Novel Vasoactive Intestinal Peptide-ELP Fusion Protein VPAC-Agonists

Induced Sustained Pulmonary Artery Vaso-Relaxation in Rats with Acute Hypoxia-Induced Pulmonary Hypertension.

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Introduction

The natural vasoactive intestinal peptide (VIP) triggers potent pulmonary vasodilatation by activating the G-protein-coupled VPAC receptors (VPAC1/VPAC2), and has been suggested as a therapeutic target in pulmonary artery hypertension (PAH); however, VIP's clinical utility is limited due to its short half-life.

PhaseBio's novel ELP fusion technology permits the creation of long-acting protein-fusion biopolymer-based VPAC-receptor agonists. Here, the pulmonary/systemic hemodynamic effects of two novel ELP-enhanced VIP analogues (ELP+VIP) were evaluated in anesthetized rats with hypoxia-induced PAH.

ELP-enhanced VPAC agonist can trigger sustained reductions in pulmonary artery pressure in the setting of hypoxic hypertension

Materials and Methods

Healthy rats (SD: 259±5 g, n=25) were anesthetized (propofol), intubated, mechanically-ventilated (95% FiO2), and instrumented for systemic (arterial) and mean pulmonary-artery pressure monitoring.

PAH was induced by decreasing the FiO2 (to ~10-11%), and the rats were assigned to receive either a novel VIP analogue (VIP+ELP, n=18: 3-6 mg/kg) or placebo (CTRL, n=11: 0.9% NaCl), delivered as acute fixed-volume single-dose boluses either intravenously (IV) or intratracheally (IT). Two novel ELP+VIP analogues, PB1120 (a VPAC1/2 agonist) and PB1046 (a VPAC2 selective agonist) were assayed in this study (n = 9/group).

In addition, the long-term hemodynamic effects of one of these analogues (PB1046, 1-9 mg/kg SQ) were evaluated in conscious telemetered SHR rats (351±4 g, n=8) during the normal/untreated state, β-AR blockade (+BB, atenolol 20 mg/kg), calcium-channel blockade (+CCB, amlodipine 5 mg/kg), and ACE-inhibition (+ACE, ramipril 1 mg/kg).

Results

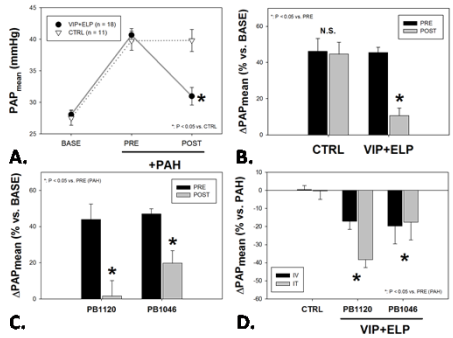

Fig. 1. Pulmonary artery pressures (PAP) after induced hypertension (+PAH) and treatment with either placebo (CTRL) or novel VIP analogues (VIP+ELP)

PAH: Reductions in the inspired FiO2 resulted in sustained pulmonary artery pressure increases (+45 ± 3%, 28 ± 1 to 41 ± 1 mmHg; P<0.05), consistent with hypoxic PAH. Induced-PAH was preserved in the absence of active treatment, as pulmonary pressures remained elevated following placebo administration (CTRL: -1 ± 2%, from 40 ± 2 to 40 ± 2 mmHg; n = 11, N.S.).

Acute administration of the VIP+ELP analogues resulted in rapid pulmonary artery pressure reductions (-24 ± 3%, from 41 ± 1 to 31 ± 1 mmHg, P<0.05) with moderate/negligible changes in systemic arterial pressures (MAP: -12 ± 6%) and heart rate (-4 ± 3%). Both VIP+ELP analogues tested triggered significant reductions in PAP (PB1120: -29 ± 7%, from 39 ± 2 to 28 ± 3 mmHg, and PB1046: -19 ± 5%, from 42 ± 4 to 34 ± 4 mmHg; P < 0.05). Pulmonary vaso-relaxation triggered by the VIP+ELP agonists was sustained (i.e., observed for at least 5min post-dosing) and independent of the route of administration (IV: -17 ± 4%, n = 8; IT: -28 ± 4%, n = 10), however, IT PB1120 (a VPAC1/2 agonist) seemed to be more efficacious in this model.

Contrastingly, sodium nitroprusside (SNP, 20 µg/kg IV bolus, n=5) triggered comparable acute PAP reductions (-23 ± 2%, from 46 ± 1 to 35 ± 0 mmHg, P < 0.05), but these changes were short lived (i.e., lasted < 2min; e.g., PAP@5min post-dosing: -2 ± 3%, 45 ± 1 mmHg, N.S.).

Conscious (long-term) Hemodynamic Effects: In SHR rats PB1046, a novel ELP+VIP analogue, induced dose-dependent blood pressure decreases that were sustained for up to 12 hours post-dosing (see 2A-B). At 9 mg/kg, PB1046 lowered MAP by 9 ± 1% (188 ± 6 to 171 ± 5 mmHg, P < 0.05), with a peak reduction of 16 ± 3% (154 ± 5 mmHg vs. 184 ± 6 in VEH, P<0.05) observed ~6hr post-dosing (see 2A). PB1046 also triggered moderate (dose-dependent) cardio-acceleration. At 9 mg/kg, for example, heart rate increased +8 ± 1% (355 ± 6 to 384 ± 8 bpm, P<0.05) after administration; however, no significant cardio-acceleration was observed at the lowest dose-level assessed (356 ± 5 to 362 ± 5 bpm).

Moreover, despite the increased HR, the rate-pressure product was unaffected (e.g., at 9 mg/kg, -2 ± 1%, from 67 ± 2 to 66 ± 2 mmHg*bpm x10^3).

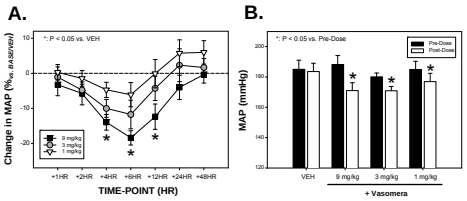

Fig. 2. Changes in mean arterial pressure (MAP) following a single-dose (SQ) administration of either three dose-levels of PB1046 (1, 3, and 9 mg/kg) or vehicle (VEH) in untreated SHR rats.

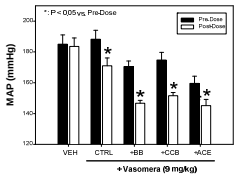

Fig. 3. PB1046 in SHR rats treated with placebo (CTRL) or anti-hypertensive drugs.

PB1046's vaso-relaxation was preserved in rats pre-treated with either atenolol (+BB: -14 ± 1%, P<0.05), amlodipine (+CCB: -13 ± 2%, P<0.05) and/or ramipril (+ACE: -9 ± 2%, P<0.05) (see Fig. 3); similar results were observed in animals pretreated with a diuretic (-8 ± 0%, P<0.05).

On the other hand, chronotropy seemed to be blunted under β-AR blockade (+6 ± 1%, 278 ± 2 to 294 ± 2 bpm), but was unaffected by amlodipine, ramipril, or hydrochlorizide (see 3, left). In all cases, no adverse clinical effects and/or drug-to-drug interactions were noted.

Disclosures: Hamlin RL: PhaseBio's consultant (modest) and QTest Labs board (significant); del Rio CL: PhaseBio's grant (modest) and consultant (modest).

Conclusion

Two novel ELP-enhanced VIP analogues triggered rapid and sustained reductions in pulmonary-artery pressures in the setting of induced (hypoxic) pulmonary hypertension (PAH). These effects were independent of the route of administration, as both intravenous/intra-tracheal administrations were efficacious. Moreover, the ELP fusion enhancement was shown, in one of these novel VIP analogues (PB1046, a VPAC2 selective agonist), to extend VIP's effects.

In collaboration with: Ohio State College of Veterinary Medicine