Cystathionine-γ-lyase (CSE), a H_2S generating enzyme, is involved in secondary bile acids induced vasodilatation

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G-protein Bile Acid Receptor (GP-BAR1) and Farnesoid X Receptor (FXR) are two bile acids activated receptors (BARs) expressed in entero-hepatic tissues and in vasculature both in endothelial and smooth muscle cells. GP-BAR1 is selectively activated by secondary bile acids, Litocholic (LCA) and Deoxycholic acid (DCA), while the primary bile acid, chenodeoxycholic acid (CDCA), is the physiological ligand for FXR (Fiorucci et al 2009; Fiorucci et al. 2014). Previous studies have shown that bile acids induce vasodilatation through the activation of smooth muscle large conductance calcium activated potassium (BK_{Ca}) channels, which regulate several physiological processes, including myogenic tone (Bukiya et al. 2011). Moreover *in vitro* studies have demonstrated that in bovine aortic endothelial cells, activation of GP-BAR1 significantly increase NO production (Kida et al. 2013). However, it is still unclear if vasodilating property of bile acids involves GPBAR1. Therefore, this study aims to provide a vascular characterization of GP-BAR1 null mice ($GPBAR1^{-/-}$) and to evaluate the possible mechanisms involved in bile acids induced vasodilatation. Functional studies have been performed on isolated aortic rings harvested from GP-$BAR1^{-/-}$ and respective background mice (GP-$BAR1^{+/+}$). Isolated aortic rings were contracted with phenylephrine and then concentration-response curves of LCA and CDCA have been carried out. In mice, CDCA and LCA induced vasodilatation in concentration-dependent manner. CDCA-induced vasodilatation was not modified in GP-$BAR^{-/-}$ mice, conversely vasodilatation induced by LCA was GPBAR1-dependent. Incubation of Iberiotoxin, a BK_{Ca} channels antagonist, abrogated CDCA caused vasodilatation, but not modified vasodilatation induced by LCA. Moreover, LCA-caused vasodilatation was abrogated by 5β-cholanic acid, a GPBAR1 antagonist, but not by N5-(1-iminoethyl)-L-ornithine (L-NIO), an eNOS inhibitor. In a separate set of experiments, GP-$BAR1^{+/+}$ aortic rings were incubated with propargyl-glycine (PAG), a selective cystathionine-γ-lyase (CSE) inhibitor, in order to evaluate the involvement of endothelial-derived Hydrogen Sulfide (H2S) synthesized by CSE. PAG significantly reduced vasodilatation induced by LCA. In conclusion we demonstrate that vasodilatation caused by CDCA involves large conductance calcium activated potassium channels. Moreover, GPBAR1 mediates the vasodilatory activity of LCA and regulates the expression/activity of CSE. These data suggest the involvement of GPBAR1/CSE pathway in vascular function and could contribute to development of hyperdynamic circulation in liver cirrhosis.

***References**:*

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