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Mini-review

PHYSIOLOGICAL CHARACTERISTICS OF THE SOMATOTROPIN-INSULIN-LIKE GROWTH FACTORS AXIS IN CALVES DURING THE FOETAL AND POSTNATAL DEVELOPMENT

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Summary

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The purpose of this review was to summarize and analyze the available information about some physiological traits of insulin-like growth factors and their cell receptors. Insulin-like growth factors (IGF-1 and IGF-2) are single-chain low molecular polypeptides with structure similar to that of proinsulin, exhibiting a very broad spectrum of physiological activity. IGF-1 and IGF-2 are formed in the liver as well as locally in almost all tissues. Due to the variety of physiological effects of IGFs and the fact that their production is stimulated by somatotropin, the term growth hormone-insulin-like growth factors axis (GH-IGFs) is commonly accepted. Apart IGF-1 and IGF-2, this system also includes insulin, somatotropin, four tissue receptor types – insulin receptor (IR), insulin like growth factor 1 and 2 receptors (IGF-1R and IGF-2R), growth hormone receptor (GHR), 6 IGF binding proteins (IGF-BP-1, IGF-BP-2, IGF-BP-3, IGF-BP4, IGF-BP5 and IGF-BP6). Despite the unclear facts related to the physiological traits of the different factors of the GH-IGFs system in animals, it is believed that they are essential for regulation of tissue growth and development via its effects on cell proliferation and differentiation and that their importance for these events changes during the foetal and postnatal periods.

Key words: development , growth, insulin-like growth factors, somatotropin

CHARACTERISTICS OF INSULIN-LIKE GROWTH FACTORS

It is acknowledged that insulin-like growth factors (IGF-1 and IGF-2; IGFs) are synthesized in the liver as well as locally in almost all tissues and exert their effect via endocrine, paracrine and autocrine pathways (Chilliard *et al.*, 1998; Gibson *et al.*, 1999; Baumrucker & Erondu, 2000; Butler & LeRoith, 2001; Pfaffl *et al.*, 2002; Georgieva *et al.*, 2003)

IGFs are considered mediators of metabolic effects of the growth hormone (GH) in some organs as the mammary gland and the muscles (Sharma *et al.*, 1994; Chilliard *et al.*, 1998; Rose *et al.*, 2005). Furthermore, they are directly

involved in the regulation of cell proliferation and differentiation, respectively in neonatal growth and development (Buts *et al.*, 1997; MacDonald, 1999; Rother & Accili, 2000; Nakae *et al.*, 2001; Blum, 2006). The role and importance of GH and IGFs as most important factors stimulating milk productivity in large ruminants are described in detail in another paper of ours (Georgiev, 1998). The purpose of this review is to summarize and analyze the current concepts about physiological traits of insulin-like growth factors and their cell receptors.

IGF-1 and IGF-2 are single-chain low molecular polypeptides. The main physiological effects of IGFs are regulation of tissue cell proliferation and differentiation and to delay apoptosis (genetically programmed cell death) (Disenhaus *et al.*, 1988; Bühler *et al.*, 1998; Jehle *et al.*, 1999; Breier *et al.*, 2000; Blum, 2006). In human medicine, the role of IGFs and their receptors in some neoplastic diseases is under extensive investigation as it is reported that their concentrations in tumour cells is several times higher than in normal cells (Gullen *et al.*, 1990; Basserga, 1995; Butler *et al.*, 1998; Nickerson *et al.*, 2001; Epa & Ward, 2006).

Due to the variety of physiological effects of IGFs and the fact that their production is stimulated by somatotropin, the term growth hormone-insulin-like growth factors axis (GH-IGFs) is commonly accepted. Apart IGF-1 and IGF-2, this system consists also of insulin, somatotropin, four types of tissue receptors – insulin receptor (IR), insulin like growth factor 1 and 2 receptors (IGF-1R and IGF-2R), growth hormone receptor (GHR), 6 IGF binding proteins (IGF-BPs), namely IGF-BP-1, IGF-BP-2, IGF-BP-3, IGF-BP4, IGF-BP5 and IGF-BP6, and specific proteases that could alter the affinity of IGFs to binding proteins and hence, their physiological activity (Gibson *et al.*, 1999; Pfaffl *et al.*, 2002).

The role of IGF-BPs is manifested in modulation of their effects by regulation of the plasma half-life of IGFs, their affinity to the respective cell receptors and their activity. It is reported that IGF-BP-1 and IGF-BP-2 concentrations are higher in foetuses and decrease sharply after birth whereas IGF-BP-3, whose concentration is low during the embryonic period begins to rise immediately after the birth and in adults is significantly higher than in foetuses (Breier *et al.*, 2000). The same authors demonstrated that IGF-BPs synthesis depended on GH, nutrition, the systemic energy status etc. For instance, the treatment with GH resulted in increased IGF-BP-3 level and reduction of that of IGF-BP-2, that was related to increased biological IGF-1 activity, i.e. to stimulation of anabolism, inhibition of protein catabolism and enhanced growth of neonates. The restricted feeding and especially dietary protein deficiency provoked a reduction of IGF-BP-2 and simultaneous impairment of relationships between changes of other components of the GH-IGFs system – increase in GH that is however not accompanied by respective increase in IGF-1 synthesis and concentration and in the amount of liver GHR (Sauerwein *et al.*, 1991; Breier *et al.*, 2000).

MECHANISMS OF ACTION OF THE DIFFERENT GH-IGF SYSTEM COMPONENTS

The receptors for insulin and IGFs are dispersed in many tissues. Despite several structural traits, insulin and IGF-1 receptors are arranged similarly and there-

fore, there are a number of similarities in their functional relationships (Siddle *et al.*, 2001; Lou *et al.*, 2006). Data about the structure of receptors for IGF-1, IGF-2 and insulin are presented in another review of ours (Georgiev, 2008)

Although GHR has been cloned long time ago, the molecular mechanisms of its activation were established only during the past 20 years. GHR belongs to class I cytokine receptors and is composed of a single-chain polypeptide transmembrane protein (Waters *et al.*, 2006). It is established that after GH binds to some of extracellular domains of the receptors, it turns into a dimer. The signal is transferred to the inner part of cells by means of binding to one of cytoplasmic domains of the receptor with a special tyrosine kinase – Janus kinase, that is activated and triggers a cascade of reactions specific for GH activity (Waters *et al.*, 2006).

The specificity of insulin, IGF-1 and IGF-2 receptors has been proved by means of concurrent binding and autoradiography. IGF-1 receptors bind mainly IGF-1 and at a lesser extent, IGF-2 and insulin (IGF-1>IGF-2>insulin). IGF-2 receptors bind mainly IGF-2, IGF-1 at a very little extent, but not insulin (IGF-2> IGF-1). The highest affinity to insulin receptors is exhibited by insulin, followed by IGF-2 and IGF-1 (insulin>IGF-2> IGF-1) (Disenhaus *et al.*, 1988; Listrat *et al.*, 1999; Hammon & Blum, 2002; Georgiev *et al.*, 2003).

According to the contemporary concepts about the IGFs mechanisms of action at a tissue level and the regulation of their synthesis, it is assumed that IGF-1 and IGF-2 circulating in blood are formed in the liver via activation of IGFs genes by GH after binding to the respective receptors – GHR. At the same time, reverse transcriptase polymerase chain reaction (RT-PCR) has provided evidence for the presence of specific i-RNA encoding the genetic information for the synthesis of IGFs in many other tissues (Cordano *et al.*, 2000; Georgieva *et al.*, 2003; Blum, 2006).

At a cellular level, IGFs could act via autocrine and paracrine pathways, i.e. to influence the metabolism, the proliferation and differentiation of IGFs-producing or adjacent cells. This is confirmed by the fact that the presence of i-RNA, carrying information about the synthesis of proteins binding IGFs and modulating their physiological action, was confirmed in peripheral tissues (Cordano *et al.*, 2000; Pfaffl *et al.*, 2002; Ontsouka *et al.*, 2004). This process is very important for the growth and development of the alimentary tract in neonate calves as in them, the system GH-IGFs is not fully functioning immediately after birth, and although present in significant quantity in colostrum (Levieux, 1999), IGFs are absorbed in very limited amounts (Hadorn *et al.*, 1997). Regardless of that fact, experimental data showed that serum insulin, IGF-1 and IGF-2 in calves fed colostrum were statistically significantly higher than in calves fed only milk replacer, due to the stimulating effect of some of colostrum ingredients upon the endogenous liver production (Blum & Hammon, 1999; 2000; Cordano *et al.*, 2000). Therefore, the timely intake of colostrum apart being vital for the immune defense, is also very important from the point of view of the maturation of the GH-IGFs system and hence, for the normal growth and development of the neonate.

Experiments with rats and pigs have shown that IGFs and insulin are among the primary factors that regulate the growth and development of the gastroin-

testinal tract and especially the proliferation, the morphological and functional maturation of enterocytes (Laburthe *et al.*, 1988; Schober *et al.*, 1990; Odle *et al.*, 1996; MacDonalds, 1999).

PHYSIOLOGICAL IMPORTANCE OF THE GH-IGF SYSTEM DURING THE PRE- AND POST NATAL DEVELOPMENT

Despite the limited number of studies, especially in large ruminants, it is believed that the relative importance of the different representatives of the GH-IGFs system varies during the pre- and postnatal period. It is supposed that GH (independently or via IGFs) is responsible for the postnatal growth, IGF-1 and insulin are important for the prenatal and particularly the postnatal growth whereas IGF-2 controls tissue growth mainly during the embryonic development (Breier *et al.*, 2000; Butler & Leroith, 2001). A positive relationship was found out between the increased liver GHR amount in the first weeks after the birth, plasma IGF-1 concentrations and neonatal growth (Breier *et al.*, 2000).

Investigations with rats demonstrated that apart the postnatal growth, insulin has probably a role for the prenatal development as insulin receptors have been identified in the foetal tissues during the intrauterine period (Frasca *et al.*, 1999; Anand *et al.*, 2002).

GH-IGFs system controls tissue growth and development via endocrine, paracrine and autocrine pathways (MacDonald, 1999; Yakar *et al.*, 2000; Butler & LeRoith, 2001). Experiments carried out in mice and rats showed that IGF-1R mediated the effects of IGF-1 and IGF-2 during the intrauterine development and IGF-1 effects during the postnatal period, whereas IR mediated the effect of IGF-2 on prenatal growth and metabolic effects of insulin after birth (Rother & Accili, 2000; Nakae *et al.*, 2001). A number of genetic evidence show that in laboratory animals, IGF-1R and IR were completely responsible for the growth-stimulating effects of IGF-1 and IGF-2 during the prenatal growth (Ludwig *et al.*, 1996; Rother & Accili, 2000). It should be noted that in rodents, the binding of IGF-2 to IGF-2 receptors results to its inactivation and destruction (Wolf *et al.*, 1998; Butler & LeRoith, 2001), that corresponds to experimental data of ours in prematurely and normally born calves (Georgiev *et al.*, 2003). The presence and the amount of GHR determined the effect of somatotropin in the prenatal and especially the postnatal period (Walker *et al.*, 1992; Yakar *et al.*, 2000; Georgieva *et al.*, 2003).

During the last decade, along with the development and implementation of methods of molecular biology and molecular genetics, a number of important facts about the physiology of the GH-IGFs system and the role of the different factors for systemic growth and development have been established (Wolf *et al.*, 1998; Yakar *et al.*, 2000; Butler & LeRoith, 2001). Experiments with mice and rats and the so-called "knockout" and transgenic models related to destruction or overexpression of genes responsible for the synthesis of some representatives of the GH-IGFs system have shown that locally produced growth factors were more important for tissue growth than those, produced in the liver, as the destruction of IGF-1 genes in the liver results in almost 80% reduction of blood IGF-1 concentrations without considerable growth delay (Butler & LeRoith, 2001). At the same time, the destruction of IGF-1 genes in all tissues

caused significantly stunted growth and thus showed that locally produced IGFs were more important in the control of cell proliferation and differentiation via their autocrine and paracrine effects (Yakar *et al.*, 2000; Butler & LeRoith, 2001). Similar investigations in other animal species and men are not available leaving open the issue of the importance of liver- and locally produced IGFs for tissue growth and development.

After discovering the role of IGF-2 in controlling prenatal growth (Wolf *et al.*, 1998; Breier *et al.*, 2000; Butler & LeRoith, 2001), arises the question about its physiological importance after the birth. The limited number of studies did not allow to make a categorical conclusion for the role of IGF-2 in the postnatal period. Moreover, several species-related differences were found out. For instance, in men, serum IGF-2 concentrations after birth remained high until the puberty and then gradually decreased, whereas in rodents, IGF-2 expression sharply decreased after birth (Wolf *et al.*, 1998), that is largely similar to our results in calves (Georgieva *et al.*, 2003). Investigations with transgenic mice have demonstrated that locally produced IGF-2 had a definite role in the postnatal growth control of some organs – skin, colon, kidneys, spleen, adrenal glands etc. It was also found out that the tissue overexpression of IGF-2 in adult individuals was an essential factor in carcinogenesis (Wolf *et al.*, 1998; Frasca *et al.*, 1999).

Receptors for binding to IGFs and insulin were discovered in the alimentary tract of rat and human foetuses as well as in neonate rabbits and pigs immediately after the birth (Schober *et al.*, 1990; Nissley *et al.*, 1993; Nowak *et al.*, 1996; Menard *et al.*, 1999). Data about the expression of IGF-1R, IGF-2R and IR in the gastrointestinal tract of prematurely and normally born calves right after birth are rather scarce. It is known that there are considerable interspecies differences with respect to the ontogenetic development and therefore, differences in both the number of IGFs receptors and the response of the alimentary tract to dietary nutrient and biologically active substances could be expected. Other possible differences could be anticipated with regard to proliferation rate and histomorphometrical parameters of intestines between prematurely and normally born calves.

In conclusion, despite the existing controversies related to the physiological traits of the members of the GH-IGFs system in animals, it is assumed that they play an essential role in the regulation of tissue growth and development through influence on cell proliferation and differentiation and that the significance of mentioned factors for these processes changes during the foetal and postnatal ontogenetic periods.

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