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EDITORIAL

Metabolic Development of the Small Intestinal Mucosa in Rodents

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The mucosa of the gastrointestinal tract is the first tissue to come into contact with food. Its response to nutrients has been well studied and the individual enzymes that break down the food are more or less well known. Much less is known about the specific metabolic pathways that are present in the mucosa. This is particularly true for the foetus and the newborn.

Basic discoveries in the adult mammals were made in the seventies. It was shown that the main source of energy for the small intestine is glutamine (Pinkus and Windmueller 1977, Kimura 1987) and that the gut produces ammonia but not urea (Malo *et al.* 1986, Hurwitz and Kretchmer 1986). These pathways are valid for the adult mucosa of rats and rabbits and probably also of most mammals. At about the same time, a number of enzymes of glycolysis was shown to be present in the mucosa and it was demonstrated that their activity depends to a large extent on the composition of the food consumed (Srivastava and Huebscher 1968, Kubát and Koldovský 1969, Saheki *et al.* 1979).

Nothing, however, was known about the infant gut even though considerable progress had been made in studies of the development of digestive enzymes (Koldovský 1969). The first report of interest was published by Nathan (1967) who described changes in the glycogen content in the small intestinal mucosa during early postnatal development. The data suggested that, as in other tissues (Hahn and Koldovský 1967), glycogen accumulates prenatally and disappears rapidly after birth. The early postnatal breakdown of glycogen suggested that glycolysis should set in postnatally when glycogenolysis commences. Alternatively glucose-6-phosphatase (G6Pase) might play a role liberating glucose from glucose-6-phosphate thus making it possible for glucose to leave the cell. This possibility seemed somewhat unlikely, since G6Pase is present only in the liver and kidney. Surprisingly, however, G6Pase was found to be present in the mucosa of infant mice (Menard and Malo 1978), activity falling to low levels at the time of weaning. Since mucosal glycogen levels are relatively low (Nathan 1967, Hahn and Smale 1983), it seemed possible that the

source of glucose-6-phosphate was not glycogen but that it was produced by gluconeogenesis. This was confirmed to be the case: the two rate limiting enzymes phosphoenolpyruvate carboxykinase (PEPCK) and fructose biphosphatase (PFB) were found to be present in infant mucosa at an activity comparable to that found in the liver (Hahn and Smale 1982, Westbury and Hahn 1984). Both enzymes showed minimal activity at the time of weaning and later in life. Furthermore, pyruvate carboxylase catalyzing the formation of oxaloacetate from pyruvate was also found to have the highest activity in early infancy (Hahn *et al.* 1988).

Using ^{14}C-labelled lactate *in vitro* it could be shown that it was incorporated into glucose (Hahn and Wei-Ning 1986). Thus the infant intestinal mucosa seems to be a gluconeogenic organ, similar to the liver. Another tissue that was found to contain PEPCK was infant brown adipose tissue (Hahn and Smale 1983). However, no PFB or G6Pase was found (Seccombe *et al.* 1977) so that only glycerol, but no gluconeogenesis, occurs in that tissue. This has also been described for white adipose tissue (Ballard 1978). In the liver the activity of PEPCK is regulated by cyclic AMP (Wicks 1971) and by hormones that induce its release, e.g. by starvation or a high fat diet. The cyclic AMP and GMP contents are higher in infant mucosa than later in life (Hahn *et al.* 1986) and rat milk contains relatively large amounts of these substances (Skála *et al.* 1981). The molecular control of PEPCK in the liver has been extensively studied (see Watford and Tatro 1989). Recently, it has been shown that the mRNA for PEPCK production by the mucosa is highest in infant rats and slows down nearly to zero at the time of weaning (Hahn *et al.* in press, Leichter and Hahn 1989). Another characteristic of the liver is the production of ketone bodies. In most tissues they are rapidly utilized as an easily accessible source of energy and this is also true for the intestinal mucosa of weaned rats which also utilize fatty acids (Windmueller and Spaeth 1978). The intestinal mucosa of infant rats, however, not only does not utilize ketones, but produces them (Hahn and Taller 1987). This occurs *via* the hydroxymethylglutaryl-CoA pathway (Bekesi and Williamson 1990).

Similarly CO_2 production from glucose and fatty acid is low in infancy (Windmueller and Spaeth 1978). The infant mucosa requires carnitine for the oxidation of fatty acids and for ketone formation. Inhibition of the action of carnitine, either by using an inhibitor of carnitine 3-acyltransferase or by adding D-carnitine, inhibits ketone formation in the infant mucosa (Hahn and Taller 1987). In agreement with the accented role of carnitine in infancy the activities of the enzymes responsible for carnitine ester formation (acetyl and acyl transferases) are higher in the intestinal mucosa from infant than from weaned rats (Hahn *et al.* 1985). It should be stressed here that in this case carnitine is not required to oxidize fatty acids to CO_2 but only to acetyl CoA, and this, of course, shows that one cannot judge the rate of fatty acid oxidation from the rate of CO_2 production. Recently, it has also been reported that carnitine is required for the transport of fatty acids across the mucosa (Leichter and Hahn 1988, Flores *et al.* 1988, Hahn 1982, 1989). Ketogenesis and gluconeogenesis are also under hormonal control. After delivery, sudden changes occur in the plasma levels of at least two hormones: insulin and glucagon (Hahn 1989). The high plasma level of insulin in the foetus is suddenly decreased, while that of glucagon, which was low in the foetus, suddenly rises steeply. Hence it is logical to assume that the changes in metabolic pattern which occur at birth are related to these perinatal changes in hormonal levels. This has

been confirmed to some extent, using antibodies to these hormones or streptozotocin (Hahn *et al.* 1986). In the infant mucosa, insulin inhibited while an insulin antiserum or streptozotocin accentuated ketone formation. Glucagon antiserum, on the other hand, suppressed ketogenesis in the infant rat intestine. PEPCK activity in the mucosa was not suppressed by insulin. The mucosa also did not respond to the antisera. However, PEPCK in the liver and brown fat were responsive to insulin, but this was not true in the mucosa, which also did not respond to the antisera, even though brown fat and liver did. Both dexamethasone and the thyroid hormone suppressed PEPCK activity (mostly in the crypts of the villi) and inhibited ketone formation (Hahn *et al.* 1986).

Conclusion

The small intestinal mucosa is metabolically more similar to the adult liver than to the adult mucosa. Further work is required to indicate the reasons for this similarity and difference. Are glucose and ketone formation necessary to feed the muscles of the intestinal wall (see Hahn and Smale 1982) in infancy? Is there another role for the infant mucosa?

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