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Roles of the Angiotensin System in Neonatal Lung Injury and Disease

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Abstract

The renin-angiotensin system (RAS) has long been known as a regulator of blood pressure and fluid homeostasis. In past several decades, local renin-angiotensin systems have been discovered in various tissues and novel actions of angiotensin II (ANGII) have emerged as an immunomodulator and profibrotic molecule. The enzyme responsible for its synthesis, angiotensin-converting-enzyme (ACE), is present in high concentrations in lung tissue. ACE cleaves angiotensin I (ANG I) to generate angiotensin II (ANGII), whereas ACE2 inactivates ANGII and is a negative regulator of the system. The RAS has been implicated in the pathogenesis of pulmonary hypertension, acute lung injury and experimental lung fibrosis. Recent studies in animal and humans indicate that the RAS also plays a critical role in fetal and neonatal lung diseases. Further investigations are needed to better understand the role of RAS, ACE and ACE-2 in neonatal lung injury. With more clarity and understanding, the RAS and/or ACE-2 may ultimately prove to constitute potential therapeutic targets for the treatment of neonatal lung diseases. This manuscript reviews the evidence supporting a role for RAS in neonatal lung injury and discusses new possibilities for therapeutic approaches.

ABBREVIATIONS

RAS: Renin-Angiotensin System; AGT: Angiotensinogen; ANG: Angiotensin; ACE: Angiotensin-Converting Enzyme; AT1: Angiotensin Type1; AT2: Angiotensin Type2; CDH: Congenital Diaphragmatic Hernia; PH: Pulmonary Hypertension; ARB: Angiotensin Receptor Blockers; BPD: Bronchopulmonary Dysplasia; MAS: Meconium Aspiration Syndrome

INTRODUCTION

The renin-Angiotensin system (RAS) has received increased attention in recent years, and our understanding of this system has changed radically over the past several decades. Originally, RAS was regarded as a systemic cascade, in which the α^2-globulin Angiotensinogen (AGT) is produced constitutively and released into the circulation, chiefly by the liver. A substrate for renin (secreted by kidneys), AGT, is converted into the decapeptide Angiotensin (ANG) I and subsequently by Angiotensin-converting enzyme (ACE) 1 to the octapeptide ANGII. By the action of ACE-2, ANGII activity is terminated by its conversion to ANG 1-7. Previous work from our lab demonstrated that ACE-2 protects against fibrosis, but is downregulated in both human and experimental lung fibrosis models [1]. Of note, both ACE-1 and ACE-2 are secreted by the lung [2].

The RAS exists not only as a systemic pathway, but as a whole in various tissues and organ systems that function independently [3-6]. Nonetheless, ACE is present in a high concentration in the lungs. ANGII produces its effects by interacting with Angiotensin type1 (AT1) and Angiotensin type2 (AT2) receptors. ANGII is a pulmonary profibrotic mediator and stimulates collagen synthesis [7]. There is increasing evidence to support the role for the activation of the renin Angiotensin system during acute lung injury in experimental lung fibrosis. ACE is predominantly expressed in the pulmonary microvascular endothelial cells, which is in contrast to that of other organs where ACE is expressed in the arteries. Because of the angiogenic function of AT2, ACE has been suggested to play a role in vascular remodeling, pulmonary hypertension [8] and in the pathophysiology of neonatal lung diseases.

The role of RAS in fetal lung development and respiratory mechanics

In the fetus, ACE protein and mRNA have been detected in a variety of tissues, including the placenta, lungs and kidneys, from early in gestation [9-11], although the pulmonary concentration *in utero* is low compared to that measured in adult life [12-14]. In several species, tissue and circulating concentrations of ACE in the fetus have been shown to increase towards term [12-17]. ACE activity was first detected in a rat lung as early as on day 17 of gestation and increased progressively to term. However, the greatest increase in lung ACE activity to adult levels occurred

between 2 and 4 weeks of postnatal life [18]. The Angiotensin receptor subtypes (AT1a, AT1b, and AT2) are known to be highly regulated during fetal development [19-22]. AT2 receptors are almost solely expressed in the fetus [20], suggesting a role in fetal development. However, the tissue distribution of Angiotensin receptors in the fetus varies considerably and the fetal lung is known to express only the ATla receptor subtype [22]. The expression of angiotensin receptors in undifferentiated fetal mesenchyme implies a possible role for ANGII as a growth and differentiation factor during development [20-22].

Increased local expression of ACE was associated with the distal muscularization that accompanies hypoxic pulmonary hypertension in the adult rat. Furthermore, in a rat model of congenital diaphragmatic hernia (CDH), associated with abnormal muscularization of the pulmonary vascular bed, ACE activity was elevated compared with the normal lung [23]. It has been proposed that increased local conversion of ANG I to ANG II in the vessel wall may contribute to the vascular remodeling associated with these conditions, because ANG II is known to stimulate hypertrophy and/or hyperplasia of vascular smooth muscle cells *in vitro*, in addition to its more traditional role as a vasoconstrictor. CDH is a severe developmental anomaly, the etiology of which remains poorly understood [24,25]. This congenital anomaly is characterized by a diaphragmatic defect that allows intrathoracic herniation of abdominal organs, and consequently, mal-development of the alveoli and pulmonary vessels. For many years, this malformation was thought to be a surgical emergence, solely related to a diaphragmatic defect, and potentially curable by surgical closure of this defect after birth which allows lung expansion. However, during 90 years, CDH pathophysiology progressed for a physiological emergence [26,27]. It is now clear that lung hypoplasia and consecutive persistent pulmonary hypertension (PH) associated with this disorder are the key determinants of mortality [24-27].

In severe human CDH, it was demonstrated that PH results from decreased number of arteries, increased thickness of media and adventitia of pulmonary arterial walls and distal muscular extension to the non- muscular intra-acinar arteries [28,29]. Despite improvements in understanding CDH pathophysiology and advances in neonatal care, the mortality (50%) and morbidity rate in CDH newborns remains exceedingly high. In humans, CDH can be accurately diagnosed at second trimester during routine ultrasound examination. Therefore, it is amenable to antenatal therapies. The *in vitro* studies demonstrated that a local RAS is functional at early stages of lung morphogenesis. More recent work showed that all RAS components, renin, ACE, Angiotensinogen, AT1 and AT2 receptors, were expressed throughout all studied gestational ages in the fetal rat lung. ANGII had a stimulatory effect on lung branching, mediated by AT2 receptor and thus ANGII-AT2 interactions might be a target useful in treating CDH [30]. Nogueira-Silva et al., studied the effect of antenatal treatment of pregnant rats with AT2 receptor antagonist on CDH fetal pup lung development. *In vivo* antenatal treatment increased lung growth, ameliorated indirect parameters of pulmonary hypertension, improved lung function and survival time in non-ventilated CDH pups, without maternal or fetal deleterious effects [30]. Further studies are needed to explore potential antenatal therapy of pathologies characterized by fetal lung hypoplasia, such as CDH.

RAS is not only involved in fetal lung development but also has an effect on respiratory mechanics. Recent experimental animal data described interesting effects of angiotensin on respiratory mechanics. The angiotensin plasma concentration is increased and potentiates bronchoconstriction in asthmatic subjects [31,32]. Angiotensin has also been shown to cause bronchoconstriction in adult guinea pigs [33] and rats [34,35], and bronchial hyper-responsiveness to metacholine in human asthmatic subjects [32,36] and adult guinea pigs [33].

Furthermore, the inhibition of angiotensin receptors of type 1, but not of type 2, has been shown to prevent in a dose-related manner the metacholine-induced bronchoconstriction in normal [33] and antigen-inhaling guinea pigs [37]. Angiotensin-elicited bronchoconstriction was also shown to be inhibited by type 1 angiotensin receptor antagonism [34] and/or angiotensin converting enzyme (ACE) inhibition in rats [35].

Rubini et al., has studied the effect of captopril on respiratory mechanics of healthy adult rats. They used end-inflation occlusion method to determine the parameters of respiratory mechanics. They observed that ACE inhibition significantly reduces the overall respiratory system resistance to inflation, hence the overall resistive inspiratory work of breathing. Thus, these experimental data suggest that ACE inhibition may exert useful pharmacological effects not only in the vascular bed, but also in the respiratory system [38]. However, whether or not any of the effects of angiotensin on pulmonary mechanics just discussed are found in neonatal animals or neonatal humans will require significant future investigation, and therefore extrapolation of the findings just discussed to neonates should be done only with extreme caution.

The role of ANG system blockers in pregnancy

The use of ACE inhibitors and angiotensin receptor blockers (ARB) in pregnant women revealed serious and deleterious effects on fetal development including renal failure, renal dysplasia, hypotension, oligohydramnios, pulmonary hypoplasia, and hypocalvaria. The fetal effects of angiotensin converting enzyme inhibitors seem to be greatest during the 2nd and 3rd trimesters of pregnancy. Many of the studies that reported adverse effects of ACE inhibitor use during pregnancy were initially conducted in animals. Use of captopril in the maternal sheep during late pregnancy (119-133 days 'gestational age term is 147 days) reduced maternal blood pressure transiently for 2 h. However, fetal blood pressure remained reduced for up to 2 days and the risk of stillbirth was significantly elevated, where 7 of 8 ewes were stillborn [39]. Orally administered captopril in the pregnant rabbit from mid-gestation until term (15 to 30th day) resulted in fetal death in 86% of newborn rabbits versus 1% in control animals [40]. Captopril administration in pregnant rabbits was also found to reduce uterine blood flow and was associated with an 86% to 92% fetal mortality, depending upon the dosage of captopril used. These investigators concluded that inhibition of Angiotensin II synthesis reduced uterine blood flow and increased fetal mortality [41].

ACE inhibitors have also been examined in the primate baboon. In a prospective placebo controlled trial, use of enalapril during pregnancy resulted in a significant rise in the incidence

of fetal death or fetal growth retardation [42]. The observation that the fetal deaths were associated with only a very modest fall in maternal blood pressure suggested that fetal mortality was likely secondary to a direct effect of enalapril on the fetal Renin-Angiotensin system, rather than to the effects of placental ischemia [42].

Since the advent of wide availability of ACE inhibitors for clinical use, numerous reports on the effects of these agents during pregnancy in humans have been published. In a survey of Michigan Medicaid recipients, there was no association between use of ACE inhibitors during the first trimester of pregnancy and congenital fetal defects [43]. The adverse fetal effects may be a consequence of the pharmacologic effect of ACE inhibitors and not a result of any dysmorphogenic or genetic effect.

The most commonly reported adverse effects of ACE inhibitors taken during second and third trimester of pregnancy include intrauterine growth retardation, neonatal hypotension, renal failure, oligohydramnios, and patent ductus arteriosus [44-47]. In many of these reported cases, oligohydramnios was noted and presumably due to reduce renal function and urine output by the fetus. The oligohydramnios was often accompanied by limb contractures, hypoplastic lungs, respiratory failure and death in the neonatal period [48,49]. The mechanism by which pulmonary hypoplasia develops is unknown, but may be related to compression of the fetal chest wall in view of oligohydramnios [50]. Overall, respiratory complications were found in 14% of newborns who were exposed to maternal ACE inhibitors [51].

Type I angiotensin II receptor blockers inhibit the binding of ANGII to AT1 receptor; thereby oppose the systemic effects of ANGII. Uses of ARBs during the second and third trimesters of pregnancies have yielded similar deleterious effects to that seen with the ACE inhibitors. High rates of mortality were observed, where 2 of 15 cases of fetal exposure to maternal ARBs were stillborn and 4 of the 15 cases died within 3 to 4 days after birth [50,52-58]. Oligohydramnios was reported in 14 of 15 cases of use of ARB late in pregnancy. Neonatal hypoplastic lungs were also reported in 3 of 15 cases of maternal use of AT1 antagonists [50].

Until recently, it was believed that pulmonary hypoplasia due to antenatal maternal exposure of ACE inhibitor and ARB results from oligohydramnios. D.N. Capelari et al., studied the role of RAS in maternal exposure to captopril during late pregnancy on postnatal lung development in rats. Treatment had no effect in serum ACE activity of pregnant rats but a significant decrease in ACE activity was observed in neonatal pups whose mother were treated with captopril [59]. They also explored the expression level of both ANGII receptor subtypes at different postnatal ages following treatment. AT1 receptor expression was high and maintained in lungs from control pups and those exposed to captopril during late pregnancy suggesting an important role of this receptor during lung development [59]. On the contrary, AT2 receptors were not detectable in control or treated animals at the different ages studied, which is same as previously reported [55].

Following treatment with captopril, lung development was evaluated by histological analysis in distal parenchyma from control and treated animals at different post-natal ages. Lung tissue sections from the captopril-treated group showed morphologic changes in the lung architecture, particularly post-natal age day 8 and 15. Lungs from the captopril-treated group showed impaired alveolar formation, resulting in enlargement of distal airway spaces. The morphological changes observed such as increased airway spaces and delayed septation, resemble the typical cytoarchitecture observed in new bronchopulmonary dysplasia (BPD) [59]. New BPD is characterized by arrest in alveolarization. The lungs of rodents are immature at birth and development completes postnatally, the histomorphological effects produced by ACE inhibition during late pregnancy suggest participation of the RAS during lung alveolarization.

The role of RAS in bronchopulmonary dysplasia (BPD)

As mentioned in previous sections, antenatal exposure of captopril disrupts normal alveolar formation in neonatal pups. Another study showed similar results after treating neonatal rats with enalapril. Animal data suggests role of RAS and ACE in lung development and potential role in BPD [59,60]. BPD is the most common complication of very preterm birth and is a multifactorial disease. BPD has evolved over several decades. The "old BPD" is characterized by airway inflammation, pulmonary fibrosis, and smooth muscle hypertrophy. These abnormalities were attributed to ventilator-induced injury as well as to oxygen therapy. Unlike the old BPD, the "new BPD" is characterized by simplification and arrest of development of alveoli and less overt fibrosis [61]. Autopsy of BPD patients showed decreased ACE expression in lungs as compared to controls without lung disease [62]. Based on these findings, ACE-targeted therapies could potentially be developed for BPD.

Supplement oxygen, which is frequently used in the treatment of pulmonary insufficiency in premature infants, has been implicated in BPD. Hyperoxia can directly cause lung injury by generation of reactive oxygen radicals. Prolonged exposure to neonatal mice hyperoxia results in impaired alveolarization and capillary development and increase in lung fibrosis [63]. Our lab has showed that ACE-2 protects against fibrosis and is downregulated in both human and experimental lung fibrosis [1]. In a cell culture study, Oarhe et al., showed that hyperoxia down regulates ACE-2 in human fetal lung fibroblasts. Both ACE-2 immunoreactivity and enzyme activity were significantly decreased in cultured fetal lung fibroblast cells treated with hyperoxia followed by recovery with normoxia compared to normoxia alone [64]. Since it is known that lung injury and fibrosis can be abrogated by ACE-2, the demonstration of a direct effect of hyperoxia on ACE-2 in human lung cells has significant implications in pathogenesis of hyperoxic lung injury, e.g. BPD.

The issue of hypoxia in the perinatal setting is an intriguing one, particularly in the context of prematurity, as the natural environment for the lungs of premature infants is hypoxic relative to that in adult lungs. Oxygen requirements are considerably lower during fetal life, and the fetal lung develops in a markedly hypoxic *in utero* environment [65]. Postnatally, despite advances in medical care, exposure to chronic or intermittent hypoxia in the neonatal period as a result of prematurity is common, typically in the setting of apnea of prematurity or as a result of immature lungs and musculature unable to adequately support the neonate in an extra uterine environment [66]. These abnormal

hypoxic perinatal exposures may compromise alveolar, airway, and pulmonary vascular development, significantly contributing to the pathogenesis of pulmonary diseases. Recent work from our lab showed that hypoxia, in contrast to hyperoxia discussed above, up regulates ACE-2 in fetal lung fibroblasts [67]. This might be an explanation for why fetal lung cells do not undergo fibrotic changes and/or develop changes of chronic lung disease in spite of hypoxemia *in utero*. These finding further suggest that ACE-2 might be potential future therapy for babies at risk for developing BPD.

The role of RAS in meconium aspiration syndrome (MAS)

Meconium aspiration syndrome (MAS) is one of the major clinical problems encountered in the neonatal period. It is an inflammatory newborn lung disease that frequently leads to severe respiratory failure [68,69]. Aspiration of meconium is known to cause airway obstruction, damage of airways and surfactant inactivation. Meconium also causes chemical pneumonitis and induces intense inflammatory reaction in the airways and alveoli [68-70].

An *in vitro* study from our lab has showed that meconium causes lung epithelial cells detachment. The substances responsible for this injury are fetal proteolytic enzymes in the meconium, as demonstrated by the finding that the cell detachment can be reversed by commercially available protease inhibitors [71]. Studies of human meconium instilled into newborn rabbit lungs suggested that apoptosis of lung epithelial cells may play an important role in meconium-induced acute lung injury of newborn [72,73]. As was demonstrated by several techniques, meconium-induced apoptosis is localized preferably in the lung and especially in the airway epithelial cells [72,73]. These data demonstrate that meconium-induced lung cell apoptosis leads to damage and that the proteolytic enzymes in meconium cause detachment of lung airway or epithelial cells.

Using a neonatal rabbit model of MAS, Zagariya et al., demonstrated that apoptosis of lung epithelial cells occurs via cytokine-induced Angiotensinogen gene expression, conversion of ANG I to ANGII, and binding of ANGII to its AT1 receptors [74-76]. They showed increase epithelial cells death via increase expression of AT1 receptors in meconium treated lungs. Although blockers of ANGII could inhibit meconium-induced epithelial cell apoptosis, the physiological effects of meconium in vivo were not completely inhibited by pretreatment of the rabbit pups with captopril or losartan. This might be related to the finding that type 2 ATR were not detectable in newborn rabbit lung before and after meconium instillation [77,78]. Nonetheless, these observations support the speculation that activation of the tissue RAS contributes to the pathophysiology of MAS.

CONCLUSIONS

The local pulmonary renin-angiotensin system plays an important role in fetal lung development and evidence suggests its involvement in CDH, BPD and MAS. Further investigations are needed to better understand the role of RAS, ACE and ACE-2 in neonatal lung injury. With more clarity and understanding, the RAS and/or ACE-2 may ultimately prove to constitute potential therapeutic targets for the treatment of these neonatal diseases.

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