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THE INFLUENCE OF CHRONIC STRESS ON THE CONTENT OF ESSENTIAL MACRO- AND MICRO-ELEMENTS IN THE BLOOD SERUM AND PANCREAS OF FEMALE RATS AND THEIR OFFSPRING

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ВПЛИВ ХРОНІЧНОГО СТРЕСУ НА ВМІСТ НЕОБХІДНИХ МАКРО- ТА МІКРОЕЛЕМЕНТІВ У СИРОВАТЦІ КРОВІ ТА ПІДШЛУНКОВІЙ ЗАЛОЗІ САМОК ЩУРІВ ТА ЇХНЬОГО ПОТОМСТВА

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Summary/ Резюме

We studied the dynamics of the content of macro- and microelements in the blood serum and pancreatic tissue of female rats that were exposed to experimentally induced combined chronic stress during pregnancy and prenatal stress in their offspring. The rats of the study group were kept daily in special individual cages-pencils in a state of prolonged, varying in time, immobilization, each time the animals were sorted into different cages and the diet was changed, which caused additional stress. Offspring from both study and control groups received balanced nutrition and were housed in standard vivarium conditions. Serum and pancreatic homogenate levels of Ca, Fe, Mg, Zn, and Cu were determined spectrophotometrically using a Stat Fax biochemical analyzer. Statistical analysis was performed using Microsoft Excel-2003, Biostat.exe-2008, and STATISTICA-10. Induced by combined chronic stress, the imbalance of macro- and microelements in different (intracellular and extracellular) sectors of organs and blood serum is accompanied by heterogeneity of changes in the content of macro- and microelements, with a tendency to reduce the content of Ca, Mg and Zn in the pancreatic homogenate, which does not coincide with the dynamics of the content of the corresponding indicators in blood serum. These disruptions are likely linked to a complex neurohumoral response to chronic stress, including increased stress hormone production and altered neurotransmitter ratios, contributing to organ damage, particularly in the pancreas, and potentially predisposing the animals to chronic pancreatitis.

Key words: *chronic combined stress, macro- and microelements, pancreas, blood serum, rats.*

Вивчали динаміку вмісту макро- і мікро елементів у сироватці крові і тканині підшлункової залози щурів-самиць, що перебували протягом вагітності під впливом експериментально викликаного комбінованого хронічного стресу і пренатального — у їх нащадків. Щури групи дослідження перебували щодня у спеціальних індивідуальних клітках-пеналах в стані тривалої, різної за часом іммобілізації, кожен раз тварин сортували до різних кліток і змінювали режим харчування, що викликало додаткове стресування. Потомство як дослідної, так і контрольної груп отримувало збалансова-

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не харчування та містилося в стандартних умовах віварію. Спектрофотометрично на біохімічному аналізаторі Stat Fax (США) в сироватці крові і гомогенаті підшлунковій залозі за допомогою відповідних наборів реагентів визначали рівень Ca, Fe, Mg (при довжині хвилі 540 нм), Zn (при довжині хвилі 550 нм), Cu (при довжині хвилі 580 нм). Статистичну обробку отриманих результатів проводили з використанням пакету аналізу програми Microsoft Excel-2003, комп'ютерної програми Biostat.exe-2008 та STATISTICA-10. Індукований комбінованим хронічним стресом дисбаланс макро- і мікро елементів в різних (внутрішньоклітинному і зовнішньоклітинному) секторах органів і сироватці крові, супроводжується неоднорідністю змін вмісту макро- і мікро елементів, з тенденцією до зниження вмісту Ca, Mg і Zn в гомогенаті підшлункової залози, що не співпадає з динамікою вмісту відповідних показників в сироватці крові. Вищенаведені порушення виникають під час реалізації складної нейрогуморальної відповіді організму на комбінований хронічний стрес (збільшення продукції стресових гормонів, порушення співвідношення нейромедіаторів), що сприяє активації механізмів ушкодження органів і тканин, в тому числі підшлункової залози, і стає передумовою розвитку хронічного панкреатиту у тварин в подальшому.

Ключові слова: хронічний комбінований стрес, макро- і мікро елементи, підшлункова залоза, сироватка крові, щури.

Introduction

The high pace and tension of life experienced by modern people in connection with responsible work, mental overload, instability of the social situation, uncertainty about the future, often leads to the development of chronic stress and neuroses, which are characterized by a violation of the management of the functioning of internal organs, primarily the digestive organs [1], posing a threat to health and life [2]. The mechanisms of adaptation to social stress and its numerous manifestations in young people are not yet sufficiently developed, and in the elderly and the elderly — they are exhausted. Therefore, it is precisely for young people that the increase in cases of acute pancreatitis associated not only with the action of alimentary factors is more characteristic. Under conditions of varying duration of experimental stress in rats, structural changes in the acinar part of the pancreas, vacuolar dystrophy of the cytoplasm, destruction, and fragmentation of the plasma membranes of acinar cells were detected, which contribute to the entry of secretory granules containing pancreatic enzymes into the interstitial space. It has been proven that intermittent stress leads to a decrease in the number of в-cells and an increase in б-cells in the pancreatic tissue of rats, while chronic stress leads to an increase in corticosterone levels against the background of a decrease in somatotropic and adrenocorticotropic hormones, which leads to damage to в-cells of the pancreas and, as a result, to a decrease in insulin levels and an increase in glucose levels [3, 4].

Prenatal stress due to maternal glucocorticoids. [5] negatively affects not only the physical development but also the structure of the pancreas of newborn rats, where a decrease in the number of endocrinocytes in the islet apparatus is observed, leading to hypoglycemia. Currently, the literature is actively considering the impact of macro- and microelements on the functioning of the body of adults and children [6,7,8,9]. Vital microelements include iron (Fe), zinc (Zn), copper (Cu), manganese (Mn), molybdenum (Mo), cobalt (Co), chromium (Cr), selenium (Se), and iodine (I). Deficiency of Cu, Fe, and Zn can disrupt the balance of almost all metabolic processes in the body [10]. while maintaining biological activity even in very low concentrations, at the same time, in elevated concentrations, even essential microelements can have a toxic effect [11,12]. Macro- and microelements are

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enzyme activators. They support the spatial configuration of enzymes in which catalytic activity is manifested [11,13]. Mineral elements (Zn, Mg, Se, flavonoids) can bind free radicals directly, blocking the activation of oxidative processes.

The lack of Fe and Zn in the body affects the processes of proliferation and differentiation of immune system cells, reducing the activity of lipid peroxidation (LPO) due to increased SOD activity [14, 15, 16, 17], which is sufficient to significantly increase the risk of complicated viral, microbial and parasitic infections. The cations K+, Na+, Ca2+, Mg2+, and Cl- anions formed during the dissociation of carbonic and phosphoric acids are also important for the body's vital processes [18,19,20,21]. They affect the state of proteins, the function of membrane excitability, muscle contraction, and energy accumulation [22], and participate in maintaining acid-base balance, osmotic pressure of the cytoplasm and other biological fluids, i.e., they are essential in maintaining homeostasis of the internal environment.

Zn and Cu deficiency cause numerous nonspecific general shifts in metabolism [23,24]. Most metalloenzymes (including antioxidants) require Zn as a catalyst and many transcription factors to maintain their structural integrity. Zn is necessary for the normal production and storage of insulin in в-cells of the pancreas, it exhibits insulinomimetic and antidiabetic effects [15,26]. There is evidence that during stress in adult rats, the accumulation of Zn in cells correlates with an increase in corticosterone and corticotropin in the blood and vice versa; a decrease in the concentration of Zn in cells is accompanied by a decrease in the level of these hormones [26]. It is necessary for the development and functioning of T-lymphocytes, the normal process of ovulation, embryo-, morpho- and angiogenesis, remodeling of the cell matrix, cell migration, axonal growth, wound healing. In the CNS, Zn plays the role of a neurotransmitter and neuromodulator. However, like glutamate and Ca, excessive Zn content can be responsible for neuronal death. Depending on the concentration, it can cause apoptosis or necrosis (brain ischemia).

Cu is an important component of various enzymes, including the one necessary for neutralizing free radicals Cu-Zn-SOD [17]. However, above-normal content, especially Cu due to its redox properties, can cause the appearance of highly toxic reactive oxygen species and cause severe oxidative damage to organs and tissues, including pancreatic acinar cells [25,26].

Magnesium (Mg), the second most abundant intracellular cation and a cofactor for over 300 enzymes, is crucial for various cellular processes. The Mg-ATP complex serves as a substrate for ATP-dependent enzymes like cyclases and protein kinases. Mg is essential for synthesizing and maintaining the structure of nucleic acids, proteins, and ribosomes; it also modulates excitable membrane permeability and electrical potential, acts as a calcium antagonist, and stimulates cholecystokinin production. Furthermore, Mg reduces blood glucose levels and oxidative stress, and it improves metabolism in rats with type 2 diabetes induced by high-fat diets.

Ca, the most abundant element in the human body, exhibits increased absorption during growth, pregnancy, lactation, and dietary deficiency. Its significant role in cell regulation stems from the steep concentration gradient across the plasma membrane. Ca's functions include skeletal mineralization, cell division, motility, excitation, muscle contraction, secretion, and platelet aggregation, influencing blood clotting. Excess Ca induces apoptosis and cell damage. In hyperglycemia, Ca stimulates insulin secretion but also triggers apoptosis in pancreatic в-cells, potentially leading to apoptosis and necrosis in acinar cells [17, 18, 20]. Literature analysis reveals that the issue of the influence of stress factors on the state of the pancreas is relevant since many aspects of the

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pathogenesis of pancreatic damage in female rats and their offspring remain insufficiently understood. In particular, this concerns issues regarding the balance of macro- and microelements in pancreatic tissue and in the blood serum of animals since this may make a negative contribution to maintaining functional and morphological changes in the pancreas. in female rats and their offspring, caused by the effect of stress on the female during pregnancy, The answers to these questions have important medical and social significance, and the new data obtained in the experiment can become the theoretical basis for the development of measures to prevent pancreatic damage, which indicates the relevance and importance of scientific developments in this area.

The study aimed to determine the characteristics of the macro- and microelements content in the blood serum and pancreatic homogenate of female rats and their offspring under chronic combined stress during pregnancy.

Research methods and materials

Female rats were divided into two experimental groups and one control group (K-group). The C-group rats were maintained in comfortable conditions and fed a balanced diet for the duration of the experiment (30 ± 1.1 days). To induce stress the rats of the study group were placed daily in special individual cages-pencils in a state of prolonged, varying in time (which makes it impossible for them to adapt) immobilization for 47.0 ± 6.1, after which the animals were returned to standard, but different cages each time, and the diet was changed, causing additional stress. Offspring from both study and control groups received balanced nutrition and were housed in standard vivarium conditions. Rats were removed from the experiment at birth and at one month of age.

Experiments on animals were conducted in accordance with the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986, revised 2006), Ukrainian Law No. 3447-IV, Articles 26, 31 "On the Protection of Animals from Cruelty to Animals," "General Ethical Principles of Experiments on Animals" (V National Congress on Bioethics, Kiev, 2013), EU Directive 2010/63/EU, and the Council of Europe Convention ETS123, adhering to all relevant ethical norms and standards for biomedical research.

Serum and pancreatic homogenate macro- and microelement content was determined spectrophotometrically using a Stat Fax biochemical analyzer and reagent kits from Filisit-Diagnostics (Dnipro) and DAC-Spectro-Med (Moldova). Specifically, Ca (540 nm; glyoxalbis- (2-oxyvinyl) (o-cresolphthalein complex)), Fe (540 nm; bathophenanthroline), and Mg (540 nm; titanium yellow) were measured using Filisit-Diagnostics kits. Zn (550 nm; 2- (5-bromo-2-pyridulazo-7- (N-propyl-N-sulfopropylamino)-phenol)) and Cu (580 nm; 4- (3.5dibromo-2-pyridula-vo0-4-ethyl-4-sulfopropylaniline)) were measured using DAC-Spectro-Med kits. Statistical analysis (Microsoft Excel-2003, Biostat.exe-2008, STATISTICA-10) involved one-way ANOVA and Mann-Whitney U tests to assess differences between groups, with significance set at $p < 0.05$.

Results and discussion

When modeling chronic stress in female rats of the study group, a decrease in the content of Ca, Mg, Zn and Cu was found in the pancreatic tissue (by 41.5 %, 40.0 %, 25.6 % and 26.7 % ($p < 0.01$) respectively) (Table 1), while the level of Fe was slightly increased (by 7.4 %, $p > 0.05$). The Ca/Mg ratio indicator almost does not differ from the average statistical value in the control group, which indicates the balance of their effects. In the blood serum of animals in the study group, less pronounced changes in the balance of macro- and microelements were found than in the pancreas (Table 1). The content of Fe and Ca C was normal (38.7 % higher than the indicator in the pancreas); the content of Mg and Zn is reduced by 32.5 % and 18.8 % ($p < 0.01$) compared to the norm and higher

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Table 1

Macro- and microelement content in blood serum and pancreatic homogenate of female rats under chronic combined stress during pregnancy

Indicators	Female rats			
	Pancreatic homogenate (*n* = 7)		Blood serum (*n* = 7)	
	experim. gr	control	experim.gr	контроль
Ca (mg/100 g of tk. — pancreas) (mM/L — blood serum)	3,44 ± 0,36**	5,88 ± 0,15	2,4 ± 0,05 ***(p_{pn} < 0,05)***	2,47 ± 0,04 ***(p_{pn} < 0,01)***
$Ca_{pn/s}$ (од.)	1,44 ± 0,14** (experim. group)			
	2,35 ± 0,05 (control)			
Mg (mg/100 g of tk. — pancreas) (mM/L — blood serum)	1,04 ± 0,06**	1,95 ± 0,04	0,76 ± 0,03** ***(p_{pn} < 0,01)***	1,12 ± 0,02 ***(p_{pn} < 0,01)***
$Mg_{pn/s}$ (units.)	1,38 ± 0,08** (experim. group)			
	1,72 ± 0,04 (control)			
Ca/Mg (units)	3,33 ± 0,32	3,02 ± 0,07	3,23 ± 0,09**	2,21 ± 0,02 ***(p_{pn} < 0,01)***
Fe (mg/100 g of tk. — pancreas) (μM/L — blood serum)	22,49 ± 0,74	20,94 ± 0,43	13,06 ± 0,31 ***(p_{pn} < 0,01)***	13,74 ± 0,29 ***(p_{pn} < 0,01)***
$Fe_{p/s}$ (units.)	1,73 ± 0,07* (experim. group)			
	0,52 ± 0,04 (control)			
Zn (mg/100 g of tk. — pancreas) (μM/L — blood serum)	4,3 ± 0,17**	5,78 ± 0,13	14,76 ± 0,2** ***(p_{pn} < 0,01)***	18,17 ± 0,29 ***(p_{pn} < 0,01)***
$Zn_{p/s}$ (units.)	0,29 ± 0,01 (experim. group)			
	0,32 ± 0,01 (control)			
Cu (mg/100 g of tk. — pancreas) (μM/L — blood serum).	5,5 ± 0,23**	7,5 ± 0,18	7,33 ± 0,26** ***(p_{pn} < 0,01)***	10,68 ± 0,16 ***(p_{pn} < 0,01)***
$Cu_{pn/s}$ (units.)	0,76 ± 0,02* (experim. group)			
	0,69 ± 0,02 (control)			

Notes: 1. **- $p < 0.01$; * — $p < 0.05$ — comparison with the control group.
2. p_{pn} — comparison with indicators in the pancreas.

than in the pancreas by 7.5 % and 6.8 % ($p < 0.01$), respectively, and the Cu level is lower than the norm by 31.3 %, which does not significantly differ from its value in the pancreas. The nature of the difference in the content of macro- and microelements in the pancreas and blood serum is clearly shown by the values of the ratio of indicators of Ca, Mg, Fe, Zn and Cu in the pancreas to those in blood serum (a decrease compared to the norm by 38.6 % and 19.7 % ($p < 0.01$) for Ca and Mg, respectively, by 8.9 % ($p > 0.05$) for Zn and an increase by 14.0 % and 10.6 % ($p < 0.05$) for Fe and Cu, respectively).

The levels of macroelements Ca and Mg were lower than the norm, but the Ca content did not differ significantly from that of the control group, while the Mg content was significantly lower (by 22.1 %). Therefore, the ratio (Ca/Mg) was 21.6 % ($p < 0.01$) higher than that in the control group.

In the pancreas of 1-month-old rats, changes in the content of microelements were observed, which consisted of a decrease in Zn and Cu (by 34.5 % and 8.7 % ($p < 0.01$), respectively), while the content of Fe was at a normal level (see Table 2).

In the blood serum of 1-month-old rats, the direction of deviations in the content of trace elements from the norm, except Cu, is identical to that in the pancreas, and the level of micro- and macroelements Ca, Mg and Zn is reduced (by 13.8 %, 45.6 % and 36.0 % ($p < 0.01$) respectively), but the level of Fe was within normal limits; the content of Cu was significantly higher than that in the pancreas (by 9.7 %, $p < 0.01$), but did not differ significantly from the control. Analysis revealed significant differences in pancreatic and serum Mg and Cu levels. The Mg pancreas/serum ratio was 52.8 % higher ($p < 0.01$), while the Cu pancreas/serum ratio was 8.1 % lower ($p < 0.01$). In one-month-old offspring of chronically stressed female rats, pancreatic tissue consistently showed lower levels of Ca, Zn, and Cu, with a tendency towards lower Mg and Fe levels.

Under the influence of chronic stress in female rats and prenatal stress in their 1-month-old offspring, a decrease in the content of macro- and microelements was observed in the pancreatic tissue and blood serum. The dynamics of individual elements

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Table 1

Macro- and microelement content in blood serum and pancreatic homogenate of female rats under chronic combined stress during pregnancy

Indicators	Female rats			
	Pancreatic homogenate (*n* = 7)		Blood serum (*n* = 7)	
	experim. gr	control	experim.gr	контроль
Ca (mg/100 g of tk. — pancreas) (mM/L — blood serum)	3,44 ± 0,36**	5,88 ± 0,15	2,4 ± 0,05 ***(p_{pn} < 0,05)***	2,47 ± 0,04 ***(p_{pn} < 0,01)***
$Ca_{pn/s}$ (од.)	1,44 ± 0,14** (experim. group)			
	2,35 ± 0,05 (control)			
Mg (mg/100 g of tk. — pancreas) (mM/L — blood serum)	1,04 ± 0,06**	1,95 ± 0,04	0,76 ± 0,03** ***(p_{pn} < 0,01)***	1,12 ± 0,02 ***(p_{pn} < 0,01)***
$Mg_{pn/s}$ (units.)	1,38 ± 0,08** (experim. group)			
	1,72 ± 0,04 (control)			
Ca/Mg (units)	3,33 ± 0,32	3,02 ± 0,07	3,23 ± 0,09**	2,21 ± 0,02 ***(p_{pn} < 0,01)***
Fe (mg/100 g of tk. — pancreas) (μM/L — blood serum)	22,49 ± 0,74	20,94 ± 0,43	13,06 ± 0,31 ***(p_{pn} < 0,01)***	13,74 ± 0,29 ***(p_{pn} < 0,01)***
$Fe_{p/s}$ (units.)	1,73 ± 0,07* (experim. group)			
	0,52 ± 0,04 (control)			
Zn (mg/100 g of tk. — pancreas) (μM/L — blood serum)	4,3 ± 0,17**	5,78 ± 0,13	14,76 ± 0,2** ***(p_{pn} < 0,01)***	18,17 ± 0,29 ***(p_{pn} < 0,01)***
$Zn_{p/s}$ (units.)	0,29 ± 0,01 (experim. group)			
	0,32 ± 0,01 (control)			
Cu (mg/100 g of tk. — pancreas) (μM/L — blood serum).	5,5 ± 0,23**	7,5 ± 0,18	7,33 ± 0,26** ***(p_{pn} < 0,01)***	10,68 ± 0,16 ***(p_{pn} < 0,01)***
$Cu_{pn/s}$ (units.)	0,76 ± 0,02* (experim. group)			
	0,69 ± 0,02 (control)			

Notes: 1. **- $p < 0.01$; * — $p < 0.05$ — comparison with the control group.
2. p_{pn} — comparison with indicators in the pancreas.

in the pancreatic tissue and blood serum in animals in the study groups had significant differences, but in general, the number of macro- and microelements, the level of which exceeded the normal range, in the pancreatic tissue is almost the same (in 1-month-old animals 60 %), and in the blood serum of female rats and their 1-month-old offspring (changes in the level of macro- and microelements 60 % and 80 %, respectively). A characteristic feature of changes in the balance of macro- and microelements due to chronic stress in female rats and prenatal stress in their 1-month-old offspring (almost in all animals) is the low Ca, Zn, and Cu in the pancreas homogenate.

Variations in macro- and microelement levels between pancreatic tissue and blood serum suggest organ-specific regulation, precluding the use of serum element concentrations to assess pancreatic metabolic status. Low calcium levels impair mitochondrial enzyme activity, the respiratory chain, oxygen consumption, and oxidative phosphorylation, thereby disrupting overall metabolism, hormone production, and neurotransmitter synthesis [15, 18].

Low Zn content affects the functional state of the antioxidant defense system and its ability to control the concentrations of nitrite and malonaldehyde, which can lead to damage to pancreatic в-cells [16, 21, 24, 26].

Low Cu content, taking into account its inclusion in many enzymes: cytochrome oxidase, superoxide dismutase, monoamine oxidase (catalyzes the oxidative deamination of catecholamines and serotonin), etc., can disrupt their functional activity, as a result of which protein metabolism slows down, inflammatory and autoimmune processes are supported [12, 13].

Given the critical roles of macro- and microelements in mitochondrial function, DNA/RNA replication, cell division, enzyme activity, immune response, free radical scavenging, antioxidant activity, carbohydrate (insulin secretion), lipid, and protein metabolism, hormone/neurotransmitter release, and pancreatic function (exocrine and endocrine, including enzyme activation) [9,28,29], macro- and microelement imbalances induced by chronic stress may predispose female rats and their offspring to pancreatic damage and chronic pancreatitis.

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Conclusions

1. Chronic stress triggers neurogenic mechanisms involving both the central and peripheral nervous systems, resulting in imbalanced macro- and microelement levels within organs, cells, and blood serum.
2. Unlike controls, there is heterogeneity in the level of macro- and microelements changes, however, a stable trend towards a decrease in the content of Ca, Mg, and Zn in the pancreas homogenate is observed, which does not coincide with the dynamics of the content of the corresponding indicators in blood serum.
3. The macro- and microelement levels imbalance arise from a complex neurohumoral response to chronic stress, likely driven by increased stress hormone production and neurotransmitter dysregulation (acetylcholine, histamine, serotonin, dopamine). These factors activate organ and tissue damage mechanisms, particularly in the pancreas, predisposing animals to chronic pancreatitis.

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