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P-65

Potential Mechanisms Involved in Sphingosine-1-phosphate Induced Coronary Flow Reduction

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1. Introduction

Sphingosine-1-phosphate (S1P) belongs to the group of lipid mediators. This sphingolipid mediator is present both in the extra- and intracellular spaces. Its concentration is ~ 1 microM in the blood plasma and is transported in free, albumin-bound or HDL-bound forms. It is produced by endothelial cells and erythrocytes and is also released in huge amounts during platelet activation [1].

Initially, it was considered to be an intracellular mediator. Later, it has been recognized also as an extracellular mediator which has 5 documented specific G-protein coupled receptors (S1P1-S1P5). Its cardiovascular (CV) effects are attributed mainly to S1P1, S1P2 and S1P3 receptors [2] which mediate various processes including the development of the CV system, anti-inflamatory responses (atherosclerosis), ischemic pre- and postconditioning and vasoconstrictor and endothelium-dependent vasodilatator actions [3-8].

In our previous study, we observed a substantial coronary flow reducing effect of S1P that was also accompanied by reduced contractile function. We showed that the S1P3 receptor plays an important, but not exclusive role in the signalling. The aim of the present study was to delineate the role of other S1P receptors and the potential intracellular signalling pathways in the S1P coronary effect [9].

2. Methods

Isolated hearts of 130-150 day-old male mice were examined in the study. S1P2 deficient (S1P2 KO), S1P3 deficient (S1P3 KO) and smooth muscle-specific (sm) S1P1 KO mice models were used, and wild type (WT) littermates served as controls.

For deep anesthesia we used pentobarbital in intraperitoneal injection. Afterwards, the heart was excised, cannulated and mounted on a Langendorff perfusion apparatus. Perfusion was executed at constant, 80 mmHg pressure with a modifiled Krebs-buffer. During experiments, we continuously monitored the left ventricular pressure and coronary flow changes.

We infused S1P (10^{-6} M) or its vehicle to the perfusate for 5 minutes with an injection pump. **(Figure 1)**

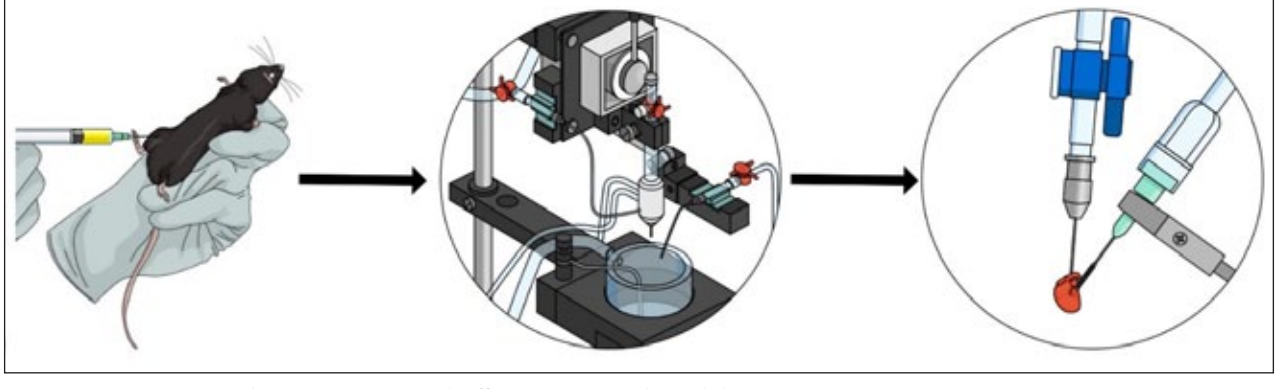

Figure 1 *Intraperitoneal injection, Langendorff-system, cannula with heart*

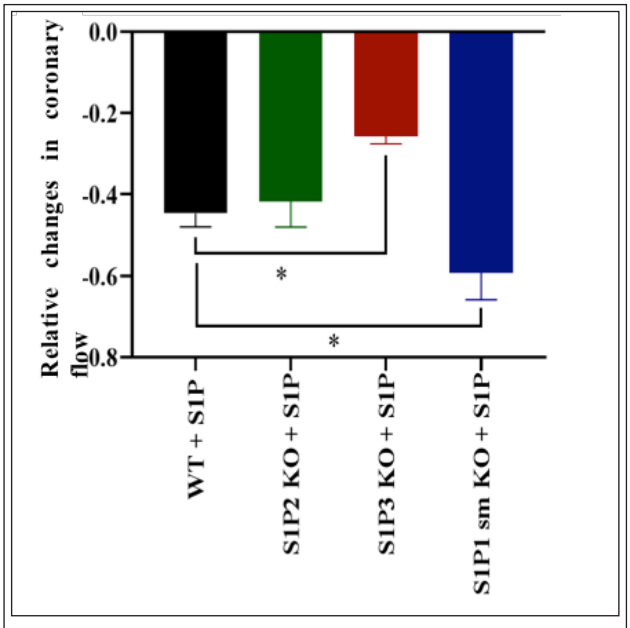

Figure 2. *Maximum relative coronary flow change in wild type (WT), S1P2 knock-out (KO), S1P3 KO and S1P1 smooth muscle specific KO hearts after application of 1 microM S1P (mean ± SEM; n=28, 8, 8, 7; * p <0.05 vs. WT + S1P, one-way ANOVA and Dunnet post hoc test)*

3. Results

The S1P-induced coronary flow reduction in hearts of S1P2-KO mice was similar to that observed in control hearts. In contrast, in S1P3-KO hearts the coronary flow effect of S1P diminished compared to WT mouse hearts. Furthermore, the coronary flow reduction in reponse to S1P was increased in sm-S1P1 KO mice. (**Figure 2**). Examination of intracellular signalling pathways showed that $G\alpha_{12/13}$ proteins may play a relevant role.

4. Conclusions

S1P causes a substantial reduction in coronary flow in murine hearts, which is mediated by the S1P3-$G\alpha_{12/13}$ pathway. In addition, the deletion of S1P1 from the smooth muscle enhances the coronary effect of S1P, suggesting that the S1P1 receptor is responsible for a vasodilatory mechanism. This process might have relevance in acute coronary events when a large amount of S1P is released due to platelet activation during thrombus formation.

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