STUDIES CONCERNING THE SITE OF RENIN FORMATION IN THE KIDNEY

IV. The Renin Content of the Mammalian Kidney Following Specific Necrosis of Proximal Convoluted Tubular Epithelium*

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Plates 3 and 4

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In the first two studies (1, 2) of the present series, it was observed that whereas the kidney of fresh water fish contained renin, the kidney of marine fish did not, regardless of whether the kidney of the latter type of fish contained glomeruli or not. In our third study (3), it was found that the mesonephros and metanephros of the developing hog fetus contained renin despite the fact that neither type of kidney possessed specialized juxtaglomerular cells as described by Goormaghtigh (4). Furthermore, in this last study, it was found that the renin content of either type of embryonic kidney was dependent not upon its arteriologlomerular component but upon the activity and structural integrity of its convoluted tubular mass.

Nevertheless, the relationship of intact tubular mass and function to the formation of renin in the adult mammalian kidney has not yet been ascertained. The dependence of both the glomerular and tubular components of the kidney upon a common blood supply makes the eradication of one component alone, quite difficult. However, it was reported by Underhill, Wells, and Goldschmidt (5, 6) and later confirmed by Potter and Bell (7), that the subcutaneous administration of tartrate to a rabbit effects a differential necrosis of its renal convoluted tubules, affecting other portions of the nephron. This method then, offers us the opportunity of comparing the renin content of a kidney possessing normal arteriologlomerular and tubular components with one possessing a normal arteriologlomerular component but a severly damaged proximal convoluted tubular mass. A significant decrease in the renin content of the latter type of kidney would indicate that this portion of the mammalian kidney was capable of forming or storing renin. The results of such a study are reported in this communication.

Methods

Thirty-two rabbits were injected subcutaneously with a neutral solution of tartaric acid as described by Underhill *et al.* (5). The amount injected, varied from 0.765

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TABLE I

The Pressor Substance (Renin) Content of the Kidney of Normal and Tartrate Injected Rabbits

Rabbit kidney	Recipient dog	Duration of life after tartrate injection	Extract injected (dry kidney powder)	Mean arterial pressure		Pressor effect (rise per gm. of dry kidney powder)
				Before injection	After injection of rabbit kidney extract	
(a) Kidney of Normal Rabbit						
		hrs.	*gm.*	*mm. Hg*	*mm. Hg*	*mm. Hg*
(1) R-40	21	—	1.00	113	165	52.0
(2) R-41	93	—	1.00	126	151	25.0
(3) R-42	82	—	1.00	134	156	22.0
(4) R-43	92	—	1.00	127	185	58.0
(5) R-49	79	—	1.00	129	148	19.0
(6) R-61	90	—	1.00	139	170	31.0
(7) R-89*a*	71	—	1.00	139	158	19.0
R-89*b*	64	—	1.00	152	184	32.0
(8) R-90	71	—	1.00	130	159	29.0
Average						32.0
(b) Kidney of Rabbit Injected with Tartrate (without Tubular Necrosis)						
(1) R-19*	87	48	1.00	109	161	52.0
(2) R-24*	21	96	1.00	97	151	54.0
(3) R-26	92	96	1.00	133	190	57.0
(4) R-27	92	144	1.00	140	156	16.0
(5) R-28	21	144	1.00	115	156	41.0
(6) R-29	85	144	1.00	121	147	26.0
(7) R-30	84	144	1.00	128	170	42.0
(8) R-32	83	96	1.00	110	122	12.0
(9) R-33	21	96	1.00	124	166	42.0
(10) R-35	21	96	1.00	117	123	6.0
(11) R-36	21	96	1.00	109	140	31.0
(12) R-37	83	96	1.00	138	178	40.0
(13) R-38*	86	96	1.00	140	154	14.0
(14) R-39	83	96	1.00	110	139	29.0
(15) R-50	88	96	1.00	119	153	34.0
(16) R-51*	92	96	2.00	130	194	32.0
(17) R-59	80	96	1.00	146	164	18.0
Average						32.0
(c) Kidney of Rabbit Injected with Tartrate (with Moderate Tubular Necrosis)						
(1) R-21	92	48	1.00	106	112	14.0
(2) R-23	86	72	1.00	153	170	17.0
(3) R-45	83*a*	48	1.00	130	132	2.0
(4) R-46	88	48	2.36	102	130	12.0
(5) R-47	95	48	1.00	119	132	13.0
(6) R-48	95	48	2.49	122	151	12.0
(7) R-52	78	96	1.00	155	168	13.0
Average						11.8

* Kidney showed marked tubular edema.

TABLE I—*Concluded*

Rabbit kidney	Recipient dog	Duration of life after tartrate injection	Extract injected (dry kidney powder)	Mean arterial pressure		Pressor effect (rise per gm. of dry kidney powder)
				Before injection	After injection of rabbit kidney extract	
(d) Kidney of Rabbit Injected with Tartrate (with Severe Tubular Necrosis)						
		hrs.	*gm.*	*mm. Hg*	*mm. Hg*	*mm. Hg*
(1) R-81	64	48	2.00	156	156	0.0
(2) R-82	97	48	2.00	148	160	6.0
(3) R-83	70	48	2.00	140	152	6.0
(4) R-84	71	48	2.00	135	135	0.0
(5) R-85	71	48	2.00	148	148	0.0
(6) R-86	64	48	2.00	157	157	6.0
(7) R-87	72	72	2.00	122	122	0.0
(8) R-88	71	48	2.00	153	153	0.0
Average						2.3

to 1.75 gm. of sodium tartrate per kilo of body weight. It was found that when the maximal amount was given, the incidence of tubular necrosis increased markedly. All rabbits were watched closely following injection and it was observed that those having severe tubular damage, became listless and obviously ill as early as 48 hours after the administration of the tartrate, whereas those rabbits showing little or no tubular damage on later histological examination appeared well even after 6 days, at which time, many were sacrificed. It is important to emphasize that all kidneys were removed and extracted immediately after the rabbits were killed.

After blocks for sections were obtained, the kidneys of the rabbits were minced, ground, defatted, and desiccated as previously described (1). The dry powder resulting from such procedures, was extracted then for renin according to the method of Helmer and Page (8). The process was carried to the "Fraction B" stage (8). The physiological assay of the pressor substance (renin) content of each kidney extract was carried out on normal, anesthetized (pentobarbital sodium) dogs according to methods previously described (1). Because the kidneys of rabbits receiving tartrate were frequently edematous on removal, the increase in blood pressure following the introduction of any kidney extract was expressed as mm. Hg rise per gram of dry kidney powder.

For control purposes, the kidneys of ten normal rabbits were treated and assayed later for renin as described above so that during any extraction and assay of a batch of kidneys obtained from rabbits injected with tartrate, a normal kidney also was extracted and assayed. Two of the control kidney extracts have not been included in Table I*a* because it was discovered that the test dog used was unduly sensitive to the pressor effect of injected renin.

Description of Rabbit Kidneys Following Tartrate Injection

The kidney of a rabbit injected with tartrate was found to appear normal, edematous, or severly necrotic, depending upon the duration of the experiment

and the amount of tartrate injected. Almost every kidney obtained from rabbits within 24 hours following tartrate administration, exhibited gross enlargement which on histological examination was found to be due to edema of the proximal convoluted tubules (Figs. 1 and 2). This portion of the nephron was identified by its characteristic ciliated epithelium. If the amount of tartrate injected were under 1 gm. per kilo, the initial edema tended usually to subside so that the kidney of a rabbit allowed to live 4 to 6 days after tartrate injection, showed little evidence of edema or of tubular necrosis.

However, the kidney of a rabbit receiving over 1 gm. of tartrate per kilo, frequently developed a severe and widespread tubular necrosis (Figs. 3 and 4), which was limited for the most part to the epithelium of the proximal convoluted tubules. The glomerulus, even in the most damaged kidneys appeared quite normal, as has been previously reported, (5–7). Red blood cells could be seen in the capillaries, there was no hyperplasia of the capillary endothelium, no accumulation of leucocytes in the glomerular tuft, and the patency of the glomerular capillary was confirmed by the detection of carbon particles in its capillary loops after postmortem injection of India ink into the renal artery.

The Renin Content of Rabbit Kidneys Following Tartrate Injection

Physiological assay of various kidney extracts made it clear that there was no essential difference between the content of pressor substance (renin) of a kidney from normal rabbit and that of a kidney obtained from a rabbit injected with tartrate unless the latter showed actual necrosis of the proximal convoluted tubular epithelium.

Thus, as Table I *a*, *b* indicates, the average pressor effect (32.0 mm. Hg per gm. of dry kidney powder) obtained from eight different extracts of kidneys, (obtained from a corresponding number of normal animals), was identical with that obtained from 17 different extracts of kidneys of rabbits injected with tartrate without a resulting necrosis of proximal convoluted tubular epithelium. In other words, the administration of tartrate *per se*, to rabbits, did not alter the renin content of their kidneys even in those cases in which marked tubular edema had occurred.

However, it was observed, as shown in Table I *c*, *d*, that a kidney sustaining tubular necrosis following tartrate injection also showed a diminution in pressor substance (renin) roughly comparable to the extent and degree of the necrosis. Thus, in seven extracts of kidneys whose proximal convoluted tubular epithelium was only partially destroyed, the average pressor effect was 11.8 mm. Hg per gm. of dry kidney powder. In eight extracts of kidneys whose proximal convoluted tubular epithelium was widely destroyed, the average pressor effect was 2.3 mm. Hg per gm. of dry kidney powder. Thus, the normal kidney was found to contain approximately 14 times as much pressor substance (renin) as the kidney whose proximal convoluted tubular epithelium was necrotized severely by tartrate injection. It should be emphasized again that in both

normal and tartrate damaged kidneys, the arteriologlomerular component, including the specialized "Goormaghtigh cells" invariably appeared normal.

DISCUSSION

In the first two studies (1, 2) of this series, the apparent absence of renin in the glomerular or aglomerular kidney of the marine fish as compared with its abundant presence in the kidney of fresh water fish, furnished the first, indirect, indications that the site of renin formation was in the tubular component of the kidney. For it is known (9) that a difference exists between the renal tubular components of the two types of fish.

In the third study (3) of this series, it became evident that the site of renin formation in the kidney (mesonephros or metanephros) of the hog fetus was tubular and had no detectable relationship with other portions of the kidney. The complete absence of specialized juxtaglomerular cells in either the mesonephros or metanephros further strengthened this view.

In the present and final study of this series, the almost complete disappearance of the pressor substance (renin) from an adult mammalian kidney whose proximal convoluted tubular epithelium had been destroyed, leads to the inescapable conclusion that in the adult mammalian kidney, the epithelium of the proximal convoluted tubules is concerned in the formation or storage of renin.

CONCLUSIONS

1. The administration of tartrate to adult rabbits was found to produce in some of them, a profound and widespread necrosis of the proximal convoluted tubular epithelium without affecting the other portions of the nephrons.

2. The markedly damaged kidneys were found to be almost completely devoid of pressor substance (renin), indicating that in the mammalian kidney, the epithelium of the proximal convoluted tubules is concerned in the formation or storage of renin.

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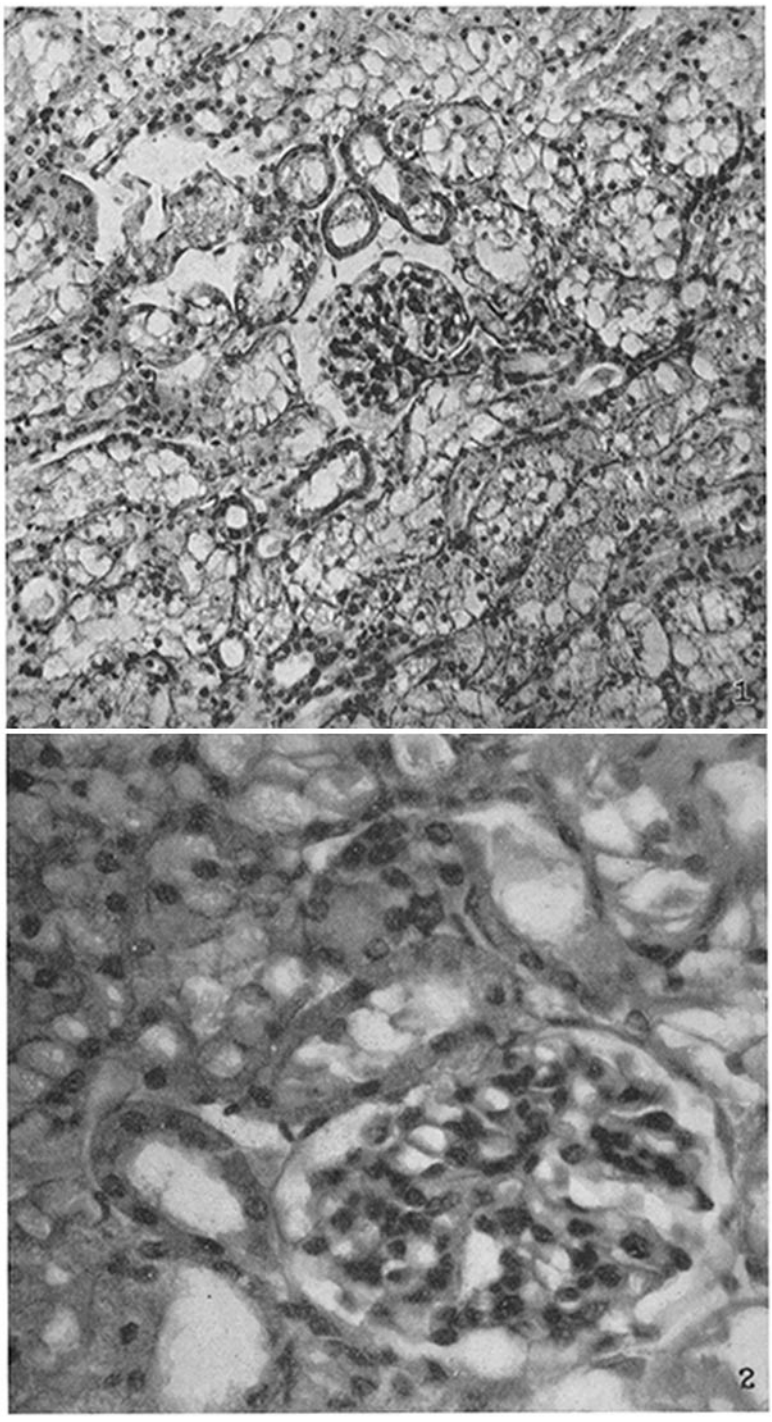
EXPLANATION OF PLATES

PLATE 3

FIG. 1. Kidney of rabbit which had received 1 gm. of tartrate per kilo 12 hours before. Note the extreme hydropic degeneration of the convoluted tubular epithelium and the normal appearance of the glomerulus. Between the edematous proximal convoluted tubules, normal appearing distal convoluted tubules can be seen. Hematoxylin and eosin. × 100.

FIG. 2. A section of same kidney as shown in Fig. 1 under greater magnification. Note the intense hydropic degeneration of proximal convoluted tubules and the normal appearance of the distal convoluted tubules immediately adjacent to the glomerulus. Hematoxylin and eosin. × 100.

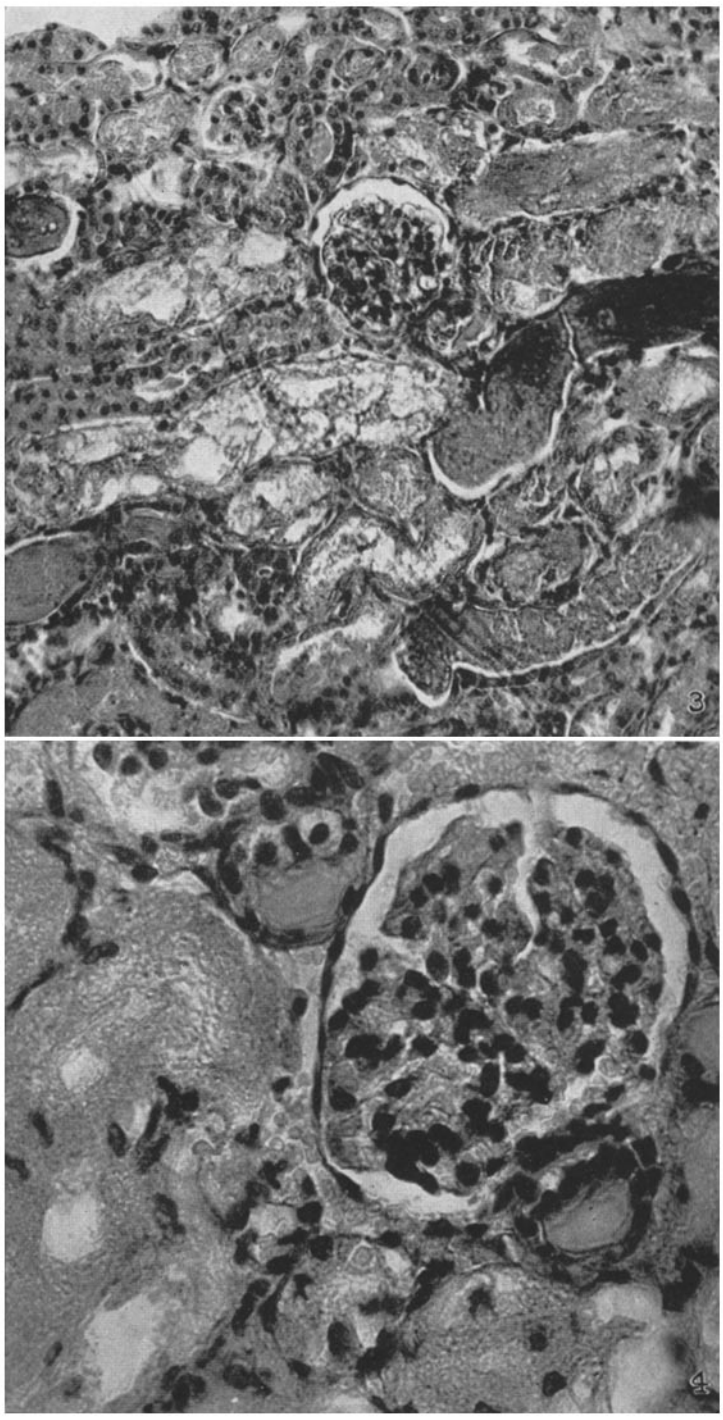


(Friedman and Kaplan: Site of renin formation in kidney. IV)

PLATE 4

FIG. 3. Kidney of rabbit which had received 1.5 gm. of tartrate per kilo, 48 hours before. Observe the complete transformation of the epithelium of the proximal convoluted tubules into hyaline necrotic masses. At the top of the section, intact epithelium of distal convoluted tubules may be seen, also normal appearing glomerulus. Hematoxylin and eosin. × 100.

FIG. 4. A section of same kidney as shown in Fig. 3, under greater magnification. Intact glomerulus can be seen, surrounded by necrotic epithelium of proximal convoluted tubules. There are several distal convoluted tubules present which have not become necrotic. Hematoxylin and eosin. × 100.



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