MECHANISM OF ACTION OF NEPHRONS FUNCTIONING IN CHRONIC RENAL FAILURE

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On the average an increase in the excretion of osmotically active substances, sodium, potassium, hydrogen, and ammonia by each nephron was found in 104 patients with chronic renal failure. The urea clearance, osmotic dilution, and concentration of the urine in the nephrons were disturbed to an extent which could not be explained by their high osmotic load. Examination of the increased excretion of these substances as a form of adaptation to the reduced number of nephrons revealed very marked insufficiency of the adaptations as a whole and differences in the adaptation of an individual function and, in particular, of different functions. Various disorders of several functions of the nephrons were found in chronic renal failure, reflecting the considerable functional heterogeneity of these structures.

There are at present two basic conceptions of the state of nephrons functioning in chronic renal failure (CRF). According to one of them, based on the results of morphological research, nephrons showing heterogeneous changes function in CRF [12]. According to the "intact nephron" hypothesis, accepted nowadays by most nephrologists [4, 6, 7, 9, 10, 13, 14], however, the activity of the kidney in CRF is carried on by a sharply reduced number of normal nephrons and the damaged nephrons play no part in urine formation.

The importance of this problem, together with some observations which contradict the "intact nephron" hypothesis [3, 16], justified further investigations in this direction.

EXPERIMENTAL METHOD

A group of 104 patients aged from 13 to 58 years, in whom CRF developed as the result of chronic inflammatory diseases of the kidneys, was studied. The urea concentration in the blood plasma varied between 39 and 468 mg % (mean 196 mg %); the creatinine concentration varied from 2.8 to 25.2 mg % (mean 9.5 mg %). The mean endogenous creatinine clearance was 9.36 ml/min. No patients with evidence of severe toxic changes from uremia were studied. A control group consisted of 25 patients aged from 16 to 40 years with functionally compensated diffuse diseases of the kidneys.

For not less than 3 days before the beginning of the investigation all patients received 20-25 g protein and not more than 20-25 meq sodium daily.

The excretion of hydrogen ions and ammonia was determined during existing metabolic acidosis. If the spontaneous decrease of the standard bicarbonate did not reach 18 meq/liter, acute acidosis was induced by the oral administration of ammonium chloride. In that case the antiacidotic function of the kidneys was determined by the method of Wrong and Davies [18]. Maximal reabsorption of "osmotically free" water was determined after dehydration for 18 h. The clearance of "osmotically free" water, the excretion of potassium and sodium ions, and the urea clearance were determined against the background of water diuresis induced by oral administration of water (20 ml/kg body weight) and was maintained throughout the period of investigation (2 h).

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TABLE 1. State of Certain Functions in Nephrons Working in CRF and in Functionally Compensated Diseases of the Kidneys (M ± m)

Function (calculated per 100 ml glomerula filtrate)	In functionally compensated diseases of the kidneys	In CRF	P
Excretion of osmotically active substances (in μosmoles/min)	380.0 ± 80.0	4517 ± 507	< 0.01
Sodium excretion (in μeq/min)	72.2 ± 9.8	496.5 ± 54.7	< 0.01
Potassium excretion (in μeq/min)	91.1 ± 9.7	486.6 ± 39.3	< 0.01
Excretion of hydrogen ions (in μeq/min)	61.8 ± 1.4	194.9 ± 13.3	< 0.01
Excretion of ammonium ions (in μeq/min)	31.5 ± 0.9	46.4 ± 3.8	< 0.01
Urea clearance (in ml/min)	54.1 ± 3.8	53.4 ± 4.6	< 0.8
Clearance of osmotically free water (in ml/min)	7.32 ± 0.68	5.25 ± 0.41	< 0.01
Reabsorption of osmotically free water (in ml/min)	0.68 ± 0.19	−0.47 ± 0.23	< 0.01

TABLE 2. Adaptation of Some Functions in Working Nephrons in CRF to a Reduced Mass of Functioning Nephrons (in %)

Degree of adaptation	Potassium excretion	Sodium excretion	Excretion of hydrogen ions	Excretion of ammonium ions
No adaptation	8,2	14,7	16,8	80,5
		P<0,01		
<50	P<0,01		P<0,01	
	61,5	34,6	80,0	20,2
		P<0,01		
			P<0,01	
		P<0,01		
50—99	24,6	26,0	3,7	—
		P<0,01		
100 or more	5,4	23,8		
	P<0,05			

Note: Adaptation (in %) was calculated as the ratio of the function performed by the total renal parenchyma in CRF to the value of the same function performed by the normal mass of healthy nephrons (× 100).

Since a definite mean volume of glomerula filtrate is always formed by an equal number of nephrons [4, 6, 7, 9, 10], the state of a particular function in each acting neuron was judged from that magnitude of the function studied which could be carried out by the mass of functioning nephrons (MFN) forming 100 ml of glomerula filtrate in 1 min. The glomerula filtrate was determined from the endogenous creatinine clearance [5] and in some patients from the mannitol clearance [17]. The urea concentration in the urine and blood was measured by a micromethod [8] and ammonia and titratable acids in the urine were determined by the method of Bulbuca et al. [1]. The osmolarity of the urine and blood plasma was measured by a cryoscopic method [2] and the potassium and sodium concentrations in the urine and blood plasma by flame photometry.

EXPERIMENTAL RESULTS

A marked osmotic diuresis (the excretion of osmotically active substances was increased by 12 times), an increase in the excretion of sodium (by about 7 times), potassium (by more than 5 times), hydrogen ions (by more than 3 times), and ammonium ions (by 1.5 times), and a decrease in the clearance of osmotically free water after water loading were discovered in CRF on the average in each functioning nephron (Table 1). The mean reabsorption of osmotically free water against the background of dehydration was so sharply reduced in CRF that it actually became negative, indicating the excretion of osmotically free water. This could be due to a severe disturbance of permeability of the nephron wall, starting from the distal tubules. The mean urea clearance in each nephron in CRF was normal. Another characteristic feature of CRF was a sharp increase in the variability of all the renal functions examined: the ratio between the maximal and minimal levels of the functions ranged from 7.9 to 138. Variability of the functions was more marked when the decrease in MFN was greatest (to 12% or below). The excretion of ammonium ions and the urea clearance were lowered in CRF in 34.7 and 42.5% of patients, respectively, increased in 55.1 and 29%, and unchanged in 10.2 and 29%.

The excretion of "osmotically free" water in dehydration and also the high variability of the clearances of the other substances in CRF could be connected with the considerable osmotic diuresis, but no correlation

was found between the latter and the clearance of osmotically free water, either during depression or during stimulation by antidiuretic hormone.

Although in CRF, as under normal conditions, direct correlation was found between the urea clearance and the intensity of osmotic diuresis ($r = 0.83$), given the same level of excretion of osmotically active substances, the values of the urea clearance were much lower in patients with CRF than in healthy subjects. Consequently, the mechanism of osmotic diuresis could not determine the differences in behavior of the functions of the nephrons in CRF.

The increase in the excretion of some substances by each nephron working in CRF could be regarded as a manifestation of the adaptation of the nephrons aimed at regulating the corresponding types of homeostasis, for it has been shown experimentally [11, 15] that if MFN is reduced, the individual functions of healthy nephrons increase in proportion to the loss of kidney tissue, or even by a greater degree. In CRF, however, differences are found in adaptation of the same function as well as statistically significant differences in the frequency of the same degree of compensation of different functions (Table 2). As regards the excretion of sodium and potassium, all four degrees of adaptation were found. Overcompensation and complete compensation of sodium excretion were observed significantly more often than of potassium excretion. The degree of adaptation of the excretion of hydrogen ions and ammonium ions to a decrease in MFN was significantly lower than the degree of adaptation not only of sodium, but also of potassium excretion. Under these circumstances compensation of hydrogen ion excretion was observed far more often than compensation of the excretion of ammonium ions.

These results cannot be explained from the standpoint of the "intact nephron" concept.

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