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Bioactive peptides in young animal nutrition

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ABSTRACT

Maternal milk contains a number of bioactive peptides and proteins important for the development of the gastrointestinal tract. This article briefly reviews information on milk insulin, insulin-like growth factors, and epidermal growth factor. Since recently leptin has been found in maternal milk, a more detailed overview of leptin's effects on gastrointestinal tract function is presented. The physiological importance of milk leptin needs, however, further investigation. In contrast to milk, artificial milk formulas contain markedly lower amounts of bioactive peptides.

KEY WORDS: EGF, IGF, insulin, leptin, colostrum, milk, newborn

INTRODUCTION

In modern animal production, increasing interest is being paid to animal physiology, but economics (a farmer's or company's profit) are usually a far more important matter. The domination of economy over the physiological needs of production animals can be observed from the first hours after birth. From the economic point of view, a shorter suckling period and feeding with either milk replacers or solid feed is better. In this case, economics means less human labour and more offspring delivered per year. From the economical point of view, it is also better to replace milk protein in the milk formula with other (read: cheaper) protein sources. Animal studies have shown, however, that the kind of feed (milk, milk replacer and weaned feed), its composition in regard to the presence of bioactive milk substances, and the mode of feeding (suckling vs bottle feeding) have a great impact on the development of the gastrointestinal tract, in particular on maturation of small intestinal mucosa, and overall animal performance. In many studies the importance of

colostrum and milk bioactive peptides and proteins for sucklings have been emphasized. However, these natural substances are readily inactivated by milk processing, for instance the concentrations of insulin, leptin, EGF and IGF-1 in infant formulas based on bovine milk are low or undetectable (Read et al., 1985; Nagashima et al., 1990; Smith-Kirwin et al., 1998). The examined porcine milk formula contained only 4% of insulin and 1% of IGF as compared with sow colostrum (Biernat et al., 2001). No commercial milk formula is supplemented so far with the growth factors and hormones relevant for the development of the neonatal gastrointestinal tract. On the other hand, however, sucklings and weaners are offered feedstuff containing a wide range of feed additives, and again economics has decided about the use of these substances, e.g., ZnO and antimicrobial feed additives, despite the hazardous effects reported by microbiologists, medical and veterinary clinicians, and ecologists (Opaliński et al., 1998; Taljański-Zygmunt et al., 1998).

DEFINITION OF BIOACTIVE PEPTIDES

The term "bioactive peptides" is wide since it covers both the peptides derived from food proteins and the peptides naturally present in the food. According to Schlimme and Meisel (1995) *bioactive peptides derived from food protein*, are protein fragments that are inactive within the sequences of their precursors but interact with appropriate receptors and affect the physiological functions of an organism after being released by proteolytic enzymes (e.g., casomorphins derived from α-and β-casein of milk). Table 1 shows some known bioactive peptides derived from milk protein and their biological activity. Since milk replacers and feed-

TABLE 1

Bioactive peptides derived from milk protein hydrolysates (Kostyra and Kostyra, 1992; Wong et al., 1996; Meisel, 1997, 1998; Rudloff and Kunz, 1997; Schanbacher et al., 1997; Tirelli et al., 1997; Dziuba et al., 1999; Yamamoto and Takano, 1999)

Bioactive peptide	Protein precursor	Bioactivity
Casomorphins	α-, β-Casein	Opioid agonists
α-Lactorphin	α-Lactalbumin	Opioid agonist
β-Lactorphin	β-Lactoglobulin	Opioid agonist
Lactoferroxins	Lactoferrin	Opioid antagonists
Casoxins	k-Casein	Opioid antagonists
Casokinins	α-, β-Casein	Angiotensin-I-converting-enzyme inhibitors
Immunopeptides	α-, β-Casein	Immunomodulators
Lactoferricin	Lactoferrin	Antimicrobial agent
Casoplatelins	k-Casein	Antithrombotic agents
Phosphopeptides	α-, β-Casein	Mineral binding agents
β-Lactotensin	β-Lactoglobulin	Ileum smooth muscle contracting agent

stuffs for early weaners contain considerable amounts of milk proteins, these bioactive peptides may appear in sufficient amounts in the gastrointestinal tract. Plant and animal proteins in the diet (e.g., wheat gluten, rye albumin, soyabean conglycinins, haemoglobin, egg ovomucin) may deliver numerous bioactive peptides, often having similar activity to those derived from milk proteins.

In contrast, *bioactive peptides naturally present in food* are active components of the food (milk) that retain their biological activity in the lumen of the gastrointestinal tract. Table 2 lists the relevant bioactive peptides, hormones and growth

TABLE 2

Bioactive peptides occurring naturally in milk and colostrum (Rao, 1991; Koldovsky et al., 1995; Smith-Kirwin et al., 1998; Xu, 1998; Zabielski, 1998)

Hormones	Insulin, somatostatin, thyroxin, calcitonin, prolactin, growth hormone, growth releasing factor, oxytocin, melatonin, atrial natriuretic peptide, endothelin-1, angiotensin I converting enzyme, gastrin, leptin
Growth factors	EGF-I, -II (epidermal growth factor-I and –II), IGF (insulin-like growth factor), NGF (nerve growth factor), TGF (transforming growth factor-α and -β) PDGF (platelet-derived growth factor)

factors naturally present in colostrum and milk. All of them have their endogenous counterparts secreted both systemically into the circulating blood and locally into the lumen of the gastrointestinal tract with saliva, gastric, intestinal, and pancreatic juices and bile (Rao, 1991). For example, saliva and enterocytes are important sources of growth factors (IGF, EGF); pancreatic juice contains remarkable amounts of insulin and gastric juice, leptin.

ROLE OF BIOACTIVE PEPTIDES PRESENT IN MILK FOR THE SUCKLING

The list of recognized colostrum and milk bioactive peptides and their biological effects is rapidly growing. These milk bioactive substances are particularly important during the first days of postnatal life for the development of the gastrointestinal tract as well as for induction of the neonate's own endocrine system. In the following pages I will briefly review only just a few of them, for more details please refer to a number of extensive reviews published in the last 15 years (Thornburg and Koldovsky, 1987; Koldovsky et al., 1988, 1995; Rao, 1991; Grosvenor et al., 1992; Schlimme and Meisel, 1995; Xu, 1996, 1998; Guimont et al., 1997; Rudloff and Kunz, 1997; Schanbacher et al., 1997; Tirelli et al., 1997; Zinn, 1997; Meisel, 1998; Zabielski, 1998; Yamamoto and Takano, 1999; Blum and Hammon, 2000; Xu et al., 2000). Following the recent discovery of leptin receptors in the

gastrointestinal tract and high leptin concentrations in the colostrum and milk (Aoki et al., 1999; Ucar et al., 2000), a new question arose on the potential involvement of leptin in the development of the gastrointestinal tract.

Bioactive peptides are present in milk at concentrations usually much higher than those found in maternal blood or in the blood and tissues of their offspring. Weström et al. (1987) have reported that the concentration of insulin in sow colostrum is over 100 times greater than in maternal plasma and that it drops gradually during lactation. Blum and Hammon (2000) have demonstrated a similar pattern with regard to insulin, prolactin and IGF-I in bovine colostrum and milk. The reduction in milk glucagon and growth hormone was far less dramatic in their study. High concentrations of insulin and IGF-1 in colostrum and milk coincide with intensive growth of the intestinal mucosa and pancreas tissue just after birth (Svendsen et al., 1986). Colostrum and milk bioactive peptides seem to be particularly important in neonates to support their neuroendocrine function and regulate the development of GI tract structure and function until the neonate's own endocrine system achieves maturity. The degradation of bioactive peptides occurs to a much lower degree in the digestive juices of neonates and sucklings than in those of weaned or adult animals (Read et al., 1987; Shen and Xu, 1996; Xu et al., 1996). There are controversies on the ability to penetrate the gut tissue and appearance of milk bioactive peptides in the circulating blood. Thornburg and Koldovsky (1987), Rao (1991), Xu and Wang (1996), Shen and Xu (2000) have found the gut permeable to numerous milk hormones and growth factors (insulin, IGF-I), on the other hand Grütter and Blum (1991), Vacher et al. (1995), Donovan et al. (1997) and Hadorn et al. (1997), observed no absorption of insulin, prolactin and IGF-I from the gut lumen into the general circulation in newborns. The discrepancy among different reports may be due to different media used to deliver the bioactive peptides (colostrum vs milk formula) since Sangild et al. (1999) reported that colostrum promotes the intestinal absorption of macromolecules. However, according to the present view, the majority of biological effects of colostrum and milk peptides is rather limited to the gastrointestinal tract (Blum and Hammon, 2000; Xu et al., 2000).

Insulin

Colostrum and milk insulin may exert local as well as general effects, although according to experiments in neonatal calves by Grütter and Blum (1991) it seems not to be absorbed in the intestine. Insulin acts through its own receptors and through IGF type I receptors due to its approximately 40% homology with IGFs. Administration of pharmacological doses of insulin increased the weight of the small intestine, in particular that of intestinal mucosa, and increased lactase and maltase activities in neonatal piglets (Shulman, 1990). Feeding a neonate pig with colostrum

devoid of insulin inhibits maturation of intestinal enzymes (Wang and Xu, 1996) and delays gut closure, thus insulin is regarded as an important maturation factor of gastrointestinal tract mucosa. Oral administration of insulin causes hypoglycaemia in neonatal pigs and calves (Koldovsky et al., 1988).

Insulin-like growth factor

Peptide growth factors, such as IGF-I, IGF–II and EGF, are present in biologically relevant amounts in maternal milk from different species. These peptides are remarkably stable in rat and pig gastrointestinal fluids suggesting that after ingestion of milk they may reach their receptors in the mucosa of the stomach, duodenum and proximal jejunum in an active form (Shen and Xu, 1996; Fellah et al., 2001). In suckling piglets, IGF-I receptors are widely distributed in the small intestinal mucosa, and located in the apical part of the enterocyte (Morgan et al., 1996). According to Donovan et al. (1997) and Hammon and Blum (1997), IGF-I is not absorbed in the small intestine in calves and pigs, even immediately after birth, though colostrum ingestion causes a marked increase of IGF-I in blood plasma (Egli and Blum, 1998). Feeding piglets with an infant formula supplemented with IGF-I and IGF-II leads to a higher DNA content in the stomach tissue and increases cell proliferation in the upper gut as compared with infant formula alone (Xu et al., 1994). In neonatal calves, orally administered recombinant human IGF-I stimulated growth of the intestine as evidenced by [^{3}H]-thymidine incorporation into the enterocyte (Baumrucker et al., 1994), but histological examination of the intestinal mucosa did not reveal any effect (Blum and Hammon, 2000). IGF-I can modulate the tight junction structures that are also associated with intestinal permeability, and enhance intestinal epithelial Na^+ and Na^+-coupled nutrient absorption (Alexander and Carey, 1999). The importance of IGF-I in rat and human milk has been questioned by others since it was found that endogenous IGF-I may be produced in sufficient amounts in the newborn and taken up selectively by the proximal gut (Burrin, 1997; Steeb et al., 1997). However, experiments on calf neonates showed that plasma IGF-I concentrations depend on the amount and timing of colostrum ingestion (Blum and Hammon, 2000).

Epidermal growth factor

EGF is stable in gastric and duodenal fluids (Thornburg et al., 1984; Rao, 1991) and acts through specific receptors located on the epithelial cells along the oesophagus, stomach and small intestine (Jaeger and Lamar, 1992). In suckling pigs the density of EGF receptors is significantly lower than in weaned pigs (Kelly et al., 1992). After ingestion, EGF stimulates epithelial cell growth and differentiation (James et al., 1987; Thornburg and Koldovsky, 1987), increases the specific acti-

vity of mucosal ornithine decarboxylase and incorporation of labeled thymidine into DNA (Ulshen et al., 1986; Berseth, 1987), and elevates jejunal lactase- and sucrase-specific activities (Jaegger et al., 1990). EGF is reported to be involved in the cessation of macromolecular transmission in newborn (Xu et al., 2000), and plays an important role in the maintenance of epithelial integrity, inhibition of intestinal bacteria translocation (Okuyama et al., 1998), as well as in the gastric and intestinal epithelium recovery after rotavirus and bacterial infections (Zijlstra et al., 1994; Buret et al., 1998).

Leptin in colostrum and milk

Leptin, a 16-kDa cytokine secreted primarily by adipose tissues, has recently been shown to be produced by the human placenta (Smith-Kirwin et al., 1998). Many functions of the placenta are replaced by the mammary gland in terms of providing critical growth factors for the newborn. Consequently, leptin is produced by the mammary epithelial cells and it has been detected in human, mice, and rat colostrum and milk (Casabiell et al., 1997; Houseknecht et al., 1997; Aoki et al., 1999; Ucar et al., 2000). Leptin is present in whole breast milk at 30- to 150-fold higher concentrations than in skim milk (Houseknecht et al., 1997; Smith-Kirwin et al., 1998). In the breast milk, leptin was found in higher (Smith-Kirwin et al., 1998), similar (Houseknecht et al., 1997) or lower (Ucar et al., 2000) concentrations than present in the maternal plasma, nevertheless, milk leptin concentrations positively correlated with maternal and/or infant plasma leptin concentrations. In other examined species, the concentration of leptin in milk was higher than in the maternal blood plasma. In lactating mice the leptin concentration of milk collected just before weaning was about two-fold higher than that of the milk collected at mid-lactating stages (Aoki et al., 1999). In experimental animals, Casabiell et al. (1997) have demonstrated that leptin is transferred from the circulation to mothers' milk, then to the infant's stomach and afterwards to the infant's blood.

Leptin function in the juvenile gut

According to Lin et al. (2000), in 50 d-old pig foetuses the long form leptin receptor mRNA is expressed in the brain, intestine, liver and umbilical cord, and in 105 d-old gilts it is expressed in the intestine, liver and pancreas. In the juvenile rat, leptin receptor expression has been found in several tissues including small intestine (Lostao et al., 1998). In mice, expression of the functional isoform leptin receptor is restricted to the jejunum and is readily detected in isolated enterocytes from this site by the RT-PCR technique (Morton et al., 1998), suggesting that the epithelium of the jejunum is a direct target of leptin action. Indeed, Lostao et al. (1998) have originally demonstrated that leptin has a rapid inhibitory effect on

sugar absorption in the rat intestinal mucosa *in vitro*. In their study, leptin inhibited D-galactose uptake by rat small intestinal rings, respectively by 33 and 56% after 5 and 30 min of incubation! However, neither at 5 min nor at 30 min did leptin prevent intracellular galactose accumulation. These results show for the first time that leptin may exert its "antiobesity" effects locally in the small intestine. Recently, Yuan et al. (2000) evaluated the effects of peripherally administered leptin on body weight changes in neonatal rats during the early suckling period (from birth to 10 d). Daily i.p. injections of leptin (0.3 and 1.0 μg/g) to neonatal rats led to a significant reduction in weight gain over 10 d compared with the control group. In addition, they also observed that 3 d after discontinuing leptin treatment, the body weight of leptin-treated pups returned to the control level. In a recent study in neonatal piglets that were fed for 6 days with either pig milk formula alone or formula supplemented with pharmacological doses of leptin, Woliński et al. (2001) have found that in the leptin- supplemented group the weight of the stomach was significantly reduced and that of the pancreas, increased. Moreover, in isolated muscle strips *in vitro* they have found that the neonates supplemented with leptin had a significantly higher amplitude of spontaneous and acetylocholine-induced contractions in the duodenum than the non-supplemented neonates. In contrast, muscle strips taken from the mid-jejunum showed opposite results (Woliński et al., 2001). The mechanism of leptin action remains obscure. Yuan et al. (1999) have demonstrated in neonatal rat *in vitro* preparations that the peripheral gastric application of leptin modulates brain stem neuronal activities *via* afferent sensory fibres (Yuan et al., 1999). In adult rats, exogenous leptin or that released endogenously by CCK or meal is accompanied by a significant rise in gastric blood flow probably mediated by NO and sensory nerves (Brzozowski et al., 1999). Data accumulated so far suggest that colostrum and milk leptin may play a role in the regulation of gastrointestinal tract function in neonates, but further studies are necessary.

FUTURE PERSPECTIVES

Bioactive peptides need to be recognized as a novel measure of protein value in addition to the essential amino acid content criterion (Friedman, 1996), and the criteria based on protein allergenicity and presence of antinutrients occurring together with proteins (Anantharaman and Finot, 1993; Matsuda and Nakamura, 1993; Bush and Hefle, 1996). This criterion should be used in particular for evaluation of artificial milk formulas, and liquid and solid feedstuffs for early weaned production animals. Research on colostrum and milk bioactive peptides, involving leptin, and their physiological role in the offspring is warranted.

Future research should be directed toward improving milk conservation technologies and the biological quality of milk replacers and feedstuffs for early weaned

production animals. Looking for better quality means: 1. protection of biological activity of native milk proteins and peptides, in particular those that are present in milk in active form, 2. supplementation of milk formula with native bioactive peptides, and 3. supplementation with selected bioactive peptides isolated from plants or obtained by biotechnological techniques. For example, spermine (Dufour et al., 1988) and kidney bean lectin (Biernat et al., 2001a) have been reported to stimulate the maturation of the gastrointestinal tract in sucklings, thus giving a chance for reduction of weaning problems.

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STRESZCZENIE

Bioaktywne peptydy w żywieniu młodych zwierząt

Mleko matki jest dla noworodka źródłem wielu bioaktywnych peptydów potrzebnych dla harmonijnego rozwoju przewodu pokarmowego. Artykuł jest krótkim przeglądem badań nad rolą pełnioną przez insulinę, insulinopodobne czynniki wzrostowe i nabłonkowy czynnik wzrostu mleka u noworodków i osesków. Leptyna w mleku została odkryta niedawno, dlatego stosunkowo więcej miejsca poświęcono na zaprezentowanie wyników badań nad rolą leptyny w rozwoju przewodu pokarmowego. Jednakże określenie fizjologicznego znaczenia tych wyników wymaga dalszych badań. Preparaty mlekozastępcze, w przeciwieństwie do mleka, zawierają znikome ilości bioaktywnych peptydów.