ON THE PECULIARITIES OF CATECHOLAMINE METABOLISM IN ACUTE POLONIUM (Po^{210}) LESIONS

(UDC 617-001.28-07 : 616-008.944.53-07)

B. B. Moroz, S. P Grozdov, and E. N. Petrovnina

(Presented by Academician P. D. Gorizontov, Academy of Medical Sciences USSR)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 61, No. 3, pp. 59-63, March, 1966
Original article submitted November 5, 1964

Excitation of the sympathico-adrenal system is one of the initial links in the reaction of the organism to the effects of ionizing radiation [2, 7]. However, it is unclear whether the reaction of the sympathico-adrenal system is adequate in this case, and what is the role of catecholamines in the appearance of adaptive and pathological processes. The catecholamine metabolism has been investigated chiefly in the study of the effect of external radiation [4, 6, 8, 10, 15]. And yet, the uniqueness of the endocrine-metabolic changes characteristic of radiation sickness, induced by incorporated polonium, may be related to a definite degree of peculiarities of the reaction of the sympathico-adrenal system.

The task of this work was to study the catecholamine content and the degree of their proteinization in the adrenals, blood, and myocardium during acute radiation sickness, induced by Po^{210}.

EXPERIMENTAL SECTION

The experiments were conducted on 33 male rabbits of the chinchilla breed, weighing 2.5-3 kg (21 experimental and 12 control). The animals received subcutaneous injections of Po^{210} in a dose of 0.1 curie/kg, which induced the development of acute radiation sickness and death after three to four weeks. Blood from the heart and organs was taken from the rabbits under hexenal narcosis. Catecholamines (adrenalin, noradrenalin, and oxidation products) in the blood, myocardium, and adrenal medulla were determined by a fluorescent-analytical method (in V. O. Osinskaya's modification) [11]. The total content of catecholamines in the free fraction and in the fractions bound to water-soluble and water-insoluble proteins were determined separately according to the procedure of M. P. Barts [1]. The degree of protein bonding of the catecholamine was represented in the form of the proteinization coefficient (K_{π}), the ratio of the amount of protein-bound catecholamine to its total amount, and it was also determined what portion of the entire amount of proteinized catecholamine (in percent) was bound to the water-soluble protein (WS). In the experiments with adrenalin loading, adrenalin was injected intravenously in a dose of 200 μg per animal, and tissue was extracted after 2 min for a determination of catecholamine.

EXPERIMENTAL RESULTS

Po^{210} lesion induced substantial changes into the catecholamine metabolism (see table), primarily into the content of catecholamines in the adrenal medulla. Thus, during early periods (sixth to seventh day), the adrenalin level in the adrenals was substantially increased (120 ±25 mg %); then on the eighth to tenth day it was normalized (70.7 mg %), while from the eleventh day on its content progressively decreased, reaching 7 mg % on the twentieth day. In the phase of reduced adrenalin level in the adrenals, noradrenalin was frequently detected, although it was very rarely determined in the normal state.

At various periods of radiation sickness, adrenalin appeared in the blood and myocardium. In the late periods (14 to 20 days), it was found in the myocardia of all the animals. Evidently during the first phase of radiation sickness, the synthesis and secretion of adrenalin are sharply increased, while subsequently there is a decrease in the synthesis, a functional "exhaustion," which is also indicated by the frequent appearance of noradrenalin—an intermediate product of the synthesis [16]—in the adrenals. Such changes had previously been observed in rats injured by Po^{210} [12], and also after x-ray irradiation [3].

Content of Catecholamines in Rabbit Tissue in the Presence of Po^{210} Lesions

Condition of experiment	No. of animals	Adrenals					
		AD (in mg %)		NAD (in mg %)		PO (in mg %)	
		n	M±m	n	M±m	n	M±m
Control: Healthy animals	6	6	70,2±8,5	1	2,0	0	—
Control: Healthy animals after adrenalin loading	6	6	80,0±11,0	0	—	0	—
Po^{210} lesion: 6—7-th day	4	4	120,0±25,0	0	—	1	2,0
Po^{210} lesion: 8—12-th »	4	4	70,7±6,0	2	(78,0 и 2,0)	2	3,0±0,5
Po^{210} lesion: 14—20-th »	4	4	21,2±3,5*	3	5,7±2,0	2	4,5±3,0
Po^{210} lesion + adrenalin loading: 6—7-th »	3	3	67,3±17,0	1	1,0	3*	5,3±4,4*
Po^{210} lesion + adrenalin loading: 8—12-th »	3	3	82,0±4,0	2	2,0	1	2,0
Po^{210} lesion + adrenalin loading: 14—20-th »	3	3	80,7±11,0	1	3,0	3*	4,6±0,9*

Condition of experiment	Blood					
	AD (in μg %)		NAD (in μg %)		PO (in μg %)	
	n	M±m	n	M±m	n	M±m
Control: Healthy animals	0	—	6	5,6±1,4	6	6,7±1,4
Control: Healthy animals after adrenalin loading	6	16,7±3,4	6	5,3±1,6	6	6,1±2,3
Po^{210} lesion: 6—7-th day	1	5,0	3	6,4±1,7	4	5,5±2,0
Po^{210} lesion: 8—12-th »	1	4,0	3	12,9±6,0	3	5,0±2,6
Po^{210} lesion: 14—20-th »	1	10,0	3	2,9±0,7	4	7,0±1,0
Po^{210} lesion + adrenalin loading: 6—7-th »	3	29,8±13,0	3	4,1±0,9	3	4,6±2,1
Po^{210} lesion + adrenalin loading: 8—12-th »	3	33,0±16,0	2	11,4±8,6	1	2,0
Po^{210} lesion + adrenalin loading: 14—20-th »	3	26,0±14,0	2	4,2±2,4	3	6,1±1,7

Condition of experiment	Myocardium of left ventricle					
	AD (in μg %)		NAD (in μg %)		PO (in μg %)	
	n	M±m	n	M±m	n	M±m
Control: Healthy animals	0	—	6	170,0±19,5	0	—
Control: Healthy animals after adrenalin loading	6	29,3±11,0	6	152,5±19,0	1	4,5
Po^{210} lesion: 6—7-th day	1	60,0	4	157,0±20,0	2	7,5±2,5
Po^{210} lesion: 8—12-th »	1	32,0	4	122,0±34,0	3*	17,0±12,0*
Po^{210} lesion: 14—20-th »	4*	33,0±14,0*	4	84,7±26,0*	3*	42,0±10,0*
Po^{210} lesion + adrenalin loading: 6—7-th »	3	53,7±27,0	3	55,0±42,0*	2	9,5±0,5
Po^{210} lesion + adrenalin loading: 8—12-th »	3	36,0±24,0	3	114,0±25,0	1	8,0
Po^{210} lesion + adrenalin loading: 14—20-th »	3	50,0±24,0	3	76,0±26,0*	1	18,0

Notes: AD—adrenalin; NAD—noradrenalin; PO—oxidation products; N—number of cases in which a given catecholamine was detected; the asterisks mark values reliably differing from the control (evaluation according to Wilcoxon and according to the ξ^2 criterion).

The presence of adrenalin in the myocardium is not only an index of increased secretion of this hormone by the adrenals, but also, according to the available observations [17], a sign of injury of the myocardium. Adrenalin was regularly detected in the myocardium during the late period of radiation sickness, when, according to the data of electrocardiography, the disturbances of heart function were the most pronounced in the rabbit. Adrenalin, as a rule, was found in the myocardium of the left ventricle, and comparatively rarely in the myocardium of the right ventricle. This may be due to the greater functional load of the left ventricle during radiation sickness. The decrease in the noradrenalin content in the myocardium during the late period of radiation sickness is also characteristic of heart injury.

There are indications that the biological effect of the catecholamines depends upon their interactions with proteins. In Po^{210}-injured rabbits, a decrease in the proteinization of catecholamines was observed in the adrenals on the eighth to fourteenth day of the disease (K_{π} = 0.45 ±0.05; norm 0.7 ±0.03). The bonds of adrenalin to the water-soluble proteins and the processes of proteinization of the noradrenalin appearing in the adrenals were not disrupted. Adrenalin loading more distinctly revealed changes in the conditions of proteinization in the adrenals. The degree of proteinization of adrenalin in this case was increased on the sixth to seventh day of the disease (K_{π} = 0.85 ±0.03; WS = 72.5 ±11%). At the second week, processes of proteinization were changed: although K_{π} was high (0.77 ±0.15), proteinization was realized exclusively on account of the water-insoluble proteins (WS = 0), In the late period, proteinization was substantially reduced (K_{π} = 0.19 ±0.12); nor was there any bond to the water-soluble proteins. It was interesting that when exogenous adrenalin was introduced; in all of the investigated periods of radiation sickness, approximately the same adrenalin concentrations were detected in the adrenals, i.e., adrenalin loading seemed to level out the radiation changes. Adrenalin loading, on the one hand, may intensify the secretion of endogenous adrenalin from the adrenals, and on the other hand may give rise to sorption of exogenous adrenalin from the blood, especially under conditions of a reduced content of endogenous adrenalin in the adrenals.

In the blood, adrenalin appearing during radiation sickness was in all cases entirely bound to the water-insoluble protein (WS = 0). The bond of noradrenalin to the water-soluble proteins was also reduced. This process may be due to a decrease in the content of the serum albumins during radiation sickness [13], as well as to an increase in the sorption capacity of the erythrocytes in connection with denaturation changes [5]. After adrenalin loading, most of it existed in the free state.

In the myocardium in the Po^{210}-injured animals, adrenalin was entirely proteinized (K_{π} = 1), but exclusively on account of the water-soluble proteins (WS = 100%). Evidently such is a peculiarity of the "sick" heart, since in healthy animals the proteinization of the endogenous noradrenalin or exogenous adrenalin in the myocardium was realized primarily by the water-insoluble proteins. Hence the adrenalin detected in the myocardium in our experiments may be considered as a deposited, temporarily inactivated form.

The increase in the water-soluble proteinization may be due to a change in the ratio of the water-soluble (myogen) and water-insoluble (myosin and myostromin) protein fractions of the myocardium, in the direction of an increase in the water soluble proteins.

Adrenalin loading revealed a definite phase character in the changes of proteinization, both in the myocardium and in the adrenals. At first water-soluble proteinization predominated, while during the late period of radiation sickness (third week), adrenalin was determined in the free state (K_{π} = 0.23 ±0.1).

The decrease in the reaction of the heart to adrenalin during the late period in Po^{210}-injured rabbits was evidently related to a decrease in the processes of proteinization [19]. As is well known, proteinization of catecholamine is a necessary condition for the realization of its effect upon the heart [1]. Undoubtedly the structural changes in the proteins in the blood and organs during radiation sickness substantially hinder the hormonal and mediator regulation. Substantial amounts of biologically active substances may be sorbed by nonspecific protein structures. Destruction of proteins may also be observed in the specific receptors of the cells, with which, in particular, the catecholamines react.

Of great importance in the catecholamine metabolism during radiation sickness after x-ray irradiation are changes in the processes of their oxidation [3, 10]. In the case of Po^{210} lesions, oxidation products of the catecholamines were detected in the adrenals and myocardium, which is evidently due to a decrease in the function of the stabilizing systems, in particular, ascorbic acid [14]. However, no increase in the oxidation processes was observed in the blood, while they were sharply intensified under the influence of x-rays.

LITERATURE CITED

1. M. P. Barts, Biokhimiya, No. 4 (1957), p. 677.
2. P. D. Gorizontov, In the book: Pathological Physiology of Acute Radiation Sickness [in Russian], Moscow (1958), p. 5.
3. B. M. Graevskaya and R. N. Shchedrina, Radiobiologiya, No. 1 (1962), p. 54.
4. V. I. Kandror, Fiziol. Zh. SSSR, No. 6 (1960), p. 744.
5. A. S. Krylov, In the book: Collection of Abstracts on Radiation Medicine for 1957 [in Russian], Moscow, 1 (1959), p. 103.
6. V. I. Kulinskii, Changes in the Catecholamine Metabolism During Experimental Acute Radiation Sickness. Author's Abstract of Candidate's Dissertation [in Russian], Khar'kov (1961).
7. A. V. Lebedinskii, Z. N. Nakhil'nitskaya, and N. P. Smirnova, Med. Radiol., No. 7 (1959), p. 3.
8. A. F. Maslova, Byull. Éksper. Biol., No. 9 (1958), p. 81.
10. B. B. Moroz, S. P. Grozdov, and E. N. Petrovnina, Radiobiologiya, No. 4 (1962), p. 543.
11. V. O. Osinskaya, Biokhimiya, No. 3 (1957), p. 537.
12. E. N. Petrovnina, Radiobiologiya, No. 6 (1961), p. 907.
13. V. M. Rodionov, et al., Transactions of the All-Union Conference on Medical Radiology. Clinic and Therapy of Radiation Sickness [in Russian], Moscow (1957), p. 112.
14. Z. Bacq and P. Alexander, Fundamentals of Radiobiology [Russian translation], Moscow (1963).
15. M. C. C. Goodal and H. Long, Am. J. Physiol., 197 (1959), p. 1265.
16. J. Malmejac, G. Neverre, M. Bianchi, et al., J. Physiol., (Paris), 50 (1958), p. 389.
17. W. Raab, In the book: Achievements of Cardiology [Russian translation], Moscow (1959), p. 67.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.