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Abstract

Pulmonary arterial hypertension (PAH) is a progressive and fatal disease. Despite the aggressive use of current selective pulmonary vasodilators, this disorder is still not curable. PAH is characterized by occlusive pulmonary vascular disease (PVD), including intimal hyperplasia, medial wall thickening, plexiform lesions, and perivascular inflammation in the small pulmonary artery. The development of occlusive PVD is accompanied by increased proliferation of pulmonary artery smooth muscle cells (PASMCs), inflammation, and epigenetic mechanisms in PAH patients and animal models. It remains unknown whether perinatal insults aggravate occlusive PVD later in life. We tested the hypothesis that perinatal hypoxia aggravates PVD and survival in rats. PVD was induced in rats with/without perinatal hypoxia (E14 to P3) by injecting SU5416 at 7 weeks of age and subsequent exposure to hypoxia for 3 weeks (SU5416/hypoxia). Hemodynamic and morphological analyses were performed in rats with/without perinatal hypoxia at 7 weeks of age (baseline rats, n=12) and at 15 weeks of age in 4 groups of rats: SU5416/hypoxia or control rats with/without perinatal hypoxia (n=40). Pulmonary artery smooth muscle cells (PASMCs) from the baseline rats with/without perinatal hypoxia were used to assess cell proliferation, inflammation and genomic DNA methylation profile.

Although perinatal hypoxia alone did not affect survival, physiological or pathological parameters at baseline or at the end of the experimental period in controls, perinatal hypoxia decreased weight gain and survival rate, and increased right ventricular systolic pressure, right ventricular hypertrophy, and indices of PVD in SU5416/hypoxia rats. Perinatal hypoxia alone accelerated the proliferation and inflammation of cultured PASMCs from baseline rats, which was associated with DNA methylation. In conclusion, we established the first fatal animal model of PAH with worsening hemodynamics and occlusive PVD elicited by perinatal hypoxia, which was associated with hyperproliferative, pro-inflammatory, and epigenetic changes in cultured PASMCs. These findings provide insights into the treatment and prevention of occlusive PVD.