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Oxidative Metabolism in Fetal Rat Brain during Maternal Anesthesia

Robert C. Vannucci, M.D., and Joan W. Wolf, B.S.†*

This study examines the effects of maternally administered anesthetics on fetal cerebral metabolism as determined by direct tissue analysis. Term pregnant rats that were paralyzed and had their lungs artificially ventilated were given nitrous oxide, halothane, or pentobarbital. Dams receiving nitrous oxide, 70 per cent, halothane, 0.4 per cent, or pentobarbital, 50 mg/kg, remained normotensive, whereas halothane, 2 per cent, or pentobarbital, 200 mg/kg, led to a 65 per cent decrease in maternal blood pressure and a threefold increase in blood lactate. Halothane, 1 and 2 per cent, was also associated with maternal hyperglycemia, while pentobarbital, 200 mg/kg, decreased blood glucose. Fetal blood lactate and glucose tended to parallel maternal lactacidemia and glycemia. Fetuses of dams anesthetized with nitrous oxide showed decreases of 45 and 8 per cent in cerebral phosphocreatine and adenosine triphosphate (ATP), respectively; cerebral lactate was comparable to that of the control unanesthetized animals. These alterations presumably resulted from cerebral hypoxia and acidosis secondary to nitrous oxide anesthesia combined with paralysis. Fetuses of dams anesthetized with halothane, 0.4 per cent, and pentobarbital, 50 mg/kg, showed concentrations of cerebral metabolites comparable to those of control animals. Halothane, 2 per cent, was associated with metabolic disturbances in fetal brain indicative of cerebral hypoxia. Pentobarbital, 200 mg/kg, although producing maternal hypotension and lactacidemia similar to corresponding changes produced by halothane, 2 per cent, preserved a more optimal fetal cerebral energy state, as reflected in a lower lactate/pyruvate ratio and normal ATP. The metabolic influence of pentobarbital may serve to protect the hypoxic fetus from neurologic damage. (Key words: Anesthesia, obstetric; Brain, metabolism; Anesthetics, gases, nitrous oxide; Anesthetics, intravenous, pentobarbital; Anesthetics, volatile, halothane.)

MODERN OBSTETRICAL PRACTICE attempts to combine safe delivery of the fetus with maximum comfort for the mother. Achievement of this goal requires judicious use of medications that produce maternal analgesia without affecting the fetus. Unfortunately, all currently used analgesics and anesthetics may affect fetal homeostasis, with possible deleterious consequences during and after birth. Agents available for general anesthesia in obstetric cases include nitrous oxide, halothane, and the barbiturates. These compounds are known to exert physiologic and biochemical effects on many maternal organ systems, and by these actions indirectly influence fetal metabolism.[1,2] In addition, volatile anesthetics, because of their low molecular weight and lipid solubility, readily diffuse across the placenta.[3,4] Barbiturates, being lipid-soluble at physiologic *p*H, also are transferred across the placental membrane barrier.[5,6] Upon entering the fetal circulation, these agents may have major influence upon fetal cardiovascular and cerebral function.

Previous studies of maternally administered anesthetics have focused on disturbances in fetal acid–base status and cardiovascular hemodynamics, but little attention has been paid to possible alterations in cerebral metabolism. The present investigation emphasized the cerebral metabolic responses of fetuses whose dams were exposed to nitrous oxide, halothane, or pentobarbital. During anesthesia, measurements of maternal blood pressure and acid–base balance were correlated with fetal oxidative metabolism and the energy state of the brain.

Methods

Dated pregnant Sprague-Dawley rats (Charles River) were individually caged and fed standard laboratory chow and water *ad libitum*. On the morning of expected delivery (gestational day 22), but prior to labor, each dam was initially anesthetized with ether, paralyzed with *d*-tubocurarine, 3 mg/kg, and a tracheostomy tube was inserted. The lungs were ventilated with nitrous oxide, 70 per cent, and oxygen, 30 per cent, with a Harvard rodent respirator at a rate and tidal volume required to attain normal arterial blood-gas values and acid–base balance (pH_a 7.35–7.41; Pa_{CO_2} 35–40 mm Hg; $Pa_{O_2} > 85$ mm Hg). Atropine sulfate, 0.12 mg/kg, was administered to minimize tracheal secretions. With local anesthesia (procaine hydrochloride, 1 per cent), a 30-gauge Teflon catheter was inserted into a tail artery for continuous monitoring of blood pressure and heart rate with a Statham pressure transducer connected to a Beckman dynograph recorder. Body temperature was monitored with a rectal thermistor probe and temperature controller (Yellow Springs Instrument Co.) and was maintained at 37 ± 0.3 C with a heating lamp. Upon completion of the surgical procedures the dam was placed in the right lateral decubitus position to de-

* Assistant Professor in Pediatrics (Pediatric Neurology).
† Research Technician, Department of Pediatrics.

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Address reprint requests to Dr. Vannucci.

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crease pressure on pelvic veins which, if increased, might collapse uterine and fetal (umbilical) blood vessels.[7]

After stabilization of the preparation, each dam was given nitrous oxide, 70 per cent: oxygen, 30 per cent, or nitrogen, 70 per cent: oxygen 30, per cent, either alone or with halothane 0.4, 1 or 2 per cent, or pentobarbital, 50 or 200 mg/kg, intravenously. As suggested by Carlsson *et al.*[8] and Nathan and Reis,[9] all surgical wounds were infiltrated with procaine hydrochloride, 1 per cent, in the animals given only nitrogen or nitrous oxide to breathe.

At the end of the 90-minute experimental period, blood samples (0.02–0.03 ml) were obtained anaerobically from the maternal tail artery for measurements of glucose and lactate. Then the dams were decapitated and three randomly selected fetuses delivered via hysterotomy and immediately frozen *in amnio* in liquid nitrogen. One additional fetus from each litter was decapitated, and a blood sample collected from the severed body for substrate analysis. Fetuses were frozen and blood samples collected within 10 seconds of maternal sacrifice, an interval insufficient to lead to alterations in cerebral metabolites during tissue fixation.[10]

All tissue and blood specimens were stored at −80 C until dissection and extraction. Forebrains (anterior to the colliculi and excluding the olfactory lobes) were dissected and finely powdered at −20 C. Weighed samples were transferred onto three volumes of frozen 3 M perchloric acid (PCA) and homogenized at −10 C. Ten volumes of 5 mM ethylenediaminetetracetic acid (EDTA) were added, and the entire contents mixed and centrifuged at 6,000 × *g* for 30 minutes at 0 C. A portion of supernatant fluid was removed and neutralized with a calculated volume of 2 M potassium bicarbonate to *p*H 6.8; precipitated potassium perchlorate was removed by centrifugation, and the supernatant fluids stored at −80 C until analysis. Exact volumes of blood were diluted tenfold in cold 0.5 M PCA and centrifuged at 5,000 × *g* for 45 minutes. Supernatant fluids were removed and stored at −80 C. Substrates were measured fluorometrically with pyridine nucleotides and appropriate enzymes.‡ Minor modifications[11] of the methods described by Lowry and Passonneau[12] were used for determination of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), phosphocreatine, glucose, lactate and pyruvate. Statistical differences were calculated by means of Student's t test.

‡ Boehringer Mannheim Corporation, New York, N.Y., or Worthington Biochemical Corporation, Freehold, N. J.

Preliminary trials were conducted to assess depths of anesthesia induced by nitrous oxide, halothane, and pentobarbital. Twelve unrestrained term pregnant rats were placed separately in a bell jar through which was circulated a gas mixture of nitrous oxide, 70 per cent: oxygen, 30 per cent, alone or with increasing concentrations of halothane in nitrogen, 70 percent: oxygen, 30 per cent. Six additional dams received pentobarbital, 50 or 200 mg/kg, intraperitoneally. After no more than 90 minutes, the rats were examined, immediately following which they were sacrificed by decapitation. Fetuses (litter sizes 8–12) were delivered by cesarean section and observed for spontaneous respirations and body movements.

Three dams exposed to nitrous oxide appear lethargic; however, they responded to non-painful stimuli and retained corneal and righting reflexes. All fetuses breathed spontaneously upon delivery but appeared hyperkinetic and tremulous. Halothane, 0.4 per cent, did not produce surgical anesthesia, as evidenced by the presence of maternal corneal and righting reflexes, as well as purposeful movements, and the majority (77 per cent) of the fetuses breathed spontaneously. Dams exposed to halothane, 1 or 2 per cent, were surgically anesthetized; none of the fetuses survived. Rats receiving pentobarbital, 50 mg/kg, were also surgically anesthetized, while pentobarbital, 200 mg/kg, produced maternal apnea and subsequent death as early as 10 minutes after administration. Fetuses of all barbiturate-treated dams were anesthetized and unable to be resuscitated by stimulation alone.

Results

Alterations in mean arterial blood pressure (MABP) were observed in pregnant rats exposed to selected anesthetic mixtures (fig. 1). During halothane anesthesia MABP decreased linearly with increasing concentrations to 1 per cent, but beyond this level, the severity of hypotension was not proportional to anesthetic dose. During anesthesia with nitrous oxide or with pentobarbital, 50 mg/kg, MABP was unchanged throughout the experimental period. The lowest recorded blood pressure (37 mm Hg) occurred in dams receiving pentobarbital, 200 mg/kg.

Arterial blood *p*H was significantly decreased in dams given halothane, 2 per cent, and pentobarbital, 200 mg/kg, indicating metabolic acidosis in these groups. Employing the Siggaard-Anderson alignment nomogram,[13] calculated base deficits were 4.7 and 8.0 mmol/l, respectively. The decreased bicarbonate (HCO_3^-) was inversely and quantitatively related to arterial lactate concentrations.

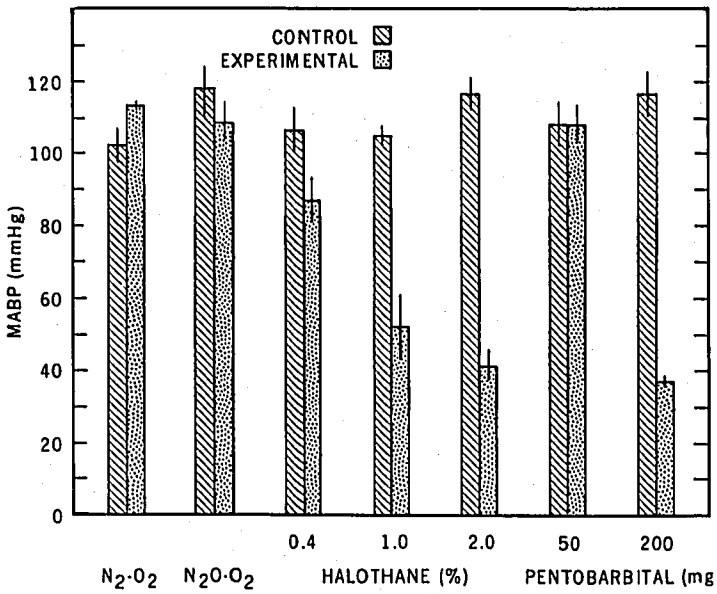

FIG. 1. Effects of anesthetics on mean arterial blood pressure in pregnant rats. Term pregnant rats were paralyzed and ventilated with 1) 70 per cent N_2–30 per cent O_2; 2) 70 per cent N_2O–30 per cent O_2; 3) halothane in 70 per cent N_2–30 per cent O_2. Dams receiving pentobarbital (iv) were ventilated with 70 per cent N_2–30 per cent O_2. Control values (mm Hg) represent means for three animals at the beginning of anesthetic exposure; experimental values are means for the same animals 90 minutes later. Vertical lines denote ±1 SEM.

Blood glucose concentrations of control, paralyzed pregnant rats were significantly higher than values (5.3 ± 0.1 mmol/l) obtained from unrestrained, decapitated dams (fig. 2). Uniform blood glucose levels were observed in animals exposed to nitrous oxide and the lowest levels of halothane and pentobarbital. Halothane, 1 and 2 per cent, was also associated with increased maternal glucose levels. Fetal blood glucose tended to follow simultaneously measured concentrations in dams, such that maternal/fetal glucose ratios approximated 1.5 under most experimental conditions. During anesthesia with halothane, 2 per cent, the glucose ratio approached unity. Pentobarbital, 200 mg/kg, actually reversed the relationship, owing primarily to a decline in the maternal glucose level.

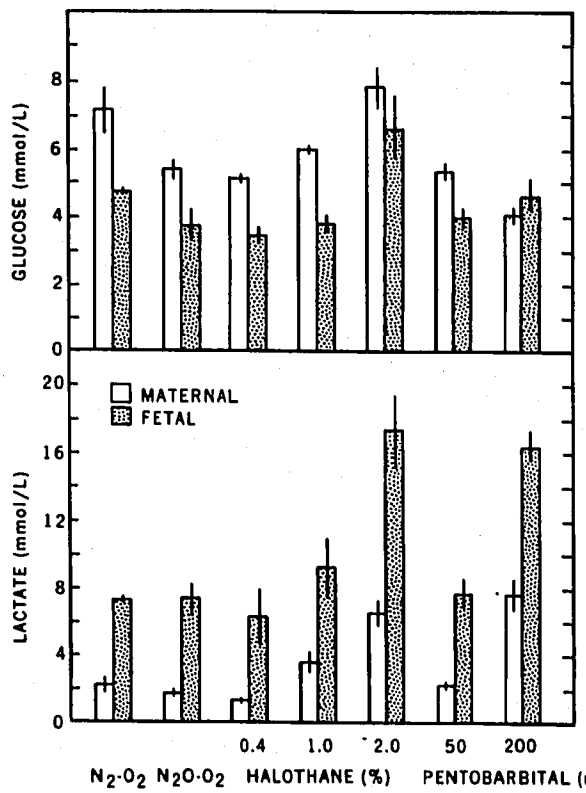

FIG. 2. Effects of anesthetics on maternal and fetal blood glucose and lactate. Pregnant rats were exposed to anesthesia as described in figure 1. Blood samples were collected after 90 minutes of anesthesia. Values, expressed as mmol/l, represent means for three animals. Vertical lines denote ±1 SEM.

Blood lactate in pregnant rats was not altered by nitrous oxide or pentobarbital, 50 mg/kg, compared with concentrations in control dams (fig. 2). Halothane, 0.4 per cent, actually depressed maternal blood lactate, while higher doses led to increasing levels of the metabolite. Pentobarbital, 200 mg/kg, produced the most severe lactacidemia of any experimental protocol. Fetal blood lactate was always greater than and closely followed respective maternal concentrations. The origin of the fetal lactacidemia was unknown, but possibilities included passage from maternal to fetal circulation, placental anaerobiosis, and endogenous fetal production. Whatever the source, the lactacidemia suggested fetal as well as maternal systemic acidosis.

Cerebral lactate concentrations were similar in fetuses of control and nitrous oxide-treated dams, although pyruvate concentration was 14 per cent lower in the nitrous oxide-treated group, resulting in an increased lactate/pyruvate ratio (table 1). Phosphocreatine and ATP levels were also lower by 45 and 8 per cent, respectively, with proportionate increases in ADP and AMP. The metabolic alterations in fetal brain induced by nitrous oxide anesthesia occurred in the absence of maternal hypotension or acidosis.

Cerebral oxidative metabolism in fetuses of halothane-treated dams was adversely influenced by increasing concentrations of the anesthetic agent (fig. 3). Halothane, 0.4 per cent, had no effect on fetal cerebral lactate, pyruvate or high-energy phosphate reserves (AMP increased slightly, $P < 0.05$) compared with the control group. Cerebral glucose was decreased by 39 per cent, although the brain-blood glucose ratio was similar to the control value of 0.48. Higher concentrations of halothane were associated with progressive increases in lactate and lactate/pyruvate ratios. Halothane, 2 per cent, led to a 58 per cent decrease in the fetal brain/blood glucose ratio. The energy state of the brain was also disrupted by halothane, 2 per cent, with near total exhaustion of phosphocreatine and a 43 per cent decrease in ATP. The altered cerebral metabolism presumably resulted from systemic hypoxemia in the fetus secondary to maternal hypotension and reduced placental diffusion of oxygen.

Pentobarbital, 50 mg/kg, was without deleterious effect on cerebral oxidative metabolism in fetuses (fig. 4). At 200 mg/kg, alterations in cerebral metabolism were similar to those observed in fetuses of dams exposed to halothane, 1 per cent. Thus, the brain/blood glucose ratio was not different from the control value, and the lactate/pyruvate ratio was increased less than twofold. Although phosphocreatine was decreased by 47 per cent, ATP was unchanged, with only slight increases in ADP and AMP. These disturbances in cerebral metabolism were not as severe as those observed in fetuses subjected to halothane, 2 per cent, even though the pentobarbital-treated dams were rendered the most hypotensive of any anesthetic group.

TABLE 1. Cerebral Glycolytic Intermediates and High-energy Phosphate Reserves in Fetuses of Unanesthetized and Nitrous Oxide-anesthetized Pregnant Rats*

Metabolite	N_2–O_2 (8)	N_2O–O_2 (9)
Glucose	2.27 ± 0.16	1.58† ± 0.13
Pyruvate	0.139 ± 0.006	0.118† ± 0.013
Lactate	2.51 ± 0.15	2.60 ± 0.21
Lactate/pyruvate	18.1 ± 0.6	24.4† ± 2.0
Phosphocreatine	1.63 ± 0.10	0.90‡ ± 0.1
ATP	2.69 ± 0.03	2.50† ± 0.04
ADP	0.340 ± 0.007	0.433† ± 0.017
AMP	0.047 ± 0.001	0.060† ± 0.005
ATP + ADP + AMP	3.07 ± 0.03	2.93 ± 0.07

* Term pregnant rats were paralyzed and artificially ventilated with either 70 per cent N_2–30 per cent O_2 or 70 per cent N_2O–30 per cent O_2. Values, expressed as mmol/kg brain wet weight, represent means ± SEM for the number of animals in parentheses.
† Different from N_2–O_2, $P < 0.05$.
‡ Different from N_2–O_2, $P < 0.001$.

Discussion

In the present study, anesthesia was associated with significant alterations in maternal blood pressure and acid–base balance, as well as in maternal and fetal blood glucose and lactate levels. The well-documented maternal hypotension during halothane anesthesia[14–16] was associated with hyperglycemia, which appeared inversely related to the mean arterial blood pressure. The increased blood glucose might have reflected epinephrine release in response to hypotension. In adult animals, epinephrine and norepinephrine secretion is known to be increased under conditions of oligemic shock,[17] and presumably also occurs during hypotension induced by halothane. The anesthetic has been reported not to be directly sympathomimetic,[18] and therefore would not of itself lead to increased blood glucose concentrations. The slight hypertensive response observed in control dams possibly also resulted from epinephrine release secondary to the stress of paralytic immobilization.[9,19,20] As with halothane anesthesia, adrenal catecholamine secretion would have accounted for the increase in blood glucose concentrations compared with values obtained from unrestrained, decapitated dams.

An alternative cause of the hyperglycemia during anesthesia with halothane, 1 and 2 per cent, may have been the change in blood lactate, which increased steadily as maternal blood pressure decreased. The hypotension undoubtedly produced tissue ischemia and a shift to anaerobic glycolysis, resulting in lactacidemia. Lactacidemia, in turn, could lead to hyperglycemia via hepatic gluconeogenesis.[21] Anesthesia with pentobarbital, 200 mg/kg, was also associated with maternal hypotension and lactacidemia, although in this instance blood glucose levels were the lowest in any experimental group. Nelson *et al.*[22] also found decreased blood glucose concentrations in adult mice subjected to prolonged (six hours) anesthesia with phenobarbital. The action of barbiturates on glucose metabolism has not been fully explored, but possibilities include enhanced transport of glucose from blood into tissue, including brain[22]; or, conversely, inhibited hepatic glycogenolysis or gluconeogenesis.[23,24]

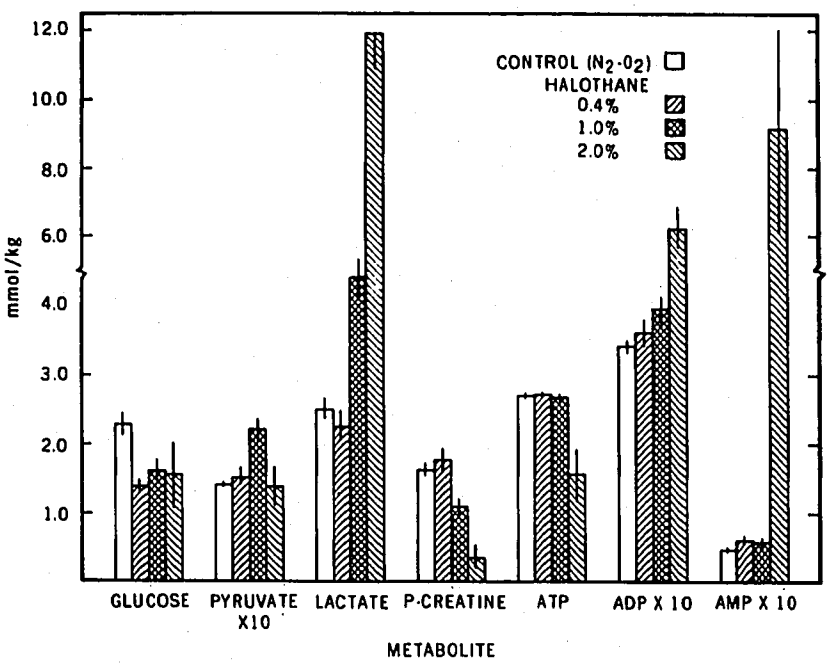

FIG. 3. Cerebral glycolytic intermediates and high-energy compounds in fetuses of halothane-anesthetized pregnant rats. Control levels are those shown in table 2 for unanesthetized, paralyzed animals. Values, expressed as mmol/kg brain wet weight, represent means for nine animals. Vertical lines denote ±1 SEM.

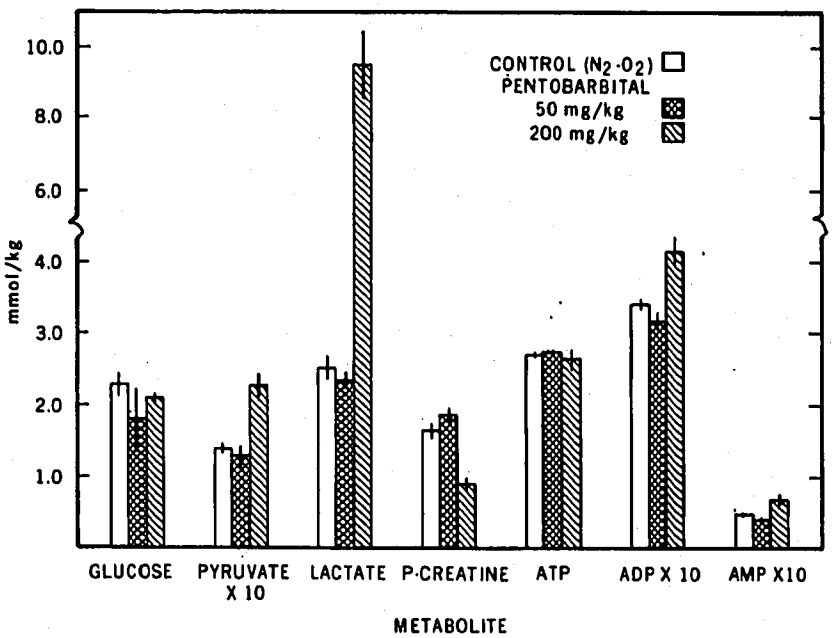

FIG. 4. Cerebral glycolytic intermediates and high-energy compounds in fetuses of pentobarbital-anesthetized pregnant rats. Control levels are those shown in table 2 for unanesthetized, paralyzed animals. Values, expressed as mmol/kg brain wet weight, represent means for nine animals. Vertical lines denote ±1 SEM.

Fetuses of dams exposed to the lowest concentrations of halothane and pentobarbital had levels of cerebral glycolytic intermediates and high-energy compounds comparable to those of fetuses from control dams. Metabolic alterations did occur in brains of nitrous oxide-treated fetuses, and included an increased lactate/pyruvate ratio and decreased phosphocreatine and ATP. Paradoxically, tissue lactate was not increased. Administration of nitrous oxide to adult animals appears to have little or no effect on cerebral oxidative metabolism, and, unlike other anesthetics, nitrous oxide does not cause energy conservation.[8,15,25] The agent also does not affect maternal cardiovascular and acid–base status, although epinephrine-mediated responses to paralytic immobilization are abolished.[9,20,26] As in adults, it is unlikely that nitrous oxide of itself would adversely influence fetal homeostasis. However, nitrous oxide anesthesia in conjunction with paralysis undoubtedly led to metabolic alterations in fetal brain suggestive of hypoxia or hypoxia combined with acidosis. In this regard, increased blood and cerebral lactate/pyruvate ratios associated with unchanged or decreased lactate concentrations have been observed during

hypercapnic acidosis in adult rats.[27] Furthermore, MacMillan and Siesjö[28] have shown that rats rendered hypercapnic and hypoxic have lower cerebral lactate and higher lactate/pyruvate ratios than those observed during hypoxia alone. Whether hypoxia and acidosis can disrupt the energy state of the brain to the extent observed in fetuses without accelerating anaerobic metabolism remains open to question.

Maternal anesthesia with pentobarbital, 200 mg/kg, appeared to have a sparing effect on cerebral metabolism in fetuses, as evidenced by the maintenance of normal ATP levels with only slight increases in ADP and AMP. This protective effect on pentobarbital occurred in spite of a 65 per cent decrease in maternal blood pressure and a two-to-threefold increase in maternal and fetal blood lactate concentrations. In adult animals, barbiturates decrease energy demands in the brain, as reflected by a decreased cerebral metabolic rate for oxygen (CMR_{O_2})[19,29,30] and a slower depletion of cerebral energy stores following decapitation.[31] Furthermore, glycolytic flux is decreased, presumably through inhibition of the phosphofructokinase (PFK) reaction.[19] The changes in oxidative metabolism may result from suppressed neuronal electrical activity with decreased requirements for energy to maintain membrane ionic gradients and to generate action potentials.[32] It is likely that similar cerebral metabolic and energy-sparing influences of barbiturates operate in immature animals, which might account for the maintenance of high-energy stores even in fetuses rendered systematically hypoxic by maternal hypotension.

Concentrations of halothane greater than 0.4 per cent were associated with major disturbances in glycolytic metabolites and the energy state of the fetal brain. At these levels of anesthesia, arterial blood pressures of dams were decreased by at least 50 per cent. Maternal hypotension, induced by halothane, leads to decreased uterine blood flow and diminished placental diffusion of oxygen and carbon dioxide, resulting in fetal hypoxemia and acidosis.[33,34] Systemic fetal hypoxia would account for the increased concentrations of blood lactate in the present study, possibly aggravated by decreased placental clearance of the organic acid. Halothane may also affect the fetus directly by producing fetal bradycarcia and hypotension, although similar disturbances in cardiovascular hemodynamics are known to result from perinatal systemic hypoxia.[35,36] Like barbiturates, halothane has direct effects on cerebral metabolism in adult animals, and presumably these effects extend to the fetus. In rats, halothane, 0.6 per cent, depresses CMR_{O_2} by 20–30 per cent, and a higher concentration (2 per cent) decreases CMR_{O_2} to an extent comparable to that seen with barbiturates in anesthetic doses.[16] In addition, cerebral energy depletion is retarded and maximal glycolytic capacity is not attained following decapitation of mice anesthetized with halothane, 0.8 per cent.[37] Unlike barbiturates, halothane is not associated with a higher cerebral energy state or with a slower rate of anaerobic metabolism, as reflected by steady-state concentrations of lactate in brain.[15,37]

The differential effects of halothane and barbiturates on cerebral metabolism may, at least in part, explain the present findings in fetuses anesthetized with halothane and pentobarbital. Halothane, 2 per cent, and pentobarbital, 200 mg/kg, led to nearly identical decreases in maternal mean arterial blood pressure and to increases in maternal and fetal lactate concentrations, alterations that suggest similar extents of fetal hypoxemia and/or acidosis. In fetal brain, deep halothane anesthesia was associated with a tenfold increase in the lactate/pyruvate ratio and a decline in ATP, with proportionate increases in ADP and AMP. In contrast, profound pentobarbital anesthesia produced a less than twofold increase in the lactate/pyruvate ratio, with no alteration in ATP. Thus, pentobarbital served to preserve an optimal cerebral energy state in the presence of systemic hypoxia. Barbiturates are known to protect fetal and newborn animals against hypoxia, both by prolonging survival and by decreasing or preventing the subsequent development of structural brain damage.[38,39] Possibly, the cerebral metabolic influence of barbiturates observed in the present study aids in protecting the hypoxic fetus from long-term neurologic damage.

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