SILDENAFIL INHIBITS VASCULAR SMOOTH MUSCLE CELL PROLIFERATION AND PLATELET AGGREGATION VIA ACTIVATION OF PROTEIN KINASE G (PKG), RESULTING IN REDUCING NEOINTIMAL HYPERPLASIA AFTER ANGIOPLASTY

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Background: Sildenafil has shown its effect in reducing cardiac hypertrophy as well as improving erectile dysfunction through Protein Kinase G (PKG) activation. Some studies have demonstrated that PKG occupies a central switching role in modulating vascular smooth muscle cell (VSMC) phenotype in response to vascular injury. In addition, the stent thrombosis after drug-eluting stent implantation is one of the hottest issues in interventional cardiology. Here, we examined the effects of PKG activation by sildenafil on neointimal formation, platelet aggregation, and re-endothelialization.

Methods and Results: Sildenafil significantly reduced neointimal hyperplasia after vascular injury in rat carotid arteries. These effects of Sildenafil were accompanied by reduction of viability, cell cycle progression, and migration of VSMCs, which was also confirmed in the injured arteries. Interestingly, in contrast to the effect on VSMC viability, Sildenafil did not reduce the viability of endothelial cells. Increased PKG activity by Sildenafil inhibited PDGF-stimulated phenotype change of VSMCs from a contractile to a synthetic form. Conversely, the use of PKG inhibitor or gene transfer of dominant-negative PKG 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 used PKG-KO mice to confirm the effect of sildenafil through PKG activation. PKG-KO mice showed no effect of sildenafil in inhibiting neointimal hyperplasia, suggesting that the effect sildenafil could be mediated via PKG pathway. Finally, Sildenafil reduced platelet aggregation, which was confirmed to be mediated via PKG activation.

Conclusion: This study demonstrated that Sildenafil inhibits neointimal formation and platelet aggregation while increasing re-endothelialization via PKG pathway. These findings suggest that Sildenafil could be a promising candidate drug of DES for the prevention of restenosis without other complications.