PRENATAL EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS (PAHS) AUGMENTS NEONATAL HYPEROXIC LUNG INJURY: ROLE OF CYTOCHROME P450 (CYP)1A1, 1A2, AND 1B1

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Background: Pregnant women exposed to high levels of polycyclic aromatic hydrocarbons (PAHs) are at increased risk for premature delivery. Preterm infants often require supplemental oxygen, a known risk factor for the development of bronchopulmonary dysplasia (BPD). The molecular mechanisms by which hyperoxia causes lung injury are not fully understood, but cytochrome P450 (CYP) enzymes have been implicated. In this study, we test the hypothesis that prenatal exposure to PAHs [i.e. a mixture of benzo[a]pyrene (BP) and benzo(b)fluoranthene (BbF)] exacerbates oxygen-mediated lung injury in neonatal mice, and that this effect is differentially altered in mice lacking the gene for cytochrome P450 1A1, 1A2, and 1B1.

Materials/Methods: Timed pregnant WT (C57BL/6J) mice were administered a PAH mixture of BP and BbF (7.5, 15, 30mg/kg each) and the dose response of prenatal PAH administration on postnatal hyperoxic lung injury was examined. In addition, timed pregnant (C57BL/6J) mice with one of four genotypes (wild type, Cyp1a1-null, Cyp1a2-null, and Cyp1b1-null) were treated orally with vehicle corn oil (CO) or mixture of PAHs BP and BbF (7.5 mg/kg each) on gestational days 16-19. Offspring were exposed to hyperoxia (80% O2) or room air (21% O2) for 14 days. Mice were sacrificed on PND15, and lung injury was assessed by morphometry (radial alveolar count, RAC) as well as real time reverse transcriptase-polymerase chain reaction (RT-PCR) for inflammatory markers IL-6 and TNF-α mRNA expression in lung tissue samples. We also performed RT-PCR for cytochrome P450 (CYP)1A1 and 1B1 expression in order to evaluate the effect of PAH exposure on the modulation of P450 enzyme expression.

Results: Results showed that hyperoxic lung injury is augmented by prenatal PAH exposure in a dose-dependent manner. This effect was differentially altered in Cyp1a1-null, Cyp1a2-null and Cyp1b1-null mice. There was significant induction of CYP1A1 expression in neonatal mice exposed prenatally to PAH in room air and suppression of CYP1A1 expression following hyperoxia, suggesting that CYP1A1 expression is protective against hyperoxic lung injury.

Conclusions: Newborn mice exposed to PAH in utero had more significant lung injury in response to hyperoxia than non-PAH exposed pups, and the degree of lung injury was varied among mice lacking the genes for cytochrome P450 1A1, 1A2, and 1B1. Our results suggest that induction of CYP1A1B by PAH may play a mechanistic role in augmenting the effects of oxidative stress in the newborn lung.

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