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INSULIN RESPONSES TO ACUTE GLUCOSE INFUSIONS IN BUŠA AND HOLSTEIN-FRIESIAN CATTLE BREED DURING THE PERIPARTUM PERIOD: COMPARATIVE STUDY

PRODANOVIĆ R*, KIROVSKI DANIJELA*, VUJANAC I*, ĐURIĆ M*, KORIĆANAC G**, VRANJEŠ-ĐURIĆ SANJA**, IGNJATOVIĆ MARIJA** and ŠAMANC H*

**University of Belgrade, Faculty of Veterinary Medicine, Serbia*
***Vinča Institute of Nuclear Sciences, Belgrade, Serbia*

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The aim of this study was to compare insulin responsevness to acute glucose infusion in cows of Holstein Friesian (HF) and Buša breeds during the peripartal period. Eight cows per each group (HF and Buša), were chosen. At day 7 prior to calving (ante partum) and day 14 after calving (post partum) animals were subjected to a glucose tolerance test (GTT). Blood samples were taken immediately before infusion and 15, 30, 60, 90, 120 and 180 min thereafter. Glucose and insulin concentrations were measured in each blood sample, while BHBA and NEFA were measured only in samples taken before the infusion. QUICKY an indicator of insulin resistance in cows was calculated. Basal glycemia did not significantly differ between the breeds. Basal insulinemia was significantly higher in Buša than in HF cows in both examined periods ($p<0.001$, respectively). Basal NEFA levels tended ($p=0.06$) to be higher in Buša cows compared with those of HF ante partum, and was significantly higher ($p<0.001$) post partum. Basal BHBA was significantly lower in Buša than HF cows in both examined periods ($p<0.01$; $p<0.001$). QUICKI was significantly lower in Buša compared to HF cows both ante partum and post partum periods ($p<0.001$, respectively). Glycemia determined during GTT were higher in Buša than HF cows, both ante partum and post partum, but significantly starting from minute 15 ante partum i.e. minute 30 post partum. Insulinemia determined during GTT was significantly lower at min 15, and significantly higher starting from min 90 in Buša than HF cows, both ante partum and post partum. Results obtained in this study indicate on difference in insulin responsevness to acute glucose infusion between the examined breeds, which is probably a consequence of the difference in the degree of negative energy balance rather than of selection on high milk production. Namely, decreased insulin tissues sensitivity and decreased insulin responsiveness in Buša compared to HF cows is probably the consequence of inadequate energy intake from alimentary sources which leads to enhanced usage of energy from body reserves.

Key words: Buša breed, glucose tolerance test, Holstein Friesian breed, insulin responsevness

INTRODUCTION

Holstein-Friesian cattle are the dominant breed of dairy cattle around the world, as well as in Serbia. Breeding programs for the Holstein-Friesian is focused on improved milk production. In contrast, Buša, as an autochthonous cattle breed characteristic for the Balkan area, is known for low milk yield and low tissue accretion of nutrients (Rogić *et al*., 2011). Selection for higher milk yields has provoked changes in cows' genotypes, physiology and metabolism (Bonczek *et al*., 1988; Veerkamp *et al*., 2003). An important issue is the possible effect of breed on the efficiency of feed use and endocrine control of nutrition partitioning. Modern, high yielding dairy cows, are capable of partitioning more energy into milk and less into depots of body tissue (Agnew and Yan, 2000; Yan *et al*., 2006), and they also express more intense mobilization of body reserves compared to their lower-yielding counterparts (Theilgaard *et al*., 2002; Beerda *et al*., 2007). This has caused a pronounced and prolonged period of negative energy balance (NEB) during lactation, which is accompanied by an increased incidence of lipid-related metabolic disorders, such as fatty liver and ketosis (Bobe *et al*., 2004; Goff, 2006; Šamanc *et al*., 2011). Thus, identifying the mechanisms that control lipid metabolism could help to develop strategies to improve lactation performance with no negative effect on cows' health and fertility.

In high yielding dairy cows, insulinemia and insulin resistance, play a key role in adjusting the balance between fatty acid mobilization and lipogenesis, as well as in the regulation of glucose uptake by insulin-dependent tissues (McNamara *et al*., 1995; Komatsu *et al*., 2005). Moreover, insulin appears to have an importance in the coordination of metabolism of carbohydrates, amino acids and lipids and the control of nutrient partitioning between the tissues and milk (Hayirly, 2006). Genetic selection for milk production has been associated with a decline in circulating insulin levels in dairy cows (Bonczek *et al*., 1988; Taylor *et al*., 2004) and insulin concentrations tend to fall in early lactation (Kunz *et al*., 1985). The euglycaemic clamp technique and glucose tolerance test (GTT) are commonly used to study insulin resistance or glucose intolerance (Hayirly, 2006; Šamanc *et al*., 2009). At the beginning of lactation dairy cows typically show reduced glucose-dependent insulin response as well as tissue sensitivity to insulin, but these effects seem to interact with genetic and metabolic factors (Hammon *et al*., 2007; Bossaert *et al*., 2008; Jaakson *et al*., 2010). However, obtained data may be confounded by the animals' nutrition, production level, body condition and medical history (Hove *et al*., 1978; Chagas *et al*., 2003, Jaaksen *et al*., 2013). Recently, Holtenius and Holtenius (2007) reported that Quantitative Insulin Sensitivity Check Index (QUICKI) could have potential as an insulin resistance index in dairy cows.

An understanding of the glucose metabolism and insulin secretion of unselected cattle may indicate which adaptive changes during the transition period are innately present in cattle. This prompted us to determine to what extent is insulin responsiveness during the transition from late gestation to early lactation modified by continued selection for high milk production.

MATERIAL AND METHODS

Cows

Sixteen clinically healthy multiparous cows of the Holstein Friesian (HF, n=8) and Buša (n=8) breeds were randomly chosen from two cattle farms and placed into the study. On both farms cows were housed in free-stall burns. Holstein Friesian dairy cows were fed TMR divided into three portions, fed at 06:00, 14:00, and 18:00 h, administering 40, 20, and 40 % of the daily ration, respectively. A detailed description of the composition of the TMR feeds during the dry and early lactation periods was reported by Prodanović *et al*. (2012). On the other hand, Buša cows grazed generous allowance of fresh pasture and were not supplemented with concentrate.

Glucose tolerance test

At 7 days prior to the predicted parturition (*ante partum*) and 14 days after parturition (*post partum*) each animal involved in the study was subjected to a glucose tolerance test (GTT). Cows were fasted 1 h before and during GTT that was conducted at approximately 10:00 h. Glucose was warmed to body temperature and administered intravenously via the jugular vein as a 50% solution (Hemofarm, Serbia) in the dose of 500 mg of D-glucose/kg of BW.

Blood sampling

Blood samples were taken from the jugular vein on the opposite side immediately before infusion (t=0) and at 15, 30, 60, 90, 120 and 180 min after glucose infusion. Blood samples were collected into 10-ml evacuated blood tubes, allowed to clot, centrifuged at 1800 × g for 10 min, and aliquoted into 2-mL microfuge tubes. Aliquots of serum were stored at -20^{o}C until analysis.

Laboratory methods

Glucose and insulin concentrations were measured in each blood sample, while BHBA and NEFA were measured only in samples taken immediately before infusion. Glucose and BHBA were enzymatically measured in whole blood samples, immediately after blood sampling, using commercial test bands (Precision *Xtra*, Abbott Diabetes, GBR). The concentration of serum NEFA was measured using a commercial kit (Randox, GBR). The radioimmunoassay technique was used for analysis of insulin (INEP, Serbia).

Statistical analysis

Glucose tolerance was measured by calculating the area under the curve (AUC_{gluc}) and the clearance of the infused glucose (CR_{gluc}) defined by the fractional turnover rate (k) and the time required for glucose concentration to fall by one-half ($T_{1/2}$) according to Holtenius *et al*. (2003). The insulin response following the glucose infusion was illustrated by measuring the maximum increase for insulin (ΔMax_{ins}) calculated as the difference between the basal concentration and the highest concentration and the area under the curve (AUC_{ins}). AUC_{gluc} and AUC_{ins} were calculated using the method described by

Bossaert *et al*. (2008). Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated as described by Holtenius and Holtenius (2007).

Data analysis was performed using STATISTICA v. 6. software package (StatSoft, Inc., Tulsa, Ok, USA). Data were expressed as the mean ± standard deviation (SD). The Student's t-test was used to evaluate the differences of means between two breeds. Differences were considered significant at $p<0.05$. Pearson's method was used to calculate correlations between NEFA and GTT characteristics.

RESULTS

Basal concentrations found before GTT and the QUICKI results are presented in Table 1. Basal glucose concentrations did not significantly differ between the breeds as well as within the same breed, but Buša had numerically higher basal concentrations of blood glucose before and during lactation. Basal insulin concentrations were significantly higher in Buša than in HF cows in both examined periods ($p<0.001$, respectively). Basal NEFA levels tended ($p=0.06$) to be higher in Buša cows compared with those of HF *ante partum*, and was significantly higher ($p<0.001$) *post partum*. There were significant differences between basal BHBA levels in both examined periods ($p<0.01$ and $p<0.001$). QUICKI was significantly lower in Buša compared to HF cows both *ante partum* and *post partum periods* ($p<0.001$, respectively).

Table 1. Basal glucose, insulin, non-esterified fatty acid (NEFA) and beta hydroxybutyric acid (BHBA) concentrations and the Quantitative Insulin Sensitivity Check Index (QUICKI) in cows of HF and Buša breeds around parturition (Mean±SD)

Breed	Period related to calving	Parameters				
		Glucose (mmol/L)	Insulin (μIU/mL)	NEFA (μmol/L)	BHBA (mmol/L)	QUICKI
HF	*ante partum*	2.78±0.50	11.72±4.0^{A}	0.46±0.20^{A}	0.40±0.09^{A}	0.70±0.12^{A}
	post partum	2.65±0.39	9.70±2.89^{A}	0.66±0.18^{A}	0.66±0.1^{B}	0.73±0.09^{A}
Buša	*ante partum*	3.10±0.58	39.66±12.90^{B}	0.69±0.32^{A}	0.24±0.08^{C}	0.49±0.05^{B}
	post partum	2.94±0.32	35.22±13.06^{B}	1.32±0.25^{B}	0.22±0.08^{C}	0.52±0.08^{B}

A-C – means within a row with different superscripts differ ($p<0.05$)

Graphic presentations of the GTT are provided in Figures 1 and 2. In both breeds glucose infusion led to an increase in blood glucose concentration from the basal level to the peak concentration 15 min after infusion. This was followed by a decrease to the pre-infusion level by 180 min in HF both *ante partum* and *post partum*, but was not in Buša neither *ante partum* or *post partum*. Blood glucose was significantly higher in Buša compared to HF 30, 60, 90, 120. and 180 min ($p<0.05$, respectively) after infusion *ante partum* and significantly higher 15 min

($p<0.05$), 30 min ($p<0.01$), 60, 90. and 120 min ($p<0.001$), and 180 min ($p<0.01$) *post partum*.

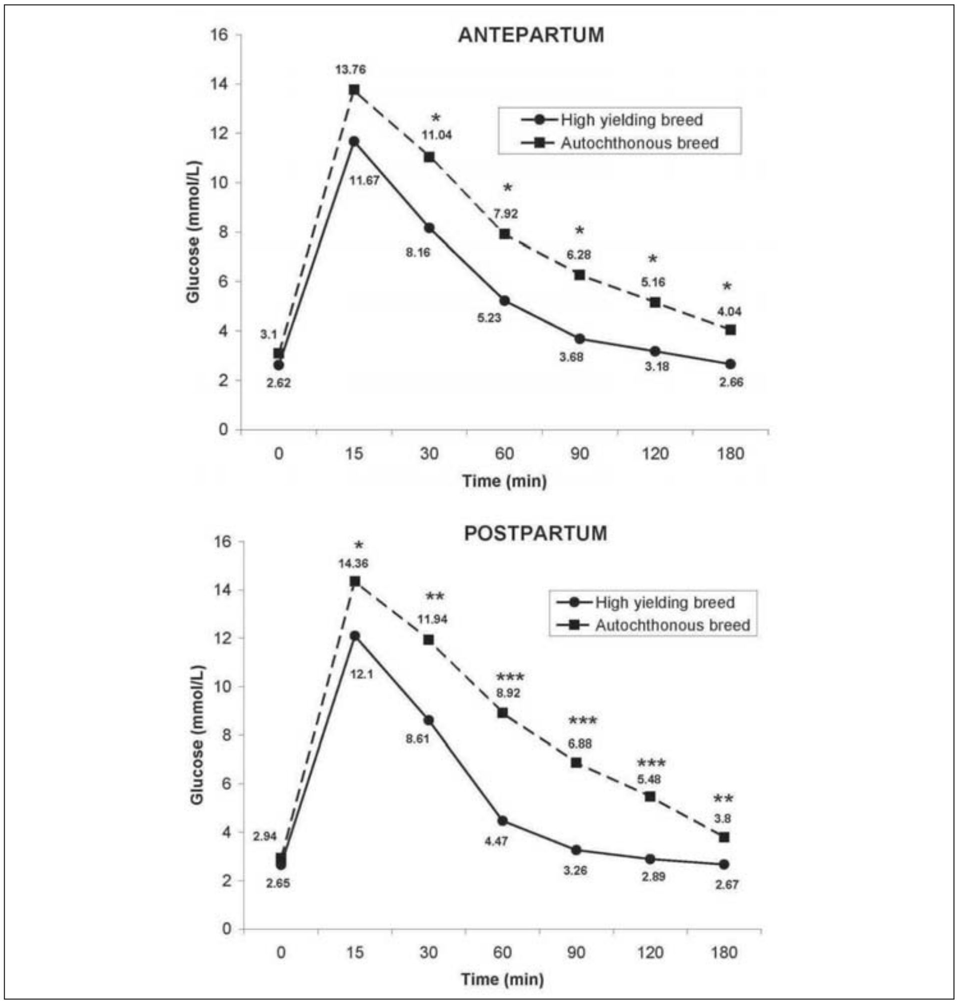

Figure 1. Glucose dynamics during the glucose tolerance test (GTT) around parturition in cows of Buša and HF breeds. Asterisks above the data points indicate significant differences between the breeds (***p<0.001; **p<0.01; *p<0.05)

Similar to responses in plasma glucose, insulin secretion in response to glucose infusion increased from basal level and reached peak level at 15 min after infusion. At this time point it was lower in Buša compared to HF both *ante partum* ($p<0.001$) and *post partum* ($p<0.05$). This was followed by a decrease to the pre-infusion level by 180 min in Buša both *ante partum* and *post partum*, as well as in HF postpartum , but was not in HF *ante partum*.

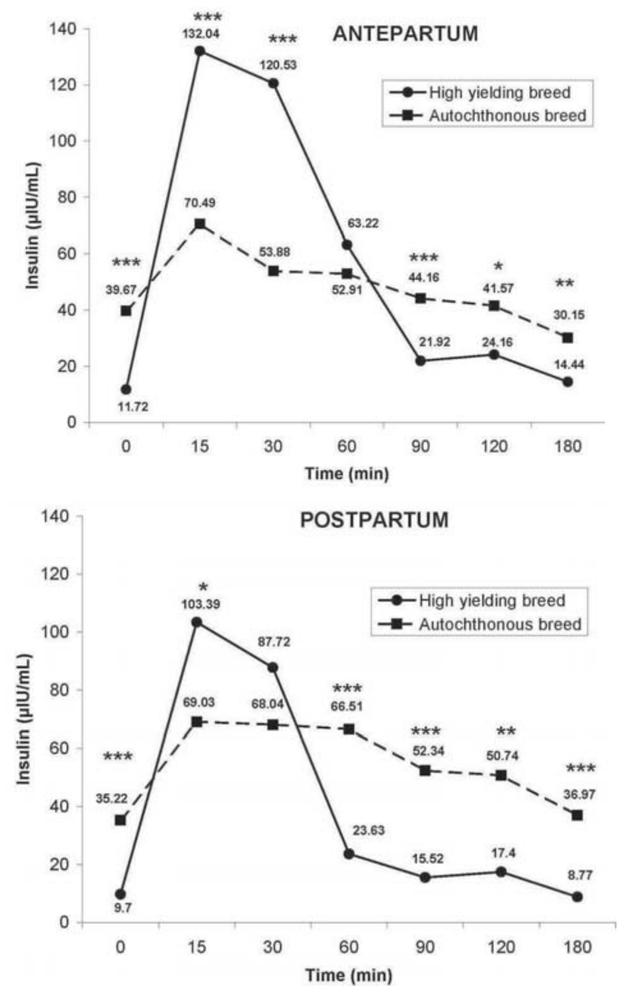

Figure 2. Insulin dynamics during the glucose tolerance test (GTT) around parturition in cows of Buša and HF breeds. Asterisks above the data points indicate significant differences between the breeds (***p<0.001; **<0.01; *p<0.05)

The resulting outcome variables of GTT are presented in Table 2. The AUC_{gluc} and the time taken to dispose of one-half the peak glucose concentrations ($T_{1/2}$) did not significantly change with time, but were lower (p<0.05 and p<0.001) before parturition as well as during lactation (p<0.001, respectively) in HF cows compared with Buša. In addition, the fractional turnover rate of glucose tended to be greater (p=0.06) in HF than in Buša cows *ante partum*, and was significantly higher (p<0.001) *post partum*. The AUC_{ins} did not differ before parturition, but were significantly lower with the onset of lactation in HF compared to Buša (p<0.001). There was significant differences between the breed' blood insulin maximum increase both *ante partum* (p<0.001) and*post partum* (p<0.01).

Table 2. Response variables to an intravenous glucose tolerance test (GTT) in Buša and HF dairy cows around parturition (Mean±SD)

Breed	Period related to calving	Parameters				
		AUC_{glu} (mmol/L x min)	K (%/min)	$T_{1/2}$ (min)	AUC_{ins} (μIU/L x min)	ΔMax_{ins} (μIU/mL)
HF	*ante partum*	869.12± 69.77^A	1.80± 0.46^A	41.22± 13.51^A	8854.78± 1857.91^A	120.33± 32.51^A
	post partum	837.47± 212.38^A	2.40± 0.74^B	31.81± 11.36^A	5819.92± 1726.31^B	93.68± 38.47^A
Buša	*ante partum*	1257.45± 410.93^B	1.29± 0.56^A	64.89± 35.64^B	8284.14± 1242.05^A	30.83± 20.25^B
	post partum	1340.7± 125.38^B	1.06± 0.30^A	69.06± 16.31^B	9794.24± 1643.17^A	33.81± 20.65^B

A-B – Means within a row with different superscripts differ (p<0.05)

DISCUSSION

A model of glucose tolerance test (GTT) was used to compare glucose metabolism and insulin secretion in HF and Buša cows during the peripartal period. As known, during this period mayor adaptive changes occurred in order to cope with the heightened energy demands of late pregnancy and lactation. Basal glucose and insulin concentrations changed with similar patterns in both breeds during the transition from late gestation to early lactation. In dairy cows, the decrease of glucose and plasma insulin concentrations was measured during the transition period (Sartin *et al*., 1988; Reist *et al*., 2003). In our study, glucose and insulin concentrations decreased with the onset of lactation in both HF and Buša cows indicating an influence of lactation on insulin-dependent glucose metabolism. Importantly, differences in serum insulin among different breeds were seen before and during lactation. Similar results were found in many previous studies in which cows with high and low genetic merit for milk production were compared (Bonczek *et al*., 1988; Gutierrez *et al*., 1999; 2006), and indicated that basal insulin concentrations could be related to breed. However, high levels of insulin may also be the consequence of low nutrition ration (Veerkamp *et al*., 2003) or caused by reduced clearance as demonstrated by Bossaert *et al*. (2008). Anyway, relatively high glucose levels associated with increased blood insulin concentrations in Buša cows both *ante partum* and *post partum* may be partly due to increased insulin resistance. Although interpretation of insulin resistance tests is complicated in lactating ruminants (Holtenius and Holtenius, 2007), major findings indicate that, after glucose challenge, Buša had higher AUC_{gluc} and lower CR_{gluc}, defined by k and $T_{1/2}$, in addition to higher AUC_{ins} compared to HF cows. If these results are combined with higher basal glucose and insulin concentrations and lower QUICKI, it may be supposed that there are breed differences in glucose partitioning and insulin responsiveness.

The physiological response to a glucose challenge differed markedly among different breeds before and during lactation, suggesting that observed differences, at least in part, are breed specific in nature. General dynamics of blood glucose and insulin during GTT are in line with literature data in dairy cows with high and low genetic merit for milk production. Namely, in high yielding dairy cows β-cell responsiveness to a glucose infusion during lactation is reduced compared to the dry period (Sartin *et al*., 1985; Holtenius *et al*., 2003), while in low milk production cows insulin release during GTT before and after onset of lactation is almost the same (Hammon *et al*., 2007). These results are in agreement with the our observations (Figure 1 and 2). Most importantly, selected animals exhibited greater insulin concentrations in response to a glucose challenge than the autochthonous breed in both examined periods, suggesting an impaired stimulation of pancreatic insulin secretion in cows with low milk production. In a number of studies (Shingu *et al*., 2002; Hammon *et al*., 2007; Jaakson *et al*., 2010) but not all (Xing *et al*., 1991; Chagas *et al*., 2003) cows selected for milk yield had a lower insulin response when submitted to a glucose challenge. However, these findings are consistent with Jaaksen *et al*. (2010), who observed that less pronounced glucose-induced pancreatic insulin release was accompanied by higher basal glucose concentrations. Furthermore, it is known that other factors may also affect the β-cell function. The outcomes of this study revealed that serum NEFA basal level correlated negatively with the ΔMax of insulin (r^2 = -0.578; $p<0.01$). Although linear correlations provide no indication of cause and effect, it is tempting to assume that elevated NEFA was responsible for insulin release differences between the breeds during GTT. In dairy cows, mediators of pancreatic insulin release and the interaction between circulating NEFA and β-cell function are not well documented, but mechanisms similar to man and rat seem eligible in Buša cows, since elevated NEFA coincide with decreased pancreatic insulin secretion in both examined periods. Consistent with this, Bossaert *et al*. (2008) also reported that elevated NEFA concentration might interfere with glucose-induced insulin secretion. In addition, we found a positive association between QUICKI and blood insulin maximum increase in both examined periods (r^2 = 0.855; $p<0.01$ and r^2 = 0.779; <0.01). The significant reduction of insulin release during GTT observed in Buša cows is therefore most likely a consequence of metabolic changes caused by insulin resistance, pointing out an important relationship between NEFA and β-cell function in dairy cows. These data seem to confirm the hypothesis that insulin dynamics may be involved in the effect of genetic strain and/or nutrition on insulin resistance (Chagas *et al*., 2003).

An interesting finding emerged from this study in that serum NEFA levels were higher during the peripartal period for autochthonous cows despite having higher insulin levels than in their high-yielding counterparts, further suggesting insulin resistance effects on adipose tissue metabolism (Dann *et al*., 2006). However, the high basal NEFA concentrations in Buša cows was unexpected, since others suggest a genetic tendency towards high NEFA levels in breeds selected for milk yield (Veerkamp *et al*., 2003; Jaaksen *et al*., 2010), but not all (Fontaneli *et al*., 2005). These results showed that Buša cows appeared to be in NEB in the late prepartum and early postpartum period perhaps because the energy requirement exceeds the level of dietary source. In addition, it has been suggested that chronic suppression of insulin responsiveness may also predispose the cow to sustained lipolysis and increase the risk for metabolic disorders (Holtenius *et al*., 2003; Kräft, 2004; Pires *et al*., 2007). In line with this, higher NEFA mobilization in low producing cows may have been due to down-regulation of insulin receptors caused by chronic hyperinsulinaemia. On the other hand, Buša had lower concentrations of blood BHBA in both examined periods that coincided with the increased rate of lipolysis compared with HF cows. This observation is not in agreement with the precursor-product relationship between the two variables as discussed elsewhere (Bobe *et al*., 2004; Goff, 2006). Thus, it is reasonable to suggest that the level of serum insulin concentration was responsible for BHBA differences between the breeds (Hayirly, 2006). The effects of insulin on the level of BHBA may be explained by enhanced peripheral tissue ketone oxidation (Kreipe *et al*., 2011). However, because of the role of adipose tissue and liver in orchestrating the adjustment of the balance between catabolism and anabolism, more specific research in the regulatory mechanism driving the observed NEFA and BHBA differences between breeds is needed.

In the present study, the characteristics of glucose tolerance in transition HF and Buša cows were clarified. The reduced clearance of glucose observed in Buša at both *ante partum* and *post partum* period was due to greater degree of insulin resistance which gave rise to more pronounced lipolysis from adipocytes. Insulin resistance differences between the breeds can, at least in part, be attributed to a greater degree of negative energy balance in Buša cows. Results indicate that impaired metabolic signals of insulin in peripheral tissues are evolutionary adaptations of mammals to ensure conceptus demands in late pregnancy and nutrients supply to the neonate.

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Address for correspondence:
Radiša Prodanović, DVM
Faculty of Veterinary Medicine
University of Belgrade
Bulevar oslobodjenja 18
11000 Belgrade, Serbia
E mail: radisaprodanovic@yahoo.com

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INSULINSKI ODGOVOR NA AKUTNU INFUZIJU GLUKOZE KOD BUŠE I HOŠTAJN FRIZIJSKE RASE GOVEDA TOKOM PERIPARTALNOG PERIODA: UPOREDNA ANALIZA

PRODANOVIĆ R, KIROVSKI DANIJELA, VUJANAC I, ĐURIĆ M, KORIĆANAC G, VRANJEŠ-ĐURIĆ SANJA, IGNJATOVIĆ MARIJA i ŠAMANC H

SADRŽAJ

Cilj ovog rada je bio da se uporedi insulinski odgovor na akutnu infuziju glukoze kod krava holštajn frizijske rase (HF) i buše tokom peripartalnog perioda. Za ispitivanja je odabrano po osam krava obe rase. Sedam dana pre teljenja (*ante partum*) i 14 dana posle teljenja (*post partum*), životinje su podvrgnute testu tolerancije na glukozu (GTT). Uzorci krvi su uzimani neposredno pre aplikacije glukoze, kao i 15, 30, 60, 90, 120 i 180 minuta kasnije. U svakom uzorku su određivane koncentracije glukoze i insulina, dok su koncentracije BHBA i NEFA određivane samo u uzorcima uzetim pre infuzije. Kao pokazatelj insulinske rezistencije kod krava je izračunat QUICKI. Bazalna vrednost glikemije se nije značajno razlikovala između krava različitih rasa, dok je vrednost bazalne insulinemije bila značajno viša kod krava rase buša nego HF u oba ispitivana perioda ($p<0,001$, pojedinačno). Bazalna vrednost koncentracija NEFA je imala tendenciju ($p = 0,06$) povećanja kod krava rase buša u odnosu na HF *ante partum*, a bila je značajno viša ($p<0,001$) *post partum*. Bazalna vrednost koncentracije BHBA je bila značajno niža kod krava rase buša nego kod HF tokom oba ispitivana perioda ($p<0,01$; $p<0,001$). QUICKI je bio značajno niži kod krava rase buša u odnosu na HF kako *ante partum* tako *post partum* ($p<0,001$, pojedinačno) ukazujući na manju senzitivnost tkiva na insulin kod krava rase buša. Koncentracija glukoze je tokom izvođenja GTT bila viša kod krava rase buša u odnosu na HF, kako *ante partum* tako i *post partum*, s tim da je ova razlika bila značajna počevši od 30. minuta testa *ante partum* i 15. minuta testa *post partum*. Koncentracija insulina je tokom izvođenja testa bila značajno niža 15. minuta, a značajno viša počevši od 90. minuta testa kod krava rase buša u odnosu na HF rasu kako *ante partum* tako i *post partum*. Razultati dobijeni u ovom radu ukazuju na razliku u insulinskom odgovoru na akutnu aplikaciju glukoze između dve ispitivane rase krava, a koja je najverovatnije posledica razlike u balansu energije, a ne selekcije na visoku proizvodnju mleka. Naime, smanjena senzitivnost tkiva na insulin i smanjeni insulinski odgovor krava rase buša u odnosu na HF je verovatno posledica smanjenog unošenja energije iz alimentarnih izvora zbog čega se u većem stepenu koriste izvori energije iz telesnih depoa.