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Title: Bone morphogenetic protein signaling in experimental nitrofen-induced congenital diaphragmatic hernia

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Body: Congenital diaphragmatic hernia (CDH) is a life-threatening cause of lung hypoplasia and persistent pulmonary hypertension of the newborn. As bone morphogenetic proteins (BMP) have been shown to play crucial roles in fetal lung and heart development, we explored the potential implication of this signaling pathway in an experimental model of CHD. Pregnant Sprague-Dawley rats were exposed to either 100 mg nitrofen or olive oil on embryonic day 9.5. On embryonic days 17 and 21, fetuses were delivered by caesarian section, sacrificed, checked for CDH and their lung and heart tissue were harvested for pathobiological evaluation. Lung and heart weight-to-body weight ratios decreased by 28% and 35% ($P<0.05$) on embryonic day 17 and by 12% and 8% ($P<0.05$) on embryonic day 21. Nitrofen administration resulted in airway septa thickening, together with lower radial alveolar count. The pulmonary expressions of the BMP receptor (BMPR) type 2, BMP4 and BMP7 decreased, while the expression of BMPR1A did not change and the expression of gremlin, a BMP antagonist, increased on embryonic day 17. The pulmonary expression of DNA binding protein 1 (Id1) decreased, together with decreased pro-apoptotic Bax/Bcl2 ratio on embryonic day 21. The myocardial expressions of BMPR2, BMPR1A, BMP7 and SERCA-2A were decreased, while the expressions of gremlin and noggin increased on embryonic day 17. On embryonic day 21, the myocardial expressions of Id1 and SERCA-2A decreased, while gremlin expression increased. These results suggest that BMP signaling is downregulated in the lungs and the heart at early and late stages of nitrofen-induced CDH.