ACTION OF 2,4-DINITROPHENOL ON DIURESIS IN DOGS

G. D. Anikin

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2,4-Dinitrophenol, in doses of 6-10 mg/kg, when injected intravenously into dogs, stimulates diuresis, increasing the excretion of sodium, potassium, and chloride ions by diminishing their reabsorption in the tubules. However, no direct action of these doses of dinitrophenol could be demonstrated on the kidney.

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2,4-Dinitrophenol (DNP) is a classical member of the group of "dissociating poisons," and the study of its action on renal function is important for the understanding of the mechanisms of urine formation. Mudge and Taggart [10], in experiments on dogs, observed no changes in the diuresis or excretion of electrolytes by the kidney following intravenous injection of DNP. However, in experiments on kidney slices [3, 6, 11, 14], changes in ion transport were found under the influence of DNP. For this reason the action of DNP was investigated on kidney function in dogs following its injection intravenously and into the renal artery.

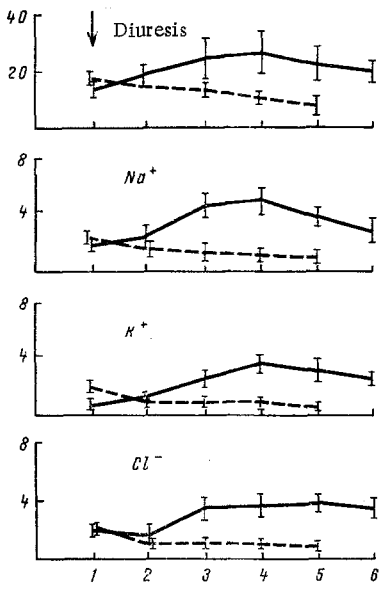

Fig. 1. Effect of intravenous injection of 2,4-dinitrophenol (9.9 ± 0.75 mg/kg) on diuresis and excretion of electrolytes (M ± t). Broken lines represent control experiments; continuous line experiments with DNP; arrow indicates injection of DNP. Abscissa, time (in h); ordinate, diuresis (in ml/h) and excretion of sodium, potassium, and chlorides (in meq/h).

EXPERIMENTAL METHOD

Chronic experiments were performed on 8 dogs with the ureteric orifices exteriorized onto the abdominal wall (by the Orbeli—Tsitovich method). The urine was collected every 15 min for 4-8 h. DNP was injected intravenously in doses of 6-12 mg/kg body weight. Acute experiments in which DNP was injected into one renal artery were carried out on 17 dogs by the method described previously [1, 2]. Urine was collected from each kidney separately. The sodium and potassium concentrations in the urine were determined by flame photometry, and chloride by Volhard's method. The glomerular filtration was estimated by determining the endogenous creatinine concentration in the urine and plasma.

EXPERIMENTAL RESULTS

In control experiments a gradual decrease in diuresis with a decrease in the elimination of sodium, chlorides, and, to a lesser extent, of potassium was observed in all dogs (Fig. 1). Injection of DNP in doses of 6-12 mg/kg in most experiments caused no change in the usual pattern of spontaneous diuresis during the first 1-1.5 h. Later, however, the diuresis was increased and after 3-5 h it was usually 1.5-2.2 times greater than its original value. More marked changes still were observed in excretion of electrolytes. The excretion of sodium and chlorides increased during this same period by 2-6 times over its initial level.

The increase in potassium excretion was particularly great: 2-3 h after injection of DNP it was 4-10 times higher than its original level.

The increase in electrolyte excretion under the influence of DNP was not associated with any change in their concentra-

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TABLE 1. Changes in Diuresis and Excretion of Electrolytes by Left Kidney Following Injection of Large Doses (191 ± 58.6 μg/kg/min) of 2,4-Dinitrophenol into Left Renal Artery (M ± t)

Function investigated	Before injection of DNP	During injection of DNP (at time of maximal changes)
Diuresis (in ml/min)	0.53 ± 0.098	1.11 ± 0.110 P < 0.002
Excretion of sodium (in μeq/min)	58.0 ± 14.1	85.0 ± 22.7 P < 0.05
Excretion of potassium (in μeq/min)	23.8 ± 6.44	54.7 ± 10.4 P < 0.05

TABLE 2. Effect of Injection of Small Doses (7.75 ± 0.96 μg/kg/min) of 2,4-Dinitrophenol into Left Renal Artery on Function of Left Kidney (M ± t)

Function investigated	Before injection of DNP	During injection of DNP
Diuresis (in ml/min)	0.56 ± 0.212	0.54 ± 0.088 P < 0.05
Excretion of sodium (in μeq/min)	45 ± 9.3	34 ± 11.8 P < 0.05
Excretion of potassium (in μeq/min)	20 ± 2.5	25 ± 3.8 P < 0.05
Filtration (in ml/min)	11 ± 1.87	10.0 ± 1.73 P < 0.05

tion in the blood plasma; in the case of sodium this remained unchanged, and the plasma potassium concentration actually fell slightly (by 0.2-0.3 meq/liter).

Under the influence of DNP the glomerular filtration either remained unchanged or increased slightly. Subsequently, the increase in diuresis was due to changes in reabsorption in the renal tubles. To identify the point of action of DNP, the compound was injected in acute experiments into one of the renal arteries. If the observed effects were due to the direct action of DNP on the renal tubules, administration in this manner should give rise to a unilateral effect — in the ipsilateral kidney only.

The results of these experiments are given in Tables 1 and 2. After injection of DNP into the left renal artery doses approximately equivalent to those injected intravenously, a marked increase in diuresis by 1.5-3 times was observed in the left kidney 1-2 h after the beginning of the injections. The excretion of sodium ions was increased on the average by 1.5 times, and that of potassium by 2.5 times. However, similar changes were found between the magnitude of the responses of the injected and control kidneys.

The changes observed in diuresis were due to a decrease in reabsorption in the renal tubules, because no regular changes in the clearance of endogenous creatinine under the influence of DNP were observed.

Changes in the function of the contralateral kidney could indicate penetration of DNP into the general blood stream. In the next experiments, the dose of the compound was therefore reduced to 5-14 μg/kg/min. When these doses of DNP were injected into the left renal artery, no significant changes were found in the diuresis and excretion of potassium ions (Table 2).

The absolute value of sodium excretion by the injected kidney 2 h after the beginning of the injection was not significantly different from its initial value, but was 46 % less ($P < 0.05$) than excretion by the con-

trol (right) kidney. Sodium excretion was reduced because of an increase in tubular reabsorption, for filtration in the left kidney remained unchanged by comparison with the right.

These results do not agree with those obtained by Mudge and Taggart [10]. However, these workers collected urine only for 30-60 min after injection of DNP. The present experiments showed that this period was too short for marked changes in kidney function to develop.

The absence of significant changes in the reaction of the kidney to injection of DNP into one renal artery is evidence of the extrarenal mechanisms of the observed changes in kidney function. Further evidence of this is the fact that the increase in diuresis coincided in time with the appearance of marked dyspnea in the animal, which can itself cause reflex changes in kidney function [4].

The doses of DNP used considerably increase the oxygen consumption in the kidneys [9], by dissociating oxidation and phosphorylation. The absence of a direct effect of DNP on reabsorption of electrolytes in the tubules may indicate that the formation of high-energy compounds in the course of tissue respiration is not essential for the supplying of energy for tubular reabsorption in dogs. The same conclusion is drawn by Strickler [13] and Fujimoto [5]. Recently a magnesium-dependent adenosine triphosphatase, activated by sodium and potassium, has been discovered in the kidneys and is ascribed a role in sodium transport [7, 12]. It is evident that amounts of ATP which can be produced independently of oxidative processes, during glycolysis for example, are adequate for the functioning of this system.

It is interesting to note that in the present experiments small doses of DNP (7.75 ± 0.96 μg/kg/min) stimulated sodium reabsorption to some extent in the injected kidney, and unlike in Strickler's experiments [13], this was not associated with a decrease in filtration. This effect can provisionally be explained either by stimulation of tissue respiration under the influence of DNP or by stimulation of the magnesium-dependent, sodium- and potassium activated adenosine triphosphatase [8].

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