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Renal Tubular Secretion of Potassium in the Normal Dog.*

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(Introduced by Alexander B. Gutman.)
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During the administration of salyrgan† (sodium salt of mercury salicyl-allylamide-ortho-acetate) to dogs, it was observed that the rate of potassium excretion frequently became constant and remained at a fixed level despite marked changes in the calculated rate of potassium filtration at the glomerulus. A constant excretory rate dissociated from filtered load is strongly suggestive of a tubular secretory mechanism. Such a mechanism for the addition of potassium to the tubular urine has, in fact, been demonstrated in the dog by experiments to be described.

Material and Methods. Experiments were performed on 4 trained, unanesthetized female dogs. To obtain stable plasma creatinine and inulin concentrations and to assure constant rates of potassium intake, solutions were administered by continuous infusion. Urine and heparinized venous blood samples‡ were collected by the usual techniques for the determination of clearances.

The plasma creatinine clearance was used as a measure of glomerular filtration rate. The equivalence of the creatinine clearance and filtration rate in the dog is generally accepted. In 2 experiments inulin clearances were simultaneously determined to check on the validity of the creatinine clearance as a measure of filtration rate under the circumstances of these experiments.

Creatinine was determined in tungstic acid filtrates of plasma and in diluted urine by a modification of the Folin method.[1] Inulin was determined by a modification of Harrison's method.[2] Both plasma and urine were treated with yeast before precipitation with zinc.

Potassium and sodium in plasma and urine were determined with an internal standard flame photometer,[3] after addition of a standard amount of lithium to each specimen and dilution. The error of the method in our hands does not exceed 1% in the recovery of added amounts. The presence of protein in diluted plasma samples did not interfere with the determination since ashed specimens gave results identical with those obtained by simple dilution. The addition of amounts of sodium greater than those present in plasma samples was found not to affect potassium determinations.

Results. An experiment showing the effect of salyrgan on potassium excretion is summarized in Table I. Soon after the administration of salyrgan the rate of excretion of potassium reached a value of about 45 μeq/min and remained at this level for a period of more than 2 hours despite a fall of 35% in the filtered potassium and during marked changes in urine flow and sodium excretion. Similar results were obtained in each of 3 other dogs. A slight rise in potassium excretion with time was sometimes observed in

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† The salyrgan used in this study was supplied by the medical research department of Winthrop-Stearns, Inc.

‡ Arterial blood samples were simultaneously obtained in several instances. The concentration of potassium in arterial plasma did not differ measurably from that in venous plasma during the infusion of KCl.

1 Shannon, J. A., and Fisher, S., *Am. J. Physiol.*, 1938, 122, 765.

2 Harrison, H. A., PROC. SOC. EXP. BIOL. AND MED., 1942, **49**, 111.

3 Berry, J. W. Chappell, D. G., and Barnes, R. B., *Ind. Eng. Chem., Anal. Ed.*, 1945, **17**, 605.

TABLE I.
Effect of Salyrgan on Potassium Excretion. Dog F. 13.9 Kilos.

Clearance period	Time, min.	Plasma concentration*			Urine flow, ml/min	Creatinine clearance, ml/min	"Filtered"†		Excreted	
		Creatinine, mg %	Sodium, meq/L	Potassium, meq/L			Sodium, μeq/min	Potassium, μeq/min	Sodium, μeq/min	Potassium, μeq/min
	0		148	3.7						
Priming creatinine 0.9 g in 200 ml isotonic NaCl.										
Start infusion 0.45% creatinine in isotonic NaCl at 2 ml/min.										
1	18-38	10.8	149	3.6	0.62	59	8800	212	105	20
2	38-59	11.6	149	3.5	0.72	58	8600	203	93	19
	62		Salyrgan 1 ml I.V.		3.2 ml Salyrgan added to 400 ml of infusion.					
3	81-104	12.6			8.89	67	10000	228	1410	31
4	104-115	12.5	149	3.4	10.03	81	12100	275	1860	44
5	115-131	12.3			6.60	69	10300	234	1270	48
6	180-196	13.8			2.12	53	7800	175	350	45
7	196-211	14.5	148	3.3	2.23	52	7700	172	353	45
8	211-232	—			2.90	—	—	—	440	46

* Plasma samples obtained at midpoint of corresponding clearance periods.
† Plasma concentration times creatinine clearance; uncorrected for Donnan equilibrium.

these experiments. The rate of potassium excretion after salyrgan was nearly constant in each experiment but varied from dog to dog, 45 μeq/min being the lowest rate observed while 150 μeq/min was the highest. Salyrgan did not always effect an increase in potassium excretion. When potassium excretion was initially increased by administration of KCl, salyrgan produced a decrease in the excretion rate.

The most direct evidence for a secretory mechanism for potassium would be the demonstration of more potassium in the urine than could be accounted for by glomerular filtration. Since the amount secreted would probably be small in relation to the amount which might be filtered, it was to be expected that some difficulty would be encountered in demonstrating a secretory mechanism. However, in each of the 4 dogs it has been possible to obtain at least one experiment in which the excreted potassium exceeded that filtered. Only in the dog with the largest potassium excretion after salyrgan was this achieved in the first attempt. In the other dogs several preliminary experiments were sometimes necessary to determine the optimum infusion rate for demonstration of this phenomenon. Achievement of the necessary conditions seemed to be facilitated by the preliminary oral administration of KCl[4] for a week before the experiment and by the administration of the KCl during experiments in hypertonic solution and at a moderate rate. One such experiment is shown in Table II. In this experiment, within 40 minutes of the time that the infusion rate was increased to 0.67 meq/min, the excreted potassium exceeded that "filtered" by 25% and ratios of excreted to "filtered" varied between 1.15 and 1.33 in 9 successive clearance periods. Inulin clearances were determined in 2 similar experiments, one of which is shown in Table III. In both experiments the inulin clearances corresponded closely with simultaneously determined creatinine clearances. In the 2 other dogs, ratios of excreted to "filtered" potassium greater than one were obtained

[4] Thatcher, J. S., and Radike, A. W., *Am. J. Physiol.*, 1947, **151**, 138.

TABLE II. Effect of Infusion of Hypertonic KCl. Dog D.† 18.6 Kilos.

Clearance period	Time, min.	Plasma* conc. Creatinine, mg %	Plasma* conc. Potassium, meq/L	Urine flow, ml/min	Creatinine clearance, ml/min	"Filtered" K,‡ μeq/min	Excreted K, μeq/min	Ratio: Excreted / "Filtered" K
	0	Priming creatinine 1.85 g in 20 ml water.						
	2	Start infusion 1.7% creatinine in 0.33 N KCl at 1 ml/min.						
	5		5.0					
1	59-78	24.8	5.5	1.05	63	346	194	0.56
2	78-104	24.9	5.5	0.84	64	352	173	0.49
3	104-124	25.7	5.4	1.17	63	340	241	0.71
	125	Increase potassium concentration of infusion to 0.67 N.						
4	164-184	25.1	6.0	2.76	75	450	556	1.24
5	184-205	25.1	6.5	2.91	76	494	615	1.25
6	205-226	25.7	7.1	2.85	74	525	625	1.19
7	226-245	25.7	7.5	3.09	76	570	670	1.18
8	245-266	25.1	6.8	3.26	78	530	702	1.33
9	266-291	24.8	6.7	2.90	78	522	678	1.30
10	291-311	25.1	7.4	2.95	77	570	665	1.17
11	311-336	25.1	7.6	3.09	79	600	715	1.19
12	336-355	24.8	7.8	2.89	80	624	720	1.15

* Plasma samples obtained at midpoint of corresponding clearance periods.
† Dog received 5 g KCl twice daily by mouth for one week before this experiment.
‡ Plasma concentration times creatinine clearance; uncorrected for Donnan equilibrium.

TABLE III. Dog M*. 11.8 Kilos.

Clearance period	Time, min.	Plasma† conc. Creatinine, mg %	Plasma† conc. Inulin, mg %	Plasma† conc. K, meq/L	Urine flow, ml/min.	Clearance Creat., ml/min.	Clearance Inulin, ml/min.	Clearance ratio: Inulin / Creat.	"Filtered"‡ K, μeq/min.	Excreted K, μeq/min.	Ratio: Excreted / "Filtered" K
	—1			4.2							
	0	Priming creatinine 1.1 g; inulin 0.6 g.									
	2	Start infusion 0.9% creatinine, 0.8% inulin in 0.35 N KCl at 1.2 ml/min.									
1	60-83	21.2	20.8	5.0	1.62	60	58	0.97	300	298	0.99
2	83-112	20.6	19.4	4.9	1.48	58	59	1.02	284	294	1.04
3	112-132	20.4	19.2	4.7	1.49	61	59	0.97	286	318	1.11
4	132-152	20.1	18.4	5.1	1.66	60	61	1.02	306	352	1.15
5	152-172	19.5	18.0	5.2	1.89	62	60	0.97	322	385	1.20
6	172-194	19.1	17.4	5.3	1.93	62	63	1.02	328	398	1.21
7	194-216	18.9	17.2	5.5	1.94	64	64	1.00	352	420	1.19

* Dog received 5 g KCl twice daily by mouth for 12 days before this experiment.
† Plasma samples obtained at midpoint of corresponding clearance periods.
‡ Plasma concentration times creatinine clearance; uncorrected for Donnan equilibrium.

in 22 clearance periods in 3 experiments; the ratios reached at least 1.15 in each dog. It is worthy of note that after preparation with oral KCl high rates of potassium excretion were attained with only minimal elevation of the plasma potassium concentration (Table III).

Discussion. The excess of excreted potassium over filtered load was well beyond the limits of experimental error. There is no reason to believe that the filtration rate actually exceeded the creatinine clearance, especially since the inulin and creatinine clearances were the same.

It should be noted that the amount of potassium filtered has been calculated simply as the product of creatinine clearance and plasma potassium. Correction of the filtered potassium for the Donnan equilibrium would lower the filtered load by about 5% and increase the excess of excreted potassium observed in these experiments.

The data obtained constitute evidence for the existence of a mechanism for the addition of potassium to the tubular urine.§ The coexistence of tubular mechanisms for both reabsorption and secretion of a single substance has not previously been demonstrated. Tubular secretion of a number of substances generally considered to undergo only filtration and reabsorption, including potassium, has been suggested by Barclay, Cooke and Kenney,[6] but the evidence on which this conclusion is based is not presented in the published abstract.

Summary and Conclusions. A constant rate of potassium excretion, dissociated from filtered load, occurring after salyrgan administration suggested a tubular secretory mechanism located, presumably, in the distal tubule. The presence of such a mechanism has been demonstrated by the intravenous administration of hypertonic KCl solutions which yielded rates of potassium excretion considerably above the rates of filtration of potassium at the glomerulus.

§ Doctors Mudge, Foulks, and Gilman[5] inform us that they have similarly concluded that potassium is secreted by the renal tubules on the basis of observations during forced osmotic diuresis.

[5] Mudge, G. H., Foulks, J. G., and Gilman, A., personal communication.

[6] Barclay, J. A., Cooke, W. T., and Kenney, R. A., XVII Internat. Physiol. Congress, Abstracts of Communications, 1947, p. 58.

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The Renal Excretion of Potassium.*

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The potassium (K) excreted in the urine under normal circumstances can be accounted for by the tubular rejection of approximately 10% of the calculated filtered K. This has been accepted as evidence that K is excreted by the process of filtration and incomplete reabsorption. The possibility of tubular secretion has been suggested by isolated observations. McCance and Widdowson[1] reported a case of alkalosis and dehydration with a low filtration rate and a K clearance greater than the inulin clearance. Keith, King and Osterberg[2] noted similar K : Inulin clearance

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[1] McCance, R. A., and Widdowson, E. M., *Lancet*, 1937, **2**, 247.

[2] Keith, N. M., King, H. E., and Osterberg, A. E., *Arch. Int. Med.*, 1943, **71**, 675.