ROLE OF THE KALLIKREIN–KININ SYSTEM OF THE KIDNEYS IN SODIUM AND WATER TRANSPORT AND ITS MODIFICATION BY INDOMETHACIN

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Direct correlation was found in intact rats between the kallikrein activity of the urine, on the one hand, and the diuresis, sodium excretion, and ability of the kidneys to concentrate the urine on the other hand. Small doses of indomethacin (2 mg/kg for 5 days) increased the kallikrein activity of the urine fourfold and, at the same time, increased the diuresis; large doses (5 mg/kg for 5 days) lowered the kallikrein activity of the urine and halved the diuresis, reduced the sodium excretion by two-thirds, and depressed the ability of the kidneys to concentrate the urine. Indomethacin may perhaps modify the synthesis not only of prostaglandins, but also of kallikrein, and this is reflected in the state of the kidney function.

KEY WORDS: *kallikrein of the urine; indomethacin; excretion of sodium and water; concentration of the urine.*

Kinins formed in the kidneys by the action of the enzyme kallikrein increase sodium and water excretion by increasing the medullary blood flow. Kinins can also affect the transport of sodium and water through the stimulation of synthesis of the renal prostaglandins [5-7].

It was decided to study the excretion of sodium and water by the kidneys under conditions of depression of prostaglandin synthesis by indomethacin and also to determine its effect on the renal kallikrein–kinin system (RKKS), for anti-inflammatory drugs inhibit the effect of kinins [2].

EXPERIMENTAL METHOD

Male Wistar rats weighing 120-150 g were subdivided into three groups: 1) control (20 intact animals), 2 and 3) rats receiving indomethacin by mouth for 5 days in doses of 2 mg/kg

TABLE 1. Excretion of Kallikrein with the Urine and Some Indices of Kidney Function in Rats Receiving Indomethacin

Index studied	Control	Indomethacin			
		2 mg/kg	P	5 mg/kg	P
		M±m		M±m	
Kallikrein excretion, KU/h	2,06±0,19	8,78±0,78	<0,002	1,25±0,22	<0,05
Diuresis, ml/h	1,4±0,1	2,15±0,23	<0,01	0,84±0,1	<0,01
Sodium excretion, meq/h	0,095±0,011	0,1±0,017	>0,1	0,031±0,007	<0,02
Potassium excretion, meq/h	0,041±0,005	0,09±0,0048	<0,001	0,04±0,0002	>0,1
Osmolarity of urine, mosm/liter	485±22,32	463,7±31,1	>0,1	337,8±19,4	<0,001
Osmotic gradient	1,8±0,1	1,8±0,11	—	1,3±0,098	<0,05
Clearance of osmotically free water	—1,04±0,11	—1,28±0,14	>0,1	—0,317±0,05	<0,01

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TABLE 2. Correlation between Level of Kallikrein Excretion and Some Indices of Kidney Function

Index studied	Control		Indomethacin			
			2 mg/kg		5 mg/kg	
	r	P	r	P	r	P
Kallikrein in urine/diuresis	+0,7	<0,025	+0,78	<0,025	+0,92	<0,001
Kallikrein in urine/sodium excretion	+0,64	<0,01	0	—	+0,76	<0,005
Kallikrein in urine/osmotic gradient	−0,67	<0,025	0	—	−0,82	<0,001

Legend. 0) Absence of correlation.

and 5 mg/kg (10 rats in each group). Urine was collected for 3-4 h on the fifth day of the experiment. The kallikrein activity of the urine was investigated by measuring the hydrolysis of benzoyl-arginine-ethyl ester and expressed in conventional kallikrein units (KU) [1]. The osmotic concentration of the plasma and urine was determined by a cryoscopic method.

EXPERIMENTAL RESULTS

The values obtained for the osmotic concentration of the urine, the clearance of osmotically free water, and the osmotic gradient indicated that the ability of the kidneys of the control rats to concentrate urine was good (Table 1). The diuresis and sodium excretion of the control animals were directly and closely dependent on the kallikrein excretion with the urine, evidence of the role of the RKKS in sodium and water transport. A reciprocal and close relationship was found between the kallikrein excretion and the osmotic gradient. The latter is known to be inversely proportional to the level of the medullary blood flow, indirect evidence that an increase in activity of the RKKS leads to an increase in the blood flow in the renal medulla.

Administration of indomethacin in a dose of 2 mg/kg body weight caused marked activation of the RKKS, as shown by the fourfold increase in the excretion of kallikrein with the urine. Meanwhile, in these animals the diuresis and the excretion of potassium with the urine increased considerably. The ability of the kidneys to concentrate the urine and to excrete sodium was unchanged. Increasing the dose of indomethacin to 5 mg/kg caused a considerable decrease in the excretion of kallikrein with the urine and in the diuresis and sodium excretion. At the same time the ability of the kidneys to concentrate the urine was reduced, as shown by the fall in its osmolarity and in the osmotic gradient, despite the increase in the clearance of osmotically free water. After administration of large doses of indomethacin correlation remained only between the excretion of kallikrein and the diuresis, whereas the excretion of sodium with the urine and the ability of the kidneys to concentrate the urine no longer depended on the level of excretion of kallikrein by the kidneys (Table 2).

The RKKS is thus closely bound with sodium and water transport in the kidneys and affects the ability of the kidneys to concentrate the urine. The action of kinins on these indices of kidney function is evidently mediated chiefly through a change in the medullary blood flow. Indomethacin, which inhibits prostaglandin synthesis, changes the state of the RKKS. Its activity increases after small doses of the drug and decreases after larger doses. The increase in the kallikrein excretion with the urine could be the result of an increase in its synthesis in the kidneys under the direct influence of small doses of indomethacin or a compensatory reaction to depression of the effect of kinins. There is evidence in the literature that the action of kinins is blocked by anti-inflamatory agents [2]. Large doses of indomethacin depress kallikrein synthesis in the kidneys, just as they depress the synthesis of renal prostaglandins.

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DISTRIBUTION OF RADIOACTIVE CORTISOL IN THE TISSUES AND MEDIA OF THE EYE

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Incorporation of cortisol-^{3}H and the dynamics of its accumulation in the tissues and media of the eye (sclera, ciliary body, cornea, iris, capsule of the lens, aqueous humor, vitreous body) were investigated. The intensity of incorporation of cortisol into the tissues and media of the eye and also the rate of its elimination from them were shown to differ. The sclera, cornea, ciliary body, and the capsule of the lens were shown to be target tissues for cortisol.

KEY WORDS: *target tissues for hormones; specific receptors; cortisol; eye.*

Hormones regulate the activity of the organs and tissues and affect the biochemical indices and processes in cells and subcellular structures [6-8]. Certain hormones have target tissues and organs in the body, which respond specifically to their action by changes in the activity of their metabolic enzymes. Evidence has recently been published on the effect of corticosteroids on the enzyme activity of some tissues of the eye [1-3] and of the incorporation of labeled steroid hormones into the retina [4, 5, 10] and lens [9].

The distribution, dynamics of accumulation and elimination, and also the specificity of the binding of cortisol-^{3}H in the various tissues of the eye were studied in the investigation described below in order to determine whether they are target tissues for the action of this hormone. The incorporation of the hormone into the sclera, cornea, ciliary body, iris, capsule of the lens, aqueous humor, and vitreous body was determined.

EXPERIMENTAL METHOD

Experiments were carried out on 50 male chinchilla rabbits weighing 1-2.5 kg. In experiments *in vivo* cortisol was injected intraperitoneally in a dose of $0.13 \cdot 10^{-3}$ mole/kg (60 μCi/kg). The animals were killed at various times (5 and 10 min; 1, 2, 4, and 24 h) after injection of the hormone. The tissues were removed in the cold and homogenized in 85% formic acid during heating (except the vitreous body and aqueous humor). Samples (0.2 ml) of the homogenates were taken and added to special flasks containing 5 ml of toluene–alcohol scintillator. The radioactivity in the sample was counted by means of the Mul'tim-212 liquid scintillation counter.

Accumulation of the hormone in the tissues and media of the eye was expressed in counts/min/g tissue.

In the experiments *in vitro* the tissues were incubated in medium containing $2.5 \cdot 10^{-6}$ M cortisol-^{3}H and 0.001 M EDTA (pH 7.4) at 37°C. The same manipulations were then carried out with the tissues as in the experiments *in vivo*, and they were homogenized after incubation for various times (from 5 min to 24 h).

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