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THE RENAL EFFECTS OF SODIUM CYANATE IN RATS

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Schütz (1946) and Birch and Schütz (1946) found that small, non-toxic doses of sodium cyanate, given intramuscularly to rats, were followed by a " marked diuresis, which in contrast to other diuretics occurred even when no excess water was given." It was therefore thought of interest to investigate the mechanism of the diuretic action of sodium cyanate in rats by means of clearance estimations.

METHODS

Experimental animals.—Adult male rats (weight 250–300 g.), adult rabbits, and adult guinea-pigs were used.

Feeding.—The rats were fed on a commercially prepared diet which was the same as that described in a previous paper (Dicker, 1949b). The rabbits and guinea-pigs were fed on oats and bran.

Experimental procedure for the determination of inulin, diodone, Cl^-, and Na^+ clearances in rats.—The routine procedure conformed to that described previously (Dicker and Heller, 1945 ; Dicker, 1949a): the subcutaneous injections of inulin and diodone were made at least 50 min. before the beginning of the urine collecting period, whether water was administered or not. The collecting period lasted from 15 to 20 min. according to the urine flow. Immediately after the end of the urine collecting period, the rats were anaesthetized, blood obtained from the carotid and jugular vessels and mixed with heparin.

Analytical methods.—Inulin in plasma and urine was determined by the method of Smith, Goldring, and Chasis (1938). The inulin used was that of Hopkins and Williams, Ltd. Diodone iodine in plasma and urine was determined by Alpert's (1941) method. The diodone used was " Per-Abrodil " (Bayer Products, Ltd.). Chloride in plasma was estimated by the open Carius tube technique (Milton and Waters, 1949), the excess of silver being estimated by the Volhard method. Chloride in urine was estimated by Volhard's method as modified by Harvey (1910). Sodium in plasma and in urine was determined by the method of McCance and Shipp (1931) and potassium in urine by Kramer and Tisdall's method as modified by McCance and Shipp (1933).

The methods for calculating Tm_D, T_W, T_{Cl}, and T_{Na} values conform with those described previously (Dicker and Heller, 1945 ; Dicker, 1946 and 1948b).

Statistical treatment of results.—Fisher's (1944) small sample method was used throughout for the estimation of the significance of means.

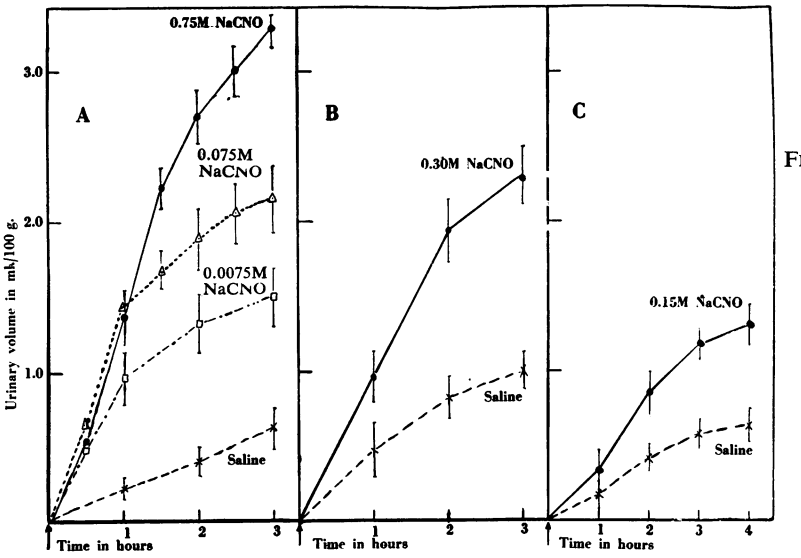

FIG. 1.—Effect of sodium cyanate on the urinary volume (ordinates) of : (A) rats, (B) guinea-pigs, and (C) rabbits. Doses administered at 0 hour (↑) : 0.3 ml./100 g. The vertical lines represent the standard error.

TABLE I

EFFECTS OF SODIUM CYANATE ON THE VOLUME (3 HOURS) AND COMPOSITION OF URINE EXCRETED BY RATS, GUINEA-PIGS, AND RABBITS IN THE 3 HOURS AFTER INJECTION OF SODIUM CYANATE

	Subcutaneous injections 0.3 ml./100 g.	Composition of urine			Urine excreted ml./100 g./3 hr.
		Cl mg./100 ml.	Na mg./100 ml.	K mg./100 ml.	
Rats (12)	Saline	37.3 ± 9.03	26.3 ± 2.04	106.0 ± 23.90	0.80 ± 0.18
	0.75 M-NaCNO	186.0 ± 22.60	92.7 ± 13.26	92.2 ± 13.00	3.30 ±0.21
Guinea-pigs (8)	Saline	286.8 ± 20.18	196.2 ± 14.78	—	1.06 ± 0.33
	0.30 M-NaCNO	404.5 ± 30.41	272.0 ± 26.51	—	2.32 ± 0.42
Rabbits (10)	Saline	182.0 ± 3.08	141.0 ± 2.00	409.0 ± 11.11	0.70 ± 0.15
	0.15 M-NaCNO	246.4 ± 4.00	195.0 ± 3.13	404.0 ± 13.12	1.43 ± 0.30

(Number of animals indicated in parentheses.)

RESULTS

Effects of intramuscular injections of sodium cyanate solutions on the urinary excretion of non-hydrated rats, guinea-pigs, and rabbits

Water and food were withheld from rats, guinea-pigs, and rabbits for at least six hours before they were injected with sodium cyanate. Fig. 1 shows the results of

injections of 0.3 ml./100 g. body weight of sodium cyanate solutions of different concentrations on urine volume. These results agree with those described previously by Schütz (1946) and Birch and Schütz (1946).

Doses of 0.3 ml./100 g. of a 0.75 M-NaCNO solution proved to be toxic in rabbits and guinea-pigs: the animals had violent convulsions 60–75 min. after the injection and died. Rats, as a rule, were more resistant: however, two out of 48 died with violent convulsions of the type described by Birch and Schütz (1946).

Table I compares the concentration of electrolytes in the urine of rats, rabbits, and guinea-pigs, excreted during three hours after an injection of a solution of sodium cyanate with that in the urine of controls injected with the same amount (0.3 ml./100 g.) of saline. It shows that sodium cyanate produced a marked increase of urinary concentration of Cl^- and Na^+, but that it had no significant effect on the concentration of K^+. The increase of urine flow accompanied by the rise in the concentration of Cl^- and Na^+ resulted in a pronounced increase of the amounts of Cl^- and Na^+ excreted.

When sodium cyanate was injected at the same time as 2.0 mU/100 g. vasopressin, into rats, no significant decrease in the diuretic effect of sodium cyanate could be noted—i.e., in the presence of NaCNO vasopressin failed to exert its usual antidiuretic effect (Fig. 2).

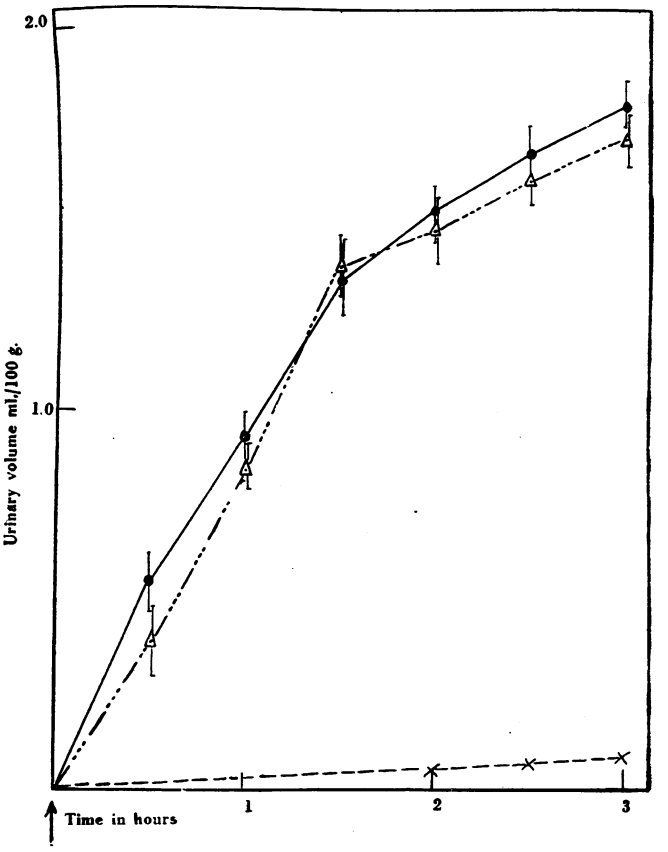

FIG. 2.—Effect of sodium cyanate and of sodium cyanate and vasopressin on the urinary volume of rats. ●——● mean urinary excretion of 12 rats injected with 0.075 M-NaCNO (dose 0.3 ml./100 g.). △— · · · —△ mean urinary excretion of 12 rats injected with 0.075 M-NaCNO (dose 0.3 ml./100 g.) and vasopressin (2.0 mU/100 g.). ×——× control rats injected with vasopressin (2.0 mU/100 g.). All the injections were given at 0 hour (↑). The vertical lines represent the standard error.

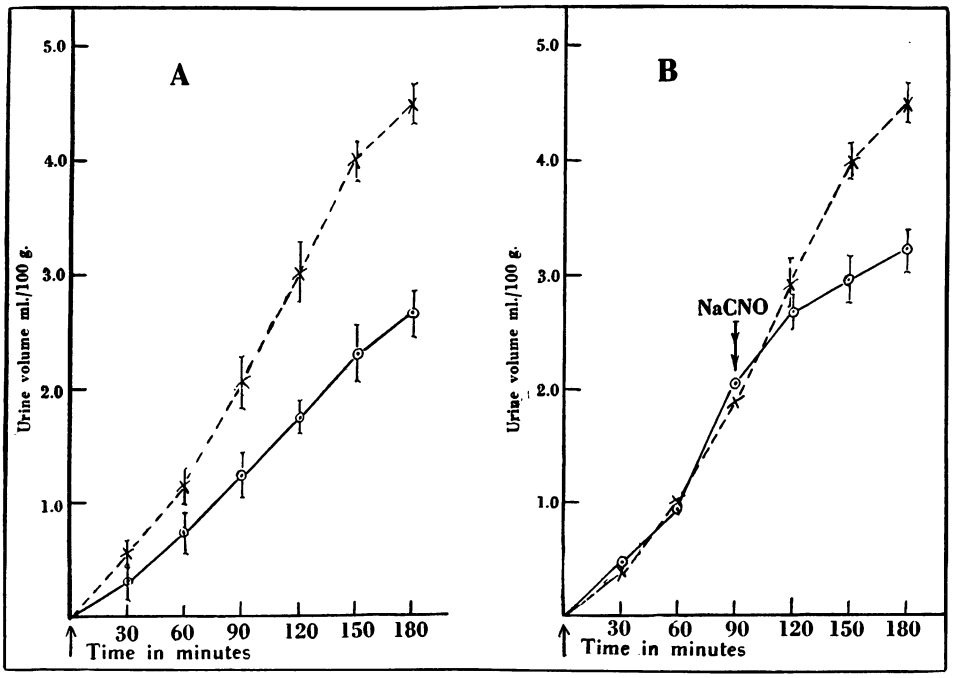

FIG. 3.—Effect of sodium cyanate on the urinary volume of hydrated rats. (A) A dose of 0.3 ml./100 g. of a 0.75 M-NaCNO is injected subcutaneously at the same time as 5.0 ml./100 g. of water is administered by stomach tube at (↑). (B) The same dose of NaCNO is injected 90 min. after (↕) the administration of the standard amount of water (↑). ×——×: control rats given 5.0 ml./100 g. of water only. ○——○: rats injected with NaCNO. The vertical lines represent the standard error.

Effects of intramuscular injections of sodium cyanate solutions on the urinary excretion of hydrated rats

When 0.3 ml./100 g. of a 0.75 M-NaCNO solution was injected into rats immediately after the oral administration of an amount of water equal to 5 per cent of their body weight urinary excretion remained comparable, in volume and composition, with that observed in non-hydrated rats, injected with the same amount of sodium cyanate (Fig. 3A).

When sodium cyanate (0.3 ml./100 g. of a 0.75 M-solution) was injected into rats 90 min. *after* water administration—i.e., at a time when the water given had been absorbed from the alimentary tract (Heller and Smirk, 1932; Dicker, 1948a)—there was a decrease in the rate of urine flow (Fig. 3B) accompanied by a pronounced increase of the urinary concentrations of Cl^- and Na^+.

A comparison of the results shown in Figs. 1 and 3 suggests that the injection of sodium cyanate in rats produced much the same renal effect, whether the animals were hydrated or not. The diuretic response to sodium cyanate was always smaller than that following the administration of water only.

Effect of sodium cyanate on the water absorption from the alimentary tract

The apparently paradoxical effect of sodium cyanate on hydrated rats could have been the result of (*a*) an impaired water absorption from the alimentary canal, (*b*) an impairment of the renal functions, or (*c*) a combination of both.

In order to investigate the rate of water absorption from the alimentary tract, 60 rats were given the standard amount of water (=5 ml./100 g.) by stomach tube, injected with 0.3 ml./100 g. of 0.75 M-NaCNO and killed after 15, 30, 45, 60, 75, 90, 105, 120, and 180 min. The stomach and intestine, with their contents, were then weighed separately. The results obtained were compared with those of rats killed at

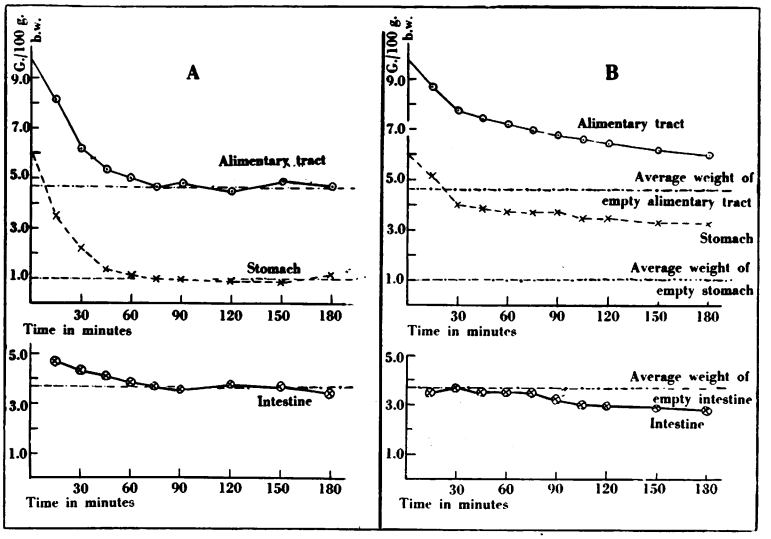

FIG. 4.—Average water absorption curves of (A) normal rats and (B) rats injected with 0.3 ml./100 g. of a 0.75 M-NaCNO solution. The average weight of the empty gastro-intestinal was 4.7 per cent of the body weight; 5.0 ml./100 g. of water was given, making 9.7 per cent the starting point of the absorption curves. ⊙——⊙ alimentary tract. ×——× stomach. ⊕——⊕ intestine.

various times after administration of the standard amount of water only. Fig. 4A shows that in the control rats stomach and intestine, and hence the alimentary tract, were empty 90 min. after water had been given (Heller and Smirk, 1932; Dicker, 1948a). In rats injected with sodium cyanate, however, the stomach still contained 2.2 ml./100 g. rat after 180 min. (Fig. 4B). On the other hand the weight of the intestine had decreased below the average weight of normal empty intestine after 180 min. These results suggested that in rats which were given water and sodium cyanate there was a marked delay in the emptying of the stomach while the intestine was losing some of its water content. The overall effect on the alimentary tract (stomach + intestine) was that in rats injected with NaCNO about 30 per cent of the administrated water had not yet been absorbed after three hours (Fig. 4B).

These results would explain why the simultaneous administration of NaCNO and water resulted in a urinary volume significantly lower than that of rats receiving water only. They do not explain, however, why the injection of sodium cyanate 90 min. after water administration reduced the rate of urine excretion.

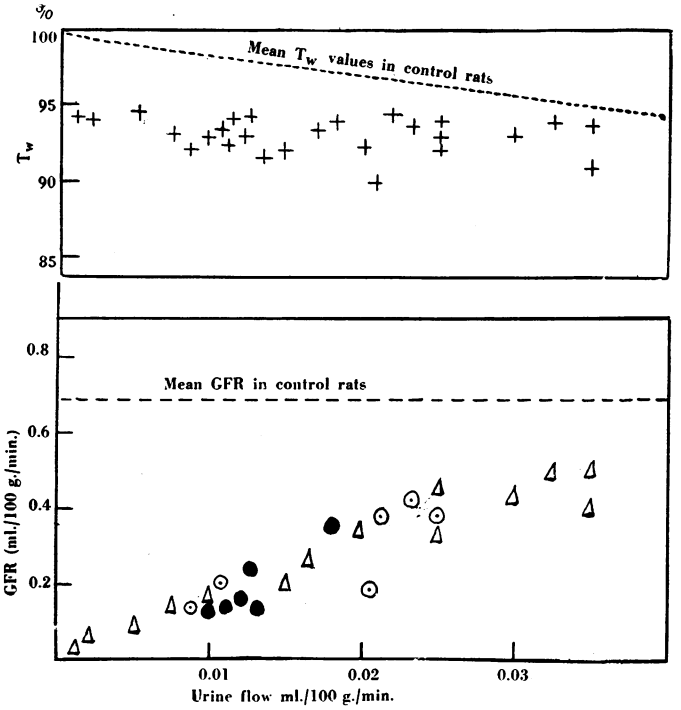

FIG. 5.—Glomerular filtration rate (GFR) and rate of tubular water reabsorption (T_w) in rats injected with a dose of 0.3 ml./100 g. of 0.75 M-NaCNO. △ : non-hydrated rats. ● : rats which were given water and sodium cyanate at the same time. ○ : rats which were injected with NaCNO 90 min. after the administration of water.

Inulin clearance estimations in rats injected with sodium cyanate

Inulin clearances (=glomerular filtration rate=GFR) were estimated (*a*) in non-hydrated rats, (*b*) in rats which were given the standard amount of water at the same time as sodium cyanate, (*c*) in rats which were injected with sodium cyanate 90 min. after water administration.

Since the results were the same in the three series, they can be examined together. It will be seen from Fig. 5 that (i) in contrast to normal rats (Dicker and Heller, 1945 ; Dicker, 1949a) the glomerular filtration rate of cyanate rats was significantly correlated with the urine flow, (ii) the highest value for GFR in rats injected with sodium cyanate was significantly lower than the mean GFR of control rats, fed on the same diet.

These changes in GFR coincided with changes in the tubular rate of water reabsorption. In control rats, T_W (=tubular water reabsorption expressed as per cent of the amount of water filtered) decreases with an increase of the urine flow—i.e., in normal rats, changes in the rate of urine flow are the result solely of changes in T_W. In rats injected with sodium cyanate, however, the values for T_W were independent

of the urine flow, suggesting that changes in the rate of urine flow were mainly the result of changes in GFR. Furthermore, it will be noticed that in rats injected with sodium cyanate the mean value of T_W was significantly lower than that of controls. The overall renal response to an injection of sodium cyanate therefore consisted in a decrease (*a*) of the amount of water filtered and (*b*) of the rate of tubular water reabsorption.

Diodone clearance estimations in rats injected with sodium cyanate

Values for Tm_D at high plasma diodone level in rats injected with sodium cyanate agreed with those found in control rats, suggesting that sodium cyanate did not impair the secretory activity of the tubules.

Clearance estimations at low diodone plasma levels (=effective renal plasma flow=RPF) showed a significant correlation with the glomerular filtration rate and, hence, with the urine flow. The ratio GRF/RPF (=filtration fraction=FF) was lower than in control animals, indicating that the glomerular efferent vessels were dilated. This fact may provide an explanation for the decrease of the glomerular filtration rate observed.

Cl^- and Na^+ clearances in rats injected with sodium cyanate

The rates of tubular reabsorption for Cl^- and Na^+ (T_{Cl} and T_{Na}) were significantly lower in rats injected with sodium cyanate than in controls. While values for T_{Cl} and T_{Na} in controls amounted to 96.8 ± 0.32 and 98.7 ± 0.52, respectively, they amounted to 95.2 ± 0.51 and 97.0 ± 0.47 in rats injected with sodium cyanate (t: 2.190 and 2.144).

Discussion and Summary

It would appear from this investigation that in contrast to other drugs—e.g., theophylline sodium acetate, mersalyl, calomel—which have a diuretic effect in rats only when extra water has been administered (Dicker, 1946) sodium cyanate has a diuretic effect on normal rats, whether they are hydrated or not (Schütz, 1946). However, the diuretic effect in hydrated animals is not due to an enhancement of water diuresis as happens with the other diuretic substances mentioned, but appears to be identical in character with that of non-hydrated rats. The reason for this seems to be that the diuretic response to water is severely impaired by sodium cyanate: the drug delays the gastric emptying time with the result that very little water is absorbed from the alimentary canal.

The renal effect of sodium cyanate seems to be resultant of a decrease in the rate of tubular water reabsorption and of a decrease of the glomerular filtration rate. The former may possibly be the result of a decrease in the rate of the tubular reabsorption of Cl^- and Na^+. This assumption is borne out by the fact that the injection of 2.0 mU/100 g. vasopressin had an effect neither on the urine flow nor on the urinary concentrations of Cl^- and Na^+ of rats injected with sodium cyanate.

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