MORPHOLOGICAL AND FUNCTIONAL CHARACTERISTICS OF CADMIUM-INDUCED ARTERIAL HYPERTENSION

L. M. Mikhaleva, A. A. Zhavoronkov, A. L. Chernyaev, and V. B. Koshelev

UDC 616.12-008.331.1-02:[615.916:546.48]-092.9-091.8

KEY WORDS: cadmium-induced nephropathy, arterial hypertension, atrial secretory granules

Cadmium poisoning is a condition due to excessive intake of the trace element by the body. It may exist in many different forms: cadmium-induced rhinitis and pharyngitis, nephropathy, osteomalacia (itai-itai disease), and a neurotoxic syndrome [1]. Data on the connection between arterial hypertension and cadmium poisoning are few in number and contradictory in nature [5, 9, 10].

EXPERIMENTAL METHOD

Experiments were carried out on 210 male albino rats receiving cadmium chloride solution by gastric tube in a dose of 2.5 mg/100 g body weight (0.25 LD), five times a week for 12 weeks, followed by a recovery period of 9 weeks. Every week the blood pressure (BP) was measured in the caudal artery, using a modified Korotkov's method [2]. Additionally, in the 7th week of the experiment the isolated posterior part of the rats' body was perfused under stabilized rate of flow conditions, by the method suggested by Folkow [6, 7]. Every week 10 rats were killed by decapitation under ether anesthesia. Parts of the heart were weighed separately, and the ventricular index (VI) determined. Pieces of heart, kidney, and tail were fixed in Lillie's buffered formalin solution, histologic sections were stained with hematoxylin and eosin and by Li's method, the PAS reaction was carried out, and semithin sections were stained with methylene blue, azure II, and basic fuchsine. The kidneys, left ventricular myocardium, and atria were investigated electron-microscopically. A morphometric study of secretory granules (SG) in the atria, containing natriuretic factor precursor (NFP), was undertaken by the method in [4] on photographic plates (magnification 7000 and 15,000). The following parameters were analyzed: diameter of SG, their area, and their number in one cardiomyocyte, and also the volume of the cytoplasm of a cardiomyocyte relative to one SG. The blood plasma NFP level was determined by radioimmunoassay using the α-ANP [^{125}I] Radioreceptor Assay System (Amersham), and the myoglobin (MG) concentration was determined by means of an RIA-myoglobin-^{125}I kit (Tashkent, USSR).

EXPERIMENTAL RESULTS

Measurement of BP revealed a significant increase in the systolic pressure after 2 weeks of poisoning to 133 ± 1.2 mm Hg (115.7 ± 1.4 mm Hg in the control), followed by an increase to 148 ± 1.8 mm Hg at the 6th week of poisoning (Fig. 1). During the next 6 weeks BP remained stable. After the end of cadmium administration, within a week BP showed a significant rise to 129.2 ± 1.9 mm Hg compared with the control, followed by a decrease to 115 ± 1.7 mm Hg after 3 weeks of rehabilitation. At the stage of stable arterial hypertension (poisoning for 7 weeks) the isolated posterior part of the rats' body was perfused. Assessment of the resistance of the arterial system of the experimental rats showed an increase of 37-40% in the structural component of resistance. Analysis of the reactivity of the vessels revealed a significant increase in the maximal constrictor response of the experimental animals to injection of high doses of noradrenalin ($2.3 \cdot 10^{-6}$ g/ml) by 14% compared with the control.

Laboratory of Geographic Pathology, Research Institute of Human Morphology, Academy of Medical Sciences of the USSR, Moscow. Department of Physiology of Man and Animals, M. V. Lomonosov Moscow State University. (Presented by Academician of the Academy of Medical Sciences of the USSR N. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 111, No. 4, pp. 420-423, April, 1991. Original article submitted July 30, 1990.

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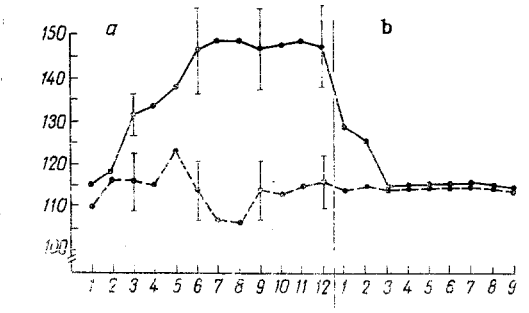

Fig. 1. Trend of systolic BP of rats during cadmium poisoning (a) and recovery period (b). Continuous line — experiment; broken line — control. Abscissa, time of investigation (in weeks); ordinate, systolic BP (in mm Hg).

On separate weighing of the heart starting with the 3rd week of the experiment a significant decrease was observed in the value of VI from 0.449 ± 0.012 in the control to 0.389 ± 0.015. In the 12th week of the experiment VI was 0.346 ± 0.007. In the recovery period VI gradually increased to reach 0.450 ± 0.008 by the 9th week of rehabilitation. Spasm and hypertrophy of the walls of the peripheral arteries (Fig. 2a) and arterioles were observed histologically. In the left ventricular myocardium of the experimental animals, with lengthening of the periods of poisoning hypertrophy of the cardiomyocytes, cloudy swelling and vacuolar degeneration of these cells, dilatation, congestion, and plasmatization of the capillaries, interstitial edema, and also the presence of segmental contractures of the myofibrils of the I-II degree, detectable under the polarization microscope, and foci of injury to individual cardiomyocytes when stained by Li's method, were observed (Fig. 2b). Radioimmunoassay yielded evidence of a sharp increase in the plasma MG concentration during the period of poisoning — up to 90.8 ± 7.6 mg/ml compared with 39.3 ± 6.2 mg/ml in the control ($p < 0.001$). Electron-microscopically the sarcolemma of the cardiomyocytes of the experimental rats became uneven, often formed arcades with a corrugated appearance, the sarcoplasm was translucent, and foci of loss of the complex structure of the myofibrils and their lysis were observed. As a rule the mitochondria showed destructive changes, with focal translucency of the matrix and lysis of the cristae, and sometimes with the presence of myelinlike structures. The nuclei of the cardiomyocytes had translucent nucleoplasm and condensation of their chromatin.

After 1 week of poisoning an increase in the number of atrial SG was observed morphometrically, whereas their diameter and area remained at the control level (Fig. 3). After 2 weeks the number of SG increased, but at the same time there was a decrease in their diameter, their area, and the volume of cytoplasm expressed per secretory granule. During this same period polymorphism of SG was found and many of them were irregularly circular in shape, and with varied electron density; most SG appeared beneath the sarcolemma (Fig. 2c). Hyperplasia and hypertrophy of the Golgi lamellar complex also was found. Radioimmunoassay revealed an almost tenfold increase in the concentration of NFP in the blood plasma in he initial period of elevation of BP (3 weeks of poisoning) — to 297.7 ± 66.7 pg/ml (30.0 ± 3.8 pg/ml in the control; $p < 0.01$). At the 4th week of the experiment the number of SG in the atrial cardiomyocytes was reduced, and this was accompanied by a simultaneous increase in the diameter and area of SG. Subsequently the above parameters of SG fluctuated, in accordance with the changes in BP during the period of poisoning and rehabilitation.

In the kidneys a picture of nephropathy was discovered at both light optical and submicroscopic levels in all the observations starting with the 2nd week of the experiment. Marked destructive changes were recorded electron-microscopically in the epitheliocytes of the proximal tubules and, in particular, in the mitochondria. In the epithelioid cells of both granular and agranular types of the juxtaglomerular apparatus (JGA) the rough endoplasmic reticulum was better developed than in the control and often formed circular structures; the Golgi lamellar complex showed hyperplasia, with an increased number of ribosomes and polysomes. An increased number of SG and protogranules could be found in the granular epithelioid cells (Fig. 2d). By the 9th week of the rehabilitation period, morphological and functional restoration of the heart and kidneys could be observed.

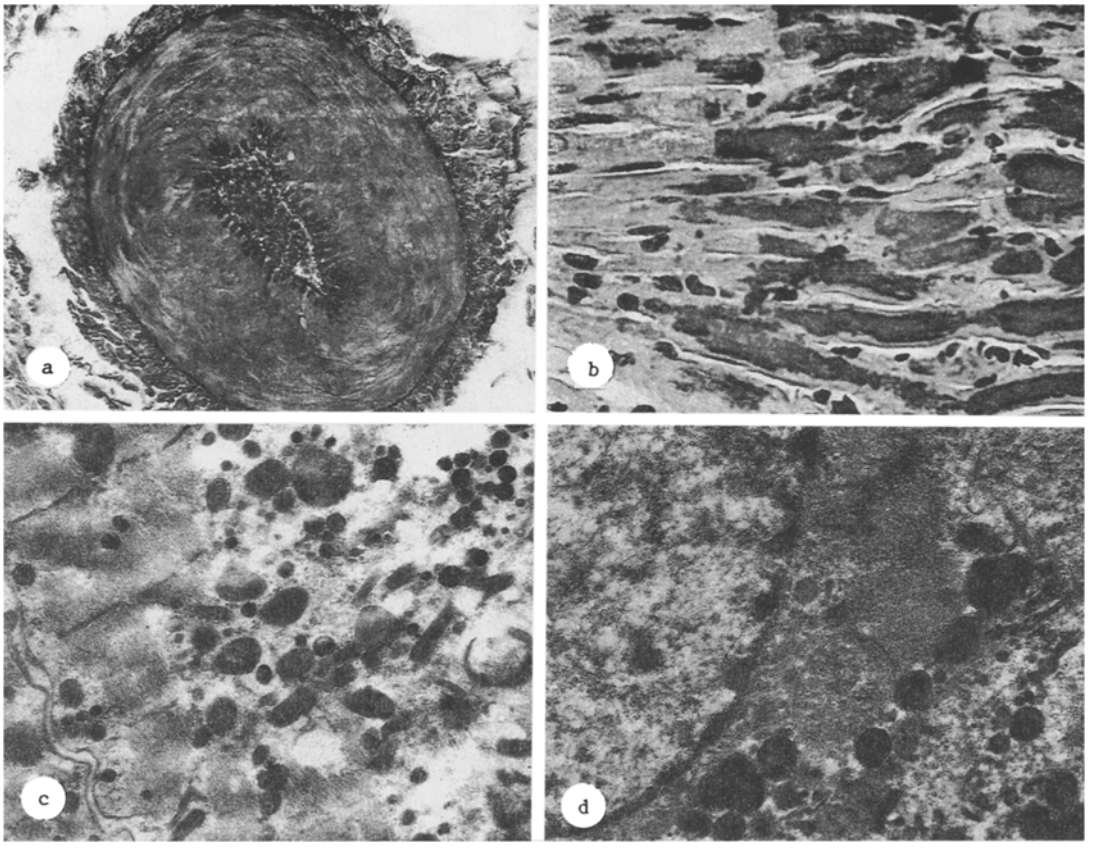

Fig. 2. Morphological characteristics of artery, myocardium, and epithelioid cells of the juxtaglomerular apparatus (JGA): a) caudal artery after 6 weeks of cadmium poisoning; corrugation of inner elastic membrane, hypertrophy of muscular layer. 125×. Stained with picrofuchsine-fuchsalin; b) foci of injury in left ventricular cardiomyocytes of a rat after 9 weeks of poisoning. 320×. Stained by Li's method; c) cardiomyocyte from right atrium of rat after 2 weeks of poisoning; SG of varied diameter and electron density, some of them located beneath the sarcolemma. 7900×; d) epithelioid cell of JGA of kidney after 2 weeks of poisoning; enlargement of secretory granules and protogranules in cytoplasm. 11,000×.

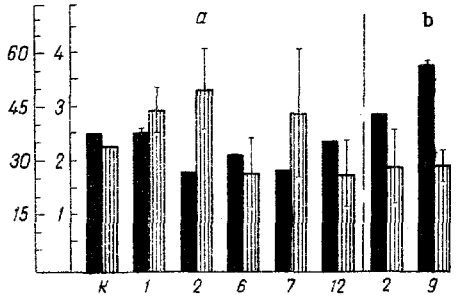

Fig. 3. Trend of diameter and number of SG of atrial cardiomyocytes during cadmium poisoning (a) and recovery period (b). Black columns — diameter of SG, vertically shaded columns — number of SG. Horizontal axis: K) control; numbers indicate times of investigation (in weeks). Ordinate, left — number of SG, right — diameter of SG ($\times 10^{-1}$).

Thus in chronic cadmium poisoning, starting with the 2nd week hypertension of the systemic circulation was observed, with hypertrophy of the left ventricular cardiomyocytes and the walls of the arterioles and arteries, with reduction of VI, and also with a sharp increase in the plasma MG concentration in the period of stable arterial hypertension. The increase in synthetic and secretory activity of the endocrine cardiomyocytes of the atria was aimed at stabilizing BP and is a secondary morphological and functional characteristic. Similar changes in the atrial cardiomyocytes also was observed in other experimental models of arterial hypertension [3]. Morphological changes in the kidneys during poisoning were characterized by the development of cadmium nephropathy, with evidence of hyperfunction of the JGA. The initial factor in the pathogenesis of cadmium-induced arterial hypertension may be considered to be the secretion of endothelin, due to the action of cadmium on the vascular endothelium [8]. The smooth muscle cells of the vascular wall are known to have specific receptors for endothelin. The mechanism of action of this endogenous vasoconstrictor peptide is linked with activation of the entry of Ca^{2+} into the cells through voltage-dependent calcium channels [11]. The rapid fall of BP during rehabilitation, and also the morphological features of recovery of the myocardium and kidneys indicate the reversible character of cadmium-induced hypertension.

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