Leukotriene Synthesis Inhibition Increases Pulmonary Blood Flow in Fetal Lambs


We considered that leukotrienes may control fetal pulmonary vascular tone because infusion of a putative leukotriene receptor antagonist (FPL57231) markedly increased pulmonary blood flow and decreased pulmonary vascular resistance in near-term fetal lambs. This hypothesis would be considerably strengthened if inhibition of leukotriene synthesis also produced similar hemodynamic changes.

Material and Methods

Pregnant ewes were operated on at 133-136 days' gestation using epidural and local anesthesia. Polyvinyl catheters were inserted into peripheral fetal vessels as well as into the fetal pulmonary artery and left atrium following left lateral thoracotomy. About 4 days' recovery were allowed before study.

The effects of \( \pm 30 \) mg/kg Piriprost (U 60257), a lipooxygenase inhibitor, given directly into the pulmonary artery over 5 minutes were evaluated in 9 fetal lambs, all with normal baseline blood gas values and pH. Pulmonary blood flow was measured before and after Piriprost with injection of microspheres and a pulmonary arterial reference sample, and pulmonary vascular resistance was calculated from the pulmonary arterial/left atrial mean pressure difference.

Results

Pulmonary blood flow increased maximally by 502% between 15 and 60 minutes after Piriprost injection (\( p<0.05 \), Friedman nonparametric ANOVA), and pulmonary vascular resistance fell by 87% (\( p<0.05 \)).

Discussion

This study further investigated the role of leukotrienes in the control of pulmonary blood flow and pulmonary vascular resistance in fetal lambs. Intrapulmonary injection of U 60257, an inhibitor of leukotriene synthesis, significantly increased pulmonary blood flow and decreased pulmonary vascular resistance in late-gestation fetal lambs—changes similar in magnitude to those seen with leukotriene receptor antagonism as well as to those that occur with the normal initiation of ventilation at birth. That structurally dissimilar compounds, one a leukotriene synthesis inhibitor and the other a leukotriene receptor antagonist, similarly increased pulmonary blood flow and decreased pulmonary vascular resistance, strongly suggests that leukotrienes play a role in controlling pulmonary vascular tone in the fetal lamb.

References


Acute and Chronic Fetal Pulmonary Hypertension Alter Pulmonary Vasoreactivity

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Persistent pulmonary hypertension of the newborn (PPHN) is the failure of the pulmonary circulation to adapt successfully to postnatal conditions. Associated with a wide variety of neonatal cardiopulmonary disorders, PPHN represents the inability to achieve or sustain a drop in pulmonary vascular resistance during the immediate newborn period. Previous clinical and experimental studies suggested that intrauterine events may play important roles in its pathogenesis. Supportive evidence includes: (1) the timing of onset of disease within hours of birth; (2) the severity of histologic findings at autopsy of infants with severe PPHN dying within the first few days, including marked smooth muscle and perivascular adventitial thickening; and (3) animal studies suggesting that fetal stressors, such as hypoxia or hypertension, can cause smooth muscle thickening of small pulmonary arteries. Recent studies, however, failed to confirm these observations. The actual mechanisms

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