Cerebral Responses to Acute Maternal Alcohol Intoxication in Immature Fetal Sheep¹

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ABSTRACT. Previous studies in mature fetal sheep have shown that alcohol depresses cerebral blood flow (CBF), cerebral O₂ consumption (CMRO₂), and cerebral glucose consumption (CMRglu). This effect earlier in gestation might contribute to the pathogenesis of fetal alcohol syndrome. Physiologic studies of immature fetal sheep have demonstrated lower CBF, CMRO₂, and CMRglu as well as a blunted vasodilatory response to hypoxia compared with mature fetal sheep. The purpose of this study was to determine whether immature fetal responses to alcohol are blunted compared with near-term fetal responses. We studied seven immature fetal sheep *in utero* at 92 ± 1 d gestation (term = 147 d) 2 d after placement of vascular catheters. Pure ethanol (1 g/kg) was infused i.v. to the mother over 1 h. We measured CBF and myocardial blood flow by radioactive microspheres and calculated CMRO₂ and CMRglu using arterial and sagittal sinus O₂ and glucose concentrations. At a fetal ethanol concentration of 33 ± 8 mmol/L (150 ± 37 mg/dL), there were no significant changes in CBF, CMRO₂, or CMRglu. There was mild hypoglycemia (glucose concentration = 1.05 ± 0.2 versus 1.33 ± 0.2 mM baseline) and lactic acidemia (lactate concentration = 1.29 ± 0.3 versus 1.07 ± 0.2 mM baseline). Cardiovascular variables were unchanged as was myocardial blood flow. The immature fetal sheep brain shows no significant cerebrovascular and metabolic response to acute alcohol intoxication compared with mature fetal sheep. Mild hypoglycemia and lactic acidemia did develop. The reason for the developmental differences in response to alcohol and their relationship to fetal alcohol syndrome remain to be elucidated. (*Pediatr Res* 31: 645–648, 1992)

Abbreviations

CBF, cerebral blood flow
CMRO₂, cerebral O₂ consumption
CMRglu, cerebral glucose consumption

Alcohol is the foremost drug of abuse in the United States, and maternal alcohol abuse, resulting in the fetal alcohol syndrome, is one of the leading causes of mental retardation (1, 2). Neurologic features of the fetal alcohol syndrome include microcephaly, hydrocephalus, abnormalities of neuronal migration ("heterotopias"), cerebellar hypoplasia, low intelligence quotient,

and behavioral problems (3). Several of these neurologic abnormalities have been produced in animals exposed to alcohol *in utero* (4). However, the mechanism(s) by which alcohol produces brain damage and the vulnerable developmental period (if any) during which damage occurs are unknown. The depressant effects of alcohol on CBF and CMRO₂ have been previously reported in several adult animal models as well as in mature fetal sheep. Richardson *et al.* (5) studied the physiologic responses of term fetal sheep to acute maternal alcohol intoxication and noted a significant decrease in both CBF and CMRO₂. In addition, they noted significant fetal hypoglycemia and a decrease in CMRglu. The fetal sheep brain is very mature near term, both structurally and functionally. Studies of immature fetal sheep have shown significantly lower CBF, CMRO₂, and CMRglu compared with mature fetal sheep (6). Furthermore, the cerebral vasodilatory response to hypoxemia is "blunted," reflecting either immature regulatory mechanisms or an inability of cerebral vessels to respond to the usual stimuli (7). We theorized that cerebral responses to acute maternal alcohol intoxication may be similarly blunted or absent in immature fetal sheep, and we therefore compared the physiologic responses to acute alcohol intoxication in immature fetal sheep with responses previously reported near term.

MATERIALS AND METHODS

Subjects. Before initiating these studies, all surgical and experimental procedures were approved by the Animal Care and Use Committee at the University of California, San Francisco. Seven mixed-breed fetal sheep were obtained from time-dated pregnancies.

Surgical preparation. One d before surgery, food was withheld from the ewe, although she was allowed free access to water. After local anesthesia (2% lidocaine hydrochloride), spinal anesthesia was achieved by injecting 4 mL of 1% tetracaine hydrochloride (Pontocaine HCl; Breon Laboratories, New York, NY). Ketamine hydrochloride (50 to 100 mg, Vetalar; Parke-Davis, Morris Plains, NJ) was administered i.v. every 15–30 min during surgery. Local anesthesia (0.25% lidocaine hydrochloride) was used for all fetal incisions. In the ewe, polyvinyl catheters were placed into the descending aorta and inferior vena cava via pedal vessels. An i.v. infusion of 10% dextrose in 0.9% NaCl was begun. Approximately 1 L was infused over 2 h during surgery. In the fetus, polyvinyl catheters were placed into the axillary artery, femoral artery, inferior vena cava (via a pedal vein), and sagittal sinus by previously described methods (6). A catheter was also placed into the amniotic cavity. All vascular catheters were filled with heparin sodium solution (500 U/mL) and sealed. Uterine and abdominal incisions were closed, and all catheters were exteriorized through the ewe's flank. Antibiotics (400 mg kanamycin, 1 000 000 U penicillin G) were given into the amniotic cavity and maternal vein on the day of surgery and each day thereafter.

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The ewe was fed a standard diet of hay and alfalfa pellets and allowed 48 h to recover before physiologic studies of the fetus *in utero*.

Physiologic measurements. Blood flow was measured by use of the radiolabeled microsphere technique (8). Approximately 800 000 microspheres (selected from ^{57}Co , ^{51}Cr , ^{153}Gd , ^{114}In , ^{54}Mn , ^{95}Nb , ^{113}Sn , ^{85}Sr , or ^{65}Zn) were injected over 0.5 min into the inferior vena cava, followed by 1.5 mL of donor fetal blood. A reference blood sample was withdrawn from the axillary artery at a rate of 2.0 mL/min, beginning 10–20 s before the microsphere injection and continuing for 1.0 min after the injection was completed. After completion of the study, the ewe was killed with an i.v. injection of sodium pentobarbital (6–10 g) followed by bilateral thoracotomy. The fetus was immediately removed from the uterus and weighed, followed by immediate removal and weighing of the brain and heart. The brain was divided at the cephalic border of the pons. All tissue rostral to that point was pooled and counted to determine CBF. The cerebellum was removed at the peduncles and counted separately, as was the pons-medulla. The tissue samples were weighed and then placed in formalin. They were later carbonized in an oven at 177°C, ground into a powder, placed in plastic vials at a uniform height of 3 cm, and counted in a 1000-channel multichannel pulse-height analyzer (Norland Corp., Fort Atkinson, WI). The activity of each isotope in each organ was determined by the least squares method. All reference blood and tissue samples contained >400 microspheres.

Blood samples for pH, respiratory blood gases, Hb concentration, oxygen saturation, and glucose, lactate, and ethanol concentration were drawn into heparinized tuberculin syringes and capped immediately. Respiratory blood gases and pH were measured at 39°C with the Corning 158 blood gas analyzer (Corning Medical, MA). Oxygen saturation and Hb concentration were measured with the OSM-2 Hemoximeter (Radiometer, Copenhagen, Denmark). Blood glucose and lactate concentrations were measured using the YSI model 2300 glucose-lactate analyzer (Yellow Springs Instrument Co., Inc., Yellow Springs, OH). Blood ethanol concentration was measured enzymatically via alcohol dehydrogenase oxidation (Sigma Diagnostics, St. Louis, MO). Arterial blood pressure (referenced to amniotic fluid pressure) and heart rate were continuously monitored using Statham P23D6 strain-gauge transducers, Beckman R612, (Beckman Instruments, Fullerton, CA) or Gould 2800S (Gould Inc., Cleveland, OH) polygraphs and a cardi tachometer.

Experimental protocol. On the day of study, 48 h after surgery, the ewe was brought to the laboratory and placed in a specially designed study cart allowing access to food and water. The ewe was allowed 1–2 h to become accustomed to her surroundings before the study began. Three measurements were obtained during the study. For each measurement, blood samples were simultaneously drawn from the maternal artery and the fetal axillary artery and sagittal sinus catheters (0.3 mL from each vessel) and analyzed for pH, blood gases, Hb concentration, and lactate, glucose, and ethanol concentrations. Immediately after blood samples were obtained, radiolabeled microspheres were injected into the inferior vena cava catheter while a reference sample was obtained from the axillary artery. All withdrawn blood was replaced immediately (mL for mL) with donor fetal sheep blood. Heart rate and blood pressure, monitored continuously, were averaged over 5 min for each measurement period. There were no changes in heart rate or blood pressure associated with microsphere injections or blood samplings.

Immediately after baseline measurements were obtained, an infusion of pure ethanol, 1 g/kg, diluted 1:2 in 0.9% saline, was begun i.v. to the ewe and continued over 1 h. The second measurement was obtained at the end of the 1-h infusion and the third measurement 2 h thereafter; henceforth, the third measurement will be called the 3-h measurement.

The 1-g/kg alcohol dose is identical to the dose used by Richardson *et al.* (5) in their studies of term fetal sheep and is

equivalent to approximately 7.5 oz. of 80-proof alcohol or six alcoholic “drinks.”

Data analysis and calculations. Organ blood flow was calculated as organ blood flow = (cpm organ/cpm ref) $\times$ reference sample withdrawal rate, in which cpm represents radioactive counts per min and ref represents the reference withdrawal sample.

CMRO_2 was calculated as $\text{CMRO}_2 = [\text{CaO}_2 - \text{CvO}_2] \times \text{CBF}$, in which CaO_2 and CvO_2 represent arterial and venous oxygen contents, respectively, and CBF represents blood flow to all cerebral tissue rostral to the pons. CMRglu was calculated similarly. Cerebral oxygen transport (OT) was calculated as $\text{OT} = \text{CaO}_2 \times \text{CBF}$. Cerebral fractional oxygen extraction (E) was calculated as $E = \text{CMRO}_2/\text{OT}$.

Measurements were calculated as mean $\pm$ SD for all the study fetuses. Measurements during alcohol intoxication were compared with baseline measurements by analysis of variance. If the *F* test was significant, specific differences were sought with the Newman-Keuls test. Significance was considered at $p \leq 0.05$.

RESULTS

We studied seven fetal sheep at a mean gestational age of 92 ± 1 d. The fetuses ranged in age from 91 to 95 d of gestation at the time of study and weighed 730 ± 50 g. Because sheep reach full term at approximately 147 d of gestation, fetuses were approximately two-thirds gestation. Four of the fetuses were one of twins. Four were males. In one of the seven fetuses, baseline blood flow measurements could not be analyzed, and in another blood could not be withdrawn from the sagittal sinus catheter.

Blood ethanol concentrations after the 1-h ethanol infusion were 32 ± 6 mmol/L (maternal) and 3.3 ± 8 mmol/L (fetal). Two h after the infusion was completed, ethanol concentrations had declined to 23 ± 9 mmol/L (maternal) and 25 ± 10 mmol/L (fetal). There were no significant differences between maternal and fetal concentrations. It is interesting to note that our immature fetal ethanol levels were similar to levels obtained by Richardson *et al.* (5) in mature fetuses, suggesting that the pharmacokinetics of placental ethanol transfer are unchanged over the last half of pregnancy. For reference, legal intoxication for driving while intoxicated in most of the United States is charged at a blood ethanol concentration of 22 mmol/L (100 mg/dL), significant narcosis occurs at 43 mmol/L (200 mg/dL), and stupor and coma occurs at 65 mmol/L (300 mg/dL) (1). During the 1-h infusion, the sheep became drowsy and unbalanced; they often sat down. They appeared fully recovered by the 3-h measurement.

Cardiovascular and systemic physiologic variables are shown in Table 1. There were no significant changes during alcohol intoxication other than a physiologically insignificant decrease in pH and mean arterial blood pressure 1 h after the infusion was completed.

The effect of acute alcohol intoxication on regional brain blood flow and myocardial blood flow is shown in Table 2. There were

Table 1. Fetal cardiovascular and physiologic variables before and during acute maternal alcohol intoxication ($n = 7$ immature fetal sheep)

	Baseline	Ethanol 1 h	Postethanol 3 h
Arterial pH	7.35 ± 0.03	$7.33 \pm 0.04^*$	7.35 ± 0.02
PCO_2 (kPa)	6.6 ± 0.4	6.8 ± 0.6	6.8 ± 0.4
PO_2 (kPa)	3.6 ± 0.2	3.9 ± 0.2	3.6 ± 0.4
Hb (g/L)	80 ± 9	80 ± 12	81 ± 11
O_2 saturation (%)	65.9 ± 5.7	70.9 ± 2.4	67.3 ± 6.9
MAP (mm Hg)†	36 ± 4	$34 \pm 3^*$	36 ± 3
Heart rate (bpm)	221 ± 19	208 ± 7	226 ± 18

* $p \leq 0.05$, compared with baseline.

† MAP, mean arterial blood pressure.

Table 2. Regional brain blood flow and myocardial blood flow (mL/100 g/min) before and during acute maternal alcohol intoxication ($n = 6$ immature fetal sheep)

	Baseline	Ethanol 1 h	Postethanol 3 h
Cerebral hemispheres and midbrain	60 ± 14	52 ± 13	56 ± 18
Cerebellum	103 ± 29	84 ± 32	93 ± 51
Brainstem	122 ± 21	96 ± 26	105 ± 38
Myocardium	171 ± 20	148 ± 26	164 ± 34

Table 3. Cerebral oxygen metabolism before and during acute maternal alcohol intoxication in immature fetal sheep

	Baseline	Ethanol 1 h	Postethanol 3 h
CaO ₂ ($n = 7$)*	3.2 ± 0.5	3.4 ± 0.5	3.3 ± 0.7
CMRO ₂ ($n = 5$)†	60 ± 11	50 ± 14	71 ± 16
OT ($n = 6$)‡	196 ± 38	183 ± 38	196 ± 71
O ₂ extraction ($n = 6$)	0.32 ± 0.04	0.30 ± 0.09	0.35 ± 0.07

* CaO₂, arterial O₂ content (mmol/L).

† CMRO₂, cerebral O₂ consumption (μmol/100 g/min).

‡ OT, cerebral O₂ transport (μmol/100 g/min).

Table 4. Cerebral glucose and lactate metabolism before and during acute maternal alcohol intoxication

	Baseline	Ethanol 1 h	Postethanol 3 h
Maternal CaGlu ($n = 7$)*	3.2 ± 0.3	2.2 ± 0.2†	1.9 ± 0.4†
Fetal CaGlu ($n = 7$)	1.3 ± 0.2	1.06 ± 0.2†	0.94 ± 0.3†
Fetal CMRglu ($n = 5$)‡	10.3 ± 3.3	9.6 ± 2.2	12.0 ± 7.8
Fetal AV glucose ($n = 6$)§	0.18 ± 0.06	0.18 ± 0.4	0.17 ± 0.09
Maternal CaLact ($n = 7$)	0.44 ± 0.16	1.27 ± 0.47†	1.61 ± 0.50†
Fetal CaLact ($n = 7$)	1.07 ± 0.23	1.29 ± 0.31†	1.23 ± 0.34†
Fetal AV lactate ($n = 6$)	0.02 ± 0.08	0.07 ± 0.1	0.0 ± 0.06

* CaGlu, arterial glucose concentration (mM).

† $p \leq 0.05$, compared with baseline.

‡ CMRglu, cerebral glucose consumption (μmol/100 g/min).

§ AV glucose (lactate), arteriovenous glucose (lactate) concentration difference (mM).

|| CaLact, arterial lactate concentration (mM).

no significant decreases in blood flow to any of the three brain regions, or to the myocardium.

The effect of acute alcohol intoxication on cerebral oxygen metabolism is shown in Table 3. There were no significant changes in CMRO₂, cerebral oxygen transport, or cerebral oxygen extraction, nor was there development of fetal hypoxemia.

Alcohol intoxication caused significant maternal hypoglycemia and lactic acidemia (Table 4). This effect was also noted in the fetus, but to a lesser extent. Despite the development of mild fetal hypoglycemia and lactic acidemia during alcohol intoxication (Table 4), there were no significant changes in fetal CMRglu or cerebral lactate flux.

DISCUSSION

The major finding of this study is that, in contrast to more mature fetal sheep, immature fetal sheep do not demonstrate significantly decreased CBF, CMRO₂, or CMRglu in response to acute maternal alcohol intoxication.

Cerebrovascular and metabolic responses to acute alcohol

intoxication have been described by many investigators in a number of species. Several of these investigators have reported that alcohol constricts umbilical and cerebral blood vessels (9–12). Alcohol is generally regarded as a “depressant,” and several studies have demonstrated that alcohol intoxication is associated with decreased CMRO₂ and CMRglu, presumably reflecting decreased functional activity (5, 10, 13–15).

Few investigators have described the effects of alcohol on fetal sheep. Richardson *et al.* (5) studied near-term fetal sheep with the same dose of alcohol as used here and reported a 41% decrease in CBF and a 35% decrease in CMRO₂ immediately after the infusion, both of which gradually returned toward baseline 1 h later. Mann *et al.* (16) also studied near-term fetal sheep but found an increase in CBF during alcohol intoxication. However, the latter studies were done acutely, in exteriorized fetal sheep under general anesthesia, a method that may result in fetal instability (17); furthermore, alcohol was infused as a dextrose solution.

Two factors could account for the absence of significant cerebral vascular and metabolic responsivity to alcohol in immature fetal sheep. One possibility is that alcohol's cerebrovascular and metabolic effects are mediated by metabolites such as acetaldehyde or other vasoactive substances whose metabolism, release, or cerebral effects may be undeveloped at midgestation. Another possibility is that CMRO₂, which at midgestation is only 25% of measurements reported near term (6), is so low that any decrease induced by alcohol may be too small to be detected by the Fick method, which is rather insensitive to small changes in CMRO₂. In fact, although our results do not demonstrate a significant decrease in CBF or CMRO₂ during alcohol intoxication, mean CBF and CMRO₂ at 1 h are slightly lower than baseline. It is possible that this decrease would become significant with the addition of more experiments. A marginal decrease in fetal CBF and CMRO₂, although blunted compared with that in mature fetuses, could affect brain development if repeated over an extended period of time.

The immature fetal sheep in this study developed mild but persistent hypoglycemia. Hypoglycemia has been reported during alcohol intoxication in mature fetal sheep (5) and adults (18). Although the mechanism is uncertain, alcohol is known to inhibit gluconeogenesis (19). Sheep depend upon gluconeogenesis to maintain glucose supply (20) and might be expected to have more severe alcohol-associated hypoglycemia. Cerebral responses to hypoglycemia have been studied in rats (21), newborn dogs (22) and preterm infants (23). There is generally an increase in CBF, a decrease in CMRglu, or both, indicating a coupling of metabolic demand to glucose supply. In the present study, CMRglu did not decrease nor did CBF increase during alcohol-induced hypoglycemia, perhaps reflecting the mild degree of fetal hypoglycemia or different responses by the immature sheep brain to hypoglycemia.

Lactic acidemia has been noted during alcohol intoxication in adults (24), and in the present study both maternal and fetal arterial lactate concentrations were increased, although the increase was most significant for the mother. Lactate could be used as an energy substrate during hypoglycemia or, alternatively, less of the glucose consumed could be used for lactate production. However, we did not note lactate uptake by the immature fetal sheep brain during alcohol intoxication, nor was there any change in cerebral lactate production.

Several studies have demonstrated depressed myocardial function during acute alcohol intoxication in fetal sheep (15, 25, 26). There was no change in myocardial blood flow in the immature fetal sheep in the present study nor were there any physiologically significant alterations in heart rate or blood pressure during alcohol intoxication.

Acute alcohol intoxication in immature fetal sheep is associated with fetal and maternal hypoglycemia and lactic acidemia but not with significant changes in CBF, CMRO₂, or CMRglu compared with mature fetal sheep. The reason for these apparent

developmental differences in the fetal responses to acute maternal alcohol intoxication and the implications of these differences with respect to mechanisms of brain damage in fetal alcohol syndrome remain to be elucidated.

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