KALLIKREIN–KININ SYSTEM OF THE KIDNEYS AND ITS ROLE IN VARIOUS MECHANISMS OF DIURESIS

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Water and salt loading and administration of frusemide increase the activity of the kallikrein–kinin system of the kidneys in rats. Direct correlation was found between kallikrein excretion, diuresis, and clearance of "osmotically free water" during water and osmotic diuresis. The greatest excretion of kallikrein by the kidneys was recorded during the "escape" phenomenon after salt loading. In osmotic diuresis the kallikrein excretion correlates directly with sodium excretion. The role of the kallikrein–kinin system in the regulation of diuresis, of sodium excretion, and of the ability of the kidneys to concentrate the urine is discussed.

KEY WORDS: mechanisms of diuresis; kidneys; kallikrein–kinin system.

Water and osmotic diuresis is accompanied by changes in the intrarenal hemodynamics and by hormonal changes determining the level of glomerular filtration and tubular reabsorption of sodium and water. One of the factors concerned in the regulation of the intrarenal hemodynamics and in sodium and water transport is the kallikrein–kinin system of the kidneys (KKSK), activation of which leads to the liberation of biologically active substances (kinins) [2-4, 7, 8].

The object of this investigation was to study the role of the KKSK in the mechanisms of water, osmotic, and salt diuresis.

EXPERIMENTAL METHOD

Male Wistar rats were used. Twenty intact animals served as the control. Twelve rats received 5 ml water/100 g body weight as a single injection by gastric tube. Six rats were given 1% NaCl solution to drink for 4 weeks. The urine of the animals was tested in the 2nd and 4th weeks of the experiment. Twelve rats received a single intraperitoneal injection of frusemide in a dose of 2 mg/100 g body weight. Urine was collected from rats receiving water and frusemide in metabolism cages during the first 2 h of the experiment at the time of maximal diuresis. Urine was collected from the rats of the other groups over a period of 3-4 h. The state of the KKSK was assessed from the kallikrein activity, determined as the rate of hydrolysis of benzoylarginine–ethyl ester [1]. The kallikrein activity was expressed in conventional units. Na^+ and K^+ were determined by flame photometry and the osmotic concentration of water by a cryoscopic method.

EXPERIMENTAL RESULTS

In the control animals (Table 1), on a standard diet (pellets) and unrestricted fluid intake, direct correlation was found between the kallikrein excretion and diuresis ($r = +0.70$; $P < 0.025$) and also sodium excretion ($r = +0.64$; $P < 0.01$). This is possible evidence of the role of KKSK in sodium and water transport. The negative correlation between the kallikrein excretion and concentration coefficient ($r = -0.67$; $P < 0.01$) may indicate that the KKSK is connected with the medullary blood flow in the kidneys [2, 6].

During water loading the diuresis increased in the rats mainly through the excretion of "osmotically free water." Sodium excretion was reduced. The urine excreted was more hypotonic than plasma; the osmotic concentration of the urine and the concentration coefficient were much lower than in the control, whereas the

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TABLE 1. Excretion of Kallikrein with the Urine and Indices of Renal Function in Rats in Various Loading Tests

Index	Control	Water loading		NaCl loading				Administration of frusemide	
				2 weeks		4 weeks			
	$M \pm m$	$M \pm m$	P	$M \pm m$	P	$M \pm m$	P	$M \pm m$	P
Kallikrein excretion, k.u./h	2,06±0,19	5,85±1,08	<0,01	10,09±0,22	<0,001	14,73±1,35	<0,001	10,59±1,66	<0,001
Diuresis, ml/h	1,4±0,10	3,23±0,56	<0,01	0,3±0,05	<0,001	1,30±0,27	>0,1	2,58±0,19	<0,001
Sodium excretion, meq/h	0,095±0,011	0,044±0,005	<0,01	0,11±0,05	>0,1	0,31±0,046	<0,001	0,26±0,02	<0,001
Potassium excretion, meq/h	0,041±0,005	0,03±0,005	>0,1	0,06±0,019	>0,1	0,06±0,02	>0,1	0,08±0,008	<0,02
Osmolarity of urine, milliosmoles/liter	485±22	149±29	<0,001	1222±131	<0,001	1163±132	<0,001	293±7	<0,001
Concentration coefficient	1,8±0,10	0,5±0,07	<0,001	4,2±0,44	<0,001	3,5±0,61	<0,001	1,01±0,33	<0,001
C_{water}	−1,04±0,11	+1,74±0,33	<0,001	−1,11±0,34	>0,1	−3,82±0,28	<0,001	−0,01±0,0075	<0,001

TABLE 2. Correlation between Kallikrein Excretion with the Urine and Indices of Renal Function Relative to Different Mechanisms of Diuresis

Correlating indices	Water loading H_2O		NaCl loading			Administration of frusemide	
			2 weeks	4 weeks			
	r	P	r	r	P	r	P
Kallikrein in urine/diuresis	+0,84	<0,01	—	+0,68	<0,1	+0,81	<0,001
Kallikrein in urine/sodium excretion	—	—	—	+0,97	<0,05	+0,80	<0,001
Kallikrein in urine/concentration coefficient	—	—	—	+0,94	<0,05	−0,88	<0.001
Kallikrein in urine/C_{water}	+0,91	<0,001	—	−0,71	<0,05	+0,73	<0,02

clearance of "osmotically free water" (C_{water}) became positive. The excretion of kallikrein was doubled during water diuresis, indicating moderate activation of KKSK. Direct correlation was found between kallikrein excretion, diuresis, and C_{water} (Table 2).

During chronic salt loading the animals developed osmotic diuresis with an increase in osmolarity and in the concentration coefficient of the urine by more than 2.5 times. Meanwhile the kallikrein excretion with the urine rose sharply. After 2 weeks the rats' kidneys were not yet adapted to the new conditions of water and salt balance. Retention of Na^+ in the body was observed (its excretion with the urine was the same as in the control), but the diuresis was considerably reduced. A phenomenon of "escape" developed after 4 weeks: The Na^+ excretion was increased threefold and, at the same time, the reabsorption of water in the distal tubules was increased in order to prevent dehydration of the animal.

The excretion of kallikrein with the urine at this period was maximal and was seven times higher than in the control. This could indicate a role of the KKSK in the development of the phenomenon of "escape" of the kidneys from overloading with Na^+. At these times of salt loading correlation was restored between the kallikrein excretion, diuresis, and sodium excretion to the level found in the control animals, but absent in the second week of salt loading. The osmotic indices of the urine in the rats of this group were those characteristic of osmotic diuresis associated with relative hydropenia and increased secretion of antidiuretic hormone. The kallikrein concentration in the urine correlated directly with the concentration coefficient and inversely with C_{water}.

Intraperitoneal injection of frusemide caused a marked increase in Na^+ excretion (three times the control level). The diuresis also was increased as the result of a marked decrease in reabsorption of water. Virtually no osmotic concentration of the urine took place because of the sharp decrease in Na^+ reabsorption in the loop of Henle. In this type of diuresis the kallikrein excretion was increased fivefold. Close positive correlation was found between the kallikrein in the urine, the diuresis, and sodium excretion, but negative correlation between the kallikrein and concentration coefficient in the urine.

The KKSK thus takes part in the regulation of excretion of Na^+ and water and it also influences the ability of the kidney to increase the osmotic concentration of the urine. Kallikrein is known to be synthesized in the cortex of the kidneys [9]; its synthesis can be activated by a change in the osmolarity of the peritubular space and in the interstitial pressure in the kidneys [4, 6]. The effect of the kinins on renal activity may be due to vasodilatation and an increase in the medullary blood flow, to direct action on Na^+ reabsorption by the epithelium of the tubules and, finally, to a change in the synthesis, secretion, and influence of other compounds, notably vasopressin and the prostaglandins [3-5, 7].

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EFFECT OF ERYTHROCYTE BREAKDOWN PRODUCTS ON STEM CELLS AND ERYTHROPOIETIN FORMATION

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In experiments on CBA mice and albino rats the effect of erythrocyte breakdown products (EBP) on the number of colony-forming units (CFU), differentiation of stem cells, and erythropoietin production was studied. After three or four injections of EBP to normal or lethally irradiated (1000 rad) mice, no changes in the number of CFU or in differentiation of the stem cells were observed after transplantation of bone marrow. Daily administration of EBP to mice for 3 days before irradiation (1000 rad) and bone marrow transplantation led to an increase in the number of colonies in the recipients' spleen, mainly on account of colonies of erythroid type. Injection of EBP into the animals did not change the erythropoietic activity of the blood serum. The possible role of EBP in the mechanism of autoregulation of erythropoiesis is discussed.

KEY WORDS: erythrocyte breakdown products; stem cells; erythropoietin.

The stimulating action of erythrocyte breakdown products (EBP) on erythropoiesis can now be taken as proven [3, 4, 6, 8, 11-13]. However, the mechanism of this stimulating action of the erythrocyte breakdown products is not clear. Some workers postulate that their effect is mediated through increased formation of erythropoietins [2, 8, 13]. A direct stimulating action of EBP on the proliferation of bone marrow erythroblasts also has been suggested [1, 2, 4, 5, 12].

Some aspects of the mechanism of action of EBP on erythropoiesis, notably their effect on hematopoietic stem cells, and also on erythropoietin production were studied in this investigation.

EXPERIMENTAL METHOD

Experiments were carried out on CBA mice weighing 20-25 g and on albino rats weighing 100-150 g. EBP were obtained from erythrocytes of these animals by washing, hemolysis with distilled water (1 volume erythrocytes + 3 volumes water), and freezing and thawing three times. Homologous EBP were injected intraperitoneally in a dose of 1 ml into rats and 0.2 ml into mice.

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