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Review article

ENDOCRINE AND METABOLIC ADAPTATIONS OF CALVES TO EXTRA-UTERINE LIFE

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The transition from intra- to extra-uterine life is one of the greatest physiological challenges that occur in the life of animals. Immediately after birth, newborn calves have to adapt to new environmental and feeding conditions. Namely, at birth a break of the thermal balance occurs, since calves abruptly pass from a 38.8°C temperature *in utero* to an environmental temperature that is generally lower than 20°C. Additionally, at birth, the energy intake shifts from a continuous parenteral supply of nutrients (mainly glucose) to discontinuous colostrum and milk intake with lactose and fat as the main energy sources. Therefore, the most important issues related to metabolic changes during the transition from intra- to extra-uterine life are related to maintaining the homoeothermic conditions and control of energy metabolism. Those metabolic adaptations are under control of the endocrine system that is relatively mature at birth, but still requires morphological and functional changes after birth. Key hormones whose concentrations are significantly changed around birth and are involved in an adequate adaptation of calves to extra-uterine life are those related to stress at birth (cortisol and cathecholamines), glucoregulatory processes (insulin and glucagon), thermogenesis (thyroid hormones) and growth (IGF axis).

Key words: calves, glucoregulation, growth, perinatal, stress, thermogenesis

INTRODUCTION

The transition from fetus to newborn is the most challenging period in the life of animals, since great morphological and functional changes occur in order to prepare the organism for extra-uterine life. Those changes include the maturation of the endocrine system, metabolic pathways, vital organs and immune system. It is not uncommon that these adaptation mechanisms fail and become risk factors for health disturbances. Therefore, morbidity and mortality rates in the perinatal period (period from day 270 of pregnancy to 24 hours of life) are the highest of all life stages of an animal [1,2]. Morbidity and mortality remain high during the neonatal period (from day 2 to day 28 of life) and then decline as calves develop and gain in body weight [3].

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Raboisson and coworkers [4] presented that mortality of dairy calves during the first month of life range up to 17%. Based on data presented by USDA for year 2007, 50% of calf mortality was directly related to inadequate passive immunity while 50% was related to non-immunological factors [5].

In order to effectively prevent losses related to health disturbances during the perinatal and neonatal periods of life, it is important to understand the conditions and factors for success and failure of adaptation mechanisms. In general, the factors influencing newborn calf morbidity and mortality may be divided between immunological and non-immunological factors. There are numerous reviews [6-10] that deal with factors that affect the maturation of the immune status of neonatal calves (immunological factors), since those factors are considered to be essential for the survival of the neonate. Namely, calves are born agammaglobulinemic and have to achive full maturity of immunity during early neonatal life [10]. On the other hand, there are only few reviews that describe non-immunological factors [11-12] that contribute to an adequate adaptation of newborn calves, but are not defined as life-threatening. Therefore, with no aim to diminish the importance of the immune system development for offspring survival, this review will emphasise the role of endocrine and metabolic factors for adequate adaptation of calves to extra-uterine life, since those factors significantlly contribute to an orchestrated physiological adaptation of newborns.

ENDOCRINE CHANGES

The endocrine status of the fetus is essential for maturation of fetal organs that have to be fully prepared for the cessation of direct maternal supply with oxygen and nutrients which occurs during birth. Nevertheless, many organs are still immature at birth and need further maturation during the early neonatal period. Coincidentally, the hormonal status of fetal and newborn calves is not fully developed and is exposed to dramatic changes during late gestation and the early neonatal period in order to provide an adequate adaptation of newborns to the extra-uterine environment.

Key hormones that are involved in the adequate adaptation of calves to extra-uterine environment are cortisol, cathecholamines, insulin, glucagon, thyroid hormones and insulin like growth factors-I and -II [IGF-I and -II). Cortisol and cathecholamines secretion is associated with birth related stress [13-15], while insulin and glucagon secretion contributes to the regulation of glucose and energy metabolism [16]. Thyroid hormones are mainly involved in thermogenesis of neonete [17]. IGF-I and –II, that are a part of the IGF system, are essential for growth and development of different fetal and neonatal organs [18].

Cortisol

Cortisol, a hormone known to be involved in the stress response, is the factor that prepares the fetus for birth, but also supports the maturation of many organs and

metabolic pathways during the transitional period from intra-uterine to extra-uterine life [13].

Most of the fetal cortisol is synthesized in fetal adrenal glands, since very little transfer of cortisol between maternal and fetal compartments seems to occur [14]. The fetus is also protected from the high maternal cortisol by the presence of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), a placental enzyme which oxidizes cortisol to the biologically inactive cortisone [19]. Placental 11β-HSD1 receptors are regulated by estrogen and the late-gestational rise in estrogen is associated with increased 11β-HSD1-enzyme expression [20]. The increase in weight of the fetal adrenal glands, as a consequence of maturation of the fetal hypothalamic-pituitary-adrenal axis, occurs mainly during the last month of gestation [14] leading to elevated concentrations of fetal cortisol. The increased fetal cortisol concentration, that is at its highest during the last 3 to 5 days of gestation, leads to the cascade of endocrine events that provokes parturition, but also to essential maturation of the fetal lungs and gastrointestinal tract in their preparation for extra-uterine life [21]. Additionally, the prenatal increase in cortisol concentration has a strong influence on maturation of glucose metabolic pathways in the fetal liver [14]. Cortisol increases the incorporation of glucose into glycogen in fetal hepatocytes, by induction of glycogen synthetase. This effect can be augmented by subsequent administration of insulin, although insulin administration with no additional cortisol does not result in glycogen accumulation in fetal hepatocytes [22].

After birth, before colostrum intake, the cortisol levels continuously rise and peak soon after delivery ("cortisol surge") as a consequence of birth-related stress. Cortisol level at birth is significantly higher than in adult animals [23]. Colostrum provides additional cortisol to the neonate since maternal cortisol taken up by the mammary gland during colostrogenesis may be transferred to the neonate. Nevertheless, 60% of the cortisol in the colostrum is protein bound [24] and therefore not available for the neonate. With no additional source of colostral cortisol and with absence of stress, cortisol level significantly decreases during the first 12 hours of neonatal life [23].

Cortisol concentration in newborn calves has a a strong impact on the adequate adaptation of the animal to extra-uterine life. Cortisol enhances the maturation of some components of the endocrine system since elevated cortisol level support catecholamine release by the adrenal tissues and maturation of the thyroid axis leading to increased conversion of T_4 to T_3. The "cortisol surge" also increases β-adrenergic receptor density in many tissues including the heart and the lungs, and provoke, in association with thyroid hormones, maturation of the surfactant system in the lung [25]. Glucocorticoids enchance the maturation of the somatotropic axis around birth. Namely, the increased cortisol concentration during the perinatal period of life plays an important role in initiating the prenatal switch of the somatotropic axis from the fetal (when growth is indipendent of growth hormone) to the postanatal status and function [26]. Literature data indicate that in farm animal species cortisol stimulates the development of immature enterocytes, and causes enhanced immunoglobulin

absorption [9]. Glucocorticoids are essential in the maturation of metabolic pathways involved in glucose metabolism in the neonatal liver [14]. It has been shown that increased cortisol levels in the newborn, like in the fetus, have major implications on glucose availability [27]. As shown by Girard [28], adrenalectomy in newborn rats inhibits glycogen breakdown by 15-20%, meaning that cortisol has a permissive role in glycogenolisis in newborns. Glucocorticoids are also essential for thermogenesis, and a marked increase in glucocorticoid concentrations has been reported in response to exposure to cold in neonatal calves [29]. It is most likely that glucocorticoides play an indirect role in supporting cold thermogeneisis through mobilization of lipids and glycogen to supply energy thermogenesis [30].

Based on data related to the impact of birth-related increased levels of cortisol on neonatal survival, it may be concluded that elevated physiological concentrations of cortisol for a short period of time (acute stress) are benificial for the long-term health of a newborn. However, prolonged or repetitive exposure to elevated cortisol concentrations (chronic stress) can negatively affect the performance of an animal [25].

Cathecholamines

Catecholamines are present in the fetal plasma and they are released from the adrenal medullar tissues into the fetal circulation in response to fetal stressors, like hypoxia and asphyxia [31]. Fetal catecholamines suppress insulin secretion and may be responsible for the rise in plasma glucagon. Therefore, in severe hypoxia the fetus survives at the expense of its glycogen reserves and the effects of catecholamines in promoting glycogen breakdown are augmented by depression of plasma insulin and rise of plasma glucagon [32]. Under physiological conditions, the fetus is partly protected from the metabolic effects of stress mediated catecholamine release because the placenta increases catecholamine clearance [33].

At delivery, transient hypoxia initiates the additional secretion of cathecholamines. Although plasma catecholamine concentrations are very high at delivery a rapid decrease during the first 30 minutes of postnatal life is found, followed by a significant increase in their concentrations at the second postnatal hour, which coincides with the highest cAMP concentrations observed in the liver and with the onset of significant liver glycogen mobilization [34, 35]. The occurrence of postnatal hypoglycemia could stimulate the increase in plasma catecholamine concentrations in the second postnatal hour. Nevertheless, it can be argued why the high plasma catecholamine concentration observed at birth is unable to promote liver glycogenolysis until then. It is tempting to speculate that high insulin concentrations observed at delivery could antagonize the catecholamine effects on liver glycogenolysis [36].

The postnatal catecholamine surge is, therefore, primarily responsible for the adaption of energy metabolism with support of the primary substrates for metabolism after birth – glucose and fatty acids, but is also responsible for other adaptive mechanisms

of the newborns, like for the increase in blood pressure following birth, and for initiating thermogenesis from brown fat. Newborns are normally exposed to very high levels of multiple vasoactive substances (catecholamines, angiotensin II and renin) that provoke increased blood pressure [37]. As far as influence of catecholamines on thermogenesis, both adrenalin and noradrenaline stimulate brown adipose tissue (BAT) thermogenesis by the activation of adenylate cyclase through binding of β-adrenergic receptors [38]. This binding leads to an increased activity of cAMP which stimulates hormone-sensitive lipase which in turn activates lipolysis to provide fatty acids for mitochondrial respiration. Free fatty acids also have been shown to stimulate uncupling protein (UCP) activity that allows energy generated by mitochondrial respiration in BAT to produce heat. Through binding of both α and β adrenergic receptors, catecholamines also stimulate the synthesis of iodothyronine 5`-deiodinase, leading to an increase of endogenous production of T_3 hormone that plays an important role in enhancing the synthesis of UCP. In addition to their role in BAT thermogenesis, catecholamines are involved in long term modulation of BAT growth and development during cold stress. Therefore, catecholamines play critical roles both in the activation of BAT thermogenesis during acute periods of cold exposure and in the recruitment and proliferation of BAT during sustained periods of cold exposure [38].

Insulin and glucagon

Insulin and glucagon are major hormones included in glucose homeostasis. In the fetal pancreas, functional maturation of glucagon and insulin secreting cells is essential for optimal growth, development and metabolism of the fetus, but also for an adequate adjustment of the neonate to extra-uterine life. It may be assumed that the need for those glucose homeostatic mechanisms may be less during fetal compared to postnatal life because the fetus is partly protected by maternal homeostatic mechanisms. However, it is not the case especially in situations of severe maternal malnutrition [39,40].

Insulin secreting B cells and glucagon secreting A cells of the pancreatic islets develop relatively early in gestation and can be detected in the islets of fetal lambs at 40 to 50 days of pregnancy. Since there is no evidence of placental flux of either hormone, it can be concluded that both hormones originated from the fetal pancreatic cells [41,42].

Insulin plays a significant role in regulating fetal glucose metabolism and the main determinant of insulin secretion is changes in the fetal plasma glucose concentration [41]. Insulin stimulates glucose metabolism within insulin sensitive tissues or incorporates glucose into glycogen in the fetal liver. As previously mentioned, the latter action of insulin is supported by cortisol [22]. Fetal insulin has also important effects on fetal amino acid metabolism which link fetal insulin status with fetal growth.

Increased fetal glucagon concentrations coordinate with fetal hepatic glycogenolysis leading to a significant increase of plasma glucose concentrations, although no direct

effect of glucagon on glycogenolysis was established in the fetal liver. Since Alexander and coworkers [42] have reported that glucagon concentrations in the fetal lamb are not influenced either by hyperglycemia or by hypoglycemia, it seems that during fasting diminished insulin concentrations will lead to a fall in the plasma insulin/glucagon ratio and increased dominance of hepatic metabolism by glucagon. Since no significant gluconeogenic activity is present before birth, it seems that glucagon contributes to the fetal glucose regulation exclusively through mobilization of glycogen [42].

Therefore, both fetal insulin and glucagon participate in the regulation of fetal metabolism during the last third of gestation, the period when the biggest part of fetal growth occurs and the maternal nutritional status has its greatest effects on weight at birth [39].

At birth, plasma insulin concentrations are very high, decreasing rapidly afterwards and reach the low level plateau between 1 and 2 hours [43], while glucagon levels rise sharply, as a consequence of adrenergic stimulation during birth-related stress, to peak at 30 minutes after birth. This leads to a big reduction of the insulin/glucagon molar ratio and favors catabolic processes that lead to glycogen mobilization, starting at the second postnatal hour [34, 35]. As previously mentioned glycogen mobilization is provoked mainly by catecholamine increase supported by a decreased insulin/glucagon molar ratio. There is a lot of evidence that proves that glucagon by itself is ineffective in triggering neonatal liver glycogenolisys [44, 45]. The partial resistance to glucagon stimulation by neonatal (and also fetal) hepatocytes could be due to (a) the lower number of high affinity receptors, or (b) an impaired coupling of the receptor with adenilate cyclase [46]. The essential role of glucagon postnatal rise is stimulation of gluconeogenesis. Glucagon stimulates the transport of pyruvate into mitochondria, which occurs during the first hour after birth, activates the components of the electron transport chain and so stimulates the phosphorylation of adenine nucleotide, and induces the appearance of PEP-carboxykinase – the rate limiting enzyme for gluconeogenesis [47].

During suckling, colostral intake leads to the postprandial release of insulin from neonatal pancreatic cells. Since insulin secretion mechanism is not fully matured, there are some speculations that partly absorbed colostral insulin may cover this insufficiency in secretion. Although neonatal gut capacity for insulin absorption is proved [43], it seems that colostral insulin, that is bound to milk casein [24], is not accessible for absorption [48]. The insulin axis in the neonate fully matures at day 7 of life in calves [48], but insulin responses to nutrients in the newborn strongly depend not only on colostrum intake but also on maternal nutrition during pregnancy that may affect it. Nevertheless, it has to be emphasised that insulin response in cattle may be breed related [49]. Plasma glucagon concentrations also rise during the first week after birth and provoke gluconeogenesis [48].

Thyroid hormones

The thyroid axis matures in late gestation parallel to the increase in cortisol level. This maturation includes increased thyroid stimulating hormone (TSH), T_3 and T_4 levels, and decreased reverse triodothironine (rT_3) levels as birth approaches [50]. The thyroid function prior to birth strongly interferes with cardiovascular and lung adaptation, as well as with thermogenesis in the newborn lamb [51]. At birth T_3 and T_4 levels are high [23, 43] and increase during the first hours of life due to both cortisol surge which supports the maturation of the thyroid axis and increased TSH secretion [52]. This peak in thyroid hormone concentration at birth considerably increases heat production and regulates cold thermogenesis. Nevertheless, acute changes of thyroid hormone concentrations at birth have a minor influence on adaptation to extra-uterine life, when compared with the impact of fetal thyroid axis maturation on postnatal adaptive mechanisms. After an initial increase, T_4 and T_3 concentrations rapidly decrease [23, 43]. Results related to the influence of suckling on thyroid hormone concentrations are inconsistent since some researchers confirmed no influence of feeding different amounts of colostrum, delayed colostral intake, and fasting on thyroid hormone concentrations in the neonate [23, 43], while others demonstrated the correlation between the nutritional and thyroid status in neonates [53].

IGF system

The IGF system includes insulin-like growth factors I and II (IGF-I, IGF-II), their receptors (type 1 and type 2), and high affinity binding proteins (IGFBPs). Six IGFBPs (IGFBP 1-6) bind blood IGFs, and the IGFBPs may alter the biological effects of IGFs action (I and II) [54]. IGFBP-3 increases the half-life of IGF-I in the blood, while enchased IGFBP-1 and IGFBP-2 enables IGF-I to pass though the capillary walls into the extracellular space where it affects glucose metabolism. In conditions of balanced energy status, IGFBP-3 is the dominant IGFBP in the blood. In a state of energy restriction, blood concentrations of IGFBP-1 are increased. There are some indications that IGFBP-2 concentrations are positively related to stress, although decreased IGFBP-2 levels in the blood may indicate on a decreased synthetic capacity of hepatocytes [55].

The IGF system regulates growth, both on systematic and tissue level, as well as metabolic adaptations of calves during all stages of fetal and neonatal development [56, 18]. Besides IGF system, growth hormone (GH) and insulin are responsible for growth of fetal and neonatal calves, and their interrelation is significantly changed during the transition from intra-uterine to extra-uterine life [57, 11]. There is a high similarity between the metabolic effects of insulin and IGF-I, due to their cross-reaction on the receptor level [58].

Fetal IGF-I and –II are synthetised in many fetal tissues including the liver, kidney, lung, heart and adipose tissue [59]. Fetal growth is mainly under IGF-II and insulin control. IGF-I concentrations are 10 fold lower in the fetus than in adult animals [60].

Syntehsis of fetal IGF-I is indirectly influenced by glucose concentration, due to the fact that increased glycemia stimulates insulin secretion that enhances IGF-I synthesis [61]. Fetal IGF-I synthesis is not under control of GH, as it is in the adult animal [57]. GH may be detected in ovine fetal circulation as early as day 130 of gestation, but its origin is still unknown since there is no precise evidence that fetal adenohypophysis may synthetise GH [62]. Abundance of IGFBPs in the fetal circulation differs from adult animals. In the human fetal serum, concentrations of IGFBP-1 and IGFBP-2 are twice higher and IGFBP-3 is three times lower than in adult animals [63].

In newborn calves, IGF system is basically functional, although it does not reach full maturity at that period. Neonatal calves are able to produce IGF-I mainly in the liver, but also in the gastrointestinal tract, spleen, thymus, lymph nodes, and kidney [64]. Effect of GH on IGF synthesis seems to be smaller in neonatal calves than in older cattle. This may be a consequence of the low GH binding capacity of the neonatal liver [65]. Therefore, it may be speculted that some other factors contribute to changes in the serum IGF-I concentration. In the condition of negative energy balance, that occurs immediately after birth, the concentration of IGF-I depends on the concentration of insulin in the circulation [66, 67]. There is a significant positive correlation between IGF-I and insulin concentrations during the first 2 hours of calf`s postnatal life, meaning that insulinemia, rather than GH, at birth affects IGF-I concentration [68]. In the condition of additional energy supply by glucose infusion, IGF-I concentration is strongly positively influenced by glucose concentration [43]. IGF system in the neonate is also influenced by thyroid hormones partly due to the influence of thyroid hormones on energy balance (metabolic rate) [69].

Kirovski and coworkers [68] showed that immediately after birth in neonatal calves the concentration of IGFBP-3 is highest and concentrations of IGFBP-2 and IGFBP-1 are lowest. This IGFBP status is opposite than in most other animals and humans [70, 71]. Thereafter, during the first 90 minutes of neonatal life, when calves are exposed to starvation, IGFBP-3 and IGFBP-2 concentrations significantly decrease and IGFBP-1 concentration significantly increases [68]. Decreased IGFBP-3/IGFBP-1 ratio enables IGF-I to pass though the capillary walls into the extracellular space where it may complement effects of insulin on glucose metabolism [72]. Murphy [73] showed that glucose concentration after birth has a strong influence on IGFBP ratio in the blood. In the study presented by Collett-Solberg and Cohen [74], hypoglycemia with hyperinsulinemia was coupled with a decrease of IGFBP-3 concentration and increased IGFBP-1 concentration. The positive relationship between insulin and IGFBP-1 is in accordance with the well-known acute effect of insulin on IGFBP-1 synthesis [75]. In a study presented by Kirovski and coworkers [43] hyperglycemia induced by glucose application immediately after birth provoked an increase of IGFBP-3, with no effect on IGFBP-1 and IGFBP-2 concentrations, leading to a retention of IGF-I in the circulation. Some authors observed a higher abundance of IGFBP-2 in neonatal calves immediately after birth [43, 68, 76] and explained it by a stress reaction that is characterized by an increased concentration of IGFBP-2 [77].

It is well known that bovine colostrum is a significant source of immunoglobulines and that the concentration of IgG in the colostrum is considered to be the hallmark for evaluating colostrum quality [78, 79]. Anyway, colostrum contains many other non-nutrient biologically active substances, such as hormones and growth factors, that are not essential for survival of the neonate but have great impact on good health of offspring [18]. This is the case not only in bovine, but also in other domestic animal species [80]. Therefore, any disturbances in milk quality of dams [81, 82] may affect the survival of young animals.

In contrast to other species where EGF is the dominant growth factor in the colostrum, IGF-I is the most abundant growth factor in bovine colostrum [83] and IGFBP-3 is the major IGFBP in mammary secretion. Colostral IGF-I is not absorbed in significant amounts [84, 85], probably due to interactions with colostral IGFBPs [85]. Because of low rate of absorption, colostral IGF-I ingestion has a minor influence on overall systemic growth and development, but has a strong impact on the neonatal digestive tract development. It reduces intestinal enzyme activity in the early postnatal period when calves are fed colostrum [86]. Although colostral IGF-I does not affect systemic IGF-I levels in a significant manner, colostrum intake increases IGF-I plasma concentrations and hepatic IGF-I expression in neonatal calves [64, 87]. Therefore, plasma IGF-I concentrations are higher in neonatal calves fed colostrum than in cows fed mature milk, glucose or water [88]. Egli and Blum [89] showed that plasma IGF-I in suckling calves increases from day 1 to day 7 of life. Therefore, in contrast to IGF-II [90], the IGF-I status can be in neonatal calves markedly modified by feeding.

METABOLIC ADAPTATIONS

During the transition from intra-uterine to extra-uterine life tremendous metabolic changes occur [91]. Those changes are strongly related to the hormonal pattern as well as to the developing rate of mechanisms involved in metabolic pathways of certain metabolites. As the previous part of this review described hormonal patterns of neonates, the maturation of components included in metabolic pathways will be presented in this section. A thermogenic response of the neonate, strongly associated with the metabolic capacity of neonates, will be presented as a separat section due to its great importance for neonatal survival. Most important issues related to the metabolic challenges during the perinatal period are related to carbohydrates i.e. energy metabolism and brown fat tissue metabolism that is strongly associated to thermal regulation.

Carbohydrate metabolism and energy homeostasis

During the life of the fetus, the calf relies on the supply with carbohydrates derived from the maternal circulation via the placenta. Carbohydrates are considered to be the most important source of energy in the fetus. Glucose is the major carbohydrate

in the fetal blood of many species but in ruminants fructose predominates. Namely, it has been shown that glucose, during its transfer from mother to fetus through the placenta, is partly converted into fructose which appears in the fetal blood [92]. Fructose is accumulated in the fetus since fructose, unlike glucose, cannot pass back into maternal circulation. Fetal blood fructose, that is highest in early pregnancy, tends to fall with increasing gestational age. Anyway, fetal fructose does not act as a reserve of carbohydrate in the fetus since the enzymes necessary for its utilization are absent in the fetal liver [93]. It is supposed that the osmotic pressure of fructose provokes the flow of water into the fetus.

The blood glucose concentration in fetal sheep is approximately 50% of maternal blood glucose concentrations. The glucose uptake by fetal lamb is a result of oxygen consumption and energy requirements [94]. Glucose is also required for the synthesis of fructose, glycogen and fat in the fetus [95]. The level of glycogen in fetal sheep liver is low very early in gestation, but it rises substantially in the last half of gestation up to parturition, when it reaches about double values compared to adults. Glycogen is also stored in skeletal muscles (five times adult concentrations) and to a lesser extend in the lung and heart. Placental stores are low. This deposition of glycogen is associated with a high activity of enzymes required for synthesis of glycogen from glucose [96]. Deposition of glycogen in the fetus is associated with functional integrity of adrenal glands [97] and, as mentioned earlier, this effect can be augmented by insulin [22]. Elevated hepatic glycogen storage in the fetus, caused by an increased cortisol concentration in the final stage of gestation, enables the neonate to provide glucose immediately after birth.

Glycogen stored in the fetus can be mobilized in time of stress. It was shown that in the case of undernutrition during late pregnancy in the sheep, fetal hepatic glycogenolysis may be stimulated, since the necessary enzymes and glucagon receptors are present in the liver of the fetal lamb [98]. All the enzymes necessary for gluconeogenesis are also present in the fetal lamb liver during this period, but studies on the incorporation of lactate into glucose suggest that no significant gluconeogenic activity is present before birth [99]. Thus it seems that mobilization of glycogen is a key mechanism that contributes to the short-term fetal glucose regulation. On the other hand, gluconeogenesis, regulated by glucagon, does not play a significant part in fetal glucose homeostasis, although such a mechanism would be possible due to the large increase in amino acid catabolism observed during prolonged fasting [100].

At birth the placental supply of carbohydrates from the mother stops abruptly and neonatal calves show hypoglycemia immediately after birth [68]. Because of that, during the first several hours of life, meaning until first colostrum intake, the newborn has to derive carbohydrates from its own endogenous sources through activation of gluconeogenesis and glycogenolysis. Several studies showed that plasma glucose concentrations increased immediately after birth, without nutrient intake [68, 101]. The rise of glucose concentration in the blood is a result of postnatal glycogenolysis that is associated with an increase in sympathetic efferent activity [102]. Sympathetic

activity at birth also increases by as much as six fold, and the plasma free fatty acid concentration in the lamb rises within 2 h of birth [103].

After parturition, liver glycogen level in the newborn ruminant falls rapidly to about 10% of fetal values within 2-3 h of birth [104]. Liver gluconeogenesis increases soon after birth due to the induction of phosphoenolpyruvate carboxykinase (PEPCK) activity, which is the key enzyme of gluconeogeneis [105]. The maturation of gluconeogenic metabolic pathways is necessary for the supply with glucose during the starvation period. The cortisol surge that occurs immediately after delivery regulates the maturation of gluconeogenic metabolic pathways [104]. Furthermore, the glucagon to insulin ratio in the blood plasma is one of the factors that may contribute to gluconeogenesis and glycogenolisis immediately after birth [12]. Regarding to fructose concentration in the blood of neonatal calves, it declines rapidly to very low values within 24 to 48 h of birth. This is not the result of metabolism of fructose but rather of excretion by means of urine. The enzymes necessary to metabolize fructose do not appear in the liver until the 5th day post partum at which no fructose remains in blood [106].

During the suckling period the young animal is again depended on its mother for carbohydrates, supplied this time in the form of milk lactose which must be hydrolyzed in the gut before it is absorbed from the small intestine. Enzymes that catabolise glucose and convert it to glycogen are present in the liver. Thus, liver glycogen, after an initial postnatal fall, rise to adult values 2 to 3 weeks post partum [104]. The maturation of gluconeogenic metabolic pathways is essential during the colostral period, because lactose intake is not sufficient to meet glucose demands in the neonate.

Glucose requirements are completed by an active gluconeogenesis process during the suckling period, in which the main gluconeogenesis substrates are lactate, glycerol and the gluconeogenic aminoacids [107]. It was shown that activities of enzymes involved in gluconeogenesis change markedly during the first week of life and are affected by feeding [108]. Colostrum feeding stimulates gluconeogenesis in the hepatocytes of newborn piglets [109].

Also, colostrum feeding impacts the glucagon to insulin ratio in the blood plasma [110]. Therefore, postnatal maturation, endocrine changes, and feeding may act in concert to stimulate metabolic processes in neonatal calves in accordance with their needs. Recently was shown [101] that endogenous glucose production, as well as gluconeogenesis, is not inhibited by insulin during euglicemic-hypergilcemic clamping, indicating a marked hepatic insulin resistance. Authors concluded that glucose production in the liver is not primarily regulated by endocrine factors, but probably by substrate availability or glucose disposal during neonatal period.

Besides lactose, colostrum supplies the neonate with fat, since colostrum, as a high-fat diet, provides the bulk of energy required for the hepatic oxidation of fatty acids [111]. The induction of this pathway occurs because of an increase in the activities of enzymes involved in the mitochondrial oxidation of fatty acids. These enzymes are

maintained at high levels of activity until weaning when a change of diet occurs. Once suckling is established, the oxidation of fatty acids results in an increase in plasma concentrations of ketone bodies, which are the energy substrate for extrahepatic tissues during this period [112].

It is interesting to emphases that in the fetal and neonatal ruminant glucose can also be converted into fat, contrary to adult animal whose activity of ATP citrate lyase, which is the key enzyme in the conversion of glucose to fat, is low [113].

Brown adipose tissue metabolism and thermogenesis

During the intra-uterine life of the calf, metabolic heat has to be expended in order not to increase the body temperature of fetus. At birth a break of the thermal balance of the calf occurs, since the calf abruptly passes from a 38.8°C *in utero* to an environmental temperature that is generally lower than 20°C [114]. Heat loss of the wet calf is directly proportional to the difference between the skin and environmental temperatures. So, the new-born calf has immediately to initiate thermolysis in physiological conditions that are not favorable due to hypoxia that occurs during parturition. This is the main reasons why hypothermia often takes place and may cause death of weaker calves [115].

In order to maintain the thermal balance, the newborn calf must adapt to extrauterine life by generating large quantities of heat. Heat production of newborn animals is a consequence of metabolic processes in body tissues, the metabolism of brown adipose tissue, shivering during physical activity and heat increment of feeding [116, 117].

The nutrient reserves accumulated in the body that affect the metabolic rate of body tissues are hepatic and muscular glycogen, labile proteins and lipids. Glycogen stores are rapidly mobilized and broken down in the starved calf [102]. Glucose is used for thermogenesis and for physical activity. Protein mobilization also occurs probably due to the high levels of cortisol after birth [23]. Body lipids are mobilized, as shown by the increase in plasma non esterified fatty acids (NEFA) [118].

Two types of adipose tissues exist in neonatal ruminants – white adipose tissue (WAT) and brown adipose tissue (BAT) [119]. BAT differs from WAT based on color and multilocular distribution of lipids within the cell. The color of BAT is from light tan to reddish brown, partly because of a lower lipid concentration and greater concentration of mitochondria and blood vessels than in WAT. As well known, the primary function of WAT is storage and release of fatty acids for use as energy source, and, the primary function of BAT is to generate heat by non-shivering thermogenesis meaning without electrical activity that occurs in the skeletal muscle that produce heat by shivering [120]. The capability of BAT thermogenesis is attributed to a unique 32 000 Mr uncupling protein (UCP) located in the inner mitochondrial membrane [121]. The UCP in BAT mitochondria allows mitochondrial respiration to be uncoupled from oxidative phosphorylation (synthesis of adenosine triphosphate-ATP) thereby using the energy generated by mitochondrial respiration in BAT to produce heat rather

than ATP [121]. On the contrary, in the mitochondria of skeletal muscles where UCP is not present, mitochondrial respiration is coupled with oxidative phosphorylation and production of ATP. Heat is produced in muscle tissue only when ATP is used (i.e. muscle contraction) [115]. Similar to shivering muscle tissue, the ability of BAT to generate heat depends on the rate of substrate (i.e. fatty acids, glucose) oxidation in the mitochondria. During the initial phase of thermogenesis the fatty acids are derived from endogenous triglyceride stores, through the action of hormone sensitive lipase [122]. The stored TAG in BAT of a newborn rabbit lasts only 30 hours under the influence of thyroid hormones [123]. Maintenance of BAT thermogenesis under prolonged periods requires provision of fatty acids from other reserves of the body as well as from the diet [120]. This requires the action of lipoprotein lipase. This enzyme increases its activity during cold exposure, which presumably reflects its increased synthesis within brown fat cells and secretion in the capillary lumen [124]. BAT has a considerably higher fatty acid releasing capacity than white fat [122].

In order to exhibit maximal thermogenesis during early postnatal life, BAT has to be fully mature at birth. It means that recruitment of functional brown adypoticites must occur during fetal development. Detectable quantities of perirenal adipose tissue first appear in the ovine fetus at 70 days of gestation, and then rapidly grow from 70 to 120 days of gestation [125]. Nevertheless, the development of major morphological and biochemical features critical to functional BAT occurs until late gestation. This was confirmed by detecting a significant increase in bovine fetal UCP from perirenal adipose tissue depots starting from day 266 of gestation [121]. BAT iodothyronine 5` deiodinase activity appeared in fetal perirenal tissue at 2 months of gestation, achieved peak at 7 months of gestation and subsequently decreased until birth [123]. It may be assumed that endogenous BAT conversion of T_4 to T_3 may be involved in the prenatal induction of UCP expression.

At birth, BAT is located in the perirenal, inguinal and prescapular regions and amounts to about 2% of body weight. Even though BAT accounts for only 2% of body weight in newborn lambs, it can account for 40% of maximal thermogenesis during cold exposure. During the first month of life BAT is rapidly converted to white adipose tissue leading to a decline in non-shivering thermogenesis in calves. The decline in non-shivering thermogenesis coincides with rapid morphological changes in the BAT and the apparent conversion of brown adipocytes to white adypocytes as demonstrated in calves [126]. Direct evidence for cellular conversion of brown to white adipocytes remains to be demonstrated, although recent studies have shown that the postnatal disappearance of morphologically identifiable BAT in neonatal ruminants is associated with a decrease in key biochemical characteristics of BAT, including the decrease in the thermogenic activity of brown adipocytes mitochondria [121], a reduction of expression of UCP mRNA [127], and a decrease in the activity of iodothyronine 5`-deiodinase enzymes [128]. Cold- and diet-induced adaptation may slow or prevent this involution [129, 130].

Shivering seems to be an important factor of thermoregulation in new-born calves and it appears soon after birth in calves held at 10°C and stops when the hair coat is almost dry. When a new-born calf struggles to get up, its heat production increases by 30 to 100%. When the animal stands up for the first time and spends 10 min standing, its energy expenditure is also increased by 100%. When it is a bit stronger and is able to stand for more than 30 min, heat production is increased by 40% on average over this period (personal results) [131].

During the suckling period, when the calf is fed, colostrum constitutes are an excellent energy source (6.7 MJ/kg) for thermogenesis. In 24 Friesian calves held at 10 °C, heat production was increased on average by 18% and 9% respectively during the first and the second hour following colostrum consumption at 12h of age. An intake of 2 kg of colostrum is able to meet the energy requirement of a 40 kg new-born calf held at 10 °C for 24h. Early consumption of colostrum is therefore very important for thermoregulation [116, 132].

CONCLUSION

Endocrine and metabolic adaptations of calves to extrauterine life are of crucial importance for neonatal survival. The main hormones that contribute to these adaptations are those related to stress (cortisol and catecholamines), glucoregulatory processes (insulin and glucagon), themogenesis (thyroid hormones) and growth (IGF axis), while the main metabolic adaptations to extrauterine life are related to carbohydrates metabolism (since *in utero* and during postnatal starving period the ruminant is provided with high levels of carbohydrates and low level of fat) and thermogenesis (since the newborn is usually exposed to lower temperature compared to intra-uterine environment). An understanding of maturation of metabolic and endocrine mechanisms that are involved in the adaptations of neonatal calves on extrauterine life, is essential for the implementation of appropriate preventive measures that may contribute to increased survival of neonatal calves.

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HORMONSKA I METABOLIČKA ADAPTACIJA TELADI NA EKSTRAUTERINE USLOVE ŽIVOTA

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Prelaz iz intrauterinog u ekstrauterini period života je jedan od najvećih fizioloških izazova koji se dešavaju tokom života životinje. Odmah nakon rođenja, novorođena telad treba da se prilagode novim uslovima ambijenta i ishrane. Naime, prilikom rođenja dolazi do prekida temperaturnog balansa organizma, pošto tele naglo prelazi iz intrauterine sredine, gde vlada temperatura od 38,8 °C, u ekstaruterinu sredinu gde je spoljašnja temperature obično niža od 20 °C. Dodatno, tada se snabdevanje energijom menja jer od kontinuiranog parenteralnog snabdevanja (pretežno glukozom) prelazi na diskontinuirano, koje se ostvaruje unošenjem kolostruma i mleka u kojima su glavni izvor energije laktoza i masti. Zbog toga su najznačajnije promene tokom prelaska iz intrauterinog u ekstrauterini život vezane za održavanje stalne telesne temperature i kontrolu energetskog metabolizama. Te promene su pod kontrolom endokrinog sistema koji je relativno razvijen u momentu rođenja ali ipak zahteva dodatne morfološke i funkcionalne promene posle rođenja. Ključni hormoni čija se koncentracija značajno menja u periodu oko rođenja i koji su uključeni u adekvatnu adaptaciju teladi na ekstrauterine uslove života su oni koje su povezani sa stresom na rođenju (kortizol i kateholamini), procesima regulacije glikemije (insulin i glukagon), termogenezom (tireoidni hormoni) i rastom (IGF osovina).