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1st International Symposium:

Modern Trends in Agricultural Production and Environmental Protection

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Tivat-Montenegro
July 02-05.
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FUNCTION AND IMPORTANCE OF HSP 70 IN METABOLIC STRESS IN DAIRY COWS IN PERIPARTAL PERIOD

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ABSTRAKT

Peripartal period in dairy cows includes 3 weeks ante partum and 3 weeks post partum (transition period). The transition period represents the most challenging phase in the life of dairy cows, because the body occurring metabolic, endocrine, immune and reproductive changes that affect the animal health and production efficiency. During the transition period (the late gestation and early lactation) in response to metabolic stress, in dairy cows can develop numerous pathophysiological mechanisms (inflammation, insulin resistance and metabolic adaptation). Numerous mechanisms are activated in the organism of dairy cows, the main role of which is maintenance of homeostatic and homeostatic functions of all tissues, organs and organ systems. In regulation of these processes, heat stress proteins HSP70 play a key role.

Key words: *dairy cows, peripartal period, metabolic stress, HSP 70.*

INTRODUCTION

Peripartal period includes 3 weeks ante partum and 3 weeks post partum (the so-called transition period). It represents a period in which the metabolism of dairy cows faces a series of changes in the homeostasis with endocrine changes, metabolic stress, and many pathophysiological mechanisms (inflammation, insulin resistance and metabolic adaptation) that develop during metabolic stress in peripartal period in dairy cows (Petrović i sar., 2018a). In this for cows during the difficult period around the partus there are numerous metabolic adaptations that arise as a result of gravity, partus and beginning of lactation (homeoretic processes), as well as the tendency of the organism to maintain homeostasis. All these processes inevitably lead to stress in the cows. The emergence of stress in cows is a consequence of the strengthening of homeotrophic, catabolic processes and the negative energy balance of cows at the beginning of lactation (Cincović 2013a).

The biggest problem with postpartum dairy cows is the imbalance between body reserves and milk production (Petrovic i sar., 2019a). The metabolic processes in the transition period are adapted to provide a sufficient amount of energy required as well as precursors for the synthesis of dairy compounds (Grummer 1995.; Overton and Valdron, 2004). Consequently, the main feature of early lactation in dairy cows is the negative energy balance (NEBAL) and the state of metabolic stress that results from reduced intake of food, calving and starting lactation. Due to the negative energy balance, the organism increases its own reserves and enters the catabolism phase.

As a result, lipomobilization intensifies ketogenesis and lipogenesis in the liver, and as a consequence, the concentration of glucose, triglycerides and total blood cholesterol (Sevinc et al., 2003.; Đoković et al., 2007, 2009, 2010a).

In NEBAL conditions, the body consumes its own energy reserves, first of all glycogen reserves, then fat, and then protein. As a consequence, there is a faty liver, a weight loss of various degrees, a decrease in production and reproductive abilities, and in some cases a death occurs (Đoković et al., 2014a).

Especially expressed is the increased mobilization of lipids from body depots in order to use fat for energy purposes, but cows become prone to the development of ketosis and fatty liver (Cincović et al., 2012; Đoković et al., 2014b). As a consequence of lipolysis in the fat tissue, the concentration of non-esterified fatty acids (NEFA) and betahydroxybutyrate (BHB) in the bloodstream increases. This phenomenon occurs as a result of endocrine and metabolic changes, primarily due to the presence of insulin resistance (Cincović et al., 2014).

Stress resulting from a disbalance of energy metabolism with numerous endocrine, biochemical, haematological, immunological and other adaptations is called metabolic stress (Cincović 2013b). Metabolic stress in early lactation in dairy cows underlies many diseases (Cincovic et al., 2018).

The transition from the state of gravidity and drying in the period of early lactation (peripartal period) is a very strenuous process for the smooth functioning of the cow organism, and is the most critical for their health and productivity. Partus and lactation start metabolically burdening cows to the extremes, so numerous adaptations can be such that the number of cows with some of the diseases (fatty liver, ketosis, metritis, mastitis, left and **right** dislocation of **abomasum**, locomotor diseases) is increasing in this period (Cincovic 2013a; Petrović et al., 2019). There may also be a persistent decline in cow productivity through reduced milk production and poor maintenance of lactation, a significant loss of body condition after calving - BSC below 3.5 (3.25 to 3.75), the occurrence of reproductive disorders such as retained placenta and cyst ovary, causing great economic damage to farmers.

It should be noted that in all this good manufacturing practice on the farm affects the economic viability of production. Therefore, efficient reproduction on farms in dairy cows is of great economic importance. However, in modern farms, increased milk production along with poor farm management (poor nutrition or reproduction) can affect reduced fertility in animals. Namely, the selection in cattle breeding is very successful in the direction of increasing milk production. But the phenotype of milk yield is only 25%. The influence of paragenetic factors on milk properties, regardless of whether their nature is fixed (the breeding area of the years and the season of birth, season of calving, lactation in order) or continuous (age at first fertilization and calving) is very pronounced and significant, and it is necessary to include them in models for assessing the breeding value of dairy cows (Petrović et al., 2005, 2006, 2009, 2010, 2012; Bogdanović et al., 2012)

Unfortunately, with the increase in milk production, fertility decreases and, consequently, the number of animals that have partus, which is reflected in the profitability of production (Gábor et al., 2016).

The main goals of modern cattle breeding are the increase in the fertility of breeding throats, the prolongation of their exploitation time, the increase in profit and the cultivation of as many genetically high-quality offspring as possible. The achievement of these goals depends on the factors determining the genetic potential of the reproductive properties of the reproductive throat and environmental factors (paragenetic factors), which enable the phenotypic expression of reproductive characteristics (Košarcic et al., 2003; Petrović et al., 2013a, b, c.).

Therefore, it is very important to understand the reproductive cycle physiology of dairy cows and its relationship with the metabolic status of cows in early lactation (Đoković et al., 2014a).

Cellular adaptation of dairy cows to peripartal metabolic stress (HSP70)

Milk production starts after calving of cows and is maintained artificially, by husband, for the next 305 days. In this period there are very significant changes in the metabolism and nutrition of cows, and the intensity and biological basis of these changes depend on the health of cows and milk production in the next lactation. The essence of metabolic changes occurring during the transition period (21 days before and 21 days after the partisans) is based on the fact that cows are exposed to negative energy balance during early lactation, that is, they can not enter through the food the amount of energy they need for maximum milk production. There are many reasons that lead to reduced food intake and a negative energy balance. Reduced food intake is the result of adaptation to the onset of lactation. On the other hand, in the cow there is a change in the main metabolic flows to maintain the lactation that follows. These processes lead to changes in the metabolism of cows, increasing the use of fat for energy purposes, in order to keep glucose for milk production. Also, in early lactation there is a deficit of vitamins and minerals, so their role in numerous metabolic processes is absent (Đoković et al., 2014c).

Namely, the basic changes in the metabolism of carbohydrates and fats in the period around calving and early lactation are: lower glycemic levels, increased gluconeogenesis, reduced glucose consumption in peripheral tissues, normal or decreased use of acetate, increased lipid mobilization from fat stores with elevated concentrations of non-esterified fatty acids (NEFA) and their increased use in peripheral tissues (Đoković 2010b)

These changes are followed by a series of endocrine changes such as insulin resistance, decreased insulin concentration (due to reduced food intake and decreased receptor sensitivity), decreased insulin-like growth factor IG and I IGF-I (due to a reduced anabolic effect of growth hormone in the peripheral tissue cow in spite of its elevated concentration), decreased thyroid hormone concentrations, catabolic effect of growth hormone on fatty tissue - increased growth hormone concentration (which allows increased use of nutrients in the mammary gland and leads to a decrease in insulin sensitivity), elevated cortisol concentration (which helps lipomobilization and gluconeogenesis), increased glucagon levels.

During the transitional period in response to metabolic stress, numerous pathophysiological mechanisms (inflammation, insulin resistance and metabolic adaptation) are developed in dairy cows. Inflammation and insulin resistance are important pathophysiological mechanisms that develop during metabolic stress. Heat shock proteins have a significant influence in the regulation of both these processes in different animal species and humans. They help to clear the protein structure of the cell and its survival. However, if they find themselves extracellularly, they show proinflammatory effects and have to do with the development of insulin resistance and diabetes (Petrović et al., 2017).

In the organism of dairy cows numerous mechanisms are activated, the main role of which is to maintain all these processes within the physiological limits. In regulation of these processes, HSP 70 heat stress proteins play a key role.

Heat schock protein (HSP) are phylogenetically conserved and ubiquitous molecules, indicating their functional importance (Petrović et al., 2017).

Heat shock protein, HSP are chaperones necessary for the proper formation of the polypeptide chain and are responsible for its translocation in the cell. These proteins were found during exposure to heat stress, when their concentration and expression in the cells grew to explain their name (Cincović 2013a.; Petrović et al., 2016).

Heat schock proteins are synthesized in response to various forms of stress. Namely, their expression can be induced in several ways: physiological (growth factors and hormones), pathophysiological (infection, inflammation, ischemia, oxidative injuries and toxins), environmental conditions (heat stress and heavy metals) (Petrović i sar., 2018b).

They are traditionally classified according to their molecular weight. (Prohaszka and Fust, 2004.). According to the molecular mass we distinguish several types, so for example: 10 kDa (Hsp10), 20-30 kDa (Hsp27, HspB1), 40 kDa (Hsp40), 60 kDa (Hsp60), 70 kDa (Hsp70, Hsp71, Hsp72, Grp78, Hsx70), 90 kDa (Hsp90, Grp94) and 100 kDa (Hsp104, Hsp110). In cattle, four types of Hsp70 genes were identified, and IRNK for this protein was found in the tissue of different cell types and in the blood plasma (Agnew and Colditz 2008; Asea 2007).

Tavaria et al., (1996.) gave a first clarification of the nomenclature of the HSPA family and showed that the family of a human heat shock protein is composed of at least 12 members and many others agree with their allegations. Modification and extension was given by Kamping et el. (2009.), where he provided updated guidelines for the nomenclature of the human HSPA family (HSP70), as well as HSPH (HSP110), HSPC (HSP90), DNAJ (HSP40) and HSPB (smoll HSP) and human chaperone families (HSP60 and CCT). Also, Kampinga et al., (2009.) stated that the guidelines for the nomenclature of human heat shock protein are also based on systemic gene symbols assigned by the HUGO Gene Nomenclature Committee (HGNC) and used as primary identifiers in databases such as Entrez Gene and Ensemble. The best known HSPs are: stress induced form HSP70 / HSP72 (HSPA1A), constitutive forms HSP70 / HSP73 / HSS73 (HSPA8), an endoplasmic reticulum form, Grp78 / BiP (HSPA5) and a form localized mainly in mitochondria HSP75 / mtHSP70 / mortalin / TRAP-1 (HSPA9) (Petrović et al., 2018c). In addition to them, and less familiar localization, there are: Hsp70-2 (HSPA1B); Hsp70-Hom / Hsp70t (HSPA1L); Hsp70-3 (HSPA2); Hsp70-6 / Hsp70B '(HSPA6); HSP70-7 / Hsp70B (HSPA7), FLJ13874 / KIAA0417 (HSPA12A), RP23-32L15.1 / 2700081N06Rik (HSPA12B), Stch (HSPA13), HSP70-4 / HSP70L1 / MGC131990 (HSPA14) (Petrović et al., 2018a).

In the cells, the HSP70 family is the most induced HSP family in response to stress. HSP72 molecular weight of 72 kDa can represent up to 20% of the total cell protein and is very rapidly induced during cell stress after appropriate stimulation (Noble et al., 2008), especially in skeletal muscle cells (Madden et al., 2008).

Namely, the two most studied proteins in the HSP70 family are HSC73 and HSP72 (Beckmann et al., 1990). Sorger and Pelham (1987) have shown that HSC73, a heat shock protein molecule mass of 73 kDa, is synthesized in most cellular organisms and is only slightly inducible. Unlike HSC73, HSP72 is present in small amounts in ungraded cells, and is thought to be primarily stress-induced (Kiang and Tsokos 1998; Hartl 1996). During the action of various stress stimulus, the organism strives to meet increased demands during stress-related events in HSP72 synthesis (Black and Subjeck 1991).

HSP70 has the ability to exert completely opposite effects depending on its localization (Rodrigues-Krause et al., 2012). Namely, heat shock proteins have long been considered exclusively cytoplasmic proteins with certain functions that are limited to the intracellular part of the cell. However, an increasing number of studies have shown that they can be released into extracellular space (eHSP72) and have different effects on other cells (Titell 2005).

A high level of intracellular HSP72 synthesized in response to stress, occupies the cell and protects it through the role of molecular chaperon (Lindquist and Craig 1988). Said cytosolic inducible HSP70 can mediate through cytoprotective, antiapoptotic and immunological regulatory effects, and is most studied.

The protective role of HSP70 is well documented, and it is interesting that HSP70-induced hyperthermia can provide protection against myocardial ischaemia, suggesting that HSP70 can be protected through cross-care (Cornelusson et al., 1994). Increased HSP70 expression in experimental models of stroke, sepsis, acute respiratory distress syndrome, renal insufficiency and myocardial ischemia is created to reduce bodily injury and in some cases improve survival (Jo et al., 2006; Weiss et al., 2002; Chen et al., 2003; Giffard and Yenari 2004). It has been shown that embryonic HSP70 plays a role in normal development (processes such as apoptosis, cell cycle regulation) and protects against stressors in sensitive embryonic stages (Luft and Dix 1999).

When it comes to extracellular HSP70, it plays a role of cytokine, an immunostimulatory role (helps synthesize proinflammatory cytokines) and improves antitumour control.

Extracellular eHSP70 comes from cells to the bloodstream from living cells exposed to stress through vesicular secretion, exosomes or lysosomes, and through intact lipid membranes that are independent of the transport of proteins through the endoplasmic reticulum-Golgi apparatus, but also passive pathways from necrotic cells and stress-stressed cells (Molvarec et al., 2007; J. Campisi et al., 2003). In a research by Campisi et al. (2003), extracellular heat shock proteins (eHSP), such as those belonging to the HSP family of 70 kDa (for example, HSP72) were presented to act as a "signal of danger" toward immune cells, promoting immune response and improving host defense.

The eHSP72 function is generally associated with the activation of the immune system (Whitham and Fortes 2008). For example, eHSP72 has been reported as an inductor of the microbicidal capacity of neutrophils (Ortega et al., 2006) and chemotaxis (Ortega et al., 2009), participates in the recruitment of NK killers (Horn et al., 2007) as well as in the production of cytokines in immune cells (Asea et al., 2000; Johnson and Fleshner 2006).

There is still no known HSP fraction in the bloodstream coming in one or the other way, and the role of extracellular HSP is contradictory. Namely, the concentration of HSP increases in various diseases, and due to the lack of HSP, metabolic syndrome occurs in humans (obesity, diabetes, cardiovascular disease and dyslipidemia) (Asea 2007; Chung et al., 2008; Krause and Rodrigues-Krause, 2011). Also, the increased concentration of extracellular HSP means better survival (Pittet et al., 2002).

Namely, although induction of iHSP72 reduces the production of cytokines, extracellular HSP (eHSP) can significantly increase the production of proinflammatory cytokines (Breloer et al., 1999; Chen et al., 1999; Multhoff et al., 1999; Asea et al., 2000).

The concentration of HSP70 during gravidity and calving depends on numerous biological variables and physiology and pathology of calving (Molvarec et al., 2010).

Molvarec et al., (2007) found that the concentration of eHSP70 was lower in pregnancy than in non-pregnant women, which is consistent with our results (Petrović et al., 2016). Expression of Hsp72 mRNA in sheep myotomy (intracellular) was elevated during lambing (Wu et al., 1996), as well as in amniotic fluid in women (extracellularly), which were conceived and produced on time (Chaiworapongsa et al., 2008).

Kristensen et al., (2004) have shown that there are numerous factors that influence the concentration of HSP70 in serum cows, such as age and stage of lactation. Although there was no statistically significant difference, plasma concentrations of HSP72 were higher in early lactation (the first 60 days) compared to the middle part of lactation. The concentration of HSP72 is significantly lower in the cows before the partus and in the first weeks after the partys, in order to grow. In dairy cows there is a positive correlation between extracellular and intracellular Hsp 72 values (Catalani et al., 2010). However, this indicates the existence of certain specificities in the regulation of extracellular Hsp72 in cows in the peripartal period. In cows in early lactation, a lower concentration of eHSP70 was found in the first two weeks after calving compared to 4 and 8 weeks (Petrović et al., 2016). These values, as well as their trend, agree with the results of Catalani et al. (2010) and Kristensen et al., (2004).

However, some studies have shown that caloric restriction, hypoglycaemia or hyperlipidemia (which occurs in early lactation) can regulate HSP expression in different parts of the body. Eitam et al., (2009) reported that an extended low-energy diet promoted cell-specific HSP response in cattle with a significant increase in HSP90, but unchanged levels of HSP70 mRNA in leukocytes and lower expression of HSP70 in somatic milk cells. Febbraio et al. (2004) showed that maintaining glucose availability during the exercise reduces the circulation response of HSP72 to healthy people. Creation of intracellular HSP72 under the effect of heat stress reduces insulin resistance and reduces fat accumulation in hepatocytes (Morino et al., 2008). HSP72 concentrations in leukocytes and plasma increased rapidly after calving and correlated with NEFA, glucose, and TNFα (Catalani et al., 2010).

In a small number of studies, the association of peripartal metabolic stress with the values of chaperones was examined. The NEFA concentration in peripartal period shows a positive correlation with the NSP72 concentration (Catalani et al., 2010). Cincović and Belić (2014) showed that the concentration of NSP70 was significantly higher in weeks after calving compared to a week before calving. A higher concentration of NEFA and BHB (beta-hydroxybutyrate) was found in the first and second weeks after calving compared to other periods. The concentration of NSP70 positively correlates with NEFA and BHB values. Partial correlation shows that ties are stronger in the first and second weeks after calving, which is the period when lipid mobilization and ketogenesis are most pronounced. The concentration of NSP70 in the first two weeks after calving is dependent on the level of lipid mobilization and ketogenesis. Metabolic stress, characterized by lipid mobilization and ketogenesis, increases the blood NSP70 concentration during early lactation.

CONCLUSIONS

Hsp70 shows significant relationships with the pathophysiological mechanisms dominant in cows in early lactation, such as inflammatory response and insulin resistance.

Consequently, there is a presumption that the indicators of metabolic stress can affect the concentration of Hsp70 in serum of cows.

In the future, Hsp70 can be a significant indicator that can be used to evaluate the metabolic adaptation of cows in the peripartal period.

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