The adenosine A1-receptor antagonist antagonist 8-CPT reverses ethanol-induced inhibition of fetal breathing movements

C. S. WATSON, S. E. WHITE, J. H. HOMAN, L. FRAHER, J. F. BRIEN, AND A. D. BOCKING

Departments of Physiology and Obstetrics and Gynecology, Medical Research Council Group in Fetal and Neonatal Health and Development, and Departments of Medicine and Biochemistry, Lawson Research Institute, University of Western Ontario, London, Ontario N6A 4V2; and Department of Pharmacology and Toxicology, Queen’s University, Kingston, Ontario, Canada K7L 3N6

Watson, C. S., S. E. White, J. H. Homan, L. Fraher, J. F. Brien, and A. D. Bocking. The adenosine A1-receptor antagonist 8-CPT reverses ethanol-induced inhibition of fetal breathing movements. J. Appl. Physiol. 87(4): 1333–1338, 1999.—Administration of either ethanol or adenosine inhibits fetal breathing movements (FBM), eye movements, and low-voltage electrocortical activity (LV ECoG). The concentration of adenosine in ovine fetal cerebral extracellular fluid increases during ethanol-induced inhibition of FBM. The purpose of this study was to determine the effect of a selective adenosine A1-receptor antagonist, 8-cyclopentyltheophylline (8-CPT) on the incidence of FBM during ethanol exposure. After a 2-h control period, seven pregnant ewes received a 1-h intravenous infusion of ethanol (1 g/kg maternal body wt), followed 1 h later by a 2-h fetal intravenous infusion of either 8-CPT (3.78 ± 0.08 µg·kg–1·min–1) or vehicle. Ethanol reduced the incidence of FBM from 44.0 ± 10.4 to 2.7 ± 1.3% (P < 0.05) and 51.2 ± 7.6 to 11.9 ± 5.0% (P < 0.05) in fetuses destined to receive 8-CPT or vehicle, respectively. In the vehicle group, FBM remained suppressed for 7 h. In contrast, during the first hour of 8-CPT infusion, FBM returned to baseline (31 ± 11%) and was not different from control throughout the rest of the experiment. Ethanol also decreased the incidence of both low-voltage electrocortical activity and eye movements, but there were no differences in the incidences of these behavioral parameters between the 8-CPT and vehicle groups throughout the experiment. These data are consistent with the hypothesis that adenosine, acting via A1 receptors, may play a role in the mechanism of ethanol-induced inhibition of FBM.

FETAL BREATHING MOVEMENTS (FBM) occur 30–40% of the time in late-gestation fetal sheep in association with low-voltage electrocortical activity (LV ECoG) and eye movements (16). Fetal exposure to ethanol inhibits FBM. In humans, maternal ingestion of ethanol (~0.2 g/kg maternal body wt) inhibits FBM for at least 3 h (18, 28). In sheep, maternal intravenous infusion of ethanol (1 g/kg maternal body wt) inhibits FBM for up to 9 h (32, 34, 37, 38). Ethanol exposure also inhibits LV ECoG and eye movements in fetal sheep, but for a shorter period of time (32, 37, 38). Therefore, ethanol-induced inhibition of FBM is not mediated solely via a decrease in the incidence of LV ECoG.

It has previously been shown that intravenous, intrarterial, or central infusions of either adenosine or the stable analog L-phenylisopropyladenosine inhibit FBM in fetal sheep (6, 22, 24, 35). In addition, intravenous infusion of the nonspecific adenosine-receptor antagonist theophylline stimulates FBM during hypoxia in fetal sheep (5, 24). Intravenous adenosine infusions also inhibit eye movements and LV ECoG (22, 24, 35), although high doses are required for this effect to be evident.

Intravenous administration of ethanol to pregnant sheep increases the concentration of adenosine in fetal cerebral extracellular fluid (37). This increase is temporally associated with the inhibition of FBM. Adenosine exerts its physiological actions via two major receptor subtypes, A1 and A2. The depressive neurobehavioral effects of adenosine are believed to be mediated by the A1 subtype (36) through a decrease in intracellular adenylyl cyclase. Furthermore, A1 receptors are found in respiratory-related areas in the ovine fetal brain (7). Therefore, the objective of this study was to test the hypothesis that adenosine, acting via adenosine A1 receptors, mediates the ethanol-induced inhibition of FBM in sheep. To provide support for this hypothesis, a selective adenosine A1-receptor antagonist, 8-cyclopentyltheophylline (8-CPT), which distributes across the blood-brain barrier (3), was infused into fetal sheep during ethanol exposure, and the incidence and amplitude of FBM were measured. Because adenosine is known to be vasodilatory in many organs (4), we also monitored fetal arterial pressure, heart rate, arterial blood gases, and pH throughout the experiments.

METHODS

Surgical procedure. Surgery was performed on seven timed-mated, mixed-breed pregnant sheep at 126 days of gestation. Anesthesia was induced with intravenous thiopental sodium (17 mg/kg maternal body wt, Abbott Laboratories, Montreal, PQ) and maintained with inhaled 1.5% halothane (Halocarbon Laboratories, Hackensack, NJ) in oxygen. Under sterile conditions, a midline incision was made in the ewe’s abdomen, and the fetal head and neck were exteriorized through an incision in the uterus. Polyvinyl catheters (V4, Bolab, Lake Havasu City, AZ) were placed in a fetal carotid artery, a jugular vein, and the fetal trachea. Stainless steel electrodes (Cooner, Chatsworth, CA) were placed over the dura of the fetal parietal cortex through burr holes in the skull 10 mm on either side of the midline for recording of the electrocortico-
gram (ECoG). The electrodes were secured with cyanoacrylate glue (Krazy Glue, Bordon, Willowdale, ON) over plastic disks on the skull. Electrodes were placed in the inner and outer canthi of one eye for recording of the fetal electrooculogram (EOG), with a common ground wire sewn into the inner surface of the scalp. A polyvinyl catheter (V11, Bolab) was sutured to the fetal skin for recording amniotic fluid pressure. The fetus was returned to the uterus, the catheters and electrodes were exteriorized through the mother’s flank, and the uterus and abdomen were closed in layers. Polyvinyl catheters (V11, Bolab) were placed 20 cm into a maternal femoral artery and vein.

Oxytetracycline (1,600 mg; Liquimycin, Roga/STB, London, ON) was given intramuscularly to the ewe at the time of surgery, and penicillin G sodium (1,000,000 IU) was infused into the fetal jugular vein and amniotic fluid at the time of surgery and daily for the following 3 days. The ewes were housed individually in metabolic cages with access to food and water ad libitum and allowed 4 days recovery before experiments were started.

Experimental protocol. The experimental protocol was approved by the University of Western Ontario and Lawson Research Institute Animal Care Committees and was in compliance with the guidelines of the Canadian Council on Animal Care. Studies began at 8:00 AM and consisted of a 2-h control period followed by a 12-h experimental period. At the end of the control period (t = 0), all ewes received a 1-h intravenous infusion of ethand (1 g/kg maternal body wt). At t = +2 h (1 h after the end of the ethanol infusion), each fetus received a 2-h intravenous infusion of ether 8-CPT (Research Biochemicals, Natick, MA) at a dose of 3.78 × 10^{-6} µg·kg^{-1}·min^{-1}, or an equivalent volume of vehicle. After the 2-h infusion, each fetus was monitored for a further 8 h. A stock solution of 0.5 mg/ml 8-CPT was prepared by dissolving 8-CPT in sterile water and adding 1 M NaOH until the 8-CPT was completely dissolved (final pH 8.0). The final solution was then filtered through a Millipore filter (pore size = 0.2 µm). An appropriate volume of this stock solution was then diluted with sterile saline to achieve the necessary dose in a final volume of 8 ml that was infused at a rate of 4 ml/h. The vehicle consisted of an appropriate volume of the filtered sterile water (pH 8.0) alone added to sterile saline for a final volume of 8 ml. Six of the seven fetuses received both 8-CPT and vehicle infusions, in random order, with 2 days between experiments, and one fetus received 8-CPT only, because of sudden fetal demise 48 h after the first experiment. The electrodes were placed with no 2-4 h throughout the experiment for measurement of blood gases, and glucose, lactate, and plasma 8-CPT concentrations. At the conclusion of the experiments, the ewe and fetus were euthanized with an overdose of intravenous pentobarbitol sodium (Euthanyl, MTC Pharmaceuticals, Cambridge, ON).

Data collection. Continuous recordings of ECoG, EOG, fetal tracheal and arterial pressures, amniotic fluid pressure, and fetal heart rate were obtained throughout each experiment and displayed on a polygraph. Pressures were recorded with Statham pressure transducers (P-23 ID; Viggo-Spectramed, Oxnard, CA) and direct-current pressure amplifiers (model 7P1, Astro-Med, Grass Division, Boucherville, PQ). FBMs were defined as episodes of repeated negative deflections in tracheal pressure of >2 mmHg that lasted for at least 30 s (8). When FBMs were present, the amplitude was measured every minute during each episode, and the hourly mean values were calculated. Mean fetal blood pressure was calculated as the diastolic pressure + 0.4 (systolic pressure – diastolic pressure) after the subtraction of amniotic fluid pressure. Fetal heart rate was measured by a cardiocochrometer (model 7P44B, Grass) triggered from the arterial pulse pressure. ECoG was recorded by using an alternating-current electroencephalogram preamplifier (model 7P511, Grass). For each animal, a minimum level for high-voltage ECoG and a maximum level for LV ECoG were determined visually from the polygraph recording during the baseline period. For each animal, if the voltage fell between the two limits, the ECoG was described as indeterminate. The minimum voltage used to define high-voltage ECoG ranged from 55 to 125 µV, and the maximum voltage used to define LV ECoG ranged from 26 to 83 µV. Each voltage level had to be present for at least 30 s to be described as a change in ECoG state. ECoG was also recorded continuously by using an alternating-current electroencephalogram preamplifier. The presence of eye movement activity was determined by visual inspection of the record. For an episode of eye movements to be identified, electrical activity must have been present for at least 30 s.

Measurement of blood gases, pH, and glucose, lactate, and 8-CPT concentrations. Fetal and maternal arterial blood samples were collected in ice-cold heparinized syringes and immediately placed on ice. A 1-ml aliquot of blood was centrifuged at 2,800 g, and the plasma was stored at −70°C until analyzed for 8-CPT concentrations. The remainder of the blood sample was used to determine glucose and lactate concentrations and for blood-gas analysis. Fetal arterial PO2, PCO2, and pH were measured by using an ABL 500 blood-gas analyzer (Radiometer, Copenhagen, Denmark) at 37°C and corrected for a fetal temperature of 39.5°C. Fetal arterial hemoglobin O2 saturation and hemoglobin concentration were measured with an OSM 3 Hemoximeter (Radiometer). The concentrations of glucose and lactate in fetal arterial blood were measured by the glucose and lactate oxidase methods with the use of a glucose and lactate analyzer (model 2300 Stat Plus, Yellow Springs Instruments).

The concentration of 8-CPT in fetal and maternal plasma was measured by high-pressure liquid chromatography. The following reagents were added to a 200-µl aliquot of plasma: 50 µl 3 M NaOH, 200 µl double-distilled H2O, and 50 ng cyclohexyladenosine (CHA; 50 µl) as the internal standard. This mixture was then extracted with 5 ml ethyl acetate. The organic layer was transferred to a clean tube and concentrated to apparent dryness in a vacuum centrifuge. The residue was dissolved in 150 µl HPLC buffer [10 mM sodium acetate buffer (pH 4.0)-methanol-acetonitrile (56:40:4, vol/vol/vol)]. A 100-µl aliquot was then injected on a Microsphere C18 column (100 × 4.6 mm). 8-CPT and CHA, the internal standard, were detected with an ultraviolet detector set at 269 nm, on the basis of the comparison with authentic standards containing 50 ng of each analyte. The plasma
concentration of 8-CPT was calculated on the basis of the area of its chromatographic signal and interpolation on a standard curve and was corrected for extraction efficiency of the CHA internal standard (27). The average extraction efficiency was 75%.

Data analysis. The data are presented as means ± SE. Statistical analysis was performed by using two-way analysis of variance for repeated measures with a post hoc Dunnett’s t-test, where significance was indicated across time in each group. Student’s t-test with a pooled variance was performed, where significance was indicated between 8-CPT and vehicle groups. Two sets of data were considered to be statistically different when P < 0.05.

RESULTS

Blood gases, pH, glucose, lactate, hemoglobin, mean arterial pressure, and heart rate. The fetal arterial P02, hemoglobin O2 saturation, PCO2, pH, and concentrations of lactate and hemoglobin remained unchanged in both the 8-CPT and vehicle groups. Fetal mean arterial pressure and heart rate also remained unchanged from control values in both groups (Table 1). Before the ethanol infusion, the fetal arterial concentration of glucose was 0.9 ± 0.05 and 1.0 ± 0.05 mmol/l in the 8-CPT and vehicle groups, respectively. Ethanol caused a decrease in the fetal arterial concentration of glucose in the 8-CPT group only (0.7 ± 0.03 mmol/l, P < 0.05). Fetal arterial concentration of glucose then returned to control values by the end of the 8-CPT infusion (t = 4 h).

At t = 12 h, fetal arterial concentration of glucose was significantly elevated above the control value in both the 8-CPT and vehicle groups (1.3 ± 0.08 mmol/l, P < 0.01, and 1.3 ± 0.2 mmol/l, P < 0.05, respectively).

Plasma 8-CPT concentrations. At the end of the infusion of 8-CPT (t = 4 h), fetal plasma concentration of 8-CPT was 38.7 ± 10.1 nmol/l. By 2 h after the end of the infusion (t = 6 h), the concentration had fallen to 6.2 ± 3.2 nmol/l and, at t = 12 h, 8-CPT was undetectable in the fetal plasma. 8-CPT was also detectable in the maternal plasma of some animals at t = 4 h and t = 6 h. At t = 4 h, the maternal plasma concentration of 8-CPT was 15.7 ± 11.0 ng/ml, and at t = 6 h it was 19.4 ± 11.0 ng/ml. 8-CPT was undetectable in maternal plasma by t = 12 h.

Table 1. Fetal arterial blood gases, pH, lactate and hemoglobin concentrations, mean arterial pressure, and heart rate during the control period for fetuses in the 8-CPT and vehicle groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8-CPT group (n = 7)</td>
</tr>
<tr>
<td>P02, Torr</td>
<td>22.4 ± 1.7</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>65.9 ± 6.0</td>
</tr>
<tr>
<td>PC02, Torr</td>
<td>50.6 ± 1.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.01</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Hemoglobin, g%</td>
<td>9.4 ± 0.6</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>43.0 ± 1.9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>161 ± 5.5</td>
</tr>
</tbody>
</table>

Values are means ± SE, n. No. of ewes; 8-CPT, 8-cyclopentyltheophylline; SaO2, arterial hemoglobin O2 saturation; MAP, mean arterial pressure.

FBM, ECoG, and eye movements. FBM occurred 44.0 ± 10.4 and 51.2 ± 7.6% of the time before the ethanol infusion in the 8-CPT and vehicle groups, respectively. During the infusion of ethanol, the incidence of FBM decreased to 2.7 ± 1.3 (P < 0.05) and 11.9 ± 5.0% (P < 0.05) in fetuses destined to receive either 8-CPT or vehicle, respectively. In the vehicle group, the incidence of FBM then remained inhibited for a further 6 h (P < 0.05). In contrast, the incidence of FBM returned to control values during the first hour of the 8-CPT infusion and was not different from control for the remainder of the experiment. The incidence of FBM was significantly greater both during, and for 5 h after, the infusion of 8-CPT when compared with the vehicle-infused fetuses (P < 0.05; Fig. 1). The amplitude of FBM was 3.9 ± 0.5 and 3.4 ± 0.3 mmHg during the baseline period in the 8-CPT and vehicle groups, respectively. There was no change in the amplitude of FBM with infusions in either group.

Maternal ethanol infusion led to a decrease in the incidence of LV ECoG for 2 h in fetuses destined to receive either 8-CPT or vehicle, respectively, from 53.5 ± 3.2 and 53.1 ± 6.3% during the control period to 31.1 ± 5.5 (P < 0.05) and 30.1 ± 7.4% (P < 0.05), respectively, during the infusion of ethanol. The incidence of LV ECoG returned to control values after t = 2 h in both groups and was not different between the 8-CPT and vehicle groups. The infusion of ethanol led to an increase in the incidence of indeterminate-voltage ECoG from control values of 14.8 ± 2.7 and 18.1 ± 4.7% to 51.3 ± 11.8 (P < 0.05) and 46.0 ± 4.3% (P < 0.05) in the 8-CPT and vehicle groups, respectively. The incidence of indeterminate-voltage ECoG returned to control values in both groups after 3 h, with no statistical difference between the two groups (Fig. 1). There was no change in the incidence of high-voltage ECoG in either group.

Eye movements occurred 51.4 ± 1.2 and 56.6 ± 7.1% of the time during the control period in fetuses destined to receive 8-CPT or vehicle, respectively. Infusion of ethanol led to a decrease in the incidence of eye movements to 27.1 ± 6.5 (P < 0.05) and 32.1 ± 8.5% (P < 0.05), respectively. The incidence of eye movements remained decreased for 3 h in the 8-CPT-infused animals and for 2 h in the vehicle-infused animals, although there was no statistical difference between the two groups during these time periods (Fig. 1).

DISCUSSION

This study demonstrates that ethanol-induced inhibition of FBM in sheep can be reversed by 8-CPT, a selective adenosine A1-receptor antagonist (10). These data provide further evidence that adenosine plays a role as a mediator of ethanol-induced inhibition of FBM, acting via the A1-receptor subtype. Furthermore, it appears that the mechanism of ethanol-induced inhibition of LV ECoG and eye movements does not involve adenosine A1 receptors, in view of the fact that 8-CPT had no effect on the incidence of these behavioral parameters. The effects on fetal behavior produced by this ethanol regimen in the absence of 8-CPT were the...
same as those observed in previous studies (32, 34, 37, 38).

FBM amplitude was not altered during these experiments, and therefore the changes in FBM incidence were used as the primary measure of respiratory activity. Measurement of tracheal pressure to determine the incidence of FBM is a standard technique used in chronically catheterized fetal sheep experiments (16). Other techniques have also been used, including recordings from phrenic nerves and diaphragmatic electromyographic (EMG) activity (9, 11). A close correlation between negative deflections in tracheal pressure and diaphragmatic EMG bursts has been demonstrated, although not all bursts in diaphragmatic EMG result in a change in tracheal pressure (26). The phasic changes in intrathoracic pressure that occur during FBM have been shown to be important in the growth and development of the fetal lung (19). Tracheal pressure is also a better measure of breath amplitude than is diaphragmatic activity (20). In our study, one person analyzed all the polygraph recordings, and the incidence of FBM during the control period is similar to that seen in previous studies (16).

Adenosine is a central inhibitory respiratory modulator (29), and the adenosine A<sub>1</sub> receptor is found in the respiratory-related centers in the fetal brain stem (7). However, the central nervous system (CNS) mechanisms by which adenosine controls FBM are not known. Adenosine decreases CNS neurotransmission presynaptically by inhibiting neuronal adenylyl cyclase via the A<sub>1</sub> receptor, and postsynaptically by hyperpolarizing the postsynaptic membrane (17). The data from our present investigation, together with the findings of our previous study (37), are in keeping with the reversal of the ethanol-induced inhibition of FBM by 8-cyclopentyltheophylline (8-CPT; solid lines; n = 7) or vehicle (dashed lines; n = 6; crosshatched bar). *P < 0.05, comparison with control period in same group. †P < 0.05, comparison between 2 groups.

![Figure 1](image-url)
ADENOSINE AND ETHANOL-INDUCED INHIBITION OF FETAL BREATHING

1337

lar adenosine through several mechanisms, such as stimulation of the transporter protein that moves adenosine out of cells (13), inhibition of the uptake of adenosine (30), or through metabolism of ethanol itself to acetate (12). Both adenosine and ethanol are thought to inhibit FBM by acting at the level of the fetal brain stem (21, 33).

In previous studies, adenosine has been shown to inhibit fetal LV ECoG for 4 h (24), effects that are similar to those of ethanol. Theophylline, which is a nonspecific adenosine A1- and A2-receptor antagonist, has no direct effect on the incidence of eye movements or LV ECoG, but it does attenuate the hypoxia-induced inhibition of these fetal behavioral parameters (5, 24). Our study indicates that the mechanism of the ethanol-induced inhibition of LV ECoG and eye movements likely does not involve the adenosine A1 receptor. It is possible that 8-CPT has intrinsic stimulatory activity on the incidence of FBM, although preliminary experiments indicate that 8-CPT does not alter FBM in the absence of ethanol exposure (N. DaSilva and A. D. Bocking, unpublished observations).

We chose in this study to infuse 8-CPT because it is a selective adenosine A2-receptor antagonist (10) that readily crosses the blood-brain barrier (3). Because we wished to intravenously infuse the adenosine antagonist to the fetus, it was important to minimize other possible peripheral effects of the pharmacological agents on fetal respiration. Adenosine can also stimulate FBM through its action on peripheral chemoreceptors (21). However, the action of adenosine at the peripheral chemoreceptors is believed to be mediated by the adenosine A2-receptor subtype, which stimulates adenylyl cyclase activity (17). Fetal heart rate and blood pressure in our study were not affected by 8-CPT, which provides further evidence that 8-CPT at this dose likely does not affect peripheral chemoreceptor activity, nor does it cause a nonspecific stimulation of the CNS.

8-CPT was infused at a dose of 4 µg·kg fetal body wt−1·min−1 on the basis of the results of a preliminary study which determined that this dose was the lowest that consistently returned FBM to control incidence during fetal ethanol exposure. 8-CPT concentration in fetal plasma was maximal at the end of the 2-h infusion and was measurable at 2 h thereafter. It is of interest that 8-CPT also was measurable in maternal plasma at the end of the fetal infusion and 2 h thereafter, indicating that it is capable of distributing across the ovine placenta. This may be a major kinetic process for elimination of 8-CPT from the fetal circulation.

Although we did not measure blood ethanol concentrations in this study, it is unlikely that the effect of 8-CPT on FBM incidence during ethanol exposure was due to a difference in blood ethanol concentrations. Diffusion of ethanol across the placenta is rapid and bidirectional, and the clearance of ethanol from the maternal-fetal unit occurs mainly by biotransformation in the maternal liver (14, 15). Although the effects of 8-CPT on uteroplacental blood flow have not been examined, theophylline is known to relax preconstricted small placental arteries (31), and the vasoactive effect of adenosine is believed to be mediated by the A2-receptor subtype (25). Thus there is no evidence to suggest that uteroplacental blood flow would be decreased by the infusion of 8-CPT.

Moss and Inman (29) have proposed a set of criteria that must be fulfilled if a specific neurochemical, such as adenosine, is to be established as a mediator in the control of respiration in developing animals. First, the system for the neurochemical (ligand, receptor, synthetic, and catabolic enzymes) in the fetal brain must be present. Second, a perturbation that inhibits FBM must be accompanied by an increase in the proposed inhibitory neurochemical. Third, infusion of the proposed inhibitory neurochemical must inhibit FBM, and its antagonist must have the opposite effect. Finally, the antagonist of the proposed inhibitory neurochemical must reverse the inhibition of FBM induced by the maneuver. For the first criterion, it is known that the A1 receptor is present in the ovine fetal brain stem (7), and adenosine has been measured in the ovine fetal brain by using microdialysis (23, 37). We have recently shown that ethanol infusion in sheep is accompanied by an increase in adenosine levels in the fetal cerebral extracellular fluid (37). Adenosine is known to inhibit FBM (6, 24), and adenosine-receptor antagonists stimulate FBM (1, 24). This study has now demonstrated that ethanol-induced fetal respiratory depression is reversed during infusion of the selective adenosine A2-receptor antagonist 8-CPT. Studies such as this, examining the mechanisms underlying pharmacological alterations in FBM, may provide new insights into our understanding of normal regulation of respiration in utero as well as during pathological conditions known to occur in human pregnancy.

This research was supported by Medical Research Council of Canada Grant MT-8073 (to J. F. Brien) and a Group Grant in Fetal and Neonatal Health and Development (to A. D. Bocking).

Address for reprint requests and other correspondence: A. D. Bocking, Dept. of Obstetrics and Gynecology, St. Joseph’s Health Centre, 268 Grosvenor St., London, Ontario, Canada N6A 4V2 (E-mail: abocking@julian.uwo.ca).

Received 18 June 1998; accepted in final form 26 May 1999.

REFERENCES

1338  ADENOSINE AND ETHANOL-INDUCED INHIBITION OF FETAL BREATHING


