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THE INFLUENCE OF SODIUM PROPIONATE ON BLOOD GLUCOSE AND SERUM CORTISOL CONCENTRATIONS IN HEALTHY AND SPONTANEOUSLY KETOTIC LACTATING COWS

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Changes in glycemia and serum cortisol concentrations after intravenous administration of sodium propionate solution (1.84 mol/L) were examined in lactating Holstein dairy cows. Propionate was given as a single dose after milking and feeding to a group of fifteen healthy cows and an equivalent group of fifteen cows showing clinical signs of ketosis between 7 and 14 days after calving.

Although very large differences were found between individual animals for both parameters at each time interval, it was established that initial glucose concentrations and the glycemic response to propionate were considerably greater in the healthy cows than in those suffering from ketosis. Moreover, the ketotic cows exhibited a significantly lower cortisol response commencing from a lower base line. While initial glucose and cortisol concentrations were positively correlated ($P<0.01$) in the whole group of cows, the size of integrated increments in glycemia and cortisol levels after propionate administration were not in correlation. However, as found in an earlier study, the animals could be subdivided into a group showing a high cortisol response to propionate ($n = 14$) and a group showing a low respones (<100 nmol/L at 60 minutes; $n = 16$). Parameters concerning cortisol levels and glycemia were not associated in the high responders, indicating mutual independence of mechanisms controlling their values. In the low responders, ten of which were ketotic, there was a statistically significant correlation between the increment in glycemia and cortisol after propionate administration ($r = 0.576$; $P <0.05$). The results obtained indicate that conditions which lead to a low cortisol status may be a predisposing factor in the appearance of spontaneous ketosis in peripartal Holstein cows.

Key words: Peripartal cows, ketosis, Na-propionate, glycemia, cortisol

INTRODUCTION

In ruminants it is characteristic that short-chain fatty acids like butyrate and propionate play a role in the regulation of certain endocrine glands such as the α pancreas (Bartoš et al., 1970; Gross et al., 1990; Istasse and ørskov, 1984; Mineo et al., 1990). In sheep at least part of the insulin response occurs through the parasympathetic nervous system and the glucagon response through the α-adrenergic system (Sano et al., 1993). Moreover, it has been shown that an infusion of sodium propionate intravenously leads to rapid increases in serum cortisol concentrations in healthy lactating cows (Šamanc et al., 1993a). It was suggested that intravenously administered sodium propionate may have a similar effect on the adrenal cortex as adrenocorticotropin (ACTH) given intramuscularly, except that the response to propionate was faster.

It is well-known that propionate is synthesized in the rumen during digestion of dietary carbohydrates and that, after absorption, it is used in the hepatocytes for the synthesis of glucose (Brockman, 1990; Demigne et al., 1991; Hart, 1983; McDowell, 1983; Lomax and Baird, 1983). In gestating and lactating cows the process of gluconeogenesis in the liver takes place very intensively. Since almost the whole amount of glucose necessary for the organism is synthesized in the liver, special attention is paid to examinations of liver function in cows with a high milk yield (Gröhn, 1985). In addition to the determination of many parameters in the blood of healthy and ketotic cows, tests to demonstrate the ability of the liver to utilise gluconeogenic precursors for glucose synthesis are being increasingly recommended. Thus, marked changes in blood glucose concentration follow intravenous injections of sodium propionate (Corse and Elliott, 1970). Moreover, it has been established that, compared with healthy cows, those suffering from ketosis exhibit much smaller increases in blood glucose concentration. This has been interpreted as a possible inability of hepatocytes in ketotic cows to utilise intravenously administered sodium propionate (Bruss et al., 1986).

Having in mind the results obtained earlier concerning changes in blood glucose levels in cows after intravenous injections of sodium propionate as a hepatic precursor for glucose synthesis, the aim of this investigation was to examine whether changes in glycemia appeared as a result of the effect of sodium propionate on the concentration of cortisol. For this reason, it was decided to determine the level of serum cortisol in healthy and spontaneously ketotic cows after intravenous administration of sodium propionate and to correlate the findings with alterations in the level of glycemia.

MATERIAL AND METHODS

Animals and sample collection. The examinations were carried out in cows of the Holstein breed (n = 30). They were in the earliest phase of lactation, from 7 to 14 days after calving. The first group (n = 15) were healthy cows which had not shown any clinical signs of ketosis, and ketone bodies were not detected in their urine. The second group (n = 15) were cows which ex-

hibited clinical symptoms of ketosis (inappetance and atony) and pathological concentrations of ketone bodies were found in their urine. Cows which had been diagnosed as suffering from other disorders such as retention of the placenta, endometritis, mastitis, dislocation of the abomasum etc. were not included.

The propionate loading test was carried out by intravenous administration of sodium propionate solution (1.84 mol/L) intravenously at 1 ml/kg body mass, always at the same time (9^{00}) after milking and feeding.

Blood was drawn by puncture of the jugular vein, when measurements of the glucose concentration were made. Blood samples were taken immediately before and 8, 30, 60, 120 and 180 minutes after administration of sodium propionate. After spontaneous coagulation of the blood, the serum was decanted and centrifuged. All further analyses were made on fresh samples of non-hemolysed blood serum.

Assays. Blood glucose concentration was determined using Dextrostix tracks and the values read on an Eyeton Refraktans colorimeter. Serum concentrations of cortisol were determined by radioimmunoassay using a commercially available kit (INEP, Zemun) and following the procedure recommended by the manufacturer.

The integral response of blood glucose and serum cortisol concentrations to propionate injection was determined by plotting the points on graph paper, connecting them linearly, cutting out the shapes and weighing them on a precise analytical balance (Metler). The weighing error for one square of paper of the size of the smallest response was 0.27% ($n = 13$), while the mean and standard deviation for thirteen similar squares cut from different sheets of paper was 28.55 ± 0.74 mg.

Statistical analyses. Student's t-test was used to detect significant differences between the two groups of cows concerning means at each time interval and integral means. The results for each group of cows were subjected, individually and combined, to analysis of variance (ANOVA). Attempts were made to derive equations describing the response and significant correlations between cortisol and glucose responses were sought.

RESULTS

Effect of sodium propionate on glucose concentrations

After intravenous administration of sodium propionate solution to healthy cows, blood glucose concentrations increased up to 60 minutes by two fold on average and then declined slowly over the next 120 minutes towards the initial values of around 2.6 nM/L (Figure 1a). The curvilinear response could be described by a quadratic equation where the calculated values were correlated with mean values obtained for the fifteen cows examined ($r = 0.885$; $P < 0.05$). The response of individual cows to sodium propionate varied widely. Thus, in Table 1 it can be seen that the effect of sodium propionate treatment

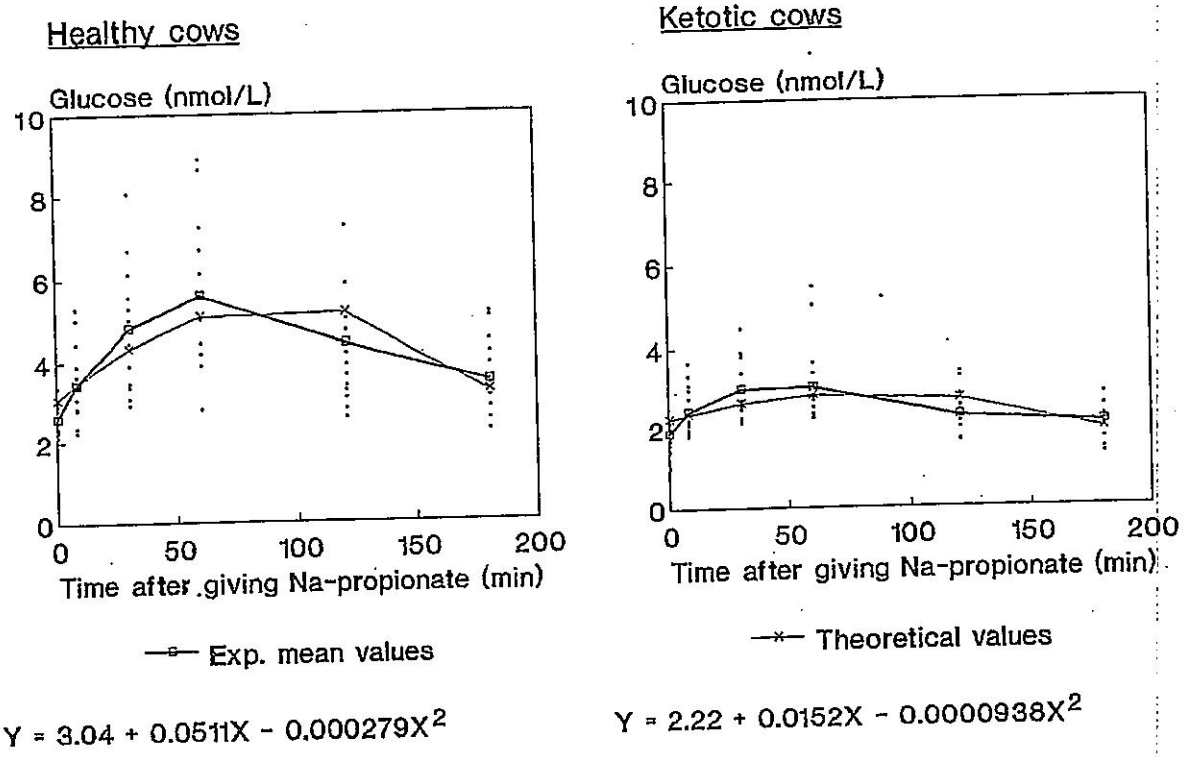

Figure 1. Changes in glycemia in lactating Holstein cows after receiving sodium propionate solution intravenously (a) healthy cows; b) cows exhibiting ketosis).

and differences between animals each accounted for about 40% of the variance within the control group of cows.

The group of cows suffering from ketosis had significantly lower initial concentrations of blood glucose (1.85 $\pm$ 0.36 nM/L) than the group of healthy cows ($P<0.001$).The response to sodium propionate was blunted so that highly significant differences between mean values for the two groups persisted at each time interval examined (Figure 1b). Maximal values about 60% higher than the initial levels were achieved earlier (30 minutes) in many cases and the subsequent decline was relatively faster. The correlation coefficient between mean values obtained experimentally and those calculated using the derived quadratic equation ($r = 0.714$; Figure 1b) was not statistically significant. Thus, gluconeogenesis from propionate was less intense in these cows and/or glucose disposal was more rapid. Analysis of variance (Table 1) showed that differences between animals again accounted for around 40% of the variance within the ketotic group, while the changes with time, although highly significant, only accounted for one third of the variance.

When the blood glucose concentrations of all the cows were subjected to analysis of variance as one block (Table 1), 58% of the variance was due to differences between animals. However, over half of this variance could be accounted for by differences associated with the appearance of ketosis (Table 1).

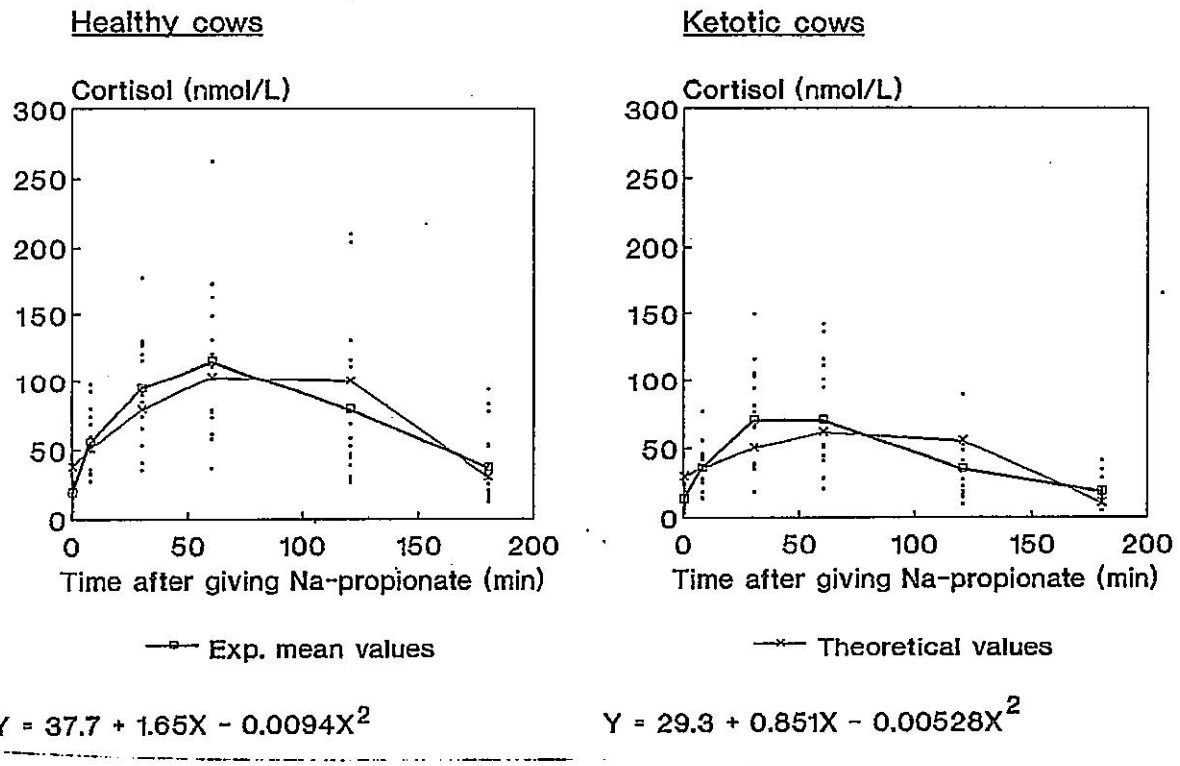

Figure 2. Changes in serum cortisol concentrations in lactating Holstein cows after receiving sodium propionate solution intravenously (a) healthy cows; b) cows exhibiting ketosis).

Table 1. Analysis of variance of blood glucose concentrations in lactating cows treated with sodium propionate

Parameter	Sum of squares	Deg. of freedom	Mean square	F value	P value	% of variance
All cows						
Total variance	387.51	179				
Effect of time	87.73	5	17.55	33.7	<0.01	22.6
Effect of cow	224.22	29	7.73	14.8	<0.01	57.8
(Control/ketos.)	(117.24)	(1)	(117.24)	(225.0)	(<0.01)	(52.2)
Error	75.56	145	0.52			19.5
Control cows						
Total variance	219.48	89				
Effect of time	89.47	5	17.89	28.5	<0.01	40.8
(Lin. regression)	(1.43)	(1)	(1.43)	(2.3)	(NS)	
(Quad. regres.)	(68.17)	(2)	(34.09)	(54.2)	(<0.01)	(76.2)
Effect of cow	86.06	14	6.14	9.8	<0.01	39.2
Error	43.94	70	0.63			20.0
Ketotic cow Total variance	50.79	89				
Effect of time	1674	5	3.35	17.8	<0.01	32.9
(Lin. regression)	(0.63)	(1)	(0.63)	(3.4)	(NS)	
(Quad. regres.)	(8.18)	(2)	(4.89)	(21.8)	(<0.01)	(48.9)
Effect of cow	20.92	14	1.49	7.9	<0.01	41.2
Error	13.14	70	0.19			25.9

The overall integrated blood glucose level in the ketotic cows was about half the value found in the healthy cows (Table 3), while the increment due to propionate administration was only just over one third of the response of the control group. These differences were statistically highly significant ($P<0.005$) and indicate either a delay in propionate utilization or diversion to pathways other than gluconeogenesis.

Table 2. Analysis of variance of serum cortisol concentrations in lactating cows treated with sodium propionate

Parameter	Sum of squares	Deg. of freedom	Mean square	F value	P value	% of variance
All cows						
Total variance	364365	189				
Effect of time	131223	5	26245	38.9	<0.01	36.0
Effect of cow	130007	29	4483	6.3	<0.01	35.7
(Control/ketos.)	(30667)	(1)	(30667)	(43.1)	(<0.01)	(23.6)
Error	103134	145	711			28.3
Control cows						
Total variance	233821	89				
Effect of time	95678	5	19136	19.2	<0.01	40.9
(Lin. regression)	(24)	(1)	(24)	(0.02)	(NS)	
(Quad. regres.)	(75905)	(2)	(37952)	(38.0)	(<0.01)	(79.3)
Effect of cow	68282	14	4877	4.9	<0.01	29.2
Error	69860	70	998			29.9
Ketotic cow						
Total variance	99876	89				
Effect of time	44335	5	8867	25.4	<0.01	44.3
(Lin. regression)	(23.86)	(1)	(2386)	(2.2)	(NS)	
(Quad. regres.)	(26287)	(2)	(13144)	(15.5)	(<0.01)	(59.3)
Effect of cow	31058	14	2218	6.3	<0.01	31.1
Error	24482	70	350			24.5

Effect of sodium propionate on cortisol concentrations

Simultaneously with the increase in blood glucose concentrations, administration of propionate led to marked increases in serum cortisol concentrations which again peaked at 60 minutes in the control group of cows (Figure 2a). Most of the variance associated with time after treatment could be described by a quadratic equation where calculated values were significantly correlated with the observed mean values ($r = 0.898$; $P<0.05$). Mean maximal values were nearly six-fold higher than mean initial values and a significant greater than two-fold response could be detected as early as 8 minutes after propionate administration. There were large differences in the response of individual cows which accounted for nearly one third of the variance (Table 2).

Mean concentrations of serum cortisol in the group of ketotic cows were generally lower than in the group of healthy cows both before and after administration of sodium propionate. The differences were statistically significant at each time interval examined ($P< 0.05$) except at 30 minutes, when values in the ketotic group approached the maximum increase of about five-fold on

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average (Figure 2b). The immediate relative increase in serum cortisol levels after injection of sodium propionate in the ketotic group of cows (2.5 fold at 8 minutes) was equivalent to the response in the control group of healthy cows. However, values plateaued between 30 and 60 minutes and then declined rapidly, so that the greatest difference between the two groups occurred at 120 minutes when the mean value for the ketotic group was less than half the value for the control group. The correlation coefficient between observed mean values and those calculated using the derived quadratic equation was 0.777 ($P>0.05$).

The distribution of variance associated with the main factors i. e. differences between individual animals and differences with time after propionate injection, was similar in both groups of cows (Table 2), although the proportion accounted for by these factors (about 70%) was somewhat smaller than for blood glucose (about 80%). Moreover, when the values for all cows were subjected to analysis of variance in one block, it was apparent that less than one tenth of the variance in cortisol concentrations was associated with the division of the cows into healthy and ketotic groups (Table 2), whereas for glucose nearly one third of the variance was associated with this division (Table 1).

Nevertheless, the overall integrated cortisol level was lower in the ketotic cows than in the healthy animals (Table 3) and the mean increment following propionate injection in the ketotic group was only half the control value. These differences approached statistical significance. There was a statistically significant correlation between initial cortisol concentrations and the increment in response to propionate which included all the cows ($r = 0.367$; $P < 0.05$). This probably reflects the metabolic state of the adrenal cortex and may indicate that a low cortisol status allows more propionate to be oxidised than be converted to glucose.

Table 3. Integral response and overall circulating glucose and cortisol levels in healthy lactating cows and cows with ketosis (arbitrary units)

	Healthy cows Mean	SD	Correl. coeff.	Ketotic cows Mean	SD	Correl. coeff.
Overall integrated glucose level	270	91	–0.186	143	31	0.615
Overall integrated cortisol level	513	246	NS	298	146	P<0.05
Integrated glucose increment	114	59	–0.204	41	24	0.464
Integrated cortisol increment	403	230	NS	210	123	NS

Glucose-cortisol interrelationships. It was found that the overall integrated cortisol level was significantly correlated with glucose only in the ketotic group ($P < 0.05$; Table 3). Since the increments due to propionate administration were not significantly correlated in either group, it appears that the net response of cortisol and glucose to propionate administration are not directly associated. Thus, the only significant correlation between parameters concerning glucose

and those concerning cortisol valid for all the cows was a positive correlation between initial glucose and initial cortisol concentrations ($r = 0.480$; $P < 0.01$).

In an earlier study in healthy Holstein cows (Šamanc et al., 1993b) the animals could be divided into two equal subgroups depending on the intensity of the cortisol response to propionate. Low responders and high responders could be identified in this investigation also, although the difference was less clear cut. The division was based on whether cortisol concentrations were above or below 100 nmol/L 60 minutes after propionate administration. The group of healthy cows contained more high responders (9 out of 15) and the ketotic cows more low responders (10 out of 15). Among the 14 high responders, which had initial cortisol concentrations of 21.6 ± 6.8 nmol/L, there was no correlation with glycemia. Namely, cortisol concentrations were probably sufficiently high for a maximal effect on glycemia, which would therefore be controlled by other hormonal pathways. However, the subgroup of 16 low responders had lower initial cortisol concentrations (12.8 ± 5.8 nmol/L and the increment in cortisol was significantly correlated with the increment in glucose ($r = 0.576$; $P < 0.05$) after propionate administration. These results do not prove a direct cause and effect mechanism but the parallelism points to interdependence. Namely, adrenal insufficiency or suppression from whatever cause is associated with the inability of the organism to give an adequate glycemic response to propionate administration.

DISCUSSION

Intravenous administration of propionate to dairy cows was developed by Gröhn (1985) as a test of hepatic function, because propionate is a major precursor of glucose in ruminants and the liver is the main site of gluconeogenesis and propionate metabolism (Elliott, 1980). Nearly all propionic acid reaching the liver from the digestive tract is either oxidised or converted to glucose. Since Hove (1978) showed that utilization of exogenous glucose given intravenously was identical in ketotic and healthy fed cows, it appears that the smaller increase of blood glucose concentrations observed in ketotic cows after administration of propionate is due to decreased gluconeogenesis. This mechanism was also suggested by Bruss and coworkers (1986) from results obtained in non-lactating cows made ketotic by fasting. The half-life of injected propionate was increased significantly from 7.6 to 10.1 minutes but increases in plasma glucagon were smaller in fasted than in fed animals. Corse and Elliott (1970) found a negative relationship between rate of intravenous propionate utilization and rate of increase in blood glucose indicating a possible difference in extrahepatic propionate uptake. However, their ketotic cows were shown to be deficient in Vitamin B_{12}, which is an essential component of the coenzyme of methylmalonyl CoA mutase. This enzyme is on the pathway of utilisation of propionate.

Normally, 46 – 55.4% of net glucose release from the liver of lactating cows is derived from propionate, while 16.5% comes from gluconeogenic amino acids and 16 – 22.9% from lactate (Seal and Reynolds, 1993). Brockman (1990)

showed that, while insulin inhibits gluconeogenesis from lactate in sheep by inhibition of pyruvate carboxylase, the pathway from propionate is not sensitive to changes in insulin concentration. Isolated sheep hepatocytes had a high capacity for propionate utilisation and conversion to glucose, which was inhibited by butyrate, ammonia and ethanol but not by the other substances examined (Demigné et al., 1991).

According to Hart (1983) high-yielding dairy cows are in negative energy balance for the first third of their lactation. In this state insulin levels are suppressed, which, however, does not appear to affect glucose uptake and lactose production in the mammary gland. Meanwhile, counterregulatory hormones are active. Thus catecholamines stimulate gluconeogenesis by increasing lactate production from muscle together with free fatty acid (FFA) and glycerol release from adipose tissue. Moreover, they inhibit insulin secretion and stimulate glucagon release from the endocrine pancreas changing their molar ratio (McDowell, 1983). Glucocorticoids stimulate mobilisation of aminoacids from muscle in order to provide the raw materials for increased gluconeogenesis. This may be counteracted by the action of growth hormone which acts to preserve body protein during situations of energy deficiency by inhibiting proteolysis and diverting glucose and FFA away from deposition towards oxidation. In healthy cows glucose production keeps pace with glucose utilisation, whereas ketosis appears when a bottle-neck occurs in one or other pathway. Bruss and coworkers (1986) state that increases in glucose concentration of less than 2mmol at 30 minutes after propionate loading (3 mmol/kg) indicates that liver function is altered. In the present experiment four cows in the control group and ten cows in the ketotic group would fail this criterion.

At any one time the relative importance of the different counterregulatory hormones in maintaining glucose levels is not known. However, Šamanc and coworkers (1993) recently showed that the nutritional regime in the peripartal period may have a profound influence on the hormone status in Holstein dairy cows. Thus, a roughage concentrate dry matter ratio of 75:25 was associated with low insulin levels, adequate glycemia and mean serum cortisol concentrations of 15 nmol/L. Feeding a 50:50 dry matter ratio was accompanied by significantly higher insulin concentrations, inadequate glycemia with the appearance of ketosis in some animals and cortisol levels of around 8 nmol/L. Namely, both cortisol and insulin status can be nutritionally manipulated. While some cows with low cortisol status may escape ketosis and some cows with high cortisol status succumb to this disorder, as occurred in the present investigation, a low cortisol status in early lactation appears to be associated with susceptibility to spontaneous ketosis. Recently, it has been shown that, besides ACTH, adrenaline can stimulate messenger ribonucleic acid production for synthesis of the enzymes necessary for steroid production in bovine adrenocortical cells (Güse-Behling et al., 1992). This offers another point of interaction between different regulatory systems.

The results obtained in our investigation confirm the earlier findings that intravenous propionate administration is followed by a rapid increase in serum cortisol concentrations. The possibility that the response was due to handling

stress was negated by the absence of an effect in saline treated controls (Šamanc et al., 1993a). In healthy cows the intensity of the cortisol response was not correlated with the intensity of the glycemic response. However, in the ketotic cows which exhibited different degrees of initial hypoglycemia, overall integrated cortisol concentrations were significantly correlated with overall integrated glucose concentrations. Moreover, when the cows were subdivided into two groups on the basis of cortisol levels rather than on the appearance of ketosis, the group of cows with a low cortisol status showed an interdependence between glycemia and serum cortisol including the response to propionate administration. This suggests that the contribution of the adrenal cortex in maintaining glucose status is important namely, adrenal insufficiency or suppression of cortisol production may be associated with the appearance of ketosis. Further work is needed to clarify these interrelationships.

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UTICAJ Na-PROPIONATA NA GLIKEMIJU I KONCENTRACIJU KORTIZOLA U KRVI ZDRAVIH KRAVA I KRAVA SPONTANO OBOLELIH OD KETOZE

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SADRŽAJ

Promene u glikemiji i koncentracijama koritzola posle ubrizgavanja rastvora natrijum propionata (1,84 mol/L) ispitane su kod krava muzara, Holštein rase, 7 do 14 dana posle telenja. Propionat je davan jednokratno posle muže i hranjenja grupi od petnaest zdravih krava i sličnoj grupi od petnaest krava koje su ispoljavale kliničke simptome ketoze.

Iako su nađene velike individualne razlike između životinja za oba ispitivana parametra u svim vremenskim intervalima, utvrđeno je da su početni nivoi glukoze i glikemijski odgovor na dati propionat bili znatno veći kod zdravih krava nego kod onih koje su obolele od ketoze. Pored toga, ketozne krave koje su imale niže početne nivo kortizola pokazivale su i signifikantno niži stepen povećanja koncentracija koritizola posle davanja propionata. Početne koncentracije glukoze i kortizola bile su u pozitivnoj korelaciji ($P < 0.01$) u celoj grupi od trideset krava. Međutim, obimi integralnih odgovora kortizola i glukoze posle davanja propionata nisu bili u korelaciji. Kao što je nađeno u ranijem istraživanju, bilo je mogućno podeliti životinje u grupu koja je pokazala visoki stepen povećanja kortizola posle propionata ($n=14$) i drugu grupu koja je imala nizak odgovor (<100 nmol/L na 60 minuta; $n = 16$). Podaci o nivoima kortizola i glikemije nisu bili u korelaciji u prvoj grupi, što je ukazalo na međusobnu nezavisnost mehanizama koji kontrolišu njihove koncentracije u krvi. Međutim, u drugoj grupi u kojoj je deset krava ispoljavalo simptome ketoze, postojala je statistički značajna korelacija između integralnog povećanja glikemije i kortizola posle davanja propionata ($r = 0.576$; $P < 0.05$). Dobijeni rezultati sugerišu da uslovi koji dovode do niskog statusa kortizola mogu biti faktor koji predisponira pojavu spontane ketoze kod visoko-mlečnih krava u peripartalnom periodu.