Relationship of Juxtaglomerular Apparatus
to Renin and Angiotensin

By Louis Tobian, M.D.

In a symposium devoted to angiotensin, it is appropriate to consider briefly the juxtaglomerular apparatus. Angiotensin makes its appearance in the body as a direct result of the proteolytic action of renin, and there is considerable evidence to support the hypothesis that all the renin in a kidney comes from the juxtaglomerular apparatus.

Before reviewing this evidence, the anatomy of the juxtaglomerular apparatus should be considered. It consists of 2 separate cell types, the granular cells and the macula densa cells. The granular juxtaglomerular cells actually lie within the medial layer of the afferent glomerular arteriole. They have small, uniform-sized granules in the cytoplasm, which can be clearly stained with Bowie's stain or with osmic acid. When examined with the electron microscope, these cells are seen to have a rich endoplasmic reticulum with an abundance of RNA granules, a Golgi apparatus, and their specific cytoplasmic secretory granules. When there are abundant granules in the cytoplasm, these cells have all the appearances of actively secreting cells. One side of the granular cell abuts the intimal layer of the afferent arteriole. On the other side, the border of the cell may interdigitate with the border of the macula densa cells. The macula densa consists of specialized cells which are part of the wall of the distal convoluted tubule. Their staining characteristics are different from the usual epithelial cells lining the distal tubule. The macula densa cells are always at the very first part of the distal tubule and are always in close proximity to the vascular pole of the glomerulus of their particular nephron. As mentioned above, there are certain areas where the membranes of the granular juxtaglomerular cells and the macula densa cells are inseparable and actually interdigitate with one another. The 2 cell types are probably also closely related physiologically. When the granular cells change their rate of secretion, certain enzymes in the macula densa cells also change their activity.

There are 3 separate lines of evidence indicating that all renin comes from the juxtaglomerular apparatus. The first line of evidence relates to the striking correlation in the rat between the abundance of granules in the juxtaglomerular cells and the content of extractable renin in the kidney. For instance, if 1 renal artery is narrowed in the rat, the juxtaglomerular granules practically disappear in the contralateral kidney. At the same time, the amount of extractable renin in this contralateral kidney also becomes vanishingly small. If the "ischemic" kidney is subsequently excised and the hypertension is "cured," both the juxtaglomerular granules and the extractable renin reappear in normal abundance in the contralateral kidney. Similarly, if desoxycorticosterone and salt are given to rats, the juxtaglomerular (JG) granules practically disappear, and there is a virtual disappearance of extractable renin. When rats are placed on a low intake of sodium, both the renin content and the JG granularity increase in their kidneys. Conversely, rats on a high intake of sodium have a concomitant reduction of both renin and JG granules. In all the studies just referred to, the amount of renin and JG granules have been determined in the same kidney.

Gross and coworkers have investigated the amount of extractable renin in many physiologic states in the rat. These results can be...
correlated with other studies of JG granularity. For instance, rats receiving desoxycorticosterone and practically no dietary sodium have a fairly normal granularity of the JG cells\textsuperscript{1,9} and a normal amount of extractable renin.\textsuperscript{10} In metacorticoid hypertension in rats, the kidneys have a subnormal amount of both renin\textsuperscript{11} and juxtaglomerular granules.\textsuperscript{9} In rats with adrenal insufficiency, there is an increased granularity of the JG cells\textsuperscript{1,9,12} and an increased content of renin.\textsuperscript{13} In all the rat experiments, the amount of renin and abundance of JG granules have shown a very strong correlation. These observations would fit in with the hypothesis that the juxtaglomerular granules contain renin.

The second line of evidence emerges from microdissection studies on kidneys. These studies were done in 2 different laboratories, that of Bing in Copenhagen and of Cook at Oxford. Originally Peart, Gordon, Cook, and Pickering found that the parts of a kidney cortex which were purely tubular contained very little extractable renin. Renin could be found only in those areas of kidney with glomeruli.\textsuperscript{14} Cook and Pickering then caused glomeruli to become clogged with magnetic iron particles. When the glomeruli were subsequently isolated magnetically, they contained most of the renin in a kidney.\textsuperscript{15} Cook then devised an ingenious procedure with a microguillotine for splitting the isolated glomeruli into a half which contained the vascular pole and another half which was opposite to the vascular pole. He extracted these halves for renin and found that all of the renin was in the half with the vascular pole. This finding indicated that renin was not in the glomerular tuft itself, since there was an equal amount of tuft in either half. The principal specialized structures present at the vascular root of the glomerulus are the granular cells and the macula densa. One or both of these structures probably contain the renin.

Bing and coworkers also discovered independently that all of the renin in a kidney was in the neighborhood of the glomeruli.\textsuperscript{16} They then isolated glomerular tufts by microdissection and found no renin in them.\textsuperscript{16} Also, on microdissection, they noted that there was very little renin in the areas between the glomeruli.\textsuperscript{17} They concluded that renin was located very near the glomeruli but not in the glomerular tufts and not in the areas between glomeruli.\textsuperscript{17} Again, the structures of the vascular pole of the glomerulus were implicated. Bing found that afferent arterioles did not contain renin.\textsuperscript{17} They dissected the arterioles free, but there is a question as to how much of the wall, or material in the wall, was removed by the dissection. Bing favors the macula densa as the locus of renin. Their work does not indicate conclusively that renin is in 1 part of the juxtaglomerular apparatus or the other, but it certainly narrows it down to an area somewhere in the juxtaglomerular apparatus. Thus, both Cook and Bing found the main locus for renin in a kidney to be the structures at the vascular pole of the kidney, the same area occupied by the juxtaglomerular apparatus.

The third line of evidence comes from Hartroft and Edelman, who prepared antibodies to renin and tagged them with fluorescent. Frozen sections of the kidney of a rabbit that had been on a low-salt diet were exposed to a layer of solution containing the fluorescent antibody. Examination of these sections showed that the fluorescent antibody localized in the cytoplasm of the granular juxtaglomerular cells. This particular experiment would emphatically point to the granular cells themselves as the locus of renin.\textsuperscript{18}

All 3 of these lines of evidence lead to the same conclusion: that renin is located mainly in the juxtaglomerular apparatus. Any 1 of these approaches would be quite suggestive, but the combination of all 3 constitutes very strong evidence for this hypothesis. Hence, when one thinks of renin, he should also be thinking of the juxtaglomerular apparatus. Renin is probably secreted by some element in the JG apparatus.

In working either with extractable renin or with stains of the juxtaglomerular granules, one is struck by the fact that opposite
physiologic maneuvers produce opposite effects on the content of granules or of renin. Hence, it is probable that the presence of abundant JG granules represents one extreme of secretion, and the complete absence of granules represents the opposite extreme. In certain situations, hypergranularity is associated with hyperplasia of the JG cells. In most secretory tissues, hyperplasia usually represents a state of hypersecretion. Therefore, hypergranularity of the JG cells probably represents a state of hypersecretion, and the absence of JG granules probably indicates a very low rate of secretion.

Certain experimental maneuvers cause a hypergranularity of the JG cells, and others cause a diminution in granularity. All the observations seem to fit in with the hypothesis that the JG cells act as stretch receptors. First, the JG cells are in the media of the afferent glomerular arteriole and, therefore, would undergo the same changes in stretch that affect the wall of the afferent arteriole. It is quite reasonable to postulate that stretch receptors, acting as volume receptors, exist in the walls of arteries. The JG cells are in an excellent anatomic location to perform such a job. Various observations would indicate that whenever the wall of the afferent arteriole with its JG cells becomes less distended, the JG cells become hypergranulated, indicating an increased rate of secretion. Conversely, when the wall of the afferent arteriole is slightly overdistended, the JG cells are increasingly stretched and, as a result, become less granulated and slow their rate of secretion.

The JG cells increase their granulation in the following situations:
1. Adrenal insufficiency.
2. Shock.
3. Experimental constriction of the thoracic inferior vena cava in the dog with resulting ascites.
4. Low sodium intake.
5. Cure of renal hypertension by removing an "ischemic" kidney. JG granules reappear abundantly in the remaining kidney.
6. Narrowing the renal artery of the kidney which is contralateral to an "ischemic" kidney. This contralateral kidney often has an increase in JG granularity.
7. Narrowing the renal artery in 1 of the 2 kidneys. The "ischemic" kidney shows the increase in JG granularity.
8. Experimental aminonucleoside nephrosis in the rat with resulting edema and ascites.
9. Chronic chlorothiazide administration in the rat.

In all of these situations, either the pressure in the renal arterial bed is reduced, or the volume of blood in the arteries is decreased. Either type of change would be expected to diminish the stretch of the JG cells.

On the other hand, juxtaglomerular granules are considerably reduced in the following situations:
1. Administration of desoxycorticosterone and salt.
2. High intake of salt.
3. The "untouched" contralateral kidney which is opposite to a kidney in which the renal artery is narrowed.
4. Kidneys in rats with metacorticoid hypertension.
5. Kidneys in rats with adrenal regeneration hypertension.
6. The lone kidney in rats with "nephrosclerotic" hypertension.
7. Isolated kidneys which have been perfused for 2 hours at a high perfusion pressure.
8. Rats receiving the sympathomimetic drug, naphazoline hydrochloride.

In all of these situations, either the blood pressure in the renal arterial bed is increased, or the volume of blood in the arteries is increased. With either type of stimulus, there would be an increased stretch of the JG cells. Therefore, when the stretch is increased, there is a reduction of JG granules; when the stretch is decreased, there is an increase in the granularity. A diminished stretch would thus be a stimulus for hypersecretion, while an increase in stretch would slow the rate of secretion. One is left with
a strong suspicion that the JG cells act as stretch receptors that are continuously monitoring the volume of blood in the afferent glomerular arteriole. If this is so, they would seem to qualify as one of the mysterious "volume receptors" for which many of us are searching.

References
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LOUIS TOBIAN

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