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Therapy of pulmonary hypertension in neonates and infants

Thomas Hoehn *

Neonatology and Pediatric Intensive Care Medicine, Department of General Pediatrics, Heinrich-Heine-University, Moorenstr. 5 D-40225 Duesseldorf, Germany

Abstract

Pulmonary hypertension (PH) in newborns and infants can present in its idiopathic form or complicate a long list of other diseases. Most of these conditions are either pulmonary or cardiovascular in origin. In the present review our currrent knowledge regarding pathophysiology, structural changes, diagnosis, and available treatment options for PH in the age group below 1 year of age is summarized. New treatment options available in adults including endothelin receptor antagonists (ETRA) and phosphodiesterase (PDE) inhibitors are presented and the need for randomized controlled trials in newborns and infants is emphasized. Future candidates for pharmacotherapy of PH in infants include among others vasoactive intestinal polypeptide (VIP), PDE-3 and PDE-4 inhibitors, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and adrenomedullin (ADM).

Keywords: Persistent pulmonary hypertension of the newborn; Pulmonary arterial hypertension; Nitric oxide; Prostacyclin; Sildenafil; Bosentan

Abbreviations: 6MWD, 6-min walking distance; ADM, adrenomedullin; EPC, endothelial progenitor cells; ETRA, endothelin receptor antagonist; HMG-CoA, hydroxymethylglutaryl coenzyme A; MCT, monocrotaline; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVR, pulmonary vascular resistance; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal polypeptide.

Contents

* Tel.: +49 211 81 18091; fax: +49 211 81 19786.
E-mail address: thomas.hoehn@uni-duesseldorf.de.

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1. Introduction

Pulmonary hypertension (PH) covers a broad clinical spectrum ranging from transient neonatal condition to permanent disabling disease in infancy or childhood. A variety of perinatal conditions can trigger persistent PH of the newborn (PPHN; Dakshinamurti, 2005). In the majority of cases, PPHN can successfully be reversed by specific treatment of the underlying condition in addition to treatment of PH. Primary PPHN is a rare event, in which cases no triggering condition of PPHN can be identified. Treatment of PPHN consists of preferably selective pulmonary vasodilation, which was first made available by the introduction of inhaled nitric oxide (NO) into neonatal clinical practice in the early 1990s (Kinsella et al., 1992; Roberts et al., 1992). While starting with considerable enthusiasm for the new drug, neonatologists began to realize, that a certain proportion of newborns with clinical PPHN did not respond favorably to NO (Hoehn & Krause, 2001; Travadi & Patole, 2003). Clinical management of this subgroup of patients combined with economic considerations and transient decreased availability of NO combined to boost the development of alternative drugs, like phosphodiesterase-5 inhibitors (PDE) or endothelin-1 receptor antagonists (ETRA) to successfully treat PH. Advantages of the latter medications include a prolonged half-life and independence from inhalational equipment. Unfortunately, due to the low number of neonates and infants treated with these substances, there are currently neither randomized controlled trials nor much experience with long-term application of these drugs available.

2. Physiology of perinatal and postnatal changes

A prerequisite for efficient postnatal gas exchange in any newborn infant is the clearance of substantial amounts of fetal lung fluid (Jain & Dudell, 2006). Rapid clearance of fetal lung fluid is a key part of perinatal adaptation and is mediated in large part by transepithelial sodium reabsorption through amiloride-sensitive sodium channels in the alveolar epithelial cells (Jain & Eaton, 2006). Failure to achieve this adaptation results in respiratory morbidity presenting as transient tachypnea of the newborn (term infant) or respiratory distress syndrome (preterm infant), depending on gestational age of the newborn. Particularly when uterine contractions are absent immediately prior to delivery, as in selective Cesarean section, there is no activation of the amiloride-sensitive sodium channels in the alveolar epithelial cells and therefore an increased risk of respiratory morbidity.

Regulation of pulmonary arterial resistance thus determining pulmonary blood flow is achieved by the interaction of 3 main players: NO, endothelin, and prostaglandins (Ziegler et al., 1995). Among these, endothelin increases pulmonary vascular resistance (PVR), whereas NO and prostaglandins lead to vasodilation and reduced vascular resistance (for details, see Fig. 1). Other genes and their products involved in the

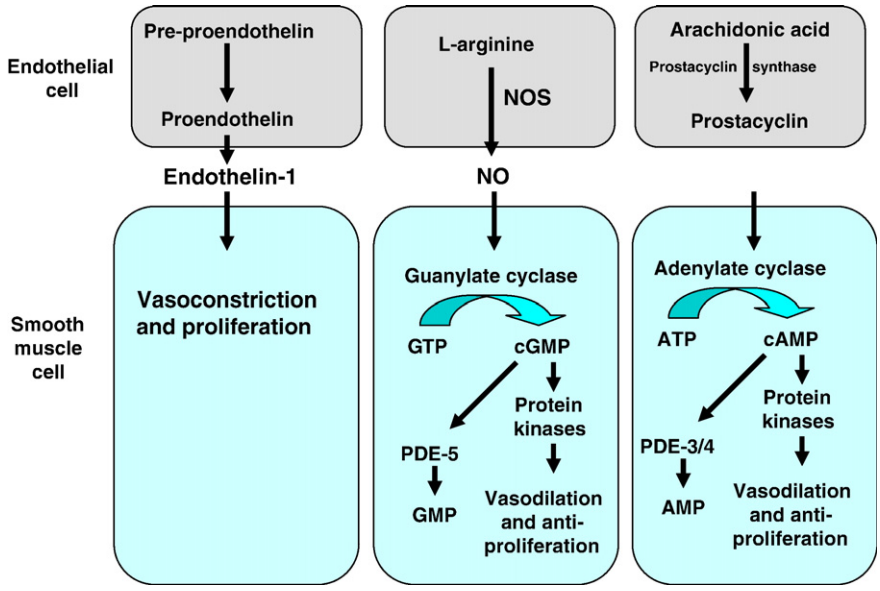

Fig. 1. Schematic interactions of endothelin, NO, and prostaglandins between pulmonary endothelial and smooth muscle cells.