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Carbohydrate Metabolism during the Postprandial Intestinal Hyperemia (41501)

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Abstract. Intestinal carbohydrate uptake and utilization were studied before and during the perfusion of the canine jejunal lumen with food. Under conditions of normal oxygen consumption (1.8 ml O_2/min/100 g) and blood flow (46.4 ± 3.5 ml/min/100 g), intestinal glucose uptake was low (2 mg/min/100 g) and glucose utilization was aerobic. When food was present in the lumen, there was a 15% increase in intestinal metabolism, as measured by oxygen consumption, while lactic acid production increased threefold. This increase in lactic acid production was not due to a shift in glycolysis toward lactic acid synthesis as the venous lactic acid/pyruvic acid concentration ratio actually decreased. Intestinal glucose utilization was offset by carbohydrate absorption as glucose uptake from arterial blood decreased. The data suggest that a relatively greater proportion of intestinal energy demand is met by glycolysis during the absorption of nutrients than at rest and supports the findings of other investigators that a portion of absorbed glucose is metabolized. In addition, the study indicates that intestinal glucose metabolism does not terminate in lactic acid synthesis as suggested by a previous study.

Recent studies indicate that the postprandial intestinal hyperemia is limited to those portions of the small intestine which have been exposed to chyme (1, 2). It has also been shown that the constituents of chyme which are responsible for this hyperemia are the products of enzymatic food digestion (3). Of these, glucose has been shown to increase jejunal blood flow and oxygen consumption when placed in the lumen in solution (4, 5). A number of studies have indicated that a portion of the glucose which is absorbed by the small intestine is metabolized (6–9) and Sit *et al.* (4) have shown that this metabolism is responsible for a significant portion of the glucose-induced increase in jejunal blood flow and oxygen consumption.

In two studies of glucose absorption (8, 9), a small fraction of the absorbed glucose appeared as lactic acid in the venous blood; however, it is not known if this lactic acid represents the end product of intestinal glucose metabolism, as suggested by Lester and Grim (10), or simply the by-product of aerobic glycolysis. In addition, in previous studies of intestinal glucose absorption, glucose was the only nutrient present in the lumen and it is not certain to what extent absorbed glucose is utilized for intestinal energy production when other substrates are available. Therefore, in this study we examined the nature of carbohydrate utilization in the canine jejunum when either saline or a nutrient solution containing fat, carbohydrate, and protein were present in the lumen.

Materials and Methods. Adult mongrel dogs of either sex (15–25 kg; $N = 12$) were fasted for 24 hr, anesthetized with sodium pentobarbital (30 mg/kg, iv) and ventilated with a positive pressure Harvard respirator to ensure normal arterial pH (7.38–7.43). Following a midline abdominal incision, a loop of the jejunum about 30 cm distal to the ligament of Treitz was exteriorized and a segment drained by a single vein was selected. After administration of sodium heparin (6 mg/kg), the vein draining the segment was cannulated and the venous effluent was directed through an extracorporeal electromagnetic flow transducer

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(Biotronex BLC-2048-E04 connected to a Biotronex BL-610 flowmeter) to a venous reservoir containing 200 ml of a dextran solution (6% in normal saline). The volume of the reservoir was maintained at 200 ml by returning the contents to the femoral vein at a rate equal to the venous outflow.

A piece of rubber tubing was placed in each end of the jejunal segment and tied in place. Both ends of the segment were tied and cut and the mesentery was cut to exclude collateral flow. The segment was covered with a plastic sheet and kept at 37° with a heat lamp. The tubing in the proximal end of the segment was connected via a Masterflex pump (Cole Parmer, Chicago, Ill.) to a reservoir containing normal saline at 37°. Warm saline was perfused through the segment at a rate of 6 ml/min. The tubing in the distal end of the segment served as a drain for the segment.

The arterial–venous oxygen ($A-VO_2$) content difference across the segment was measured continuously by perfusing femoral arterial blood and a portion of the venous outflow from the segment through the cuvettes of an $A-VO_2$ content difference analyzer (AVOX Systems, San Antonio, Tex.). The analyzer was previously calibrated with a Lex-O_2 Con TL oxygen content analyzer (Lexington Instruments, Waltham, Mass.) and the output signal was recorded continuously on a Hewlett-Packard recorder (Waltham, Mass.). The signal from the flowmeter was also recorded continuously and the flow transducer was calibrated periodically during the course of the experiment by measuring the venous outflow with a graduated cylinder and stopwatch. Systemic arterial pressure was monitored continuously through a femoral artery cannula.

After surgery had been completed, saline was perfused through the lumen until blood flow and the $A-VO_2$ content difference had reached a steady state (approx. 30 min). At that time, duplicate blood samples were taken from the femoral artery and the venous outflow of the segment for the measurement of blood pH, pO_2, pCO_2, lactic acid, pyruvic acid, and glucose. The perfusate was then changed to a mixture of digested food and bile, at 37°, and, when a new steady state had been achieved, duplicate arterial and venous blood samples were taken as before. The animal was then killed with an overdose of anesthetic and the segment was excised, trimmed of all mesentery, and weighed. Blood flow, oxygen consumption, glucose uptake, and lactic acid and pyruvic acid production were expressed in units per 100 grams tissue weight.

Care was taken during the collection of the arterial and venous blood samples for the measurement of pH, pO_2, and pCO_2 to ensure that the samples were not contaminated with room air. Arterial and venous blood samples for the determination of arterial and venous glucose, lactic acid, and pyruvic acid concentrations were collected on ice in test tubes containing 10 mg of NaF. The NaF served to inhibit red blood cell glycolysis. The portion of blood to be used for the measurement of the pyruvic acid concentration was pipetted from each blood sample immediately after collection and vortexed with an 8% perchloric acid solution to precipitate the blood proteins. This served to block enzymatic degradation of the pyruvic acid.

The arterial and venous blood gases were measured with a BMS 3 MK II Blood MicroSystem and Acid–Base Analyzer (London Co., Cleveland, Ohio). The glucose concentration in each blood sample was measured in a YSI Glucose Analyzer (YSI, Yellow Springs, Ohio). The pyruvic acid and lactic acid concentrations were measured spectrophotometrically using a lactic acid dehydrogenase assay (Sigma Chemical Co., St. Louis, Mo.).

The oxygen consumption of the segment was determined by multiplying the appropriate values from the blood flow and $A-VO_2$ content difference recordings after correcting for the lag time between the recordings due to the distance between monitoring points. Glucose uptake was calculated as the product of the arterial–venous concentration difference and jejunal blood flow while lactic acid and pyruvic acid production were taken as the product of the venous–arterial concentration difference and blood flow.

The nutrient solution used in this study

TABLE 1. MEAN SYSTEMIC ARTERIAL PRESSURE (SAP) AND JEJUNAL BLOOD FLOW (BF), $A-VO_2$ CONTENT DIFFERENCE (ΔAVO_2), OXYGEN CONSUMPTION ($\dot{V}O_2$), AND VENOUS HEMATOCRIT (Hct) BEFORE AND DURING THE PERFUSION OF FOOD THROUGH THE LUMEN

	Lumen contents		
	Saline	Food	Food−saline
SAP (mm Hg)	117 ± 5	117 ± 5	0 ± 3
BF (ml/min/100 g)	46.4 ± 3.5	54.6 ± 4.2	8.2 ± 1.3*
ΔAVO_2 (ml O_2/100 ml)	4.1 ± 0.3	4.0 ± 0.3	−0.1 ± 0.1
$\dot{V}O_2$ (ml O_2/min/100 g)	1.78 ± 0.08	2.06 ± 0.10	0.28 ± 0.05*
Hct	41 ± 1	40 ± 2	−1 ± 2

Note. Values are means ± SEM; $N = 12$.
* $P < 0.05$.

contained equal parts by weight of fat, protein, and carbohydrate. Fifty grams of this food mixture was combined with 500 mg of a pancreatic enzyme preparation (Viokase, Viobin Co., Monticello, Ill.) and mixed at room temperature for 5 hr in 400 ml of 0.1 *N* $NaHCO_3$. Prior to each experiment, nine parts of the digested food solution were mixed with one part of bile from the dog's gallbladder. The osmolarity of the final solution was adjusted to 300 ± 20 mosmole/kg with NaCl or distilled water and the pH was adjusted to 7.0 ± 0.2 with HCl or NaOH.

The data are expressed as the mean ± SEM and comparisons between treatments were made using Student's *t* test modified for paired comparisons. Statistical significance was set at *P* values less than 0.05.

Results. As seen in Table I, mean systemic arterial pressure was 117 ± 5 mm Hg and it did not change during the course of the experiment. Also, as shown in Table I, jejunal blood flow was 46.4 ± 3.5 ml/min/100 g and the $A-VO_2$ content difference was 4.1 ± 0.3 ml O_2/100 ml when saline was in the lumen yielding an oxygen consumption of 1.78 ± 0.08 ml O_2/min/100 g. Glucose uptake was 1.96 ± 0.24 mg/min/100 g and jejunal lactic acid and pyruvic acid production were 0.26 ± 0.10 mg/min/100 g and 0.059 ± 0.012 mg/min/100 g, respectively (Fig. 1). The venous lactic acid/pyruvic acid concentration ratio (*L/P* ratio) was 26 ± 2 (Fig. 1). This indicates that when saline is present in the lumen, jejunal glucose metabolism is aerobic and does not terminate in lactic acid synthesis (11).

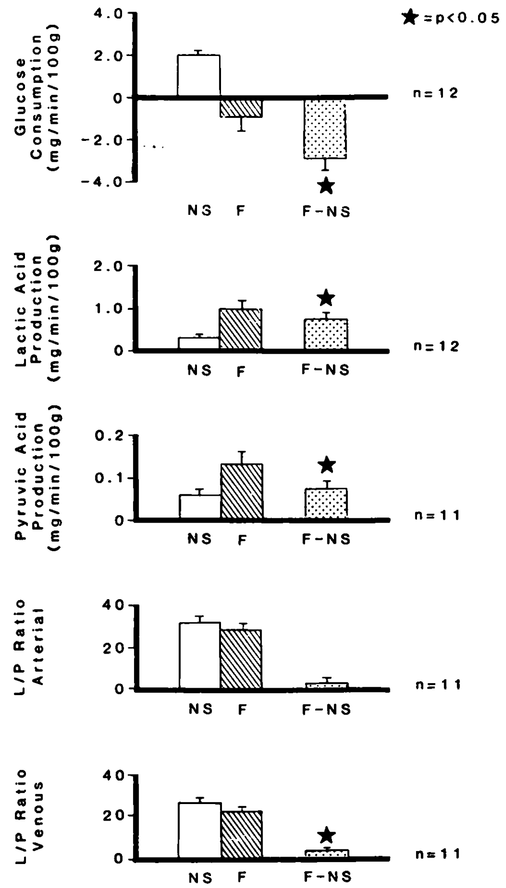

FIG. 1. Mean ± SEM of jejunal glucose consumption and lactic acid and pyruvic acid production and the arterial and jejunal venous lactic acid/pyruvic acid concentration ratios with either normal saline (NS) or food (F) in the lumen.

TABLE II. ARTERIAL AND VENOUS BLOOD pH, pO_2, AND pCO_2 BEFORE AND DURING PERFUSION OF THE JEJUNAL LUMEN WITH FOOD

	Arterial	Venous	A-V Difference
	Saline in the lumen		
pH	7.41 ± 0.01	7.40 ± 0.01	0.01 ± 0.004*
pO_2	86 ± 4	37 ± 1	49 ± 4*
pCO_2	33 ± 1	34 ± 1	−1 ± 1
	Food in the lumen		
pH	7.41 ± 0.01	7.38 ± 0.01	0.03 ± 0.04*,†
pO_2	85 ± 4	38 ± 2	47 ± 3*
pCO_2	34 ± 2	38 ± 2	−4 ± 1*,†

Note. Values are means ± SEM; $N = 12$.

* $P < 0.05$.

† $P < 0.05$ relative to the corresponding value with saline in the lumen.

The arterial pH was 7.41 ± 0.01, the pO_2 was 86 ± 4 mm Hg and the pCO_2 was 33 ± 1 mm Hg (Table II). The venous pH (7.40 ± 0.01) was only slightly less than arterial pH but the difference was statistically significant. In addition, the venous pO_2 (37 ± 1 mm Hg) was significantly less than arterial pO_2 but there was no significant arterial–venous pCO_2 difference. The venous hematocrit was 41 ± 1 (Table I).

When food was perfused through the lumen, there was a significant increase in jejunal blood flow and oxygen consumption (Table I). Jejunal blood flow increased 8.2 ± 1.3 ml/min/100 g (18 ± 3%) to 54.6 ± 4.2 ml/min/100 g. Oxygen consumption increased 0.28 ± 0.05 ml O_2/min/100 g to 2.06 ± 0.10 ml O_2/min/100 g, an increase of 15 ± 3%. The increased demand for oxygen was met entirely by the increase in blood flow as the $A-VO_2$ content difference did not change (Table I).

The luminal presence of food significantly decreased jejunal glucose uptake from the blood to −0.88 ± 0.63 mg/min/100 g, a decrease of 2.84 ± 0.68 mg/min/100 g (Fig. 1). At the same time both lactic acid and pyruvic acid production increased significantly. Lactic acid production increased to 1.02 ± 0.18 mg/min/100 g, an increase of 0.76 ± 0.17 mg/min/100 g or nearly 300%. Pyruvic acid production increased by 0.07 ± 0.024 mg/min/100 g to 0.128 ± 0.027 mg/min/100 g. There was no significant change in the arterial *L/P* ratio while the venous *L/P* ratio decreased slightly (−4 ± 1).

There were no significant changes in arterial pH, pO_2, or pCO_2 when food was present in the lumen (Table II); however, there were significant increases in the arterial–venous pH and pCO_2 differences. The arterial–venous pCO_2 difference increased from −1 ± 1 to −4 ± 1 mm Hg and the arterial–venous pH difference increased from 0.01 ± 0.004 to 0.03 ± 0.004, reflecting the increased CO_2 and lactic acid production. There was no significant change in either the arterial–venous pO_2 difference (Table II) or the venous hematocrit (Table I).

Discussion. Recent studies indicate that when glucose is placed in the lumen of the small intestine, 15–40% of the glucose which is absorbed does not appear in the venous blood (6, 7, 9). This net loss of glucose across the intestinal wall has been attributed to the utilization of absorbed glucose for energy production within the mucosal layer (8–10). This concept is supported by the fact that there is an increase in the venous lactic acid concentration during glucose absorption which is equivalent to 5–10% of the absorbed glucose (8, 9). It has even been suggested that this intracellular conversion of glucose to lactic acid in the small intestine and its subsequent release into the portal circulation where it can be utilized as a substrate for hepatic gluconeogenesis may serve as another mechanism of intestinal glucose absorption (12).

In this study, we examined the nature of jejunal glucose metabolism with either saline or food in the lumen in order to determine if glucose utilization increases when a variety of nutrients are present in the lumen. Furthermore, we wished to determine if lactic acid is the end product of intestinal glucose metabolism as suggested by Lester and Grim (10).

The carbohydrate used in this study was sucrose (4 g/100 ml) which consists of one molecule each of glucose and fructose and is broken down to its constituents by the intestinal brush border enzyme, sucrase.

Although fructose was not measured in this study, 60–95% of absorbed fructose is converted to either glucose or lactic acid within the small intestine (9, 13–15) so that, in this experiment, venous glucose and lactic acid represent at least 80% of the absorbed carbohydrate.

The data indicate that, when saline is present in the lumen, there is a low level of glucose uptake and lactic acid and pyruvic acid production. These findings support those of Shoemaker *et al.* (9), who reported a control lactic acid production of only 2.8 mg/min for the entire nonhepatic splanchnic area in conscious dogs, and contradict those of Lester and Grim (10), who found that in canine jejunal mucosa 80% of metabolized glucose was converted to lactic acid *in vitro*. The reasons for this discrepancy in results between *in vivo* and *in vitro* studies are not readily apparent. It is possible that portions of the tissues in the *in vitro* studies were anoxic and relied on anaerobic glycolysis for energy production; however, Wilson (12) presents strong evidence against such a possibility in similar studies using everted rat gut sacs.

It is interesting to note that Wilson has also reported a sixfold increase in lactic acid production by everted rat ileal sacs when glucose was placed on the mucosal rather than the serosal side (12). Therefore, it is possible that the difference between the *in vivo* and *in vitro* studies of canine jejunal glucose metabolism may be due to the fact that in the *in vitro* studies glucose was exposed to the mucosal surface while in the control period of the *in vivo* studies it was not. It is not clear, however, if these results are applicable to other species as the nature of glucose metabolism in the rat and mouse intestines is considerably different from other species such as the guinea pig, hamster, and rabbit (12).

When food was perfused through the lumen, there was an increase in jejunal oxygen consumption, a decrease in glucose uptake from arterial blood, and an increase in both lactic acid and pyruvic acid production. As it was not possible to accurately measure the disappearance of carbohydrate from the lumen in these studies, the conclusions which may be drawn from the available data must be based on certain assumptions and are therefore tentative.

In the saline-perfused jejunal loop, glucose was taken up from the blood at a rate of 66 μmole $C \cdot min^{-1} \cdot 100\ g^{-1}$. Of this, lactic acid and pyruvic acid production accounted for 11 μmole $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$. Oxygen consumption during this period was 80 μmole $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$. If the remaining 55 μmole $C \cdot ^{-1} \cdot 100\ g^{-1}$ were converted entirely to CO_2, then 70% of the oxygen consumed by the segment was used for glucose metabolism. However, Lester and Grim (10) have reported that only 50% of jejunal oxygen consumption is used for carbohydrate metabolism *in vitro*. If these results are representative of conditions *in vivo*, then approximately 25% of the glucose metabolized by the saline-perfused jejunal loop was converted to products other than CO_2, lactic acid, and pyruvic acid.

When food was perfused through the lumen of the jejunal loop, there was a threefold increase in the rate of lactic acid production by the segment. This increase could have been due to either a shift in carbohydrate metabolism toward lactic acid synthesis while total carbohydrate metabolism remained unchanged or to an increase in the overall rate of carbohydrate metabolism. The former conclusion would support Wilson's findings that the metabolic fate of glucose depends upon which surface of the cell it must cross, i.e., serosal or mucosal. However, a shift in carbohydrate metabolism toward lactic acid synthesis is usually associated with an increase in the venous *L/P* ratio (11). This did not occur, rather the venous *L/P* ratio decreased slightly in this study. Therefore, it would seem likely that the increased rate of lactic acid synthesis represents an increase in the overall rate of carbohydrate metabolism.

There is some evidence to support the conclusion that a portion of absorbed glucose is metabolized by the canine jejunum in a recent study by Sit *et al.* (4). In that study, the authors examined the effect of placing either glucose or 3-*O*-methyl glucose in the jejunal lumen on jejunal oxygen consumption. While both glucose and 3-*O*-methyl glucose are actively transported by the mucosal epithelia, only glucose is metabolized by intestinal tissues. Sit *et al.* found that although the jejunal loops absorbed equal amounts of each carbohydrate, only glucose increased intestinal oxygen consumption. The authors attributed this difference in response to metabolism of absorbed glucose.

If jejunal carbohydrate metabolism did increase when food was perfused through the lumen, the amount of absorbed carbohydrate which was metabolized depends upon which assumptions regarding the nature of intestinal carbohydrate metabolism which we have discussed previously are correct. If, as Lester and Grim have reported (10), 50% of intestinal oxygen consumption is directed toward carbohydrate metabolism, then total carbohydrate utilization in the food-perfused loops was 84 μmole $C \cdot min^{-1} \cdot 100\ g^{-1}$ (38 μmole $C \cdot min^{-1} \cdot 100\ g^{-1}$ converted to lactate/pyruvate; 46 μmole $C \cdot min^{-1} \cdot 100\ g^{-1}$ converted to CO_2). This would represent an increase in the rate of carbohydrate metabolism over control of 18 μmole $C \cdot min^{-1} \cdot 100\ g^{-1}$ or 16% of the absorbed glucose. The rate of glucose absorption in this case being equal to the sum of the decrease in the rate of glucose uptake from the blood (96 μmole $C \cdot min^{-1} \cdot 100\ g^{-1}$) and the assumed increase in the rate of carbohydrate metabolism (18 μmole $C \cdot min^{-1} \cdot 100\ g^{-1}$). If 70% of the oxygen consumed were directed toward carbohydrate metabolism or if glucose were degraded to compounds other than lactic acid or pyruvic acid, then the percentage metabolized would be even greater.

Although resting glucose utilization by the small intestine is low (4, 9, 10), it should not seem surprising that the rate of glycolysis should increase during periods of nutrient absorption. There is no reason to believe that absorbed nutrients are compartmentalized as they pass through the cells of the mucosa and therefore one would expect that a portion of those nutrients would be metabolized according to the laws of mass action. If the increase in the rate of lactic acid production is proportional to the overall increase in the rate of glycolysis, then it would appear that the relative proportion of energy demand met by glycolysis increased when food was present in the lumen as there was a threefold increase in the rate of lactic acid production while total intestinal metabolism increased only 15%. Again, this should not seem surprising as glucose is available for immediate utilization while the fats, tripeptides, dipeptides, and amino acids require additional catabolism before they can be utilized for energy production.

The results of this study indicate that when blood flow and oxygen delivery are adequate, there is a low level of intestinal glucose metabolism which does not appear to terminate in lactic acid synthesis. When food is present in the lumen, there is an apparent increase in the rate of glucose utilization which is proportionally greater than the overall increase in the rate of intestinal metabolism. The demand for glucose by the small intestine is apparently offset by carbohydrate absorption as glucose uptake from the arterial blood actually decreases. These findings lend support to the conclusions of other investigators (4, 6–9) that a portion of the glucose absorbed from the lumen of the small intestine is metabolized and suggests that metabolism is directed through the Kreb's cycle rather than terminating in lactic acid synthesis.

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