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Placental Transfer and Fetal Effects of Maternal Sodium β-Hydroxybutyrate Infusion in the Baboon

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ABSTRACT. We examined the effects of maternal sodium β-hydroxybutyrate (NaBOHB) on the primate fetus to investigate the impact of ketosis not associated with acidosis on fetal metabolism. After a loading dose (600 mg/kg), NaBOHB was infused for 70 min (300 mg/kg·hr) into the maternal femoral vein of eight pregnant baboons, and placental transfer and fetal and maternal metabolic changes were observed during an acute experimental protocol. Maternal arterial levels rose from 0.70 ± 0.21 to 5.42 ± 0.93 mM ($p < 0.001$), and fetal arterial levels from 0.34 ± 0.09 to 2.76 ± 0.64 mM ($p < 0.01$). A maternal-fetal gradient of approximately 2:1 was observed in both baseline and steady-state infusion conditions and is similar to the human maternal-fetal ketone gradient. This is in contrast to the sheep where significantly higher gradients have been described. The elevated lactate, from 1.90 ± 0.34 to 2.88 ± 0.54 mM ($p < 0.05$) and somewhat decreased pO_2 values in the fetus from 54.8 ± 8.9 to 45.0 ± 3.8 mm Hg ($p > 0.05 < 0.1$), without change in oxygen consumption (2.00 ± 0.28 *versus* 1.73 ± 0.15 mM/min) are features common to conditions of increased levels of fetal energy substrate. NaBOHB does not appear to contribute to oxidative energy metabolism of the whole fetus but may contribute to lipid stores. The significance of higher levels of BOHB in the primate fetus compared to the sheep fetus remains to be elucidated. (*Pediatr Res* 25:435–439, 1989)

Abbreviations

BOHB, β-hydroxybutyrate
NaBOHB, sodium β-hydroxybutyrate

Ketoacidosis during human pregnancy has deleterious effects on both mother and fetus. Serious consequences for the fetus include increased mortality and increased prevalences of malformations and intellectual deficits (1–3). Human placental ketone body transport has not been well studied. A number of reports have described placental transfer and metabolic effects of BOHB infusion in the pregnant sheep. However, the human maternal-fetal gradient for ketones, 2:1 (4), is different from that reported for the sheep, 7–10:1 (5). The sheep placenta is epitheliochorial in contrast to the hemochorial placentation of the primates. To better define the metabolic effects of hyperketonemia in the nonhuman primate, we studied placental transfer of ketones during an acute experimental infusion of NaBOHB into the maternal circulation of eight pregnant baboons in late gestation.

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MATERIALS AND METHODS

Baboons of known gestational age were obtained from the Biologic Resources Laboratory, University of Illinois, Chicago, and studied between 164 and 171 d of gestation (term 184 d). Individually caged pregnant animals had food and water removed 16 h before surgery. After initial tranquilization with phencyclidine and endotracheal intubation, anesthesia was maintained with halothane and an 80% oxygen-air mixture. This mixture increases maternal oxygenation (303 ± 14 mm Hg), but was used so that data would be comparable to previously published acute studies in the baboon (6–8). As previously described (6–8), fetal catheters were placed in the femoral vein, femoral artery, and umbilical vein. Maternal catheters were placed in a femoral artery and femoral vein. The experimental protocol lasted 3½ h, beginning with the start of the antipyrine infusion into the fetal femoral vein. During the 1st h, fetal catheter placement was completed. As described in Table 1, during the next 80 min four sets of samples were drawn from the fetal femoral artery, umbilical vein and maternal artery for substrate analyses. Additional sample sets were obtained for antipyrine and blood gas analyses. The umbilical vein was sampled for glucose, ketones, antipyrine, and blood gases only.

During the last period of the protocol, a maternal loading intravenous infusion of 600 mg/kg of NaBOHB was administered over 10 min and an infusion continued at 300 mg/kg·hr for the next 70 min. During this period, the earlier sampling protocol was repeated. Four sets of blood samples were drawn for substrate analyses. Additional sample sets were obtained for antipyrine and blood gas analyses. The sampling protocol used a total of 26 mL of fetal blood. To maintain fetal blood vol, maternal blood was collected at the beginning of the protocol. Fetal blood samples were then replaced vol for vol with maternal blood after each sampling. At the end of the protocol, the fetus was delivered and killed humanely. The mother was returned to the breeding colony after surgical repair and recovery.

ANALYSES

Plasma samples were analyzed for glucose using a glucose oxidase, oxygen electrode technique (Beckman Instruments Inc., Fullerton CA) and for glycerol (9), lactate (10), pyruvate (11), alanine (11), and BOHB (12), using enzymatic fluorometric methods (13). Samples for pyruvate were analyzed immediately. Others were frozen at −70°C until measurement. All samples for enzymatic analysis, except those for glucose, were assayed after preparation of 1:10 dilution of a protein-free filtrate using Cen-

triflo membrane cones (CF-50, Amicon Corp. Scientific Sys. Div., Danvers, MA). All analyses of each sample were performed in triplicate and each replicate set was analyzed in the same assay. Replicate assays were rejected and repeated if determinations varied more than 5% from the mean. Mean values for these determinations were reported.

Enzymes for substrate analyses were obtained from Boehringer-Mannheim Biochemicals, NY (glycerokinase, glycerophosphate dehydrogenase) and Sigma Chemical Co., St. Louis, MO (lactate dehydrogenase, D-β-hydroxybutyrate, glutamic-pyruvic transaminase). Reagents used to construct standard curves were purchased from Sigma (lactic acid, DL-β-hydroxybutyrate, α-ketoglutarate, alanine, pyruvate) and Sargent-Welch, Chicago, IL (glycerol). NADH and NAD were purchased from Sigma.

Table 1. *Experimental protocol**

		MA	FA	UV
−75 min	Start of surgical procedure			
−60 min	Start of antipyrine infusion into fetal femoral vein			
0 min	Start of sampling protocol			
	Blood gas #1, antipyrine #1	×	×	×
20 min	Substrates #1, antipyrine #2	×	×	×
30 min	Substrates #2	×	×	×
40 min	Substrates #3, antipyrine #3	×	×	×
50 min	Substrates #4	×	×	×
60 min	Antipyrine #4	×	×	×
70 min	Blood gas #2	×	×	×
80 min	Maternal infusion of 600 mg/kg NaBOHB over 10 min, then 300 mg/kg/h			
90 min	Blood gas #3, antipyrine #5	×	×	×
110 min	Substrates #5, antipyrine #6	×	×	×
120 min	Substrates #6	×	×	×
130 min	Substrates #7, antipyrine #7	×	×	×
140 min	Substrates #8	×	×	×
150 min	Substrates #8	×	×	×
160 min	Blood gas #4	×	×	×
	End experiment and deliver fetus			

* Abbreviations: MA, maternal femoral artery; FA, fetal femoral artery; UV, umbilical vein.

Fluorometric analyses were performed on an Aminco-Bowman SPF-125 spectrophotofluorometer.

Antipyrine was measured colorimetrically using an Auto-Analyzer (Technicon Instruments Corp., Tarrytown, NY). Blood gases (pH, P_{CO_2}, and P_{O_2}) were determined at 37°C using Radiometer (Radiometer America Inc., Westlake, OH) electrodes and meter, PHM71, and oxygen content measured with a Lex-O_2-Con (Lexington Instruments Corp., Waltham, MA).

Data obtained before and during NaBOHB infusion are presented as mean ± SEM and were compared by ANOVA (15).

RESULTS

Before NaBOHB infusion, fetal concentration of alanine, lactate, and pyruvate were higher than maternal levels ($p < 0.05$) (Table 2). Fetal glucose concentrations were the same as maternal and fetal ketone levels and were significantly lower than maternal values ($p < 0.05$).

Maternal infusion of NaBOHB resulted in an increase in maternal arterial levels from 0.70 ± 0.21 to 5.42 ± 0.95 mM ($p < 0.001$) and in fetal arterial levels from 0.34 ± 0.09 to 2.76 ± 0.64 mM ($p < 0.01$). During NaBOHB infusion, maternal and fetal lactate and pyruvate increased significantly ($p < 0.05$); glucose, alanine, and glycerol did not change. Maternal and fetal levels of ketones (BOHB and acetoacetate) increased during infusion so that the preinfusion maternal-fetal gradient was maintained. In addition, both fetal and maternal lactate and pyruvate increased, so that the fetal:maternal relationship remained the same.

Maternal acid-base status (Table 3) was maintained within normal limits before and did not change during NaBOHB infusion. The elevated maternal and fetal P_{O_2} values were due to the oxygen enriched inhalation mixture. Fetal acid base values were consistent with the mild mixed metabolic and respiratory acidosis seen during acute experimental protocols. Fetal acid-base status did not change, but umbilical vein P_{O_2} and O_2 content showed a trend towards lower values ($p > 0.05 < 0.1$) during NaBOHB infusion.

Umbilical blood flow 148 ± 17.8 mL/kg·min was within the normal range for the late gestation baboon fetus and did not

Table 2. *Maternal and fetal blood levels of ketones, glucose, alanine, lactate, pyruvate and glycerol before and during infusion of NaBOHB**

	Maternal artery		Fetal umbilical vein		Fetal femoral artery	
	Before ($n = 8$)	During ($n = 7$)	Before ($n = 8$)	During ($n = 7$)	Before ($n = 8$)	During ($n = 7$)
BOHB	0.70 ± 0.21	5.42† ± 0.93	0.38 ± 0.10	3.08‡ ± 0.73	0.34 ± 0.09	2.76‡ ± 0.64
Acetoacetate	0.34 ± 0.06	1.62† ± 0.33	0.15 ± 0.03	0.80† ± 0.11	0.12 ± 0.03	0.69† ± 0.09
Ketones	1.04 ± 0.26	7.06† ± 1.11	0.53 ± 0.13	3.87‡ ± 0.73	0.66 ± 0.12	3.65‡ ± 0.65
Glucose	3.25 ± 0.33	3.08 ± 0.48	3.41 ± 0.47	3.43 ± 0.74	3.56 ± 0.52	3.55 ± 0.82
Alanine	0.17 ± 0.04	0.16 ± 0.03			0.31 ± 0.05	0.33 ± 0.05
Lactate	0.70 ± 0.11	0.94§ ± 0.12			1.90 ± 0.34	2.88§ ± 0.54
Pyruvate	0.07 ± 0.01	0.10§ ± 0.01			0.19 ± 0.03	0.31§ ± 0.06
Glycerol	0.14 ± 0.04	0.13 ± 0.04			0.10 ± 0.03	0.13 ± 0.03

* All values in mM expressed as mean ± SEM.
† In before-during comparisons: $p < 0.001$.
‡ In before-during comparisons: $p < 0.01$.
§ In before-during comparisons: $p < 0.05$.

Table 3. *Maternal and fetal pH and blood gas values before and during infusion of NaBOHB**

	Maternal artery			Fetal umbilical vein			
	pH	P_{O_2} mm Hg	P_{CO_2} mm Hg	pH	P_{O_2} mm Hg	P_{CO_2} mm Hg	O_2 content mM
Before ($n = 8$)	7.39 ± 0.01	303.2 ± 13.8	35.3 ± 1.6	7.27 ± 0.02	54.8 ± 8.9	44.2 ± 7.8	4.75 ± 0.47
During ($n = 7$)	7.41 ± 0.02	302.1 ± 29.9	36.9 ± 1.3	7.27 ± 0.03	45.0+ ± 3.8	47.8 ± 2.9	4.31 ± 0.43

* All values expressed as mean ± SEM. In before-during comparison: $p > 0.05 < 0.1$.

change significantly during NaBOHB infusion (Table 4). Fetal arteriovenous substrate concentration differences were multiplied by umbilical blood flow to calculate oxygen, glucose, and ketone turnover by the fetus (Table 5). During the maternal NaBOHB infusion, fetal ketone uptake increased 6-fold from 9.12 ± 1.84 to 61.6 ± 11.1 μmol/kg·min without change in oxygen consumption or net glucose transfer. Oxygen delivery to the fetus (umbilical vein flow × umbilical vein oxygen content) did not change significantly. It was 0.71 ± 0.12 before and 0.61 ± 0.14 mM/kg·min during NaBOHB infusion.

DISCUSSION

As shown in Figure 1, the baboon fetus maintains a BOHB level of 0.38 ± 0.10 mM, about one-half that of the mother, 0.70 ± 0.21 mM. When maternal levels are elevated to 5.42 ± 0.93 mM, this ratio is rapidly resumed with fetal levels of 3.08 ± 0.73 mM. In contrast, Morriss *et al.* (5) demonstrated maternal BOHB levels 7–10 times those found in the fetus in both fed and fasting states in chronically catheterized sheep (Table 6). Also in the sheep (16), during acute induced ketonemia after 2 h of BOHB infusion, the maternal-fetal gradient was nearly 20 times that seen in the primate. The peak maternal level reported was 6.93 ± 1.32 mM, and the peak fetal level was 0.15 ± 0.03 mM. The maternal-fetal gradient in these experiments by Miodovnik *et al.* (16) appears to be increased over that reported by Morriss *et al.* (5), perhaps because of failure to reach a maternal steady state concentration during the experiment. In that study, as in ours, ketonemia was induced by infusion of a potential alkalinizing agent, NaBOHB. In human neonates, Paterson *et al.* (4) reported cord blood ketone levels of 0.47 ± 0.11 mM at the time of normal delivery; paired maternal levels were 0.93 ± 0.19 mM. There was a similar maternal-fetal ratio when maternal levels were elevated. At midgestation, results were similar (17): maternal levels were 0.49 ± 0.06 mM and fetal levels were 0.25 ± 0.03 mM.

The data presented here were obtained during acute experiments. The high level of maternal oxygenation (303 ± 14 mm Hg) was used to obtain experimental conditions comparable to those previously reported in the baboon preparation (7, 8). The acid-base data indicate a mild maternal metabolic acidosis and a mixed acidosis in the fetus. Before BOHB infusion in this acute experimental protocol, the baboon fetus showed evidence of stress, with fetal arterial glucose elevated above maternal arterial levels; this difference was not significant. During the experiment, the lack of change of maternal or fetal glucose levels indicated

Table 4. *Gestational age, maternal and fetal wt, and fetal umbilical blood flow**

	Maternal wt (kg)	Gestational age (d)	Fetal wt (g)	Umbilical blood flow mL/min	Umbilical blood flow mL/kg·min
Before	15.5 ± 0.3	167.6 ± 0.7	822.5 ± 37.6	111.1 ± 11.9	147.5 ± 17.8
During				112.1 ± 20.4	131.4 ± 20.4

* All values expressed as mean ± SEM.

Table 5. *Net fetal exchange of oxygen, glucose and ketones before and during infusion of NaBOHB**

	Fetal oxygen uptake		Net glucose loss by fetus		Ketone uptake	
	mM	mL/kg·min	mM	μmol/kg·min	mM	μmol/kg·min
Before (n = 8)	2.00 ± 0.28	5.90 ± 0.82	0.10 ± 0.06	14.40 ± 9.30	0.06 ± 0.00	9.12 ± 1.84
During (n = 7)	1.73 ± 0.15	5.10 ± 0.83	0.12 ± 0.08	17.31 ± 9.96	0.42† ± 0.07	61.59‡ ± 11.12

* All values expressed as mean ± SEM.
† In before-during comparisons: $p < 0.001$.
‡ In before-during comparisons: $p < 0.01$.

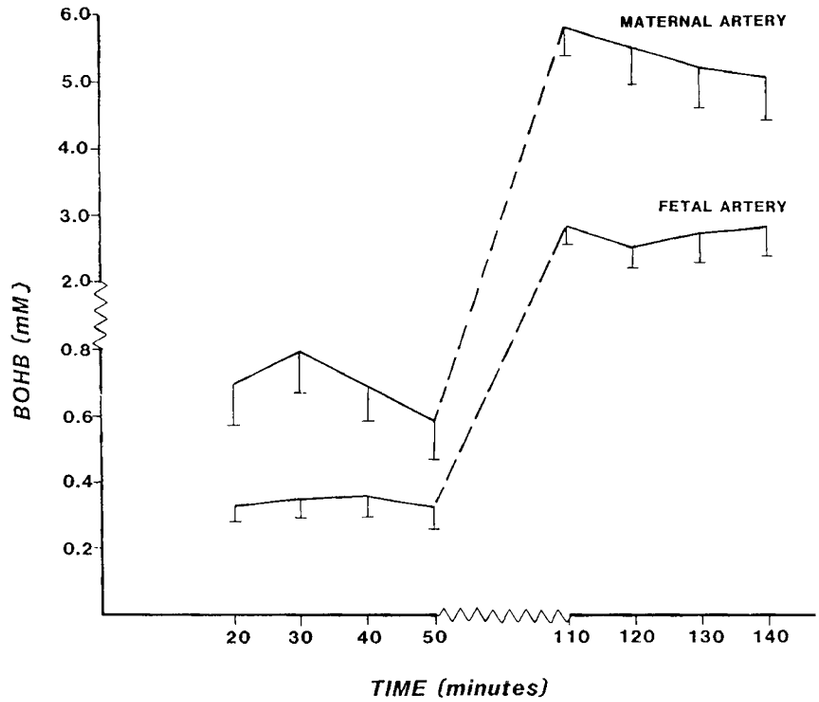

Fig. 1. Fetal and maternal levels of BOHB before and during maternal infusion of NaBOHB (mean ± SEM).

Table 6. *Species differences in maternal:fetal ratios of ketones in this study and from literature review**

	BOHB (mM)		Ketones (mM)		Ratio
	Maternal	Fetal	Maternal	Fetal	(maternal/fetal)
Present study (baboon)	0.70 ± 0.21	0.38 ± 0.10			1.84
			1.04 ± 0.26	0.53 ± 0.13	1.96
	5.42 ± 0.93	3.08 ± 0.73			1.76
			7.06 ± 1.11	3.87 ± 0.73	1.82
Paterson *et al.* (4) (human)			0.93 ± 0.19	0.47 ± 0.11	1.98
			1.81	0.78	2.32
Aynsley-Green *et al.* (17) (human)			0.49 ± 0.06	0.25 ± 0.03	1.96
Morriss *et al.* (5) (sheep)	0.602 ± 0.072	0.082 ± 0.003			7.43
	1.208 ± 0.123	0.118 ± 0.008			10.23
Miodovnik *et al.* (16, 22, 25) (sheep)	0.76 ± 0.20	0.01 ± 0.01			7.80
	0.49 ± 0.14	0.12 ± 0.08			4.08
	5.93 ± 1.32	0.15 ± 0.03			39.53

* All values expressed as mean ± SEM.

an absence of BOHB-induced stress hyperglycemia. The rise in lactate and fall in Po_2 are similar to results induced by infusion of hypertonic glucose into the fetal lamb (17–20). These changes, although similar to those induced by asphyxia, are not asphyxia-induced in these experiments, as indicated by umbilical blood flow and fetal oxygen consumption data (6).

As an explanation for the low umbilical vein fetal Po_2, Clark *et al.* (21) demonstrated increased oxygen extraction by the sheep placenta. This is compatible with our data in that fetal oxygen extraction was maintained in the presence of somewhat decreased umbilical vein Po_2 ($p < 0.1 > 0.05$). The umbilical blood flows were variable in this acute preparation and we could not definitively measure significantly decreased fetal oxygen delivery, although seven of eight animals had decreased umbilical vein oxygen content, six of eight had decreased umbilical vein blood flow, and six of eight had decreased computed oxygen delivery during NaBOHB infusion. The absence of change in fetal and maternal pH usually associated with increased levels of lactate is probably related to the fact that BOHB was infused as the sodium salt. In a chronic fetal sheep preparation in which β-hydroxybutyrate was infused to the mother, mild maternal alkalosis was a consequence (22). Therefore, we believe that this technique permits the evaluation of the effects of ketones without the additional effects of acidosis.

Changes in endogenous substrate levels noted in these fetuses are associated with the decreased fetal Po_2 after ketone infusion. The above normal fetal Pao_2 before infusion allows examination of relative changes in fetal Pao_2 and oxygen delivery without the superimposition of the effects of reduced oxygenation—anaerobic metabolism and metabolic and physiologic decompensation. The increases in lactate and pyruvate in the fetus may be related to placental metabolism of BOHB (23). The small, but significant changes in maternal lactate and pyruvate could relate to continuing anesthetic and surgical stress as well. Of interest is the fact that glycerol levels did not rise, indicating that stress induced lipolysis was minimal. Inhibition of lipolysis by ketones may be an explanation for the lack of change in glycerol levels during anesthetic and infusion stress (24). Previous investigators, working with other animal models, have demonstrated that the placenta is the most active site of ketone body oxidation (23). It is likely, therefore, that the placental utilization of ketones is responsible for the decreased Po_2 of fetal blood during ketone body infusion (25). The fetus itself does not increase oxygen utilization during the uptake of large quantities of β-hydroxybutyrate. It must be assumed, therefore, that ketones are taken up by the fetal primate to be used for fat synthesis, a major nonoxidative pathway of ketone body utilization (24). The utilization of ketones for lipogenesis has been documented in the fetal rat. Also, the necessary enzymatic pathways for lipogenesis from ketones are present in human fetal tissue.

In conclusion, the placenta appears more permeable to BOHB in the baboon and in humans than in the sheep. No significant contribution of BOHB to fetal oxidative metabolism could be identified; BOHB may, however, contribute to fetal lipid energy stores (23). Why placental transport of BOHB is so different as well as the role of higher levels of BOHB in the primate fetus compared to the sheep remains to be elucidated. Studies using chronically maintained ketoacidosis and the use of isotope-labeled ketone substrates may contribute to our understanding of maternal-fetal ketone dynamics.

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