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Theophylline Stimulates Fetal Breathing Movements during Hypoxia

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ABSTRACT. The respiratory responses to theophylline during normoxia and hypoxia were determined in 13 unanesthetized fetal sheep. Theophylline (plasma levels ~111 μmol/L) increased the incidence of fetal breathing movements measured over 120 min from 37.7 ± 4.8% to 61.1 ± 5.7% (SEM) in normoxic fetuses. In isocapnic hypoxia (arterial O_2 tension ~1.86 kPa), theophylline increased the incidence from 20.0 ± 6.3 to 52.0 ± 6.1%. Theophylline also resulted in an increase in the slope of inspiration during both normoxia and hypoxia. We conclude that adenosine modulates fetal respiratory drive during normoxia and hypoxia. (*Pediatr Res* 28: 83–86, 1990)

Abbreviations

ECOG, electrocorticogram

In unanesthetized fetal sheep, acute hypoxia causes a depression in the incidence of fetal breathing movements (1, 2). This response is present in fetuses as early as 75–95 d gestation (3, 4). Despite a number of investigations (5–9), a satisfactory explanation of the mechanisms involved in this response to hypoxia has not been forthcoming.

In vagotomized, glomectomized adult animals, the depressive response to hypoxia can be attenuated by the adenosine receptor antagonist theophylline (10). In addition, a long acting analog of adenosine [N^6 (L-2-phenylisopropyl) adenosine] causes respiratory depression in these preparations (11), and this effect can be reversed by theophylline (12). Similarly, in neonatal rabbits, phenylisopropyl adenosine results in depression of respiration, and this effect can be reversed with theophylline (13–15). Moss and Scarpelli (16) have shown that theophylline increases the fetal respiratory responses to CO_2. Some of the fetuses studied were acidemic and hypoxic, but these authors did not specifically determine if the adenosine antagonist would reverse the hypoxic depression of fetal breathing movements. Smith *et al.* (17) produced prolonged fetal apnea by injecting i.v. phenylisopropyl adenosine into fetal sheep. Because the dose used resulted in a loss of low voltage electrocortical activity that is the permissive state for fetal respiratory activity (18), the specific effect on fetal breathing is difficult to evaluate.

Our studies were performed to determine if the respiratory response to hypoxia could be altered by pretreating the fetus with theophylline. Because theophylline has been shown to stimulate fetal respiration during normoxia (16), this poses a difficulty in interpreting an effect during hypoxia. However, we reasoned that if adenosine contributes to the respiratory depression seen with hypoxia, then the stimulatory effect of theophylline during hypoxia should be similar to that during normoxia. Although other studies indicate that theophylline does not cause a change in neonatal cerebral blood flow (19), we measured sagittal vein blood gases and pH to determine if these stimuli to the central chemoreceptors were altered.

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MATERIALS AND METHODS

Thirteen pregnant ewes were used for these studies. Sterile surgery was carried out between 122 and 130 d gestational age under nitrous oxide and fluothane anesthesia in oxygen. The methods used for placement of catheters in the fetal trachea, axillary artery, sagittal vein, hind limb vein, and amniotic fluid and placement of electrodes above the dura have been described in detail (6). A polyvinyl catheter was inserted in the ewe's trachea and sutured to the s.c. tissues. This catheter was used for the addition of N_2 and CO_2 to the ewe's inspired air (20). The flow rates were 8–11 L/min for nitrogen and 0.8–0.9 L/min for CO_2. After surgery, the animals were housed in 1.5 × 3 m pens with free access to food and water.

Experiments were initiated 4–8 d after surgery and carried out over the following 2–6 d. The fetuses were between 127 and 142 d gestation at the time experiments were performed. The studies were conducted between 1000 and 1400 h, a period during which we have not observed differences in the incidence of fetal breathing (21). The animals ate *ad libitum* during the studies. Four protocols were used, each consisting of a 2.5-h period. For the normoxia studies, 0.9% saline (15 mL bolus, followed by 0.5 mL/min) was infused into the fetal hind limb vein, after which air was added to the ewe's inspiratory flow. The theophylline protocol was similar to the normoxia except that the bolus infusion of saline and the subsequent constant infusion contained 27.8 mmol/L theophylline (Sigma Chemical Co., St. Louis, MO). The hypoxia and hypoxia theophylline protocols were similar to those described above except that N_2 and CO_2 were added to the ewe's inspiratory air at flow rates adjusted to decrease fetal arterial P_{O_2} to less than 2.26 kPa and maintain P_{CO_2} at the control level. After the initial 0.5 h during which the blood theophylline levels were established and fetal blood gases stabilized, fetal respiratory variables were recorded for the next 120 min. Fetal blood was sampled for theophylline concentrations, pH, and blood gases at 30 and 90 min of this 120-min period. The order of the four protocols was chosen at random and only one protocol was used on a single day. A total of 38 experiments were carried out in the 13 animals. The pregnancy continued for 2–6 d after the last experiment in seven animals and the remaining six were killed because the four protocols were completed. No differences in results were seen between these two groups.

The tracheal, amniotic fluid, and arterial catheters were connected to pressure transducers (model 23 Db, Statham, Oxnard, CA) that were calibrated with a mercury manometer. The leads for the fetal ECOG were connected to an amplifier and filtered (0.5- to 30-Hz band pass, Beckman type 9853A coupler, Beck-

man Instruments, Schiller Park, IL). The signals from the transducers and ECOG were displayed on a chart recorder (Beckman R611). The data were converted to digital form and stored for later analysis of the respiratory variables (model xT286, IBM Instruments, Inc., Danbury, CT). Fetal blood samples were analyzed for pH, P_{O_2}, and P_{CO_2} at 39°C with standard electrodes (Radiometer Ltd., Copenhagen). Fetal arterial and sagittal vein blood was sampled at 30 and 90 min of the 120-min study. Theophylline was measured in fetal blood at 30 and 90 min using a fluorescence polarization immunoassay (22). The coefficient of variation for this assay in our laboratory is 3%.

Single-breath analysis of the respiratory variables was performed by methods similar to those of Wickham and Walker (23), although not in real time. Tracheal pressure and amniotic fluid pressure were digitized at 95 Hz and stored for later analysis. Amniotic pressure was subtracted from tracheal pressure; the difference was filtered digitally (Gaussian, cutoff frequency 2.85 Hz) and subjected to a rule-based breath recognition algorithm. A breath was defined by the time and pressure at the initiation of an inspiratory effort and the time and pressure at the peak negative pressure. The initiation of a breath was considered to be the time and pressure that preceded negative rate of change of pressure that was at least 0.20 kPa (taken over 50 ms) and led to at least a 0.13 kPa change in pressure. The inspiratory time was the time from initiation to peak negative pressure and breath-to-breath interval the time from the initiation of one breath to the initiation of the next. Breath amplitude or depth was the difference between the initiation pressure and the peak negative pressure. Inspiratory slope was calculated by dividing amplitude by inspiratory time. Each breath was visually inspected before its parameters were included in the statistical analysis. Depending on the length (range 0.5–32 min) of a breathing episode, 1–5 separate min representative of the episode were selected for breath-to-breath analysis. Each breathing episode during the 120 min had a portion analyzed. The median number of breaths analyzed in each protocol was 340 with a range of 118–559. The lower number was from a single hypoxia saline study in which the incidence of breathing movements was only 4%. The arithmetic means for each experiment were used to calculate respiratory parameters.

Fetal breathing movements were defined as repeated transient negative pressures recorded from the trachea (relative to amniotic fluid pressure) that were greater than 0.13 kPa and occurred at a frequency >0.25 Hz. The incidence of fetal breathing movements was calculated as the percent of the 120-min period during which breathing was present. Fetal ECOG was assessed visually into periods of low voltage (<50 μV) and high voltage (50–200 μV). The incidence of low voltage ECOG was similarly calculated.

All data are reported as the means ± SEM. The incidence of fetal breathing movements and the respiratory variables for the four experimental situations were compared by one way analysis of variance. Significant differences between groups were determined by the least significant difference test (24).

RESULTS

The fetal arterial blood gases and pH for the four protocols are shown in Table 1. Control blood gases and pH obtained before infusing gases in the maternal trachea or fetal i.v. infusions were not different among the four groups before beginning the protocols. Theophylline at concentrations of 112.2 ± 8.9 μmol/L in fetal arterial blood did not cause any changes in arterial blood gases or pH. The theophylline levels at 30 and 90 min of the study were not different. Hypoxia induced by adding N_2 and CO_2 to the ewe's inspired air resulted in a 0.93 kPa fall in arterial O_2 tension in both the fetuses infused with saline and those that received theophylline. Fetal arterial theophylline concentrations (103.3 ± 6.7 μmol/L) in the fetuses that were then rendered hypoxic were similar to that achieved in the normoxia group. There were no differences in arterial CO_2 tension and pH between the four groups. Table 2 lists the O_2 and CO_2 tensions and pH in the sagittal vein for the four experimental conditions. As for fetal arterial measurements, hypoxia produced significant decreases in sagittal vein P_{O_2} (~0.60 kPa), but theophylline had no effect; sagittal vein P_{CO_2} and pH were unchanged under all conditions.

In studies in which fetuses were pretreated with theophylline, the incidence and depth of fetal breathing movements were increased. This occurred in both normoxia and hypoxia (Table 3). Although the incidence of breathing was less in hypoxia theophylline experiments than in normoxia theophylline, this difference was not significant. Respiratory timing was not affected by theophylline. Theophylline caused a significant increase in inspiratory slope during both normoxia and hypoxia. As was observed for the incidence of fetal breathing movements, the difference in inspiratory slope was not significant between normoxia theophylline and hypoxia theophylline. In the normoxia experiments, the fetuses spent 58.6 ± 2.8% time in low voltage electrocortical activity, and this was unaffected by hypoxia (56.2 ± 2.4%). Theophylline pretreatment was associated with an insignificant increase to 67.4 ± 2.7% during normoxia and 65.1 ± 2.9% during hypoxia.

DISCUSSION

Previous studies have examined a number of mechanisms concerning the depression in respiration seen with hypoxia in the fetus. The response is present in fetuses that have been subjected to peripheral chemodenervation (5). Fetal cerebral metabolism does not change during the moderate levels of hypoxia that result in respiratory depression (6), although it is not possible to determine the metabolic rate of the medulla itself. Transection of the fetal brain stem at various levels suggests that there is an area rostral to the pons, but caudal to the hypothalamus, that is involved in the hypoxic depression (7, 8). Further studies with smaller bilateral lesions have localized this area to the upper lateral pons (8), although these lesions do not define whether nuclei at the site or fiber tracts running through it are responsible. In addition, these lesion studies do not establish a neurochemical mechanism for the hypoxic depression.

In our experiments, sagittal vein pH and P_{CO_2} were unchanged with theophylline pretreatment in both the normoxic and hypoxic studies. Therefore, a differential stimulus to central chemoreceptors cannot be invoked to explain the stimulatory effects of theophylline. In addition, the level of central hypoxia was similar in the control and theophylline studies. Theophylline produced a much greater increase in the incidence of fetal breathing movements during hypoxia than during normoxia. Because adenosine is released during hypoxia, this observation is consistent with theophylline's action as an antagonist to adenosine receptors. Theophylline concentrations of 50 μmol/L produce minimal inhibition of intracellular phosphodiesterase activity (25). Because at least half of the drug is bound (25), the plasma levels of free theophylline in our studies would have been about 50 μmol/L, and it is unlikely that the major site of action was at the level of phosphodiesterase activity.

Previous studies (26, 27) have shown that the inspiratory slope of tracheal pressure increases as a linear function of arterial CO_2 tension in fetal sheep. In our experiments, theophylline resulted in an increase in this parameter of respiratory drive in both normoxic and hypoxic fetal sheep. Hypoxia resulted in no change in inspiratory slope or depth of inspiration in agreement with earlier observations (3, 27). Our observation of no change in the components of the respiratory cycle with hypoxia was consistent with the observations of Sameshima and Koos (28), although other studies (3, 4) have reported a fall in respiratory rate.

Responses to theophylline in various parameters of respiratory activity have been variable. Moss and Scarpelli (16), in studies of fetal sheep, noted an increase in both frequency and tracheal deflection at 100 ms. Lagercrantz *et al.* (13) noted an increase in

Table 1. *Fetal arterial blood gases and pH**

	Normoxia saline	Normoxia theophylline	Hypoxia saline	Hypoxia theophylline
Pa_{O_2} (kPa)				
Control	2.90 ± 0.05	2.73 ± 0.09	2.70 ± 0.12	2.65 ± 0.11
30 min	2.82 ± 0.09	2.69 ± 0.09	1.88 ± 0.13†	1.82 ± 0.07†
90 min	2.77 ± 0.08	2.67 ± 0.11	1.92 ± 0.09†	1.86 ± 0.13†
Pa_{CO_2} (kPa)				
Control	6.53 ± 0.15	6.50 ± 0.11	6.46 ± 0.11	6.29 ± 0.17
30 min	6.45 ± 0.17	6.40 ± 0.13	6.24 ± 0.13	6.05 ± 0.17
90 min	6.48 ± 0.20	6.37 ± 0.15	6.22 ± 0.16	6.06 ± 0.19
pHa				
Control	7.38 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.36 ± 0.01
30 min	7.37 ± 0.01	7.36 ± 0.01	7.37 ± 0.01	7.36 ± 0.01
90 min	7.37 ± 0.01	7.37 ± 0.01	7.36 ± 0.01	7.35 ± 0.01

* All values mean ± SE. $n = 11$ for normoxia saline and normoxia theophylline and $n = 8$ for hypoxia saline and hypoxia theophylline. Pa_{O_2}, arterial O_2 tension; Pa_{CO_2}, arterial CO_2 tension; pHa, arterial pH. The control samples were obtained before beginning tracheal infusions in the ewe or i.v. infusions in the fetus. The 30- and 90-min samples were obtained 30 and 90 min after the desired fetal blood gases had been obtained.

† $p < 0.05$ compared with normoxia saline.

Table 2. *Fetal sagittal vein blood gases and pH**

	Normoxia saline	Normoxia theophylline	Hypoxia saline	Hypoxia theophylline
Psv_{O_2} (kPa)				
30 min	2.22 ± 0.07	2.12 ± 0.07	1.48 ± 0.12†	1.44 ± 0.08†
90 min	2.10 ± 0.08	2.03 ± 0.11	1.53 ± 0.13†	1.48 ± 0.12†
Psv_{CO_2} (kPa)				
30 min	6.90 ± 0.20	6.86 ± 0.20	6.57 ± 0.15	6.60 ± 0.20
90 min	7.18 ± 0.23	6.96 ± 0.15	6.44 ± 0.21	6.69 ± 0.21
pHsv				
30 min	7.34 ± 0.01	7.33 ± 0.01	7.35 ± 0.01	7.34 ± 0.01
90 min	7.33 ± 0.01	7.33 ± 0.01	7.35 ± 0.02	7.33 ± 0.01

* Number of experiments as in Table 1. Time of blood sampling (30 and 90 min) as in Table 1. Psv_{O_2}, sagittal vein O_2 tension; Pv_{CO_2}, sagittal vein CO_2; pHsv, sagittal vein pH.

† $p < 0.05$ compared to normoxia saline.

Table 3. *Respiratory variables in fetal sheep during four experimental conditions**

	Normoxia saline	Normoxia theophylline	Hypoxia saline	Hypoxia theophylline
Fetal breathing movements (%)	37.7 ± 4.8	61.1 ± 5.7†‡	20.0 ± 6.3†	52.0 ± 6.1‡
T_i (s)	0.32 ± 0.03	0.36 ± 0.01	0.38 ± 0.05	0.38 ± 0.03
T_{tot} (s)	0.75 ± 0.08	0.86 ± 0.06	0.87 ± 0.14	0.98 ± 0.10
Depth (kPa)	0.41 ± 0.03	0.76 ± 0.07†‡	0.40 ± 0.04	0.63 ± 0.07†‡
Inspiratory slope (kPa/s)	1.53 ± 0.23	2.30 ± 0.23†‡	1.20 ± 0.09	1.85 ± 0.24‡

* Number of experiments as in Table 1. T_i, inspiratory time. T_{tot}, breath-to-breath interval.

† $p < 0.05$ compared with normoxia saline.

‡ $p < 0.05$ compared with hypoxia saline.

respiratory rate but no change in tidal volume in newborn rabbits, whereas Eldridge *et al.* (11) reported a small increase in frequency and a large increase in phrenic nerve output in adult cats. Direct comparisons cannot be made, inasmuch as the above studies involved either anesthesia or anesthesia and peripheral chemodenervation. In unanesthetized fetal sheep, we have found an increase in inspiratory slope and no change in respiratory rate.

The site of action of theophylline is an unsettled question. In an extensive set of experiments, Eldridge *et al.* (29) eliminated muscular and mechanical factors, carotid body and vagal reflexes, spinally mediated mechanisms arising below the 7th cervical vertebra, changes in arterial CO_2 or medullary extracellular fluid hydrogen ion concentration, and changes of whole body metabolic rate or release of substances from the adrenal glands. They concluded that the neural respiratory response to theophylline is mediated at the level of the brainstem. Because both a dopamine receptor antagonist and an inhibitor of dopamine biosynthesis reduced but did not abolish the stimulatory effects of aminophylline (29), Eldridge *et al.* conclude that dopamine is involved in the respiratory responses to the methylxanthines. The stable sagittal vein CO_2 tension measurements obtained in

our studies indicate that altered CO_2 stimulus of respiratory centers is not responsible for the effects of theophylline. This would not have been expected, inasmuch as it has been shown in newborn piglets that theophylline does not alter cerebral blood flow in either normoxia or hypoxia (19). This increased respiratory drive at the same CO_2 concentration is consistent with the left-shifted CO_2 response after theophylline, which has been seen in fetal sheep (16) and premature human infants (30).

In adult male subjects, theophylline at plasma levels similar to those we obtained in fetal sheep caused a 21% increase in diaphragmatic contractility measured after stimulation of the phrenic nerve (31). We have observed a 50 and 54% increase in inspiratory slope during normoxia and hypoxia, respectively. Transdiaphragmatic pressure generated at functional residual capacity with bilateral electrical stimulation of the phrenic nerves to mimic a constant input to the diaphragm in air-breathing man cannot be directly compared with the slope of intrathoracic pressure deflections in the sheep fetus *in utero*. Nevertheless, the fact that a much greater change from control was observed after theophylline in our studies, coupled with the observations made concerning the central site of theophylline's actions (discussed above), is consistent with the conclusion that the effect is not confined to an improvement in diaphragmatic contractility.

Our studies have shown that theophylline stimulates fetal breathing movements during both normoxia and hypoxia. They also have implications about the adaptation that takes place when hypoxia is maintained in the fetus (6, 9). It may be that adenosine secretion in the CNS is not sustained or, alternately, that there is a down regulation of the adenosine receptors responsible for the inhibitory effects on respiration.

Note: After this manuscript was accepted for publication, a paper appeared (Koos BJ, Matsuda K 1990 Fetal breathing, sleep state, and cardiovascular responses to adenosine in sheep. J Appl Physiol 68:489–495) showing that theophylline stimulated the incidence of fetal breathing during hypoxia, although to a lesser extent than we have observed.

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