Novel Vasoactive Intestinal Peptide-ELP Fusion Protein VPAC-Agonists

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

Yeh ST¹, Youngblood BL¹, Georgopoulos L², Arnold S², Hamlin RL¹,³, del Rio CL¹.

1: QTest Labs; OH (USA). 2: PhaseBio Pharmaceuticals, Inc, Malvern, PA (USA), and 3: The Ohio State University, OH (USA).

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.

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 = 8/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

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% (168 ± 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 x10¹). 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 hydrochlorothiazide (see 3, left). In all cases, no adverse clinical effects and/or drug-to-drug interactions were noted.

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.

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