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ASSESSMENT OF OCCUPATIONAL RISK OF HEALTH DISORDERS OF NON-FERROUS METALLURGY WORKERS

Annotation. The assessment of workers' health requires the development of scientific approaches to detect early changes in the body as a result of exposure to production factors. There is very little scientific literature on the effect of unfavourable toxic factors of titanium-magnesium production on the organism. Currently, the issues of prenosological diagnostics are becoming more relevant, and the methods are being actively developed. Tissue metabolism plays a major role in the formation of prenosological conditions. Chronic stressor influence of production factors cause changes in the regulation of blood circulation. We have studied the influence of toxic chemical substances Ust-Kamenogorsk Titanium-Magnesium Plant (UKTMP) on the organism of workers, namely on the indicators of the kallikrein-kinin system of workers of the main workshops depending on the length of service at this enterprise, we determined the level of kininogen and prekallikrein, the activity of kininase and kallikrein. It was revealed that workers under the influence of a complex of production factors on the organism have activation of indicators of the kallikrein-kinin system, the changes depend on the length of service and the workshop. Kinins are necessary products of vital activity, they are contained in all organs and tissues, fulfil the role of chemical regulators of local and general blood flow rate. Our studies are necessary for early detection of changes in the body of workers and comprehensive treatment procedures, can prevent the development of occupational diseases.

Keywords: Unfavourable production factors; indicators of the callecrein-kinin system; workers of the main workshops; occupational risks.

Introduction

At JSC ‘UK TMP’ the most unfavourable areas from the hygienic point of view is the area where work is carried out with sulphuric acid and caustic magnesite in the production of magnesium sulphate. In these working premises the concentration of magnesite aerosol in the air of the working zone is 4-5 times higher than maximum permissible concentration (MPC). In the winter period of the year the air temperature in the workplaces reaches 18-200 C. In the areas of cleaning, solution packing and filtration are carried out at air temperature in summer 38-400 C. Workers at washing, drying, packing of the preparation have a prolonged contact of skin of workers with this substance. Air pollution of working premises with chemical substances, as well as unfavourable microclimatic conditions depend on the state of exhaust and inlet ventilation [1].

However, there is no doubt that complete exclusion of unfavourable factors from the work environment is impossible due to technological, economic and other difficulties [2; 3].

Information on the effect of titanium and its compounds on individual organs and systems in the literature is limited.

It has been established that when white mice are baited with titanium tetrachloride ($TiCl_4$), not only $TiCl_4$ but also its hydrolysis products - hydrogen chloride and aerosols of titanium compounds - have an effect [4;5]. At action of $TiCl_4$ products high mortality was noted, rapid development of pulmonary oedema occurred. Toxic effect of $TiCl_4$ hydrolysis products, apparently, are connected with the fact that HCl vapours are carried into deep parts of lungs, and particles of intermediate products of $TiCl_4$ hydrolysis getting into alveoli, further affect the lung tissue.

Purulent conjunctivitis developed during application of $TiCl_4$ solution, as well as corneal opacity, i.e. irritating effect of $TiCl_4$ and its hydrolysis products was observed. Animals died with oedema and pulmonary haemorrhage.

It is known that under the action of insoluble titanium compounds, changes in the respiratory tract develop [6;7;8]. Development of pneumoconiosis is established in workers, whose production activity is connected with the action of titanium and titanium carbide [9;10].

Highly dispersed particles of condensation of welded stainless steel, as well as a small admixture of gaseous substances (ozone, nitrogen oxides, hydrogen fluoride and others) were detected in the breathing zone of electric welders. The concentration of aerosol at the workplace of electric welders ranged from 4.0 to 22.0 mg/m3, chromic anhydride 0.3-0.4 mg/m3 (MPC 0.01 mg/m3), the content of chromium in electrodes reached 20%, nickel 9%, manganese 7%. When fitters and electric welders worked together in closed, poorly ventilated rooms, conditions for the summarised effect of the above factors were created [11; 12; 13].

Intratracheal administration of TiO_2 to rats causes transient pneumotoxic effect. When studying bronchoalveolar lavage fluid in experimental animals, an increase in the activity of lactate dehydrogenase and alkaline phosphatase enzymes was detected. Acid phosphatase did not change significantly, the amount of total protein and glucose increased [14].

The results of experiment on rabbits indicate that both in isolated form and in mixture with other elements (zinc, lead, iron, arsenic, antimony, copper, fluorine, cadmium), titanium dioxide has an effect, disturbing the functions of many organs and systems, including the activity of enzymes such as aldolase, cholinesterase, alkaline phosphatase, aspartataminotransferase, alanineaminotransferase [15].

In animal experiments it was found that titanium dioxide and titanium metal dust can cause changes both in lung tissue and bronchial lymph nodes. In white rats with intratracheal injection of titanium dioxide, metallic titanium and titanium carbide dust, proliferative cellular reaction around dust accumulations, hyperplasia of lymphatic follicles around bronchi was observed in 6-8 months [16;17;18].

A number of modern improvements have been introduced in the technological process of titanium sponge production, but labour conditions remain unfavourable.

The influence of harmful factors of TMP and their role in the occurrence of health disorders is necessary in a number of studies, which can become the basis for the development of a set of health-improving measures aimed at improving health and increasing working capacity.

There are few works in the literature on the effect of harmful components of magnesium, titanium and their compounds on the organism, and no such works have been found on their effect on the kallikrein-kinin system.

Materials and methods of research

The workers of the main shops were examined: shop 1 - magnesium production; shop 2 - titanium tetrachloride production; shop 3 - titanium sponge production (Table 1).

The control group consisted of 100 employees of the administrative and economic department of JSC “UKTMP”, whose production activities were not associated with occupational hazards, divided into the same seniority groups.

Kallikrein-kinin system indices were determined according to the method of Paskhina T.S. and Egorova T.P. (1973): level of kininogen and prekallikreinogen, activity of kininase and kallikrein. The principle of the bradykininogen determination method is based on the release of bradykinin from plasma denatured by trypsin.

Table -1- Distribution of subjects by length of service (in per cent and absolute number)

No.	Survey groups	Experience								Total	
		up to 3 years		3-5 years old		6-10 years old		Over 10 years			
		abs	%	abs	%	abs	%	abs	%	abs	%
1	Control group	29	29	25	25	24	24	22	22	100	100
2	Workers	125	29	116	27	99	23,1	90	20,9	430	100

Kininogen content in the blood of healthy humans is 4.2 ± 0.1mg/ml.

Total kininase activity was estimated according to the method of Paskhina T.S. and Egorova T.P. (1968). The principle of the method is based on the measurement of residual activity of bradykinin after its incubation with the enzyme. The results obtained were expressed in mg Br*10-3 g/l min. Determination was carried out on a spectrophotometer SPh-4a.

Blood kininase activity in healthy individuals averages 1.2 µg/ml of serum in 1 min.(1mg of bradykinin corresponds to approximately 1 mmcmol).

Kallikrein and prekallikreinogen in blood were determined by the chromatographic method of Paskhina T.S. and Yarova G.A. The principle of the method: cationic properties of kallikrein were used, due to which it is not adsorbed at pH 7.0 and low ionic A-50 and can be determined in the unadsorbed blood fraction by the rate of hydrolysis of the ester bond with ethyl ester hydrochloride of N-benzoyl-alpha-arginine. The amount of prekallikreinogen was expressed in mkU/ml, the amount of kallikrein - in mkU/ml x min.

Kallikrein activity in healthy subjects: 30.6±1.2 milikallikrein units (mkU) in 1 ml of serum at one minute(mkU/ml-min).

Norms for prekallikreinogen activity in healthy human serum: 404.4 ± 8.09 mkU/ml.

Statistical analysis of the obtained data was carried out according to the method of O.Y. Rebrova [22], the significance of differences between the studied values was determined by Student's t test according to the formula:

$$\boldsymbol{t} = -\frac{\boldsymbol{M}\text{study group} - \boldsymbol{M}\text{control group}}{\sqrt{\boldsymbol{m^2}\text{study group} + \boldsymbol{m^2}\text{control group}}}$$

where Mstudy group- mah (the largest number in the variation series of the study group);

Mcontrol group- mah (the largest number in the variation series of the control group);

m (study) - mean error - this is a measure of fluctuations in the mean of the study group itself;

m (counter) is the mean error, a measure of the variation in the mean of the control group.

These values are determined as follows: $m = \frac{G}{\sqrt{n}}$

where G- is the mean square deviation, which is a measure of variation in the variation series;

n- is the number of those studied.

$G = \frac{Mmax-Mmin}{Ermolaeva\ coefficient}$, coefficient is found by the well-known table of Ermolaev

$$M = \frac{Z(variation\ series\ sum)}{n(number\ of\ investigated)}$$

if t≤1.96, P>0.05; if t≥1.96, P<0.05; if t>2.06-3.0, P<0.01; if t>3.0, P<0.001.

Results and Discussion

Indicators of the kallikrein-kinin system (KKS) were determined in 176 people working in shops no. 1,2 and 3 of JSC “UKTMP” The average analysis of all workers for KKS components revealed activation of the enzyme forming free kinins 2.2 times in comparison with the control (p<0.01) against the background of an increase in the blood of its precursor precollikrein (PK) by 25% (p<0.001).

The analysis by length of service revealed activation of the enzymatic link of KKS at the length of service up to 3 years: increase in the activity of blood kallikrein (KK) by 2 times up to 25.6± 0.3 mkU/ml-min compared to control values (12.6±0.3 mkU/ml-min) against the background of some increase (by 19%) of its precursor - prekallikrein, indicating some adaptive increase in its synthesis (Tables 2 and 3.). The activity of kininases - enzymes that break down free kinins was also increased by 8% due to the need of the workers' organism during this period.

With 3-5 years of experience, kallikrein activity slightly decreases, but remains quite high, exceeding the values in the control group by 1.5 times (Figure 1).

The level of prekallikrein continued to increase by 34% up to 401±1.2 in comparison with the content in the blood of the control group subjects. Kininase activity significantly decreased by 38%, which indicated some insufficient functional activity of this enzyme in this age group.

Table -2- Indicators of kallikrein-kinin system in workers of JSC "UKTMP" by length of service

No.	Years of experience	n	Contents		Activity	
			kininogen	prekallikrein	kallikrein	kininases
			Br*10^{-3} g/l	mkU/ml-min	Br*10^{-3} g/l	mkU/ml-min
1	up to 3years	28	3,7±0,3	427,0±2,2^{xx}	25,6±0,3^{xxx}	4,1±0,1^{x}
2	3-5 years old	30	3,5±0,2	401±1,2^{xxx}	21,1±0,5$^{xxx}{}_{o}$	5,8±0,2$^{xxx}{}_{ooo}$
3	6-10 years old	22	3,6±0,2^{x}	399±1,0^{xxx}	38±0,8$^{xxx}{}_{ooo}$	6,0±0,2^{xxx}
4	Over 10 years	20	3,8±0,1^{x}	396±2,0^{xxx}	57±1,2^{xxx}	3,5±0,05$^{xxx}{}_{ooo}$
Total, M±m		100	3,6±0,2	405,7±1,6^{xxx}	35,4±1,4^{xxx}	4,8±0,1

Note –

^{x} – p<0,05; ^{xx} -p< 0,01:

^{xxx} – p<0,001 compared to the control group (Table 3); ^{o} – p<0,05;

^{ooo} – p<0,001 compared to the previous group.

Table - 3- Indicators of kallikrein-kinin system in workers of the control group by length of service

No.	Years of experience	n	Contents		Activity	
			kininogen	prekallikrein	kallikrein	kininases
			Br*10-3 g/l	mkU/ml-min	Br*10-3 g/l	mkU/ml-min
1	up to 3years	30	4,0±0,3	360±3,6	12,6±0,3	3,6±0,1
2	3-5 years old	28	3,8±0,2	300±2,8	14,2±0,1	4,2±0,2
3	6-10 years old	26	4,1±0,1	320±3,0	16,1±0,2	5,0±0,1
4	Over 10 years	21	4,2±0,2	318±2,8	20,6±0,1	5,2±0,3
Total, M±m		105	4,0±0,2	324,5±3,05	15,8±0,2	4,5±0,2

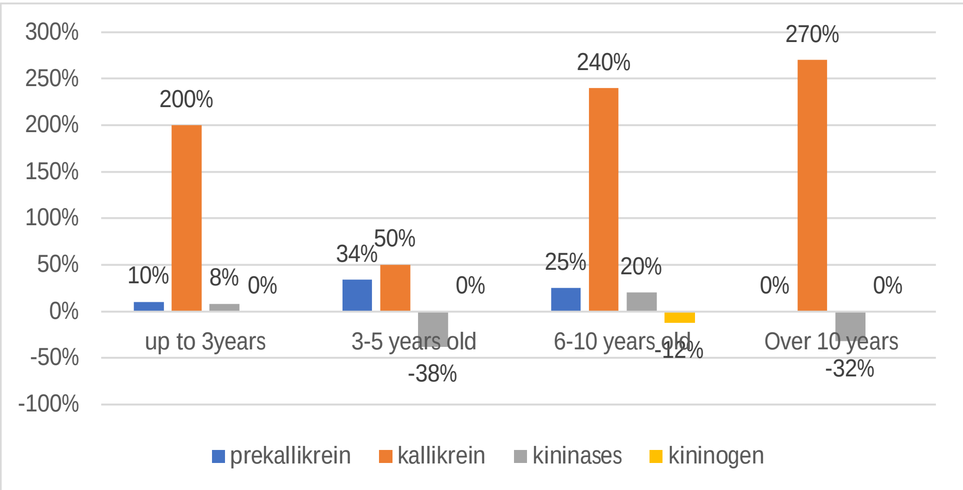

Figure 1- Changes in indicators of the kallikrein-kinin system in workers of JSC “UKTMP” by length of service

In the age group of 6-10 years the changes in the KKS parameters begin to progress, besides the reaction of the enzyme system and the KK-PK precursor, there is a significant decrease in the precursor of free kinins - kininogen, which indirectly indicates an increased increase in the physiological active forms of kinins: Kininogen level decreases significantly ($p<0.05$) by 12% to 3.6±0.2 Br*10-3 g/l compared to control (4.1±0.1 Br*10-3 g/l). The activity of kallikrein increases again by 2.4 times compared to control, in parallel with the increase of its inactive protein-bound precursors - prekallikrein - by 25% ($p<0.001$) and against the background of secondary adaptive increase of kininase activity (by 20%, p<0.001), which indicates deeper changes in the redistribution of structural elements of KKS.

At the age of workers working at the mill for more than 10 years, changes in kininogen and prekallikrein content remained at the level of the previous group. However, the continuing increase in kallikrein activity-2.7 times to 57±1.2 mkU/ml-min compared to the control - 20.6±0.1 mkU/ml-min, as well as the continuing decrease in kininase activity by 32 % to 3.5±0.05 Br*10-3g/l-min, p<0.001, indicate the progression of changes in the KKS system. Consequently, when exposed to the complex of factors of JSC “UKTMP”, conditions for hyperactivation of KKS are created, which depend directly on the length of service. With increasing length of service mutually balanced processes of formation and decay of kinins are disturbed (Paskhina T.S.); decay of free active kinins decreases, especially at 3-5 years of service and more than 10 years, though it stabilises somewhat at 6-10 years of service, as evidenced by phase adaptive changes of protease enzymes-kininases. The activity of kallikrein, which controls the release of free kinins from kininogen, changes in parallel.

All this has a certain importance in humoral regulation of homeostasis, as the KKS is one of the most important physiological systems of the organism, closely related to the coagulation system, catecholamines to other neurotransmitters and biologically active compounds.

When analysing the KKS indices in workers located in different workshops, it was revealed that in the blood of workers in workshop No.1 (magnesium production) the most significant increase in the enzyme (trypsin-like serine proteases) activating the formation of free kinins from kininogen kallikrein was detected compared to other workshops - 3.3 times to 52 ±1.5 mkU/ml-min against control values, p<0.001 (Table 4, Figure 2), in parallel with a decrease in the activity of enzymes that cleave physiologically active free kinins to inactive products. The activity of kininases decreased by 24% compared to the control group, p<0.001. The synthesis of PK in the liver was adaptively increased by 20% to compensate for the need for kallikrein.

Table - 4- Indicators of kallikrein-kinin system in workers of the main workshops of JSC “UKTMP”

No.	Persons under observation	n	Contents		Activity	
			kininogen	prekallikrein	kallikrein	kininases
			Br*10^{-3} g/l	mkE/ml-min	Br*10^{-3} g/l	mkE/ml-min
1	Shop 1	46	3,4±0,3	390±2,0^{xx}	52±1,5^{xxx}	3,4±0,05^{xxx}
2	Shop 2	62	3,8±0,4	420±1,5^{xxx}	32±2,0$^{xxx}_{ooo}$	5,2±0,3^{xx}
3	Shop 3	68	3,7±0,4	427±2,0^{xxx}	34±4,0^{xxx}	5,6±0,1^{xxx}
	Total	176	3,6±0,4	412±1,8^{xxx}	39±2,5^{ooo}	4,7±0,15^{o}
Note –						

xx – $p<0,01$;
xxx – $p<0,001$ compared to the control group (Table 3);
o – $p<0,01$;
ooo – $p<0,001$ by previous group

In Shop 2 (for tetrochloride production) and in Shop 3 (for titanium sponge production), the changes in KKS indicators were also manifested at the level of the enzyme link of KKS.

Thus, in shop No.2 (for production of titanium tetrochloride) in the blood of workers the activity of kallikrein increased 2 times and in shop No.3 (for production of titanium sponge) 2.2 times compared to the control.

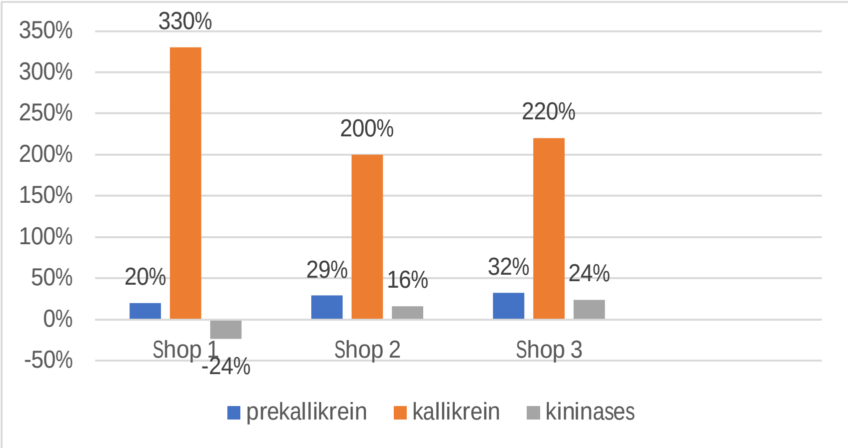

Figure 2- Changes in indicators of the kallikrein-kinin system in workers at the main workshops of JSC "UKTMP"

Analysis of kininase activity revealed an adaptive increase in its values in workshop No.2 and in workshop No.3 to 5.2± 0.3 (by 16%) and to 5.6±0.1 Br*10-3 g/l*min (by 24%) compared to control, ($p<0.001$).

A 24% decrease in kininase activity was found in the blood of workers in workshop No. 1, indicating an increased need for the enzyme to bind free kinins.

The level of protein-bound precursor of kallikrein-precallikrein reveals an increase in its synthesis in the blood of workers in all workshops most pronounced in the blood of workers in workshops 3 and 2 (32% and 29% higher than the control).

In the blood of workers of workshop 1, these values increased by 20% ($p<0.01$).

Conclusions

Thus, as a result of the conducted researches activation of KKS was revealed in workers of different shops of the plant and with different work experience. Apparently, when the homeostatic balance is disturbed, activation (or inhibition) of the enzymatic link of KKS indicates excessive formation of free kinins (compensated by bradykinin synthesis by the liver).

This mechanism, acquiring a cascade character, participates in the formation of the ultimate resistance of the workers' organism to the extreme impact of production factors.

It is known that kinins act as tissue hormones, being formed from precursors under the influence of specific enzymes and being peptides with high biological and pharmacological activity, they are one of the humoral factors significantly influencing the regulation of body functions and homeostasis processes.

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ТҮСТІ МЕТАЛЛУРГИЯ ҚЫЗМЕТКЕРЛЕРІНІҢ ДЕНСАУЛЫҒЫНЫҢ БҰЗЫЛУЫНЫҢ КӘСІБИ ТӘУЕКЕЛІН БАҒАЛАУ

Андатпа. Жұмысшылардың денсаулығын бағалау өндіріс факторларының әсерінен организмдегі ерте өзгерістерді анықтаудың ғылыми тәсілдерін әзірлеуді талап етеді. Ғылыми әдебиеттерде титан - магний өндірісінің қолайсыз уытты факторларының ағзаға әсері өте аз кездеседі. Қазіргі уақытта донозологиялық диагностика мәселелері өзекті бола түсуде және әдістер белсенді түрде әзірленуде. Донозологиялық жағдайлардың қалыптасуында тіндік метаболизмге үлкен рөл беріледі. Өндірістік факторлардың созылмалы стресстік әсері қан айналымын реттеудің өзгеруіне әкеледі. Біз Өскемен титан - магний комбинатының (ӨТМК) улы химикаттарының жұмысшылардың ағзасына әсерін, атап айтқанда, осы кәсіпорындағы жұмыс өтіліне байланысты негізгі цехтардың каллекреин-кинин жүйесінің көрсеткіштерін зерттедік, кининоген мен прекалллекреиногеннің деңгейін, кининаза мен калликреиннің белсенділігін анықтадық. Өндірістік факторлардың жұмысшылар ағзасына әсері кезінде калликреин-кинин жүйесінің белсенділігі артып, бұл еңбек өтілі мен цехқа байланысты өзгеретіні анықталды, олар барлық органдар мен тіндерде болады, жергілікті және жалпы қан ағымының химиялық реттегіштерінің рөлін атқарады. Біз жүргізген зерттеулер жұмысшылардың ағзасындағы өзгерістерді ерте анықтау

және кешенді емдеу процедураларын жүргізу үшін қажет, кәсіби аурулардың дамуына жол бермейді.

Кілтті сөздер: Өндірістің қолайсыз факторлары; калликреин-кинин жүйесінің көрсеткіштері; негізгі цехтардың жұмысшылары; кәсіби тәуекелдер.

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ОЦЕНКА ПРОФЕССИОНАЛЬНОГО РИСКА НАРУШЕНИЙ ЗДОРОВЬЯ РАБОТНИКОВ ЦВЕТНОЙ МЕТАЛЛУРГИИ

Аннотация. Оценка состояния здоровья рабочих требует разработки научных подходов к выявлению ранних изменений в организме в результате воздействия факторов производства. Влиянии на организм неблагоприятных токсических факторов титано- магниевого производства в научной литературе очень мало. В настоящее время вопросы донозологической диагностики становятся более актуальными, а методы активно разрабатываются. В формировании донозологических состояний большая роль отводится тканевому метаболизму. Хроническое стрессорное воздействие производственных факторов вызывают изменения в регуляции кровообращения. Нами изучены влияние токсических химических веществ титано- магниевого комбината (УК ТМК) на организм рабочих, а именно на показатели каллекреин-кининовой системы рабочих основных цехов в зависимости от стажа работы на данном предприятии, определяли уровень кининогена и прекаллекреинногена, активность кининазы и калликреина. Выявлено, что у рабочих при воздействии комплекса производственных факторов на организм происходит активация показателей каллекреин – кининовой системы, изменения зависят от стажа работы и цеха Кинины являются необходимыми продуктами жизнедеятельности, они содержатся во всех органах и тканях, выполняют роль химических регуляторов скорости местного и общего кровотока. Проведённые нами исследования необходимы для раннего выявления изменений в организме рабочих и проведения комплексных лечебных процедур, могут предотвратить развитие профессиональных заболеваний.

Ключевые слова: Неблагоприятные факторы производства; показатели каллекреин-кининовой системы; рабочие основных цехов; профессиональные риски.