NASA TECHNICAL MEMORANDUM

NASA TM-76010

THE CONTENT OF CATECHOLAMINES IN THE ADRENAL GLANDS AND SECTIONS OF THE BRAIN UNDER HYPOKINESIA AND INJECTION OF SOME NEUROTROPIC AGENTS

B. E. Mel'nik and E. S. Paladiy

(NASA-TM-76010) THE CONTENT OF CATECHOLAMINES IN THE ADRENAL GLANDS AND SECTIONS OF THE BRAIN UNDER HYPOKINESIA AND INJECTION OF SOME NEUROTROPIC AGENTS (National Aeronautics and Space HC A02/MF A01

N80-28044

G3/52 Unclas 28017

Translation of "Soderzhaniye katekholaminov v nadpochechnikakh i otdelakh golovnogo mozga pri gipokinezii i vvedenii nekotorykh neyrotropnykh sredstv," Biologicheskiye nauki, Vol. 15, No. 11, 1972, pp. 45-49.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D.C. 20546 MARCH 1980

STANDARD TITLE PAGE

1. Report No. NASA TM-76010	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle THE CONTENT OF CATECHOLAMINES IN THE ADRENAL GLANDS AND SECTIONS OF THE BRAIN UNDER HYPOKINESIA AND INJECTION OF SOME NEUROTROPIC AGENTS		5. Report Date March 1980
		6. Performing Organization Code
7. Author(s) B. E. Mel'nik and E. S. Paladiy, Department of Human and Animal Physiology, V. I. Lenin Kishinev State University		8. Performing Organization Report No.
		10. Work Unit No.
9. Performing Organization Name and Address Leo Kanner Associates, Redwood City, California 94063		11. Contract or Grant No. NASW-3199
		13. Type of Report and Period Covered Translation
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration, Washington, D. C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes
Translation of "Soderzhaniye katekholaminov v nadpochechnikakh i otdelakh golovnogo mozga pri gipokinezii i vvedenii nekotorykh neyrotropnykh sredstv," Biologicheskiye nauki, Vol. 15, No. 11, 1972, pp. 45-49.

16. Abstract
White rats (75) were studied. Profound changes in body catecholamine balance occurred as a result of prolonged acute restriction of motor activity. Adrenalin retention increased and noradrenalin retention decreased in the adrenal glands, hypothalamus, cerebral hemispheres, cerebellum and medulla oblongata. Observed alterations in catecholamine retention varied depending upon the type of neurotropic substance utilized. Mellipramine increased catecholamine retention in the tissues under observation, while spasmolytin brought about an increase in adrenalin concentration in the adrenals and a decrease in the brain.

17. Key Words (Selected by Author(s))	18. Distribution Statement Unclassified-Unlimited

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	10	

NASA-HQ

THE CONTENT OF CATECHOLAMINES IN THE ADRENAL GLANDS AND SECTIONS OF THE BRAIN UNDER HYPOKINESIA AND INJECTION OF SOME NEUROTROPIC AGENTS

B. E. Mel'nik and E. S. Paladiy

Department of Human and Animal Physiology
V. I. Lenin Kishinev State University
Kishinev, USSR

In experiments on rats it was established that, under the influence of comparatively prolonged acute restriction of motor activity, profound alterations in the catecholamine balance occur, manifested as an increase in the content of epinephrine and decrease in the content of norepinephrine in the adrenals, hypothalamus, cerebral hemispheres, cerebellum, and medulla oblongata. It was shown that the observed alterations in catecholamine content may be compensated through the use of corresponding neurotropic substances. Mellipramine facilitates an increase in the content of catecholamines in the tissues under study, while spasmolytin causes an increase in the concentration of epinephrine in the adrenals and a decrease in the brain. /45*

The harmful effects of decreased motor activity (hypokinesia) on the condition of human and animal body physiological functions have recently become of increasing interest to biologists and physicians. It has been established that restriction of motor activity invariably leads to disorders in a number of metabolic processes and physiological systems which function as regulators, for example, those producing hormones and mediators, in particular catecholamines [2,3,5,7,8].

Catecholamines are present in various functional and structural regions of the brain and adrenals, and play an important role in the mechanisms of physiological processes. In this connection, the search for substances which normalize disordered catecholamine metabolism in the body and ways of using neurotropic pharmacological substances is assuming great practical significance.

We studied the dynamics of catecholamine content in the adrenals and in various regions of the brain during acute restriction of body motor activity.

Experiments were conducted on white laboratory rats of both sexes. 75 animals were used, having pre-experiment weights of 160-200 g.

In experiments of the first series, the change in catecholamine content in the organs under study was examined following 7, 14, and 21 days of acute motor activity restriction. In experiments of the second series, the same indices were studied following 7 and 14 days of motor activity restriction, with daily injection of neurotropic substances into the experimental animals. One of the animal groups received injections of mellipramine, 6mg. per 1kg. body weight, and the other received spasmolytin, 4mg /kg over the course of the entire experiment. Intact rats kept under normal vivarium conditions without restricting activity served as the control. /46

In order to create hypokinesia, the animals were placed in special panelled cages, set up according to the shape and size of the animal. The construction of the cages permitted systematic removal of food wastes, urine, and fecal substances, and supplied water and feed to the animals. The animals received unlimited quantities of water and food. The cages and animals were kept at a relatively constant temperature and received moderate natural illumination. Before placing the rats in the cages, they were weighed and their temperatures taken. Over the course of the entire experiment, body weights of the experimental and control rats were taken and rectal temperature was recorded daily. The results of the measurements were worked up using variation statistics and Student's method.

At a preselected time, the rats were decapitated and the content of catecholamines (epinephrine and norepinephrine) in the organs and tissues was determined. Epinephrine and norepinephrine content in the adrenals and various regions of the brain (hypothalamus, cerebral hemispheres, cerebellum, and medulla oblongata) was determined using V. O. Osinskaya's fluorometric method [6]. Fluorescent intensity was measured using a PF-1 domestic brand fluorometer, using excitation waves of 360 nanometers, obtained from a URS-3 primary light filter. Maximum fluorescence corresponded to a frequency of 510 nanometers, obtained through a secondary interference light filter.

Analysis of the statistical data indicates that hypokinesia over the course of the entire experiment caused a trustworthy progressive increase in epinephrine content in the adrenals (Table 1). Thus, following seven days of hypokinesia, epinephrine content in the adrenals increased almost two times, while following 21 days it increased almost five times relative to the controls.

Change in norepinephrine content in the adrenals occurred in two phases: a decrease took place on the 7th day of the experiment, while on the 14th day there was a maximum increase in the quantity of this substance in the adrenals. The decrease in norepinephrine concentration in the adrenals, apparently, was a consequence of elevated output of it into the blood, and was probably associated with the passive anxiety of the animals.

Acute restriction of motor activity caused considerable fluctuations in the concentration of catecholamines in the brain tissues under study, which undoubtedly is evidence of alteration in the mechanisms of nervous processes. By the 7th day of the experiment, epinephrine content in the hypothalamus increased almost 5 times relative to controls, and in the cerebral hemispheres increased 3 times. A noticeable increase in the quantity of epinephrine was also established in the cerebellum and medulla oblongata following 7 days of acute hypokinesia. Further increase in epinephrine content in both the hypothalamus and cerebral hemispheres occurred by the 14th day of the experiment. In the cerebellum and medulla oblongata, the quantity of epinephrine did not change, or perhaps decreased somewhat, in comparison to the 7th day of the experiment; by the 21st day, a further moderate increase in epinephrine content was noted in the hypothalamus, cerebellum, and medulla oblongata (Table 1).

Acute restriction of the animals' motor activity caused an increase in the concentration of norepinephrine in all the regions of the brain under study: in the medulla oblongata - over the course of the entire experiment, in the hypothalamus, cerebellum, and cerebral hemispheres - by the 14th and 21st days of the experiment.

The considerable alteration in the distribution of catecholamines in various regions of the brain during hypokinesia must be examined within the framework of autoregulatory neurohumeral processes. The high content of epinephrine an. products of its oxidation were evidence of intensification of metabolic processes, which may lead to tissue hypoxia. Moreover, the large quantity of catecholamines changes the energy balance, which is harmful to the overall functional condition of the body. In particular, energy balance disorders manifest themselves in processes associated with acetylcholine synthesis, and may have an effect on the functional condition of the nervous system as a whole.

Results of experiments using injection of neurotropic substances into immobilized animals are of considerable interest (Table 2). In the first stage of the experiment, the neurotropic preparation mellipramine caused a distinct increase in epinephrine and norepinephrine content in the animal tissues under study, in comparison to the tissues of animals which were kept immobilized but did not receive mellipamine. Epinephrine concentration in brain tissues began to gradually decrease on the 14th day. /47

Norepinephrine content in brain tissues grew sharply in the 1st half of the experiment, and on the 14th day it continued to be higher than in animals subjected only to immobilization. Upon the injection of mellipramine, norepinephrine content decreased so abruptly that we could not detect it. This fact may be evidence of sympatico-adrenal system function exhaustion, which is an unfavourable symptom and must be taken into account when making an overall evaluation of the reactivity of the body to prolonged hypokinesia. It has been suggested [4] that mellipramine, as an antidepressant, has an effect at least on 2 regions of the brain: the hypothalamus, in its posterolateral regions, and the amygdaloid complex, in its basiolateral part.

Injection of the immobilized animals with spasmolytin caused a two phased change in epinephrine content in the adrenals: a considerable increase was noted following 7 days, and a sharp decrease of epinephrine content in the adrenals relative to controls (immobilized animals) was noted following 14 days.

Injection of spasmolytin and immobilization over the entire course of the experiment caused a moderate decrease in epinephrine content in the brain tissues under study. Following injection /49
of spasmolytin, norepinephrine quantity in the adrenals of the immobilized rats decreased sharply following seven days and continued to decrease for 14 days of the experiment. Norepinephrine content increased in the brain tissues, with the exception of the cerebellum.

The effect of spasmolytin on the indices we studied may be explained by blocking of the cholinergic system of the cerebral cortex and hippocampus, since we know that expanded cortical inhibition causes an increase in the content of norepinephrine in brain tissue[1].

The results of the second series of experiments indicated that alterations in catecholamine content observed in various tissues during immobilization may be successfully modified through injection of the corresponding neurotropic substances.

All of the above leads us to conclude that protracted hypokinesia causes profound changes in catecholamine metabolism in animals, which is manifested by an increase in epinephrine content and decrease in norepinephrine quantity in all tissues under study. The nervous system stimulator mellipramine causes an increase in catecholamine content for the tissues under study in such animals. The N-cholinolytic spasmolytin increases epinephrine content in the adrenals during hypokinesia, and decreases its quantity in brain tissues.

TABLE 1. CHANGE IN CATECHOLAMINE CONTENT IN THE ORGANS OF RATS FOLLOWING ACUTE RESTRICTION OF MOTOR ACTIVITY

Cond'ns of Exprmnt	Number of Animals	Catecholamine content, micrograms per 1g. raw tissue: adrenals A	adrenals N	hypothalamus A	hypothalamus N	cerebral hemispheres A	cerebral hemispheres N	cerebellum A	cerebellum N	medulla oblongata A	medulla oblongata N
Control..	6	1315±75	353±31,3	1,9±0,32	3,73±0,31	0,389±0,126	0,512±0,142	0,525±0,095	1,01±0,012	0,888±0,282	0,51±0,093
7 days Immobil'n	9	2315±98 P<0,001	282±30,77 P<0,1	6,24±0,90 P<0,001	2,0±0,75 P<0,05	3,24±0,67 P<0,001	0,49±0,079 P<0,1	2,2±0,35 P<0,001	0,55±0,095 P<0,001	1,28±0,27 P<0,1	0,92±0,19 P<0,05
14 days Immobil'n	8	3163±198 P<0,001	465±36,5 P<0,02	7,27±0,58 P<0,001	1,62±0,37 P<0,001	4,39±0,94 P<0,001	0,844±0,1 P<0,1	2,17±0,27 P<0,001	1,21±0,15 P<0,1	1,08±0,2 P<0,1	1,40±0,20 P<0,02
21 days Immobil'n	9	5220±416 P<0,001	351±29,27 P<0,1	10,73±0,95 P<0,001	5,48±0,51 P<0,01	1,81±0,3 P<0,001	1,91±0,28 P<0,001	2,22±0,31 P<0,001	1,78±0,19 P<0,002	1,53±0,26 P<0,1	ʒ1,61±0,41 P<0,02

Key: A -- adrenaline
N -- noradrenaline

TABLE 2. CATECHOLAMINE CONTENT IN THE ORGANS OF RATS FOLLOWING ACUTE RESTRICTION OF MOTOR ACTIVITY AND INJECTION OF NEUROTROPIC SUBSTANCES

Cond'ns of Exprmnt	Number of Animals	Catecholamine content, micrograms per 1g. raw tissue: adrenals A	adrenals N	hypothalamus A	hypothalamus N	cerebral hemispheres A	cerebral hemispheres N	cerebellum A	cerebellum N	medulla oblongata A	medulla oblongata N
7 days Immobil'n	5	2274±95,57	270±22,8	5,5±0,508	2,45±0,562	2,48±0,481	0,45±0,077	2,8±0,106	0,5±0,111	1,13±0,185	0,89±0,13
14 days Immobil'n	6	2992±150,6	470±35,5	6,93±0,542	1,75±0,2	4,02±0,71	0,871±0,012	2,07±0,278	1,28±0,15	1,12±0,153	1,31±0,111
7days Imm. +melliprmn	8	3206±385 P<0,05	0	11,25±2,6 P<0,05	20,0±2,88 P<0,01	4,24±0,45 P<0,1	2,33±0,45 P<0,05	3,5±0,62 P<0,1	2,33±0,54 P<0,05	2,77±0,57 P<0,02	4,42±0,6 P<0,002
14 days Immobil'n +melliprmn	8	2723±424,4 P<0,1	0	1,66±0,41 P<0,001	12,08±2,31 P<0,05	1,25±0,38 P<0,02	2,1±0,86 P<0,1	1,41±0,54 P<0,002	1,70±0,63 P<0,1	1,27±0,14 P<0,1	2,08±0,24 P<0,05
7 days Immobil'n +spasmoltn	8	7376±592 P<0,001	0	2,08±0,41 P<0,002	4,58±0,41 P<0,01	2,2±0,93 P<0,1	1,86±0,19 P<0,001	1,33±0,77 P<0,1	0	1,05±0,46 P<0,1	3,86±1,37 P<0,02
14 days Immobil'n +spasmoltn	8	136±12,0 P<0,001	22υ±90,7 P<0,1	3,3±0,42 P<0,01	5,83±0,41 P<0,1	1,16±0,3 P<0,01	1,5±0,29 P<0,001	1,25±0,29 P<0,05	7,16±0,91 P<0,001	0,6±0,005 P<0,02	3,99±1,06 P<0,05

Key: A -- adrenaline
B -- noradrenaline

REFERENCES

1. Andreyev, S. V., and I. D. Kobkova, in: Rol' katekholaminov v zdorovom i bol'nom organizme [The Role of Catecholamines in the Healthy and Diseased Body], "Medicine" Publishing House, Moscow, 1970.

2. Artyukhina, T. V., "The Structural Condition of the Hypothalamo-hypophyseal System during Hypokinesia", in: Eksperimental'nyye issledovaniya gipokinezii, izmenennoy gazovoy sredy, uskoreniy, peregruzok i drugikh faktorov [Experimental Studies on Hypokinesia, Altered Gaseous Environments, Acceleration, G-forces, and Other Factors], Moscow, 1968.

3. Korobkov, A. V., L. A. Ioffe, M. A. Abrikosova, Yu. M. Stoyda, "The Dynamics of Orthostatic Stability in Athletes as Affected by 40-day Hypokinesia", Kosmicheskaya biologiya i meditsina, 2, 3 (1968).

4. Lapin, I. G., and L. Kh. Allikmete, "A Hypothesis Concerning the Role of the Amygdaloid Complex and Hypothalamus in the Action of Antidepressants", in: Sovremennyye psikhotropnyye sredstva [Contemporary Psychtropic Remedies], 2nd Edition, Moscow, 1967.

5. Mel'nik, B. E., and E. S. Paladiy, "Alterations of Catecholamine Content in Various Regions of the Brain and in the Adrenals during Acute Hypokinesia", Materialy nauchnoy konferentsii professorsko-prepodavatel'skogo sostava Kishinevskogo gosuniversiteta po itogam nauchno-issledovatel'skoy raboty za 1969 god. [Materials from the Scientific Conference of the Kishinev State University Faculty Summarizing Research Work in 1969], Kishinev, 1970.

6. Osinskaya, V. O., "Research on Epinephrine and Norepinephrine Metabolism in the Tissues of the Animal Body", Biokhimiya, 22, 3 (1957).

7. Parin, V. V., V. N. Vinogradov, A. N. Razumov, "Problems in Space Pharmacology", Kosmicheskaya biologiya i meditsina, 1 (1969).

8. Parin, V. V., B. M. Fedorov, V. S. Nevstruyeva, "Alterations in Corticosteroid and Catecholamine Metabolism during Acute Restriction of Body Motor Activity", Dokl. AN SSSR, 184, 1 (1969).