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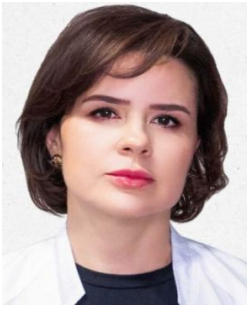
LABORATORY INDICATORS IN RATS EXPOSED TO ISOLATED AND COMBINED EXPOSURE TO LEAD AND CHROME

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ҚЎРҒОШИН ВА ХРОМНИНГ КОМБИНАЦИЯЛАНГАН ВА ИЗОЛЯЦИЯЛАНГАН ТАЪСИРИГА ТУШГАН СИЧҚОНЛАРНИНГ ЛАБОРАТОР КЎРСАТГИЧЛАРИ

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ЛАБОРАТОРНЫЕ ПОКАЗАТЕЛИ У КРЫС, ПОДВЕРГАВШИХСЯ ИЗОЛИРОВАННОМУ И КОМБИНИРОВАННОМУ ВОЗДЕЙСТВИЮ СВИНЦА И ХРОМА

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Резюме. *Оғир металларнинг таъсири натижасида ошқозон ости бези эндокрин аппарати бузилишларининг табиатини билиш ва бу шароитда қандли диабет ривожланиши ушбу касалликнинг патогенезини чуқурроқ тушунишга ёрдам беради ва натижада касалликларнинг рационал профилактика усулларини яратишга ёрдам беради. Шу муносабат билан, мақолада қўрғошин ва хром бирикмаларининг сичқонлар ошқозон ости безинг эндокрин функциясига зарарли таъсири патогенези баъзи жиҳатлари келтирилган. Тажрибани ўтказиш учун интоксикацияни келтириб чиқарган моддага қараб ҳайвонларнинг 4 та гуруҳи тузилди: 1 гуруҳ - "қўрғошин" (n=33); 2-гуруҳ – "хром" (n=40); 3-гуруҳ – "қўрғошин+хром" (n=108); 4-гуруҳ – "интакт" (n=47). Металларнинг комбинацияланган таъсири эркин радикалли оксидланиш жараёнларининг янада аниқ фаоллашишига олиб келади, бунинг натижасида ортиқча липид пероксидланиши қўзғатилади, бу эса ўз навбатида ошқозон ости бези В-ҳужайраларининг кўпроқ шикастланишига ва буларда гипоинсулинемиянинг ривожланишига олиб келади, бунда изоляция қилинган металлар билан зарарланган ҳайвонлар билан солиштирганда, гипоинсулинемия кузатилмаган. Таққослаш гуруҳларидан фарқли ўлароқ, "қўрғошин+хром" гуруҳида ўлимнинг мавжудлиги ва тана вазнининг кўпроқ камайиши, шунингдек, изоляция қилинган таъсирга нисбатан металлар бирикмасининг танага янада аниқ токсик таъсирини кўрсатади.*

Калит сўзлар: *қўрғошин, хром, ошқозон ости бези, сичқонлар, липид пероксидацияси, антиоксидант тизим.*

Abstract. *Knowledge of the nature of disorders of the endocrine apparatus of the pancreas as a result of exposure to heavy metals and the development of diabetes mellitus under these conditions will contribute to a deeper understanding of the pathogenesis of this disease and, consequently, the creation of rational methods of prevention. In this connection, the article presents some aspects of the pathogenesis of the damaging effects of lead and chromium compounds on the endocrine function of the pancreas of rats. To conduct the experiment, depending on the substance that caused the intoxication, 4 groups of animals were formed: 1 group – "lead" (n=33); Group 2 – "chrome" (n=40); Group 3 – "lead+chromium" (n=108); Group 4 - " intact " (n=47). It has been shown that combined exposure to metals leads to more pronounced activation of free radical oxidation processes, as a result of which excess lipid peroxidation is induced, which in turn leads to greater damage to pancreatic β- cells and the development of hypoinsulinemia in these animals, compared with isolated exposure metals, where hypoinsulinemia was not observed. The presence of mortality and a greater decrease in body weight in the "lead + chromium" group, in contrast to the comparison groups, also indicate a more*

pronounced toxic effect of the combination of metals on the body compared to their isolated effect.
Key words: *lead, chromium, pancreas, rats, lipid peroxidation, antioxidant system.*

Introduction. Environmental pathology, which previously more often developed in narrow populations, under the influence of specific xenobiotics, has today acquired a spontaneous character [1]. Among the many organic and inorganic substances that enter nature, heavy metals occupy a special place, since they do not decompose, are included in food chains and accumulate in living organisms, having mutagenic and toxic effects [2,3]. Lead and chromium, as well as their compounds, are considered the most toxic. Despite the fact that numerous researchers have studied diabetes mellitus in detail and in depth, there is very little information in the literature about how heavy metals influence the occurrence and course of this disease [4,5]. Meanwhile, it has been shown that in regions with high technogenic load, the incidence of diabetes mellitus in people is higher than in environmentally favorable areas [6,7,8,9]. It is quite obvious that knowledge of the nature of disorders of the endocrine apparatus of the pancreas as a result of exposure to heavy metals and the development of diabetes mellitus under these conditions will contribute to a deeper understanding of the pathogenesis of this disease and, consequently, the creation of rational methods of prevention. Thus, the study of the prepathological state in diabetes mellitus seems very relevant. These provisions determined the purpose of the study.

Purpose of the study: to study some aspects of the pathogenesis of the damaging effects of lead and chromium compounds on the endocrine function of the pancreas.

Materials and methods of research. Studies included 3 series of experiments on white outbred male rats with an initial weight of 230-270g. The maintenance, care of animals and removal from the experiment were carried out in accordance with the order of the Ministry of Health of the Republic of Kazakhstan dated July 25, 2007 No. 442 «On approval of the rules for conducting preclinical studies, medical and biological experiments and clinical trials in the Republic of Kazakhstan». The animals were kept on a standard vivarium diet with free access to water and food. The following groups were formed to conduct the experiment:

Group 1 – rats that received per os 1% lead acetate solution - “lead” group (n =33);

Group 2 – rats that received per os 0.5% solution of potassium dichromate – “chromium” group (n =40);

Group 3 – rats that simultaneously received per os combination of lead acetate and potassium bichromate in the same dosages - the “lead + chromium” group (n = 108);

Group 4 - intact rats that received per os 0.9% NaCl solution - “intact” group (n= 47).

Lead intoxication was caused by oral administration of a 1% solution of lead acetate at a dose of 15 mg/kg body weight for 30 days, daily, except Sunday. Chromium intoxication was modeled by oral administration of a 0.5% solution of potassium dichromate at a dose of 5 mg/kg body weight for the same period. Combined intoxication - by administering the specified metals in the same dosages at the specified times. Animals were removed from the experiment by decapitation under ether anesthesia.

During the entire experimental period, the general condition of the animals was monitored. In animals of all experimental groups, the number of sick rats, the percentage of their death were taken into account, body weight indicators, levels of glucose and ketone bodies in the blood on an empty stomach were studied (glucometer Optium from MediSense with a set of test strips), immunoreactive insulin (IRI) in blood serum by radioimmunological method.

To study the processes of lipid peroxide oxidation (LPO) and the state of the antioxidant system (AOS), a homogenate was prepared from liver cells and the activity of superoxide dismutase (SOD) was studied according to the method of V.G. Verbolovich (1987); catalase activity according to the method of M.A. Korolyuk (1988) [10]. The activity of oxidative metabolism in hepatocyte membranes was determined by the content of diene conjugates (DC) and malonic acid. dialdehyde (MAD), by E.I. Lvovskoy, I.A. Volegorodsky, S.E. Shemyakova (1991) [11].

The concentration of lead and chromium in the blood of rats was determined at the end of a 30-day priming using inductively coupled plasma atomic emission spectrometry.

Static processing of the material was carried out using the statistical software package Statistica 6 (“StatSoft” USA). The reliability of intergroup differences was assessed using Student's t-test.

Research results and their discussion. Observing the condition of rats exposed to isolated and combined exposure to lead and chromium for 30 days, we noted that in the “lead + chromium” group, signs of intoxication were observed for the first time during the experiment. This was expressed in a sharp decrease in appetite, up to refusal of the offered food, diarrhea, which was observed in some animals, decreased motor activity, lethargy, drowsiness, changes in grooming and deterioration in the condition of the coat. Over 30 days, the death rate of animals in this group was 31% (out of 108 rats, 34 died), meanwhile, in the groups with isolated influence of the metals “lead” and “chrome” there was no mortality.

Table 1. Effect of lead and chromium on body weight of rats (M±m)

Groups of animals	Body weight (g)		
	The initial state	On the 15th day	On the 30th day
Intact	240±3.3	256±3.8*	260±4.3*
Chromium	270±3.1	266±4.2	254±4.7*
Lead	254±5	247±4.7	268±3.6*▼
Lead+chrome	268±4.8	241±3.6▼	229±5.9*

Note: ▼ - statistically significant differences compared to 15 days (p≤0.05);
** - compared with the corresponding initial data (p<0.01)*

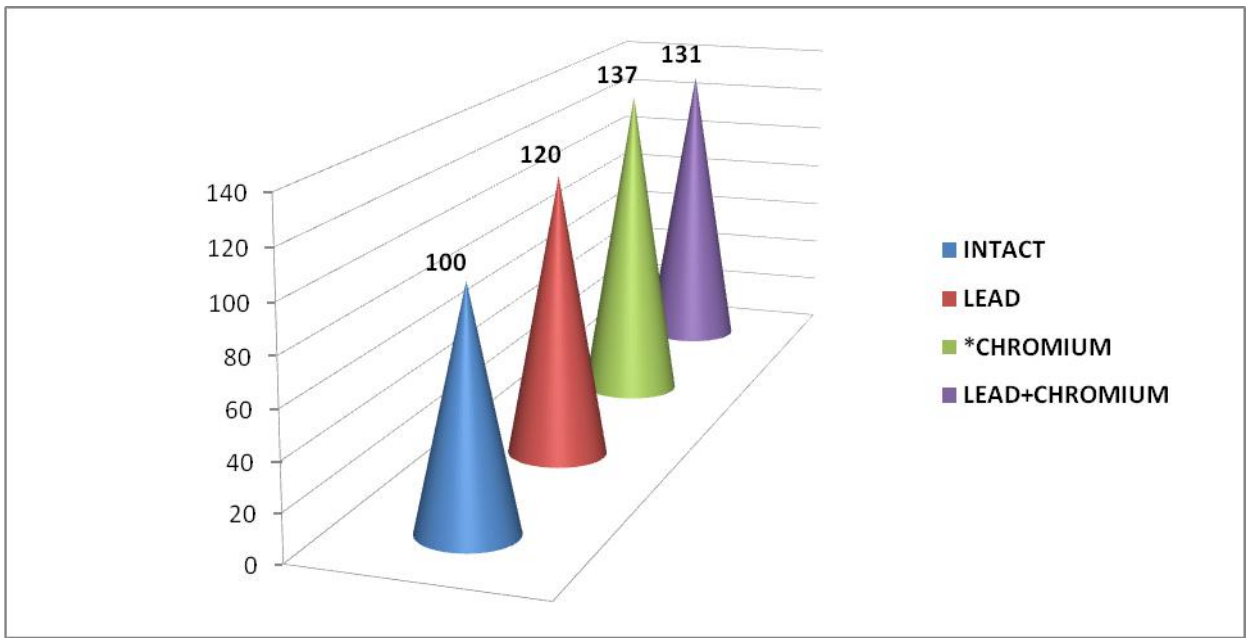
Table 1 presents data on the effect of the combination of lead and chromium on the body weight of animals. In the available literature, we have not found information about the effect of this combination of metals on changes in body weight, either in experimental animals or in humans.

Table 1 shows that if in intact rats on the 15th day there was an increase in body weight by 7%, then in rats that were under the simultaneous influence of lead and chromium for 15 days, body weight decreased by 10% compared to the initial data. During the same observation periods, the body weight of rats with isolated exposure to lead and chromium did not change. On the 30th day of the experiment, the body weight of intact rats was 108% compared to the initial indicator; in the "lead + chromium" group, the animals continued to lose weight and their body weight was 85% of the original. Meanwhile, in rats exposed to isolated chromium, the body weight on the 30th day of the experiment was 94%, and in the "lead" group it was 106% compared to the corresponding initial conditions.

Mortality and decrease in body weight in the group of animals receiving a mixture of metals indicate the toxic effect of metals on the body of rats.

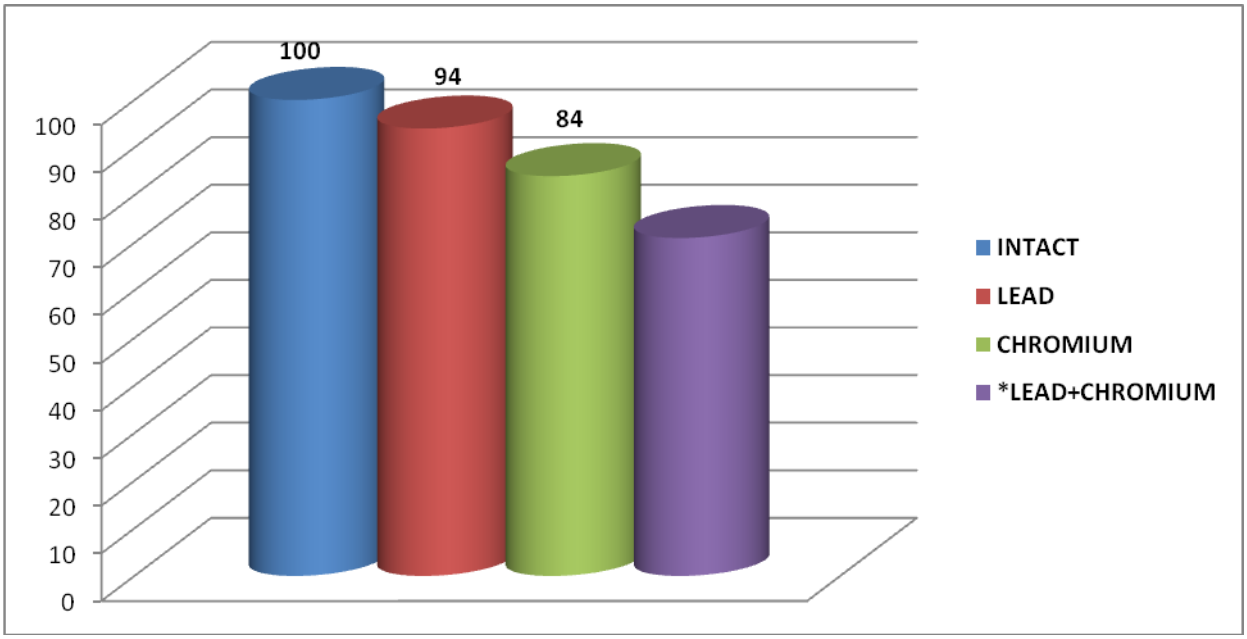
Studies of the isolated and combined effects of these metals on the content of glucose and insulin in the blood of rats showed that simultaneous administration of lead and chromium to rats for 30 days led to a decrease in the level of IRI by 29% compared to intact rats; accordingly, there was a tendency to increase the glucose content in blood from these animals. On the contrary, isolated administration of lead to rats did not affect the levels of glucose and IRI, while the administration of chromium led to an increase in glucose levels by 35%, while the level of IRI only tended to decrease in relation to intact animals (Fig. 1, 2). So, in contrast to the isolated effect of lead and chromium, the combined administration of these metals caused hypoinsulinemia in animals.

The system of LPO and AOP is a criterion for predicting the harmful effects of metals on the body [12]. The results of the study are in Table 2.



Indicators in intact rats were taken as 100%
** - statistically significant differences from intact animals (p<0.05)*

Figure 1. Blood glucose levels in rats after 30 days of metal priming



Indicators in intact rats were taken as 100%

** - statistically significant differences from intact animals (p<0.05)*

Figure 2. IRI content in the blood of rats after 30 days of metal priming

Table 2. Indicators of LPO and AOD in the liver of rats on the 30th day of the experiment (M±m)

Groups animals	DK µmol /ml	MAD µmol /ml	SOD (U/ml/min)	CAT (cat/l)
Intact	0.8±0.05	0.8±0.04	8.36±0.1	678±1.2
Lead	0.9±0.03	0.9±0.03* p ≤0.05	9.0±0.2* p≤0.01	682±1.9
Chromium	0.94±0.02* p≤0.01	0.9±0.01* p≤0.01	10.1±0.2* p ≤0.001	680±6.4
Lead+chrome	1.2±0.02*	1.34±0.02*	12.1±0.6*	766.9±9.1*

*Note: *- statistically significant differences from intact animals (p≤0.001)*

The study revealed significant changes in the studied indicators. So, in the "lead+chromium" group, the level of DC increased by 50%, MAD – by 68% compared to intact animals, which indicates an intensification of the processes of lipid peroxidation. Against the background of SRO induction, the AOD system was also activated: the level of SOD increased by 45%, catalase - by 13% in relation to intact rats.

Meanwhile, in the comparison groups (animals with isolated administration of metals), LPO processes were not as active. Thus, in the "lead" group only the MAD content increased by 13%, in the "chrome" group the level of both DC and MAD increased by 18% and 13%, respectively. As for AOD, in the comparison groups only SOD activity significantly increased by 8% in the lead group and 21% in the chromium group.

Thus, the simultaneous influence of lead and chromium, compared with their isolated effect, caused a more intense activation of lipid peroxidation processes and increased activity of SOD and catalase.

Determination of the coefficient K LPO/ AOD, reflecting the balance of the work of the LPO-AOD system, showed that in rats of the "lead" group there was an increase in this indicator to 1.1, which exceeded the limits of the accepted norm (in intact animals K LPO/ AOD = 1) by 10% and indicated a slight shift towards pro-oxidants.

In addition, the correlation analysis revealed a positive functional relationship between changes in indicators of lipid peroxidation processes and antioxidants r = + 1, indicating that in response to an increase in lipid peroxidation products, antioxidant protection also increases.

Analysis of the balance in the LPO-AOD system in animals of the "chrome" group showed that the administration of potassium dichromate for 30 days led to the accumulation of intermediate and final products of LPO – DC and MAD and to the parallel activation of antioxidant defense enzymes, resulting in the indicator balance of functioning of the LPO-AOD system K LPO/ AOD was equal to 1.3.

Along with this, we have established a negative close correlation between the indicators of LPO and AOD r = -1, indicating that with an increase in LPO processes, the activity of antioxidants will decrease.

An analysis of the balance in the LPO- AOD system in rats of the "lead + chromium" group revealed a predominance of DC and MAD over protective factors, as evidenced by a K LPO/ AOD equal to 2, i.e. was 100% higher than the value of that coefficient in intact animals (K LPO/ AOD = 1).

In support of this result, a close negative correlation was obtained between lipid peroxidation products and AOD factors: r = -1, indicating that a further increase in lipid peroxidation will lead to a decrease in the activity of SOD and catalase.

So, in the rats of the "lead" group there was no pronounced imbalance in the LPO-AOD system; in the rats of the "chrome" group there was a slight shift in the balance towards pro-oxidants, with the possible subsequent development of oxidative stress, although moderate activation of SOD may also indicate the control of antioxidants over pro-oxidants.

A comparative analysis of the "lead + chromium" group with animals under conditions of isolated exposure to metals revealed that the shift in the equilibrium in the LPO-AOD system in the case of simultaneous exposure to metals was more significant (K LPO/ AOD = 2) than in the "lead" groups (K LPO/ AOD = 1.1) and "chrome" (K LPO/ AOD = 1.3). Thus, the combination of lead and chromium causes a more pronounced imbalance in the LPO-AOD system than the isolated effect of these metals.

In our case, apparently, in the animals of the "lead" group, a new ratio of pro-oxidant and antioxidant factors was formed, promoting adaptation to new living conditions; in addition, the presence of adaptation is evidenced by the absence of mortality in the group and the increase in body weight, as well as the appearance of the rats, which remained mobile, had thick, white, shiny fur. Animals under these conditions, despite exposure to lead, had normal levels of IRI and blood glucose.

Conclusion. Summarizing the above, it can be noted that the combined effect of metals leads to a more pronounced activation of FRO processes, as a result of which an excess of free radicals induces LPO, which in turn leads to greater damage to pancreatic β-cells and the development of hypoinsulinemia in these animals, compared to isolated exposure to metals, where hypoinsulinemia was not observed. The presence of mortality and a greater decrease in body weight in the "lead + chromium" group, in contrast to the comparison groups, also indicate a more pronounced toxic effect of the combination of metals on the body compared to their isolated effect.

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ЛАБОРАТОРНЫЕ ПОКАЗАТЕЛИ У КРЫС, ПОДВЕРГАВШИХСЯ ИЗОЛИРОВАННОМУ И КОМБИНИРОВАННОМУ ВОЗДЕЙСТВИЮ СВИНЦА И ХРОМА

Ким Т.А., Мавлянова З.Ф.

Резюме. *Не только знание характера нарушений инкреторного аппарата поджелудочной железы как результат воздействия тяжелых металлов, но и формирование в этих условиях сахарного диабета позволит более глубоко понять патогенез вышеназванного заболевания, а значит, разработать рациональные методы профилактики. Именно поэтому в данной статье приводятся некоторые аспекты патогенеза у крыс повреждающего действия соединений хрома и свинца на эндокринную функцию поджелудочной железы. Для проведения эксперимента в зависимости от вещества, вызвавшего интоксикацию, было выделено 4 группы подопытных животных: в первую группу вошли n=33 – «свинец»; вторую группу n=40 – «хром»; третья группа – «свинец+хром», n=108; четвертая группа - «интактные», n=47. Выявлено, что у крыс комбинация металлов привела к активации процессов свободнорадикального окисления, в результате индуцированного ПОЛ, что в конечном итоге привело к выраженному повреждению β-клеток поджелудочной железы и развитию гипоинсулинемии. В отличие от данной группы животных при изолированном воздействии металлов гипоинсулинемия не развивалась. Летальность и снижение массы тела у животных в группе «свинец+хром» в отличие от групп сравнения указывали на выраженное токсическое действие комбинации металлов в сравнении с их изолированным воздействием.*

Ключевые слова: *свинец, хром, поджелудочная железа, крысы, ПОЛ, антиоксидантная система.*