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EFFECT OF COLOSTRUM INSULIN-LIKE GROWTH FACTORS ON GROWTH AND DEVELOPMENT OF NEONATAL CALVES

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Summary

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The purpose of the present paper is to review the role of colostrum growth factors in the growth and development of neonatal calves. An emphasis is put on insulin-like growth factors (IGF-1 and IGF-2), that are abundant in cow's colostrum. Although these factors are absorbed in rather limited amounts, they exert an effect upon both the growth and development of the gastrointestinal tract, and on the functional maturation of the organism and its adaptation to the novel environment after the birth, when a transition from parenteral to enteral nutrition takes place. A number of systemic effects of colostrum on the organism of neonates are described and discussed, as well as the role of endogenous growth factors.

Key words: colostrum, growth and development, insulin-like growth factors, neonatal calves

INTRODUCTION

There are considerable differences in mechanisms that regulate systemic growth and development during the foetal period and after the birth. The regulation of the foetal growth depends mostly on maternal phenotype and the gestational stage. Endocrine factors play a key role, influencing the distribution of nutrients among the maternal organism, the placenta and the foetus, and the ability of the foetus to utilize absorbed substrates. Thus, the foetal growth and development are controlled from endogenous (foetal) and exogenous (maternal nutrients, hormones and growth factors) factors, provided to the foetus by the placenta and with swallowed amniotic fluid (Peng *et al.*, 1996; Kimble *et al.*, 1999; Breier *et al.*, 2000; Trahair & Sangild, 2000).

The growth during the neonatal period is determined mainly by the genotype and feeding conditions (Breier *et al.*, 2000). In large ruminants, somatotropin – insulin-like growth factors axis (GH-IGFs), that includes the growth hormone (GH), IGF-1, IGF-2, insulin, the respective cell receptors (GHR, IGF-1R, IGF-2R and insulin receptor) and six plasma IGF binding proteins, is the most important for systemic growth and development. At present, the quantitative changes in the different components of the GH-IGFs axis during the different physiological developmental periods (embryonic and neonatal) are subject to extensive research and analysis.

In this review, we should go through the effect of feeding colostrum (where the concentration of growth factors is the highest) upon the growth and development of neonatal calves. A special attention is paid on the gastrointestinal (GI) tract as its mucous coat makes the first contact with colostrum. Also, it is determined that growth factors are absorbed in rather limited amounts and therefore they are expected to have a most profound influence on the growth and functional development of intestines (Blum & Hammon, 2000; Blättler *et al.*, 2001; Blum, 2006).

PHYSIOLOGICAL FEATURES OF INSULIN-LIKE GROWTH FACTORS

Insulin-like growth factors (IGF-1 and IGF-2; IGFs) are formed both in liver and locally in almost all tissues, including the mammary gland. The hepatic synthesis of IGFs is stimulated by adenopituitary somatotropin (growth hormone; GH) that possesses specific receptors in hepatocytes – the growth hormone receptor, GHR (Disenhaus *et al.*, 1988; Chilliard *et al.*, 1998; Gibson *et al.*, 1999; Baumrucker & Erondu, 2000).

IGF-1 and IGF-2 are single-chained low-molecular weight polypeptides with proinsulin-like structure, with a very large spectrum of physiological activity. The more important physiological effects of IGFs are related to their effect upon the transmembrane transport and metabolism of glucose, amino acids, nucleotides etc. Moreover, IGFs stimulate the synthesis and inhibit the breakdown of proteins, DNA, RNA and regulate cell proliferation and differentiation in tissues, and simultaneously, inhibit apoptosis (genetically programmed cell death) (Disenhaus *et al.*, 1988; Bühler *et al.*, 1998; Jehle *et al.*, 1999; Breier *et al.*, 2000; Blum, 2006). In animals, especially in large ruminants, investigations are mostly aimed at elucidation of IGFs role in systemic growth and development during the foetal and neonatal periods (Breier *et al.*, 2000; Hammon & Blum, 2002; Roffler *et al.*, 2003; Bittrich *et al.*, 2004, Ontsouka *et al.*, 2004; Blum, 2006). IGF-1 and IGF-2 exert their effects on a cellular level after binding to specific membrane receptors – IGF-1R and IGF-2R, respectively.

IGF-1R and IGF-2R are found in many tissues, including the epithelial cells of the mammary gland. IGF-1R is a membrane-bound glycoprotein with molecular mass of 420 kDa. It consists of two chains (α and β), linked with disulfide bonds. The α- and β-chain form a α, β-heterodimer, and two heterodimers, connected with 2 disulfide bonds, form the receptor itself. The α-chain is entirely extracellular, and the β-chain is composed of 3 segments – extracellular, transmembrane and intracellular (possessing tyrosine kinase activity mediating the intracellular effects). The extracellular part of receptors, consisting of the α-chain and the extracellular segment of the β-chain, are built from 6 structurally independent domains that accomplish the binding to the respective ligands (insulin and IGF-1) and transmit the signal to the transmembrane and intracellular components (Marino-Buslje *et al.* 1999; Listrat *et al.*, 1999; Hammon & Blum, 2002; Epa & Ward, 2006).

The structure of IGF-2R is quite different from that of IGF-1R. It is a monomeric glycoprotein with molecular mass of 275–300 kDa, and consists of a single chain with extracellular, transmembrane and intracellular parts (Dahms *et al.*, 1989). On the extracellular part, 15 homologous domains are located, each one

built of 147 amino acids, and the active centre for binding to IGF-2 is located on the 11th domain (Dahms *et al.*, 1989; Devi *et al.*, 1998).

SYSTEMIC EFFECTS OF COLOSTRUM IN NEONATAL CALVES

Intake of colostrum and IGFs in particilar affect metabolic and endocrine status of neonate and has long-lasting effect on the immune protection as well (Blum, 2006). The intake of colostrum during the first hours after birth has a considerable effect on immune, metabolic and hormonal profile of neonatal calves, stimulates the systemic growth and development and contributes to the further adaptation and vitality of neonates (Blum & Hammon, 1999; 2000; Blum, 2006). Statistically significant blood concentrations of total protein, IgG, essential and non-essential amino acids, triglycerides, phospholipids, cholesterol, essential fatty acids, fat-soluble vitamins (A, E, D) are reported in calves fed colostrum during the first 7 days after the birth compared to calves deprived of colostrum and receiving it with a 24-hour delay (Blum *et al.*, 1997). Also, significantly higher levels of insulin, IGF-1, glucagon and GH were reported, whereas cortisol levels were reduced, and those of thyroid hormones and prolactin were unaltered (Blum *et al.*, 1997; Hadorn *et al.* 1997; Hammon & Blum, 1997; 1998; Rauprich *et al.*, 2000 a, b). An intriguing fact is that the blood concentrations of insulin and IGFs in neonatal calves are significantly higher after feeding colostrum regardless of the very limited absorption of these substances from the GI tract of calves (Vacher & Blum, 1993). This was probably due to the stimulating effect of other factors ingested with colostrum on the endogenous production of insulin and IGFs. Furthermore, it is shown that apart in the liver, IGFs in neonatal calves could be also locally formed in many other tissues (Cordano *et al.*, 2000). During the first week after birth, there was a statistically significant positive correlation between IGF-1 blood concentration in newborn calves and colostrum intake, weight gain and body weight (Egli & Blum, 1998; Breier *et al.*, 2000). Unlike IGF-1, IGF-2 concentration is not dependent on colostrum intake (Hammon & Blum, 1997). In addition, plasma IGF-1 concentration is found to be significantly higher in neonatal calves fed colostrum compared to calves fed only milk, glucose or water (Hammon & Blum, 1997). Therefore, the intake of colostrum in the first hours after birth is extremely important not only for passive immunization of neonatal calves and the supply of nutrients – proteins, carbohydrates, lipids, vitamins, minerals etc. but also for the normal growth and the morphological and functional maturation of the GI tract and thus, for the adequate systemic adaptation to the new environment after birth, including feeding. The research on this subject showed that this is due to the high content of various biologically active peptides, growth factors, hormones, cytokines etc. in colostrum that regulate the normal occurrence of these processes (Hammon & Blum, 1997; 1998; Hadorn *et al.*, 1997; Blum & Hammon, 2000; Blum, 2006).

EFFECT OF COLOSTRUM INSULIN-LIKE GROWTH FACTORS ON GASTROINTESTINAL GROWTH AND DEVELOPMENT IN NEONATAL CALVES

At birth, the GI tract of calves is relatively mature. Nevertheless, its successful adaptation to the new environment, including feeding, requires marked alterations in

gastrointestinal structure and function affected by the nutrition and numerous factors in the intestinal lumen, either locally produced or present in the circulation (Sangild, 2001; 2006; Blum & Baumrucker, 2002; Blum, 2006). In the newborns, including calves, an abrupt change from parenteral feeding during the intrauterine development to almost enteral feeding after birth does occur (Sangild, 2001; 2006; Blum, 2006). The timely intake of biologically valuable colostrum is essential for the survival of neonatal calves. It is recognized that colostrum provides all necessary nutrients to the organism of the neonate but relatively few is known about the role and the physiological importance of some of non-nutrient ingredients and growth factors in particular.

With regard to IGFs origin in colostrum and milk, it is believed that the major part (over 50%) of IGFs is brought in the mammary gland with circulating blood. The other part is locally produced, not in glandular epithelial cells, but in the stroma, the fibroblasts, the vascular walls and its physiological effect is realized via a paracrine or autocrine manner (Plath-Gabler *et al.*, 2001).

The IGFs supplied with colostrum are absorbed in rather restricted amounts by the GI tract of calves. Although not fully known, it is thought that they exert a local stimulating effect on gastrointestinal growth and development and that along with endogenous growth factors, they are very important for the growth and development of other organs. This assumption is highly supported by the fact that IGFs concentration is the highest in the first portions of colostrum and afterwards, rapidly decreases (Rauprich *et al.*, 2000a, b).

For the first time, the stimulating effect of colostrum on the morphofunctional maturation of the GI tract in newborns is demonstrated by Widdowson *et al.* (1976) in experiments with neonatal piglets, and Klagsbrun (1978) was the first to show *in vitro* that milk and especially colostrum contains substances that stimulate cellular division and these compounds differ in men and cattle.

Functionally, newborn calves are pseudomonogastric animals, whose GI tract is characterized by a marked growth rate (Blum, 2006). The observed changes are directly related to the growth and maturation of other digestive organs such as the liver and the pancreas (Guilloteau *et al.*, 2002). During the first week of life, a gradual replacement of lysosomal digestion of proteins in the enterocytes with digestion in the lumen and the brush border surface (so-called membrane digestion) is observed in calves. It should be noted that the delayed functional maturation of the GI tract is one of the commonest causes of gastrointestinal disorder leading to considerable morbidity and death rates in neonatal calves (Blum, 2004).

GROWTH AND DEVELOPMENT OF GI TRACT IN PRETERM NEONATAL CALVES

It is known that the first 2–3 postnatal weeks of life in calves are characterized by high morbidity and mortality rates. Gastrointestinal disorders (i.e. severe diarrhoea) are particularly frequent and are often followed by fatal systemic diseases (Blum, 2006). The inadequate morphological and functional adaptation of the GI tract is considered to have a central role in the etiology of GI diseases during the neonatal period (Guilloteau *et al.*, 2002), especially in preterm neonatal calves (Sangild, 2001; 2006; Bittrich *et al.*, 2002; 2004).

Calves born between the 248th and the

268th gestation days are considered as prematurely born (Sangild, 2006). Bittrich *et al.* (2002) observed that calves born 2 weeks prior to the term, are able to ingest and utilize nutrients but that at the same time, there were a number of deviations in their physiological adaptation – enhanced heart and respiratory rates, increased blood glucose and insulin concentrations, and reduced response of GH to exogenous somatotropin-releasing factor compared to full-term neonatal calves. Also, their GI tract is structurally and functionally immature and reacts to a lesser extent to nutritive and growth factors supplied with colostrum. Compared to full-term calves, the GI tract of prematurely born ones possesses a lower proliferation and growth rate and reduced activity of membrane-bound enzymes (Bittrich *et al.*, 2002).

Considerable species-related features with regard to the morphological and functional maturity of the GI tract are available. According to Sangild (2006), the GI tract of neonatal children is sufficiently mature and could digest milk and non-milk carbohydrates and proteins, so it undergoes a considerable growth during the intrauterine period. At the same time, GI tract of small rodents (rats and mice) and some carnivores (cats) at the time of birth is extremely immature and is characterized with a rapid postnatal growth. The GI maturity in piglets, lambs, calves and foals at birth is intermediate and its growth and development occurs both prior to and after birth. A common trait for all animal species is that GI growth and development are particularly intensive in the immediate postnatal period and by the time of weaning, when the type and mode of nutrition are changing. This is shown to be due both to feed and to endocrine alterations during these periods, with several inter-species differences. Thus, in animals that are born with a relatively mature GI tract such as calves, the prevailing growth occurs in the period close to the time of birth (Blum & Baumrucker, 2002; Blum, 2006).

During the intrauterine period in calves and lambs and particularly in the second half of gestation, the substances supplied by maternal placental circulations as well as the absorption of biologically active substances (IGFs) with the amniotic fluid are the most important for GI growth and development (Kimble *et al.*, 1999; Trahair & Sangild, 2000, 2002).

INFLUENCE OF IGFs ON GASTROINTESTINAL GROWTH AND DEVELOPMENT IN FULL-TERM NEONATAL CALVES

During the early postnatal period, GI tract of calves undergoes considerable morphological and functional alterations that are largely influenced by the amount and composition of colostrum (Guilloteau *et al.*, 1997; Bühler *et al.*, 1998; Blum & Hammon, 2000). The adequate knowledge of factors that stimulate the functional maturation of the GI tract during that period would contribute to reduced incidence of digestive disorders and to more effective digestion, health status, growth and development of neonatal calves.

It is known that small and large intestines are composed of several layers, each of them with specific functions. Initially, consumed colostrum enters in contact with epithelial cells and therefore, the primary effect of colostrum growth factors is manifested at that level. Intestinal epithelial cells are situated in one layer, that covers the crypts and the villi and are of different types – cylindrical, mucosal, Panet's, enteroendocrine cells. These cells are characterized by a rapid turnover rate,

and the new cells originate from the proliferation zone within the crypts. The role and physiological significance of these cells in calves are still poorly studied.

The growth and development of the GI tract are subject to external and internal control. Generally, there is a negative correlation between the size of villi and the size of crypts and their rate of cell proliferation.

Numerous factors are known to affect the morphological and functional maturation of the GI tract: (1) nutrients and growth factors provided by colostrum and milk; (2) the presence of a number of locally produced biologically active substances, regulating gastrointestinal growth and development – growth factors, cytokines, neuromediators etc. with auto- and paracrine mode of action; (3) substances, produced in intestinal cells and released in the lumen, the so-called lymokines; (4) the circulatory supply of biologically active substances – hormones (insulin, IGFs, GH, thyroid hormones, cortisol etc.) formed outside the GI tract and exerting their effect by an endocrine route.

Among the gastrointestinal regulatory factors in neonatal calves, the physiological importance of gastrin, cholecystokinin, secretin, vasointestinal polypeptide, motilin, pancreatic polypeptide, somatostatin and glucose-dependent insulinotropin polypeptide (Guilloteau *et al.*, 1977; 2002) are fairly well studied, whereas the role of IGFs is not entirely clear despite the extensive research during the last 10–15 years.

Of endocrine factors, cortisol should be mentioned, as it is proven to have a key role in gastrointestinal development and cell proliferation and differentiation during the early neonatal period (Sangild, 2001). It is experimentally shown that the higher release of cortisol in the prenatal and the early postnatal period in animals, including calves, is of critical importance for the enhanced maturation of the GI tract (Schmidt *et al.*, 2004; Sauter *et al.*, 2004).

In neonatal calves, glucocorticosteroids stimulate the growth and the development of the GI tract as their exogenous administration results in enhanced cell proliferation (Sauter *et al.*, 2003; 2004). The role of glucocorticosteroids for the growth and development of lungs, heart, endocrine system and other tissues is also well known (Breier *et al.*, 2000). These effects should be however interpreted in a broader sense, i.e. as one of the most important humoral factors controlling the changes and the adaptation of physiological events after the birth. Immediately before and especially after birth, the GH-IGF system undergoes significant alterations at various levels – significant increase in plasma IGF-1 concentration, of GH receptors (GHR) and the respective mRNA in the liver and acute reduction of blood IGF-2 content (Breier *et al.*, 2000). Although the mechanism of regulation of these changes is still under extensive investigation, it is assumed that the marked increase in foetal blood cortisol level just before the parturition has essential role for the functional maturation of GH-IGF axis in a manner characteristic for the postnatal period (Breier *et al.*, 2000). Thus, the elimination of the prenatal cortisol peak in the foetus inhibits these alterations in the GH-IGF system (Li *et al.*, 1996; Breier *et al.*, 2000).

The studies of Sauter *et al.* (2004) showed that feeding colostrum and the exogenous treatment with cortisol increased crypt depth in the colon; also, a positive correlation between crypt depth and cell proliferation along the entire GI tract was shown. Furthermore, the treat-

ment with cortisol enhanced the rate of proliferation in the total small intestine and especially in the ileum.

IGFs exert an important stimulating effect on the growth and development of neonates, and thus, on their adequate adaptation to the new environment after the birth (Hammon & Blum, 1998). For instance, a positive correlation between plasma IGF-1 concentration and the body mass of neonatal calves is reported (Hammon & Blum, 1997). Nutrients and growth factors have a direct local effect on intestines. Colostrum alters GI tract development, influencing the activity of digestive enzymes, locally produced gastrointestinal hormones and the absorption capacity (Hammon & Blum, 1997; Bühler *et al.*, 1998; Guilloteau *et al.*, 2002). It is established that these effects are due not only to the intake of colostrum energy sources, nutrients, vitamins and minerals, but also to growth factors, particularly IGFs, both supplied with colostrum and synthesized *in situ* (Xu, 1996; Burrin *et al.*, 1996; Blum & Hammon, 2000; Blum & Baumrucker, 2002; Blum, 2004). It is established that the exogenous application of recombinant somatotropin in calves during the first week of life results in increased plasma IGF-1 concentration (Hammon & Blum, 1997). These data demonstrate that although immature, the GH-IGFs system is functioning and could be modulated by internal and external factors (amount and composition of consumed colostrum and milk, local production of growth factors and other biologically active compounds, systemic hormonal status of neonatal calves etc.). Thus, calves fed only water, milk or glucose, showed lower IGF-1 levels than calves fed colostrum (Hammon & Blum, 1997).

Histomorphometrical studies showed that neonatal calves, fed colostrum 6 times during the first 3 days of life, exhibited bigger circumference, area and height of villi on total length of the small intestine, especially in the duodenum when compared to calves fed only milk replacer (Bühler *et al.*, 1998). Furthermore, the circumference and area of villi was higher in calves fed colostrum once than in those given no colostrum (Bühler *et al.*, 1998). These data evidenced that feeding colostrum to calves stimulated the growth of intestinal epithelium.

The intake of colostrum stimulates at a significantly greater extent the growth of the GI tract in neonatal calves than the application of some growth factors alone (Roffler *et al.*, 2003). The oral or parenteral administration of IGF-1 alone under the form of the preparation Long-R3-IGF-1, did not influence significantly the morphology and the absorptive capacity of the GI tract in neonatal calves (Bühler *et al.*, 1998), whereas the feeding of a milk-based formula that did not contain any growth factors (IGF-1, 2, lactoferrin, insulin) and colostrum extract rich in these growth factors, enhanced the proliferation in intestinal crypts and increased the size of intestinal villi (Roffler *et al.*, 2003). Morphological and histomorphometrical studies demonstrated that calves fed colostrum exhibited enhanced epithelial cell proliferation in intestinal crypts, bigger height and area of intestinal villi compared to calves fed milk-based formula without growth factors (Bühler *et al.*, 1998).

It is reported that the *per os* administration of recombinant IGF-1 (rIGF-1) stimulates the mitosis of intestinal cells and the incorporation of ^{3}H-labeled timidine in enterocytes of 8-day-old calves, indicating enhanced synthesis of DNA (Baumrucker *et al.*, 1994).

The recent experimental data show

that IGFs (colostral, endogenous and locally produced), apart their stimulating effect on proliferation and differentiation of the intestinal epithelium, are among the most important physiological factors inhibiting apoptosis (genetically programmed cell death) thus extending the life of cells and the term of their functional activity (Blum & Baumrucker, 2002).

Growth factors such as those from the GH-IGF system preserve their structure and functional activity in the intestine of neonatal calves because the production of hydrochloric acid and the proteolytic activity of the gastric juice are rather low in newborns and at the same time, colostrum contains compounds that inhibit proteolysis (Xu, 1996). There is evidence that colostrum IGFs are more important for ruminants than for men, pigs and rodents, where the so-called epidermal growth factor is prevailing (Kelly, 1994; Blum & Hammon, 2000; Vachkova, 2008).

According to Smith *et al.* (2002) the development of the GH-IGFs system in calves after the birth is influenced at a significant extent by the intake of nutrients with colostrum and milk. By means of radioreceptor analysis, it is shown that small and large intestines of 8-day-old calves possess specific receptors for binding to insulin and IGFs (Baumrucker *et al.*, 1994). Thus, IGFs ingested with colostrum, locally produced or supplied through the blood circulation could influence the growth and development of intestines, respectively their morphological and functional maturation after binding to respective receptors (IR, IGF-1R and IGF-2R). The effects of these growth factors and hormones are largely dependent on both the affinity to and the number of receptors. The factors (external and internal) that determine the number and the affinity of IGFs and insulin receptors and therefore, their effects in calves are not investigated. The ontogenesis of these receptors is neither studied.

In experiments with rats and pigs, it is determined that IGFs and insulin are among the primary factors that regulate the development of the GI tract and more specifically, the proliferation and the morphological and functional maturation of enterocytes (Laburthe *et al.*, 1988; Schober *et al.*, 1990; Odle *et al.*, 1996; MacDonald, 1999; Menard *et al.*, 1999).

Despite the limited number of studies, especially in large ruminants, it is believed that the relative importance of the different members of the GH-IGFs system varied during the prenatal and the postnatal period. It is presumed that GH, on its own or via IGFs, is responsible for the postnatal growth; IGF-1 and insulin were important in the prenatal and mainly the postnatal growth, whereas IGF-2 was thought to control tissue growth, particularly during the foetal period (Breier *et al.*, 2000; Butler & LeRoith, 2001; Lee *et al.*, 2001).

Investigations with rats illustrate that apart its role in the postnatal growth, insulin was probably essential for the prenatal development as well (Margolis *et al.*, 1990; Goya *et al.*, 2001). The maturation of the GI tract and the liver in the foetus could be influenced by the GH-IGF system via endo-, para- and autocrine routes (MacDonald *et al.*, 1999; Lee *et al.*, 2001; Butler & LeRoith, 2001). The observed significant effect of IGF-1 from swallowed amniotic fluid on sheep foetuses, proved the exceptional importance of amniotic fluid growth factors for gastrointestinal growth and development in the prenatal period (Kimble *et al.*, 1999; Trahair & Sangild, 2002). However, little is known about the role of the GH-IGF system for the foetal growth in large ruminants.

Experimental data in mice and rats showed that IGF-1R mediated the effects of IGF-1 and IGF-2 during the intrauterine development and postnatal effects of IGF-1, whereas IR mediated the impact of IGF-2 on prenatal growth and the metabolic effects of insulin after birth (Rother & Accili, 2000; Nakae *et al.*, 2001). There is evidence that in laboratory animals, IGF-1R and IR are fully responsible for the growth-stimulating effect of IGF-1 and IGF-2 throughout the prenatal period (Ludwig *et al.*, 1996; Rother & Accili, 2000). The presence and the amount of GHR determined the effect of somatotropin in the prenatal and mostly, in the postnatal period (Walker *et al.*, 1992; Lucy *et al.*, 1998; Smith *et al.*, 2002). There are no analogous studies with regard to the role and functional importance of IGF-1R, IGF-2R and IR during the different periods of ontogenesis in calves.

Receptors for binding to IGFs and insulin are found out in the GI tract of rat and human foetuses, as well as in neonatal rabbits and piglets immediately after birth (Schober *et al.*, 1990; Nissley *et al.*, 1993; Nowak *et al.*, 1996; Menard *et al.*, 1999). No data are available for the presence of IGF-1R, IGF-2R and IR in the GI tract in preterm and full-term calves immediately after birth. Significant interspecies differences are known to exist with regard to the ontogenetic development and therefore, similar differences in both the number of receptors and the GI tract response to ingested nutrients and biologically active substances could be anticipated. Also, variations in intestinal proliferation rates and histomorphometric indices between preterm and full-term calves could be expected.

In vitro trials with growing intestinal crypt cells (IEC-6) and differentiating jejunal enterocytes (CaCo-2) in rats showed that IGF-2 and insulin participated mainly in the regulation of cell differentiation of enterocytes while IGF-1 is more closely related to mechanisms, controlling proliferation in intestinal crypts (Jehle *et al.*, 1999). Both cell classes possessed specific IGFs receptors, but while intensively proliferating IEC-6 cells had more receptors and higher affinity to IGF-1, on the cell membrane of differentiating cell (CaCo-2), mainly IGF-2 and insulin receptors were detected. On the basis of these facts it could be assumed that IGF-1 stimulated mainly cell mitosis and proliferations, whereas the effects of IGF-2 and insulin were related to cell differentiation of enterocytes as well. It is important to note that the receptors were primarily situated in intestinal crypts, where the proliferating cells giving rise to membrane epithelial cells after a short differentiation period are located (Buts *et al.*, 1997; Jehle *et al.*, 1999). The IGFs effect however could be manifested if the concentration of plasma binding proteins (IGFs-BP) are reduced. This process is controlled by IGF-1 that inhibits mRNA expression, responsible for the synthesis of IGF-1 binding proteins (Jehle *et al.*, 1999).

Circulating IGF-1 in the blood and the tissue expression of the respective mRNA are highly influenced by the altered plasma GH levels and the amount of liver GHR (Breier *et al.*, 2000). PCR-based investigations of Cordano *et al.* (2000) in neonatal calves proved the existence of mRNA coding for IGF-1 synthesis in many tissues, including the liver and the different parts of the GI tract. Also, a statistically significant positive correlation was found out between plasma IGF-1 concentration and the expression of IGF-1 mRNA in the liver, thus showing that IGF-1 in the circulation is mainly produced in the liver. A number of other facts

however prove that locally produced IGFs are more important for the tissue growth (Yakar *et al.*, 2000; Butler & LeRoith, 2001).

There is evidence about the expression of mRNA coding the synthesis of different components of the GH-IGFs system in tissues of rats, pigs, sheep, monkeys and men in both prenatal and postnatal periods (Peng *et al.*, 1996; Birnbacher *et al.*, 1998; Lee *et al.*, 2001; Goodyer *et al.*, 2001; Li *et al.*, 2002). However, little data are available for the quantitative expression of mRNA responsible for the synthesis of IGF-1, IGF-2, IGF-1R, IGF-2R, IR and GHR in full-term and preterm neonatal calves.

In conclusion, it could be summarized that colostrum and the nutrients (proteins, carbohydrates, lipids, vitamins, minerals) and non-nutrients (growth factors, immunoglobulins, cytokines, enzymes etc.) it contains, have an essential role in gastrointestinal growth and development as well as on systemic functional maturation during the early neonatal period, when the type of feeding switches from parenteral during the intrauterine development to entirely enteral after birth. Insulin-like growth factors of colostrum, and those produced in the GI tract and circulating in the blood, are of primary importance for the regulation of these processes.

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