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Impact of the nitric oxide – independent soluble guanylate cyclase activator cinaciguat on restenosis after arterial injury in rats

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Restenosis is a major limitation of percutaneous coronary intervention (PCI). The advent of drug-eluting stents (DES) drastically decreased the risk of restenosis. However, owing to the enormous number of revascularization procedures performed each year the clinical and economic burden of restenosis remains immense.
Restenosis is the arterial wall's maladaptive healing response to trauma inflicted during PCI. It comprises three different elements: elastic recoil, neointimal hyperplasia and vascular remodeling. Together they culminate in postprocedural lumen loss.
Today repeat revascularization using DES is the preferred approach for treating in-stent restenosis. So far clinical trials investigating the use of various drugs for the primary prevention of restenosis have yielded altogether disappointing results. Mounting evidence that impaired nitric oxide (NO) - soluble guanylate cyclase (sGC) - cyclic guanosine monophosphate (cGMP) signaling is involved in the pathophysiology of cardiovascular diseases has prompted intense research into the pharmacological enhancement of this pathway. The NO- and heme-independent sGC activator cinaciguat has produced promising results in numerous experimental models of cardiovascular and non-cardiovascular diseases. However, its potential for the treatment of restenosis has not been tested yet. The present work is the first to investigate the effects of cinaciguat in an experimental model of injury-induced arterial stenosis.
To this end, 100 male Sprague-Dawley rats underwent wire injury of the right common carotid artery. Animals were randomly assigned to treatment with cinaciguat (10 mg/kg body weight per day via oral gavage) or no treatment. Morphometric data and expression of relevant genes (inducible nitric oxide synthase [iNOS], proliferating cell nuclear antigen [PCNA], alpha smooth muscle actin [αSMA], $sGC\beta_1$, cGMP - dependent protein kinase [PKG], matrix metalloproteinase-9 [MMP-9]) were recorded at different time points (one day, two days, three days, one week, three weeks).
Arteriel injury promotes the phenotypic transition of vascular smooth muscle cells (VSMCs) towards a dedifferentiated phenotype which is associated with a decreased expression of $sGC\beta_1$ and αSMA and an increased expression of MMP-9. These changes enable VSMC proliferation and migration ultimately resulting in neointima formation. The importance of PKG in the pathology of restenosis is unclear.
Cinaciguat curbs injury-induced neointimal hyperplasia by limiting VSMC migration and to a lesser degree VSMC proliferation through downregulation of MMP-9 and inhibition of phenotypic modulation.
This study confirms that cinaciguat selectively targets heme-oxidized sGC independently of NO. However its mode of action downstream of cGMP seems to be context-specific and its influence on sGC expression apparently depends on the given pathophysiological conditions, particularly the prevalence of oxidative stress. The detection of a truncated 51-kDa MMP-9 fragment which was unknown until recently represents an intriguing issue that should be dealt with in subsequent studies.
The methodological shortcomings of the study demand a judicious assessment of the aforementioned results. Nevertheless, sufficient evidence is provided to justify the hypothesis

that cinaciguat is a promising compound for the prevention of restenosis. Hence, this study adds yet another pathological entity to the broad spectrum of diseases which could be potential future indications for the use of cinaciguat.