ROLE OF THE KIDNEYS IN THE PATHOGENESIS OF LITHIUM POISONING

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Lithium poisoning was produced in rats by intraperitoneal injection of lithium chloride in a dose of 200 mg/kg (0.22 LD_{50}) daily for 6 days. Polyuria, connected with pathological changes in the epithelium of the convoluted tubules and inhibition of the antidiuretic hormone–acid mucopolysaccharides system in the zone of the straight tubules of the kidney, was observed on the sixth day of the experiment. Oliguria and death of some of the animals on the seventh day of the experiment were due to severe pathological changes in the kidney structure. Later during the experiment (30 days), besides regeneration, considerable sclerosis of the kidney tissue developed. It is concluded that severe lithium poisoning is associated with the development of acute renal failure. The functional reserves of the kidneys remained depressed for a long time after stopping the course of injections of lithium chloride.

KEY WORDS: lithium poisoning; acute renal failure.

During the treatment of effective states with lithium salts, disturbances of kidney function are observed as a serious complication [1]. Most of the lithium entering the body is known to be excreted through the kidney; more of the metal accumulates in the kidneys than in other organs [6, 9]. The state of the kidney function determines the rate of elimination of lithium, but its role in the pathogenesis of lithium poisoning has been inadequately studied.

The state of the kidneys during lithium poisoning and the reversibility of their morphological and functional disturbances were studied in view of the absence of such information in the literature [5, 7].

EXPERIMENTAL METHOD

Experiments were carried out on 62 male albino rats weighing 180–220 g. Once a day for 6 days the experimental animals received an intraperitoneal injection of a 5% solution of lithium chloride in a dose of 200 mg/kg (0.22 LD_{50}). The control animals received equal volumes of distilled water. The rats were decapitated 24 h after the first injection or 1, 7, and 30 days after the sixth injection of the compound. The kidneys were fixed in 10% formalin solution and in Carnoy's fluid and embedded in paraffin wax. Sections were cut to a thickness of 5–7 μ and stained with hematoxylin–eosin and by Mallory's method. Neutral mucopolysaccharides were detected by the PAS reaction according to McManus, and acid mucopolysaccharides by Lyson's metachromatic reaction with toluidine blue with appropriate enzyme and chemical control [2]. The state of the kidney function was judged by the usual histophysiological criteria and the diuresis [4]. The diuresis was measured in metabolism cages on the 6th and 7th days of the experiment. The rats received neither food nor water while the urine was collected.

EXPERIMENTAL RESULTS AND DISCUSSION

A single injection of lithium chloride caused moderate changes in the kidneys in the form of congestion of the glomeruli and the initial signs of cloudy swelling of the epithelium of the convoluted tubules. The brush border and basement membranes of these tubules accumulated neutral mucopolysaccharides intensively. The quantity of acid mucopolysaccharides in the medulla of the kidney, on the other hand, was appreciably reduced. The histophysiological picture was evidence of increased renal activity at this stage of the experiment.

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The capillaries of the glomeruli 24 h after the sixth injection of the compound appeared collapsed, their endothelium showed cloudy swelling, and their cell nuclei pycnosis and lysis. In the dilated spaces of the glomerular capsules an accumulation of fluid with desquamated epithelial cells and erythrocytes was found. Besides widespread cloudy swelling of the epithelium in the proximal convoluted tubules there were foci of hyaline droplets and vacuolar degeneration of the cells with pycnosis or lysis of their nuclei. The brush border of most tubules was fragmented or detached from the cytoplasm. The lumina of the tubules were irregularly widened and filled with homogeneous PAS-positive masses, among which cell nuclei with gross structural changes were seen. The changes were much more severe in the distal convoluted tubules, where over wide areas the epithelial cells were completely separated, the basement membranes torn, and the filtrate had escaped into the interstitial tissue. The medulla of the kidney was highly edematous and contained foci of hemorrhage and a greatly increased quantity of acid mucopolysaccharides. The epithelial cells of the tubules in this part were in a state of cloudy swelling and their lumina were filled with numerous casts. In some animals extensive areas of kidney tissue showed necrosis with complete disorganization of its structure.

The polyuria observed on the 6th day of the experiment (9.8 ± 0.86 ml compared with 4.0 ± 0.17 ml in the control; $P < 0.001$) was replaced on the 7th day of the experiment by oliguria (2.7 ± 0.21 ml; $P < 0.05$); one third of the experimental animals had died by the end of the seventh day from anuria.

Seven days after the end of the course of injections of lithium chloride into the rats the morphological picture of the kidneys was one of the development of active regeneration in the damaged structural elements of the organ. The lumina of the capsules and tubules of the nephrons appeared irregularly widened. Degenerative changes were observed in the epithelial cells of all parts of the nephrons. Beneath the layer of necrobiotically changed epithelial cells, small cells with indistinct boundaries, containing small amounts of neutral mucopolysaccharides in their cytoplasm and a large, hyperchromic nucleus, were observed on the basement membranes of some of the tubules. The number of mitoses in the cell nuclei of the tubular epithelium was sharply increased. The lumina of some tubules were filled with desquamated epithelium and homogeneous PAS-positive masses or shaped casts. Marked signs of edema with multiple foci of lymphocytic and histiocytic infiltrations and the initial features of sclerosis were observed in the interstitial tissue of the kidney, especially in the medulla. The quantity of acid mucopolysaccharides in the medulla was rather less than in the control.

The normal structure of most elements of the kidney was restored after 30 days. However, the considerable sclerosis of the kidney tissue and the incomplete maturation of the newly formed epithelium points to incomplete restoration of the initial morphological and functional state of the organ.

Analysis of the results suggests the following mechanisms of the toxic action of lithium on the kidney. The causes of the polyuria in the initial stage of poisoning were, first, a decrease in reabsorption in the convoluted tubules of the nephron on account of loss of the brush border and degeneration of their epithelium, and second, a decrease in reabsorption in the straight tubules as a result of reduced activity of the antidiuretic hormone–acid mucopolysaccharides system. Later, pathological changes in the glomeruli lead to a sharp decrease in renal filtration, and the developing necrosis of the epithelium of the convoluted tubules and the occlusion of their lumina by casts lead to tubulorrhexis. The escape of filtrate into the interstitial tissue, together with the vascular disorders, are responsible for its edema, for the rise in intrarenal pressure, and for the cessation of renal activity. Consequently, severe lithium poisoning ends with the development of acute renal failure. This may explain the increase in toxicity of lithium chloride when it is given in conjunction with diuretics [6]. For the reasons given above the administration [8, 10] of diuretics to increase diuresis and so accelerate the elimination of lithium from the body is, in the writers' view, hard to justify. It would be more rational to use more physiological methods of detoxication whose effectiveness as a means of accelerating the excretion of toxins by the kidney rests on a firm experimental basis [3].

It can accordingly be concluded from these results that severe lithium poisoning is associated with the development of acute renal failure. The functional reserves of the kidneys remained depressed for a long time after the course of injections of lithium chloride had ceased, and this must be taken into account when the strategy of future treatment with lithium salts is chosen.

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EFFECT OF FETAL HYPOXIA AND HYPEROXIA ON GROWTH AND FUNCTIONAL ACTIVITY OF THE ADRENAL CORTEX

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The content of lipids, cholesterol, and ascorbic acid in the adrenal cortex was investigated in rabbit fetuses developing under conditions of normal gestation and during exposure in the last third of pregnancy to hypoxia and hyperoxia. During exposure to hypoxia (of moderate degree) activation of the adrenal cortex was reflected by a marked decrease in the content of lipids, cholesterol, and ascorbic acid. The total weight of the fetal muscle mass was increased under these circumstances. During exposure to hyperoxia the adrenal cortex was inactivated, as reflected in a marked increase in the content of the above-named substances. The total weight of the fetal muscle mass was reduced.

KEY WORDS: fetus; growth; adrenal cortex; motor responses; hypoxia; hyperoxia.

Investigations in the writers' laboratory have shown that, during fetal life, growth and formation of the body take place under conditions of natural physiological stress, brought about by episodic deficiencies in the supply of nutrients and oxygen on account of the limited area of the placental surface [1-6]. Acute experiments have shown that the fetus responds to the production of moderate maternal hypoxia by generalized movements of increased intensity and frequency, whereby the necessary supply of nutrients and oxygen is maintained to the fetal blood, whereas during inhalation of a gas mixture with a high oxygen concentration, these generalized movements are inhibited or even disappear completely [2, 3]. Other investigations in the laboratory have shown that motor responses of the developing organism stimulate anabolism, resulting in an increase not only in the mass of the skeletal muscles, but also correspondingly in other systems of organs [2-4, 6].

The object of this investigation was to study the features distinguishing adrenal growth and function in fetal rabbits exposed during the last third of pregnancy to the action of hypoxia or hyperoxia. Fetal adrenocortical activity in rabbits is known to be controlled by the hypothalamic–pituitary system at the beginning of the fetal period [5, 7].

EXPERIMENTAL METHOD

The state of adrenocortical function was assessed from the content of chemical substances participating in steroid production in the glands: lipids, cholesterol, and ascorbic acid. Histochemical methods of determination were used: lipids by Sudan Black B and Sudan IV, cholesterol by means of the polarization microscope, and ascorbic acid by Backhus' method. The oxygen supply to the fetal blood was reduced by exposure

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