Cardiovascular Pharmacology: Open Access
ISSN: 2329-6607
Yang and Sun, Cardiol Pharmacol 2013, 3:1
DOI: 10.4172/2329-6607.1000e123

Editorial Open Access

Perinatal and Neonatal Hypoxia in Pulmonary Vascular Dysfunctions

Qiwei Yang* and Miranda Sun

Department of Pediatrics, College of Medicine, University of Illinois at Chicago, USA

Unlike in the adult, the perinatal/neonatal pulmonary vascular response to chronic hypoxic exposure is much more rapid and severe and results in the failure of the fetal/neonatal circulation to adapt to a response supporting postnatal life. This, in turn, contributes to the pathogenesis of persistent pulmonary hypertension of the newborn and pulmonary vascular dysfunction later in life. As such, furthering our understanding of the mechanisms and pathology of perinatal/neonatal pulmonary hypertension development leading to adult diseases is important to support more effective therapeutic target identification.

There is increasing evidence in humans and experimental animal models that perinatal/neonatal factors may be linked to the development of adult diseases such as chronic obstructive pulmonary disease and hypertension. Experimental studies have shown that adverse stimuli, especially hypoxia, can impair lung growth and function during a critical period of lung development in a variety of animal species [1,2]. In addition, early exposure to hypoxia alters the pulmonary circulation and increases the susceptibility to diseases later in life. In infant rats, brief perinatal hypoxia resulted in a greater increase in the right ventricular systolic pressure and right ventricular hypertrophy after re exposure to hypoxia [3].

The role of cytokines and transcriptional factors in the pathogenesis of pulmonary hypertension in neonatal animal models has been characterized. Transforming growth factor-β (TGF-β) signaling has been demonstrated to be involved in hypoxia-induced pulmonary hypertension in newborn animals. Neonatal hypoxia led to thicker, more muscularized resistance pulmonary arteries and impaired alveolarization, which was accompanied by increases in active TGF-β and phosphorrylated Smad2 [4]. The hypoxia-induced increase in pulmonary artery pressure and inhibition of alveolar development were greatly attenuated in mice with an inducible dominant-negative mutation of the TGF-β type II receptor (DNTGFβRII). The stimulatory effects of hypoxic exposure on pulmonary arterial cell proliferation and lung extracellular matrix proteins were abrogated in inducible DNTGFβRII mice. These data support the conclusion that TGF-β plays an important role in hypoxia-induced pulmonary vascular adaptation and inhibition of alveolar development in the newborn animal model. A following study was performed to determine whether inhibition of TGF-β signaling attenuates endothelin-1 (ET-1) expression and thereby reduces the effects of hypoxia on the newborn lung [2]. The data demonstrated that hypoxia increased ET-1 synthesis. BQ610 (an endothelin-A receptor antagonist), but not BQ788 (an endothelin-B receptor antagonist), improved lung function without altering alveolar development or increased TGF-β signaling in hypoxia-exposed animals. On the other hand, inhibition of TGF-β signaling reduced ET-1 in vivo, which was confirmed in vitro in mouse pulmonary endothelial cells. Endothelin-A receptor blockade improved function but not development of the hypoxic newborn lung. Reduction of ET-1 via inhibition of TGF-β signaling indicates that TGF-β is upstream of ET-1 during hypoxia-induced signaling in the newborn lung [2]. It was also demonstrated that hypoxia-induced inhibition of lung development is attenuated by the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist rosiglitazone, which increased PPAR-γ signaling and improved lung development and compliance in association with reduced TGF-β signaling [5]. Nuclear factor of activated T cells isoform c3 (NFATc3), a transcriptional factor, is also reported to be involved in chronic hypoxia-induced pulmonary hypertension in neonatal mice. Chronic hypoxia caused NFAT activation in the whole lung as well as nuclear accumulation of NFATc3 in both pulmonary vascular smooth muscle and endothelial cells. In addition, heterozygous NFATc3 neonates showed less right ventricular hypertrophy and pulmonary artery wall thickening in response to chronic hypoxia compared to wild-type neonates, suggesting that NFATc3 mediates pulmonary hypertension and vascular remodeling in neonatal mice [6].

The role of stromal cell-derived factor 1 (SDF-1) and chemokine receptor type 4 (CXCR4) in neonatal hypoxia-induced pulmonary hypertension has been described [7,8]. Neonatal mice exposed to normoxia and hypoxia were assigned to receive daily intraperitoneal injections of AMD3100, a CXCR4 antagonist, or anti-SDF-1 antibody from postnatal day 1 to 7 (preventive strategy) or postnatal day 7 to 14 (therapeutic strategy). As compared to normal saline, inhibition of the SSF-1/CXCR4 axis significantly improved lung alveolarization and decreased pulmonary hypertension, right ventricular hypertrophy, vascular remodeling, and right ventricular stem cell expression to near baseline values, suggesting that the inhibition of the SDF-1/CXCR4 axis prevents and reverses hypoxia-induced cardiopulmonary remodeling in neonatal mice [7]. Another animal experiment was performed to determine the role of chemokine receptor type 7 (CXCR7) in neonatal hypoxia [8]. Mice exposed to neonatal hypoxia had a significant increase in the lung protein expression of CXCR7, and the administration of CCX771, a CXCR7 antagonist, markedly attenuated the hypoxic-induced increase in right ventricular hypertrophy, right ventricular systolic pressure, and pulmonary vascular remodeling. These studies suggest that chemokine (s) and their receptor(s) may play an important role in the pathogenesis of neonatal chronic hypoxia-induced pulmonary hypertension.

Rho-kinase is one of several factors that contribute to the normally elevated pulmonary vascular resistance of the fetus and newborn [9]. Pulmonary arteries from near-term fetal sheep in the model of antenatal chronic hypoxia have increased expression and activity of rho-kinase [10,11]. The effect of chronic perinatal hypoxia on the role of rho-kinase in pulmonary artery contraction in newborn lambs was reported, and inhibition of rho-kinase resulted in significantly greater attenuation of serotonin constriction in high altitude compared to low altitude arteries. High altitude lambs had higher baseline pulmonary artery pressure in addition to greater elevations in pulmonary artery

***Corresponding author:** Qiwei Yang, Department of Pediatrics, College of Medicine, University of Illinois at Chicago, USA, Tel: 312-413-8502; E-mail: qiwei@uic.edu

Received January 10, 2014; **Accepted** January 11, 2014; **Published** January 18, 2014

Citation: Yang Q, Sun M (2014) Perinatal and Neonatal Hypoxia in Pulmonary Vascular Dysfunctions. Cardiol Pharmacol 3: e123. doi:10.4172/2329-6607.1000e123

pressure during acute hypoxic exposure compared to low altitude lambs [12]. This study suggests that chronic hypoxia in utero results in increased vasopressor response to both acute hypoxia and serotonin, but that rho-kinase is involved only in the increased response to serotonin. Evidencing this, in a neonatal rat model of pulmonary hypertension, inhibition of rho-kinase both prevented and reversed the effects of chronic hypoxia-induced pulmonary hypertension [13,14].

Nitric oxide/cGMP signaling deficiency has been described in pulmonary hypertensive disease and is a current target of therapeutic agents in humans [15-17]. The long-term effects of perinatal hypoxia on the lung circulation with particular attention to the nitric oxide/cGMP pathways have been investigated [18]. Adult mice exposed to perinatal hypoxia displayed an altered regulation of pulmonary vascular tone with higher right ventricular pressure in normoxia and increased sensitivity to acute hypoxia compared to control mice. Perinatal hypoxia dramatically decreased responsiveness of adult pulmonary arteries to acetylcholine (ACh), an endothelium-dependent relaxing agent, but not to nitric oxide, an endothelium-independent agent. Muscarinic M1 ACh receptor (AChR) mRNA expression was increased in lungs and pulmonary arteries of mice born in hypoxia. Inhibitors of M1 AChR abolished the adverse effects of perinatal hypoxia on ACh-induced relaxation. A phosphodiesterase 1 (PDE1) inhibitor also reversed the decrease in ACh-induced relaxation following perinatal hypoxia, suggesting that M1 AChR-mediated alteration of ACh-induced relaxation is due to the activation of calcium-dependent PDE1. Therefore, perinatal hypoxia leads to an altered pulmonary circulation in adulthood with vascular dysfunction characterized by impaired endothelium-dependent relaxation. BAY 41-2272 is a direct activator of soluble guanylate cyclase independent of nitric oxide and is effective as an acute pulmonary vasodilator in an animal model of persistent pulmonary hypertension of the newborn. Prolonged BAY 41-2272 treatment during chronic hypoxia reduced right ventricular hypertrophy and attenuated pulmonary artery wall thickening in neonatal rats. However, BAY 41-2272 did not protect animals from hypoxia-induced inhibition of alveolarization and vessel growth [14,19].

Determining the developmental origins of adult diseases including pulmonary vascular disease and their associated effects is quite challenging. Understanding the molecular mechanism underlying early hypoxia–induced pulmonary vascular disease could therefore be conducive in providing new insights for improved treatment and prevention of later adult diseases.

References

1. Jones RD, Morice AH, Emery CJ (2004) Effects of perinatal exposure to hypoxia upon the pulmonary circulation of the adult rat. Physiol Res 53: 11-17.
2. Olave N, Nicola T, Zhang W, Bulger A, James M, Oparil S, et al. (2012) Transforming growth factor-beta regulates endothelin-1 signaling in the newborn mouse lung during hypoxia exposure. Am J Physiol Lung Cell Mol Physiol. 302: 857-865.
3. Tang JR, Le Cras TD, Morris KG Jr, Abman SH (2000) Brief perinatal hypoxia increases severity of pulmonary hypertension after reexposure to hypoxia in infant rats. Am J Physiol Lung Cell Mol Physiol 278: L356-364.
4. Ambalavanan N, Nicola T, Hagood J, Bulger A, Serra R, et al. (2008) Transforming growth factor-beta signaling mediates hypoxia-induced pulmonary arterial remodeling and inhibition of alveolar development in newborn mouse lung. Am J Physiol Lung Cell Mol Physiol 295: 86-95.
5. Nicola T, Ambalavanan N, Zhang W, James ML, Rehan V, et al. (2011) Hypoxia-induced inhibition of lung development is attenuated by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. Am J Physiol Lung Cell Mol Physiol 301: 125-134.
6. Bierer R, Nitta CH, Friedman J, Codianni S, de Frutos S, et al. (2011) NFATc3 is required for chronic hypoxia-induced pulmonary hypertension in adult and neonatal mice. Am J Physiol Lung Cell Mol Physiol 301: L872-880.
7. Young KC, Torres E, Hatzistergos KE, Hehre D, Suguihara C, et al. (2009) Inhibition of the SDF-1/CXCR4 axis attenuates neonatal hypoxia-induced pulmonary hypertension. Circ Res 104: 1293-1301.
8. Sartina E, Suguihara C, Ramchandran S, Nwajei P, Rodriguez M, et al. (2012) Antagonism of CXCR7 attenuates chronic hypoxia-induced pulmonary hypertension. Pediatr Res 71: 682-688.
9. Parker TA, Roe G, Grover TR, Abman SH (2006) Rho kinase activation maintains high pulmonary vascular resistance in the ovine fetal lung. Am J Physiol Lung Cell Mol Physiol 291: L976-982.
10. Gao Y, Portugal AD, Negash S, Zhou W, Longo LD, et al.(2007) Role of Rho kinases in PKG-mediated relaxation of pulmonary arteries of fetal lambs exposed to chronic high altitude hypoxia. Am J Physiol Lung Cell Mol Physiol 292: 678-684.
11. McNamara PJ, Murthy P, Kantores C, Teixeira L, Engelberts D, et al. (2008) Acute vasodilator effects of Rho-kinase inhibitors in neonatal rats with pulmonary hypertension unresponsive to nitric oxide. Am J Physiol Lung Cell Mol Physiol 294: 205-213.
12. Blood AB, Terry MH, Merritt TA, Papamatheakis DG, Blood Q, et al. (2013) Effect of chronic perinatal hypoxia on the role of rho-kinase in pulmonary artery contraction in newborn lambs. Am J Physiol Regul Integr Comp Physiol 304: R136-146.
13. Ziino AJ, Ivanovska J, Belcastro R, Kantores C, Xu EZ, et al. (2010) Effects of rho-kinase inhibition on pulmonary hypertension, lung growth, and structure in neonatal rats chronically exposed to hypoxia. Pediatr Res 67: 177-182.
14. Xu EZ, Kantores C, Ivanovska J, Engelberts D, Kavanagh BP, et al. (2010) Rescue treatment with a Rho-kinase inhibitor normalizes right ventricular function and reverses remodeling in juvenile rats with chronic pulmonary hypertension. Am J Physiol Regul Integr Comp Physiol 299: 1854-1864.
15. Dumitrascu R, Weissmann N, Ghofrani HA, Dony E, Beuerlein K, et al. (2006) Activation of soluble guanylate cyclase reverses experimental pulmonary hypertension and vascular remodeling. Circulation 113: 286-295.
16. Ghofrani HA, Osterloh IH, Grimminger F (2006) Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. Nat Rev Drug Discov 5: 689-702.
17. Klinger JR, Abman SH, Gladwin MT (2013) Nitric oxide deficiency and endothelial dysfunction in pulmonary arterial hypertension. Am J Respir Crit Care Med 188: 639-646.
18. Peyter AC, Muehlethaler V, Liaudet L, Marino M, Di Bernardo S, et al. (2008) Muscarinic receptor M1 and phosphodiesterase 1 are key determinants in pulmonary vascular dysfunction following perinatal hypoxia in mice. Am J Physiol Regul Integr Comp Physiol 295: 201-213.
19. Deruelle P, Balasubramaniam V, Kunig AM, Seedorf GJ, Markham NE, et al. (2006) BAY 41-2272, a direct activator of soluble guanylate cyclase, reduces right ventricular hypertrophy and prevents pulmonary vascular remodeling during chronic hypoxia in neonatal rats. Biol Neonate 90: 135-144.