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FACTORS AFFECTING THE UTILIZATION OF KETONE BODIES AND OTHER SUBSTRATES BY RAT JEJUNUM: EFFECTS OF FASTING AND OF DIABETES

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SUMMARY

1. The utilization of some metabolic fuels has been measured *in vitro* in a preparation of rat jejunum to which the substrates were supplied *via* the perfusate flowing through the vascular bed.

2. In jejunum from 48 hr-fasted rats, the combined rates of utilization of 1 mM-acetoacetate and 2 mM-D-3-hydroxybutyrate are similar to that of 7·5 mM-glucose.

3. The utilization of glucose is reduced in jejunum from animals fasted for 48 hr (45–63 % reduction) and also from animals after 3–6 days of diabetes induced by streptozotocin (29 % reduction). The addition of ketone bodies or of Na-oleate to the vascular perfusate does not reduce the utilization of glucose by the jejunum of either fed or 48 hr fasted rats.

4. Ketone bodies in the vascular perfusate reduce the oxidation of glucose by the jejunum of fed rats. In the jejunum of 48 hr-fasted rats, ketone bodies completely inhibit the oxidation of glucose so that all the glucose utilized by the tissue is converted to lactate.

5. The findings are discussed in relation to other work and it is concluded that substrates for the oxidative metabolism of the jejunum of fasted rats are likely to be ketone bodies, glutamine and fatty acids; at the same time the utilization of glucose is reduced and its oxidation completely abolished.

INTRODUCTION

Metabolic fuels can be supplied to the intestinal mucosal epithelium by two different routes, from the intestinal lumen and from the blood. The first route is clearly only open when absorption is occurring; the second route is always available and may contain substrates of oxidative metabolism such as the ketone bodies that are not normally found within the intestinal lumen. There is no reason to suppose that the metabolic fate of a particular substrate is the same when presented alternatively from the lumen and the blood. Indeed, we have already shown that a higher proportion of glucose is oxidized when presented to the rat jejunum from the blood than from the lumen when up to 50 % of the glucose metabolized is converted to

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lactate. The metabolic fate of glutamine similarly depends on whether it is presented to the intestine *via* the blood or *via* the lumen (Hanson & Parsons, 1977*a*, *b*). A preparation of intestine perfused through the vascular bed *in vitro* is well suited to the investigation of the metabolism of the intestine from rats in differing nutritional states, and it enables substrates to be presented to the intestinal mucosal epithelium *via* the blood. There are, nevertheless, some complications arising from the fact that the mesenteric arteries supply blood not only to the epithelium but also to the intestinal smooth muscle.

Hülsmann (1971) showed that D-3-hydroxybutyrate (5·4 mM) was taken up from the vascular medium by vascularly perfused small intestine taken from fed rats. Oxidation of D-3-hydroxybutyrate has been demonstrated in mitochondria isolated from crypt and villus cells of rate small intestine (Hülsmann, Iemhoff, Van Den Berg & De Pijper, 1970; Iemhoff & Hülsmann, 1971), and the enzymes D-3-hydroxybutyrate dehydrogenase (EC 1.1.1.30), 3-oxoacid-CoA transferase (EC 2.8.3.5) and acetoacetyl-CoA thiolase (EC 2.3.1.9) have been found in such mitochondria (Iemhoff & Hülsmann, 1971). Epithelial cells of rat small intestine therefore have the capacity to metabolize ketone bodies, but rates of metabolism using physiological concentrations of ketone bodies appear not to have been assessed. Nor have the effects of fasting or the influence of ketones on metabolism been investigated.

It has also been shown that long chain fatty acids are taken up by perfused rat small intestine from the vascular medium, and are oxidized in preference to glucose (Hülsmann, 1971), but the effects of fasting on this process have not been studied.

We have attempted to answer some of the questions posed above and, in particular, to determine the extent to which fatty acids and ketone bodies are fuels for the intestine of fed and fasted rats. Csáky & Fischer (1977) have suggested that hyperglycaemia has an effect on the movement of sugars across the basolateral membrane of intestinal epithelial cells, and that this may be related to the enhanced transport activity of the intestine in early diabetes (Crane, 1961; Leese & Mansford; 1971; Schedl & Wilson, 1971*a*). We have therefore also measured the uptake of glucose from the vascular bed of jejunum taken from 3–6 day diabetic rats.

METHODS

Animals

Male Wistar rats (175–225 g body wt.) supplied by OLAC Ltd, Bicester, Oxon., were fed on Oxoid Breeding Diet. Experiments were performed between 1 p.m. and 5 p.m., and where necessary rats were fasted by removing food at noon 2 days before they were required for use. Diabetes was induced by a single I.V. injection of streptozotocin at a dose of 65 mg/kg body wt. The streptozotocin (50 mg/ml.) was dissolved in isotonic saline that had been adjusted to pH 4·5 with citric acid. Rats showing a positive glucosuria, which developed within 24 h (Boehringer test strip), were used 3–6 days after injection. The results obtained showed no obvious relationship to the period of diabetes and have been pooled.

Materials

Bovine serum albumin (fatty acid-poor, fraction V) was supplied by Miles Laboratories, Stoke Poges, Slough, England and by Calbiochem Ltd, Bishop's Stortford, Herts, England. In some experiments where fatty acids were added to the perfusate, the albumin (Miles Laboratories) was not fatty acid-poor. Streptozotocin and sodium D,L-3-hydroxybutyrate, containing 41% D-3-hydroxybutyrate, were from Boehringer Ltd, Lewes, East Sussex, England. Sodium

acetoacetate was prepared by the hydrolysis of ethyl acetoacetate (B.D.H. Chemicals Ltd, Poole, Dorset, England) by the method of Krebs & Eggleston (1945). Ethanol formed during the reaction was removed by freeze-drying. Sodium oleate was obtained from the Sigma Chemical Co. Ltd, Kingston-upon-Thames, Surrey, England. The requisite volume of a solution of Na oleate (0·1 M) in isotonic saline at 50 °C was added in drops to about 30 ml. of a vigorously stirred solution of dialysed bovine serum albumin (7·5 g/100 ml.) at 37 °C. The sources of other materials are given by Hanson & Parsons (1977*b*).

Perfusion procedure

20 cm segments of jejunum, with their origin about 5 cm below the ligament of Trietz, were perfused by recycling through the vascular bed a Krebs-Ringer bicarbonate medium containing dialysed bovine serum albumin, 3 g/100 ml.; washed bovine erythrocytes, haematocrit 40%; benzylpenicillin, 10,000 u./100 ml.; streptomycin sulphate, 5 mg/100 ml.; glucose, and in some cases additional substrates. Krebs-Ringer bicarbonate medium was recycled through the lumen of the segment. Further details of the procedure are given in Hanson & Parsons (1976, 1977*b*).

Analytical methods

Substrates and metabolites were estimated spectrophotometrically as follows: L-lactate (Hohorst, 1963); D-3-hydroxybutyrate (Williamson & Mellanby, 1974); acetoacetate (Mellanby & Williamson, 1974); and glucose using hexokinase and glucose-6-phosphate dehydrogenase (Boehringer kit).

Calculation and expression of results

Rates of metabolism were obtained by regression analysis of the linear part of the curve relating changes in the amounts of substrates or products (μmole/g dry wt.) to time. In all experiments where there was uptake of glucose from the vascular perfusate this was linearly related to time for the period 20–50 min after the onset of perfusion. The same was true of the appearance of lactate except for the experiments with jejunum from rats fasted for 48 h with oleate and glucose in the vascular perfusate. Here lactate appearance consistently did not become steady until 30 min. Uptake of acetoacetate and D-3-hydroxybutyrate was linear over a period of 20–40 min.

Results have been corrected for the metabolism of glucose by the erythrocytes, and for the breakdown of acetoacetate upon incubation of the perfusate in the absence of an intestine. As the concentration of glucose appears to be very low inside the bovine erythrocytes used in the perfusate, the concentrations of glucose are presented as m-mole/l. of perfusate plasma. Concentrations of other substrates are given in terms of m-mole/l. of whole perfusate.

On the assumption that exogenous glucose is the only source of lactate, the expression (lactate production × 0·5)/glucose utilization is taken as a measure of the proportion of glucose converted to lactate.

RESULTS

Utilization of ketone bodies

Ketone bodies, at concentrations similar to those found in the blood of rats fasted for 48 h (Hawkins, Alberti, Houghton, Williamson & Krebs, 1971), were taken up from the vascular perfusate by rat jejunum (Table 1). The rate of uptake by jejunum from fed rats did not differ significantly from that found with jejunum from 48 hr-fasted rats. In an experiment with jejunum from a fed rat, and with concentrations of ketone bodies in the vascular perfusate much closer to those found *in vivo* in the blood of a fed animal (D-3-hydroxybutyrate, 0·12 mM; acetoacetate, 0·2 mM), the slopes of the lines relating the uptake of D-3-hydroxybutyrate and the corrected uptake of acetoacetate (μmole/g dry wt.) to time over the period 20–50 min were $1{\cdot}72 \pm 2{\cdot}84$ and $1{\cdot}43 \pm 4{\cdot}46$ μmole/g dry wt. hr respectively. Neither of these slopes is significantly different from zero.

With jejunum from both fed and fasted rats the addition of ketone bodies to the

vascular perfusate increased lactate production expressed as a percentage of glucose utilization (Tables 2 and 3). This change was associated with a reduction in the expression: glucose utilization-(lactate production × 0·5), which should at least in part reflect glucose oxidation. Indeed with fasted rats this term was insignificantly different from zero, and all of the glucose utilized appeared to be converted to lactate.

TABLE 1. Utilization of ketone bodies in presence of glucose by vascularly perfused rat jejunum

Dietary status	Acetoacetate	D-3-hydroxy-butyrate	Total ketone body utilization
Fed	44 ± 4	41 ± 4	85 ± 5
Fasted, 48 hr	28 ± 9	36 ± 5	64 ± 13

Initial concentration of substrates in the vascular perfusate were: glucose, 7·5 mM, acetoacetate, 1 mM; D-3-hydroxybutyrate, 2 mM. No substrates were present in the luminal fluid. Results expressed as μmole/g dry wt. hr, are means ± S.E. of mean of four experiments, and were calculated from measurements made 20–40 min after the start of perfusion.

There was no production of ketone bodies by jejunum when they were not added to the vascular perfusate; in such experiments concentrations of acetoacetate and D-3-hydroxybutyrate were often undetectable (below 0·01 mM), and when present, the concentrations were below 0·04 mM and changed little during the experiment. Glucose utilization was not influenced by the presence of ketone bodies.

Sodium oleate

The only significant change caused by the addition of sodium oleate was to increase lactate production by jejunum from rats fasted for 48 hr (Table 3). Glucose utilization was not influenced by the presence of sodium oleate.

Fasting

Rats fasted for 48 hr exhibited significantly reduced rates of total glucose utilization and values of glucose utilization − (lactate production × 0·5), irrespective of the substrates present in the vascular perfusate (Table 4). This has also been found when glucose is present in both the luminal fluid and vascular perfusate (Table 5). With glucose only in the vascular perfusate, lactate production was decreased in jejunum from rats fasted for 48 hr (Table 4). Lactate production expressed as a percentage of glucose utilization was increased by fasting if glucose, or glucose and ketone bodies, were the substrates in the vascular perfusate (Table 4).

Diabetes

Utilization of glucose was reduced in diabetic rats as was the rate at which glucose was converted to metabolites other than lactic acid; lactate production expressed as a percentage of glucose utilization was increased (Table 2). Short-term diabetes did not change the length of the small intestine, the dry wt. jejunum/cm length, the hydration of the jejunum, or the proportion of the mucosa in the jejunal wall (Table 6; Lal & Schedl, 1974). Longer periods of diabetes are associated with changes

TABLE 2. Effect of ketone bodies, fatty acids and diabetes on glucose utilization and lactate production by vascularly perfused jejunum taken from fed rats

		μmol/g dry wt. hr			
Initial concentration of additional substrate	n	Glucose utilization	Lactate production	Glucose utilization − (lactate production × 0·5)	$\frac{\text{(Lactate production} \times 0{\cdot}5)}{\text{Glucose utilization}}$ (%)
None	5	170 ± 2	113 ± 8	113 ± 6	33 ± 3
D-3-hydroxybutyrate 2mM; acetoacetate 1 mM	4	156 ± 14	167 ± 35	73 ± 12**	52 ± 7*
Na oleate 1 mM	4	165 ± 6	114 ± 34	108 ± 20	35 ± 11
None, diabetic rat	4	120 ± 12***	118 ± 12	61 ± 12***	51 ± 7*

In all cases glucose (7·5 mM) was present in the vascular perfusate. No substrates were added to the luminal fluid. Rats were made diabetic by intravenous injection of streptozotocin at a dosage of 65 mg/kg body wt. Rats with positive glucosuria were used 3–6 days after injection. Results are expressed as means ± S.E. of mean; n, number of animals. P, where significant, for comparison with fed controls without additional substrate, denoted as follows: * $P < 0{\cdot}05$; ** $P < 0{\cdot}02$; *** $P < 0{\cdot}01$.

TABLE 3. Effect of ketone bodies and fatty acids on glucose utilization and lactate production by vascularly perfused jejunum taken from rats fasted for 48 hr

Initial concentration of additional substrate	n	μmole/g dry wt. hr: Glucose utilization	Lactate production	Glucose utilization − (lactate production × 0·5)	$\frac{\text{(Lactate production} \times 0{\cdot}5)}{\text{Glucose utilization}}$ (%)
None	3	62 ± 12	59 ± 14	33 ± 5	46 ± 3
D-3-hydroxybutyrate 2 mM; acetoacetate 1 mM	4	57 ± 11	118 ± 16*	−2 ± 5***	113 ± 16**
Na oleate 1 mM	3	90 ± 7	110 ± 11*†	34 ± 12	63 ± 11

In all cases glucose (7·5 mM) was present in the vascular perfusate. No substrates were added to the luminal fluid. † Lactate appearance in the vascular perfusate measured during the steady state over the period 30–50 min after the start of perfusion. Results are expressed as means ± S.E. of mean; n, number of animals. P, where significant, for comparison with fasted controls without addition substrate, denoted as follows: * $P < 0{\cdot}05$; ** $P < 0{\cdot}02$; *** $P < 0{\cdot}01$.

in the length of the small intestine and also the dry wt./cm length (Table 6; Jervis & Levin, 1966; Schedl & Wilson, 1971*b*). However, such alterations cannot be the reason for the changes seen in rats diabetic for only 3–6 days.

Concentrations of glucose in the plasma of diabetic rats were high, but concentrations of ketone bodies were little higher than the levels found in fed rats (Hawkins *et al.* 1971).

TABLE 4. Values of P for comparisons between results from fed and 48 hr-fasted rats

Concentration of additional substrate	Glucose utilization	Lactate production	Glucose utilization − (lactate production × 0·5)	$\frac{\text{(Lactate production} \times 0{\cdot}5)}{\text{glucose utilization}}$
None	0·001	0·02	0·001	0·05
D-3-hydroxybutyrate 2 mM; acetoacetate 1 mM	0·01	n.s.	0·01	0·02
Sodium oleate 1 mM	0·001	n.s.	0·05	n.s.

Values of P are less than the numbers shown, except where n.s. is written when $P > 0{\cdot}05$. The results are those in Tables 2 and 3. In all cases glucose (7·5 mM) was present in the vascular perfusate.

TABLE 5. Effect of fasting rats for 48 hr on glucose utilization and lactate production by vascularly perfused jejunum with glucose present in the vascular perfusate and luminal fluid at initial concentrations of 15 and 10 mM respectively.

	μmole/g dry wt. hr			
Dietary status	Glucose utilization	Lactate production	Glucose utilization − (lactate production × 0·5)	$\frac{\text{(Lactate production} \times 0{\cdot}5)}{\text{Glucose utilization}}$ (%)
Fed	401 ± 31	421 ± 59	190 ± 27	52 ± 5
Fasted, 48 hr	192 ± 47*	225 ± 48	79 ± 26*	60 ± 5

Results are expressed as means ± S.E. of mean of three experiments. The results for fed rats are taken from Hanson & Parsons (1976). P, where significant, for the comparison between results from fed and fasted animals, denoted as follows: $*P < 0{\cdot}05$.

DISCUSSION

Utilization of ketone bodies

The rate of uptake of ketone bodies present at physiological concentrations in the vascular perfusate by jejunum of rats fasted for 48 hr was similar to that of glucose (Tables 1 and 3). It seems likely that the ketone bodies were being oxidized, because oxidation of glucose in both fed and fasted rats appeared to be inhibited, indeed in the fasted rats glucose oxidation appeared to be completely abolished (Table 3). Glucose may not therefore be a fuel of oxidation by the intestine from fasted rats.

Ketone bodies are not fuels for the intestine of resting, fed rats, because we find a negligible uptake from perfusate containing ketones at concentrations close to those existing in the plasma *in vivo* in such animals. The absence of a significant difference between jejunum of fed and fasted rats in the utilization of acetoacetate

TABLE 6. Effects of streptozotocin diabetes on the composition of the wall of rat jejunum and on the concentration of some substrates in the plasma

Days after injection of streptozotocin	Length (cm)	Dry wt./cm. (mg/cm)	Dry wt. of mucosa / Dry wt. of wall (%)	Hydration of whole wall (g of H_2O/g dry wt.)	Plasma concentration (mM)		
					glucose	acetoacetate	D-3-hydroxy-butyrate
Control	100 ± 2 (10)	13·9 ± 0·3 (6)	72 ± 2 (6)	3·52 ± 0·04 (6)	—	—	—
3–6	98 ± 2 (6)	13·0 ± 0·4 (6)	71 ± 5 (6)	3·60 ± 0·03 (6)	23 ± 3 (4)	0·09 ± 0·02 (3)	0·13 ± 0·01 (3)
17–19	123 ± 2 (4)****	18·6 ± 1·2 (4)***	78 ± 2 (4)	3·55 ± 0·05 (4)	31 (1)	0·22 (1)	0·38 (1)

Samples of blood were withdrawn with a heparinized syringe from the aorta of rats anaesthetized with ether. The methods used to determine the composition of the intestinal wall are described by Hanson & Parsons (1977*b*). The length of the small intestine was taken as the distance from the ligament of Trietz to the ileocaecal valve. Results are expressed as means ± S.E. of mean with the number of animals in parentheses. *P*, where significant, for the comparison with control values denoted as follows: *** $P < 0.01$; **** $P < 0.001$.

(1 mM) and D-3-hydroxybutyrate (2 mM) suggests that, as in some other tissues (Krebs, Williamson, Bates, Page & Hawkins, 1971), ketone body metabolism in the jejunum is primarily affected by changes in the concentrations of ketone bodies in the plasma, rather than by alterations in the capacity of the tissue to take up or metabolize ketone bodies. In the intestine, rates of uptake of acetoacetate and D-3-hydroxybutyrate are similar to each other; this is in contrast to skeletal muscle where the uptake of acetoacetate is much greater (Ruderman, Houghton & Hems, 1971). It is probable that these differences depend upon the fact that intestine has a higher activity of D-3-hydroxybutyrate dehydrogenase than muscle. It seems likely that ketone bodies are being utilized both by the intestinal epithelial cells, which do contain the enzymes necessary for ketone body metabolism (Iemhoff & Hülsmann, 1971), and also the intestinal smooth muscle. Metabolism of ketone bodies at a number of sites within the intestinal wall is supported by the presence of ketone bodies causing a complete abolition of glucose oxidation in jejunum taken from rats fasted for 48 hr (see below). If muscle were the only site of ketone body metabolism oxidation of glucose by the epithelial cells should have been unaffected.

Ketone bodies and metabolism of glucose

With jejunum from both fed and 48 hr-fasted rats, the presence of ketone bodies in the vascular perfusate appeared completely to inhibit glucose oxidation but did not affect glucose utilization. Similar effects of ketone bodies have been observed with brain *in vitro* (Rolleston & Newsholme, 1967) and in the perfused hind-limb (Berger, Hagg, Goodman & Ruderman, 1976); in the perfused heart (Randle, Newsholme & Garland, 1964), frog sartorius and gastrocnemius muscles (Newsholme, Sugden & Williams, 1977), and brain *in vivo* (Ruderman, Ross, Berger & Goodman, 1974) glucose uptake was also decreased. Maizels, Ruderman, Goodman & Lau (1977) have suggested that ketone bodies do not inhibit glucose utilization in tissues that exhibit a low glycolytic rate because citrate levels are not sufficiently increased to inhibit phosphofructokinase (EC 2.7.1.11). However, glucose is utilized at a high rate by perfused jejunum, and glucose utilization may be controlled mainly by the rate at which glucose can reach the sites of its metabolism (Hanson & Parsons, 1977*b*) rather than by the activity of phosphofructokinase (Tejwani & Ramaiah, 1971; Tejwani, Kaur, Ananthanarayanan & Ramaiah, 1974). If the presence of ketone bodies does not affect this availability then glucose utilization may also not be affected.

The mechanism by which ketone bodies decrease glucose oxidation probably involves inhibition of pyruvate dehydrogenase (EC 1.2.4.1) by a decrease in the active form (Lamers & Hülsmann, 1974), and by increases in the ratios [acetyl-SCoA]/[CoASH] and [NADH]/NAD] (Lamers, 1975).

Effects of fatty acids

In agreement with the results of Hülsmann (1971) for the whole small intestine, the addition of 1 mM sodium oleate to the vascular perfusate did not alter the rate of glucose utilization by jejunum (Table 3). However, the presence of fatty acids in the perfusate did not abolish glucose oxidation (cf. Hülsmann, 1971), although lactate production was increased in jejunum from fasted rats. It is possible that the

discrepancy between our results and those of Hülsmann may be related to differences in the levels of glucose oxidation in the controls (*viz.* maximum possible rate of glucose oxidation expressed as a percentage of total glucose utilization by fed intestine: 67%, this work; 28%, Hülsmann, 1971). Other complicating factors are the possible utilization of endogenous fatty acids in the controls, or the esterification of added fatty acids by glycerol phosphate derived from glucose (Brindley, 1977).

Fasting

The reduction of glucose utilization caused by fasting, which has also been found *in vitro* with non-vascularly perfused preparations of intestine (Newey, Sanford & Smyth, 1970; P. J. Hanson & D. S. Parsons, unpublished work) seems to be associated in the intestinal mucosa with reductions in the activities of such glycolytic enzymes as hexokinase (EC 2.7.1.1.) phosphofructokinase and pyruvate kinase (EC 2.7.1.40) (Srivastava, Shakespeare & Hübscher, 1968; Shakespeare, Ellis, Mayer & Hübscher, 1972; Anderson & Tyrrell, 1973) or, in the case of hexokinase, by a redistribution in activity between particulate and soluble fractions (Mayer, Shakespeare & Hübscher, 1970). It is not known whether there is any effect of fasting upon the transport of glucose into the intestinal epithelial cells from the blood, e.g. across the basolateral membrane. In our experiments 48 hr-fasting has little effect on glucose uptake from the lumen into the jejunum (unpublished observations).

Diabetes

The metabolic state in streptozotocin diabetes is similar to fasting in that it is a condition of hypoinsulinaemia, although of course in diabetic rats the lumen of the small intestine is exposed to nutrients when the animals feed. We find that both in fasting and in diabetes the uptake of glucose by the jejunum from the vascular bed is reduced; a reduction in glucose uptake has been found in other diabetic tissues, e.g. rat heart (Randle *et al.* 1964). In our preparation the jejunal epithelium and the muscle coats are perfused in parallel circulation; however, we believe it likely that in diabetes the oxidative utilization by the epithelium of glucose derived from the vascular bed is likely to be reduced. Thus, from *in vitro* measurements using tissue slices, it has been estimated that the muscle layers contribute between 7 and 14% of the oxygen consumption and lactate production of the jejunal wall (Bronk & Parsons, 1965; Sherratt, 1968). On this basis we can estimate that if in the diabetic rats the muscle glucose metabolism was completely abolished, but that there was no change in the glucose metabolism of the epithelium, then the glucose metabolism of the whole wall would be about 150 μmole per unit weight per hour, whereas we find the rate to be 120 ± 12 μmole per unit weight per hour (see Table 2).

We have previously shown (Hanson & Parsons, 1976) that the metabolic fate of glucose depends on whether it is presented to the jejunum from the intestinal lumen or from the blood. It is therefore of interest that Leese & Mansford (1971) found that for everted sacs of mid-intestine with glucose available for metabolism from both mucosal and serosal surfaces, the glucose oxidation and lactate formation were enhanced after 7 days of diabetes.

Csáky & Fisher (1977) have shown that in rats made hyperglycaemic over periods of from 4 to 12 hr, there is an increase in the flux of glucose from the epithelium into

the blood. In these experiments the hyperglycaemia was presumably accompanied by a hyperinsulinaemia. However, it is possible that the membranes of the jejunal epithelial cells that face the blood (basolateral) contain two sorts of transport system for sugars. One sort would represent an export system through which movement occurs from the epithelium into the blood and which is operating during absorption; the other sort would represent a nutrient system through which glucose passes into the epithelium from the blood. If this is so, then the two systems may respond differently to metabolic conditions such as hyperglycaemia and diabetes mellitus.

Fuels for the jejunum of fasted rats

The findings that we have presented here, and also elsewhere (Hanson & Parsons, 1977*a*, *b*) suggest that while glucose will not be a fuel for oxidation by the jejunum of 48 hr-fasted rats, important substrates will be ketone bodies, fatty acids and glutamine. Indeed, Windmueller & Spaeth (1977) found that after only an overnight fast, the oxidation of glucose accounted for only 8% of the total CO_2 produced by rat jejunum *in vivo*; glutamine contributed 36%, so that the remaining CO_2 was presumably derived from fatty acids and the ketone bodies. The contribution of the ketone bodies as a fuel for the jejunum will become more important as the length of the fast increases and their concentration in the plasma rises.

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