ULTRASTRUCTURE OF COMPONENTS OF THE FUNCTIONAL UNIT OF THE ADRENAL MEDULLA IN THE EARLY PERIOD OF ENDOTOXIN SHOCK

Yu. G. Kirichenko, B. A. Saakov,
and É. A. Bardakhch'yan

UDC 576.8.097.29:612.452:616-076.4

KEY WORDS: endotoxin shock; sympathico-adrenal system; catecholamines; permeability.

The role of catecholamines in the development of endotoxin shock has frequently been studied by many workers. In particular, an increase in their plasma concentration has been found within minutes of administration of an endotoxin [3, 7]. However, changes in the ultrastructure of the adrenal medulla in response to toxins of gram-negative bacteria have not yet been investigated.

It was accordingly decided to undertake an electron-microscopic analysis of functional units of the adrenal medulla in the early period of endotoxin shock. In any organ the term functional units is given to cells which perform a specific function, connective tissue cellular and fibrous structures oriented along the microcirculatory unit, and also neural formations [1, 2].

EXPERIMENTAL METHOD

Endotoxin shock was produced in seven rabbits weighing 2-3 kg into which typhoid endotoxin was injected intravenously (5 mg/kg). Three rabbits receiving physiological saline served as the control.

Pieces of adrenal medulla, fixed in the usual way with glutaraldehyde and osmium tetroxide, were dehydrated with acetone and embedded in Epon 812 or a mixture of Epon with Araldite. Sections cut on the LKH-8800 Ultrotome were stained with uranyl acetate and lead citrate and examined in the IEM-100 electron microscope.

To facilitate the search for chromaffin tissue cells, before each series of ultrathin sections, semithin sections were cut from the same blocks.

EXPERIMENTAL RESULTS

Intravenous injection of physiological saline in doses equivalent to those in the experimental group caused virtually no change in the fine structure of the adrenal medulla.

After intravenous injection of endotoxin the chromaffin cells, performing a specific function, were evidently the most vulnerable part of the functional unit of the medulla.

The first feature to be noted was a considerable decrease in the number of electron-dense granules containing catecholamines. Despite the known mosaic character of this process, which varies in different cells, the general tendency could be discerned sufficiently clearly.

The osmiophilic dense center, included in a membrane, becomes reduced during the outflow of biologically active substances, with the result that only empty vesicles remain in its cytoplasm (Fig. 1A). Catecholamines are discharged into the blood stream not only by transendothelial transport through pinocytotic vesicles (Fig. 1B), but also on account of secretion of holocrine character. Nuclei of the chromaffin cells, which were oval or circular in shape in the control group, were often changed in animals with endotoxin shock: their membrane became convoluted and sometimes was deeply invaginated into the karyoplasm, resulting in fragmentation of the nucleus (Fig. 1C). The mitochondria were usually small and the

Central Research Laboratory and Department of Pathological Physiology, Rostov Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 10, pp. 500-503, October, 1980. Original article submitted November 29, 1979.

 0007-4888/80/9010-1464$07.50

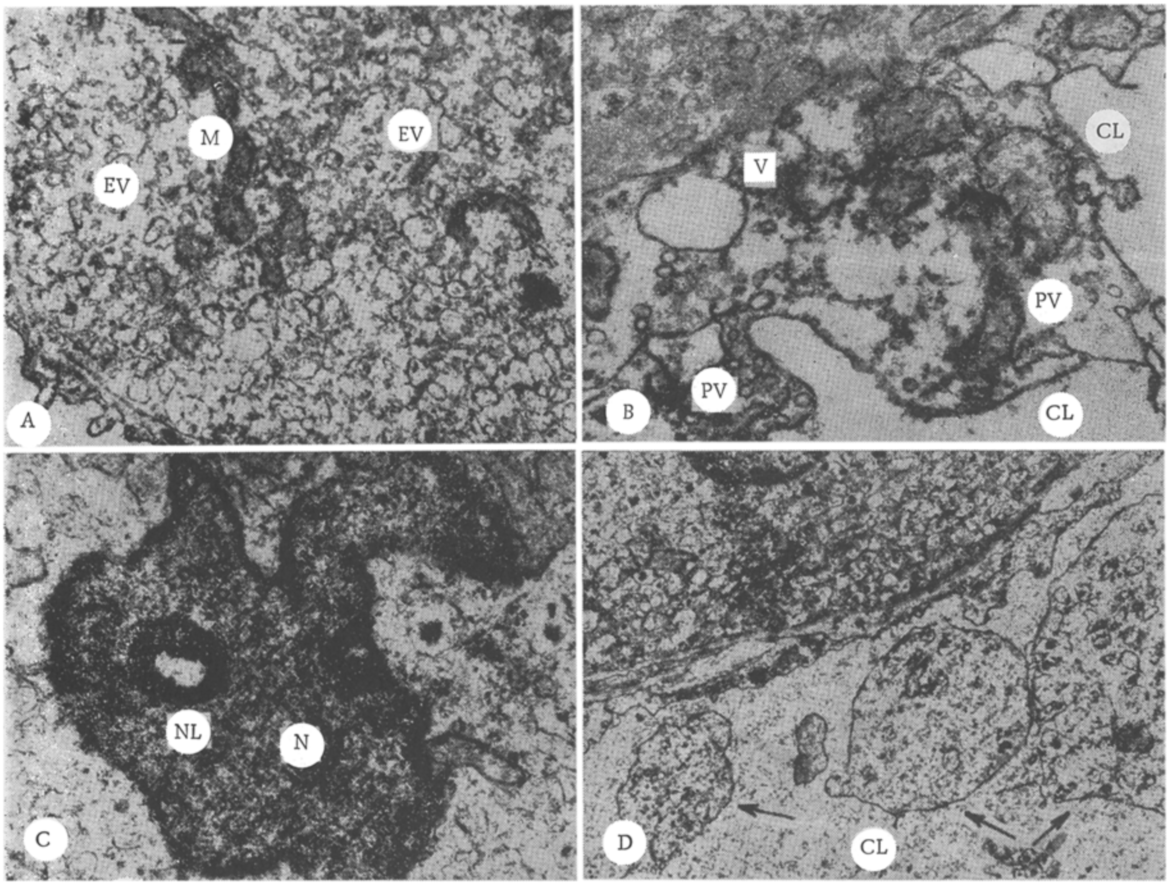

Fig. 1. Ultrastructural changes in adrenal medulla in endotoxin shock. A) Sudden discharge of catecholamines and presence of numerous empty vesicles (11,400 ×); B) vesiculation and vacuolation of endothelium (12,000 ×); C) invagination of nuclear membrane (16,000 ×); D) appearance of fragments of cytoplasm of chromaffin cells (arrows) in capillary lumen (5600 ×). M) Mitochondria, EV) empty vesicles. V) vacuoles, PV) pinocytotic vesicles, N) nucleus, NL) nucleolus, CL) capillary lumen.

cristae few in number and palely stained (Fig. 1A, C). In some cases these organelles were swollen or arranged in groups of 12-17 mitochondria.

Single granules, their membranes, and fragments of cytoplasm of chromaffin cells can be seen in the capillary lumen (Fig. 1D). It will be noted that as a result of increased permeability of the blood—adrenomedullary barrier, diapedetic hemorrhages and egress of leukocytes into the pericapillary spaces were observed. Sometimes blood cells were found completely in the parenchyma far from blood vessels (Fig. 2A).

Endotoxin shock also was accompanied by disturbances of the ultrastructure of the innervation system. In particular, in the zone of junctions between axons and chromaffin cells, where thickenings and concentrations of synaptic vesicles typical of synapses were present, the latter were relatively rare. Furthermore, myelin figures and residual bodies could be seen constantly in the axoplasm (Fig. 2B, C). Similar structures also were found in fibers of Schwann cells. It must be emphasized that the presence of osmiophilic inclusions is evidence of the development of degenerative processes of the dark type, which may be local or total in character.

The results of the electron-microscopic study of changes in the adrenal medulla thus reveal a triad of the most important disturbances in the functional units. First, ultrastructural changes were found in the cells of the medulla, where signs of mass discharge of catecholamines and corresponding structural changes in the microcirculatory unit were found, indicating increased vascular permeability. Finally, irreversible alteration of nerve fibers (degeneration of the dark type) is evidence of a disturbance of nervous regulation.

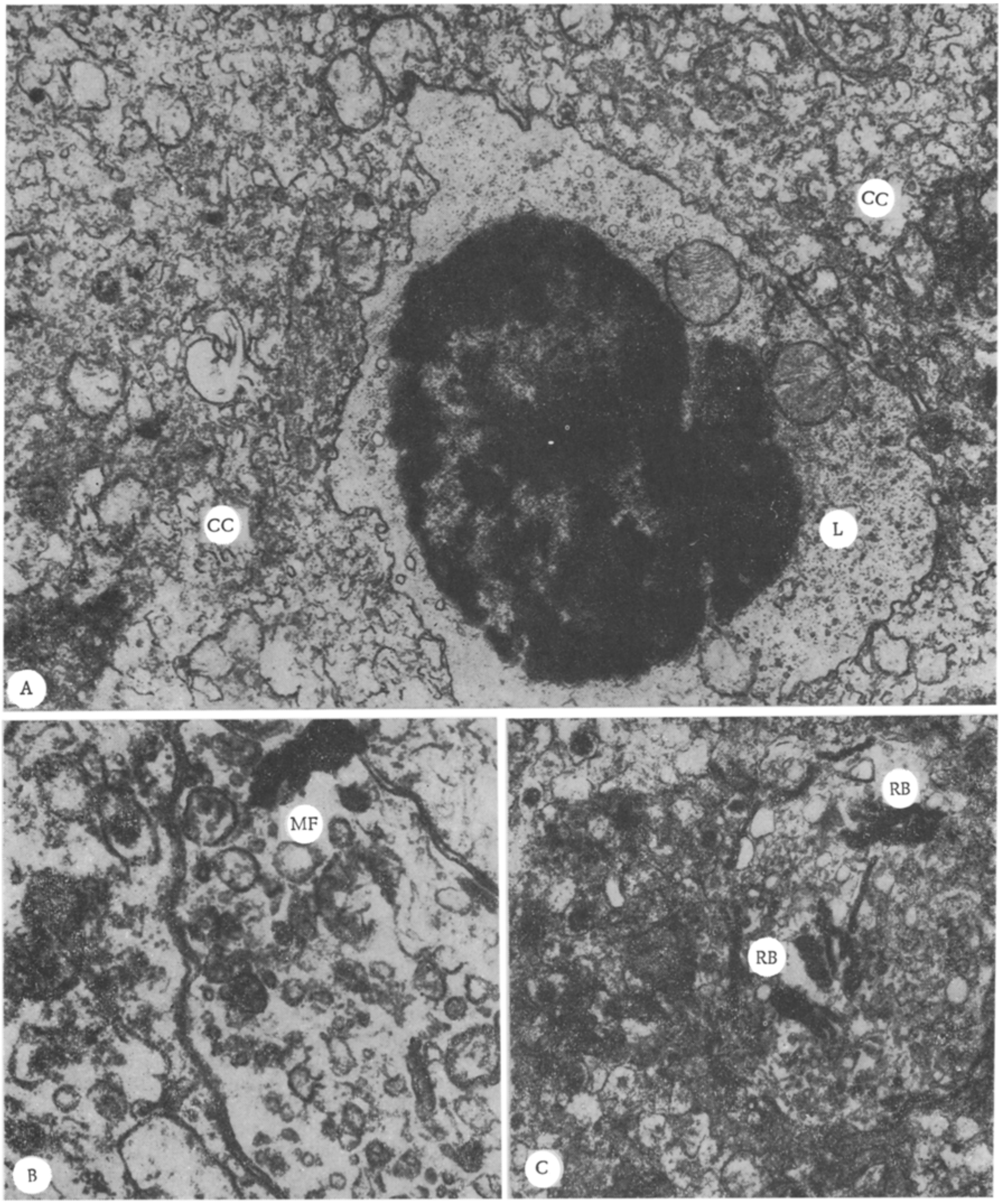

Fig. 2. Ultrastructural changes in adrenal medulla in endotoxin shock. A) Lymphocyte surrounded by chromaffin cells (16,800 ×); B) myelin figure in axoplasm of adrenergic fiber (46,000 ×); C) residual bodies in axoplasm of adrenergic fiber (22,000 ×). L) Lymphocyte, CC) chromaffin cell, MF) myelin figure, RB) residual bodies.

The results of these investigations are in agreement with data of other workers indicating that endotoxemia is accompanied by an increase in the plasma catecholamine concentration [7, 9]. It is a noteworthy fact that the adrenalin level is rapidly restored to normal, whereas the noradrenalin concentration remains high, reflecting its secretion from the adrenal medulla and sympathetic nerve endings [8].

The main stimulus for liberation of catecholamine-like substances into the blood after intravenous injection of endotoxin is considered to be the developing systemic hypotension [6]. Stasis in the blood vessels of the abdominal organs in endotoxemic shock leads to a decrease in the venous return to the heart, a decrease in reactivity to pressor agents, and an increase in ractivity to depressor substances [5]. Moreover, despite the liberation of adrenalin, the reaction of the vessels to it (especially in the postcapillary segment) is distorted and histamine-like in character [4], and this aggravates the systemic hypotension. Whatever the case, there is disparity between the circulating blood volume and the capacity of the vascular bed [3].

Of all the homeostatic mechanisms initiated by acute hypotension, the most important role is played by activation of the sympathico-adrenal system. Increased secretion of catecholamines from the adrenal medulla and of noradrenalin from the postganglionic sympathetic nerve endings is evidently the fastest and most effective mechanism of defense.

LITERATURE CITED

1. A. M. Chernukh, Patol. Fiziol., No. 4, 3 (1977).
2. A. M. Chernukh, Inflammation [in Russian], Moscow (1979).
3. D. Cavanagh, P. S. Rao, D. M. C. Sutton, et al., Am. J. Obstet. Gynecol., 108, 705 (1970).
4. L. B. Hinshaw and D. L. Nelson, Am. J. Physiol., 203, 870 (1962).
5. L. B. Hinshaw, J. A. Vick, M. M. Jordan, et al., Am. J. Physiol., 202, 103 (1962).
6. L. B. Hinshaw and C. M. Brake, J. Okla. State Med. Assoc., 57, 421 (1964).
7. P. S. Rao, B. D. Bhagat, and D. Cavanagh, Proc. Soc. Exp. Biol. (New York), 141, 412 (1972).
8. J. C. Rosenberg, R. C. Lillehei, J. Longerbeam, et al., Ann. Surg., 154, 611 (1961).
9. W. W. Sink, J. Reddin, S. J. Zak, et al., J. Clin. Invest., 45, 78 (1966).