Contractions of human coronary vessels induced by Prostaglandin E$_2$ are mediated via EP3 receptor and modulated by perivascular adipose tissue

Introduction: Most of the blood vessels are surrounded by perivascular adipose tissue (PVAT) which could regulate vascular functions. Prostaglandin E2 (PGE$_2$) released by PVAT could regulate vascular tone depending on which PGE$_2$ receptors (EP) are expressed by the vessel (vasocontriction via EP1 / EP3, vasodilatation via EP2 / EP4 receptors). During vascular pathologies associated with inflammation such as atherosclerosis, the release of PGE$_2$ is increased. The aim of this study is to determine the effects of PVAT and PGE$_2$ on vascular tone of human coronary vessels (HCV), with or without atherosclerosis).

Methods: Some of HCV were obtained after heart transplantation for myocardial ischemia (n=17) and named as atherosclerotic while the others were obtained after heart transplantation for cardiomyopathy (n=14) and called as healthy preparations. The vascular preparations were used with or without PVAT and set up in organ bath system. Cumulative dose-response curves (1 nM - 10 microM) were established with various EP receptor agonists in the presence of different antagonists in healthy and atherosclerotic vascular preparations with or without PVAT. The release of endogenous PGE$_2$, the expression of microsomal PGE synthase 1 (mPGES-1, responsible for PGE$_2$ synthesis) and EP3, EP1 receptor mRNA have been measured in HCV and their isolated PVAT by ELISA, Western Blot or real time PCR.

Results: (Biochemical) the release of PGE$_2$ and expression of mPGES-1 were significantly higher in atherosclerotic HCV or their PVAT compared to healthy preparations. The EP3 and EP1 receptor mRNAs were detected in HCV and PVAT. (Physiological results) in HCV without PVAT, PGE$_2$, the EP3-agonist (ONO-AE-248) and the two EP1/EP3-agonists (17-phenyl-PGE$_2$ and sulprostone) induced concentration-dependent contractions. The EP3-antagonist (L-826266, 3 µM), inhibited the contraction induced by PGE$_2$, while the EP1-antagonists (SC-51322, ONO-8713; 10 µM) were ineffective. Moreover, the IP/EP1-agonist (iloprost), and another EP1-agonist ONO-DI-004 failed to contract HCV. These results and the rank order of potency (sulprostone>17-phenyl-PGE$_2$) suggest the involvement of the EP3 rather than EP1 receptor. Interestingly, in the presence of PVAT, the contractile response to PGE$_2$ was reduced (by 45%) in healthy HCV, this reduction was abolished only after incubation with the EP3 antagonist L-826266. This relaxant effect of PVAT completely disappeared in atherosclerotic HCV.

Conclusion: Taken together these results suggest that endogenous PGE$_2$ is responsible for HCV contraction via EP3 receptors present in vascular wall. In addition, PVAT could stimulate the release of relaxing factor(s) and reduce its former contractile effect in healthy HCV. This vasorelaxant effect is abolished in atherosclerotic HCV and could accelerate atherosclerosis and plaque rupture. Finally, we suggest that PGE$_2$ via EP3 receptor activation is a key bioactive lipid in coronary physiopathology.