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Development of Gastrointestinal Functions

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Summary

Data are summarized about digestion and absorption of carbohydrates, lipids and proteins during mammalian perinatal development including human fetuses. Corresponding with the high fat intake in suckling rats, absorption of triglycerides was found to be approximately 2–3 times higher in suckling than in adult rats. Carnitine contents of the small intestinal mucosa of rats decrease postnatally, reaching adult levels at the time of weaning. Other studies suggested that gluconeogenesis may occur in the small intestine in the neonatal period. The intestinal mucosa of infant rats produces ketones; it was suggested that ketone production is to a large extent due to a breakdown of long-chain fatty acids. Studies dealing with the development of colonic sodium transport in rats are described. Other studies on the developing colon showed that the proximal colon resembles ileum during the early postnatal period. Developmental changes of the "specialization" of intestinal segments are reviewed. In all studies attention is given to the maturative effects of hormones of the adrenal cortex and thyroid gland (88 references).

Key words

Pancreatic amylase – Sucrase-isomaltase – Maltase-glucoamylase – Lactase-phlorizinhydrolase – Sialylation of brush border enzymes – Glucose transport – Pancreatic and small intestinal lipases – Esterification capacity – Absorption of triglycerides – Formation of phospholipids – Carnitine absorption – Metabolism of the developing small intestine – Colonic sodium transport – Human fetal studies – Adrenal cortex and thyroid gland hormones – "Specialization" of intestinal segments – Enterocyte migration

Digestion of carbohydrates

Activity of pancreatic amylase was found to be low in suckling rats, however, an increase in pancreatic amylase activity was evoked by exogenous glucocorticoids (Procházka *et al.* 1964).

The activity of sucrose appeared at the beginning of the third postnatal week in suckling rats (Yiezuitova *et al.* 1964) and in isografts of foetal small intestine implanted in adult rats (Kendall *et al.* 1977, 1979). Preparation of guinea-pig antisera to purified adult rat sucrase-isomaltase (Kolínská and Kraml 1972) allowed detection of enzymatically inactive antigens of sucrase-isomaltase during early postnatal development of rat by the indirect immunofluorescence method (Kolínská *et al.* 1984, Slabý *et al.* 1977), as well as their isolation and purification by the immunoadsorbent technique (Kolínská *et al.* 1984). Studies of rat foetal small intestinal isografts in adult hosts (Kendall *et al.* 1979) have shown that the appearance of sucrose activity and of its proximodistal gradient in the small intestine is programmed in the foetal intestine; contact with digesta appears to have a "tuning" effect. Interestingly, sucrose activity which is not present in the large intestine of adult human subjects, was detected in the proximal colon of 4-month-old foetuses (Jirsová *et al.* 1968).

Glucocorticoid administration to sucklings accelerated the developmental increase of sucrose activity which normally occurs during the weaning period (Koldovský *et al.* 1965a, 1972b, Herbst and Koldovský 1972), foetal rats (Celano *et al.* 1977), and foetal organ cultures (Kolínská *et al.* 1990a). It is noteworthy that the precocious increase of sucrose activity was shown to be dependent on *de novo* protein synthesis in experiments where actinomycin D inhibited

the cortisone-evoked increase of sucrose activity (Koldovský *et al.* 1972b). Adrenalectomy of suckling rats was found to delay (but not to prevent) the increase of sucrose activity (Koldovský *et al.* 1965a, 1975, Boyle and Koldovský 1980) and of the host in foetal small intestinal isografts (Kendall *et al.* 1977). The decisive role of adrenal stimulation during the precocious increase of sucrose activity evoked by the premature weaning in the small intestine (Boyle and Koldovský 1980) and due to early intake of sucrose in suckling rats (Goda *et al.* 1985a, 1985b) was clearly established; no direct effect of dietary change was found. Thyroidectomy also caused a delay in the increase of sucrose activity (Koldovský *et al.* 1975).

Antiserum to rat brush-border maltase-glucoamylase (M-G) was used for differentiation of soluble neutral M-G of suckling rats and acid lysosomal M-G; the latter at variance from the former does not react with the antiserum to adult membrane-bound M-G (Kolínská *et al.* 1991). Maltase-glucoamylase is a glucocorticoid-stimulated enzyme; demonstrated also in foetal and early postnatal jejunal organ cultures of the rat (Kolínská *et al.* 1990a). Antiglucocorticoid onapristone suppresses not only the effect of exogenously applied glucocorticoids at the level of the glucocorticoid receptor, but also acts as an antagonist suppressing the postnatal development of maltase-glucoamylase and lactase in which the involvement of endogenously secreted glucocorticoids is assumed (Kraml *et al.* 1995).

Rat lactase was isolated as a complex with phlorizinhydrolase (Kraml *et al.* 1972) using affinity chromatography of β-thioglucoside Sepharose column as the last purification step (Ledvina *et al.* 1977). Phlorizin was found as a competitive inhibitor of lactase towards lactose as a substrate (Kraml *et al.* 1972, Hiršová *et al.* 1972, 1977).

Sialylation

The pH values of brush-border enzymes increased due to a progressive loss of bound sialic acid during the weaning period (Kraml *et al.* 1983). Injected glucocorticoids speed up the process of postnatal decrease of bound sialic acid to brush-border membranes and enzymes (Kraml *et al.* 1984). This change starts in the differentiating cells of Lieberkuehn crypts (Kolínská *et al.* 1986) as a result of the suppression of sialyltransferase activity (Kolínská *et al.* 1988); it may be antagonized by actinomycin D, a known inhibitor of transcription (Kolínská *et al.* 1990b). Administration of an antiglucocorticoid inhibits the hydrocortisone-induced pH shift of the brush-border enzyme dipeptidyl peptidase IV (Kraml *et al.* 1995). Thus the hydrocortisone effect on sialylation processes in the small intestine of infant rats is apparently mediated through glucocorticoid receptors and through transcription of a sialyltransferase, apparently of the alpha 2,6-type (Hamr *et al.* 1993, Kolínská *et al.* 1990b, 1993).

Glucose absorption

Faltová *et al.* (1963) and Koldovský *et al.* (1963) demonstrated the increasing capacity for absorption of glucose in the rat postnatal period. These studies were then extended to human foetuses using *in vitro* methods. The presence of an active process for glucose transport was demonstrated in the small intestine of a 3-month-old human foetus (Koldovský *et al.* 1965b, Jirsová *et al.* 1966, 1968, Levin *et al.* 1968) that exhibited a considerable increase of glucose absorption with development. Glucose was transported against a concentration gradient even in the absence of oxygen, and Levin *et al.* (1968) also found an active transport of amino acids. A functional differentiation of jejunum and ileum was also noted in these studies. The glucose transport capacity increased more in the jejunum than in the ileum, thus establishing a proximodistal gradient during foetal life that is present in adult subjects.

Lipid absorption

Other studies concentrated on the developmental aspects of lipid absorption (Hahn and Koldovský 1967). In spite of the high fat intake in milk during the suckling period, the activity of pancreatic and small intestinal lipases (Rokos *et al.* 1963) and nonspecific esterase (Pelichová *et al.* 1967) were found to be low during the suckling period. Glucocorticoids caused an increase in the activity of pancreatic lipase (Rokos *et al.* 1963). The low lipolytic activity of the developing gastrointestinal (GI) tract contrasts to similar (or even higher) esterification capacity of the small intestine of suckling rats, when compared to adult rats (Holtzapple *et al.* 1975, Shiau *et al.* 1979). This discrepancy stimulated research in other laboratories that demonstrated the significance of milk-borne and gastric lipases in fat digestion during the suckling period.

Corresponding with the high fat intake in suckling rats, GI absorption of triglycerides was found to be approximately 2–3 times higher in suckling than in adult rats (Flores *et al.* 1989). The formation of phospholipids during fat absorption was demonstrated in the intestine of suckling rats. In the adult rat a proximodistal gradient was observed, but in the suckling it was absent (Koldovský *et al.* 1964). In contrast to other functions, the villus-to-crypt gradient of fatty acid esterification was very steep. This was correlated with the fact that fat digestion and absorption are very often the first damaged function in compromised intestine (Shiau *et al.* 1980). Interestingly, contact with digesta was necessary to

preserve the activity of fatty acid esterification processes.

Lipids in the small intestine of suckling rats were characterized both morphologically (Vacek *et al.* 1962) and biochemically (Dobiášová *et al.* 1963, 1964). The biochemical studies showed a correlation of individual fatty acids in triglycerides of milk and small intestinal mucosa, however, no correlation being seen in the case of fatty acids in phospholipids. An interesting phenomenon was found using histochemical methods to detect lipids in the lungs of suckling rats. Fed and fasted-refed rats (with milk or olive oil) exhibited strong staining with "oil red O" in the lungs whereas in fasted rats this staining showed either low or negative.

Hahn *et al.* (1985) have shown that the carnitine contents of the mucosa (free, acetyl-, palmitoyl- and total) of the small intestine of rats decrease postnatally, reaching adult levels at the time of weaning. Activities of carnitine acetyltransferase and palmitoyltransferase in the mucosa rise after birth and fall at the time of weaning. Orally administered ^{14}C-carnitine is only slowly absorbed so that radioactivity is still high in plasma and organs 6 hours later, whereas the label given subcutaneously disappears from the plasma and tissues more rapidly. The intestinal mucosa also takes up carnitine from ^{14}C-carnitine administered subcutaneously. Using the *in vitro* everted small intestinal technique, Leichter and Hahn (1988) studied further the intestinal transport of carnitine. The release of endogenous carnitine and its esters into the serosal medium was greatest in the suckling and lowest in the postweaning period. In contrast, the transport of carnitine from the mucosal to the serosal compartment was lowest in the suckling and higher in the older groups.

Metabolism of the developing small intestine

Phosphoenolpyruvate carboxykinase activity was found to be high in the mucosa of the small intestine of suckling rats and mice; it decreased to very low values at weaning. Since fructose-biphosphatase was also found in the intestinal mucosa of suckling rats, it was suggested that gluconeogenesis may occur in this tissue in the neonatal period (Hahn and Smale 1982b). Other studies showed that the activities of glutaminase and glutamate dehydrogenase in the small intestinal mucosa of infant increased at the time of weaning. On the other hand, pyruvate carboxylase activity, was very high during the suckling period and decreased to negligible values at weaning (Hahn *et al.* 1988). Fructose-biphosphatase activity was found to increase to a maximum on about the 10th postnatal day and to decrease thereafter.

3-hydroxy-3-methylglutaryl-CoA reductase activity was found to be high perinatally. It decreased postnatally and increased again at weaning. Activity in the mitochondrial fraction of the small intestine showed no developmental changes (Hahn and Smale 1982a). Whereas the intestinal mucosa of infant rats produces ketones, no production was found in weaned rats. Since ketogenesis could be inhibited by D-carnitine or tetradecylglycidic acid, an inhibitor of long-chain acylcarnitine transferase, it was suggested that ketone production is to a large extent due to a breakdown of long-chain fatty acids (Hahn and Taller 1987). Injections of triiodothyronine and glucocorticoid decrease the high activity of phosphoenolpyruvate carboxykinase (Hahn and Smale 1983) and of fructose-biphosphatase in the small intestinal mucosa of suckling rats (Westbury and Hahn 1984). An injection of insulin or dexamethasone *in vivo* or of an antiglucagon antiserum decreased ketone formation in the mucosa of rats, whereas injection of antiinsulin antiserum increased mucosal ketogenesis (Hahn *et al.* 1991).

Formation of glucose from uniformly labelled ^{14}C-lactate was found to occur in the small intestinal mucosa of infant rats and rabbits, but not in adult animals (Hahn and Wei-Ning 1986). The rate of cholesterol *in vitro* synthesis from $^{3}H_2O$ in the small intestine decreased from birth to day 14 and then increased again by day 21 (Kroeger and Hahn 1983).

Ion transport

Pácha published a series of studies dealing with the development of colonic sodium transport in rats. They found that Na^+ transport in the rat distal colon is electrogenic and amiloride-sensitive during the early postnatal period (Pácha *et al.* 1987b). This transport is very high during the suckling period, decreasing around the time of weaning, and then disappearing after the 5th week of life. It is decreased by adrenalectomy and restored by aldosterone treatment (Pácha *et al.* 1988). The increased Na^+ absorption *via* a amiloride-sensitive pathway was demonstrated in other mammals (Pácha 1993a) and in chicks (Pácha 1993b).

It was found that the electrogenic amiloride-sensitive Na^+ absorption is accompanied by increased K^+ secretion (Pácha *et al.* 1987b). Potassium enters colonocytes through the basolateral membrane, together with Na^+ and Cl^-, through a furosemide-sensitive pathway. Sodium is recycled across the basolateral membrane through the Na^+,K^+-pump, and apical barium-sensitive K^+ channels, allowing K^+ extrusion into the lumen (Pácha *et al.* 1987a). The increased Na^+ absorption and K^+ secretion reflect the influence of mineralocorticoids (Pácha *et al.* 1987c, 1988). The mineralocorticoid selectivity of distal colon depends upon 11β-hydroxysteroid dehydrogenase; its activity is high in colonic epithelium of adult (Pácha and Mikšík 1994) and immature rats (Pácha *et al.* 1995). This enzyme converts physiologically active

glucocorticoids (corticosterone, cortisol) to their 11-keto analogs (11-dehydro-corticosterone, cortisone) which are biologically inactive. Studies indicate that very high Na^+ absorption and K^+ secretion during early postnatal life reflect an elevated pump turnover rate and increased affinity for Na^+ of a single isoform of the Na^+,K^+-ATPase, which is the biochemical equivalent of the Na^+-pump (Pácha *et al.* 1991). It is possible that the higher pump turnover rate is induced by corticosteroids. However, there was no demonstration as to what effect adrenalectomy has on Na^+K^+-ATPase activity (measured under V_{max} conditions) and maximum Na^+-pumping activity in the colon of weaning rats (Pácha *et al.* 1991) and chickens (Pácha 1993b). The presence of the amiloride-sensitive pathway in suckling and weaning rats (but not in adult rats) reflects a 10 times higher plasma aldosterone level in early postnatal life (Pácha *et al.* 1995). These high levels indicate that early life is the period of life when growing animals are threatened by relative Na^+ deficiency.

Proximodistal gradient

Several previously mentioned studies led to the exploration of changes in the development of the "specialization" of intestinal segments; in other words, of the establishment of a proximodistal gradient of other functions. In the human foetus the gradient of several enzyme activities was established after the third month of foetal life (Heringová *et al.* 1966, Pelichová *et al.* 1966, Jirsová *et al.* 1965a, 1968). Activities of lysosomal enzymes in suckling rats were found to be higher in the ileum than in the jejunum (Heringová *et al.* 1965, 1968, Koldovský and Chytil 1965, Koldovský and Herbst 1971, Koldovský *et al.* 1966a, 1972a, Jirsová *et al.* 1965b, Noack *et al.* 1965, 1966, Pelichová *et al.* 1967, Coates *et al.* 1977). Studies on colon development have shown that the proximal colon resembles the ileum during the early postnatal period (Litin and Koldovský 1982, Masnerová *et al.* 1966); expression of the proximodistal gradient of villus height present in suckling and adult rats was found to be programmed during the foetal period (Jolma *et al.* 1980).

Above mentioned experiments concerning the effects of hormones on the developing gastrointestinal tract were further extended. Adrenalectomy delayed the normal developmental decrease of activity of lysosomal enzymes (Koldovský *et al.* 1965a, 1975, Koldovský and Herbst 1971, 1973). Glucocorticoids caused an increase of luminal proteolysis (Britton and Koldovský 1988) and a precocious decrease in developmental activity of lysosomal hydrolases (Koldovský and Palmieri 1971, Koldovský and Herbst 1973); the decrease of the latter was also enhanced by thyroxine (Koldovský *et al.* 1974) and delayed by thyroidectomy (Koldovský *et al.* 1975). Developmental activity of several colonic enzymes were also found to be under the control of these hormones (Litin *et al.* 1983).

Finally, it is noteworthy that the rate of enterocyte migration is considerably slower in sucklings than in adult rats and increases during the weaning period (Koldovský *et al.* 1966b, Herbst and Koldovský 1972, Koldovský and Herbst 1973).

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