Prostacyclin analogues: the next drug-eluting stent?

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Abstract
Recent concern over existing drug-eluting stents, for the treatment of myocardial ischaemia, has led to the development of approaches that seek to inhibit restenosis while promoting the recovery of a functional endothelium. Prostacyclin analogues may be worthy candidates for use within a drug-eluting stent by virtue of their wide profile of vasoprotective effects. This article reviews recent developments in this area, and in so doing, reveals the future challenges for the further development of this technology.

Background
Drug-eluting stents have dramatically reduced restenosis rates after percutaneous coronary interventions. However, they remain unsuitable for certain high-risk lesions, and recent evidence of delayed healing and long-term endothelial dysfunction has led to renewed efforts to find alternative approaches. Broadly, the aim of these approaches is to inhibit ISR (in-stent restenosis), while promoting the recovery of a functional endothelial cell layer.

ISR
ISR is generally viewed as a natural healing response to the injury invoked by arterial expansion and stent placement. This healing process has been described as a cascade of events, where the end result is the development of a neointima consisting primarily of SMCs (smooth muscle cells) and extracellular matrix components. The individual processes leading to neointima formation have been summarized as follows [1]. Stent injury activates platelets, leading to thrombus formation. In combination with the vessel injury and thrombus, the metallic surface of the stent causes activation of circulating neutrophils and macrophages within arterial tissue. Consequently, various cytokines and growth factors are produced that activate SMCs, resulting in a switch from a contractile to a proliferative phenotype. Finally, up-regulation of matrix metalloproteinases leads to SMC migration from the medial layer to the intimal layer. Existing drug-eluting stents inhibit SMC proliferation, but there is evidence that such an approach can impair endothelial cell proliferation and hence the recovery of the endothelium [2].

PGI2 (prostacyclin) as an anti-restenotic agent
PGI2 has a wide profile of action, and is an important physiological regulator of vascular haemostasis via its antithrombotic and vasodilatory actions [3]. It has been shown to inhibit SMC proliferation while having little effect on endothelial cell proliferation [4]. Such a profile of action provides a strong rationale for examining the potential of PGI2 to inhibit ISR.

PGI2 has not yet been reported. Indeed, in this study [6], only 15% of the iloprost loaded on to the stent was released at 90 days, compared with 65% release of the PEG–hirudin complex. However, the effect of any PGI2 analogue alone delivered from a stent has not yet been reported. Indeed, in this study [6], only 15% of the iloprost loaded on to the stent was released at 90 days, compared with 65% release of the PEG–hirudin complex. Meaningful interpretation of such results and how they may translate into future clinical efficacy, requires an understanding of the actions of PGI2 analogues at the receptor level.

PGI2 and its receptors
The protective actions of PGI2 analogues are thought to be mediated through activation of the prostanoid IP receptor [7]. The seven-transmembrane IP receptor is coupled with the Gs-type G-protein, leading to activation of adenylate cyclase and increases in intracellular cAMP signalling. However, it has been demonstrated that the leading PGI2 analogues developed to date have non-specific agonist activity at prostaglandin E2 receptors, EP1 and EP3. The EP1 receptor causes increases in intracellular calcium,
producing vasoconstriction. The EP3 receptor has various splice variants capable of coupling with G12, G13 and G14-type G-proteins. However, in general, EP3 receptor activation leads to inhibition of adenylate cyclase, and activation of phospholipase C, and is associated with vasoconstriction [7]. Consequently, activation of these receptors by PGI2 analogues may lead to paradoxical vasoconstriction, and limit their antiproliferative potential via an inhibitory effect on cAMP. In determining what effect such non-specific actions may have on the therapeutic potential of PGI2 analogues, it is necessary to examine what is known of the prostanoid receptor distribution on the human coronary artery.

Prostanoid receptors on human coronary artery

In a limited number of in vitro studies, PGI2 has been demonstrated to produce submaximal relaxation in human coronary arteries [8]. Similarly, intracoronary delivery of iloprost produced an increase in vessel diameter in vivo, suggesting the presence of a functional IP receptor population [9]. In addition to a vasodilatory role, iloprost has been shown to inhibit human coronary artery SMC proliferation [10]. An IP receptor-mediated inhibition of cellular migration has also been demonstrated in SMCs isolated from the human mammary artery [11]. In the same study, the potent EP3 prostanoid receptor agonist, M&B 28.767, increased migration, supporting the presence of an EP3 receptor population.

Preclinical models of restenosis

Given that PGI2 analogues produce relaxation and inhibit SMC proliferation in the human coronary artery, it is likely that the ideal preclinical model would produce similar responses. Of the animal models used to study the development of ISR, the PCA (pig coronary artery) model has gained the most widespread acceptance, largely due to the similarity in the anatomy and physiology of the pig and human cardiovascular systems. In vivo, it has been shown that endogenous prostanoids play an important vasorelaxant role in maintaining haemostasis in PCAs [12]. While this may indicate a role for PGI2, it is not clear if other prostanoids such as PGE2 were involved in this response.

In vitro, PGI2 produced near complete relaxation of PCA, which was significantly attenuated by removal of the endothelium [13]. This suggests that PGI2, at least in part, exerts its vasodilatory effect by endothelium-dependent mechanisms. It also suggests that there is a limited population of IP receptors on PCA SMC, or that their function is limited given the limited direct relaxation. A weak contractile effect of PGI1 on isolated PCA has also been reported [14].

In quiescent PCA SMC, iloprost had a mild stimulatory effect on DNA synthesis, with no effect at lower concentrations (<0.1 µM) [15]. A similar work has demonstrated no inhibitory effect on serum-stimulated SMC proliferation (C. McCormick, R.M. Wadsworth, R.L. Jones and S. Kennedy, unpublished work). These results are in contrast with the antiproliferative effect obtained in human coronary artery cellular proliferation studies. Taken together with the conflicting results obtained in functional studies, these results indicate significant differences between the human coronary and PCA with regard to the distribution of functional prostanoid receptors.

Conclusion

PGI2 analogues may have potential for use in a novel drug-eluting stent via IP receptor-mediated vasoprotective effects. However, it has proven difficult to produce a truly IP receptor-selective PGI2 analogue. The non-specific activity of the current analogues at prostanoid EP1 and EP3 receptors may produce vasoconstriction, and limit the antiproliferative and antimitagatory effects of these compounds. Whether such activity significantly limits their therapeutic potential will depend, at least in part, on the distribution and function of these receptors in the human coronary artery. Equally, effective preclinical assessment of such compounds requires animal models that closely reflect the human coronary prostanoid receptor distribution. Different functional and cellular responses to PGI2 analogues have been observed between the PCA and the human coronary artery. Therefore the distribution and function of these receptors, in the human coronary artery and the leading models of restenosis, need to be determined if further progress is to be made towards better preclinical assessment of these compounds and understanding of how they may be used in the treatment of coronary vascular disease.

References


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