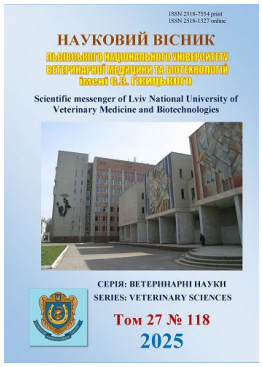

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The impact of stress factors on metabolism in horses with insulin resistance

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Horses have unique adaptive mechanisms for maintaining a stable metabolism under physical or stressful conditions. However, stress factors have a significant impact on metabolism in horses, especially in animals with insulin resistance. The aim of our research was to determine the effect of stress factors on the main metabolic parameters in horses with insulin resistance. The studies were conducted on twenty horses, 10 of which formed the control group and 10 – the experimental group with signs of obesity. Serum glucose concentration, insulin, cortisol, triglycerides, cholesterol, lactate and electrolytes (sodium and potassium) were measured. Urine levels of ketone bodies, ammonia and creatinine were measured. It was found that stress causes serious metabolic changes in obese horses, including hyperglycaemia, hyperinsulinaemia, activation of lipolysis and anaerobic metabolism in the blood serum, and an increase in ketone bodies, ammonia levels and creatinine concentration in the urine confirm the need to control metabolic changes in animals with insulin resistance, especially under stressful conditions.

Key words: *insulin resistance, metabolism, stress, carbohydrates, proteins, lipids, electrolytes.*

Вплив стресових факторів на метаболізм у коней з інсулінорезистентністю

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Коні мають унікальні адаптаційні механізми для утримання стабільного метаболізму в умовах фізичних або стресових навантажень. Проте стресові фактори мають значний вплив на метаболізм у коней, особливо у тварин з інсулінорезистентністю.

Метою наших досліджень було встановлення впливу стресових факторів на основні показників метаболізму у коней з інсулінорезистентністю. Дослідження були проведені на двадцяти конях, 10 з яких склали контрольну групу, а 10 – дослідну з ознаками ожиріння. У сироватці крові визначали концентрацію глюкози, рівень інсуліну, кортизолу, тригліцеридів, холестерину, лактату та електролітів (Натрій та Калій). В сечі визначали рівень кетонових тіл, аміаку та креатиніну. Встановлено, що стрес викликає серйозні метаболічні зміни у коней із ожирінням, включаючи гіперглікемію, гіперінсулінемію, активацію ліполізу та анаеробного метаболізму в сироватці крові, а підвищення кетонових тіл, рівня аміаку та концентрації креатиніну в сечі підтверджують необхідність контролю метаболічних змін у тварин з інсулінорезистентністю, особливо в умовах стресових навантажень.

Ключові слова: *інсулінорезистентність, метаболізм, стрес, вуглеводи, білки, ліпіди, електроліти.*

Introduction

The metabolism of horses maintains energy homeostasis, which is necessary for normal life, physical activity and adaptation to environmental conditions. The main substrates of energy supply are carbohydrates, fats and proteins. Glucose, which is formed during the digestion of carbohydrates, is a key source of energy. Its level in the blood is maintained through the interaction of insulin and glucagon, which regulate the processes of glycogenolysis and gluconeogenesis. In a state of rest or light physical activity, carbohydrates are the main source of energy, while during intense exercise, especially under stress, the role of lipolysis increases (van der Kolk et al., 2020). Exposure to stressors, especially transport stress as one of the most common factors, activates the hypothalamic-pituitary-adrenal axis, which stimulates the release of corticotropic hormone and adrenocorticotropic hormone (Miller et al., 2021). This leads to an increase in the secretion of cortisol, the main stress hormone, which has a wide range of effects, including increased gluconeogenesis in the liver, which increases blood glucose levels; inhibition of protein synthesis and activation of catabolic processes; increased lipolysis, accompanied by an increase in free fatty acids in the blood (Fryk et al., 2021). Horses also demonstrate unique adaptive mechanisms for maintaining the homeostasis of metabolic processes under the influence of physical and stress factors. For example, an increase in plasma lactate levels indicates the activation of anaerobic metabolism, but long-term use of the anaerobic pathway can lead to metabolic acidosis, which in turn leads to the development of metabolic syndrome and requires correction of the diet, as well as physical and emotional stress (Durham et al., 2019).

It is known that a key component of metabolic syndrome in horses is insulin resistance. It is characterised by a decrease in the sensitivity of peripheral tissues to insulin, which leads to impaired glucose utilisation and the development of hyperglycaemia. The pathogenesis of insulin resistance is associated with insulin receptor dysfunction, which can be caused by both genetic factors and external influences such as obesity, stress, sedentary lifestyle and a high-carbohydrate diet (Kaczmarek et al., 2015). It is known that insulin resistance is a risk factor for chronic diseases, including laminitis, which occurs as a result of impaired microcirculation in the hoof. In addition, obesity, especially in the neck and withers, is a powerful indicator of insulin resistance in horses. Horse breeds genetically predisposed to fat accumulation, such as ponies and Friesians, are particularly vulnerable to this condition (Frank et al., 2006).

Stress affects a wide range of metabolic processes in horses. Studies have shown that increased blood triglyceride and cholesterol levels in insulin-resistant horses are a typical response to stress due to activation of lipolysis (Pleasant et al., 2013; Bourebaba et al., 2023).

In terms of protein metabolism, stress causes increased protein catabolism, which is accompanied by an increase in ammonia levels and a decrease in blood albumin concentration. This may indicate an increased burden on the liver, which performs the function of ammonia detoxification. Stress also causes changes in the water-salt balance, although in most cases compensatory mechanisms prevent significant disturbances in sodium and potassium levels. However, in horses with electrolyte metabolism disorders, stress can lead to the development of hypokalemia or hyponatremia, which requires additional monitoring (Lindinger, 2022).

Thus, according to current research, stress factors have a significant impact on metabolism in horses, especially in animals with insulin resistance. It has been established that changes such as increased levels of glucose, insulin, triglycerides and ketone bodies are associated with the activation of stress-induced metabolic pathways. This emphasises the need to implement preventive measures to reduce the impact of stress, especially in sports horses and animals with metabolic disorders.

Aim of the study

To determine the influence of stress factors on the main metabolic parameters in horses with insulin resistance on the background of obesity.

Materials and Methods

Horses kept in private stables of Kharkiv and Poltava regions were examined, from which 2 groups were formed: 10 clinically healthy animals and 10 horses with insulin resistance. A total of 20 animals were examined.

Feeding and housing conditions met the physiological needs of the animals. The animals' diets were balanced in terms of essential nutrients, and all animals had free access to water and enjoyed walking. All animals underwent a general clinical examination according to generally accepted methods.

The physical condition of the horses was assessed using the Body Condition Score (BCS) scale, which is based on visual inspection and palpation of key body areas: neck, withers, ribs, lower back, tail base and shoulders. The assessment was carried out by a veterinarian, who assigned points to the animals on a scale from 1 (extremely emaciated) to 9 (overweight). The average score was determined for each horse, which reflects the level of fat deposits and general physical condition.

Blood was taken from the jugular vein on an empty stomach into 10 cm^3 Vacuette tubes for further serum collection. Biochemical parameters of blood and urine were determined using an automatic COBAS analyser (Roche® analytical platform) (Roche Diagnostics, Mannheim, Germany) using standardised methods, reagents and in accordance with the manufacturer's protocols. Glucose levels were determined by the hexokinase test, in which glucose was oxidised to glucose 6 phosphate, and the resulting NADH was determined spectrophotometrically. For the analysis of insulin and cortisol, electrochemiluminescent immunoassay (ECLIA) was used, which provides accurate determination of the concentrations of these hormones by the intensity of the chemiluminescent signal. Triglycerides and cholesterol were measured using enzymatic photometric tests. Triglycerides were hydrolysed to glycerol, which was oxidised to form a coloured product, and cholesterol was oxidised to hydrogen peroxide, which formed a coloured product in the presence of chromogen. Lactate level was determined by the photometric enzymatic test, in which lactate was oxidised to pyruvate to form a coloured product.

The concentration of sodium and potassium in the blood was analysed by the method of ion-selective analysis (ISE), which is based on measuring the potential of an ion-selective electrode sensitive to the corresponding ions.

Photometric enzymatic methods were used to analyse urine biochemical parameters. The level of ketone bodies was determined using test strips from ACON (USA). The level of ammonia was assessed by the oxidation reaction to glutamate, which was accompanied by the formation of a coloured product. The creatinine concentration was determined by the Jaffe reaction method, where creatinine reacted with picrate in an alkaline medium to form a coloured complex, the intensity of which was measured photometrically.

All animal studies were performed in accordance with the basic principles of bioethics, in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986) and the General Ethical Principles for Animal Experiments approved by the First National Congress on Bioethics (2012).

Statistical analysis of the data was performed using Minitab 19 (Minitab Inc) in a free trial version. The arithmetic mean (M) and the statistical error of the arithmetic mean (m) were determined. The probability of the difference between the arithmetic mean of two variation series was determined by the reliability criterion (td) and by Student's tables and the nonparametric method of Van der Warden. The difference between two values was considered significant at * – $P \leq 0.05$; ** – $P \leq 0.01$; *** – $P \leq 0.001$.

Results

We examined 20 horses from private stables in Kharkiv and Poltava regions. Two groups were formed for the study: 10 clinically healthy animals and 10 horses with diagnosed insulin resistance. The physical condition was assessed by the Body Condition Score (BCS) scale, which takes into account the level of body fat.

In the group of clinically healthy animals, the average BCS score was 5.8 ± 0.4 points, which corresponds to the optimal condition. In animals with insulin resistance, this index was significantly higher – 7.2 ± 0.6 points ($P < 0.01$). The results obtained indicate a link between increased BCS and the development of metabolic disorders, in particular insulin resistance.

The results of our study indicate a significant effect of stress on metabolic processes in horses with insulin resistance, which significantly exceeds similar changes in clinically healthy animals (Table 1).

Table 1
Biochemical parameters of blood in horses before and after stress (n = 10)

Index	Clinically healthy horses		Obese horses	
	Before transporting	After transporting	Before transporting	After transporting
Glucose, mmol/l	5,3 ± 0,41	5,7 ± 0,56	7,2 ± 0,55	8,5 ± 0,62**
Insulin, µU/ml	15,8 ± 2,12	17,0 ± 2,31	35,0 ± 3,21	40,5 ± 4,05*
Cortisol, nmol/l	190,5 ± 15,2	210,6 ± 18,7	280,5 ± 20,3	340,8 ± 25,5**
Triglycerides, mmol/l	0,5 ± 0,15	0,6 ± 0,11	0,9 ± 0,11	1,2 ± 0,13*
Cholesterol, mmol/L	2,1 ± 0,17	2,3 ± 0,21	2,8 ± 0,26	3,2 ± 0,33*
Lactate, mmol/L	1,52 ± 0,24	2,07 ± 0,25	1,84 ± 0,21	3,58 ± 0,34**
Sodium, mmol/L	144,5 ± 2,17	143,6 ± 2,23	142,3 ± 2,6	139,8 ± 2,5
Potassium, mmol/L	4,0 ± 0,22	4,2 ± 0,26	4,1 ± 0,25	4,5 ± 0,30

Blood glucose levels in the insulin-resistant group increased from 7.2 ± 0.55 to 8.5 ± 0.62 mmol/L ($P < 0.01$), which is 18.0 %, while in the control group the changes were less pronounced: from 5.3 ± 0.41 to 5.7 ± 0.56 mmol/L, which is 7.5 %. This indicates a disturbance in carbohydrate metabolism under the influence of stress in animals with insulin resistance. Similar results were described by Jacquay, Harris and Adams (2024), who noted that the increase in glucose levels after stress in animals with metabolic disorders can reach 20–30 %, while in healthy animals these changes are limited to 10 %. The main cause of hyperglycaemia is the activation of gluconeogenesis in the liver, caused by high levels of cortisol, which acts as a counterinsulin hormone. According to our research, insulin levels in the insulin-resistant group also increased from 35.0 ± 3.21 to 40.5 ± 4.15 mU/ml ($P < 0.05$), while in the control group this increase was less significant (from 15.8 ± 2.12 to 17.0 ± 2.31 mU/ml). According to research by Marycz et al. (2018), compensatory hyperinsulinemia is a typical response of the body in

animals with metabolic syndrome, but its effectiveness is reduced due to impaired insulin receptor function at the cellular level. Under these conditions, stress exacerbates the situation by increasing cortisol levels, which further reduces tissue sensitivity to insulin. The increase in cortisol levels in animals with insulin resistance from 280.5 ± 20.3 to 340.8 ± 25.5 nmol/L ($P < 0.01$) is more pronounced than in the control group (from 190.5 ± 15.2 to 210.6 ± 18.7 nmol/L). Hart et al. (2016) noted that a 20–30 % increase in cortisol levels is typical for animals with metabolic disorders under stressful conditions, while in healthy animals these changes are about 10 %. Cortisol plays a central role in the mobilisation of energy resources by stimulating lipolysis and gluconeogenesis, which ensures the body's adaptation to stress. However, in horses with insulin resistance, these processes are accompanied by significant metabolic disorders, such as increased triglyceride and cholesterol levels.

Triglyceride levels in the insulin-resistant group increased from 0.9 ± 0.11 to 1.2 ± 0.13 mmol/L ($P < 0.05$), while in the control group they increased from 0.5 ± 0.15 to 0.6 ± 0.11 mmol/L. Similarly, cholesterol levels in the insulin-resistant group increased from 2.8 ± 0.26 to 3.2 ± 0.33 mmol/L ($P < 0.05$), and in the control group from 2.1 ± 0.17 to 2.3 ± 0.21 mmol/L.

Discussion

Raje et al. (2020) confirm that the activation of lipolysis under stressful conditions is a typical adaptive response, but in animals with insulin resistance, these changes are more pronounced due to reduced efficiency of low-density lipoprotein utilisation. This creates an additional burden on the liver, increasing the risk of secondary complications, including laminitis.

Lactate levels in the insulin-resistant group increased from 1.84 ± 0.21 to 3.58 ± 0.33 mmol/L ($P < 0.01$), while in the control group they increased from 1.52 ± 0.24 to 2.07 ± 0.25 mmol/L. Kenéz et al. (2018) note that an increase in lactate indicates the activation of anaerobic metabolism due to insufficient oxygen supply to tissues. In horses with insulin resistance, these changes are more pronounced due to the limited efficiency of the aerobic energy supply pathway, which leads to a significant accumulation of lactic acid.

In horses with insulin resistance, changes in blood sodium and potassium levels may be observed after stress, which are associated with physiological responses to stress, as well as with metabolic disorders caused by insulin resistance. Data show that in the short term, compensatory mechanisms effectively maintain electrolyte balance. However, the possible increase in aldosterone as a compensatory response should be evaluated in further studies.

Sodium is an important electrolyte involved in maintaining osmotic balance, cell function and blood pressure regulation. Horses with insulin resistance may experience a decrease in sodium levels after stress due to the activity of stress hormones such as adrenaline and cortisol. These hormones can affect kidney function, promoting sodium retention or, conversely, increased sodium excretion (Wan et al., 2018). However, based on our data, we only found a tendency toward a decrease in this element in the blood of horses with insulin resistance after stress.

Potassium is important for proper muscle and heart function. Insulin resistance and stress can cause an increase in blood potassium levels (hyperkalaemia). This is due to a disruption in cellular metabolism, where insulin normally promotes the transport of potassium into cells. In insulin resistance, this process is disrupted and potassium can accumulate in the blood. Stress, in particular the activation of the sympathetic nervous system, can also promote the release of potassium from cells into the blood (Murao et al., 2018). The results regarding blood potassium levels in horses with insulin resistance after stress are consistent with the literature (an 8.9 % increase in electrolyte levels was observed).

Overall, the results of the study demonstrate that stress causes serious metabolic changes in horses with insulin resistance, including hyperglycaemia, hyperinsulinaemia, activation of lipolysis and anaerobic metabolism. This highlights the importance of monitoring metabolic parameters for the development of preventive and therapeutic strategies. Further research should focus on evaluating insulin receptor function, lipid metabolism enzyme activity, and the effects of pharmacological agents, such as HMG CoA reductase inhibitors, to optimise the metabolic status of these animals.

The results of the study revealed significant metabolic changes in the urine of horses with insulin resistance (IR) under stress conditions (Table 2).

Table 2
Metabolic indicators in horse urine before and after stress (n = 10)

Index	Clinically healthy horses		Obese horses	
	Before transporting	After transporting	Before transporting	After transporting
Ketone bodies, mmol/L	0,25 ± 0,14	0,36 ± 0,18	0,84 ± 0,21	1,52 ± 0,18*
Ammonia, mmol/L	0,65 ± 0,11	0,75 ± 0,12	0,91 ± 0,22	1,29 ± 0,11*
Creatinine level, mmol/L	6,86 ± 0,31	7,07 ± 0,43	6,54 ± 0,40	8,29 ± 0,52**

The level of ketone bodies in this group increased from 0.84 ± 0.21 to 1.52 ± 0.18 mmol/L ($P < 0.05$), indicating mitochondrial dysfunction and energy imbalance in the body associated with impaired carbohydrate utilisation and, as a result, activation of alternative energy supply pathways through lipolysis. In the control group, this increase was minimal (from 0.25 ± 0.14 to 0.36 ± 0.18 mmol/L). Research by Rojas Morales et al. (2019) confirms that ketone bodies are markers of energy deficiency and are often observed in animals with impaired glucose uptake. In their study, ketone body levels in horses with metabolic disorders increased after stress. A significant

increase in ketone bodies in animals with insulin resistance is explained by the fact that under such conditions, the body switches to fatty acid oxidation due to the inability to effectively use glucose. This is a typical compensatory response to insulin resistance, which limits the availability of glucose to tissues. In healthy animals, lipolysis is activated less intensively due to the preserved ability to absorb glucose, which explains the lower levels of ketone bodies.

The level of ammonia in the urine of horses with insulin resistance also increased from 0.91 ± 0.22 to 1.29 ± 0.11 mmol/L ($P < 0.05$), while in the control group the increase was insignificant (from 0.65 ± 0.11 to 0.75 ± 0.13 mmol/l). According to Karaca et al. (2018), ammonia is a by-product of amino acid breakdown, which is used by the body as an alternative source of energy during stress. In animals with insulin resistance, this process is more pronounced due to impaired carbohydrate metabolism, which forces the body to break down proteins more actively. High ammonia levels place an additional burden on the liver, which must neutralise it by forming urea.

The level of creatinine in the urine of horses with insulin resistance increased from 6.54 ± 0.40 to 8.29 ± 0.52 mmol/L ($P < 0.01$), indicating increased muscle protein breakdown. In the control group, the changes were less pronounced (from 6.86 ± 0.31 to 7.07 ± 0.43 mmol/L). Gomes Marcondes and Tisdale (2002) note that increased creatinine levels are the result of increased muscle protein catabolism, especially under stress. In their study, creatinine levels increased by 10–15 % in horses with metabolic disorders, while in healthy animals this increase was only 3–5 %. Elevated creatinine in horses with insulin resistance may be due not only to energy deficiency but also to carbohydrate metabolism disorders that limit the availability of glucose for energy, forcing the body to use muscle protein as an alternative energy source. In healthy animals, these changes are less pronounced due to the preserved efficiency of glucose utilisation.

Overall, the results indicate a significant impact of stress on metabolism in horses with insulin resistance. Increased ketone bodies indicate the activation of lipolysis as the main source of energy. The increase in ammonia levels indicates increased protein catabolism, and the increase in creatinine reflects the breakdown of muscle protein. These data are consistent with scientific sources and confirm the need to monitor metabolic changes in such animals. Monitoring these indicators allows for the timely detection of disorders and adjustment of housing conditions, diet and workload to minimise the negative effects of stress, and the development of strategies to minimise the effects of stress should become an important area of focus in veterinary medicine.

Conclusions

Glucose, insulin and cortisol levels remain the most important markers of stress-induced metabolic disorders in horses with insulin resistance, as they are elevated by an average of 18.0 %.

The established disorders of lipid and protein metabolism under the influence of stress are confirmed by a significant increase in triglyceride levels by 33.0 % and cholesterol by 14.2 % in blood serum, ketone bodies by 87.0 % and ammonia by 33.0 % in urine.

The data obtained can be used to develop preventive strategies aimed at minimising the impact of stress on horses with insulin resistance.

Conflict of interest

The authors declare that there is no conflict of interest.

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