Digestion and Absorption of Carbohydrates by the Fetal Lamb *In Utero*

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Summary

Intestinal digestive function was studied in 12 chronically catheterized third trimester fetal lambs by instilling glucose, fructose, lactose, maltose, and sucrose into their duodenum. Glucose was absorbed rapidly with the peak circulating glucose concentration reached within 1 hr. Fructose was absorbed well, but in contrast to glucose, blood fructose concentration did not peak; it continued to climb for 4 hr. Intraduodenal lactose administration resulted in a rapid rise in blood glucose with the maximum value reached in 1 hr. After receiving either glucose or lactose fetuses older than 130 days showed a faster rise in blood glucose, a greater total increase in glucose and a more rapid return to control levels than the younger fetuses. No change in blood glucose occurred with either maltose or sucrose administration. An increase in lactate concentration and a rise in fetal $[H^+]$ were noted after glucose and lactose administration, the only studies in which an increase in blood glucose concentration occurred.

Speculation

The demonstration that the fetal lamb *in vivo* is able to digest and absorb glucose, fructose, and lactose, but not maltose or sucrose, provides functional validation of prior *in vitro* studies. Similar *in vitro* studies lead to the prediction that the human fetus is able to absorb glucose and digest all three disaccharides (18). *In vitro* studies, however, cannot predict whether the human fetus will also develop an increase in $[H^+]$ and lactate with carbohydrate feeding.

Fetal swallowing of amniotic fluid occurs *in utero* (13). It may, therefore, be possible to inject nutrients into amniotic fluid and have the fetus absorb them through its digestive tract. Fetal carbohydrate absorption has been studied in the past using *in vitro* methods and acute animal preparations (11, 14, 24). Using chronically catheterized fetal lambs, fetal intestinal glucose and fructose absorption, lactase, maltase, and sucrase activity and fetal acid base status after gastrointestinal administering carbohydrates, were evaluated. It was found that lamb fetuses in the last third of gestation readily absorb intraduodenally administered glucose and fructose. They have considerable intestinal lactase activity, but no functional maltase or sucrase activity. The increase in fetal blood glucose concentration that occurs after glucose and lactose feeding is accompanied by a drop in pH and a rise in circulating lactate. No decrease in pH accompanies the increase in fructose concentration that occurs after fructose feeding.

MATERIALS AND METHODS

ANIMAL PREPARATION

The authors used 12 third trimester pregnant ewes of known gestational age. All animals were fasted for 48 hr before surgical

preparation. Surgery was performed under low spinal anesthesia with 1% tetracaine hydrochloride. Polyvinyl catheters (French No. 8) were placed in the maternal femoral artery and vein. Sodium pentobarbital, 60 mg/ml, was given through the maternal vein for sedation as needed during the operation. A midline abdominal incision was made and the uterus opened. Polyvinyl catheters (0.030 inch I.D. and 0.048 inch O.D.) were placed in the fetal femoral artery and vein. A left abdominal incision was made in the fetus and the rumen exposed. A feeding tube (French No. 8) was inserted into the rumen through a stab wound and threaded 2-3 cm past the pylorus into the duodenum. After closure of the fetal abdomen an open ended polyvinyl catheter (French No. 8) was placed in the amniotic fluid and the maternal uterus closed. All catheters were brought out through a stab wound in the maternal flank and protected by a waterproof cloth patch. Immediately after surgery, one million units of penicillin and 400 mg of kanamycin were injected into the amniotic fluid and maternal vein. Kanamycin, 200 mg, was instilled into the amniotic cavity for 2-4 days after surgery. All catheters were flushed with heparin 1000 μ /ml daily. After surgery, the ewes were allowed to feed on alfalfa, alfalfa pellets, and water *ad libitum*.

EXPERIMENTAL DESIGN

Each day after surgery the ewes were brought into the laboratory from their stalls in mobile cages. During this time they had access to food and water. All animals were allowed to recover at least 24 hr after surgery before any studies were done (range 1-25 days, mean 8 days). All studies were done on separate days and more than 2 days before delivery or intrauterine demise. Seven of the lambs were born healthy at term. At delivery or autopsy, all fetal wounds were completely healed and difficult to locate.

Gastric contents move slowly through the compartments of the fetal ruminant stomach. After fructose is instilled into the esophagus of the fetal lamb, there is no rise in circulating fructose concentration for at least 3 hr (14). In order to evaluate the ability of the fetal intestine to digest and absorb carbohydrates, without obscuring absorption by slow gastric emptying, sugar solutions were administered directly into the duodenum.

Forty-two studies were performed by injecting 2 gm/kg boluses of either glucose, fructose, lactose, maltose, or sucrose into the fetal duodenum and measuring the change in fetal levels of glucose, fructose, pH, PaO_2 , $PaCO_2$, and lactate. The sugars were administered as 20% solutions in distilled water, except for glucose which was given as a 50% solution. The pH of the solutions at 25°C were: glucose, 4.0; fructose, 7.1; lactose, 6.5; maltose, 3.9; and sucrose, 7.1. The quantity of carbohydrate to be administered was calculated using an estimated fetal weight for gestation. This was taken from an ovine fetal growth chart (20). The volume of carbohydrate given ranged from 6-12 ml for glucose and from 20-45 ml for the other sugars.

During studies of glucose, lactose, sucrose, and maltose absorption, 1.0 ml aliquots of blood were withdrawn from the fetal femoral artery into heparinized syringes and analyzed for glucose

concentration. Samples were drawn before carbohydrate administration and at 15, 30, 60, 90, and 120 min after. An additional 1.0 ml of femoral arterial blood was drawn and pH, PaO_2 , and PaCO_2 measured before the sugar bolus and at 60 and 120 min after. Maternal femoral arterial blood was analyzed for glucose concentration before fetal sugar administration and at 30, 60, and 120 min.

Studies of fructose absorption were carried out as for the other sugars except that 1.50 ml of fetal blood was drawn and analyzed for both fructose and glucose concentration in the fetus and mother. Four of the fructose studies were carried out for 4 hr with additional measurements of fetal and maternal monosaccharides and fetal blood gases made at 180 and 240 min after fructose administration.

In 22 studies, measurements of fetal arterial lactate concentration were made before administration of carbohydrate and hourly thereafter during the study.

ANALYTICAL METHODS

Blood samples were deproteinized immediately and analyzed in duplicate for whole blood concentrations of glucose, fructose, and lactate. Glucose was measured by a glucose oxidase method (23). Our mean percent of error between duplicate glucose samples was 3.2%. Fructose was measured enzymatically using hexokinase (1), with a mean percent of error of 2.7% between duplicate samples. Lactate was measured using lactic dehydrogenase (19), with a mean percent of error of 5.2% between duplicate samples.

Measurements of pH, PaO_2 , and PaCO_2 were made using a Copenhagen Radiometer (3) that is calibrated in our laboratory several times a day.

Statistical analyses of our data were performed using the paired and unpaired *t* test and the correlation coefficient, where appropriate. Multiple *t* tests between study and control values were performed on our carbohydrate tolerance test data (Fig. 1-5). In analyzing these results, the *P* value which was accepted as significant was decreased to 0.01 to reduce our chance of committing a Type I error.

GLUCOSE

Twelve studies of glucose administration were performed using 9 fetuses of 121-141 (mean 131) days of gestation and 1-9 (mean 3) days postsurgery. The changes observed in fetal femoral arterial glucose concentration after intraduodenal glucose are graphed in Figure 1. In all studies, the fetal glucose concentration peaked by 60 min. The six studies done on the oldest fetuses (132-141 days of gestation) were compared to the six studies done on younger fetuses (121-129 days of gestation). The older animals had: a greater increase in glucose concentration over the first 15 min, 17.2 ± 2.1 vs. 9.3 ± 1.0 SEM mg% ($P < 0.01$); a greater peak increase in glucose concentration; 22.7 ± 3.3 vs. 13.1 ± 1.2 SEM mg% ($P < 0.025$); and a larger decline in glucose concentration back towards baseline levels by 120 min ($P < 0.05$). There was no difference in the number of days the fetuses in the two groups had recovered from surgery, before study.

The femoral arterial blood gases obtained from our fetuses just before glucose administration showed a mean hydrogen ion concentration, $[\text{H}^+]$, of 40.9 ± 1.4 SEM nmole/liter (pH equal to 7.39 ± 0.01 SEM), a mean PaO_2 of 20 ± 1 SEM torr and a mean PaCO_2 of 44 ± 1 SEM torr. There were no changes in PaO_2 or PaCO_2 after glucose, but there was a significant increase in $[\text{H}^+]$ to 43.7 ± 1.5 SEM nmole/liter (pH of 7.36 ± 0.01) by 120 min ($P < 0.025$). There was no difference between older and younger fetuses with respect to starting blood gases and changes in $[\text{H}^+]$, PaO_2 , and PaCO_2 .

Fetal arterial lactate concentration was measured in six of the glucose studies. The mean starting lactate concentration was 11.2 ± 1.8 SEM mg% that rose to 13.9 ± 2.0 SEM mg% at 60 min, ($P < 0.025$), and remained elevated at 13.6 ± 2.2 SEM mg% at 120 min.

The mean maternal arterial glucose was 43.1 ± 2.3 SEM mg% at the start of these studies and did not change.

FRUCTOSE

Seven studies of fructose administration were performed using four fetuses of 125-141 (mean 133) days of gestation and 2-20 (mean 10) days postsurgery. There was much variability in baseline fructose concentration between animals. The changes in fructose that occurred after intraduodenal fructose are graphed in Figure 2. There was a large, rapid increase in fructose concentration that was observed in all of the animals. The rate of rise slowed after an hr, but fructose levels continued to climb gradually throughout the study period, even in the four experiments carried out for 4 hr. No differences in the fructose curve were found when studies done on older and younger fetuses were compared. The mean increase in fructose concentration by 1 hr was 45.1 ± 6.2 SEM mg% ($P < 0.001$).

The fetal femoral arterial blood gases done immediately before fructose administration had a mean $[\text{H}^+]$ of 46.3 ± 1.3 SEM nmole/liter (pH of 7.33 ± 0.01 SEM), a PaO_2 of 22 ± 1 SEM torr and a PaCO_2 of 42 ± 2 SEM torr. No change in $[\text{H}^+]$, PaO_2 , or PaCO_2 occurred during these studies.

The mean fetal glucose concentration at the start of the fructose studies was 16.8 ± 0.8 SEM mg% that had dropped slightly to 15.5 ± 0.6 SEM mg% ($P < 0.1$) by 120 min and stayed down. The mean maternal glucose was 48.6 ± 2.6 SEM mg% before sugar administration and did not change. In all cases, maternal fructose was < 1 mg% and below the sensitivity of our assay.

Fetal lactate concentration was measured in six fructose studies. The mean arterial lactate concentration at the start was 11.0 ± 2.2 SEM mg% and did not change even over the 240 min observation period.

LACTOSE

Eleven studies of intraduodenal lactose administration were performed using five fetuses of 122-143 (mean 133) days of gestation and 1-23 (mean 8) days postsurgery. The changes observed in fetal glucose concentration after lactose are graphed in

Fig. 1. Glucose studies. Fetal femoral arterial glucose concentration (mean $\pm$ SEM) after intraduodenal glucose administration is graphed vs. time. Studies done in younger and older fetuses are shown separately. All values after glucose was given are significantly higher than the control values with $P < 0.005$, unless indicated (* denotes $P < 0.01$; ** denotes not significant).

Fig. 2. Fructose studies. Fetal femoral arterial fructose concentration (mean $\pm$ SEM) after intraduodenal fructose administration is graphed vs. time. All values after fructose was given are significantly higher than the control value with $P < 0.001$ unless indicated. (* denotes not significant).

Figure 3. The six studies done on the older fetuses (130–143 days of gestation) were compared with the five studies done on younger fetuses (122–129 days of gestation). The older animals had: a greater increase in glucose concentration over the first 15 min, 14.0 ± 1.4 SEM mg% vs. 7.4 ± 0.9 SEM mg% ($P < 0.005$); a greater peak increase in glucose concentration, 18.8 ± 1.7 SEM mg% vs. 11.9 ± 1.8 SEM mg% ($P < 0.025$); and a larger decline in glucose concentration back towards baseline by 120 min ($P < 0.05$). There was no difference in the number of days the fetuses in the two groups had recovered from surgery, before study.

The femoral arterial blood gases before lactose administration showed a mean $[H^+]$ of 45.6 ± 1.1 SEM nmole/liter (pH of 7.34 ± 0.01 SEM), a mean PaO_2 of 21 ± 1 SEM torr, and a mean $PaCO_2$ of 43 ± 1 SEM torr. There were no changes in PaO_2 or $PaCO_2$ after lactose, but there was a significant increase in $[H^+]$ to 48.5 ± 1.3 SEM, nmole/liter (pH of 7.31 ± 0.01 SEM) by 120 min ($P < 0.05$). There was no difference between the older and younger fetuses with respect to starting $[H^+]$ and PaO_2 and changes in $[H^+]$, PaO_2 , and $PaCO_2$. The older animals had a higher starting $PaCO_2$, 44 vs. 39 ($P < 0.01$).

Fetal arterial lactate concentration was measured in five lactose studies. The mean lactate concentration increased from 10.2 ± 2.1 SEM mg% at the start to 15.5 ± 3.1 SEM mg% at 60 min ($P < 0.025$) and stayed elevated at 13.1 ± 5.6 SEM mg% at 120 min.

The mean maternal arterial glucose concentration was 47.2 ± 1.6 SEM mg% at the start of the lactose studies and did not change significantly.

MALTOSE

Five studies of maltose administration were performed on four fetuses of 127–147 (mean 135) days of gestation and 2–25 (mean 11) days postsurgery. Fetal glucose concentration did not change after intraduodenal maltose as can be seen in Figure 4. There were no differences between older and younger fetuses. The mean peak increase in glucose concentration was 1.8 ± 1.3 SEM mg%.

The femoral arterial blood gases at the start of the five studies showed a $[H^+]$ of 47.8 ± 2.1 SEM nmole/liter (pH 7.32 ± 0.02 SEM), a PaO_2 of 20 ± 2 SEM torr and a $PaCO_2$ of 43 ± 2 SEM torr. There were no changes in PaO_2 or $PaCO_2$ during these

studies, but there was a fall in $[H^+]$ to 45.9 ± 2.2 SEM nmole/liter (pH rise to 7.34 ± 0.02 SEM) by 120 min ($P < 0.05$).

Fetal arterial lactate was measured in three maltose studies and is discussed with the sucrose data below.

Maternal glucose concentration had a mean value of 43.2 ± 2.5 SEM mg% before giving the fetus maltose and did not change during the studies.

SUCROSE

Seven studies of sucrose administration were performed on five fetuses of 128–145 (mean 138) days of gestation and 2–25 (mean

Fig. 3. Lactose studies. Fetal femoral arterial glucose concentration (mean $\pm$ SEM) after intraduodenal lactose administration is graphed vs. time. Studies done in younger and older fetuses are shown separately. All glucose values after lactose was given are significantly higher than the control values with $P < 0.005$, unless indicated. (* denotes $P < 0.01$; ** denotes not significant).

Fig. 4. Maltose studies. Fetal femoral arterial glucose concentration (mean $\pm$ SEM) after intraduodenal maltose administration is graphed vs. time. Glucose values after maltose was given are not significantly different from the control value.

9) days postsurgery. Fetal glucose concentration did not increase after intraduodenal sucrose as can be seen in Figure 5. The mean peak change in glucose concentration was -0.1 ± 0.5 SEM mg%. There were no differences between older and younger fetuses.

The fetal femoral arterial blood gases at the start of these studies showed a $[H^+]$ of 45.0 ± 1.6 SEM nmole/liter (pH of 7.35 ± 0.01 SEM), a PaO_2 of 21 ± 1 SEM torr and a $PaCO_2$ of 45 ± 2 SEM torr. There were no changes in blood gases after sucrose administration.

The mean starting maternal glucose concentration was 46.7 ± 2.7 SEM mg% and did not change during the sucrose studies.

Fetal lactate concentration was measured in two sucrose and three maltose studies. The mean baseline arterial lactate was 16.4 ± 3.3 SEM mg% and remained the same after the disaccharides were administered.

REPEAT CARBOHYDRATE CHALLENGES

Repeat challenges of a fetus with the same sugar, 4 or more days after the initial dose, were performed 13 times. Three such studies were done with glucose, four with lactose, two with fructose, two with maltose, and two with sucrose. Glucose and lactose showed no increase in carbohydrate absorption beyond that seen with advancing gestation in other fetuses, of the same age, tested for the first time. Fructose, maltose, and sucrose showed no increase in absorption.

Four animals had multiple testing with different sugars. None of them showed improved absorption of subsequent sugars.

None of the fetuses had impaired absorption of the same or different sugars on repeat testing.

POOLED DATA

There were no significant differences in $[H^+]$, PaO_2 , or $PaCO_2$ between the groups of fetuses used in the study of the five sugars. There were no differences in fetal gestational age or postoperative days between the groups except that the animals given glucose were younger than those receiving sucrose (131 vs. 138 days of gestation, $P < 0.05$), and closer to surgery than those receiving maltose (3 vs. 11 postoperative days, $P < 0.05$). There were no significant differences in baseline fetal lactate concentration or maternal glucose concentration between groups.

When data from all the studies were pooled, a strong correlation was found between the change in arterial glucose concentration

and the change in lactate concentration (Figure 6). No correlations were found between fetal gestational age or postoperative day and development of acidosis.

DISCUSSION

Duodenal feedings of glucose are rapidly absorbed by the third trimester fetal lamb. Peak circulating glucose concentrations are reached within an hr and decline toward starting levels by 2 hr. Chez *et al.* (2) found a similar pattern of absorption in third trimester fetal monkeys after intragastric glucose administration. Their fetuses' glucose levels rose 18–34 mg% and peaked within 45 min. They were interested in insulin responses and did not continue their studies past an hr nor did they evaluate changes with gestation. As gestation progresses in fetal lambs, the increase in glucose concentration achieved with a 2 gm/kg dose of the sugar becomes greater. The rise in glucose also becomes more rapid and the subsequent fall towards baseline becomes faster. The smaller, slower rise in glucose seen in the younger fetuses might be explained by either increased utilization of glucose or decreased intestinal absorption. Because younger fetuses have the same umbilical uptake of glucose (4, 9) and a smaller, delayed insulin response to hyperglycemia than older fetuses (7), increased utilization of glucose is unlikely. The blunted insulin response to glucose is probably reflected in the younger animals' slow return of glucose to baseline levels. The mechanism of the decreased absorption of glucose seen in the younger fetuses cannot be determined from our experiments. The activity of the glucose carrier may be decreased or total surface area for absorption may be decreased, as has been described in acquired monosaccharide intolerance of infancy (10).

Fructose is absorbed well after instillation into the fetal lamb's gastrointestinal tract. The majority of the increase in blood fruc-

Fig. 5. Sucrose studies. Fetal femoral arterial glucose concentration (mean $\pm$ SEM) after intraduodenal sucrose administration is graphed vs. time. Glucose values after sucrose was given are not significantly different from the control value.

Fig. 6. Relationship between the change in fetal glucose concentration and the change in lactate concentration.

tose concentration occurs by 1 hr, but fructose concentration continues to climb gradually for at least 4 hr. Nixon and Wright (14) found a similar pattern of fructose absorption in acute fetal lamb preparations studied for 3 hr. The longer time course, as compared to glucose absorption, may reflect the slower facilitated diffusion of fructose in contrast to the rapid active transport of glucose (5). The high levels of fructose achieved with fetal gastrointestinal administration are exaggerated by the slow fetal metabolism of fructose (22). The decline in fetal glucose levels seen may be due to fructose induced insulin release (6).

Considerable functional lactase activity is present in the third trimester fetal lamb. After intraduodenal lactose, blood glucose rises rapidly, peaks within an hr and falls towards starting values by 2 hr. As with glucose administration, the older fetuses have a greater increase in glucose concentration, a more rapid rise in glucose and a faster decline from peak levels. Because the ability of the younger fetuses to absorb glucose is decreased, their small rise in glucose concentration after lactose feeding cannot be attributed to a deficiency in lactase activity. In fact, lactase activity *in vitro* appears to be present in other ungulates in appreciable concentrations throughout the last half of gestation (15) and is present in sheep in high amounts at birth (21). The greater increase in glucose concentration after lactose seen in older fetuses is probably due to improved glucose absorption rather than increasing lactase.

No functional sucrase and maltase activity is seen in the fetal lamb. There is no rise in blood glucose after sucrose and maltose feedings. This is in agreement with the observation that lambs after birth, still lack sucrase and only have very low levels of maltase (21). It is in contrast to the situation in the human fetal intestine where high levels of sucrase and maltase are present by the third trimester (18). Because the pH optimum for maltase is close to 6 (12), the low pH of the maltose solution may hinder the activity of small quantities of maltase. If significant amounts of fetal maltase are present, some rise in blood glucose would be expected.

Repeat intraduodenal administration of sugars does not improve or impair fetal digestive capability. There is, therefore, no evidence of inducibility of any of the enzymes by duodenal feeding and no evidence of intestinal injury from the solutions instilled.

After intraduodenal administration of glucose and lactose, the only two sugars which result in a rise in blood glucose, lactate concentration and $[H^+]$ increase. In all our studies, a very significant correlation is found between changes in glucose concentration and changes in lactate. The observation that a change in glucose concentration leads to a change in lactate is not new and is attributed to variations in pyruvate concentration with changes in glucose metabolism. Lactate accumulates when there is a lack of alternative pathways for pyruvate utilization (8, 17). Shelley *et al.* (17) have noted an increase of lactate in fetal lambs when their plasma glucose is raised above 40 mg% by iv glucose infusion. In addition to a rise in lactate, there is a rapid drop in pH when glucose is infused, if the fetuses have been made hypoxic by having their mothers' breath 9% O_2 . Hypoxia may decrease the fetus' capacity for oxidative metabolism and increase the accumulation of lactate. Robillard *et al.* (16) have found that glucose infusion into nonhypoxic fetal lambs results in a progressive fall in pH and rise in lactate concentration. These become significant only after the fetal blood glucose has been raised above 150 mg% (16). The latter experiments appear to have been conducted by increasing fetal glucose concentration in a stepwise fashion so that higher fetal glucose levels are achieved later in a study. After glucose or lactose feeding, our nonhypoxic fetuses increase their blood glucose to between 30 and 35%, yet lactate concentration rises and $[H^+]$ increases significantly after 2 hr. The duration of fetal exposure to elevated glucose, rather than the absolute glucose concentration, may be what is important in past studies. Duodenal feeding may also alter fetal oxygen consumption or umbilical oxygen uptake and accentuate the effects of hyperglycemia in our fetuses.

Alternate explanations for the increase in $[H^+]$ and lactate in our glucose and lactose fed fetuses, independent of the rise in blood glucose, were considered. The acid load given to the fetuses with the sugar solutions could not have caused the observed increase in $[H^+]$, because a decrease in $[H^+]$ was seen when maltose feedings, pH 3.9, were given. The volume of blood drawn from the fetuses could not have led to the change in $[H^+]$ because it was the same for other sugars. The fructose studies were even carried out longer, with additional blood sampling. All sugars were administered as hypertonic solutions and would have drawn large volumes of fluid into the intestine. If the osmolality of the administered solution was responsible for the increase in $[H^+]$ and lactate, the effect of lactose and the other 20% solutions should have been the same, while the effect of glucose should have been the most pronounced. The number of days that the fetuses had recovered from surgery before study was appreciably less for glucose feedings than feedings of the other sugars and could have made the glucose animals more vulnerable to acid-base changes. This was not true of the lactose studies, however. When the number of postoperative days, or the gestational ages of the fetuses from all our studies were compared against their change in $[H^+]$, no relationship was found.

The authors believe that the rise in blood glucose after intraduodenal glucose and lactose administration is most likely responsible for the increase in $[H^+]$ and lactate seen. The physiologic changes that occur in the fetus as a consequence of gastrointestinal absorption are, however, still unknown and could contribute to $[H^+]$ and lactate accumulation.

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