DIFFERENTIAL CONTRIBUTION OF CYCLOOXYGENASE-ISÖZYMES 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-1\(\beta\) (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-1\(\beta\) 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-1\(\beta\). 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-1\(\beta\). 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.