S1PR1, S1PR3 and FTY720 in vascular tone and blood pressure regulation

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Nitric oxide is one of the major endothelial-derived vasoactive factors that regulate blood pressure and the bioactive lipid mediator sphingosine-1-phosphate is a potent activator of endothelial nitric oxide synthase through G-protein coupled receptors. Recently, it has been discovered that local production of sphingosine-1-phosphate and autocrine/paracrine activation of sphingosine-1-phosphate receptors on the endothelium is an important pathway preserving vascular functions and blood pressure homeostasis. Furthermore, FTY720, binding to four out of five S1PRs recently approved by the FDA to treat autoimmune conditions, induces a modest and transient decrease in heart rate in both animals and humans, suggesting that drugs targeting sphingolipid signaling affect cardiovascular functions in vivo. However, the role of specific S1P receptors in BP homeostasis remains unknown.

The aim of this study is to determine the role of the key vascular sphingosine-1-phosphate receptors, namely, S1PR1 and S1PR3 in BP regulation in physiological and hypertensive conditions. The specific loss of endothelial S1PR1 decreases basal and stimulated endothelial-derived NO, and re-sets blood pressure to a higher-than-normal value. Interestingly, we identified a novel and important role for S1PR1 signaling in flow-mediated mechanotransduction. FTY720, acting as functional antagonist of S1PR1, markedly decreases endothelial S1PR1, increases blood pressure in control mice and exacerbates hypertension in Ang-II mouse model, underlining the anti-hypertensive functions of S1PR1 signaling.

Our study identifies S1P-S1PR1-NO signaling as a new regulatory pathway in vivo of vascular relaxation to flow and blood pressure homeostasis, providing a novel therapeutic target for the treatment of hypertension.