EFFECT OF FLUOROACETATE ON KIDNEY FUNCTION IN DOGS

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Injection of fluoroacetate into the renal artery of dogs is accompanied by a marked unilateral increase in diuresis. The excretion of sodium, potassium, calcium, chlorides, and inorganic phosphates is increased because of inhibition of their reabsorption. Intravenous injection of fluoroacetate causes similar changes in renal function.

Farah and co-workers [5] found that fluoroacetate causes a marked decrease in the accumulation of p-aminohippurate by rat kidney slices. Mudge [6], on the other hand, states that fluoroacetate has no effect on the accumulation of potassium ions by kidney slices.

In the present investigation the action of fluoroacetate on kidney function was studied in dogs in chronic and acute experiments.

EXPERIMENTAL METHOD

The chronic experiments were carried out on dogs with ureters exteriorized on the skin of the abdominal wall. Fluoroacetate was injected intravenously in doses of 37-936 μg/kg. The volume of urine was measured every 15 min and the concentration of sodium and potassium in it determined with a flame photometer, calcium was estimated by trilonometric titration, inorganic phosphates by the Fiske-Subbarow method, chlorides by Volhard's method, and endogenous creatinine in the urine and plasma by the Folin–Wu method.

The acute experiments were carried out on dogs anesthetized with nembutal. Fluoroacetate was injected into the left renal artery in doses of 4.5-15 μg/kg/min for 90-240 min. The urine was collected separately from each kidney by means of vinyl chloride catheters. The urine was analyzed by the same method.

EXPERIMENTAL RESULTS

In the chronic experiments when fluoroacetate was injected in a dose of 37-44 μg/kg (4 experiments), changes in diuresis were minimal or absent, but if the dose injected was 87 μg/kg or more (4 experiments) the animals died 1.5-3 h after injection of the compound. With doses of 50 μg/kg and more, the diuresis increased sharply 45-60 min after injection. Simultaneously with the increase in diuresis, a still more marked increase took place in the excretion of sodium, potassium, and inorganic phosphates. The mean results of all the experiments are given in Table 1. Glomerular filtration also increased to some extent (to 154% of its initial level), but to a lesser degree than the diuresis and, in particular, the excretion of electrolytes. Consequently, fluoroacetate decreases the tubular reabsorption of the investigated components of the urine.

To examine the mechanism of the changes in diuresis, in acute experiments fluoroacetate was injected into one renal artery so that its effect on the kidney tissue could be studied directly. Just as after intravenous injection, the action of fluoroacetate when injected into the renal artery began after a long (40-80 min) latent period, during which all indices of renal function were within control limits. The diuresis then gradually increased, with a simultaneous increase in excretion of electrolytes. The function of the contralateral kidney was unchanged during this period, indicating a direct action of the compound on the kidney (Fig. 1).

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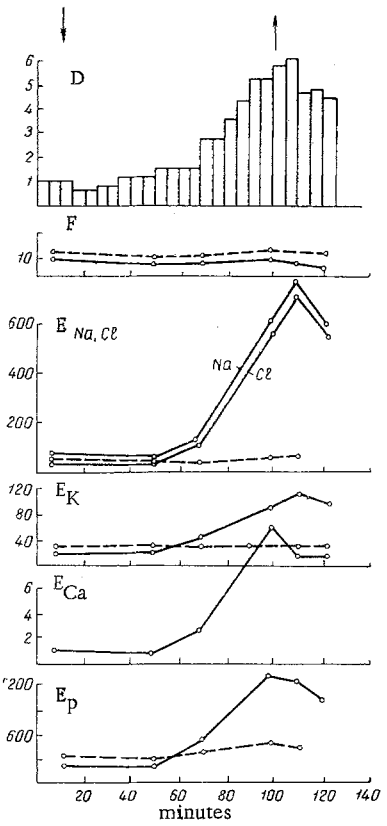

Fig. 1. Changes in renal function after injection of fluoroacetate into the left renal artery. D, diuresis; F, filtration (in ml/min); E_{Na}, K, Cl, Ca represents excretion of sodium, potassium, chlorides, and calcium, respectively (in μeq/min); E_p, excretion of inorganic phosphates (in μg/min). Abscissa, time (in min). Arrows indicate beginning and end of infusion of fluoroacetate in a dose of 8.5 μg/kg/min into the left renal artery. Continuous line gives indices of left (experimental) kidney, broken line those of right (control) kidney.

TABLE 1. Effect of Intravenous Injection of Fluoroacetate on Diuresis, Filtration, and Excretion of Electrolytes in Dogs (M ± m)

Function tested	Number of experiments	Before injection of fluoroacetate	After injection of fluoroacetate 1	After injection of fluoroacetate 2
Diuresis (in ml/h)	14	10,0±1,30	9,1±1,21	16,6±1,99*
Filtration (in ml/min)	14	16,7±1,50	16,0±1,23	25,9±3,24*
Na excretion (in meq/h)	10	1,38±0,278	1,35±0,201	2,77±0,47*
K excretion (in meq/h)	12	0,48±0,086	0,69±0,200	1,08±0,211*
Ca excretion (in μeq/h)	5	14,2±3,48	12,3±2,28	29,0±8,03†
P excretion (in mg/h)	5	5,5±0,80	7,3±1,19	15,0±3,96*

*P< 0.05, †P > 0.05.

The results of all the acute experiments are summarized in Table 2. For simplicity, the indices of function of the experimental kidney only at the time of maximal development of the effect are given in this table. In contrast to the chronic experiments, after intra-arterial injection of fluoroacetate no consistent changes in glomerular filtration were found. This function is evidently modified after intravenous injection as a result of extrarenal influences.

The excretion of sodium and chlorides showed the greatest increase (on the average by 8.75 and 11.22 times, respectively). On this basis it can be postulated that the magnitude of the diuresis increases secondarily on account of a decrease in the reabsorption of these ions. However, it must be noted that the sodium concentration in the urine was significantly increased only if its initial values were low, and if the control values were high they were actually decreased slightly.

The action of fluoroacetate was thus mainly directed toward the reabsorption of sodium, chlorides, and other ions. Fluoroacetate, which blocks aconitase and condensing enzyme, is known to disturb oxidation in the Krebs cycle at the citrate stage. According to data in the literature [7], after injection of lethal doses of fluoroacetate into rats the accumulation of citrate is greater in the kidneys than in any other organ.

On the other hand, the activity of enzymes of the Krebs cycle (especially succinate dehydrogenase) is particularly high in those structural elements of the kidney in which active reabsorption of sodium takes place [2,3], and inhibitors of succinate dehydrogenase disturb the transport of this ion [1,3]. Possibly, therefore, the disturbance of reabsorption of electrolytes may be associated with blocking of the enzyme systems of the Krebs cycle in the tubules.

The action of fluoroacetate develops after a long latent period (65 ± 7.4 min). This also suggests that the compound does not act directly on ion transport but blocks particular enzyme systems participating in the reabsorption of electrolytes.

TABLE 2. Direct Action of Fluoroacetate on Renal Function

Statistical index	Time of development of effect (in min)		Diuresis (in ml/min)		Filtration (in ml/min)		Excretion of ions (in μeq/min)								Excretion of phosphates (in μg/min)	
							Na		K		Cl		Ca			
	onset	maximum	C	E	C	E	C	E	C	E	C	E	C	E	C	E
M	65,0	117,0	0,53	4,2	12,9	12,4	52,1	456	16,3	80,1	49,3	553	1,06	7,74	161,7	841,5
$\pm m$	7,4	7,4	0,11	0,39*	4,16	3,76	15,6	53,8*	3,48	10,18*	16,3	61,5*	0,23	1,30*	15,1	124,9

Legend: C represents control, before injection of compound; E experiment, during administration of fluoroacetate.

*P < 0.001.

LITERATURE CITED

1. V. G. Leont'ev and Yu. V. Natochin, Dokl. Akad. Nauk SSSR, 165, No. 4, 962 (1965).
2. Yu. V. Natochin and T. V. Krestinskaya, Fiziol. Zh. SSSR, No. 3, 388 (1961).
3. Yu. V. Natochin, Tsitologiya, No. 4, 457 (1962).
4. Yu. V. Natochin, Biofizika, No. 4, 626 (1966).
5. A. Farah, F. Koda, and M. Frazer, J. Pharmacol. Exp. Ther., 113, 169 (1955).
6. C. H. Mudge, Am. J. Physiol., 167, 206 (1951).
7. V. R. Potter and H. Buch, Cancer Res., 10, 353 (1950).