SILDENAFIL INHIBITS PLATELET AGGREGATION AND REDUCES NEOINTIMAL HYPERPLASIA AFTER VASCULAR INJURY

Background: Stent thrombosis and restenosis after stent implantation are one of the main issues in interventional cardiology. Sildenafil has shown its effect in reducing cardiac hypertrophy as well as improving erectile dysfunction through cGMP-dependent kinase (cGK) activation. Some studies have demonstrated that cGK occupies a central switching role in modulating vascular smooth muscle cell (VSMC) phenotype in response to vascular injury. In this study, we investigated the effects of cGK activation by sildenafil on platelet aggregation and neointimal hyperplasia.

Methods and Results: Sildenafil significantly reduced platelet aggregation induced by ADP or thrombin. This effect was reversed by cGK inhibitor, suggesting that sildenafil inhibits platelet aggregation through cGK pathway. Furthermore, assays for VASP phosphorylation and P-selectin activation showed the same inhibitory effect of sildenafil on platelet activation. In terms of restenosis after vascular injury, sildenafil significantly reduced neointimal hyperplasia in rat carotid arteries compared to control group. This effect of sildenafil was accompanied by the reduction of viability, cell cycle progression, and migration of VSMCs. This was also confirmed in the injured arteries in vivo. Further studies showed that the increased cGK activity by sildenafil inhibited PDGF-stimulated phenotype change of VSMCs from a contractile to a synthetic form. Conversely, the use of cGK inhibitor or gene transfer of dominant-negative cGK reversed the effects of sildenafil, resulting in the increased viability of VSMCs and neointimal formation. In addition, the mice treated with sildenafil showed the facilitated re-endothelialization, compared to control group. Furthermore, we confirmed the effect of sildenafil through cGK activation using cGK-KO mice.

Conclusions: Our study showed that sildenafil inhibits not only platelet aggregation, but also neointimal hyperplasia via cGK pathway. These findings suggest that sildenafil could be a promising candidate drug of drug-eluting stents for the prevention of restenosis without other complications such as stent thrombosis.