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FUNCTIONAL-MORPHOLOGICAL PARALLELS OF THE HYPOTHALAMO-PITUITARY-ADRENAL SYSTEM RESPONSE REACTION TO LONG-TERM HYPOKINESIA

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16. Abstract

The effect of 2- and 4-week hypokinesia regimens on the hypothalamo-pituitary-adrenal system (HPAS) was investigated in 110 inbred mice (2.5 months old; line C57Bl and BAlb/C) and rats (Wistar). The results revealed progressive exhaustion and pathological reorganization of the HPAS morphofunctional structures. On the basis of established facts of interlineary and interspecies differences in the HPAS response, it is suggested that the animal body response reaction to the long-term effects of hypokinesia depends largely on it HPAS resistance and the values of this system's defensive-adaptation potential.

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FUNCTIONAL-MORPHOLOGICAL PARALLELS OF THE HYPOTHALAMO-PITUITARY-ADRENAL SYSTEM RESPONSE REACTION TO LONG-TERM HYPOKINESIA

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The negative effects on the body of motor activity restriction -- hypodynamia and hypokinesia -- have long been familiar in medical practice. Pathological conditions of such a type are relatively infrequently encountered, and are seen chiefly in the chronically ill and in persons leading sedentary life styles. /9

Tremendous progress in developing the material and technological foundation of contemporary society (automatization, development of means of control and transportation, space travel, etc.) has resulted in a steady increase in restriction of motor activity and its unfavorable effects on the body. In this connection, the problem of hypokinesia is assuming an increasingly important social significance.

We do know that, during protracted hypokinesia, complex combinations of defensive-compensator and pathological responses develop in the body (G. P. Tikhonova, Yu. I. Bizii, 1974), considerable disruptions of metabolism are found (Ye. A. Kovalenko et al., 1970), as are progressive growth of the clinical syndromes of autonomic-vascular dystonia and nervous and psychological exhaustion (A. Ya. Tizul et al., 1972) and acute and chronic alteration of higher nervous activity (L. N. Khruleva, 1969). /10

Hence, it has been established that prolonged hypokinesia has an unfavorable effect on practically all organs and systems of the adult organism. Its effects on the developing organism and on the condition of its defensive-compensator system under these conditions have been less extensively studied. The relationship between individual (genotypic) peculiarities and environmental factors has insufficiently shown.

*Numbers in the margin indicate pagination in the foreign text.

Study of the response reaction of the hypothalamo-pituitary-adrenal system (HPAS) of the developing body during hypokinesia is thus of definite interest, since this system is an extremely labile adaptive device which regulates the function of other organs and systems and reacts sensitively to any stressful influences.

In this work we shall cite the results of prolonged hypokinesia in the young, developing body, its effects on morpho-functional changes in the HPAS, and the specific response reaction of this system in representatives of various genotypes. To do this, regimes of two and four weeks of hypokinesia were utilized, since, according to the literature, it is during these periods that the most rapid response reactions of various morpho-functional systems of the body to this influence may be seen.

Two-and-a-half month old inbred animals -- mice and male rats (to rule out hormonal shift cyclicity) -- were studied. We used 110 animals: 50 mice of the C_{57}Bl strain, 30 mice of the BAlb/C strain, and 30 Wistar rats. After the background animal group was sacrificed (10 from each strain), the experimental mice (C_{57}Bl and BAlb/C) were kept hypokinetic for two weeks (10 from each strain). The same number of animals was used for a two week control (normodynamia) in order to study growth-related changes for comparison with the effects under investigation. In addition, 10 C_{57}Bl mice and the same number of Wistar rats were kept in hypokinesia for four weeks and in normodynamia for four weeks. Hypokinesia was simulated by maintaining the animals in specially-built paneled cages which sharply limited their movements. The most active (nocturnal) period of these animals' circadian rhythm was included in the experiment. At the end of the experimental period, the animals were withdrawn from it, decapitated, and the weights of the bodies were determined; adrenals and brains with hypophyses were removed. The adrenals were weighed on a torsion balance. Variation statistics were used to work up weight-related data. After fixing the hypothalami and hypophyses in Bouin's solution and the adrenals in 10% neutral formalin, the organs were enclosed in paraffin. Neurosecretory substance (NSS) content in the frontal sections of the hypothalamus in the supraoptic (SON) and paraventricular (PVN) nuclei, and the hypothalamo-pituitary tract (HPT), was determined using the Gomori-Gabou method, sections of the hypophysis were Helm-Dyban stained, and those from the adrenals were stained with hematoxylin-eosin. In addition, adrenal sections obtained on a freezing microtome were stained with Sudan-III to determine lipids.

Analysis of the obtained data indicated that a decrease in weight/11 and cessation of growth are found during two- and four-week hypokinesia in young animals. Interstrain and interspecies differences in reaction to the applied influence are quite clearly seen. Thus, following two weeks of motor activity restriction, a reliable decrease in body weight (in comparison to controls) of 9.6% and 22.6% occurred in the C_{57}Bl and BAlb/C mice, respectively, and after four weeks a 27.8% decrease took place in the C_{57}Bl mice and a 28.1% decrease in the Wistar rats.

Noting a deceleration in the growth of rats during hypokinesia, I. V. Fedorov et al. (1970) established that this phenomenon was associated with a reduction in tissue protein synthesis and an increase in their lysis. Moreover, these facts are confirmed by data from I. L. Yurens and O. I. Kirillova (1972) on the more exhausting effects of hypokinesia on the young organism relative to the adult. These authors note that adrenal weight in rats sharply increased following 12 hours and 2 and 6 days of hypokinesia, and that the hypertrophy markedly weakened after 9, 11, and 19 days. This weakening is viewed as one of the symptoms of animal exhaustion. According to our data, relative adrenal weights decreased somewhat in young C_{57}Bl and BAlb/C mice, and in Wistar rats of the control group, over the course of two and four weeks of normodynamia, while, in experimental animals of these strains which were subjected to hypokinesia, gland weight progressively increased in a direct relationship to the length of the experiment (fig. 1). Analysis of adrenal relative weight indices in experimental mice and rats demonstrated an essential difference in glandular reaction to hypokinesia for various species and strains of animals. Thus, following two weeks of restricted motor activity, adrenal weights in mice of the C_{57}Bl strain were greater than those in BAlb/C animals.

Hypokinesia lasting four weeks caused a more pronounced adrenal weight increase in C_{57}Bl strain mice than in Wistar rats (fig. 2). /12

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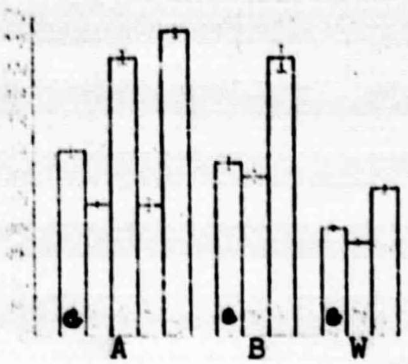

Fig. 1. Relative adrenal weight in mice and rats during hypokinesia.
A -- C_{57}Bl strain, B -- BAlb/C; W -- Wistar, G -- Background, K_1 and K_2 -- control after 2 and 4 weeks; H_1 and H_2 -- hypokinesia for 2 and 4 weeks.

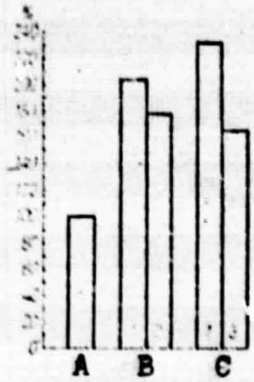

Fig. 2. Relative adrenal weight in mice and rats (in % relative to controls) during hypokinesia.
A -- control; B and C -- hypokinesia for 2 and 4 weeks, respectively.
1 -- C_{57}Bl strain; 2 -- BAlb/C; 3 -- Wistar strain.

Morphological changes in experimental animal adrenals following /12 two weeks of hypokinesia are characterized by hypertrophy of the fascicular layer. Cells here are enlarged, alveolar, and vacuolized. A considerable number of the nuclei are hyperchromatic and pyknotic. Lipids form rough droplets which merge with one another. Fascicular layer alterations are more pronounced in mice of the BAlb strain than in those of C_{57}Bl. After four weeks of hypokinesia, it is impossible to discern the boundaries between layers. Clear cells with rounded and pyknotic nuclei are frequently encountered. A small quantity of large-drop lipids are found in the sudanophobic zone. Besides the appearance of lipids in the sudanophobic zone, a general decrease of their presence in the glomerular layer is observed in rats.

When comparing preparations from backgound and control group animals (two and four weeks of normodynamia), an increase can be seen in the number of cells with hyperchromatic and pyknotic nuclei in the glomerular and reticular layers. The mass of small-droplet lipids in the

the glomerular layer is increased. Division of the cortical material into glomerular, fascicular, and reticular layers becomes more and more distinct. These discrepancies are caused by the continuing growth and development processes in the young animals. The significantly greater content (relative to controls) of spongiocytes in the fascicular layer is a growth factor index in rats.

Study of the hypothalami and hypophyses in background group animals (mice and rats) showed that the predominant elements of the SON and PVN are clear cells of the 1-b type (using the classification system of A. L. Polenov, 1968), containing sparse quantities of NSS in the form of small granulations situated in the central perinuclear zone. Small, solitary dilatated axons filled with NSS are encountered along the course of the HPT. A moderate quantity of Herring bodies, located in the area of axon terminations, are found in the neurohypophysis. Epithelial trabeculae formed into cells are seen in the adenohypophysis.

In the control group (two and four weeks of normodynamia), SON and PVN regions are distinguished by abundant vacuolization. Actively functioning elements -- large, clear cells of the 1-a type -- represent a significant number of the cells. Hypertrophied neurons with considerable peripheral cytoplasmic vacuolization are encountered. Along the course of the HPT, dilatation of axons filled with NSS in the form of Herring bodies around dilated sinusoidal capillaries is revealed. Gomori-positive colloid is discerned in the lumens of adenohypophyseal glandular cells. These data confirm the high degree of differentiation and maturity in these formations and their functional activity.

Dilatated vascular nets are clearly seen in the preparations from experimental animals (two weeks of hypokinesia) of the PVN and SON areas. Dark type 2 cells are present along with a large quantity of type 1-a ones. A large number of dilatated axons, filled with NSS, are seen along the course of the HPT. There is a massive accumulation of NSS around the dilatated sinusoidal capillaries in the neurohypophysis. Discomplexation of epithelial trabeculae and some reduction in acidophilic cells is found in the adenohypophysis. In BAlb/C strain mice, in distinction to the C_{57}Bl strain, solitary degenerate pyknomorphic cells are seen in the PVN and SON, while in the adenohypophysis there is an increased number of amphophil-type transitional forms, which, together with the previously noted facts, is a sign of the rapid response reaction of the neurosecretory system to the extreme influence.

The number of dark cells, hypertrophied neurons with alveolar cytoplasms, and degenerate pyknomorphic cells, sclerosed in places (in rats), increases in the PVN and SON of the hypothalamus following four weeks of hypokinesia -- figs. 3 & 4. Solitary dilatated axons containing Gomori-positive granules are encountered in the HPT. In the neurohypophysis, the amount of NSS in Herring bodies decreases markedly (in comparison to two weeks of hypokinesia, but they remain at a higher level than in the controls). In the adenohypophysis, a significant decrease is noted in the number of acidophilic cells and amphophils, and chromophobic secretions are seen. These facts show the increasing depletion of the neurosecretory system. /13

Fig. 3. Rat supraoptic nucleus following four weeks of hypokinesia. In the background of the bright cells -- vacuolization and degenerative changes. Gomori-Gabou aldehyde-fuchsin staining. 10 X 40 mag.

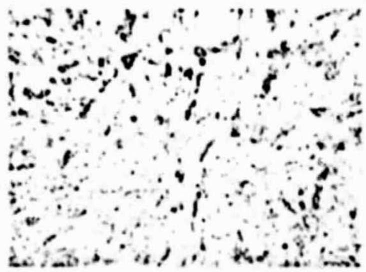

Fig. 4. Supraoptic nucleus of C_{57}Bl mouse following four weeks of hypokinesia. In the background of the bright cells -- axon sections filled with neurosecretions. Gomori-Gabou aldehyde-fuchsin staining. 10 X 40 mag.

The data we obtained confirm that the model of hypokinesia that was created is a powerful stress factor, the action of which on the young, growing organism is accompanied by an acutely pronounced reaction of the HPAS. At the very beginning, this reaction was of a defensive-adaptational nature, while progressively increasing depletion and pathological restructuring of the system appeared later on. It is quite understandable that the changes occcurring in it with increasing periods of hypokinesia necessarily bespeak an unfavorable effect in all spheres of metabolism, insofar as the HPAS is a basic hormonal regulator of body autonomic functions. The cited data on changes in animal weights and cessation of growth testify to this.

The established facts concerning interstrain and interspecies discrepancies in HPAS reaction furnish a basis for proposing that the resistance of the body functional systems of animals representing differing genotypes to the effects of prolonged hypokinesia is, to a considerable extent, conditioned by the resistance of their HPAS and its defensive-adaptational potential.

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