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Studying the Benefits of Green Workplace Environment on Health Promotion in Sympathoadrenal and Kallikrein-Kinin Systems

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Abstract

This study is performed to study the positive effects and benefits of going green and creating green physical environments of work on health promotion and stressors reduction on workers in Sympathoadrenal and Kallikrein-Kinin Systems. It also evaluates environmental conditions of work-place, as well as sympathoadrenal and kallikrein-kinin systems for early (prenosological) sings of de-adaptation to work-related stressors in workers engaged in non-ferrous metallurgy. Workplace health promotion (WHP) has been proposed as a preventive intervention for stress, possibly operating by promoting positive organizational culture or via programs promoting healthy lifestyles. In order to do this a trial experiment was done on animals (white rats). Adrenaline and noradrenaline (AD and NAD) levels in the liver, adrenal glands and hearts of rats were measured throughout 2, 4 and 12 trial weeks. Changes in sympathoadrenal system, detected in workers, who were working at the main workshops for a long time, reflect all the stages of non-specific adaptation process to work-place environment, defined as a standard activation of stress-realizing system. At the last stages of stress, the KKS, which represents a cascade, promotes body resistance to work-related stressors and negative environmental conditions. Signs of early de-adaptation were found in healthy workers to identify who of them are at risk of adaptive breakdown. Our tests were used at five times as part of health examination, and some related guidelines were published.

Keywords: green workplace environment, healthy lifestyle, going green, Sympathoadrenal, Kallikrein-Kinin, stressors

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INTRODUCTION

Studies have shown that poorly designed offices can negatively affect workers. Poor lighting, bland walls, and a lack of sunlight create a stagnant and uncomfortable work environment. Some factors like bad lighting and uncomfortable chairs can also cause injuries. Improving lighting, adding windows, repainting the walls, and adding plant life can all improve the work environment. Research has shown that employees of environmentally responsible companies are more productive than average recorded productivity rates. Being green allows for greater participation and interaction amongst employees which in turn leads to greater levels of motivation, togetherness and sense of achievement. Employees of green companies also tend to receive higher levels of training and coaching which benefits not only their moral but your business performance too. Numerous scientific studies have proven the positives of having more greenery in your workspace. They help to reduce stress, and increase productivity. They also have positive environmental effects as they clean the air and reduce pollution.

Functional status of the human body during labor is known to be influenced primarily by work-related stressors that stress regulatory mechanisms (nervous,

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humoral, and metabolic) in the central nervous system. That how strong will those factors be depends on environmental conditions of work, type of work and severity. At the end, a worker will 'pay' for adaptation with his/her functional status. At the current stage of human ecology and biomedical science development, health status classification system is guided by the concept of a General Adaptation Syndrome (GAS) and the R.M. Baevsky's General Adaptation Theory, and includes 4 items, correlating with adaptation stages (Andujar et al. 2011):

1) body is generally healthy, with good adaptive capabilities;

2) borderline state, originating from high stress experienced by regulatory systems;

3) Premorbid state/adaptation tension. The latter is divided into 2 sub-stages that come with non-specific and specific changes, respectively, but not causing auto-regulation disturbances;

4) Adaptive breakdown, characterized by a sharp decrease in the functional capabilities.

The occupational stress, like any other type of stress, encourages reorganization in those physiological and metabolic functions that boost body resistance and mobilize those energetic resources essential for homeostasis and normal functioning of organs and systems. Hence, stress response consisting of alarm and resistance stages is considered preferable kind of reaction if expressed by mammals. Biochemical mechanism of resistance implies an increased catabolism of endogenous nutrients that results in higher exogenous nutrient intake. In this case, metabolism strategy is hypercatabolic and requires a lot of energy to run essential processes in the body. This allows a human body to run these essential processes even if it reached its limits. Thus, ability of a human body to adapt is a continuous process that is driven by non-specific adaptive reactions that provide a relatively stable physical status with regard to body's capabilities that come up in a particular situation, and by its direct dependence on the range of adaptive reactions possible. Based on the above stated, investigating over occupational stress, adaptive and compensatory mechanisms is of great importance. Indicators of prenosological changes in the worker's body have not been studied or developed yet, not to mention the fact that they could be useful in developing early preventive measures usable attitanium magnesium plants ecology.

In health and human ecology-related research, it is essential to evaluate the body protection systems and adaptive capabilities of healthy experienced workers. The role of the sympathoadrenal system (mediators and hormones-catecholamines) is considered as one of the main adaptation and stress triggers mobilizing the energetic and functional reserves of the human body. Human sympathoadrenal system (SAS) is proved one of the most important non-specific connection between adaptation stages a neurohumoral regulation system goes through. The SAS produces specific neurotransmitters, called catecholamines. Aschemical regulators of cellular processes, they are essential for human life, running adaptation and compensatory processes through the activation of pituitary-adrenocortical system. They also affect the nerve trophism and metabolic process (foremost, energy metabolism, then –carbohydrate, fat and protein metabolism processes).The KKSis a part of the contact activation system, and it is considered as a mechanism, which triggers the activation of clotting, fibrinolysis, complement and the renin-angiotensin system, the cooperative action of which is a key in adaptation and protection of the human body (Bayevsky, Chernikova 2014).If homeostatic balance is disturbed, the body (often the KKS cascade pathway) will produce an excessive amount of biologically active kinins to enhance body resistance to extreme factors, or to a certain pathological syndrome. From this, we know the pathogenetic role of kinins in vascular diseases and lead intoxication. There are some papers reflecting the changes in KKSthat occur throughout the course of pneumatic hammer disease. A general modest tendency of KKS's activation was evaluated from a decreased KG (kininogen) level and a decreased kallikrein activity in workers with pneumatic hammer disease. Recently, kinins were suggested to be part of regulatory system organization, since a connection was revealed between them, the SAS, and the adrenal cortex hormones. We have found no data on the role that sympathetic regulation and KKS have in response to occupational stress in workers of the ecology of the titanium magnesium plant. Based on the above stated, we have focused on evaluating biochemical parameters of SAS and KKS in healthy TMP workers using a full-scale trial in order to allocate theborderline signsof de-adaptation to work-related stressors.

MATERIALS AND METHODS

The full-scale trial was performed directly on the territory of three main workshops of TMP (Workshop 1 – Magnesium Production; Workshop 2 –Titanium

Table 1. Survey samples by length of employment (in percentages and in absolute values)

№	Survey samples	Years in Position								Total	
		less then 3 years		3-5 years		6-10 years		more than 10 years			
		ab.v.	%	ab.v.	%	ab.v.	%	ab.v.	%	ab.v.	%
1	Reference group	29	29	25	25	24	24	22	22	100	100
2	Healthy workers	30	28.1	29	27.1	25	23.3	23	21.5	107	100

Tetrachloride Production; Workshop 3 – Titanium Sponge Production; Trial period: 2, 4 and 12 weeks). Animals were placed in tailored cages (25:1 ratio)at the level of human breath. The reference group consisted of animals that were on the territory of the plant ecology, but at a considerable distance from the main workshops – in clean and well-ventilated rooms. The trial was approved by the Ethics Commission of the S. Amanzholov East Kazakhstan State University (Protocol No. 38 of 12.09.2014) (Bazarova 2015). At the end of the trial, animals were decapitated, according to the "International recommendations of medical and biological researches conduction with a use of animals".

Clinical (biochemical) trials involved healthy workers, engaged in production process at the three main workshops of TMP. The trials were guided by the Order No. 654 of 02.09.2014"On conducting a preventive examination". The workers have given a written consent after learning the purpose of the study (107 people). The reference group consisted of 100 employees, working at the Administrative and Housing Division of TMP, and not exposed to the negative impact of TMP factors. All workers (including the reference group) were divided into groups by experience (**Table 1**) (Bonner et al. 2013).

All methods have been modified and published in guides. Activity of the SAS was evaluated by measuring the catecholamine (adrenalineand noradrenaline) level using the Matlina's method. Its idea is to isolate catecholamines from the animal tissue (adrenal glands, liver and heart) and from daily worker's urine by column chromatography (adrenaline, noradrenaline, dopamine and their precursor in the metabolism-DOPA chain).The KKS parameters (bradykininogen level and kininase activity) were evaluated using the Paskhina-Egorova method. The bradykininogen level was estimated by the amount of bradykinin liberated from denatured plasma by an excess of trypsin. Kallikrein and prekallikrein levels in blood were measured using the Paschina-Yarova chromatographic method. The idea is that cationic properties cause kallikreinnot to absorbon DEAE-Sephadex A-50 at pH 7.0 and low ionic strength, so it can be found in fractions by the hydrolysis rate of esters and the N-α-Benzoyl-L-arginine ethyl ester hydrochloride (BAEE HCI). Measured prekallikrein was expressed in μU/ml, kallikrein– in μU/ml/min. All parameters of the KKS were evaluated in blood samples isolated from animals and humans (in our case, workers). Statistical data analysis was carried out using the Rebrova's method. Thus, we have achieved the maximum possible accuracy of calculated results. Studied values were compared using the Student's T-Test, and following formulas:

$$t = -\frac{\mathrm{M}exp - \mathrm{M}ref}{\sqrt{\mathrm{м}^2exp + \mathrm{м}^2ref}} \quad (1)$$

where: M (exp) – Max value in the ordered sample (trial group);

M (ref) – Max value in the ordered sample (reference group);

m (exp)– mean absolute error – measure of difference between two extreme values in the trial group with average outcomes;

m (ref) –mean absolute error – measure of difference between two extreme values in the reference group with average outcomes;

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

where: G – mean square deviation – measure of difference between values in the ordered sample, n – number of examined subjects

$$G = \frac{\mathrm{M}max - \mathrm{M}min}{Ermolaev\ coefficient} \quad (2)$$

The coefficient is found according to Ermolaev's table

$$\mathrm{M} = \frac{Z\ (Sum\ of\ values\ of\ the\ ordered\ sample)}{n(\ number\ of\ examined\ subjects)} \quad (3)$$

If $t \leq 1.96$ .then$P>0.05$

If $t \geq 1.96$, then$P<0.05$

If $t> 2.06 – 3.0$, then$P<0.01$

If $t> 3.0$, then$P<0.001$

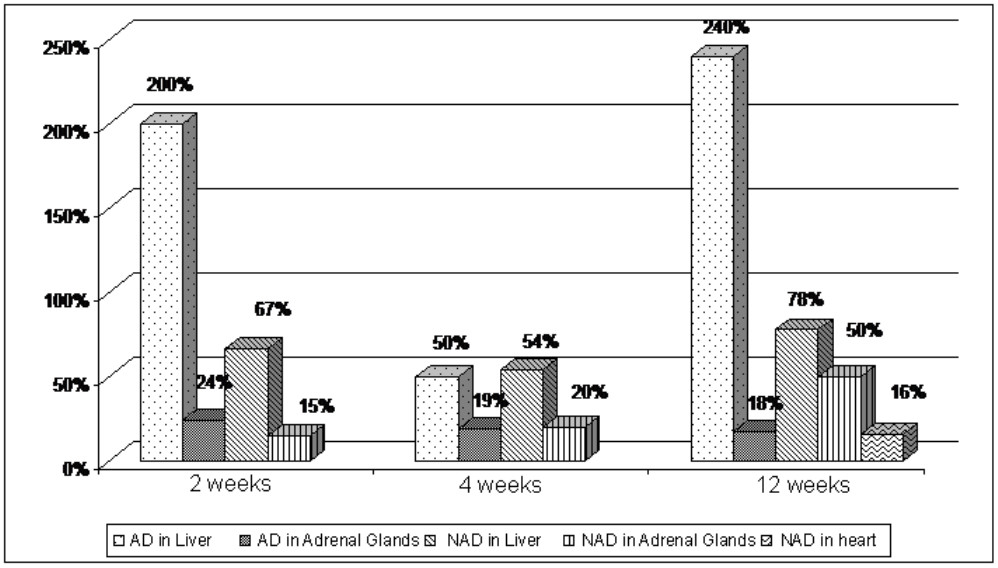

Fig. 1. Catecholamine Levels in the Insides of Animals from the Workshop 1: Pattern of Changes, (+, -)

RESULTS

Full-scale trial on animals placed in the workshops (1, 2 and 3) of the TMP. After 2 weeks of the trial, we have examined the animals that were in Workshop 1, and found an increase in the stress hormone (AD) level in the liver (up to 0.08±0.006 μg per 1 g of crude tissue) that was higher by 200% compared to the reference group (0.04±0.004), p <0.001 (**Fig. 1**). After 4 trial weeks of the tral, AD level has decreased, but was still was by 50% higher than the reference values (0.06±0.005) – 0.09±0.002, p <0.001. After 12 weeks, AD level in the liver increased again by 240%,up to 0.12±0.09, while the reference value was 0.05±0.004 μg per 1 g of crude tissue.

In parallel with the changing AD level in the liver tissue, AD level has increased in the adrenal glands (2 weeks) by 24%, up to 1012±56.2 μg per 1 L of fresh weight (reference value: 814±76.2), p <0.01. This indicates an increase in AD synthesis in this tissue. However, after 4 and 12 trial weeks, AD level has slightly decreased by 19% and 18%, respectively. Although, it was above the reference value (826±81.2 and 870±79.4) – 968±69.4, p <0.05, and 1026±42.4, p <0.01, respectively. There was a gradual increase in the NAD level in the livers of animals that were in the Workshop 1 for 2, 4 and 12 weeks – by 67%, 54% and 78% (up to 0.68±0.09; 0.86±0.07 and 1.09±0.06, p <0.001). The NAD level in adrenal glands has increased by 15% after 2 weeks, up to 450±19, p <0.05 (reference value: 379±9.0 μg per 1 g of crude tissue). After 4 weeks, NAD level increased by 20%, up to 469±29 (reference value: 392±12.0), p <0.05. After 12 weeks, the increase was by 50%, up to 620±15.0, p <0.001 (reference values: 410±9.0). The NAD level in heart tissues of animals from the Workshop 1 has increased by 16% (up to 0.840±0.05) only after 12 trial weeks.

The AD level of animals that were in theWorkshop 2 has increased in the liver tissue by 33%, 66% and 80% after 2, 4 and 12 weeks (**Fig. 2**). The AD level in adrenal glands began to increase by 15% only after 4 weeks (up to 948±56.2, p <0.05) and after 12 weeks, reaching the final 1221±30.1 μg per 1 g of crude tissue, p<0.001. Thus, AD level in adrenal glands was by 40% higher than in the reference group. The NAD level in liver tissue has decreased by 27% –down to 0.41±0.03, p <0.05, apparently due to its enhanced conversion to adrenaline in the metabolic chain. The NAD level in adrenal glands has moderately increased by 17% and 19% after 2 and 4 trial weeks, up to 442±8.0 and 466±10 μg per 1 g of crude tissue, p <0.001. After 12 weeks, the increase was more significant –by 66%, up to 466±10.0, p <0.001.

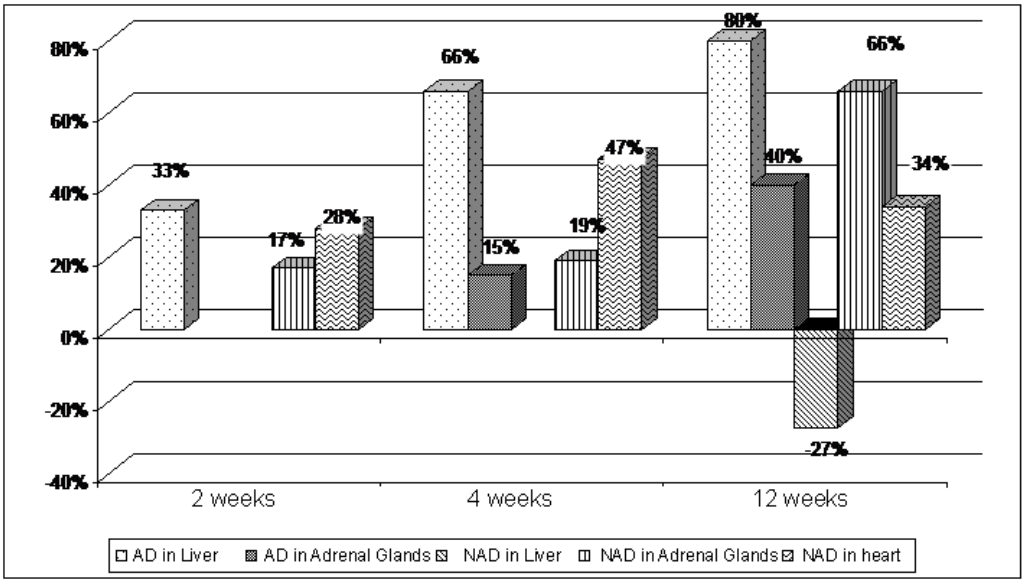

Fig. 2. Catecholamine Levels in the Insides of Animals from the Workshop 2: Pattern of Changes, (+, -)

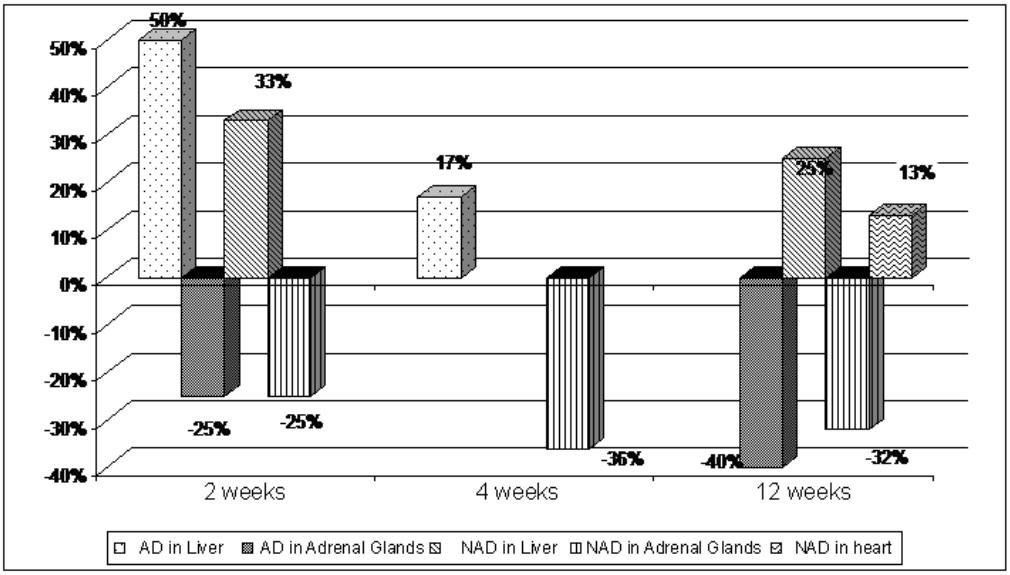

Fig. 3. Catecholamine Levels in the Insides of Animals from the Workshop 3: Pattern of Changes, (+, -)

Workshop 2 shows an increased NAD level (by 28%, 47% and 34%) in the heart, up to 0.78±0.08; 0.968±0.04 and 0.996±0.08 μg per 1 g of crude tissue, $p < 0.001$, compared to reference values (0.660±0.04; 0.669±0.05 and 0.720±0.06).We have found an increase in the AD level in liver tissues of animals from the Workshop 3 – by 50% after 2 weeks (up to 0.06±0.003, $p < 0.001$),and by 17% after 4 weeks (up to 0.07±0.004, $p < 0.05$) (**Fig. 3**). The AD level in adrenal glands has decreased by 25% ($p < 0.01$) and 40% ($p < 0.001$) after 2 and 12 weeks, due to greater amounts of it released from organs that stored it.

The NAD level in the liver tissue has increased by 33% and 25%, $p < 0.01$ and $p < 0.05$, after 2 and 12 trial weeks. In the adrenal glands, we have recorded a decrease in NAD level by 25%, 36% and 32% down to 286±5.0; 251±8.0 and 278±6.0, $p < 0.001$, due to an increased release of mediators into the bloodstream. We have found an increase in NAD level(by 13%) in the hearts of animals from the Workshop 3after 12 trial weeks, up to 0.810±0.09, $p < 0.001$.We have recorded an increased kininase activity (by 28% and by 200%) in animals, placed in the Workshop 4, after 4 and 12 trial weeks, up to 0.32±0.02 and 0.40±0.02, $p < 0.001$ (**Fig. 4**). This indicated that this enzyme is required to bind free kinins and to maintain them at normal level in blood in order to maintain homeostasis under stress.

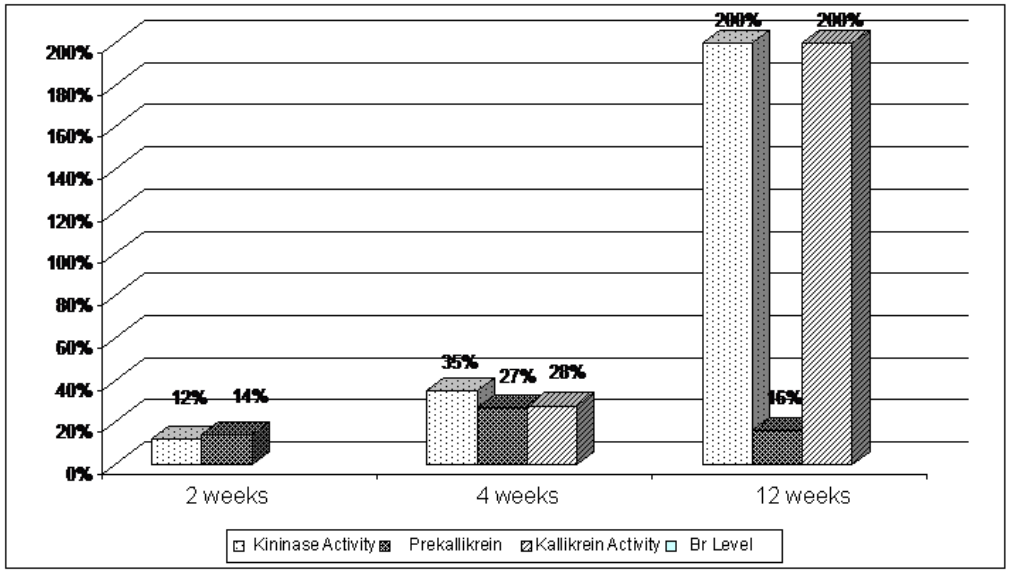

Fig. 4. Changes in the KKS of Trial Animals from the Workshop 1, (+, -)

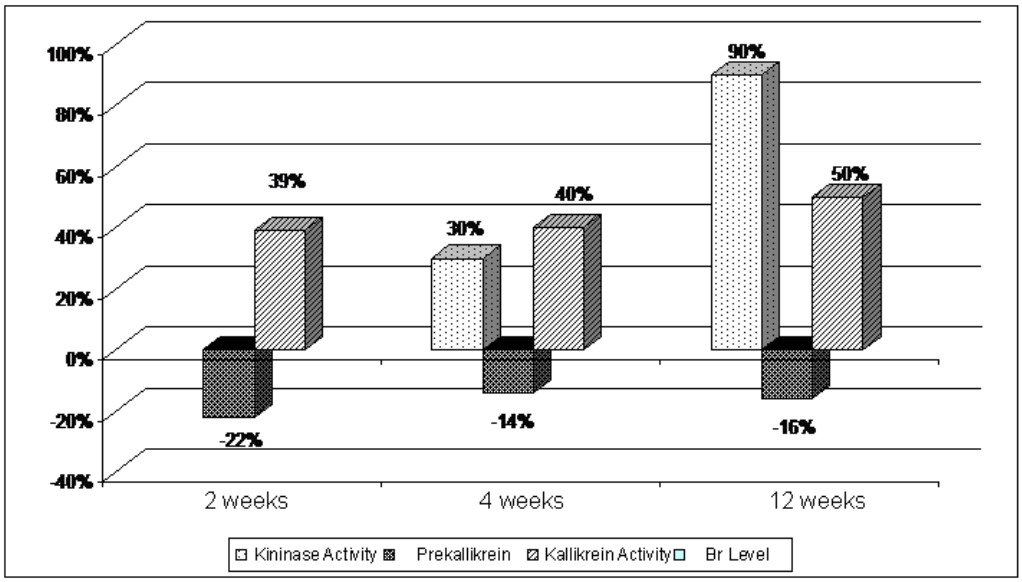

Fig. 5. Changes in the KKS of Trial Animals from the Workshop 2, (+, -)

After 2 trial weeks, kallikrein activity begins to increase by 12%, up to 99.6±3.5 μU/ml•min (reference value: 88.9±3.1); after 4 weeks – by 35%, up to 102.4±4.0, p <0.001 (reference value: 75.6±2.5); after 12 weeks – by 200%, up to 122.7±3.0, p <0.001 (reference value: 62.8±2.0 μU/ml•min). In parallel, there was an increase in the prekallikrein (PK) level – by 14%, 27% and 16% (up to 76.6±2.0, p <0.05; 88.5±3.0 and 80.48±2.5 μU/ml, p <0.001).The kallikrein activity in animals from the Workshop 2 (**Fig. 5**) has increased by 30% and 90% only after 4 and 12 weeks, respectively, indicating a late activation of the KKS. The values have reached 98.7±3.0 and 118.4±2.0μU/ml•min, p <0.001 (reference values: 75.6±2.5 and 62.8±2.0 μU/ml•min). However, the level of kallikrein precursor (kallikreinogen) began to decrease. After 2 weeks, it was52.3±2.5, p <0.001. This mark is by 22% lower than in the reference group (67.4±3.9). After 4 and 12 weeks, we have recorded a moderate decrease in the PK level – down to 61.8±3.0 and 70.2±2.0, p <0.01. These marks are by 14% and 16% lower than in the reference group. In parallel, the kininase activity has increased after 2 and 4 weeks, up to 0.25±0.02, p <0.001, and 0.35±0.03, p <0.01.These marks were by 39-40% higher than in the reference group (0.18±0.02 and 0.25±0.03 μU/ml•min). After 12 weeks, kininase activity has increased by 50%, up to 0.10±0.01, p <0.001 (reference value: 0.20±0.002).

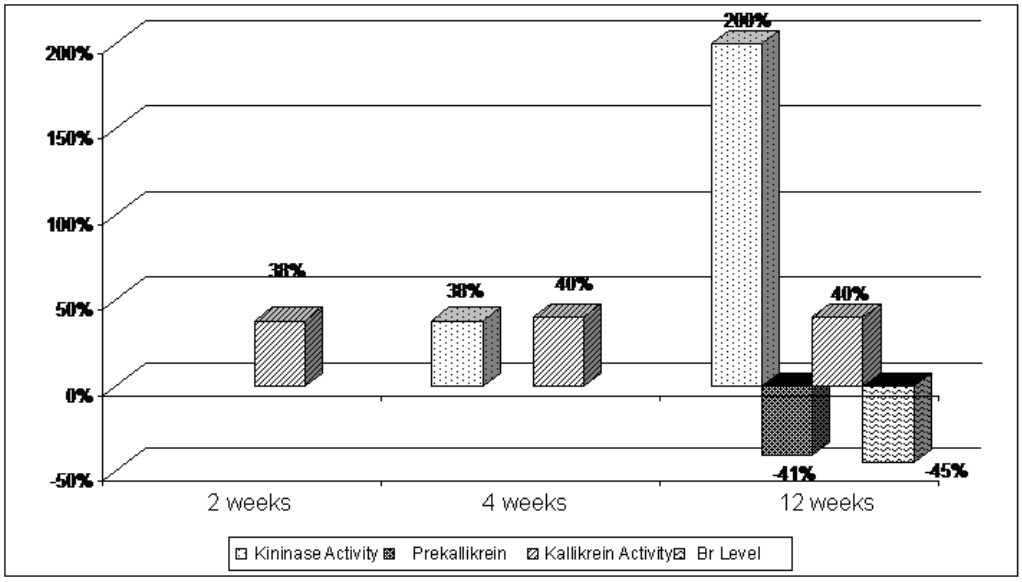

Fig. 6. Changes in the KKS of Trial Animals from the Workshop 3, (+, -)

Table 2. Indicators of catecholamine excretion in healthy workers, depending on their experience rate

№	Experience rate	N.	Daily urine excretion			
			AD	NAD	DA	DOPA
			µg/sec			
1	Less than 3 years	30	41.1±3.9	80.6±5.2	2006.0±121.4	230.7±18.2
	Reference group		36.6±4.1	92.6±10.0	2290.1±186.4	250.6±21.1
2	3-5 years	29	39.2±2.9	90.7±4.1	1920.8±97.7 xx	180.7±12.1
	Reference group	30	32.4±3.5	80.3±8.2	2300.1±156.4	200.4±16.0
3	6-10 years	25	45.6±5.2xx	106.4±4.0xx	1560.4±56.8xx	120.6±9.0xxx
	Reference group	25	34.8±3.8	89.80±5.1	1900.6±120.3	180.6±13.2
4	More than 10 years	20	35.9±3.0xx	122.2±9.0xx	1160.3±37.2xx	96.8±8.9xxx
	Reference group	20	41.2±4.0	106.8±5.2	1500.7±96.7	200.8±18

Note 1: xx - <0.01 and xxx< 0.001
Note 2: N – number of workers

In the Workshop 3 (**Fig. 6**), bradykininogen level in blood has decreased by 45% after 12 trial weeks– down to 1.2±0.14, p <0.001 (reference value: 2.2±0.25). However, kininase activity turned to be highereach time the measurements were made. It has increased by 38%, 40% and 40%, up to 0.25±0.01; 0.35±0.01 and 0.28±0.02, p <0.001.The kallikrein activity began to increase by 38% and 200% after 4 and 12 trial weeks (up to 104.6±3.0, and 128.9±3.4, p <0.001, compared to reference values).In parallel, the PK level began to decrease by 41% only after 12 trial weeks– down to 48±2.5 µU/ml compared to reference values.

Thus, we have observed different cases of KKS activation in the workshops, depending on the work-related exposure and the trial period.

Parameters of the SAS and KKS in experienced workers of the main workshops. Evaluation of healthy TMP workers (107 people) with different length of employment (**Table 2**) revealed an adaptive increase in the AD level in workers being for less than 3 years in position, and some unreliable changes in dopamine (DA) level and its precursor (DOPA). The revealed changes remained stable in those, who was working for 3-5 years. In the group of workers, who were in position for 6-10 years, we recorded a statistically significant increase in the AD level (by 30%), an increase in the NAD level (by 18%) and a decrease in DA and DOPA levels (by 22% and 50%, respectively) that indicated a higher catecholamine intake. In the group of workers, who were in position for 10 years, we recorded a significant decrease in the AD level (by 15%), an increase in the NAD level (by 14%). In parallel, we have recorded a further decrease in the DA level (by 29%) and a double increase in the DOPA level that indicated an increased catecholamine synthesis (Bork 2014).

Analysis of catecholamine excretion in healthy workers revealed a significant decrease in DA level (by 20%) in the Workshop 1, due to its conversion to NAD in the metabolic chain. The Workshop 2 shows a decreased DA (by 37%) and DOPA (by 37%) levels.

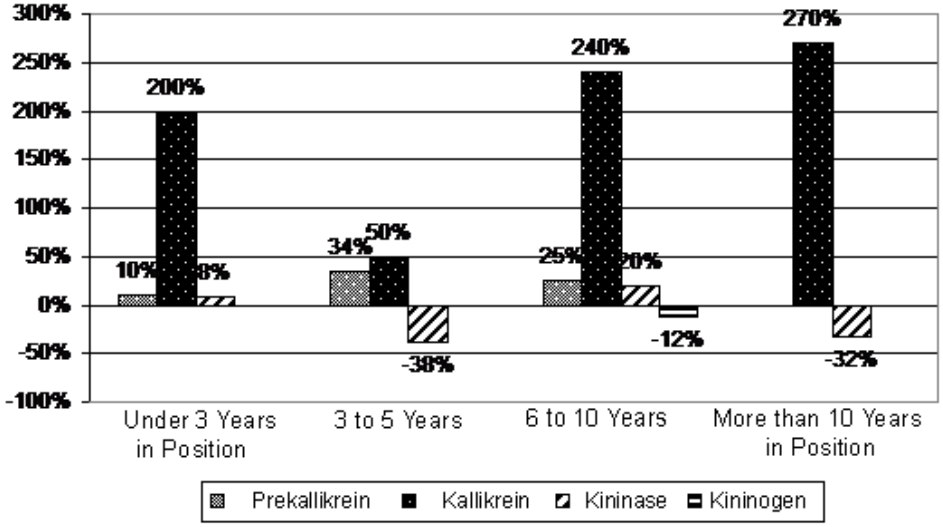

Fig. 7. Changes in the KKS of Workers by Length of Employment, (+, -)

These marks indicate a depletion of catecholamine stores in synapses and organs, when poorly synthesized. The Workshop 3 shows a tendency of increasing AD and NAD levels with a simultaneously decreasing DA level (by 20%) and DOPA synthesis (by 50%).From biochemical evaluation of healthy experienced workers, we can assume that catecholamine level characterizes the compensation degree for stress in workers, who are in position for 3-5 years. As for those, who have been working for 6to over 10 years, it is important to allocate groups with borderline sings of de-adaptation to work-related stressors, manifested as early adaptive breakdown, evident from catecholamine excretion. These signs are a decrease in AD and DA, and increase in NAD and catecholamine synthesis (DOPA stage) (Chandrasekar 2011).

In the group of workers, who were in position for 6-10 years, KKS parameters begin to change progressively, except for the response of enzyme system and the kallikrein-prekallikrein precursor (KLK-PK). There is a significant decrease in bradykininogen, indirectly indicating an increase in the level of physiologically active kinins. The bradykininogen level decreases reliably ($p < 0.05$) by 12%, down to 3.6 ± 0.2 Br$\times 10^{-3}$ g/l in comparison with the reference values ($4.1 \pm .1$ Br$\times 10^{-3}$ g/l). The kallikrein activity becomes 2.4 times higher if compared to reference values. In parallel, there is an increase (by 25%, $p < 0.001$) inits inactive protein-bound precursor (prekallikrein), and a secondary adaptive increase in kininase activity (by 20%, $p < 0.001$) that indicates a profound change in the way the structural elements of the KKS redistribute (Cryer 2009).

Workers, who have been in position for more than 10 years, show changes in kininogen and PK levels similar to previous groups. However, kallikrein activity continued to increase. It has increased in 2.7 times, up to 57 ± 1.2 μU/ml•min compared reference values (20.6 ± 0.1 μU/ml•min) (Karabalin 2014).By contrast, kininase activity continued to decrease. It has decreased by 32%, down to 3.5 ± 0.05 Br$\times 10^{-3}$ g/l•min, $p < 0{,}001$. These results indicate progressive changes in the KKS. Consequently, work-related stressors in the TMP trigger the activation of KKS, which is linked to the length of employment. The longer a worker stands in position, the more imbalanced is the formation and degradation of kinins. There can be recorded a lower degradation of free active kinins, especially if a worker has been there at the ecology of plant for more than 10 years. Although, the process is rather stabilized when the employment length is about 6-10 years, as evidenced form the phased adaptive changes in the level of protease. In parallel, there are changes in the activity of kallikrein, regulating the conversion of kininogen to free kinins (Neuhof et al. 1989).

Evaluation of KKS parameters in workers (**Table 3**) from different workshops reveales the most significant increase in the kallikrein level (trypsin-like serine proteases) in blood samples of workers from the Workshop 1 compared to other workshops. The kallikrein level was 3.3 times higher, up to 52 ± 1.5 μU/ml•min, $p < 0.001$, compared to reference values. In parallel, we have recorded a lower activity of enzymes that convert physiologically active free kinins into their inactive forms. The kininase activity has decreased by 24% compared to reference values, $p < 0.001$. The PK

Table 3. Parameters of the KKS in workers according to their work location at the TMP

Workplace	Number of workers	Level		Activity	
		Kininogen	PK	Kallikrein	Kininase
		Br ×10^{-3} g/l	μU/ml•min	Br ×10^{-3} g/l	μU/ml•min
Workshop 1	46	3.4±0.3	390±2.0^{xx}	52±1.5^{xxx}	3.4±0.05^{xxx}
Workshop 2	62	3.8±0.4	420±1.5^{xxx}	32±2.0$^{xxx}_{ooo}$	5.2±0.3^{xx}
Workshop 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 in comparison with the reference values

synthesis in the liver was adaptively increased by 20% to compensate for kallikrein (Nyakas et al. 2015).

The Workshops 2 and 3 also show a change in the KKS parameters related to the enzymatic action. Thus, kallikrein activity in blood plasma was twice as higher in workers from the Workshop 2, and 2.2 times higher in workers from the Workshop 3, compared to reference values. The kininase activity analysis revealed its adaptive increase in the Workshops 2 and 3, up to 5.2±0.3 (by 16%) and 5.6±0.1 Br×10^{-3} g/l×min (by 24 %), compared to reference values (p <0.001). Prekallikrein level indicates an increase in its synthesis in the blood plasma of workers from each of the workshops. The most pronounced levels have been recorded in workers from the workshops 3 and 2 (by 32% and 30% higher than in the reference group) (Perlman and Chalfie 2007, Piazza et al. 2010).

DISCUSSION

There are few research papers devoted to the work-related exposure at the TMP that illustrate the clinically apparent form of an adaptive breakdown in long-term workers, manifested as chronic non-specific diseases of bronchopulmonary system that may come with pronounced respiratory insufficiency. At the same time, part of examined workers had non-specific abnormalities in their CNS, vascular systems and neuromuscular apparatus. These days, prenosological diagnostics is becoming more relevant, and associated methods are being actively developed. At the same time, integrated approaches that allow evaluating the consequences of disrupted adaptation process before conditions start to progress are priority. Along with this, the preference is given to methods essential for diagnosis, related to integral indicators of homeostasis that are associated with energy supply and body regulation. Thus, changes in neurohumoral regulation and tissue metabolism bring the body to a borderline state. These studies are of interest, due to a recently generalized concept, indicating that constant stress, including from work-related exposure, cause changes in the nervous system (in both the CNS and the PNS) (Saralaya and Mahesh 2010, Shibata et al. 2010). The latter negatively affect the neurographic processes and blood flow regulation.

It is well known that there are several groups of physiological substances, including neurotransmitters (AD, NAD, DA, etc.) and local regulators (kinins), that affect the metabolic processes in cells, tissues and organs, and the blood flow regulation. Our research compares the catecholamine levels in workers, and shows that their early adaptive changes originate from inside changes, in particular – from a change in catecholamine released into the bloodstream from the catecholamine-storing organs, such as liver, adrenal glands and heart. Our research shows that changes in the parameters of SAS, detected in the first groups, apparently reflect the stage of a non-specific adaptation process, defined as a standard activation of a stress-realizing system, when oxygen consumption increases. At the later stages of work-related exposure (when being in position for a longer time), adaptation process is compensated for by increased catecholamine synthesis in the internals (liver, adrenal glands). Certain increase in catecholamine level in the heart causes negative effects on the heart and blood vessels. As chemical regulators of cellular processes, catecholamines are essential for human life, running adaptation and compensatory processes through the activation of pituitary-adrenocortical system. They also affect the nerve trophism and metabolic process (primarily, energy metabolism, then – the carbohydrate, fat and protein metabolism processes) (Siegrist 2016).

Catecholaminesboost oxygen consumption simply by stimulating mitochondrial oxidative function, which implies the accumulation of substrates, or the activation of oxidative enzymes. It is well known that stress activates α-adrenoreceptors, which cause spasm of the coronary arteries, activation of the arachidonic acid cascade, and formation of thromboxane, which has pronounced adhesive properties that increase and prolong vasospasm. In this regard, one should note proof studies related to the involvement of catecholamines in the formation and destruction of free active kinins, in particular, through the Hageman factor

- the starting link in the mechanism of cascade kinin formation. It is assumed that the adaptogenic effect of free kinins (in particular, kallikreins) is mediated through the adrenal cortex, and isto reduce the production of glucocorticoids, and boost the synthesis of mineralocorticoids. In other words, this effect is to prevent the imbalance of these hormones under stress. At the initial stages of stress, activation of the KKS, being a non-specific reaction of the organism, is generally protective. Thus, work-related stress causes a common adaptation syndrome, which is a universal response to stress. With sufficient functional capabilities, human body responses by putting regulatory systems at stress. In this case, mobilization of the SAS, which is the trigger mechanism and the main metabolism intensifier, is the most pronounced response (Sorensen et al. 2011). The sympatheoadrenal system is involved in stress mobilization of the hormonal system (kinins, glucocorticoids, etc.). If the organism has insufficient functional reserves at this stage, adaptation process will fail. This can be predicted through checking the parameters of SAS and KKS during the preventive examinations of workers, and allocating workers at risk.

Practical Relevance of Research Results

Prognostic and diagnostic tests are recommended for use in Healthcare as additional tests to detect pre-pathological changes during periodic medical examinations of TMP workers. There are five documented attempts of their implementation in the health care practice. Practical guidelines were included into the innovation patent, two monographs and two guide books, as well as into a scientific copyrighted work.

CONCLUSIONS

Trials on animals (white rats), placed in the main workshops of TMP for 2, 4 and 12 weeks, revealed that adaptive changes in catecholamine, which triggers the body to respond to stress at early stages, manifest in the increasing/decreasing levels in the insides (liver, adrenal glands). After 2 trial weeks, AD level in the liver was higher by 200%, compared to the reference group, and after two weeks more, it increased by 50% more. Over the same intervals, NAD level in adrenal glands increased by 15%, 20% and 50%, respectively. After 12 trial weeks, the increase was by 240%. At the last stages, higher catecholamine level in the heart negatively affects the cardiovascular system. Twelve weeks since the trial started, NAD level in the hearts of animals from the Workshop 1 increased by 16%. In the Workshop 2, NAD level increase by 28%, 47% and 34% throughout the intervals. In Workshop 3, NAD level changed only after 12 weeks, and increased by 13%.

Changed catecholamine levels in the groups of healthy workers, working in the main workshops at the TMP, reflect the stages of a non-specific adaptation process, defined as a standard activation of the stress-realizing system. In workers, who've been employed for less than 3 years, and for 3 to 5 years so far, catecholamine levels did not change dramatically, but those, who have been working for 6 to 10 years, experienced a statistically significant increase in AD (by 30%) and NAD (by 18%), and a decrease in DA and DOPA (by 22% and 50%, respectively). Workers, who've been at the plant ecology of plant for more than 10 years, experienced a decrease in AD (by 15%) and DA (by 29%), and an increase in NAD (by 14%) and DOPA (twofold).Excretion analysis revealed in Workshop 1 a significant decrease in dopamine, by 20%; in Workshop 2, it was a decrease in both DA and DOPA, by 37% each. The Workshop 3 shows a tendency of increasing AD and NAD levels with a simultaneously decreasing DA level (by 20%) and DOPA synthesis (by 50%) (Udut et al. 2005).

The KKS activation was tracked throughout the trial. After 2 trial weeks, its activity in animals from the Workshop 1 increased by 12%. After 4, and then 12 weeks, the increase was by 35% and 200%, respectively. In parallel, there was an increase in the prekallikrein, by 12%, 27% and 16%. In animals from the Workshop 2, kallikrein was found to increase after 4 weeks (by 30%). A significant increase was observed after 12 weeks (by 90%). After 2 weeks, kallikreinogen level decreased by 22%. Prekallikrein decreased after 4 and 12 weeks (by 14%, and 16%). There was a parallel increase in kininase activity by 39% and by 40%. After 12 weeks, the increase was by 15%. In the Workshop 3, bradykininogen level in blood has decreased by 45% after 12 trial weeks. However, kininase activity turned to be higher each time the measurements were made. It has increased by 38%, 40% and 40%. The kallikrein activity began to increase by 38% and 200% after 4 and 12 trial weeks. In parallel, the PK level began to decrease by 41% only after 12 trial weeks. Thus, the sharpest responses of the KKS in animals were detected in the Workshop 1.

At the last stages of stress, cascade activation of KKS boosts the resistance of the body to the work-related stress in the TMP. This is why workers from the Workshop 1 had better adaptive capabilities compared to other Workshops. Thus, kallikrein level in their blood was the highest among other workers, and was 3.3

times higher compared to reference values. At the same time, enzymatic activity decreased. The kininase activity decreased by 24%, compared to the reference group. The PK synthesis in the liver was adaptively increased by 20% to compensate for kallikrein. The kallikrein activity in blood of workers from the Workshop 2 was as twice as higher, compared to reference values, while the same parameter in workers from the Workshop 3 was 2.2 times higher. The kininase activity increased in the Workshops 2 and 3, by 16% and 24 %, respectively. The patterns of changes in the SAS and KKS that were tracked during the preventive examinations will help to identify those, who are at risk of balancing between normal and abnormal physical status.

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