Proceedings of the Nutrition Society (1995), **54**, 83–94

Fuel selection in intestinal cells

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Sélection de substrats énergétiques dans les cellules intestinales

RÉSUMÉ

Compte tenu de ses fonctions multiples, l'intestin, première cible de l'aliment, joue un rôle crucial dans le maintien de l'état de santé. Les fonctions d'hydrolyse et de transport assurées par les cellules intestinales différenciées, et d'une façon générale, l'intégrité des membranes intestinales nécessitent un métabolisme intense de certains nutriments, d'origine luminale et/ou vasculaire. La demande énergétique est, en effet, très élevée puisque la consommation intestinale d'O_2 s'élève à 20–25% de la consommation totale de l'organisme. Parmi les nutriments, qui rendent compte de cette consommation énergétique élevée, le rôle de la glutamine a été démontré. Les raisons pour lesquelles cet acide aminé, prélevé du côté luminal (avec le glutamate et l'aspartate) comme du côté vasculaire est utilisé d'une façon privilégiée, sont évoquées (activité et affinité de la glutaminase (*EC* 3.5.1.2), décarboxylation incomplète de la glutamine conduisant à la génération de composés à trois carbones, interactions métaboliques avec les autres nutriments). Par ailleurs, le faible rôle énergétique dans l'intestin grêle du glucose et des acides gras à longue chaine est expliqué. Néanmoins, dans la partie distale de l'intestin (colon), les acides gras à courte chaine, et plus particulièrement, le butyrate, représentent des substrats énergétiques majeurs des cellules épithéliales. Enfin, les modifications du métabolisme énergétique des cellules intestinales en fonction de l'âge et de l'état pathologique sont abordées. L'adaptation du métabolisme énergétique de l'intestin grêle au cours du développement fait ainsi apparaître des voies métaboliques transitoires telles que la voie de la gluconéogenèse et de la cétogenèse.

The gastrointestinal tract is a site of high O_2 uptake, the latter amounting to 20–25% of the whole-body O_2 consumption, even in the post-absorptive or fasting state (Yen *et al.* 1989; Vaugelade *et al.* 1994). The consumption of a meal in humans as well as in animal models is generally accompanied by a rise in energy expenditure. In humans, half the enhanced O_2 consumption occurs in splanchnic organs (Brundin & Wahren, 1991). As demonstrated in animal models, this enhancement of intestinal O_2 uptake is explained by an increase either in blood flow to the digestive organs or O_2 extraction rate (Granger & Norris, 1980; Sit & Chou, 1984). This high energy demand of the gastrointestinal tract parallels a high fractional rate of protein synthesis linked to a rapid turnover rate of epithelial cells and a high rate of intracellular protein synthesis.

Table 1. *Contribution of nutrients to respiratory carbon dioxide in rat jejunum (% CO_2 yield)*

(Experiments were performed with autoperfused jejunal segments of rats, as described in Windmueller & Spaeth (1978, 1980). Post-absorptive animals were 16 h-fasted and fed rats were perfused luminally with an Earle's balanced salt solution plus glucose (70 mM) and nineteen L-amino acids (0·5–6·5 mM each) to simulate a meal)

	Post-absorptive state	Fed state
Glutamine	35	77*
Ketone bodies	50	7
Glucose	7	6
Fatty acids	3	nd

* With luminal glutamate and aspartate.
nd, Not determined.

Measurements based on arterial–venous differences across autoperfused segments of rat jejunum have shown that glutamine, glucose and ketone bodies are widely taken up by intestinal tissues (Windmueller & Spaeth, 1974, 1978, 1980). Because glutamine and ketone bodies account for 35 and 50% respectively of the total CO_2 produced, they represent the major oxidative substrates of the rat small intestine in post-absorptive conditions (Table 1). However, in fed rats, glutamine available both from the intestinal lumen (with glutamate and aspartate) and from the vascular bed provides the main source of energy for the intestinal tissues. Conversely, whatever the nutritional conditions, fatty acids and glucose do not represent significant energy sources for the gastrointestinal tissues even though glucose uptake by intestinal tissues is as high as that of glutamine (Windmueller & Spaeth, 1978, 1980). These metabolic data were obtained with preparations containing different cell types. To explain why the gastrointestinal tissues use such a range of fuel substrates, it is necessary to examine simplified preparations based on a single cell type.

Investigating the metabolic capacities of epithelial cells which represent the predominant cell population in intestinal tissues confirms that glutamine is an important respiratory fuel for enterocytes or colonocytes (Watford *et al.* 1979; Roediger, 1982; Ardawi & Newsholme, 1985; Ashy & Ardawi, 1988; Fig. 1). However, these *in vitro* measurements also point to a high capacity for glucose oxidation, which conflicts with the *in vivo* observations. Moreover, cells isolated from the distal part of the gastrointestinal tract (colon) exhibit a high capacity for short-chain fatty acid oxidation, suggesting a variable metabolic response of intestinal cells according to their location. Thus, the main objective of the present review is to provide some information about the metabolic characteristics of intestinal cells and their adaptation.

WHY INTESTINAL CELLS SELECT GLUTAMINE AS A FUEL SUBSTRATE

Glutamine is the main vehicle for the transfer of N between muscle and splanchnic tissues (Souba, 1991). The first reaction in glutamine degradation is catalysed by a mitochondrial phosphate-dependent glutaminase (*EC* 3.5.1.2), whose activity is higher

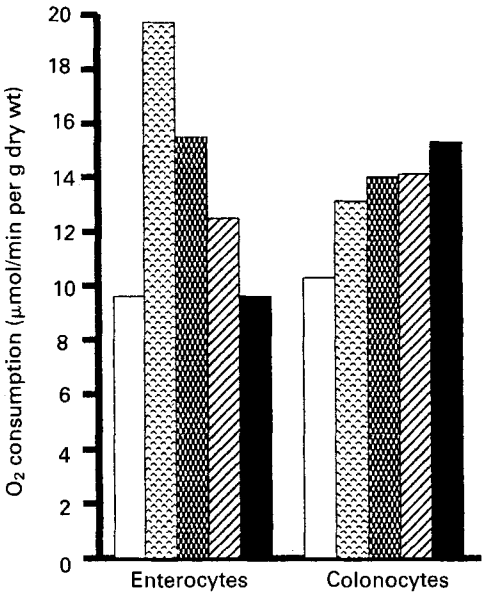

Fig. 1. Effects of added substrates on oxygen consumption rate of intestinal cells. Rates of O_2 consumption were measured in rat enterocytes as described by Watford *et al.* (1979) and in rat colonocytes as described by Ardawi & Newsholme (1985). Concentrations of substrates were 5 mM (glutamine (▩), acetoacetate (▨)) or 10 mM (glucose (▦), *n*-butyrate (■)). (□), Basal.

in the intestine than that in most other tissues (Newsholme & Carrié, 1994). However, a slightly lower activity of glutaminase is found in the distal part of the intestine. Glutaminase activity is detected in mature epithelial cells from the villi as well as in rapidly-dividing cells from the crypts (Pinkus & Windmueller, 1977). The apparent K_m of glutaminase for glutamine is about 2·2 mM at pH 8·1, which is tenfold lower than that of the liver (Pinkus & Windmueller, 1977). The high affinity of the intestinal enzyme, also, could explain the very low concentration of the amino acid found in the intestinal mucosa. Glutamate generated through glutaminase may be further metabolized via transamination reactions or by glutamate dehydrogenase (*EC* 1.4.1.2). Since the activity of glutamate dehydrogenase is very low in intestinal mucosa, this suggests that glutamate is metabolized through the transaminase reactions leading to alanine and aspartate formation. Indeed, as demonstrated by Windmueller & Spaeth (1980), glutamine-N is mainly recovered in NH_3 and alanine (65%), and also in citrulline (28%).

CO_2 production from glutamine is concentration-dependent in cells isolated from the jejunum or the colon of fed rats and may be saturated at a glutamine concentration several times those found in the blood or in the intestinal lumen (Kight & Fleming, 1993). The large recovery of glutamine-C in CO_2 (60% from *in vivo* preparations), lactate, other organic acids and alanine suggests that an extensive but incomplete glutamine oxidation prevails in intestinal mucosa (Windmueller & Spaeth, 1978, 1980). The fate of glutamine-C was recently followed in rat enterocytes by comparing the rate of $^{14}CO_2$ production from differentially labelled L-[^{14}C]glutamine (Watford, 1994). The

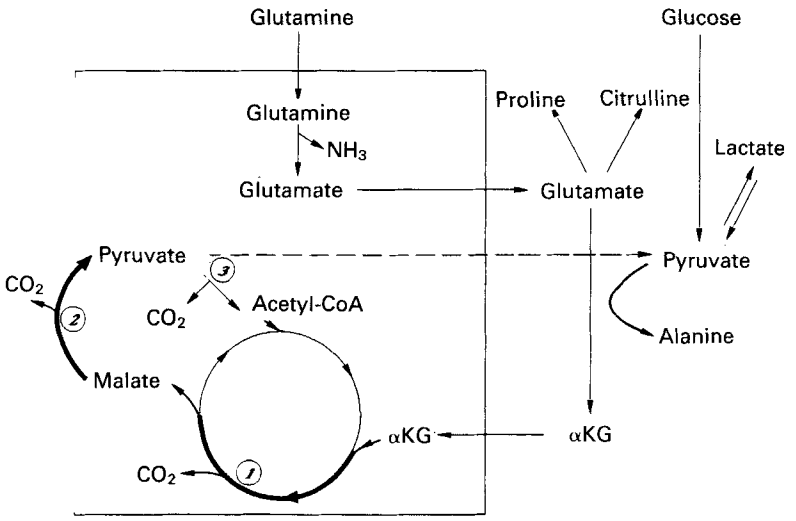

Fig. 2. A proposed scheme for the decarboxylation of glutamine in intestinal cells. The predominant steps in glutamine decarboxylation are those catalysed by α-ketoglutarate (αKG) dehydrogenase (*EC* 1.2.4.2; 1) and $NAD(P)^+$-dependent malic enzyme (*EC* 1.1.1.38, 1.1.1.40; 2). The pyruvate dehydrogenase (*EC* 1.2.4.1) reaction (3) is not important in glutamine decarboxylation. C_3 endproducts are alanine and lactate. (Adapted from Hanson & Parsons, 1980; Mallet *et al.* 1986*b*; Watford, 1994.)

results indicate that glutamine undergoes two decarboxylations and that the labelled C_3 endproduct is either alanine or lactate depending on the flux rate through the pyruvate pool. Glutamine metabolism has also been studied using the CO_2 ratio technique (Mallet *et al.* 1986*a*,*b*). Calculations based on this technique estimate the probability that a molecule which enters the tricarboxylic acid cycle will either remain in the cycle for one complete turn or will leave and re-enter as acetyl-CoA. Calculations from succinate-CO_2 ratio ($^{14}CO_2$ from [1,4-^{14}C]succinate: $^{14}CO_2$ from [2,3-^{14}C]succinate) or from acetate-CO_2 ratio ($^{14}CO_2$ from [1-^{14}C]acetate: $^{14}CO_2$ from [2-^{14}C]acetate) in the presence of glutamine predicts that glutamine molecules entering the tricarboxylic acid cycle have a low probability of remaining in the cycle for a complete turn (Mallet *et al.* 1986*b*; Fleming & Kight, 1994). The first step of glutamine decarboxylation is presumably via the α-ketoglutarate dehydrogenase (*EC* 1.2.4.2) reaction. Several enzymes could play a potential role in the second step of decarboxylation: phosphoenolpyruvate carboxykinase (*EC* 4.1.1.32; PEPCK) plus pyruvate kinase (*EC* 2.7.1.40), malic enzyme ($NAD(P)^+$-dependent; *EC* 1.1.1.38, 1.1.1.40) and oxaloacetate decarboxylase (*EC* 4.1.1.3). Because the addition of 3-mercaptopicolinate, an inhibitor of PEPCK, has no effect on glutamine oxidation, PEPCK plus pyruvate kinase may play only a minor role in the second decarboxylation of glutamine-C and the generation of pyruvate and alanine (Hanson & Parsons, 1977; Watford *et al.* 1979; Watford & Tatro, 1989; Watford, 1994). Similarly, the step catalysed by oxaloacetate decarboxylase probably does not make a significant contribution to the decarboxylation of glutamine. This suggests that the mitochondrial $NAD(P)^+$-dependent malic enzyme is the enzyme responsible for the second step of glutamine decarboxylation (Hanson & Parsons, 1980), as proposed in Fig. 2.

In enterocytes isolated from rat small intestine the presence of glucose does not generally modify the rate of glutamine utilization, but stimulates CO_2 production from glutamine by 20–35%; this reinforces the argument for glutamine as a major respiratory substrate for intestinal cells (Ashy & Ardawi, 1988; Fleming & Kight, 1994; Watford, 1994). Stimulation by glucose of intestinal glutamine metabolism and oxidation, also, has been demonstrated in other conditions (Weber *et al.* 1982; Rhoads *et al.* 1992). Indeed, glucose generates pyruvate which is used in the transamination of glutamate (Fig. 2). Moreover, in experiments on isolated enterocyte mitochondria, O_2 consumption related to glutamine oxidation is significantly enhanced by the presence of malate (Evered & Masola, 1984), suggesting that the entry of glutamine into the tricarboxylic acid cycle and/or the efflux of intermediates from the cycle may be stimulated by glucose metabolism (Fleming & Kight, 1994). Under fasting conditions, a high capacity for glutamine oxidation is maintained in isolated enterocytes (Vaugelade *et al.* 1994), although glutaminase activity is slightly depressed (Newsholme & Carrié, 1994). In contrast, glutamine oxidation is profoundly altered during fasting in isolated colonocytes (Firmansyah *et al.* 1989).

The overall balance of ATP and the acid–base balance for the metabolic processes occurring in the gut have been calculated recently (Jungas *et al.* 1992). The calculations based on a daily intake of 110 g protein by a human adult indicate that 80% of total O_2 uptake of the human jejunum results from the oxidation of lumen and arterial glutamine, in addition to that of lumen glutamate and aspartate, which confirms previous data from Windmueller & Spaeth (1980). The role of glutamine in the gastrointestinal tract is not limited to being a major energy source because it also provides amide-N for nucleotide synthesis and other N compounds (proline, citrulline). Dietary arginine, also, is highly metabolized during intestinal transport to provide urea, ornithine and citrulline but, unlike glutamine, arginine does not represent a significant energy source for the small intestine (Blachier *et al.* 1991*a*).

WHY INTESTINAL CELLS DO NOT SELECT GLUCOSE AND FATTY ACIDS AS FUEL SUBSTRATES

Although intestinal uptake of glucose seems to be high in rats in the post-absorptive state, glucose does not represent an important energy source in the mucosa (Windmueller & Spaeth, 1978). This is true also in the fed state when lumen glucose is available (Windmueller & Spaeth, 1980). Since the capacity for glucose oxidation is high in intestinal cells from fed rats (Watford *et al.* 1979; Fleming *et al.* 1991; Kight & Fleming, 1993), this involves a rapid adaptation of glucose metabolism during glucose transport and absorption. Glucose oxidation corresponds to CO_2 production (in the pyruvate dehydrogenase complex and tricarboxylic acid cycle). The pentose phosphate pathway contributes weakly to CO_2 generation (Mallet *et al.* 1986*a*; Blachier *et al.* 1991*b*). Thus, the generation of pyruvate and its oxidation determines the rate of glucose oxidation. Because glycolysis is the main pathway of glucose metabolism, the generation of pyruvate from glucose has not been identified as a limiting step in glucose oxidation. The probability that pyruvate derived from glucose will be oxidized is high (Mallet *et al.* 1986*a*; Fleming & Kight, 1994). Moreover, a stimulation of pyruvate dehydrogenase activity by the addition of dichloroacetate does not further increase glucose oxidation (Vidal *et al.* 1988). In contrast, the presence of glutamine profoundly reduces glucose

oxidation without effect on glucose utilization (Watford *et al.* 1979; Kimura, 1987; Ashy & Ardawi, 1988). This result is probably explained both by the diversion of pyruvate towards glutamate transamination (see p. 87) and by a direct effect of NADH generated by glutamine metabolism on the activity of pyruvate dehydrogenase complex (Fleming & Kight, 1994). Pyruvate dehydrogenase activity and pyruvate oxidation, also, are profoundly depressed by the intramitochondrial generation of acetyl-CoA and NADH during fatty acid oxidation in enterocytes (Lamers & Hülsmann, 1974; Vidal *et al.* 1988). Although the rate of fatty acid oxidation seems to be very low in enterocytes (see below), the latter probably gives rise to a rapid increase in the acetyl-CoA concentration, because the potential pathways for acetyl-CoA utilization (in the citrate or ketone-body synthesis) are limited. Conversely, the high capacity for ketone-body synthesis in colonocytes (Henning & Hird, 1972) probably could explain a slightly higher capacity for glucose oxidation in colonocytes than in enterocytes (Kight & Fleming, 1993). Similarly, the addition of *n*-butyrate moderately reduces the rate of glucose oxidation in pig colonocytes (Darcy-Vrillon *et al.* 1993).

Although the main fate of glucose in intestinal cells is always to generate C_3 products (pyruvate, lactate, alanine), this glycolytic activity can be altered by the nutritional conditions, for example during fasting in the rat (Butler *et al.* 1992; Newsholme & Carrié, 1994) or immediately after a meal in the pig (Vaugelade *et al.* 1994). Hexokinase (*EC* 2.7.1.1) and 6-phosphofructokinase (*EC* 2.7.1.11) are identified as the limiting steps of the glycolytic pathway in intestinal cells (Newsholme & Carrié, 1994). However, high activities of both enzymes prevail even in conditions of reduced glycolytic flux. This suggests that the flux through hexokinase and/or 6-phosphofructokinase could be controlled by the modulation of one or several factors, as suggested by Newsholme & Carrié (1994). One possible mechanism of control could be the setting of a substrate cycle (glucose–glucose-6-phosphate cycle) due to the presence of an active glucose-6-phosphatase (*EC* 3.1.3.9) in enterocytes (Bismut *et al.* 1993; Newsholme & Carrié, 1994). Hexokinase activity which represents the sum of several isozyme activities (Srivastava *et al.* 1968) is inhibited by glucose-6-phosphate. A specific control of the flux through hexokinase by one of these isozyme activities and/or by variations of the glucose-6-phosphate concentration via the activity of 6-phosphofructokinase (Kellett *et al.* 1984) represent other possible mechanisms for the regulation of glucose metabolism.

Although the metabolic fate of lumen fatty acids in the intestinal cells is incorporation into triacylglycerol, contradictory results have been previously obtained concerning the role of plasma long-chain fatty acids (LCFA) as fuel substrates in enterocytes (Gangl & Ockner, 1975; Windmueller & Spaeth, 1978; Mansbach & Dowell, 1992). Because high plasma LCFA levels generally prevail during fasting (Robinson & Williamson, 1980), LCFA represent a potential source of energy in intestinal cells. However, recent observations in isolated pig enterocytes confirm that the rate of oleate oxidation determined in the presence of glucose and glutamine was limited even after a 3 d fasting period, representing only 10% of the amount of oleate metabolized (M. T. Morel, B. Darcy-Vrillon, F. Blachier and P. H. Duée, unpublished results). The primary regulatory step of LCFA oxidation in the liver is mitochondrial entry at the level of carnitine palmitoyltransferase I (*EC* 2.3.1.21; CPTI). The concentration of malonyl-CoA which acts as a potent inhibitor of CPTI and the sensitivity of CPTI to inhibition by malonyl-CoA represent predominant factors to explain the repartition of LCFA between

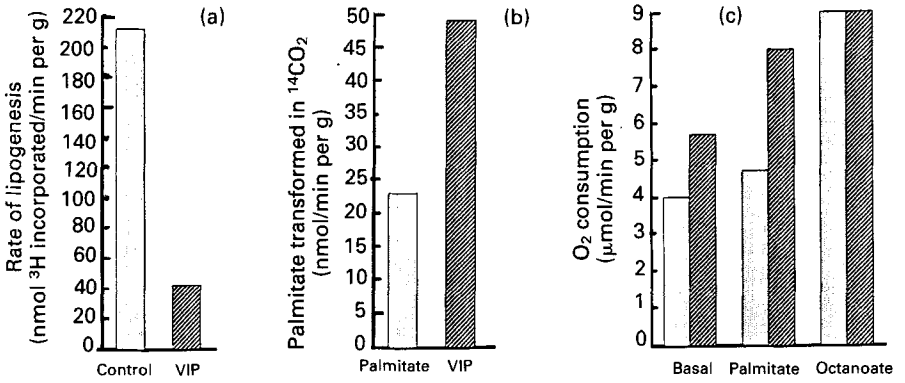

Fig. 3. Vasoactive intestinal peptide (VIP, ▨) effects on the rates of (a) lipogenesis, (b) palmitate oxidation and (c) oxygen consumption of isolated rat enterocytes. (Adapted from Vidal *et al.* 1988, 1989.)

oxidation and esterification (McGarry & Foster, 1980). Metabolic data obtained by Vidal *et al.* (1988, 1989) suggest that such a control could operate in rat enterocytes. Indeed, unlike LCFA, the presence of octanoate which enters the mitochondrion by a carnitine-independent mechanism stimulates the rate of O_2 consumption (Fig. 3). Although low in enterocytes, the rate of lipogenesis is inhibited by the addition of vasoactive intestinal peptide (VIP) which probably induces a lower malonyl-CoA concentration. Also, the rate of LCFA oxidation and the rate of O_2 consumption are enhanced by VIP (Fig. 3). These findings also suggest that the hormonal milieu could promote the role of LCFA as fuel substrates. Finally, in the colon only, short-chain fatty acids produced by bacterial colonic fermentation are considered to be the major oxidative substrates (Roediger, 1982; Ardawi & Newsholme, 1985). CO_2 production accounts for about 40% of butyrate metabolism and total ketone-body production accounts for the remaining 60% (Darcy-Vrillon *et al.* 1993; Clausen & Mortensen, 1994). Thus, despite its capacity to utilize ketone bodies as fuel substrates as in other tissues (Robinson & Williamson, 1980), the colon has the capacity for a net ketone-body production. The hydroxymethylglutaryl-CoA (HMG-CoA) synthase (*EC* 4.1.3.5) pathway would be the major route for ketogenesis from butyrate in the colon (Henning & Hird, 1972). Even though the colonic epithelial cells possess the capacity to utilize acetate, propionate and butyrate, only butyrate suppresses the oxidation of the other short-chain fatty acids (Clausen & Mortensen, 1994). Moreover, butyrate metabolism is not significantly affected by the presence of metabolic substrates from vascular origin, i.e. glucose and glutamine (Fleming *et al.* 1991; Darcy-Vrillon *et al.* 1993), which could explain its predominant role as a fuel substrate in the colon.

ADAPTATIONS OF FUEL METABOLISM IN INTESTINAL CELLS

Birth is accompanied by important modifications in several physiological functions and particularly dramatic changes of nutrition (Girard *et al.* 1992). The gastrointestinal tract

becomes operative and undergoes marked structural and functional changes. Most of these changes occur at different times after birth, according to the species concerned (Darcy-Vrillon *et al.* 1994). The postnatal period is also associated with marked modifications in fuel metabolism of intestinal cells (Girard *et al.* 1992). Because milk is a high-fat diet, the question of the contributions of fatty acids as fuel substrates may arise. In the intestinal mucosa of sucking rats, fatty acids can be oxidized and even produce ketone bodies (Békési & Williamson, 1990). The enzymes of the mitochondrial HMG-CoA pathway have been detected in the small intestine mucosa of the sucking rat. Moreover, the concentration of mitochondrial HMG-CoA synthase mRNA increases markedly in the rat jejunum after birth and remains elevated during the sucking period (Thumelin *et al.* 1993). Ketogenesis from endogenous substrates can be strongly inhibited by tetradecylglycidic acid, an inhibitor of LCFA oxidation, suggesting that LCFA are the main precursors for intestinal ketogenesis (Békési & Williamson, 1990). When rats are weaned on a high-carbohydrate diet the ketogenic rate falls, as do the HMG-CoA synthase activity and the concentration of HMG-CoA synthase mRNA. Since the expression of HMG-CoA synthase gene could be reinduced when rats are weaned on a high-fat diet, the absorption of large amounts of fatty acids or hormonal changes could promote the transcription and/or the stabilization of intestinal HMG-CoA synthase mRNA (Thumelin *et al.* 1993).

In isolated mitochondria from rat small intestine, the production of $^{14}CO_2$ from [1–^{14}C]palmitoyl-CoA is low during the sucking period and increases threefold after weaning (Kimura & Warshaw, 1988). The removal of [1–^{14}C]palmitoyl-CoA by mitochondria from adult and sucking rats is similar, although CPTI activity decreases slowly after weaning (see Girard *et al.* 1992). These data suggest that the capacity to oxidize LCFA remains fairly constant during the sucking period and after weaning, but that the fate of acetyl-CoA differs, reversing from ketone-body synthesis to oxidation in the tricarboxylic acid cycle.

Glutamine oxidation is high during the sucking period in rat intestinal tissue slices (Kimura, 1987) or isolated pig enterocytes (Darcy-Vrillon *et al.* 1994). In contrast, glucose and 3-hydroxybutyrate oxidation are lower during the sucking period than after weaning in the rat (Kimura, 1987). Glucose oxidation in rat intestinal tissue slices is

Table 2. *Relative contribution of glucose and glutamine to ATP turnover in newborn pig enterocytes** (Adapted from Posho *et al.* 1994)

	Birth	2 d old†
Total ATP turnover (nmol/min per 10^6 cells)	26·0	42·5
Percentage of ATP supported by:		
Glucose metabolism	16	36
Oxidation	9	11
Glycolysis	7	25
Glutamine metabolism	60	49
Endogenous fuels	24	15

* Total ATP turnover rate was estimated from O_2 consumption in the presence of 2 mM-glucose and 2 mM-glutamine. Potential ATP production from glucose or glutamine was calculated on the basis of measured endproducts.

† Sucking animals in the post-absorptive state.

100-fold lower than the conversion of glucose to lactate. Since the rates of lactate and CO_2 production from glucose slightly increase after weaning in the rat, these changes in glucose utilization could be explained by the concomitant variations in fatty acid metabolism (Kimura *et al.* 1984). However, in contrast to the rat situation, the rate of glycolysis is profoundly enhanced after birth in isolated pig enterocytes, while the rate at which glucose is completely oxidized remains constant (Darcy-Vrillon *et al.* 1994; Posho *et al.* 1994). Thus, the production of ATP from glucose through glycolysis is increased in sucking-pig enterocytes (Table 2). Besides a high glycolytic capacity, enterocytes isolated from sucking pigs also have the capacity to generate glucose from galactose or dihydroxyacetone (Darcy-Vrillon *et al.* 1994). Similarly, there is a sizeable generation of glucose from lactate in the intestinal mucosa of sucking rats (Hahn & Wei-Ning, 1986). The emergence of a transient gluconeogenic pathway in sucking-pig enterocytes depends on colostrum ingestion and could be required for the synthesis of glycerol-3-phosphate needed for the high rate of intestinal re-esterification of fatty acids. Whether these metabolic adaptations in small intestinal cells are linked to parallel changes in both structure and function of enterocytes and could be controlled by hormonal changes during this period needs further investigation. The influence of ageing on glucose and glutamine metabolism has been investigated recently in rat jejunal cells (Fleming & Kight, 1994). Compared with cells from young (4 months) fed animals, cells from fed aged (24 months) rats show lower O_2 uptake in either the absence or presence of both substrates. Moreover, total CO_2 production from glucose and glutamine is depressed, suggesting that intestinal fuel metabolism may require other additional substrates with ageing. In general, profound changes in intestinal fuel metabolism are observed in pathological states or when the hormonal milieu is substantially modified (Souba, 1991). Thus, intestinal glucose metabolism in the rat seems to be stimulated by insulin (Kellett *et al.* 1984) or inhibited by glucocorticoid treatment (Ardawi *et al.* 1988). Conversely, glucocorticoid administration increases the rate of glutamine utilization (Ardawi *et al.* 1988).

In enterocytes isolated from septic rats, rates of both glucose and glutamine utilization are decreased (Ardawi *et al.* 1990), suggesting that the response to sepsis induces different metabolic responses in the gut compared with other tissues. Finally, in streptozotocin-diabetic rats, glucose and glutamine metabolism, also, are profoundly altered: an increased rate of glucose metabolism parallels a lower rate of glutamine utilization (Anderson, 1974; Watford *et al.* 1987; Ardawi, 1988). Moreover, during prolonged diabetes, a more important role for ketone bodies and fatty acids as fuel substrates becomes evident (Watford *et al.* 1987; Ardawi, 1988). Again, the mechanism for such an adaptation remains to be elucidated.

CONCLUSION

The main functions of the gastrointestinal mucosa are digestion and nutrient transport as well as defence against noxious substances. The gut is not an inert tube, because its mucosa displays a central role in the whole-body metabolism. This high metabolic activity of the mucosa can be modulated according to the nutritional, physiological or pathological conditions. Additional information is needed on the role of hormonal pattern on fuel selection in intestinal cells, and also on the relationship between this metabolic activity and the function and integrity of the intestine.

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Printed in Great Britain