Nanoparticles delivery of vascular endothelial growth factor promotes fetal lung growth in the nitrofen rat model for congenital diaphragmatic hernia

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Objective

To determine whether sustained prenatal intra pulmonary delivery of vascular endothelial growth factor (VEGF) using slow release nano diamonds (NDS; over 48-72 hours), has advantageous effects in lung growth in nitrofen-induced congenital diaphragmatic hernia (CDH).

Methods

CDH was induced in fetuses of pregnant sprague-dawley rats by gavage feeding nitrofen on e9, 5 (term=22). Maternal laparotomy and hysterotomy were performed at e19, and NDS (2-8nm nanoparticles; 75μg/ml in 50μl vehicle/saline) were administered into the fetal trachea followed by tracheal occlusion (TO). NDS were fluorescently-labelled (ND-fl) or conjugated with recombinant VEGF 164 (ND-VEGF; 2μg/ml VEGF164). Blinded assessment of lung-to-body weight ratio (LBWR) and morphometric parameters was performed at e21. 5 in CDH offspring. Comparisons were made between fetuses receiving nd-vegf+to, unconjugated vegf+to, vehicle+to, and sham surgery.

Results

Prenatal ND administration did not have noticeable adverse feto-maternal effects. Although unconjugated VEGF+TO led to improvements in LBWR and lung architecture, the effects did not exceed those seen in the vehicle+TO group. ND-VEGF+TO was associated with improved lung growth (LBWR: 5. 9±0. 2%), which was significantly greater than that observed in VEGF+TO (3. 5±0. 4%; p<0. 01), vehicle+TO (3. 9±0. 1%; p<0. 01), and sham (2. 0±0. 2%; p<0. 001). Moreover, ND-VEGF+TO resulted in thinner alveolar septa (mean transection length/airspace: 18. 9±0. 5) and increased alveolar size (mean airspace chord length: 31. 4±0. 6) compared to other treatment groups (p<0. 01 vs. VEGF+TO and vehicle+TO; p<0. 001 vs. sham).

Conclusion

Fetal airway delivery of VEGF gradually released by NDs under to induce additional lung growth as compared to to alone. The lack of effect of unconjugated VEGF delivery suggests that gradual release is a requirement for bioactivity in this experimental model.