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Review

Development of gastrointestinal and pancreatic functions in mammals (mainly bovine and porcine species): influence of age and ingested food

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Abstract — This review summarizes recent advances in knowledge on the development of digestive tissues and their productions as well as mechanisms of regulation in response to age and ingested food in mammalian species (mainly bovine and porcine species). In the first two sections, changes are reported for stomach, pancreas and small intestine, and examined in relation to different situations (colostral, milk feeding and weaned periods). The implication of some regulatory substances (growth factors, gut regulatory peptides and neurohormonal substances) in regulation mechanisms is discussed over these periods. For example, the plasma pattern of several gut regulatory peptides and the expression of their specific receptors could explain certain phenomena of digestive development. Recent cellular and molecular aspects of regulation of the digestive enzyme production are also reported. Finally, an approach to interactions existing between age and ingested food is given in the last section. In conclusion, although some phenomena are well established, it is often difficult to distinguish what the age- and food-dependent events are in the development of the digestive function.
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age / food / gastrointestinal tract / pancreas / digestive enzyme / gut regulatory peptide / growth factor / dietary bioactive substance

Résumé — Développement des fonctions gastrointestinales et pancréatiques chez les mammifères (principalement chez les bovins et les porcins) : effets de l'âge et de l'aliment. Cet article de synthèse résume les nouvelles connaissances concernant l'influence de l'âge et de l'aliment sur le développement des tissus digestifs et de leurs productions ainsi que sur leurs régulations chez les mammifères (principalement chez les bovins et les porcins). Dans les deux premières parties, les modifications observées au niveau de l'estomac, du pancréas et de l'intestin grêle sont examinées dans différentes situations (périodes colostrale et d'allaitement, et après le sevrage). Pendant ces périodes, l'implication de substances régulatrices (telles que des facteurs de croissance, des peptides régulateurs digestifs, des substances neurohormonales) est décrite. Par exemple, les profils plasmatiques de plu-

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seurs peptides régulateurs digestifs et l'expression de leurs récepteurs spécifiques peuvent expliquer certains phénomènes observés au cours du développement. Les aspects moléculaires et cellulaires récents de la régulation de la production des enzymes digestives sont aussi rapportés. Dans la dernière partie, les interactions pouvant exister entre les effets de l'âge et de l'alimentation sont discutées. En conclusion, bien que certains phénomènes soient bien établis, il est souvent difficile de distinguer les effets respectifs de ces deux facteurs majeurs au cours du développement de la fonction digestive.
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âge / aliment / tractus gastrointestinal / pancréas / enzyme digestive / peptide régulateur digestif / facteur de croissance / substance alimentaire bioactive

1. INTRODUCTION

Fetal development is determined by the genome, the placenta and maternal factors. Important interactions exist between these three systems. The genetic program lays down the ontogenic specification of a tissue and the temporal sequence of events. However, it can be highly modulated by a complex interplay of intrinsic regulatory factors and extrinsic factors (nutrients, growth factors, polyamines, antinutritional factors, bacteria). Indeed, genetic factors are considered of great importance in early gestation, but in late gestation, fetal growth is also constrained by nutrition. During the first days or months after birth, marked adaptations of digestive organs and functions are required in young mammals. Luminal nutrition, which represents one of the most significant modulatory influences on the developing gastrointestinal (GI) tract and pancreas, depends on the nature of the ingested food (colostrum versus milk versus a diversity of solid food). It has been suggested that changes in the secretion of pancreatic juice in pigs at weaning are greatly influenced by nutrition [103, 105]. However, the genetic program can also be important, e.g. as a factor limiting the early weaning of pigs and calves.

This paper describes in review form the development of digestive tissues and digestive productions of stomach and small intestine mucosa and of pancreas as well as the changes in regulatory substances (growth

factors, gut regulatory peptides and neuro-hormonal substances) in response to age and ingested food in mammalian species (mainly bovine and porcine species). These aspects are discussed in relation to different situations (colostral, milk feeding and weaned periods) and are reported in the first two sections. An approach to interactions existing between age and ingested food is given in the last section. Understanding the digestive functions would help to optimize animal production since the GI tract and the pancreas play a fundamental role in the development and health of young animals.

2. EFFECT OF AGE ON DIGESTIVE PRODUCTIONS AND ENZYME EXPRESSIONS

The GI tract develops intensively in the perinatal period. Most of the structural elements appear in the prenatal period; however, their intensive growth occurs in the early postnatal period. The length, diameter and weight of GI organs increase in the first days of life. Interestingly, the stomach, small intestine and pancreas of pigs as well as the forestomach and small intestine (but not the abomasum and pancreas) of calves and sheep grow disproportionately faster than the rest of the body, with the most intensive growth present within the first 24 h after birth [34, 46, 133, 135, 140, 141]. The small intestinal mucosa layer possesses the highest growth-rate as compared to submu-

cosal or smooth muscle layers. Intensive growth in the neonatal GI tract mucosa is associated with an increased DNA synthesis and a decreased cell turnover [90]. The development of the small intestine's neonatal digestive function follows the so-called 'gut closure' period that is particularly important for passive immunization as well as for supplementation with other bioactive substances, such as hormones, regulatory peptides and growth factors, via the colostrum [63, 129, 130, 136, 144]. Before the gut is 'closed', large macromolecules may be absorbed [126]. The gut closure was suggested to be time-programmed; however, it also seems to be nutrient-related. Thus the period of the 'open gut' may be influenced by feeding, e.g. late feeding with colostrum or feeding with a modified colostrum [50, 127, 139]. The colostrum contains a number of bioactive substances which may also regulate 'gut closure'. Svendsen et al. [120] demonstrated that intestinal absorption of marker molecules is inhibited in insulin-treated neonatal piglets. After the first week of life, the rate of GI tract development slows down, and a second stage of intensive growth is observed during weaning, i.e. when the transition from milk or milk replacer to a solid food takes place. Nevertheless, some age-related developments have been observed at that time as discussed further below.

2.1. Stomach and small intestine

During the early postnatal period the stomach and small intestine epithelium grow very intensively [140, 141]. No GI mucosa growth is observed if the neonates are prevented from suckling or are fed only with water [133], thus suggesting that the first ingestion of colostrum plays a key role as a triggering mechanism. The total weight, mucosal weight and protein content, the length and surface area of the small intestine increase dramatically during the first hours of life. This rapid growth is mainly attributed to the increased protein concentration in

relation to a transient retention of colostrum molecules (i.e. immunoglobulins) and to an enhanced protein synthesis [96, 141].

In the abomasum of ovine fetus, the quantity of parietal cells is very low until birth and the intragastric pH is about 7.0. Three days after birth, the number of cells is 3-fold higher, leading to an intragastric pH of about 3.0 [53]. In pigs, the gastric mucosa is capable of secreting HCl and enzymes shortly before birth; the late fetal life is characterized by a marked decline in stomach pH, from pH 7 to 2–3 [110]. Just after birth, the capacity to secrete gastric acid increases about 5-fold during the first week postpartum followed by a slower increase up to weaning [137]. At birth, in calves and pigs, gastric tissues are at maximum chymosin content, the major milk-clotting protease produced by the gastric mucosa, whereas pepsin is present in trace amounts only in pigs. In calves, pepsin activity is 4.4-fold higher at birth than in a 37-week-old fetus [44, 110]. Agarose gel electrophoresis of gastric mucosa extracts from neonatal cats shows that the majority of changes appear during the neonatal period as compared to adults [109].

During the suckling period, the capacity to secrete gastric acid slowly increases up to weaning in pigs. In calves, it increases during the first month of life [108], and then the quantity of electrolytes secreted by calf abomasal pouches decreases [35, 44]. In gastric mucosa, chymosin and lysozyme activities decrease sharply during the first week of life and decrease at a lower rate afterwards. The activity of pepsin remains stable in calves, and it increases after the first week of life in pigs and the second or third week of life in cats [19, 24, 25, 38, 75, 109, 111]. In contrast, the quantities of gastric juice and enzymes (chymosin, pepsin) secreted per kg of body weight (BW) by the abomasal pouch tend to decrease with age [44]. The total estimated quantities of gastric juice secreted by the whole abomasum is about 60–100 g·kg⁻¹ BW in 1–1.5-month-

old and 20–45 g·kg⁻¹ BW in 3–5-month-old calves. However, even in 20-week-old calves, the amounts of enzymes produced daily are sufficient enough to rapidly coagulate 10–15 times the daily milk intake of intensively-fed preruminant calves [34].

Intestinal enzymes show distinct temporal and spatial expressions. In newborn pigs and calves, lactase activity is high and exhibits maximum expression in the proximal jejunum. In contrast, sucrase and maltase activities in pigs and calves are present in low or undetectable levels at birth [74, 85, 124]. In pigs, sucrase and maltase exhibit a mid-jejunum peak, whereas aminopeptidase N is expressed uniformly between the duodenum and the terminal ileum [60]. In calves, aminopeptidase A is fairly equally distributed along the small intestine, and aminopeptidase N is high in both the median and distal jejunum and the ileum. Alkaline phosphatase is mainly located in the proximal jejunum and to a lesser extent in the median jejunum and duodenum. The distributions of maltase and isomaltase are greatly influenced by age since at birth and at 2 d of age, they are fairly equally distributed and, thereafter, these two disaccharidases exhibit maximum activity in the distal segments of the small intestine [74]. In milk-fed calves, the activities of aminopeptidases A and N, alkaline phosphatase, lactase and isomaltase in the whole small intestine, expressed on a BW basis, are maximum at 2 d of age, and then decline sharply between days 2 and 7, but do not change significantly thereafter. In contrast, maltase activity increases during the milk period [74]. In pigs, similar changes are observed with age, i.e. the activities per kg BW of lactase, dipeptidase and aminopeptidase decrease and those of maltase and sucrase increase [1, 122].

2.2. Pancreas

The development of the pancreas starts in the prenatal period, and in general, the activity of pancreatic enzymes in tissue homoge-

nates increases with fetal age up to birth in calves and pigs [126, 131]. Pancreatic enzymes are detected in 2-month-old bovine fetuses. In fetal samples, amylase and chymotrypsin activities are very low, trypsin and phospholipase A2 show a gradual increase and lipase remains almost constant over the gestation period [126]. Therefore, in calves, most of the pancreatic enzymes are present at birth, except for amylase [30, 75], while in newborn pigs enzyme activities are relatively low, except for elastase II which exhibits a maximum activity [12, 29].

Following birth, in pigs and lambs, there is a positive allometry and an isometry of the pancreas, respectively, associated with age [46, 84]. Based on DNA and RNA measurements in pancreas, Corring et al. [12] ascribe the increase in pancreas weight before 4 weeks of age to a hyperplasia of pancreatic cells; subsequent increases involve both hyperplasia and hypertrophy. In lambs, the pancreas shows an extensive hyperplasia without growth until day 2; its weight increases thereafter owing to hypertrophy [37], as also observed in calves [30].

The secretion of pancreatic juice increases with age from the first day of life in calves with a minimum at day 2 [153]. During the colostrum period, daily volume of pancreatic juice secreted is below 2 mL·kg⁻¹ BW, and in 6-day- and 2-month-old calves it is 3–4- and 6-fold higher, respectively. The most prominent changes in the amount of secreted pancreatic juice, protein and trypsin output are observed when colostrum is replaced with milk formula and after weaning (our unpubl. data, [151]). However, it is important to mention that these changes also involve the kinetics of preprandial and postprandial pancreatic secretion in milk-fed calves, which is different in the morning and evening [71, 151]. In experiments with conscious or anaesthetized pigs, no age effect is observed between 1–2 and 4–5 weeks; daily basal secretion of pancreatic juice is about 5–14 mL·kg⁻¹ BW [49, 101].

In addition, following birth, there is a major change in the nature of the enzymes

present in pig pancreas with the gradual appearance of chymotrypsin C, cationic trypsin and protease E [103, 131]. According to these authors, elastase I does not appear until about 5 weeks of age in pigs, while Gestin et al. [29] detected the elastase I activity as early as birth. Trypsin undergoes some age-related modifications as observed by the reduction of anodal trypsin that is irrespective of weaning. Generally, in pigs and calves, the tissue activities of pancreatic enzymes (excluding elastase II and chymotrypsin in some studies) decrease during the first 2 days of life, i.e. during the colostrum period, and thereafter increase in variable amounts during the first month of life (*figure 1*). Increase in amylase activity is surprising since amylase shows a significant increase in sucklings which ingest no or very little starch [12, 75, 103]. Similar conclusions are drawn for amylase studies in cat pancreas. Moreover, in cats, the pancreatic proteolytic activity does not change with age [109].

In preruminant calf, during postnatal development, the lack of parallel variations in the levels of mRNAs specific for pancreatic enzymes suggests that the protein synthesis of each enzyme is specifically regulated [73] (*figure 1*). The levels of mRNA specific for amylase, lipase and trypsin increase 10-, 8- and 5-fold, respectively, between 0 and 17 weeks of age, while those of chymotrypsin decrease by 44 % during the first month of life. These changes probably resulted from the transcriptional control of gene expression, but variations in mRNA stability can not be excluded. Moreover, translational regulation could explain the existence of enzyme levels non-proportionally related to mRNA profiles. In the calf and pig, elastolytic activities evolve similarly with age. Elastase II activity peaks at birth before decreasing sharply during the postnatal development phase. Conversely, elastase I, similarly high at birth, does not vary subsequently. In both species, a quantification of mRNA rates reveals a mechanism of regulation of biosynthesis at pre-

translational and translational levels for elastase I and essentially at translational levels for elastase II. In pigs, the elastase II activity is higher than in calves while the number of corresponding mRNA copies is similar in both species. Thus, it would appear that the efficiency of translation differed according to species [30].

2.3. Regulation of digestive productions with age

The growth of the gastrointestinal mucosa and pancreas tissue is regulated by a milieu of hormones, regulatory peptides and growth factors (insulin growth factor-I (IGF-I), epidermal growth factor (EGF), transforming growth factor- α (TGF- α), etc.), and the development of neuro-hormonal regulations seems to be in relation to the development of the GI tract [32, 56, 61, 94, 138]. Mammals secrete some of these substances in their milk in a species-specific manner, and the concentration in colostrum is several times higher than in mature milk. For example, the concentration of IGF-I in porcine colostrum is 10 to 20 times higher than in milk [117]. Growth factors and gut regulatory peptides are remarkably stable in the gastrointestinal lumen of suckling neonates and the stability decreases after weaning [114, 143]. These factors can act locally on the GI mucosa and can be partially absorbed by the pathway independently of gut closure, as has been demonstrated for IGF-I in neonatal pigs [139, 142]. Moreover, growth factors are synthesized in tissues of neonates, including the GI tissue, and the relevance of endogenous synthesis increases in the postnatal period. Experiments showed that either parenterally or orally administered growth factors induce neonatal intestinal and pancreas tissue growth. For example, TGF- α and EGF administered parenterally similarly increase proliferation of gastric, duodenal and colonic mucosa; TGF- α is more active on pancreatic tissue, whereas EGF is more active on jejunal cell proliferation in suckling rats [56, 119]. Grasslander et al. [32]

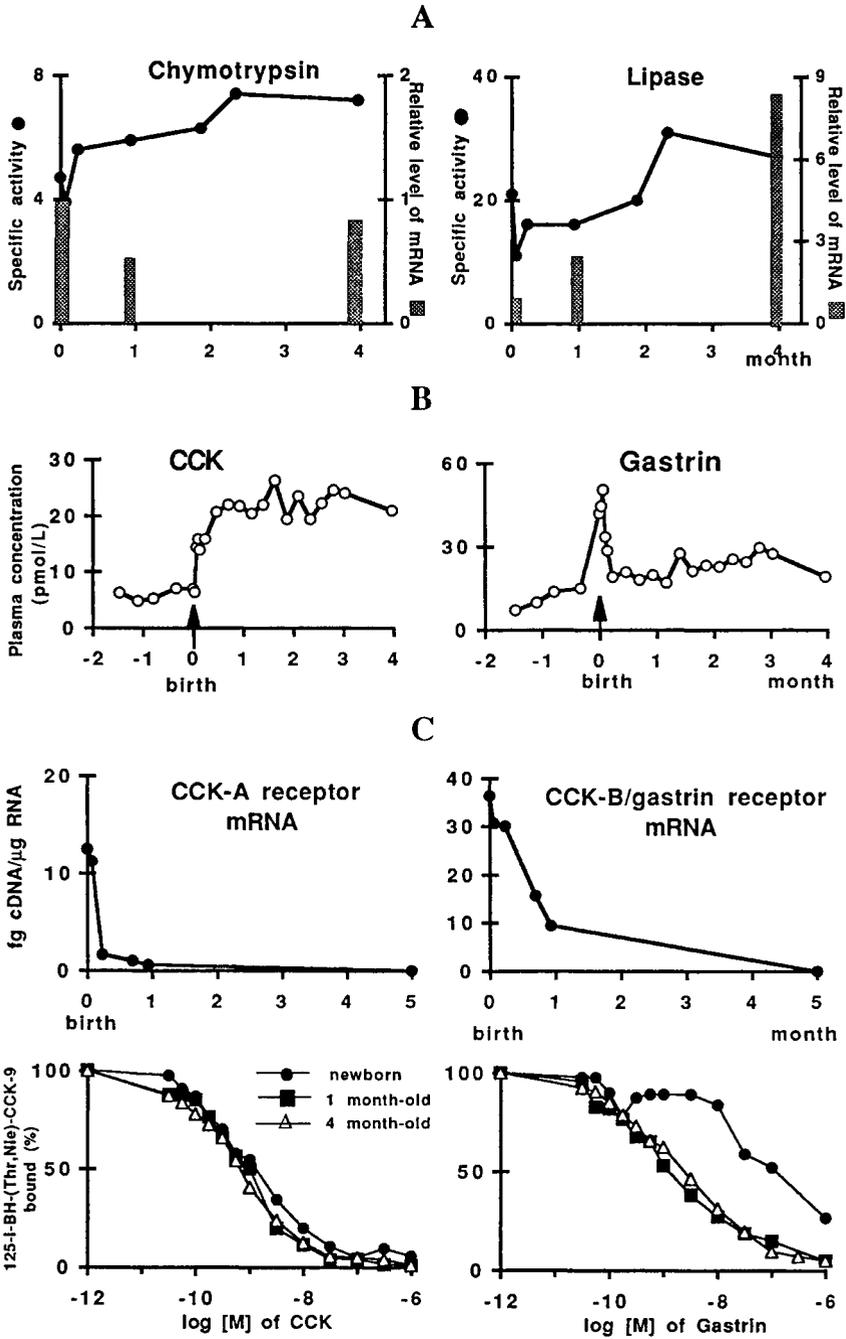


Figure 1. Pancreatic enzyme activities and mRNA (A), plasma gut regulatory peptide concentrations (B) and pancreatic CCK-A and CCK-B/gastrin mRNA and binding (C) during fetal and postnatal development in calves [20, 41, 42, 45, 73, 75, 78, 125].

showed in rats that EGF is selectively extracted from the plasma by the duodenal mucosa and pancreas tissues. IGF-I added to artificial formula increases intestinal mucosal growth (mucosa protein and DNA content, villus height) in neonatal pigs although without elevation of IGF-I concentration in the circulating blood plasma [10]. These findings are strongly supported by the work of Morgan et al. [91] who showed a specific binding of IGF-I in the jejunum (mucosa and muscularis propria) of newborn, suckled and weaned piglets using *in vitro* autoradiography. Receptors within the epithelium are localized by immunohistochemistry both in crypts and villi. Interestingly, the distribution of IGF-I receptors is bilateral, on apical and basolateral membranes in the jejunal epithelium of piglets, supporting the hypothesis of a luminal action by IGF-I. However, the density of IGF-I receptors has been shown to decrease during postnatal development and this pattern mainly concerns the apical (microvillar) membranes [91]. Growth hormone is not required for normal postnatal maturation of the small intestine, although it acts by promoting homeostasis or steady-state regulation of mucosal epithelial growth [21]. Somatostatin and luteinizing releasing hormone (Lh-RH) inhibit the proliferation of gastric epithelium cells in rats [27].

In bovine fetuses, some gut regulatory peptides are synthesized and secreted as early as the third month of gestation (*figure 1*). Moreover, plasma levels of gut regulatory peptides seem to be independent of maternal levels and are high at the end of gestation [45, 106]. Therefore, the ontogenesis of GI and pancreatic endocrine cells (gastrin, cholecystokinin (CCK), pancreatic polypeptide (PP), somatostatin) in porcine fetuses [57] and the high concentrations of gut regulatory peptides during gestational age in bovine fetuses [45] suggest that these peptides participate to some extent in the regulation of the growth and morphogenesis of the digestive system of endodermal origin.

Somatostatin infusions in fetal lambs depress levels of plasma gastrin and PP, thereby possibly leading to a decreased gut mucosa development [115]. Gastrin probably enhances the growth of the digestive tract as well as the enzyme content of the gastric mucosa. Positive correlations in calves after birth are observed between plasma PP levels and digestive organ development [75]. Since PP is considered to reflect the vagal input [112], it may also reflect a pro-trophic effect of vagal nerves on digestive tract tissue. Such a role for pancreatic development in lambs and calves has already been suggested and related to the maturation of vagal nerve function by Shulkes and Hardy [116] and Reddy and Elliot [106].

In the newborn calf, high concentrations of plasma CCK, gastrin and secretin parallel the storage of digestive enzymes in the pancreas at birth (*figure 1*). High concentrations of these peptides as well as of vasoactive intestinal polypeptide (VIP) observed after the first colostrum meal could result in the decrease of enzymatic content of the pancreas during the 24 h postnatal period [35, 37, 38, 42, 75] by stimulating the secretion of enzymes stored during the end of the fetal period. However, according to our recent studies on neonatal conscious calves during the first week and to those of Pierzynowski et al. [100] during the first 2 weeks in piglets, intravenous infusion of CCK does not seem to affect pancreatic secretion. In contrast, intraduodenal administration of CCK-A receptor antagonist reduces pancreatic secretion suggesting the involvement of some mucosal duodenal mechanism for pancreatic secretion (*figure 2*), and alters intestinal mucosa morphology [5, 150, 153]. During the first postnatal week, a rapid decrease in gastrin concentration could favor chymosin reduction and a steady-state in pepsin and HCl secretion since gastrin stimulates pepsin and acid secretion [35, 128]. The growth of the pancreas in young calf and sheep and the increase of enzymatic activities [36–38, 75,

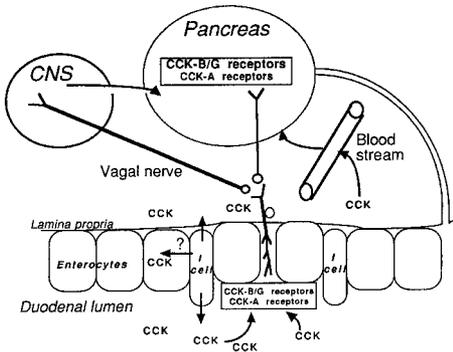


Figure 2. Hypothesis on the different mechanisms of action of CCK.

123] are parallel to the increase of CCK (*figure 1*) and secretin levels and to the decrease of somatostatin levels [125].

After birth, the regulatory peptides can act on the synthesis and release of secretions because their receptors are present and functional in digestive glands. We have recently determined the levels of CCK-A and CCK-B/gastrin receptor mRNAs in several tissues during postnatal development in calves [20]. In the calf fundus, the levels of CCK-B/gastrin receptor mRNA are 10-fold higher than those detected in the antrum, while the CCK-A receptor mRNA is expressed at very low levels in gastric tissues. CCK-A receptors are expressed on chief cells producing pepsin and on D cells producing somatostatin. Somatostatin released from these cells is thought to mediate CCK-induced acid secretion inhibition. CCK-B/gastrin receptors expressed on parietal cells and on enterochromaffin-like (ECL) cells producing histamine mediate gastrin-stimulated acid secretion [128]. In the calf, the enhancement of the parietal cell number and of the CCK-B/gastrin receptor transcript in fundus could explain the rise in gastric acid secretion between 7 and 31 d of age. In addition, the high levels of plasma gastrin and of CCK-B/gastrin receptor mRNAs in newborn calves support the role of gastrin as a growth factor for the stomach

throughout the gastric CCK-B/gastrin receptor. VIP-secretin family receptors [77] and CCK-gastrin family receptors have also been detected in calf and pig pancreas [71, 78, 92, 99]. Furthermore, a pharmacological analysis using selective agonists and antagonists shows expression of the CCK-A receptor (great affinity for CCK) at birth whereas the CCK-B/gastrin receptor (similar affinity for CCK and gastrin) predominates at the postnatal stage, which shows the existence of a differential expression of CCK-A and CCK-B/gastrin receptors in the developing calf pancreas (*figure 1*). These results suggest that CCK and gastrin may play a predominant role during postnatal development in regulating proliferation and exocrine secretion in the calf pancreas. This is partly in agreement with the recent results of Lhoste et al. [82] in growing pigs. As discussed above, studies with CCK-A and CCK-B/gastrin receptor antagonists provide more critical information on the relevance of CCK and gastrin as trophic factors for the pancreas tissue. However, the trophic role of CCK and gastrin seems to be species-specific. In the guinea pig, the CCK-A receptor antagonist has no effect either on the pancreas tissue development or on the secretion of juice [51]. In the rat, CCK is an important trophic stimulus for the pancreas but gastrin is not [2, 11, 121]. However, the increase of pancreas weight during the first month of life when CCK-B/gastrin transcript and its corresponding receptor protein are predominantly expressed, supports the idea that gastrin could be involved in the control of pancreatic growth in calves.

Recently, a new indirect mechanism of CCK action on pancreatic juice secretion has been postulated in preruminant calves [146, 148] as well as in pigs and rats [64, 83, 145] (*figure 2*). In preruminant calves, infusions of CCK-8 into the duodenal lumen and duodenal arteries markedly increase the secretion of pancreatic juice (similar results are obtained with intra-arterial infusions of secretin and VIP). The effects are blocked by both atropine and cold vagal blockade sug-

gesting the involvement of neural pathways in this mechanism. This local indirect mechanism may be physiologically relevant since significant amounts of CCK are found in the duodenal lumen in calves. Furthermore, the amount of luminal CCK increased during electrical stimulation of the vagus [147, 149]. The presence of CCK receptors in the small intestinal mucosa has been reported in rats and ferrets [6, 88]. Moreover, the stability of gastrin in the GI lumen and its protection by colostrum from luminal hydrolysis in the small intestine [143] suggest a potential physiological role for luminally released gastrin as well as the other luminally released gut regulatory peptides in suckling animals.

3. EFFECT OF INGESTED FOOD ON DIGESTIVE PRODUCTIONS AND ENZYME EXPRESSIONS

3.1. Stomach and small intestine

In preruminant calves, the substitution of fish protein (which does not coagulate in the abomasum) for milk protein (which coagulates in the abomasum) substantially modifies digestion and absorption (gastric evacuation, transit time, motility, secretion of gut regulatory peptides). The gastric secretion is, however, barely affected. In animals fitted with an innervated pouch, the daily quantity (expressed in kg BW) of electrolytes (Cl^- , H^+ , Na^+ and K^+) and enzymes (chymosin and pepsin) secreted are generally not affected. It is modified only for H^+ which decreases with fish protein or meals with low or high level of dietary protein [34, 43]. These results confirm those obtained by Guilloteau et al. [40] with soya protein, but do not agree with those of Williams et al. [134] and Garnot et al. [28] who found a decrease of chymosin and pepsin secretion following the replacement of skim milk powder protein by soya or fish protein. These differences in results could be due to the animal model used (abomasal pouch versus abomasal and duodenal cannulas)

and/or to the technology used for preparing protein concentrates. Overall, in pigs, there is no effect of diet (sow or cow milk, soybean diet, etc.) on the gastric mucosa weight and protease activities or on the postprandial pH of gastric content [84, 93]. Nevertheless, it seems that the increase in proteolytic activity in relation to age is more pronounced in artificially reared pigs [19].

Weaning induces a sharp increase in gastric pepsin and lysozyme activities but a decrease in chymosin activity, which does not disappear in ruminant animals [24, 39, 75]. In calves, daily quantities of juice, pepsin and electrolytes largely increase; however, those of chymosin decrease [34, 44]. These results concerning abomasal enzymes agree with those of Hill et al. [54], Garnot et al. [28] and Guilloteau et al. [37], using another methodological approach. Moreover, creep-fed pigs have higher stomach weight expressed per kg BW and greater secretory capacity for both gastric acid and pepsin [15]. In cat gastric mucosa extracts, no obvious food-related changes are observed in the activity of proteolytic enzymes [109].

Little is known on the influence of diet composition on intestinal enzyme activities. Nutritional adaptation of enzymes to the quantity of substrates present in the diet is more or less obvious. Thus, in calves and pigs, lactase activity is stimulated when lactose-rich diets are offered to the animals [22, 44]; while in rats, a lactase activity fall occurs to a smaller extent, even if feeding of lactose is maintained [79]. Maltase and sucrase activities change when a diet rich in starch is offered instead of a high oil-rich diet [23]. In contrast, no specific modification of intestinal peptidase activities is observed in weaned pigs when different levels of casein or different sources of protein (wheat and soya versus milk) are introduced in the diet [97].

The distribution of enzymes along the small intestine is not at all influenced by weaning. In most species, weaning results in

a decrease in lactase activity parallel to a decline in lactase mRNA, suggesting that, similarly to pancreatic enzymes, developmental regulation of this enzyme in sheep is mediated primarily at the mRNA level [67]. The increases in sucrase, maltase and glycoamylase activities in pigs and maltase, isomaltase and aminopeptidase N activities in calves observed rapidly after weaning could result from stimulation by dietary substrates. However, in pigs, the abrupt change from a predominantly sow milk diet to a weaning diet high in complex carbohydrate and protein induces striking alterations in intestinal productions consisting of a transient depression in the immediate post-weaning days. For example, sucrase activity is sharply decreased during the first 5 post-weaning days [62]. On the other hand, in calves, weaning has short-lasting effects on the intestinal enzymatic activities.

Polyamines, spermidine and spermine, are important factors regulating functional and structural maturation of the upper gut. In suckling rats, dietary polyamines directly induce cell maturation of the small intestinal mucosa. In addition, the effects of spermine may involve corticosterone and the adrenocortico-trophic hormone (ACTH) [58]. Short-lasting spermidine administration (8 h) transiently reduces intestinal DNA and protein content as well as lactase specific activity and increases cell desquamation on the top of the villi. However, the gut atrophy is recovered 24 to 48 h later, and the mucosa appears more mature as evidenced by a dramatic increase in maltase and sucrase specific activity [58]. Moreover, within the weaned food components, there are numerous bioactive substances that enhance the exocrine pancreas and gastrointestinal mucosa's growth and function. Much research has been recently directed toward the substances present in seeds (soybean, kidney bean, cowpea). Soybean contains moderate lectin and high Kunitz and Bowman-Birk trypsin inhibitor levels, whereas kidney bean contains high lectin, low Bowman-Birk and no Kunitz trypsin inhibitors.

Lectins and Kunitz trypsin inhibitor survive the passage through the stomach and small intestine in rats, whereas the Bowman-Birk trypsin inhibitor shows a low rate of survival [48]. Long-lasting feeding of young rats with a kidney bean lectin, phytohemagglutinin (PHA), induced polyamine dependent, hyperplastic and hypertrophic growth of the small intestine [4, 95, 104]. As a consequence, animals lose weight continuously and the energy of the diet is used to maintain gut growth. However, only a 3-d application of PHA is necessary to double the growth of juvenile rat intestinal mucosa [3, 4].

3.2. Pancreas

The effects of diet composition on pancreatic enzymes are rather unclear. For instance, in calves and pigs, milk protein was found to stimulate or to decrease tissular enzyme activity compared to plant protein [29, 40]. In calves, the outflows of pancreatic fluid, protein and trypsin during 5 h postfeeding were 40 % lower, unchanged and 82 % higher, respectively, when soybean protein was fed as compared to milk protein [72]. It is clearly established that the adaptation of the pancreatic function is specific to each enzyme. The level of regulation was also studied with protein substitutes. For instance, amylase-specific activity increased with pea diets but showed opposite tendencies with soybean products [70]. Proteolytic enzyme activities in pancreas are slightly influenced by dietary protein source [70] but this is not as obvious as in the reviewed literature; technological treatments applied to these dietary proteins would be of greater importance [70]. Specific messenger RNAs corresponding to amylase, trypsin and chymotrypsin seem to increase with soybean diets. However, further investigations are required before any conclusions may be drawn concerning regulation levels of pancreatic adaptation to dietary protein. Furthermore, the modification of the quantity of dietary substrates ingested results in

significant modifications in outputs and specific activities of pancreatic enzymes. Thus, in pigs, pancreatic lipase increases before weaning; however, there is no age effect since sow milk is rich in lipids and lipid content increases within the first 3–4 weeks of lactation [65]. In weaned pigs, pancreatic amylase and proteases also undergo large increases with increasing starch and protein intake, respectively [16, 80].

The mechanisms of pancreas development modulation at weaning probably involve several factors including the stage of development, feed intake and the source of dietary nutrients. As with intestinal enzymes, during the first post-weaning days pancreatic enzymes present in the tissue are markedly reduced in pigs. Thus, 3 to 7 d after weaning, pancreatic enzymes are 30–75 % depressed [16]. However, activities are recovered 2 weeks after weaning. In contrast, Rantzer et al. [105] indicate a 2.6- to 7.4-fold gradual increase in volume, protein and trypsin levels during the first 5 d after weaning in relation to the progressive increasing consumption of solid feed. These changes are maintained or increase 2 weeks after weaning [103]. The composition of pancreatic juice is also modified as indicated by variations in some enzyme/protein ratios. While elastase II and chymotrypsin are probably the predominant pancreatic proteases during the neonatal period, elastase I, trypsin and amylase are probably more specifically expressed after weaning [29]. Studies on pigs showed that changes in cathodal trypsin and chymotrypsin are apparently related to the weaning time, thus the change of diet from milk to solid food could contribute to the differences [12, 103]. In calves, weaning induces a large increase in all pancreatic enzyme activities (*figure 3*). Thus, at 4 months of age, tissular chymotrypsin, carboxypeptidase A, amylase and lipase activities are 1.6- to 4-fold higher in weaned calves than in milk-fed calves. The daily pancreatic secretion, as well as the prefeeding and post-feeding secretions, of fluid, protein and trypsin are also increased by 20–240 % in

weaned calves [71]. Larger digestive contents, more regular flow of digesta into the duodenum with lower pH, and different end products may be responsible for the enhancement of enzyme expression. In sharp contrast to the multiple control of protein synthesis during postnatal development in preruminant calves, weaning was found to induce increases in specific activity and in mRNA levels for amylase, lipase, trypsin, chymotrypsin and elastase I, suggesting that pretranslational modulation of gene expression was mainly, if not exclusively, concerned [30, 73] (*figure 3*).

Recent experiments in weaned pigs revealed that the amount of pancreatic juice trypsin secreted into the duodenum is negatively correlated with the feed conversion ratio (FCR), i.e. the greater the secreted trypsin activity, the lower the obtained FCR value (Pierzynowski and Botermans, pers. comm.). In a similar manner, recent experiments on milk-fed calves showed that pancreatic insufficiency correlates with an increase of FCR and a decrease of digestibility. Supplementation with pancreatic juice normalized the digestibility. Moreover, in normal preruminant calves, the supplementation with pancreatic juice tended to increase the digestibility of soya protein (Guilloteau and Le Huërou-Luron, unpubl. data). These results do not agree with the common belief that the exocrine pancreas produces excess juice, at least in growing animals. This may only be true in adult animals in which removing 80 % of the pancreas does not lead to apparent digestive dysfunction. In human patients suffering from chronic pancreatitis, malabsorption does not usually develop until the inflammatory process destroys 90–95 % of the secretory tissues [68].

3.3. Regulation of digestive productions in relation to ingested food

In the newborn calf, the ingestion of four colostrum meals during the first 22 h after

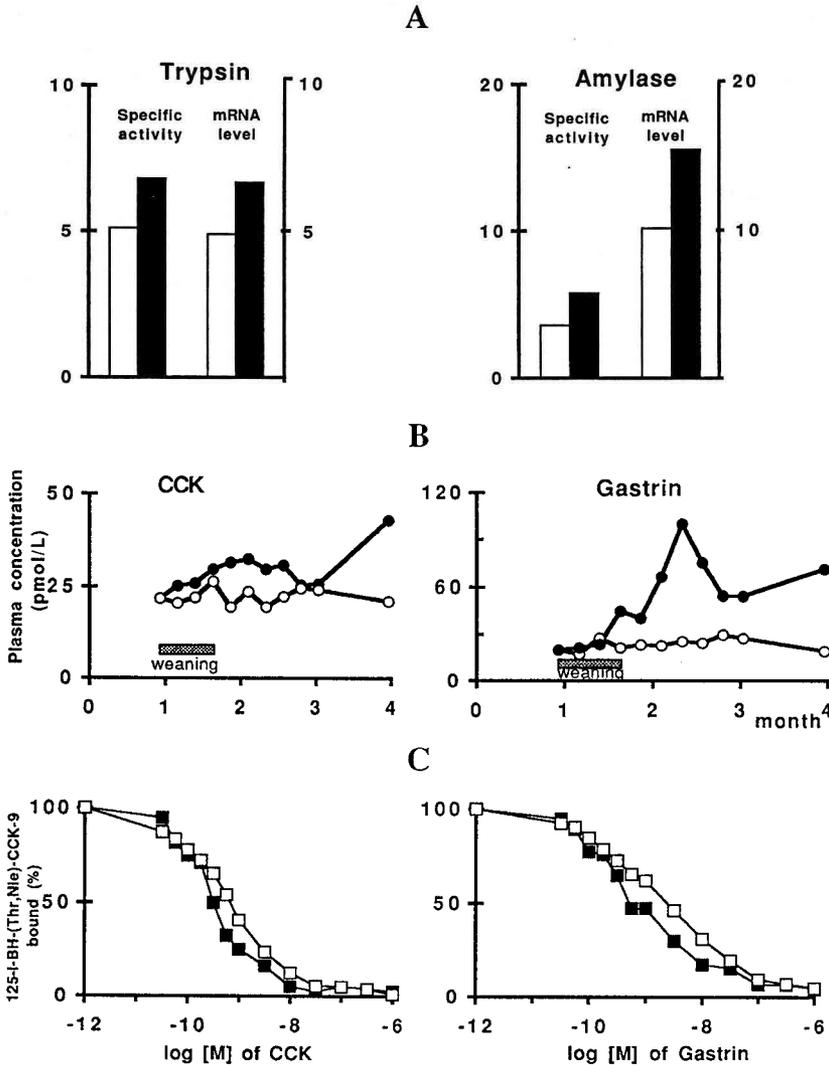


Figure 3. Pancreatic enzyme activities and mRNA (A), plasma gut regulatory peptide concentrations (B) and pancreatic CCK-A and CCK-B/gastrin binding (C) in milk-fed (white symbols) and weaned (black symbols) calves [42, 73, 75, 78, 125].

birth causes a marked rise in plasma concentrations of gastrin, CCK, secretin, VIP and PP and, after the first colostrum meal, of GIP as well as a decrease in motilin and somatostatin levels [41]. If the first colostrum meal is replaced by purified immunoglobulins dissolved in saline then

the responses of plasma gastrin, CCK, secretin, somatostatin and GIP are reduced, while those of VIP, PP and motilin are not significantly affected (Guilloteau et al. unpubl. data). The increase in GIP could be related to fats contained in colostrum since Martin et al. [86] showed that the con-

sumption of whole milk or an emulsion of milk fat but not a solution of lactose or glucose alone or an emulsion of casein plus lactose, stimulated GIP secretion in prerinant goat kids. In the same manner, gastrin and GIP increase in 1-d-old calves in response to colostrum feeding, but not when calves are only fed water or glucose [47]. The increased circulating amounts of gastrin and CCK could have a favorable effect on gastrointestinal growth (marked hyperplasia of the pancreas observed in lambs) and on digestive functions (decrease in the enzyme content in the pancreas during the first 24 h of extrauterine life) [37, 38, 75].

In milk-fed calves, parallel patterns of juice flow and secretin, as well as protein and trypsin concentrations, CCK and gastrin have been found [71]. The role of these peptides in the regulation of pancreatic secretions is in agreement with the results of Mineo et al. [87] for secretin and of Pierzy-

nowski et al. [101] and Le Dréan [69] for CCK and gastrin after IV infusion of peptides in chronically cannulated sheep and calves. The replacement of casein by protein substitutes (hydrolysed fish, whey protein concentrate, soybean protein concentrate) does not greatly modify the patterns of peripheral plasma gut regulatory peptide responses to feeding in comparison with a milk diet [72, 76]. However, in prerinant calves and in pigs, pre-feeding and/or post-feeding plasma levels of many peptides were highly affected [14, 40]. It seems that the most important characteristic influencing plasma gut peptide concentrations is the ability of dietary protein to clot in the abomasum (consequently determining the pattern of gastric emptying), the composition and the origin of diets and the pH of duodenal contents (*figure 4*). Thus, in pigs, carbohydrates and fats are a strong stimulus for gastric inhibitory polypeptide (GIP) and (GLP 1-36) amide [66] and for CCK [18], as

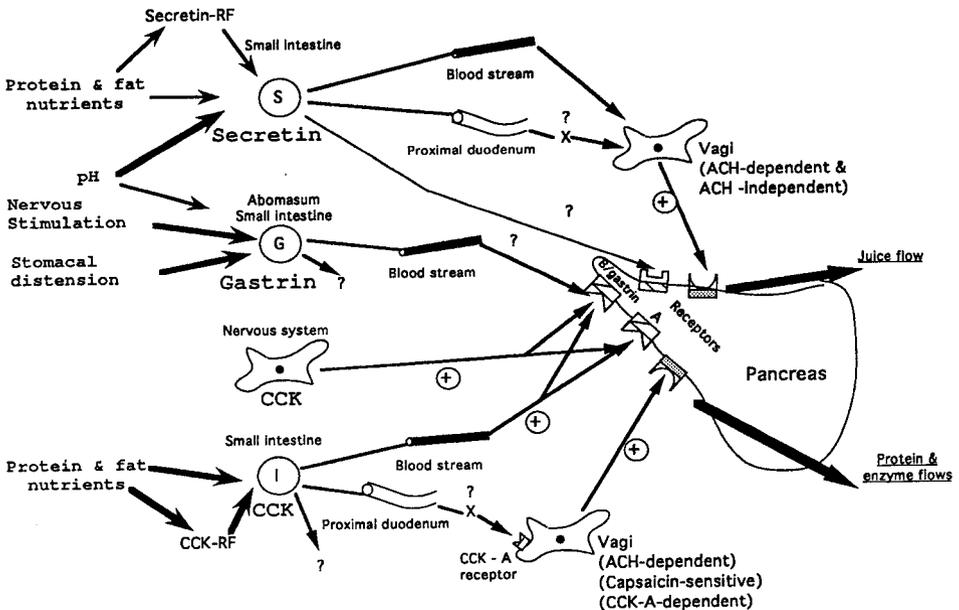


Figure 4. A scheme of the postprandial regulation of the pancreatic secretion in milk-fed calves (synthesis of the recent results [75, 76, 142, 143]).

well as for the amounts of protein (α amino nitrogen) absorbed for gastrin, glucagon, insulin and PP [107]. Moreover, a modification of the vagally dependent cephalic phase of pancreatic secretion with a soybean diet is noteworthy and is described in preruminant calves [71, 102]. The higher pancreatic prandial protein and especially trypsin concentrations and trypsin outflows with a soybean diet as compared with a milk diet could be related to the higher basal levels of CCK and gastrin which have been shown to stimulate pancreatic juice outflow in preruminant calves [69, 146]. Similar explanations could be given for fish proteins [152]. As observed with trypsin inhibitors in rats [33], undigested soybean protein may form a complex with duodenal trypsin that could stimulate CCK release by activation of a trypsin-sensitive CCK-releasing factor.

In calves progressively weaned between 28 and 56 d of age and in weaned pigs, concentrations of gastrin, CCK and PP are higher, while those of secretin and somatostatin are lower than in milk-fed animals [9, 17, 42, 101] (*figure 3*). Increased gastrointestinal emptying before feeding and greater distension of the stomach in milk-fed compared to weaned animals could be responsible for the differences observed. Changes of basal gastrin, CCK and somatostatin concentrations induced by weaning and especially after weaning completion, as well as the expression of CCK-A and CCK-B/gastrin receptors [78, 89], are expected to favor the development of the forestomach, abomasal mucosa and pancreas and to increase the secretion of acid and of some gastric and pancreatic enzymes [17, 44, 75] (*figure 3*). Thus, G cells, which produce gastrin, may be more responsive to solid than liquid feed [55]. Higher concentrations of PP possibly reflect a prolonged stimulation of the parasympathetic system [7] which could also have a trophic effect on the pancreas [115].

In contrast to results obtained in milk-fed calves, feeding has no effect on the

plasma concentration of regulatory peptides in weaned calves (except for GIP whose plasma concentration increased), as well as in adult cattle [26, 71, 98, 118], in agreement with the pattern of pancreatic secretion which is not affected by feeding [71, 101, 151]. The lack of post-feeding changes could be explained by the more regular abomasal distension and digesta flow rate as well as by the stability of the duodenal content pH which is about 2.75.

The biological effects of lectins and trypsin inhibitors, also called 'antinutritional factors', on the gastrointestinal tract are presently being re-evaluated [132]. When used in small doses and for a short period of time, several beneficial effects are reported. Grant et al. [31] demonstrate that lectins and trypsin inhibitors stimulate the growth of the exocrine pancreas in young rats, although by using different mechanisms since the effect of lectins is diminished after several weeks and that of trypsin inhibitors is long-lasting. Lectins are shown to stimulate the release of CCK from the intestinal neuroendocrine cells, thereby inducing pancreatic growth in rat [52]. Intestinal growth is stimulated by a mechanism independent of CCK in their study. Lectins do not stimulate the tissue or the plasma concentrations of gastrin, enteroglucagon, glucagon and peptide YY (PYY) [3]. It is therefore possible that by adjusting the doses of dietary 'antinutritional factors' beneficial effects alone will be preserved, leading to a controlled maturation of the gastrointestinal and pancreas function in young animals. This approach may be of interest in nutritional manipulations in piglets, whereas in calves the antigenic properties of seeds should be taken into account.

A microbial ecosystem interference with the development of the gastrointestinal function is still not clear. Microbial flora begins to colonize the gastrointestinal tract at birth and the process is maintained in balance throughout the life-time. Bry et al. [8] demonstrated that normal intestinal microflora reg-

ulates the production of fucosylated glycoconjugates (mediators of pathogen attachment to the epithelial surface) in the small intestinal epithelium of the host. This process in mouse neonates is very intensive and interferes with crypt cell proliferation in small intestine. Sharma and Schumacher [113] in their study of normal and germ-free rats demonstrate that the number of endocrine cells in the intestine is related to dietary composition, the presence or absence of microflora as well as to the interactions between diet and microflora in the intestinal lumen. In theory, the germ-free animal has characteristics which should permit better utilization of the ingested diet (cecal hypertrophy, slower small intestinal cell renewal, slower gastric emptying and intestinal transit). Data on digestive enzymes do not currently provide a complete picture of their digestive enzyme equipment. Indeed, information on intestinal enzymes is scarce and we have no data on gastric proteolytic enzymes. In general, data on exocrine pancreatic enzymes show that the digestive equipment is similar in germ-free and conventional animals such as the mouse, rat, chicken and rabbit. But a recent study indicates that the protein content of the pancreas and the chymotrypsin activity are higher in germ-free than in conventional rats; however, the weight, DNA content and other digestive enzyme activities of the pancreas are not modified [13, 81]. Moreover, this issue is usually overlooked in most gastrointestinal studies.

4. CONCLUSION: AGE-FOOD RELATIONSHIPS IN DIGESTIVE SECRETIONS

What is the physiological implication for a low capacity of GI secretion and digestive processes just after birth? The neonate, although having little digestive capacity can grow intensively during the first few days of life. This is due to the fact that colostrum and milk provide structural and fuel sub-

strates in a form which is ideally adjusted to the digestive capabilities of the neonate. Low digestive capacity during early postnatal life is then beneficial for the neonate. Colostrum and milk contain a large number of substances that must reach the GI tract or the peripheral tissues after absorption in an intact form (i.e. immunoglobulins, hormones, regulatory peptides, growth factors, milk mucins, other bioactive proteins and peptides, nucleic acids and polyamines) [58, 59, 61, 110, 136, 144]. This postnatal regulatory information addressed by the mother to offspring would not survive high secretion of gastric HCl and gastric and pancreatic proteolytic enzymes; however, there are certain mechanisms protecting the bioactive compounds in colostrum and milk [135]. Therefore, from a physiological stand-point, we should be more critical of early milk deprivation of neonates in animal production. Manipulation of 'gut closure' in order to regulate the closure of gut permeability to macromolecules is a very promising tool. But our knowledge on the consequences is scanty especially concerning later effects, i.e. in adult animals.

As discussed above, it is difficult to precisely distinguish what the age- and food-dependent events are in the development of the digestive function. If we compare the digestive function in the piglet and the calf, we may conclude that in intensive pig and dairy calf productions, the digestive productions follow an ontogenic pattern which is modified by ingested food. The inherited program, if carried out for a prolonged period of time can limit or slow down the rate of animal development (e.g. in the late suckling period). Moreover, it provides a harmony between the development of the GI tract and other organs. Early transition, e.g. from colostrum to artificial formula or from milk/milk replacer to solid food, may lead to serious disorders in the GI tract. At present, the main problem is to find out how to accelerate growth and maturation of the GI tract epithelium and pancreas tissue in order to obtain an optimum digestive secre-

tion without producing dangerous shifts in GI homeostasis. For example, the addition of a creep feed in suckling piglets reduced the weaning problems in some experiments, although piglets show little interest in creep feed at the age of 2–4 weeks of life. Another approach would be to supplement the young with growth factors or hormones (i.e. EGF, IGF and insulin, since artificial milk formulas do not contain them) or to stimulate their endogenous production by nutritional manipulation. It should be considered that weaning in calves actually starts some days after birth, since artificial milk formulas, although they provide the suckling with nutrients, fail to provide the bioactive substances present in colostrum and fresh milk.

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