

Oral presentation

## Exploiting the natriuretic peptide system for the treatment of pulmonary hypertension

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### Introduction

Pulmonary hypertension (PH) is characterised by increased pulmonary arterial blood pressure, vascular remodelling of the small pulmonary arteries, right ventricular hypertrophy and ultimately right ventricular failure. Whether idiopathic (primary PH) or secondary (due to chronic lung disease, congenital heart disease or HIV infection), the disease carries a high mortality and morbidity, primarily because of the lack of selective pulmonary vasodilators. Current treatment options include prostacyclin analogues (e.g. epoprostenol) and the endothelin receptor antagonist bosentan; however, these agents suffer from many drawbacks including the need for parenteral administration and, like other vasodilators (e.g. calcium channel blockers), have significant systemic hypotensive effects. Recently, the phosphodiesterase 5 (PDE V) inhibitor sildenafil has been licensed for the treatment of PH. Sildenafil is orally active, has selective pulmonary vasodilator effects and improves exercise tolerance in patients with PH [1], thus representing a significant advance over existing therapy. In addition, attention has focused on novel combination therapies for PH (e.g. sildenafil plus iloprost) [2] or by increasing cGMP levels by activating soluble guanylate cyclase (sGC; e.g. inhaled NO, BAY 41-2272) [3].

The mechanism(s) underlying the pulmonary selectivity of sildenafil remain unclear. Although sildenafil reduces functional and structural changes in many animal models of PH, the pulmonary selectivity of sildenafil is blunted in

animals lacking the natriuretic peptide receptor (NPR)-A [4]. This suggests that the mechanism of pulmonary selectivity of PDE V inhibition is dependent, at least in part, on the bioactivity of natriuretic peptides and activation of the particulate isoform of guanylate cyclase. Thus, we have explored the interaction(s) of PDE V inhibitors and the natriuretic peptide system *in vitro* and *in vivo*, including an animal model of PH, to more fully elucidate the (patho)physiological relationship between these two cGMP-regulating systems.

### Results

Using classical organ bath pharmacology to assess the reactivity of isolated aortic and pulmonary artery smooth muscle from the rat, we observed that sildenafil augments relaxations to the NO-donor, spermine NONOate, in both vessel types. In marked contrast, sildenafil only enhances the vasodilator activity of atrial natriuretic peptide (ANP) in the pulmonary artery. Furthermore, the *in vivo* hypotensive effect of ANP is augmented by sildenafil specifically in the pulmonary resistance vasculature. These data suggest a specific role for PDE V in the modulation of pulmonary (but not systemic) responses to natriuretic peptides in the mouse *in vitro* and *in vivo*. This gives rise to the possibility of effecting organ- or vessel-specific alterations in the vasodilator activity of natriuretic peptides, which may represent an important physiological regulatory mechanism and may be of therapeutic benefit in PH.

To address the latter possibility, we explored the beneficial effects of sildenafil, the neutral endopeptidase inhibitor ecadotril (prevents natriuretic peptide breakdown and thereby augments plasma levels of these peptides), and a combination of sildenafil plus ecadotril, on vascular function and pulmonary remodelling in an animal model of hypoxia-induced PH. Our results indicate that a combination of sildenafil plus ecadotril is superior to either drug alone in reversing many indices of disease progression and severity including increased pulmonary artery pressure, right ventricular hypertrophy and pulmonary vascular remodelling. Importantly, a combination of sildenafil plus ecadotril had no significant effect on systemic blood pressure.

### Conclusion

These data imply that manipulating the natriuretic peptide system can enhance the pulmonary selectivity of PDE 5 inhibitors and may offer a better means of treating PH than PDE V inhibitors alone or in combination with activation of the soluble isoform of GC (particularly in terms of avoiding systemic hypotension). Moreover, these findings give clear evidence for compartmentalisation of cGMP-dependent signalling between the soluble and particulate guanylate cyclases and differential regulation of cGMP metabolism by PDEs between vascular beds.

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