involved in PGI_2 biosynthesis in response to LSS and IL-1β. In fact, it was suppressed by 60% and 90%, respectively, by the compound. Interestingly, PGE_2 was produced principally by COX-1 in response to LSS while only COX-2 contributed to the generation of the prostanoid in response to IL-1β . In conclusion, our results show that in endothelial cells PGI_2 biosynthesis is coupled preferentially with COX-2. Preservation of PGE_2 biosynthesis in front of profound suppression of PGI_2 in endothelial cells, at physiological level of steady LSS, by selective inhibitors of COX-2 might contribute to the acceleration of the developing CV risk, in subjects at initial low-risk.