MORPHOLOGY AND PATHOMORPHOLOGY

Morphofunctional Changes in the Kidneys in Chronic Endotoxemia against the Background of Hypothyroidism

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We studied morphological structure of the kidneys in chronic endotoxemia modeled against the background of hypothyroidism. The detected changes did not differ from those under conditions of basic endotoxemia model and were characterized by the development of glomerulosclerosis and glomerulohyalinosis. The changes were less severe in rats with hypothyroidism and appeared at the late terms of the experiment. This indicated a moderate protective effect of preexisting thyroid hormone deficiency.

Key Words: *hypothyroidism; hormonal dysregulation; kidney; endotoxemia*

Adaptive reaction to destructive environmental factors depends on the hypothalamic-pituitary-thyroid status. Hormonal activity of the thyroid gland is largely determined by the nature, type, and intensity of exposure [2,8,9]. Thyroid hormone deficiency is associated with inhibition of renal blood flow and impairment of renal filtration, tubular reabsorption, and secretory functions [1,3].

Hyperthyrosis preceding the development of endogenous intoxication augments renal injury by endogenous toxic compounds and stimulates the development of the nephrotic syndrome [4]. Specific features of the renal injury in chronic endotoxemia (ET) under conditions of thyroid hormone deficiency were virtually never studied.

We studied the changes in the renal morphology and functions in chronic ET under conditions of hypothyroidism.

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MATERIALS AND METHODS

The study was carried out on 66 outbred male rats. Chronic ET with predominant involvement of the kidneys was induced in 18 animals by daily intraperitoneal injections of gentamicin (nephrotoxic antibiotic; 20 mg/kg). On day 6, the animals received an additional intraperitoneal injection of LPS (0.2 μg/kg). Day 7 was free from manipulations. The formation of ET was verified by biochemical markers of endogenous intoxication (increase of plasma concentrations of medium molecular weight substances (MMWS), oligopeptide fraction, and MDA concentration). Hypothyroidism was modeled by oral thiamasole (antithyroid drug; 20 mg/kg/day) for 5 days followed by maintenance doses 5 mg/kg/day [5]. The group with hypothyroidism alone consisted of 15 animals. Endotoxemia was created as described above in 18 rats with hypothyroidism. Control group consisted of 15 intact animals. Animals of all groups were sacrificed by Nembutal overdosage on days 30, 60, and 90.

Morphology of the renal tissue was studied in paraffin preparations stained with hematoxylin and eosin [6,7]. Morphometric analysis of histological prepara-

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tions included evaluation of the volume percent of the connective tissue, urinary space index (proportion of Shumlyansky–Bowman's capsule area/glomerular capillary area, arb. units), tubular index (tubular outer/lumen diameter, arb. units), and percentage of sclerotic glomeruli.

Serum levels of thyroid stimulating hormone (TSH), triiodothyronine, and thyroxin were measured by ELISA using Vector-Best and DRG kits. The results were statistically processed by Excel 7.0 and ARKADA software.

RESULTS

Simulation of hypothyroidism in animals led to changes in serum thyroid hormone profiles. The maximum reduction of peripheral hormone (thyroxin and triiodothyronine) levels was recorded in 90 days of experimental ET created under conditions of hypothyroidism. Changes in the thyroid indicating suppression of its functional activity served as morphological substrate of the thyroid imbalance. The thyroid in isolated hypothyroidism and in chronic ET with hypothyroidism had large follicular structure. The epithelium consisted of cubical cells with elongated nuclei oriented along the greater axis parallel to the basal membrane. Appreciable amounts of compact colloid without marginal vacuolation were found in the follicular lumen.

In chronic ET without previous thyroid imbalance, the morphological changes in the thyroid by the end of the experiment (day 90) were characterized by more intense proliferation of the follicular and intrafollicular epithelium, signs of micro- and macrofollicular transformation, and greater volume fraction of the stroma.

Biochemical analysis of the serum showed less severe endogenous intoxication in rats with the underlying hypothyroidism than in rats with the basic ET model (without hormone imbalance). On day 90, plasma concentration of MMWS in animals with ET was 3.64 times higher ($p<0.05$) than in controls. In rats with ET and underlying hypothyroidism this parameter was 1.9 times higher than in the controls at the end of experiment (Fig. 1). Similar data were obtained for oligopeptide fraction and MDA.

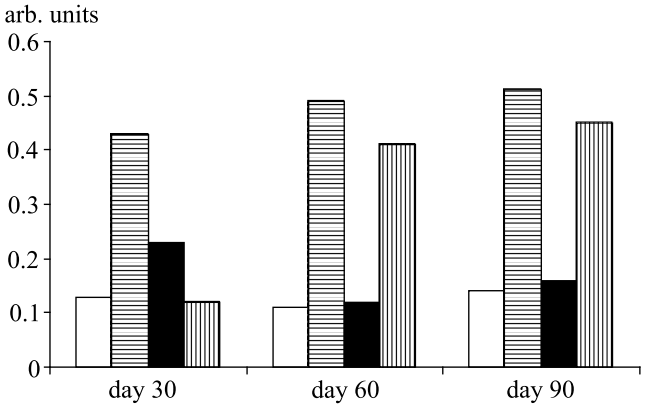

Fig. 1. Time course of MMWS in peripheral blood serum in experimental animals. Light bars: intact rats; horizontal cross-hatching: ET; dark bars: hypothyroidism; vertical cross-hatching: hypothyroidism+ET.

Morphological changes in the renal tissue in animals with the basic chronic ET model were characterized by the development of nephropathy. Signs of reversible and irreversible lesions, necrosis of some nephrocytes were found on day 30. Lymphohistiocytic infiltration of the glomeruli and the periglomerular zone, circulatory disorders (paretic dilatation of the vessels and development of leukostasis) were found after 60 days. The lesions and necrosis of tubular epithelium were paralleled by connective tissue growth; fibrosis foci were located mainly perivascularly. By day 90, the connective tissue foci were seen far from the peritubular arterioles.

The changes were less severe in ET with underlying hypothyroidism than in the classical ET model.

TABLE 1. Morphometric Values of Renal Tissue ($M\pm m$)

Group; time after ET induction		Volume percent of interstitial tissue	Urinary space, arb. units	Tubular index, arb. units	Sclerotic tubules, %
Control		7.2±0.4	1.4±0.1	0.8±0.1	0
LPS+gentamicin (basic model)	day 30	9.2±0.9	1.2±0.1	1.6±0.2*	8.0±0.3*
	day 60	14.5±1.3*	1.2±0.1	0.6±0.1	8.9±0.9*
	day 90	19.7±4.4*	1.1±0.6*	0.5±0.1*	9.3±1.4*
Hypothyroidism	day 30	10.7±0.9*	1.4±0.1	1.1±0.1	1.20±0.09*+
	day 60	11.3±0.9*	1.2±0.2	0.9±0.1	1.90±0.01*+
	day 90	11.7±0.1*+	1.2±0.1	0.9±0.1+	3.10±0.01*+

Note. $p<0.05$ in comparison with *control, +basic model.

Vacuolation of the nephrocyte cytoplasm was found on day 30, scanty lymphohistiocytic infiltration after 60 days. Signs of the proximal tubular epithelial lesions and slight fibrosis of the renal tissue were detected on day 90 of experiment.

Morphometric analysis of histological preparations at the end of experiment showed a 1.6 and 2.7 times lesser connective tissue increment in rats with chronic ET induced in the presence of hypothyroidism in comparison with the basic ET model (Table 1).

The tubular index of rats with ET and underlying hypothyroidism virtually did not differ from that of control rats throughout the entire experiment. The number of sclerotic glomeruli in rats with chronic ET and underlying hypothyroidism was 3-fold less than in animals with the basic chronic ET model ($p<0.01$).

Hence, morphologic changes in the kidneys in chronic ET induced under conditions of hypothyroidism did not differ from the lesions in basic ET model and were characterized by the development of glomerulosclerosis and glomerulohyalinosis. The changes in rats with hypothyroidism were less pronounced and developed during later periods of experiment, indicating a moderate protective effect of previous thyroid hormone deficiency.

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