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THE STATE OF CATECHOLAMINE METABOLISM DURING INTOXICATION WITH A COMPLEX OF TOXIC GASES AND DUST

In professional conditions, adaptation to unfavorable production factors is most often implemented through a resistance strategy that provides changes in the function of molecular and supramolecular systems. Unfavorable factors of the working environment can cause two differently directed reactions in a person – an increase in resistance (increase in resistance) and an increase in tolerance (tolerance, endurance). We conducted experimental studies of laboratory animals directly in the main workshops of the titanium-magnesium plant, where their body is exposed to a complex of toxic gases and dust (aerosol of titanium dioxide, dust of metallic titanium, titanium tetrachloride and its hydrolysis products, as well as chlorine and phosgene). In the experiment, the activity of the sympathetic-adrenal system was determined by the excretion of catecholamines – adrenaline, norepinephrine, dopamine and DOPA. We have revealed significant changes in the level of catecholamines in the organs of experimental animals. Adrenaline and norepinephrine in the liver tissue increased significantly in laboratory animals at 2; 4 and 12 weeks, kept in 1,2 and 3 shops compared with the control. The content of norepinephrine in the tissue of the adrenal glands, in the tissue of the heart in animals kept in the main workshops changed significantly compared to the control. These studies are of interest in the light of early detection of changes in the body when exposed to a complex of toxic gases and dust, the timely implementation of therapeutic, preventive measures prevents the development of occupational and somatic diseases.

Key words: *titanium-magnesium plant (TMP), main workshops, laboratory animals, catecholamines*

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Улы газдар мен шаңдар кешенімен улану кезіндегі катехоламин алмасуының жағдайы

Кәсіби жағдайларда қолайсыз өндірістік факторларға бейімделу көбінесе молекулалық және супрамолекулалық жүйелер қызметінің өзгеруін қамтамасыз ететін қарсылық стратегиясы арқылы жүзеге асырылады. Жұмыс ортасының қолайсыз факторлары адамда екі түрлі бағытталған реакцияларды тудыруы мүмкін – қарсылықтың және төзімділіктің жоғарылауы (толеранттылық, төзімділік). Біз зертханалық жануарларға тікелей титан-магний зауытының негізгі цехтарында тәжірибелік зерттеулер жүргіздік, олардың денесіне улы газдар мен шаңдар кешені әсер етілді (титан диоксидінің аэрозолі, металл титанның шаңы, титан тетрахлориді және оның гидролиз өнімдері, сондай-ақ хлор және фосген). Экспериментте симпатикалық-бүйрек үсті жүйесінің белсенділігі катехоламиндердің – адреналиннің, норадреналиннің, дофаминнің және ДОФА-ның бөлінуімен анықталды. Тәжірибе жануарларының ағзаларында катехоламиндер деңгейінде айтарлықтай өзгерістерді анықтадық. Бауыр тінінде адреналин мен норадреналин бақылаумен салыстырғанда 1,2 және 3 цехтарда сақталған зертханалық жануарларда 2;4 және 12 аптада айтарлықтай жоғарылаған. Негізгі цехтарда ұсталатын жануарларда бүйрек үсті бездерінің тіндеріндегі, жүрек тіндеріндегі норадреналиннің мөлшері бақылаумен салыстырғанда айтарлықтай өзгерді. Бұл зерттеулер улы газдар мен шаңдар кешені әсер еткенде ағзадағы өзгерістерді ерте анықтау, емдік, профилактикалық шараларды дер кезінде жүргізу кәсіптік және соматикалық аурулардың дамуын болдырмайды.

Түйін сөздер: *титан-магний өндірісі, негізгі цехтар, зертханалық жануарлар, катехоламиндер.*

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Состояние метаболизма катехоламинов при интоксикации комплексом токсических газов и пыли

В профессиональных условиях адаптация к неблагоприятным факторам производства наиболее часто реализуется через стратегию резистентности, которая обеспечивает изменения функции молекулярных и надмолекулярных систем. Неблагоприятные факторы производственной среды могут вызывать у человека две разнонапраленные реакции – увеличение резистентности (увеличение сопротивляемости) и увеличение толерантности (переносимости, выносливости). Нами проведены экспериментальные исследования лабораторных животных непосредственно в основных цехах титано-магниевого комбината, где на их организм происходит воздействие комплекса токсических газов и пыли (аэрозоль двуокиси титана, пыль металлического титана, четыреххлористый титан и продукты его гидролиза, а также хлор и фосген). В эксперименте определяли активность симпато – адреналовой системы по экскреции катехоламинов – адреналина, норадреналина, дофамина и ДОФА. Нами выявлены значительные изменения уровня катехоламинов в органах экспериментальных животных. Адреналин и норадреналин в ткани печени значительно увеличился у лабораторных животных в 2;4 и 12-недельный срок, содержащихся в 1,2 и 3 цехах по сравнению с контролем. Содержание норадреналина в ткани надпочечников, в ткани сердца у животных, содержащихся в основных цехах, значительно изменились по сравнению с контролем. Эти исследования представляют интерес в свете раннего выявления изменений в организме при воздействии комплекса токсических газов и пыли, своевременное проведение лечебных, профилактических мероприятий предотвращает развитие профессиональных и соматических заболеваний.

Ключевые слова: титано-магниевое производство, основные цеха, лабораторные животные, катехоламины.

Introduction

Health assessment at the present stage urgently requires the development of scientific approaches to identifying early changes in the state of the body under the influence of the environment, including the negative consequences of production factors [1;2;3]

It is known that the functional state of the body during labor activity is influenced, first, by the factors of the labor process, which cause tension in regulatory mechanisms (nervous, humoral, metabolic) under the regulatory influence of the central nervous system [4;5]. Their severity correlates with the conditions, nature, and severity of labor [6;7;8]. The functional state of the organism that is formed at the same time at a new stage of regulation is evaluated as the “price” of adaptation. [9;10;11].

In healthy people and animals, the constancy of homeostasis is ensured by a balanced state between assimilation processes, i.e. processes of decay and synthesis of metabolites, maturation and degradation of cellular elements that form the basis of every minute adaptation of the body’s function to constantly changing conditions of the external and internal environment [12;13;14]. At the same time, the constancy of homeostasis is ensured by the mechanisms of antagonistic regulation and duplication of functions, the polyfunctionality of cells by recombination transformations of tissue structures [15;16].

These mechanisms form the basis of the adaptation syndrome, which, according to G. Selye, is a clinical manifestation of a stress reaction that occurs when deviations in the living conditions are unfavorable for the body [17;18].

Occupational stress, like any other, causes a restructuring of the body’s physiological functions and metabolism, aimed at increasing the body’s stability and mobilizing energy resources necessary to maintain homeostasis and normal functioning of organs and systems [19;20].

In the formation of prenosological states, an important role is assigned to indicators of neurohumoral regulation and tissue metabolism. These studies are of interest in the light of the general concept created in recent years, according to which chronic stressful effects of production factors cause changes in the nervous system (both in the central and peripheral ones), which negatively affect the neurographic processes and the regulation of blood circulation [21, p. 38].

It is well known that several groups of physiologically active substances act on metabolic processes in cells, tissues and organs, as well as on the regulation of the circulatory system, some of which are neurotransmitters (adrenaline, norepinephrine, dopamine, acetylcholine), others are local regulators – kinins, etc.

Information about the effect of titanium and its compounds on individual organs and systems is limited in the literature. It is known (that the action of insoluble titanium compounds develops changes in the respiratory tract) [22;23]. The development of pneumoconiosis was found in workers whose production activities are associated with the action of titanium and titanium carbide [24, p.5].

The influence of harmful factors of TMP and their role in the occurrence of health disorders is necessary in several studies that can become the basis for the development of a complex of recreational activities aimed at improving health and increasing efficiency.

Even though several modern improvements have been introduced in the technological process of obtaining titanium sponge, working conditions remain unfavorable.

Material and research methods

Our research includes a section – experimental, performed on laboratory animals. In order to clarify the nature of pathological changes in the body of animals developing under the influence of a complex of toxic gases and dust (aerosol of titanium dioxide, dust of metallic titanium, titanium tetrachloride and its hydrolysis products, as well as chlorine and phosgene), experimental studies were carried out directly under conditions of titanium-magnesium production. Such an approach, from our point of view, can create the most advantageous experimental model, which makes it possible to carry out the corresponding clinical and experimental parallels with maximum completeness. Therefore, a series of experimental animals was placed on the territory of three main workshops (shops 1, 2 and 3) of JSC TMP Management Company. The animals were placed in specially made cages of 25-26 animals each, which were installed at the level of the human respiratory organs. The experimental animals of the control series of the experiment (28 animals) were kept on the territory of the plant, but at a considerable distance from the main production shops in a separate, clean, well-ventilated room. Animals of the control group were killed at the same time as the experimental animals (2, 4 and 12 weeks).

The activity of the sympathetic-adrenal system was assessed by the excretion of catecholamines – adrenaline, norepinephrine, dopamine and by the DOPA method Matlina E.Sh. et al. (1965), which is based on their isolation from urine by alumina column chromatography. Adrenaline, norepinephrine and almost half of the adsorbed DOPA were eluted with 0.25 mol/l acetic acid solution. The DOPA remaining on the adsorbent was removed with a mol/L solution of hydrochloric acid. Catecholamines were differentiated by their oxidation with potassium ferrocyanide in a medium with different pH values and fluorimetrically on a spectrofluorimeter using different sets of light filters. Dopamine was determined using iodine as an oxidizing agent.

Results and its discussion

In animals that were on the territory of shop №1, after 2 weeks, an increase in the stress hormone – adrenaline in the liver to 0.08 ± 0.006 μg / 1 g of raw tissue was found, which is 200% more than in the control group (0.04 ± 0.004), $p<0.001$.

After 4 weeks of the experiment, the level of adrenaline decreased slightly, but was higher than the control values (0.06±0.005) by 50% and amounted to 0.09±0.002, $p<0.001$.

After 12 weeks, liver epinephrine again increased by 240% to 0.12±0.09 against the control – 0.05±0.004 μg/1g of raw tissue.

Apparently, changes in adrenaline in the liver tissue reflect the stages of the adaptation process of animals to the factors of the production environment of shop No. 1.

In parallel with the change in adrenaline in the liver tissue, there was an increase in adrenaline in the adrenal tissue after 2 weeks by 24% to 1012 ± 56.2 μg / 1 l of wet weight (in control – 814 ± 76.2) $p<0.01$, which indicates an increase in synthesis adrenaline in this tissue. However, after 4 and 12 weeks, the level of adrenaline slightly decreased by 19 and 18%, but was higher than the control values (826±81.2 and 870±79.4) up to 968±69.4, $p<0.05$ and 1026± 42.4, $p<0.01$.

Table 1 − Levels of epinephrine and norepinephrine in the internal organs of animals located on the territory of JSC "MC TMP" shops, (M±m)

№	Indicators / Animal series	Adrenalin		Noradrenalin		
		Liver mcg/1 gram wet weight	Adrenal gland mcg/1 gram wet weight	Liver mcg/1g wet weight	Heart mcg/1g wet weight	Adrenal gland mcg/1g wet weight
1	Control: 2 weeks	0,04±0,004	814±76,2	0,42±0,03	0,660±0,04	379±9,0
	4 weeks	0,06±0,005	826±81,2	0,56±0,04	0,669±0,05	392±12,0
	12 weeks	0,05±0,004	870±79,4	0,61±0,06	0,720±0,06	410±9,0
2	Workshop 1: 2 weeks	$0,08±0,006^{xxx}$	$1012±56,2^{xx}$	$0,68±0,09^{xxx}$	0,596±0,02	$450±19^{x}$
	4 weeks	$0,09±0,002^{xxx}$	$968±69,4^{x}$	$0,86±0,07^{xxx}$	0,729±0,09	$469±29,0^{x}$
	12 weeks	$0,12±0,09^{xxx}$	$1026±42,4^{xx}$	$1,09±0,06^{xxx}$	$0,840±0,05^{x}$	$620±15,0^{xxx}$
3	Workshop 2: 2 weeks	$0,08±0,001^{xxx}$	910±81,1	0,37±0,02	$0,78±0,08^{xxx}$	$442±8,0^{xxx}$
	4 weeks	$0,100±0,002^{xxx}$	$948±56,2^{x}$	$0,41±0,03^{x}$	$0,968±0,04^{xxx}$	$466±10,0^{xxx}$
	12 weeks	$0,09±0,001^{xxx}$	$1221,4±30,1^{xxx}$	0,50±0,04	$0,966±0,08^{xxx}$	$682±12,0^{xxx}$
4	Workshop 3: 2 weeks	$0,06±0,003^{xxx}$	$612±51,1^{xx}$	$0,56±0,04^{xx}$	0,76±0,06	$286±5,0^{xxx}$
	4 weeks	$0,07±0,004^{x}$	784±73,9	$0,62±0,04^{x}$	0,680±0,03	$251±8,0^{xxx}$
	12 weeks	0,04±0,002	$526±28,9^{xxx}$	$0,76±0,07^{x}$	$0,810±0,09^{xxx}$	$278±6,0^{xxx}$

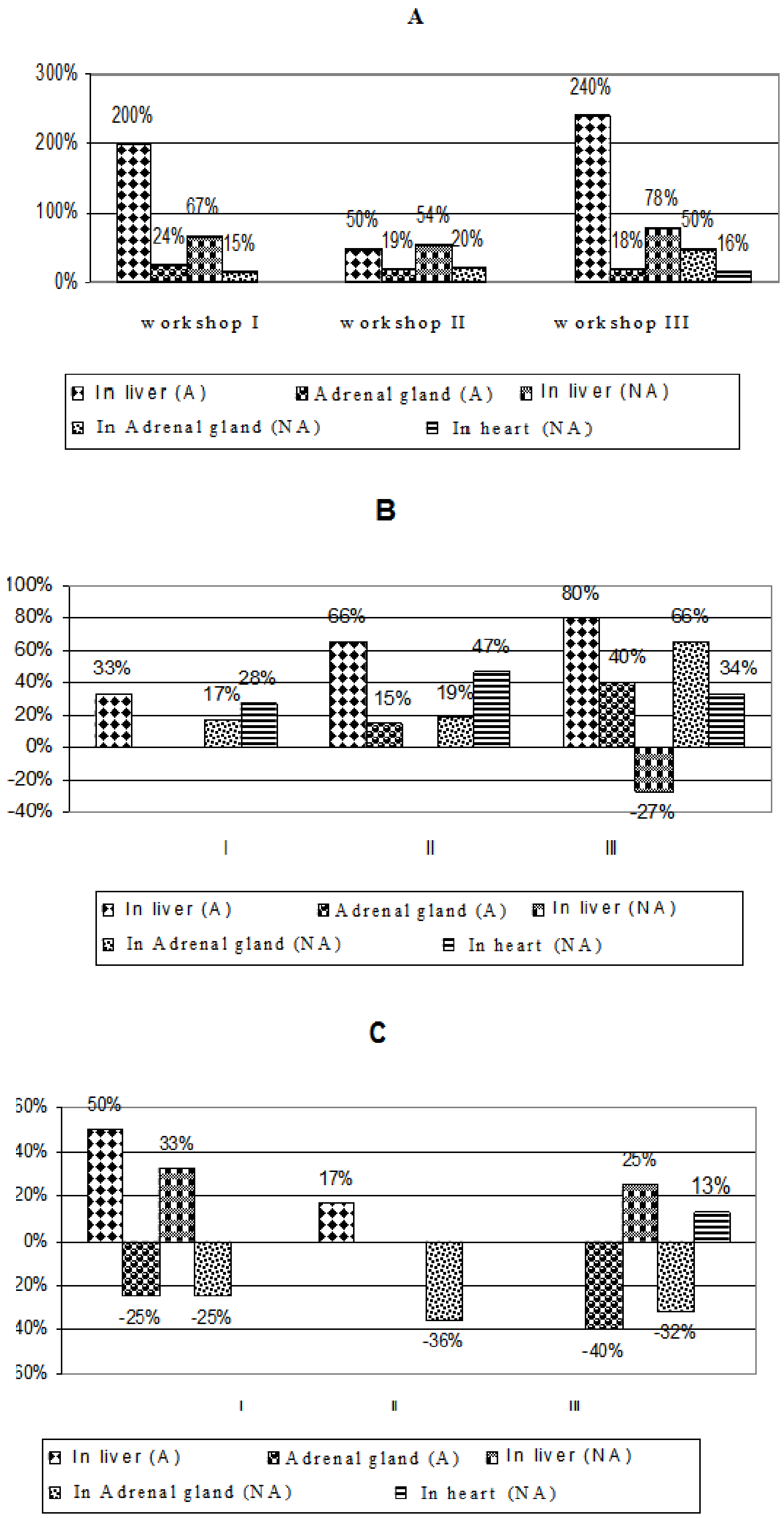
The content of norepinephrine in the liver of animals that were on the territory of shop No. 1 gradually increased after 2, 4 and 12 weeks by 67, 54 and 78% to 0.68±0.09; 0.86±0.07 and 1.09±0.06, $p<0.001$. The control figures for norepinephrine in the liver tissue were 0.42±0.03; 0.56±0.04 and 0.61±0.06 corresponding to the terms of the experiment. The content of norepinephrine in the tissue of the adrenal glands increased after 2 weeks by 15% to 450±19, $p<0.05$ (in control – 379±9.0 µg/1g) of raw tissue, after 4 weeks by 20% to 469±29 (control – 392±12.0), $p<0.05$ and after 12 months by 50% to 620±15.0, $p<0.001$, against control – 410±9.0.

The content of norepinephrine in the heart tissue in animals of shop No. 1 increased by 16% to 0.840±0.05 only after 12 months of the experiment.

In animals that were on the territory of shop No. 2, adrenaline increased in the liver tissue after 2, 4 and 12 weeks by 33, 66 and 80% to 0.08±0.001; 0.100±0.002 and 0.09±0.001, $p<0.001$. The content of adrenaline in the adrenal glands began to increase only after 4 weeks by 15% to 948±56.2, $p<0.05$, and by 12 weeks it reached 1221±30.1 µg/1g of raw tissue, which was 40% higher than the control, $p<0.05$ <0.001. The level of norepinephrine in the liver tissue decreased by 27% to 0.41±0.03, $p<0.05$, apparently due to its increased conversion into adrenaline in the metabolic chain. In the adrenal tissue, the content of norepinephrine moderately increased after 2 and 4 weeks by 17 and 19% to 442±8.0 and 466±10 µg/1g of raw tissue, $p<0.001$, and significantly increased by 66% after 12 weeks to 466±10 .0, $p<0.001$.

Shop No. 2 is characterized by an increase in norepinephrine in the heart, starting from 2 and 4 weeks to 12 weeks – by 28, 47 and 34% to 0.78±0.08; 0.968±0.04 and 0.996±0.08 µg/1g of raw tissue, $p<0.001$, against control values in the same terms of the experiment – 0.660±0.04; 0.669±0.05 and 0.720±0.06.

In animals that were on the territory of shop No. 3, an increase in adrenaline in the liver tissue was found after 2 weeks – by 50% to 0.06±0.003, $p<0.001$ and after 4 weeks – by 17% to 0.07±0.004, $p<0$ .05. The content of adrenaline in the adrenal glands decreased during the period of the experiment of 2 and 12 weeks – by 25%, $p<0.01$ and 40%, $p<0.001$. The content of norepinephrine in the liver increased after 2 and 12 weeks to 33 and 25%, $p<0.01$ and $p<0.05$.



Terms of the experiment: I – 2 weeks, II – 4 weeks, III – 12 weeks.
A – workshop 1, B – workshop 2, C – workshop 3.

Figure 1 − The content of catecholamines in the internal organs of animals located on the territory of the workshops of Ust-Kamenegorsk "JSC TMP"

In the adrenal glands, a decrease in norepinephrine was found by 25, 36 and 32% to 286±5.0; 251±8.0 and 278±6.0, $p<0.001$ due to increased release of the mediator into the blood. An increase in norepinephrine by 13% after 12 weeks to 0.810±0.09, $p<0.001$, was found in the hearts of the animals of shop No. 3.

Thus, the action of production factors on the territory of JSC "MC TMK" shops causes a restructuring of neurohumoral regulation, which is expressed in changes in catecholamines in organs.

Conclusion

The titanium-magnesium plant in Ust-Kamenogorsk functions as one of the most advanced enterprises in Kazakhstan and as one of the leading enterprises in the CIS countries in terms of the integrated use of raw materials, the degree of extraction of metals, and product quality.

Ust-Kamenegorsk "JSC TMP"includes 3 main workshops:

workshop 1 – magnesium production;

workshop 2 – for the production of titanium tetrachloride;

workshop 3 – for the production of titanium sponge.

Currently, a magnesium-thermal method for producing titanium sponge is used, based on the implementation of the interaction of titanium chloride and magnesium.

Magnesium-thermal, as well as less common sodium-thermal methods of reduction of titanium tetrachloride are used in world practice.

The choice of magnesium or sodium titanium tetrachloride as a reducing agent is determined by technological and economic considerations, the availability of appropriate raw materials and experience in the production of these metals. In particular, in England, where magnesium raw materials are practically absent, but sodium production is developed, the titanium industry is based on the sodium-thermal method of titanium reduction, while in the USA and Japan, the magnesium-thermal method is mainly used. The magnesium-thermal method is also used in the domestic titanium industry.

As a result of experimental studies carried out on the territory of TMP workshops, we found a change in adrenaline in the liver in the 1st workshop after 2 weeks by 200% more than in the control group $p<0.001$, after 4 weeks the level of adrenaline is 50% higher than the control $p<0.001$ and the 12-week period of the experiment adrenaline in the liver increased by 240%.

In parallel with the change in adrenaline in the liver tissue, there was an increase in adrenaline in the tissue of the adrenal glands after 2 weeks by 24% compared with the control $p<0.01$, and after 4 and 12 weeks the level of adrenaline slightly decreased by 19 and 18%, but was higher than the control values $p<0.01$. <0.05 and $p<0.01$.

The content of norepinephrine in the liver of animals that were on the territory of shop No. 1 gradually increased after 2, 4 and 12 weeks by 67, 54 and 78% $p<0.001$. The content of norepinephrine in the tissue of the adrenal glands increased after 2 weeks by 15%, after 4 weeks by 20% $p<0.05$ and after 12 months by 50% $p<0.001$, against the control.

The content of norepinephrine in the heart tissue in animals of shop No. 1 increased by 16% only after 12 months of the experiment.

In animals that were on the territory of workshop No. 2, adrenaline increased in the liver tissue after 2, 4 and 12 weeks by 33, 66 and 80%, $p<0.001$. The content of adrenaline in the adrenal glands began to increase only after 4 weeks by 15% $p<0.05$ and by 12 weeks by 40% higher than the control, $p<0.001$. The level of norepinephrine in the liver tissue decreased by 27%, $p<0.05$. In the adrenal tissue, the content of norepinephrine moderately increased after 2 and 4 weeks by 17 and 19%, $p<0.001$, and significantly increased by 66% after 12 weeks, $p<0.001$.

Workshop No. 2 is characterized by an increase in norepinephrine in the heart, starting from 2 and 4 weeks to 12 weeks – by 28, 47 and 34%, $p<0.001$, against control values at the same time of the experiment.

In animals that were on the territory of shop No. 3, an increase in adrenaline in the liver tissue was found after 2 weeks – by 50%, $p<0.001$ and after 4 weeks – by 17%, $p<0.05$. The content of adrenaline in the adrenal glands decreased during the period of the experiment of 2 and 12 weeks – by 25%, $p<0.01$ and 40%, $p<0.001$. The content of norepinephrine in the liver increased after 2 and 12 weeks to 33 and 25%, $p<0.01$ and $p<0.05$.

In the adrenal glands, a decrease in norepinephrine by 25, 36 and 32% was found, $p<0.001$. An increase in norepinephrine by 13% after 12 weeks was found in the hearts of animals from shop No. 3, $p<0.001$.

Thus, we have identified significant changes in the level of catecholamines in the organs of experimental animals when exposed to a complex of chemicals such as titanium dioxide aerosol, metallic titanium dust, titanium tetrachloride and its hydrolysis products, as well as chlorine and phosgene. The revealed changes can cause changes in the function of molecular and supramolecular systems, causing maladjustment and presonic manifestations.

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