Control of Renin Release

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DURING THE PAST 5 YEARS there have been remarkable advances in our understanding of the functions of the renin-angiotensin hormonal system. It is now clear that angiotensin is the primary regulator of aldosterone secretion (40). Moreover, evidence is accumulating to indicate that angiotensin exerts an important direct regulatory control over arterial blood pressure under a variety of normal physiological states via its vasoconstrictor actions. Many of the functions and properties of this system have been reviewed in recent years (40, 80, 115, 117; see also Can. Med. Assoc. J. 90(4): 1964). However, there exists at present a considerable controversy in a particularly critical area, namely, the control of renin release. This review is an attempt to analyze the various theories proposed and the rapidly expanding body of literature underlying them.

I. THEORIES PROPOSED FOR CONTROL OF RENIN RELEASE

Introduction

A brief description of the relevant renal anatomy is essential for an understanding of the possible control mechanisms; more detailed descriptions may

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be found elsewhere (4, 82–85, 97, 113). There is general agreement that renin is formed in the specialized area of each nephron known as the juxtaglomerular (JG) apparatus, which is composed of three anatomical structures: 1) granular cells; 2) the macula densa; 3) mesangial cells. The granular cells, which appear to be differentiated smooth muscle cells in the media of the arterioles (particularly the afferent) just adjacent to the glomerulus, are presumed by most investigators to be the site of renin formation, storage, and release. The macula densa is the specialized tubular area that marks the transition from ascending loop of Henle to distal tubule. This nephron segment always lies in contact with the vascular pole of its glomerulus of origin, and the cells themselves are closely associated anatomically with the granular cells (see below). The mesangial cells appear to be interstitial cells in contact with both the granular cells and macula densa.

After the early experiments of Goldblatt and others (see refs. 13, 115) on the production of renal hypertension by partial constriction of the renal artery, it was assumed that the factor stimulating renin release was renal ischemia. There is little question today, however, that ischemia is not a necessary requirement for renin release. Huidobro and Braun-Menendez (94) demonstrated that arterial pressor activity in the dog was not increased by breathing 7–8% O₂, carbon monoxide, or 2–5% CO₂, nor by the production of histotoxic anoxia with cyanide. The lack of effect of low inspired Po₂ on acute renin release in dogs has recently been confirmed by Skinner et al. (129). Divry (47) demonstrated that no detectable renin release occurred during perfusion of a dog kidney with venous blood at normal perfusion pressures. Perhaps the strongest evidence against the concept that renal ischemia is the stimulus for renin release is the recent demonstration that renin release can be stimulated by reductions of renal perfusion pressure too small to cause significant decreases in renal blood flow (127, 129, 153). Finally, the alterations of sodium balance that affect renin release (see section II) clearly do not produce renal ischemia. A possible role for chronic hypoxia, however, has been suggested by the demonstration that prolonged hypoxia causes increased JG granulation in rats (114).

With the recognition that ischemia is not required for renin release, most investigators have come to stress two other concepts as to possible mechanisms controlling renin release; these have been labeled the intrarenal baroreceptor theory and the macula densa theory. Because either of these theories by itself can explain most but not all of the experimental observations, the bulk of this review consists of a critical analysis of the data supporting each theory.

Both the baroreceptor and macula densa theories are completely intrarenal in the sense that detection of the afferent stimulus occurs within the kidney itself. The development of such theories was a natural result of the concentration of research efforts on renal hypertension. Recently, however, as a consequence of observations relating sodium balance to the renin-angiotensin system, attention has been drawn to the possible role of extrarenal “volume” receptors acting via the renal nerves and adrenal catecholamines (149). Interaction of the sympathetic nervous system with the intrarenal receptor, whether baroreceptor or macula densa or both, is probably of considerable importance and may well explain the inadequacies of the previous theories.
Baroreceptor Theory

In 1940 Kohlstaedt and Page reported (95) that in perfused dog kidneys a decrease in pulse pressure without change in mean pressure was an adequate stimulus for renin release. Their experiments, however, were complicated by changes in urine flow and renal blood flow. In contrast, Kolff (96) reported that renal pressor output could be increased by reduction of renal perfusion pressure, but that no difference was observed between pulsatile and nonpulsatile perfusion. This problem has recently been carefully restudied by Skinner et al. (127, 129), who measured renal venous and arterial pressor activity during graded aortic constriction. Renin release was not observed when pulse pressure was reduced, but did occur with very slight reductions (10 mm Hg) in mean renal arterial pressure. Renin release was not stimulated even when pulse pressure was virtually abolished (without change in mean pressure) by a combination of aortic constriction and vagotomy. A combination of reduced mean pressure and increased pulse pressure was achieved by the administration of ganglionic blocking drugs and stimulation of the peripheral end of a severed vagus nerve; this combination resulted in increased renin release. Further evidence against pulse pressure as a primary stimulus has been provided by Davis et al. (41), who observed increased renin concentrations in renal venous and peripheral blood despite elevation of the arterial pulse pressure in experimental high-output cardiac failure achieved by an aortic-caval fistula. Their dogs did have a reduced mean arterial pressure. It seems clear, therefore, that the intrarenal receptor mechanism that responds in some manner to changes in mean arterial pressure does not respond to changes in arterial pulse pressure. Yet a word of caution seems in order before dismissing pulse pressure completely; if, as seems likely, the renal nerves play an important role in renin release, reflex control of release might well be influenced by extrarenal vascular receptors such as the carotid sinus (28, 91) and aortic arch, which are, in part, responsive to pulse pressure. (See below for a discussion of the possible role of extrarenal receptors and renal nerves.)

The concept of a renal baroreceptor sensitive to changes in mean arterial pressure was postulated quite early by several groups of investigators (see ref. 13), but has received its most cogent expression more recently by Tobian (141, 142). Tobian has suggested that because the JG granular cells are located in the media of the afferent arteriole they undergo the same changes in stretch that affect the wall of the afferent arteriole. In this manner, the granular cells could act as stretch receptors; an increased blood pressure would stretch the granular cells and inhibit renin release, whereas a decreased blood pressure would reduce granular cell distention and enhance renin release. The lack of responsiveness to pulse pressure is compatible with this theory, since the arterial pulse would be considerably damped at the level of the JG apparatus.

In order to evaluate this postulated baroreceptor, it is necessary to define the actual stimulus being detected. Obviously, it cannot be arterial pressure per se, since the granular cells are located in the arterioles, not the arteries. The following seem to be the most likely possibilities: 1) intravascular pressure within the afferent arterioles at the site of the granular cells; 2) transmural pressure of the afferent
arterioles at the site of the granular cells; 3) tension within the granular cells, i.e., the product of the transmural pressure and the arteriolar radius, as given by Laplace's law.

What factors will alter the magnitude of these three possible stimuli?

1) **Arterial blood pressure.** A change in arterial blood pressure will obviously tend to produce similar directional changes in afferent arteriolar intravascular pressure, transmural pressure, and wall tension. However, this need not always be the case since a change in arterial pressure can be either blunted or amplified at the site of the granular cells by a change in active tone in the afferent arteriole.

2) **Active afferent arteriolar vascular tone.** Pressures at the site of the granular cells reflect, in large part, the activity of the afferent arteriolar smooth muscle. Thus, for example, an increased renin release not accompanied by decreased arterial pressure (as in simple salt deprivation) does not in itself provide evidence against the baroreceptor theory, because it ignores possible changes in afferent arteriolar tone. An increased afferent arteriolar constriction would have an effect on granular cell "stretch" similar to that caused by a decreased arterial pressure (see ref. 102 for an interesting theoretical treatment of this problem). The possible role of the sympathetic nervous system in mediating such changes is discussed below.

3) **Renal interstitial pressure.** Under most physiological conditions the renal interstitial pressure is relatively constant, so that transmural pressure will vary directly with intravascular pressure. However, many of the experimental manipulations used to study renin release (including osmotic diuresis, ureteral occlusion, renal venous occlusion, congestive heart failure, perinephritis, and others) may cause large increases of renal interstitial pressure and thereby may decrease transmural pressure. Because of the location of the granular cells, it might also be postulated that the critical extravascular pressure is the macula densa intratubular pressure rather than the interstitial pressure. This distinction is probably of little importance, however, since it has been shown that renal tubular and interstitial pressures generally change in a similar manner (76, 77).

**Macula Densa Theory**

The anatomy of the JG apparatus undoubtedly has played the primary role in stimulating speculation concerning a function for the macula densa. Now, a generation after Goormaghtigh (71, 72) proposed that the glomerular filtration rate (GFR) is, in some manner, controlled by the macula densa fluid via the JG cells, the controversy still persists. Indeed, the possibility has not been ruled out that renin is actually synthesized in the macula densa rather than the granular cells (8). The anatomical and histochemical evidence suggesting a functional relationship between the macula densa and renin secretion may be summarized as follows.

1) Both in light and electron microscopy an intimate anatomical relationship may be seen between the macula densa and granular cells (4, 84, 97, 113). The cell groups seem separated at times only by an incomplete basement membrane.
with possible cytoplasmic bridges between them (84). All the above authors have pointed out, with Goormaghtigh, that this relationship might permit either sampling of macula densa fluid or transferal of information concerning its composition to the granular cells.

2) McManus (106) first demonstrated that the Golgi apparatus of the macula densa cells was unusual in that it was located in the basal rather than the luminal portion of the cell, and he suggested that some substance passed from macula densa cell to granular cell.

3) A positive correlation has been found between JG granulation and activity of hexose monophosphate shunt enzymes of the macula densa (as studied histochemically) under a variety of experimental conditions (17, 52, 88, 89).

4) Friedberg (58) has demonstrated an inverse relationship between loop of Henle length and JG granulation. He has also observed (59) that the adult distribution of JG granularity is achieved in mice at the 3rd week of intrauterine life, a time that correlates well with the maturation of the long loops of Henle. These findings led him to suggest the possibility of a functional relationship between renin secretion and loop function.

5) Barajas and Latta (5) observed the appearance of dense cytoplasmic bodies in the macula densa in association with increased JG granulation in adrenalectomized rats.

6) Reeves et al. (120) have described an increased height and hydropic changes in the macula densa in patients with cirrhosis. Reeves and Sommers have recently demonstrated (121) a specific increase of macula densa height in rats fasted (with free access to water) for 24 hr; this increase showed a significant reciprocal correlation with urinary sodium excretion. Brown et al. (17) have reported increased macula densa height in kidneys with chronic renal artery constriction.

These anatomical observations, as well as a growing body of physiological studies (see section II), have led numerous investigators to propose that renin release is controlled primarily by the macula densa. The specific macula densa parameter most commonly suggested as a possible signal is either the tubular fluid osmolality or sodium concentration (19, 87, 97, 98, 113, 121, 137, 153). The concept stems largely from micropuncture studies, which have established that early distal tubular fluid (and presumably the macula densa fluid, which has never actually been sampled) always has an osmolality and sodium concentration less than those of plasma (66, 74, 75, 78, 164). This phenomenon results from the fact that the ascending loop of Henle actively reabsorbs sodium but is apparently relatively impermeable to water. Unfortunately, existing micropuncture data are inadequate to validate either the osmolality or sodium concentration theory. Moreover, the countercurrent functioning of renal medullary structures is not yet understood well enough to warrant dependable predictions concerning even the direction of changes in macula densa fluid composition resulting from manipulations known to inhibit or stimulate renin release. These problems are well illustrated by the data for osmotic diuresis, virtually the only condition for which data on both early distal micropuncture and renin release are available, albeit in different species. The administration of hypertonic mannitol caused an increase early distal osmolality
(78, 147), whereas infusion of hypertonic saline actually reduced early distal osmolality below the level seen in antidiuresis (78). Since both mannitol and hypertonic saline are known to inhibit renin release (153), these data militate against osmolality as the macula densa stimulus. It should be stressed, however, that the micropuncture data cited above were limited in number, highly variable, and for portions of the tubule slightly distal to the macula densa. The data concerning sodium concentration in early distal tubule are also perplexing. Intuitively, one might expect hypertonic saline infusion to increase early distal sodium concentration, but just the opposite has been demonstrated (67); the mass of sodium was increased but the sodium concentration was unaltered or decreased (67). Similar results have also been reported for osmotic diuresis induced by urea, glucose, and mannitol (78). Since all these diuretics are known to inhibit renin release (153), the data are consistent, and Thurau and Schnerrmann have postulated (137, 140) that renin release varies directly with macula densa sodium concentration. In support of this theory, Thurau and his co-workers have performed ingenious experiments in which fluids of varying solute compositions were injected, by a micropipette, into the early distal tubule. They have observed that isotonic sodium chloride or bromide caused rapid collapse of the proximal tubule of the same nephron, a result they believed was caused by the local release of renin, generation of angiotensin, and cessation of GFR. Equiosmolar solutions of mannitol did not produce collapse, nor did sodium chloride when the kidneys were depleted of renin by salt-loading and unilateral nephrectomy. Unfortunately, there are other possible reasons for tubular collapse in their experiments, and the authors should provide direct evidence that the collapse was due to renin release. Moreover, Cortney et al. (38) have perfused loops of Henle with isotonic saline and observed that early distal sodium concentration varied directly with perfusion rate. These data seem to be in conflict with the micropuncture data for saline diuresis described above, but the differences may be due to the concentration and rate of their perfusions. In conclusion, it is evident that we need micropuncture studies of early distal fluid in the many experimental situations known to be associated with changes in the rate of renin release (see section II). Otherwise, all theories concerning the role of tubular fluid osmolality or sodium concentration will remain speculative.

It seems to this reviewer, however, that a correlation is discernible; renin release may vary inversely with the total load, rather than concentration, of sodium delivered to the macula densa (80, 148, 153). This relationship could make renin release highly responsive to changes in body fluid balance and cardiovascular function. A stepwise analysis based on micropuncture studies in rats and dogs follows.

1) A decrease in the filtered load of sodium either does not alter or may increase fractional proximal sodium reabsorption (46, 65, 69, 119, 134, 157). The studies cited utilized renal artery or aortic constriction. Similar studies during reduction of plasma volume will be important.

2) Conversely, expansion of extracellular volume (accomplished by infusion of isotonic or hypertonic saline) usually increased GFR and either does not alter or may reduce fractional proximal sodium reabsorption (37, 46, 67, 157).
Therefore, changes in salt balance or cardiovascular function that increase GFR or decrease proximal sodium reabsorption will enhance the load of sodium entering the loop of Henle. Conversely, decreased GFR or increased proximal reabsorption will diminish loop sodium load.

These changes will be partially cancelled because the ascending loop of Henle adjusts its rate of transport to the load of sodium presented to it (32, 37, 66, 67, 147, 161). However, the compensation is incomplete, and the delivery of sodium to the macula densa will be altered. Thus, Landwehr, Schnerrmann, Klose, and Giebisch (personal communication) have reported that reduction of GFR in the rat by means of an arterial clamp caused decreased total sodium delivery to the early distal tubule.

I propose that, by some mechanism, the sodium load to the macula densa is detected and that there exists a reciprocal relationship between sodium load and renin release. It should be noted that Thurau and Schnermann (137, 140) have postulated the opposite conclusion—that an increased sodium load stimulates the release of renin. They have theorized that this system, by generating angiotensin in response to an increase GFR, would autoregulate renal blood flow and GFR. It is difficult for me to accept their hypothesis, because virtually all measurements during acute reduction of renal arterial pressure (accomplished by aortic or renal artery constriction) have demonstrated increased renin release. I should like to emphasize, however, that regardless of the validity of Thurau’s general theory of autoregulation, his data (described above) concerning macula densa sodium concentration will be important for any understanding of the specific stimulus to the macula densa.

It is possible that the macula densa cells might detect changes in their sodium load via changes in their own intracellular sodium concentration. As described above, the proximal tubules and the ascending loops of Henle transport sodium at rates directly related to the total load of sodium presented to them. If the macula densa cells operate similarly, then their rate of sodium uptake and their cellular sodium concentration might vary directly with the total sodium load rather than with the sodium concentration of the intraluminal fluid. Reeves and Sommers (121) have suggested an intriguing mechanism by which intracellular sodium concentration might control renin secretion; they have observed that “biochemically and histochemically the effect of sodium on glucose-6-phosphate dehydrogenase in vitro is inhibitory.” As described above, this is one of the macula densa enzymes known to vary directly with renal renin content and might be involved in the synthesis of renin or a transmitter substance controlling renin release.

In concluding the discussion on this perplexing problem, it seems fitting to point out that Stamey (133) has postulated the antithesis of the theory proposed above. He has suggested that renin release is directly, rather than inversely, related to macula densa sodium reabsorption rate. According to his theory, complete cessation of glomerular filtration should inhibit renin secretion, and he has cited as evidence the lack of JG granulation of human kidneys not forming filtrate (133). However, Luciano and Vander (manuscript in preparation) have observed high rates of renin release in dogs whose kidneys were being perfused at 25–30 mm Hg so as to prevent glomerular filtration.
Sympathetic Nervous System Theory

There is no question that a completely intrarenal mechanism exists that can alter the rates of renin synthesis and release. The previous two sections have described the major concepts concerned with this mechanism, namely the baroreceptor and macula densa theories. Recently, however, evidence has accumulated to indicate the existence of reflex neural and humoral control of renin secretion.

Taqini et al. (136) reported that denervation of a rat kidney decreased renin content in that kidney as compared to the opposite intact kidney. This work has been confirmed by Tobian et al. (143), who reported 40% fewer JG granules in the denervated kidney. Vander (149) demonstrated in dogs that direct electrical stimulation of the renal nerves caused increased renin release; renin release was also induced in these experiments by the intravenous infusion of either epinephrine or norepinephrine during maintenance of a constant renal arterial pressure by means of aortic constriction. Wathen et al. (155) and Bunag et al. (28) have observed that infusion of catecholamines directly into a renal artery produced an increase in renin release. However, when given via intravenous infusion, pressor amounts of catecholamines failed to increase renin release (155). Scornik and Paladini (126) have demonstrated that intravenous infusions of norepinephrine caused small but significant increases in plasma angiotensin. Norepinephrine infusion combined with reduction of renal perfusion pressure resulted in a marked increase in plasma angiotensin despite the fact that perfusion pressure reduction alone did not alter plasma angiotensin. Finally, Bunag et al. (28) have reported that renin release was stimulated by infusion of tyramine or dimethylphenylpiperazinium (DMPP) directly into the renal artery.

These experiments, therefore, have conclusively demonstrated that the sympathetic nervous system can alter renin synthesis and release. There are at least three mechanisms by which the renal nerves (and adrenal catecholamines) might control renin release: 1) direct control of the granular or macula densa cells [the JG apparatus receives a rich supply of nonmyelinated nerve fibers presumed to be sympathetic (3, 44)]; these nerves might be important, not only in directly altering renin release, but also in setting a basal “tone,” i.e., a permissive role facilitating other types of stimuli; 2) amplification of the signal to the postulated JG stretch receptors by inducing afferent arteriolar constriction; and 3) amplification of the signal to the postulated macula densa receptor by reducing GFR as a result of afferent arteriolar constriction. It has also been claimed that the renal nerves directly influence tubular sodium reabsorption (11), but this question remains unsettled.

It will be a difficult but critical task to distinguish between these possibilities. What seems especially important, however, is that we recognize the likelihood that our hope of finding a single “volume” receptor controlling renin release (and thereby aldosterone secretion) may well be ended. It is possible that the receptors that initiate renin-releasing reflexes are the same intrarenal receptors that participate in the wholly intrarenal control system. However, it seems more likely that other receptors, extrarenal in location, are involved. The entire problem of the
location of volume receptors has been well summarized by Smith (191), Farrell and Taylor (49), and by Gauer and Henry (60). Although the emphasis in their reviews was on the control of aldosterone secretion, the same discussion might well apply to renin. Indeed, the neural reflexes controlling renin release (see section II) may be the link that will reconcile theories concerned with neural and renal pathways for control of aldosterone secretion. Recently, Hodge et al. (91) demonstrated that occlusion of the common carotids increased plasma angiotensin (presumably because of increased renin) in 10 of 17 dogs. Bunag et al. (28) were able to stimulate renin release more consistently during carotid occlusion, probably because they maintained renal arterial pressure constant despite the systemic hypertension caused by the occlusion. Thus, these experiments demonstrated that extrarenal baroreceptors can alter renin release and that their reflex contribution may be obscured by other direct influences on the kidney.

**Hormonal Control of Renin Secretion and Role of Angiotensin**

It has recently been demonstrated (29, 43, 64, 148, 150) that angiotensin exerts a negative feedback control over renin release that is independent of changes in renal arterial blood pressure or aldosterone secretion. Vander and Geelhoed (150) observed that the increased renin release induced in dogs by aortic constriction (or ureteral occlusion) was suppressed by small quantities of angiotensin infused intravenously during maintenance of constant reduced renal arterial pressure. Moreover, even the very low rates of renin release observed under normal conditions (i.e., without aortic constriction of ureteral occlusion) were further reduced by antihypertensive infusion during maintenance of constant arterial pressure. This inhibitory effect of angiotensin on renin release in dog has been confirmed by Bunag et al. (29). Genest et al. (43, 64), working with humans, were able to reduce the elevated plasma renin concentration induced by salt depletion by infusing subpressor quantities of angiotensin. In both the dog (61) and human (43), aldosterone administration failed to lower plasma renin in similar experiments. The specific mechanism by which this negative feedback is exerted is at present unknown. It is evident, however, that the plasma angiotensin concentration may play an important role in the control of renin secretion and may help to explain, at least in part, such phenomena as the decreased renin secretion exhibited by the unclamped kidney in Goldblatt hypertension.

The possibility also exists that renin release may be altered by circulating hormones other than angiotensin and catecholamines. Bunag et al. (29) have reported that vasopressin, but not oxytocin, was a powerful inhibitor of the renin release induced by reduction of renal perfusion pressure. The doses used in their study were large, and their important observations should be extended. Fasciolo (50) was unable to induce renin release in dogs with acetylcholine, histamine, vasopressin, growth hormone, or ACTH. Interestingly, intravenous kallikrein induced renin release in anesthetized but not unanesthetized dogs. Vander and Luciano (152) failed to induce renin release in dogs by the renal intra-arterial
infusion of kallidin, bradykinin, acetylcholine, histamine, serotonin, or dopamine. Bunag et al. (28) reported that renal intra-arterial infusion of isoproterenol, serotonin, or acetylcholine did not cause renin release. Vander (unpublished observations) has observed that intravenous infusion into dogs of very small quantities of freshly voided dog urine usually caused renin release without significant changes in arterial blood pressure. The interpretation of these preliminary observations awaits further investigation. There is also suggestive, but indirect, evidence from studies of salt depletion (described below) that may indicate the importance of other hormones, as yet unidentified, in the control of renin release. In conclusion, it should be noted that hormones other than aldosterone may regulate proximal sodium reabsorption (46, 67). These hormones could indirectly influence renin release by altering the sodium load to the macula densa.

II. ANALYSIS OF RENIN RELEASE DATA

Introduction

Section I presented a primarily theoretical description of the major theories invoked to explain the control of renin release. There now exists a rapidly increasing number of experiments in which renin release has been evaluated by one or more of several criteria (see below). The remainder of this review analyzes these experiments and attempts to answer the following questions: 1) Are the proposed theories (either individually or in combination) adequate to explain the experimentally observed changes in renin release? 2) Are any of the theories either favored or excluded by the experimental data?

The analysis of section I emphasizes the difficulties encountered in attempting to distinguish between the baroreceptor and macula densa theories; a decreased afferent arteriolar pressure will usually be associated with a reduced macula densa sodium load resulting from a decreased GFR. Therefore, the experiments designed to separate these phenomena (see below) have generally involved manipulations of either tubular sodium reabsorption, renal interstitial pressure, or plasma sodium. These experiments, therefore, receive predominant emphasis in the following discussion.

Methodological Considerations

A quantitative evaluation of renin release requires measurement of total renin secretory rates. The data required are renal venous-arterial renin differences and total renal plasma flow. For obvious reasons, studies providing these data have been relatively few. Instead, the concentration of renin-like material in peripheral or renal venous plasma (or lymph) has generally been used as a measure of renin release. The deficiency of this approach is that no account is taken of the other determinant of plasma renin concentration, namely, the rate of renin destruction.
Very little is known about this latter process, and the ultimate validation of plasma renin as a measure of renin release awaits the study of renin destruction and secretory rates in each situation associated with changes in plasma renin.

A second method of evaluating renin secretion utilizes the measurement of renal renin content or juxtaglomerular granulation. Such data obviously bear only indirectly on the question of renin release because renal renin content is the resultant of both synthesis and release. However, there appears to be a significant positive correlation between renal renin content (or JG granulation) and plasma renin concentration in chronic experiments. In contrast, several investigators have demonstrated a poor correlation between renin content and plasma renin during relatively short time periods (80, 110, 132).

Finally, several types of studies are not cited: 1) experiments involving the experimental production of hypertension but lacking data on renin concentration in plasma or kidney; 2) studies concerned with the secretion of aldosterone but lacking data on renin; 3) data for human hypertension (with the exception of primary aldosteronism). This last area presents exceptional hazards for the interpretation of renin control mechanisms, and there still exists no general agreement as to the role of renin in essential and renovascular hypertension (see Can. Med. Assoc. J. 90 (4): 1964).

Hemorrhage and Systemic Hypotension

Acute hemorrhagic hypotension increased renin release in the dog (24, 45, 81, 94, 122, 124, 126), rat (166), and rabbit (105). Acute systemic hypotension due either to histamine (81) or to intestinal manipulation (94) also increased renin release in the dog, as did nitroprusside infusion in humans (146). These data are obviously consistent with both the baroreceptor and macula densa theories. Also consistent is the observation by Brown et al. (24) that a 500-ml hemorrhage without arterial pressure diminution failed to increase plasma renin in supine human subjects. In contrast, Bunag et al. (28) demonstrated that slow hemorrhage (15–20 ml/kg) in the absence of arterial pressure decrease produced increased renin release in anesthetized dogs. The release was prevented or greatly reduced by the administration of tetraethylammonium or local infiltration of the renal hilus with lidocaine. Similar experiments have been reported by Hodge et al. (92), who measured plasma angiotensin rather than renin. These investigators observed that hemorrhage in dogs produced increased plasma angiotensin despite a constant or negligibly reduced arterial pressure. Local anesthesia of the renal nerves prevented the response. Clearly, the renin response to mild hemorrhage is primarily mediated by the sympathetic nervous system. Under these conditions, do the renal nerves increase renin release by a direct effect or by amplifying the signal to the JG cells or macula densa? The final interpretation of these important experiments will await simultaneous measurement of renal blood flow, GFR, sodium excretion, and intratubular fluid composition.

Although the renal nerves may play an essential role in nonhypotensive hemor-
rhage, there is no question that they are not required for the increased renin secretion observed during hypotension (28, 81, 94). Despite their lack of essentiality, however, they almost certainly are influential in determining the magnitude of renin release during hypotension. This is strongly indicated by the experiments of Paladini and Scornik (116), who reported increased plasma angiotensin during hemorrhagic hypotension but not during similar hypotension induced by ganglionic blocking agents. In addition, Kaneko and co-workers (personal communication) have observed that, in humans, ganglionic blockade did not abolish the renin response to hypotension (induced by nitroprusside) but did reduce it.

**Acute Local Reduction of Renal Arterial Pressure**

During Oliguria or Natriuresis

Renal arterial pressure can be locally decreased in the absence of systemic pressure reduction by one of the following procedures: employment of a pump-perfused kidney; partial constriction of the aorta just above the renal arteries; partial constriction of a renal artery; inflation of an intra-aortic balloon just above the renal arteries. Because these experiments do not reduce the arterial pressure in the rest of the animal’s body, extrarenal cardiovascular reflexes that might alter the intrarenal receptor response are eliminated. Regardless of the experimental method employed, all investigators have reported, in anesthetized dogs not receiving diuretics, increased renin release during local reduction of renal perfusion pressure (47, 96, 99, 127–130, 153, 160). The intrarenal receptor was sensitive to as little as 10 mm Hg reduction of pressure (129). Similar studies should be performed in trained, unanesthetized animals to evaluate the receptor’s sensitivity under more physiological conditions.

These experiments in nondiuresing dogs meet the criteria for both the macula densa and baroreceptor theories; a decreased perfusion pressure (90 mm Hg) significantly lowered the GFR (153, 160), and invariably reduced sodium excretion (153; see this paper for further references). There was a significant inverse correlation between sodium excretion and renal venous renin concentration (153).

In order to produce a combination of decreased arterial pressure and increase macula densa sodium load, Vander and Miller (153) administered various osmotic diuretics (including urea, mannitol, sodium sulfate, isotonic and hypertonic sodium chloride), chlorothiazide, and acetazolamide during or prior to arterial pressure reduction. The diuretics prevented or reversed the usual increase in renin release. White (160) has demonstrated that injection of mercapto merlin or renal intraarterial infusion of 1 M NaCl or sucrose suppressed the renin release induced by reduction of renal arterial pressure. Vander and Luciano (151) have reported similar data using chloromerodrin. The following analysis indicates that these effects of diuretics are not explainable by the baroreceptor theory. The suppression of renin release occurred despite the maintenance of mean renal arterial pressure at 80–90 mm Hg. Therefore, for the diuretics to have increased JG cell stretch, as required by the baroreceptor theory, they must have induced either afferent arteri-
olar dilation or a reduction in renal interstitial pressure (thereby increasing transmural pressure). Did such changes occur?

Interstitial pressure. It is well documented that osmotic diuretics increase renal interstitial pressure (77, 138, 163) and decrease vascular transmural pressure (138). Therefore, according to the baroreceptor theory, they should stimulate rather than inhibit renin release. This concept is analyzed further in the section on ureteral and venous occlusion.

Afferent arteriolar tone. Many investigators have demonstrated that osmotic diuretics generally induce renal vasodilation. However, Vander and Miller (153) observed that suppression of renin release occurred during osmotic diuresis without significant change in renal plasma flow as long as renal perfusion pressure was maintained at 90 mm Hg. These seemingly contradictory findings become consistent when one analyzes current theories concerning the mechanism of vasodilation usually produced by osmotic diuretics. It has been postulated (68, 112, 138) that the vasodilation occurs as a result of myogenic reflex initiated by the reduced vascular transmural pressure associated with osmotic diuresis. It has also been shown that local reduction of renal perfusion pressure to 80–90 mm Hg produces maximal myogenic vasodilation and that, under these conditions, increasing interstitial pressure will cause no further vasodilation (138, 139). As predicted by this analysis, Vander and Miller (153) observed in several dogs that osmotic diuresis at 80–90 mm Hg perfusion pressure induced large decreases in renal plasma flow, probably due to increased venous resistance resulting from elevated tissue pressure (138). Despite this plasma flow reduction, suppression of renin release still occurred. Finally, in the experiments of Vander and Miller (153), both chlorothiazide and acetazolamide tended, if anything, to decrease renal plasma flow.

In summary, the ability of diuretics to inhibit the renin release produced by reduction of renal arterial pressure does not appear explainable on a hemodynamic basis and constitutes strong evidence for a nonbaroreceptor intrarenal receptor. The data are consistent with the macula densa theory since these diuretics increase the sodium load to the macula densa despite the decreased arterial pressure. It should be restated (148), however, that these experiments do not rule out the possibility of a baroreceptor, the action of which might be masked by a more potent inhibitory input from the postulated macula densa receptor.

To date only one study has reported the effect of a local increase in renal perfusion pressure on renin secretion (145). Degranulation of JG cells was observed in rats 2 hr after the onset of perfusion and was interpreted as an indication of decreased renin synthesis. This interpretation may not be warranted because of the difficulties involved in the analysis of acute JG granulation changes.

Acute Sodium Depletion by Natriuretic Drugs

As described in the section above, chlorothiazide and mercurial diuretics inhibit the increased renin release induced by reduction of renal arterial pressure. In contrast, it has recently been demonstrated that the administration of these
same (25, 26, 151) or similar-acting (57, 108) natriuretics to the normotensive dog (25, 26, 151) or human (57, 108) increased renin release within 1–2 hr, i.e., at a time when the natriuresis still was present and the macula densa sodium load was almost certainly greater than normal. Vander and Luciano (131) and Meyer et al. (108) have reported that this did not occur when salt depletion secondary to the diuresis was prevented by administration of fluids. Under these conditions, changes in plasma sodium or mean arterial blood pressure usually did not occur. Thus, it was the fluid depletion rather than the drugs or diuresis per se that stimulated renin release.

In summary, it is evident that natriuretic drugs exert dual, seemingly paradoxical effects on renin release: 1) the diuresis itself can inhibit the renin release usually produced by renal arterial pressure reduction; 2) the acute salt depletion resulting from the diuresis causes enhanced renin release despite the continued presence of the diuresis. Perhaps the most important implication of these effects is that the mechanisms controlling renin release during pressure reduction and during salt depletion must, at least in part, be different. The data are consistent with the following, admittedly speculative, hypotheses: 1) both renal arterial pressure and the state of diuresis influence renin release primarily by altering macula densa sodium load; 2) salt depletion causes reflex enhancement of renin release by a mechanism(s) that can operate, at least in part, independently of the macula densa. Vander and Luciano (152) have demonstrated that the sympathetic nervous system may play a modifying role in this latter response but that it is not an essential pathway; mercurial-induced acute salt depletion caused increased renin release despite renal denervation and the administration of ganglionic, alpha, and beta blocking agents. Therefore, they suggested the possible existence of an unidentified hormonal pathway controlling renin release. It may be important to note that the sympathetic nervous system, on the basis of present evidence (see above), appears to play a more important role in the renin response to hemorrhage than in the response to salt depletion. Obviously, this area requires further investigation, and it seems likely to this reviewer that the resolution of these dual effects observed for natriuretic agents will aid in elucidating and relating the various theories proposed for control of renin release.

Ureteral or Renal Venous Constriction

Experiments utilizing ureteral or renal venous constriction, when compared with the data concerning osmotic diuretics described above, offer a fascinating spectrum of results (all data for anesthetized dogs): acute elevation of ureteral pressure increased renin release (153); partial renal venous constriction did not significantly alter renin release (199; Vander, unpublished observations); osmotic diuretics inhibited the renin release induced by aortic constriction (153). These data are important because the procedures all produce very similar changes in intrarenal pressures (76, 77). Specifically, they all increase intratubular pressure and interstitial pressure, but decrease vascular transmural pressure (see ref. 138).
Therefore, the lack of similar effects of the procedures on renin release militates against any of these pressures being the critical controlling input. In contrast, the data are consistent with the macula densa theory, because early distal sodium load is increased by osmotic diuretics and decreased by ureteral occlusion. The lack of effect of venous constriction on renin release is also consistent because, as recently demonstrated by Wathern et al. (156) and Vander (unpublished observations), partial venous occlusion in antidiuretic dogs causes a natriuresis. This reflects inhibition of sodium reabsorption, which, if located proximally to the macula densa, would maintain a constant macula densa sodium load despite moderate GFR reduction. In support of this interpretation, Lewy and Windhager (personal communication), using micropuncture, have recently demonstrated that partial renal venous constriction inhibits proximal sodium reabsorption.

Chronic Sodium Depletion or Sodium Loading

Induction of chronic (24 hr or more) sodium depletion by dietary sodium deprivation, either alone or in combination with natriuretic agents, consistently produced elevated plasma renin in humans (1, 2, 18, 19, 35, 49, 51, 154, 162) and dogs (9, 27). Studies of JG granulation and renal renin content (80, 83) demonstrated increased renal renin during chronic salt depletion or water deprivation in rats. Conversely, increased dietary sodium intake reduced renin release in humans (18, 19, 154) and in rats (see 80, 83).

The above data are generally consistent with both the baroreceptor and macula densa theories. It seems reasonable that arterial pressure, GFR, and plasma sodium would all tend to decrease during salt depletion and would increase during high salt intake. However, even under conditions of relatively large depletion, such changes have not been consistently observed. For example, Binnion et al. (9) reported that arterial pressure and plasma sodium did not change when dogs were given a 1–2 meq sodium diet and 2 ml of mercuhydrin daily for 3 days (on the 4th day, plasma sodium did decrease). A reduction in pulse pressure was observed. Brubacher and Vander (27; manuscript in preparation) demonstrated, in dogs maintained on 10 meq Na/day, an increased plasma renin without significant change in mean or pulsatile arterial pressure, GFR, renal plasma flow, or plasma sodium. Salt deprivation in man frequently is not associated with changes in plasma sodium (7, 10). GFR reduction, particularly in man, seems a relatively consistent finding (see ref. 159), but there are conflicting data (93, 103). The fact remains that sodium excretion is decreased during sodium deprivation or depletion, and the uncertainty as to what happens to GFR may reside in the extreme difficulty of detecting small GFR changes (159). Clearly, under these conditions, small changes in either JG cell stretch or macula densa sodium load may be the result of increased renal sympathetic tone. Brubacher and Vander (manuscript in preparation) using dogs have observed that after bilateral surgical renal denervation, the renin response to dietary salt deprivation was delayed and reduced in magnitude for several days. However, on the 4th day, the plasma renin increased to the same de-
After administration of ganglionic, alpha, and beta blocking agents did not reduce the elevated renin. Similarly, Lewis et al. (101) and Greene and Vander (manuscript in preparation) have demonstrated that humans with renal transplants show a normal rise in plasma renin in response to low-sodium diet. It is evident, therefore, that the sympathetic nervous system may play a modifying role in the renin response to chronic sodium deprivation but is not essential. This situation is similar to that described above for acute salt depletion and is suggestive of an unidentified hormonal control mechanism. Finally, it should be noted that Malnic et al. (104), using micropuncture, have reported decreased delivery of sodium to the early distal tubule in rats on a low-sodium diet.

Adrenal Steroid Excess or Deficit

Numerous investigators have demonstrated that a primary excess or deficit of adrenal mineralcorticoids is generally associated with decreased or increased renin secretion, respectively (see 80, 83). This problem is of special clinical importance because human primary aldosteronism is associated with markedly reduced plasma renin (21, 35, 43), plasma angiotensin (62), and JG granulation (33). Conversely, Addison's disease in humans is associated with an increased plasma renin (18). Present data indicate that the changes in renin secretion are due to alterations in sodium balance rather than to a direct negative feedback of aldosterone on renin secretion: 1) prolonged therapy of primary aldosteronism with aldosterone or natriuretics caused an increase plasma renin concentration (21); 2) the decreased JG granulation induced by deoxycorticosterone in rats was prevented by reducing dietary sodium intake (see ref. 83); 3) neither acute nor chronic administration of exogenous aldosterone reversed the plasma renin increase caused by sodium depletion in humans (43, 64) and dogs (61). It is unnecessary, therefore, to analyze these data in terms of renin control theories since the previous discussion of sodium depletion and loading is applicable.

Experimental Renal Hypertension

Peripheral plasma renin concentrations in animals with one Goldblatt (or perinephritic) kidney and one intact kidney cannot be used for the interpretation of renin control mechanisms because these concentrations are the resultant of different secretory rates by the two kidneys. On the other hand, a study of the individual kidneys is revealing. This subject has been extensively reviewed (80, 141), and the following observations are generally accepted and well documented: 1) placing a clamp on one renal artery (or inducing unilateral perinephritis) but leaving the other kidney untouched causes increased renin content of the clamped (or perinephritic) kidney and decreased renin content of the untouched kidney; 2) unilateral nephrectomy combined with renal artery clamping of the remaining kidney results in unchanged renin content of that kidney.
These findings are generally compatible with both the baroreceptor and macula densa theories. Thus, the baroreceptor theory interprets the changes as reflecting a decreased pressure in the clamped kidney (or a decreased transmural pressure in the case of perinephritis) and an increased pressure in the untouched kidney. Presumably, in some manner, the removal of the untouched kidney allows the pressure beyond the clamp to reach normal levels and restore renin content to normal. There are, however, several findings that are difficult to reconcile with the baroreceptor theory in its simplest form: 1) the renin content of the untouched kidney decreases regardless of whether hypertension develops (12, 80); 2) the renin content of the untouched kidney increases during dietary sodium restriction despite little or no change in the hypertension (59, 144). These findings could be explained by the baroreceptor theory if changes in afferent arteriolar constriction were occurring in the untouched kidney. Simultaneous studies of renal hemodynamics, the renal nerves, and rates of renin release under these conditions will be critical.

The macula densa theory can explain the renin data as due to changes in GFR or sodium reabsorption in the clamped and unclamped kidneys. Such changes form the basis of clinical renal function tests for renovascular hypertension in patients and have received confirmation from experimental work in the dog (111, 135). Chronic constriction of one renal artery decreased GFR and sodium excretion in the clamped kidney and increased these parameters in the opposite kidney. Removal of the normal kidney was followed by a rise in GFR and sodium excretion back to (or above) preconstriction levels. The mechanisms mediating these changes are unknown.

Another factor that may be important in reducing the renin content of the untouched kidney in hypertension is the inhibition of renin release produced by angiotensin. If this is true, however, it requires that plasma angiotensin concentration be increased in experimental hypertension, a phenomenon not yet established.

Congestive Heart Failure, Cirrhosis, and Nephrosis

Plasma renin concentration in humans is usually elevated in all three diseases (18, 51, 64, 107, 154, 165). Davis and his co-workers (41, 89, 90) have also demonstrated increased renin secretion in dogs with experimental secondary hyperaldosteronism. Genest et al. (64) have presented evidence indicating that the control of renin release may be different in these diseases, generally classified together as secondary hyperaldosteronism; treatment by natriuretics and sodium restriction caused a decrease plasma renin in cardiac patients, no consistent change in patients with cirrhosis, and consistent increases in patients with nephrosis. Analysis of renin release mechanisms operative in these diseases would require a review of disease-induced hemodynamic changes beyond the scope of this review (see ref. 39). The tendency toward reduction of arterial pressure and GFR in these diseases is consistent with both the macula densa and baroreceptor theories. A possible role for the renal nerves is also suggested by the studies of Barger et al. (6), who demon-
strated a unilateral increase in sodium excretion after the renal intra-arterial injection of Dibenzyline in a dog with congestive failure. In contrast, Carpenter et al. (31) have reported that hyperaldosteronism and sodium retention resulted from thoracic inferior vena cava constriction even in dogs having only a transplanted kidney. Plasma renin measurements under such conditions will be critical.

Miscellaneous Situations Associated With Changes in Renin Release

**Pregnancy.** Increased plasma renin has been demonstrated throughout normal pregnancy (18, 51, 64). There is little reason at present to speculate on the stimulus for renin release since the renin may originate in the placenta rather than the kidneys (14).

**Postural changes.** It has been demonstrated that assumption of the upright position (36) or tilting (15) results in a rapid increase in plasma renin. In light of the well-documented hemodynamic changes associated with postural changes, these data are consistent with both the baroreceptor and macula densa theories. Participation of the sympathetic nervous system is strongly suggested by the work of Gordon et al. (73), who observed that four patients with sympathetic nervous system disease (postural hypotension) had subnormal increases in plasma renin in response to upright posture. The response was normalized by infusion of catecholamines.

**Exercise.** Helmer (86) has demonstrated an increased plasma renin in normal humans during exercise. Conn et al. (36) observed little change in renin when subjects were exercised in the supine position. More data are needed in this interesting area.

**Evidence concerning the regional distribution of renin within the kidney.** In rats (16, 48) and in mice (58, 59), there is a greater renin content or JG granulation in the superficial zone of the cortex (excluding the subcapsular agglomerular zone) than in the juxtamedullary zone. As pointed out by Brown et al. (16), this regional distribution is consistent with both the baroreceptor and macula densa theories.

**Correlations between renin and plasma sodium or urine sodium.** Pitcock and Hartroft (118) studied JG granulation in an unselected group of 200 patients at necropsy and observed that JG granularity was significantly correlated reciprocally with the plasma sodium concentration but showed no correlation with blood pressure of the patient before death. Brown et al. (21) have reported a significant inverse correlation between plasma sodium and renin in a series of hypertensive patients. A significant inverse correlation between plasma renin concentration and urine sodium excretion but not arterial blood pressure has been observed in anesthetized dogs (153) and in humans (43). These relationships offer indirect support for the macula densa theory but are not necessarily incompatible with the baroreceptor theory, as described above in the section on sodium balance.

**“Conditioning” effect of dietary sodium.** Bunag et al. (30) have reported that placing dogs on a low-sodium diet increased their renin release in response to aortic constriction, hemorrhage, and norepinephrine infusion. The mechanism of this “con-
ditioning" effect is unknown, but it may be secondary to the increased renal renin content induced by a low-sodium diet.

**Concluding Remarks**

Figure 1 is a diagrammatic summary of presently considered pathways for the control of renin release. A change in "effective" blood volume is presented as the initiating event because such changes probably do represent the adequate stimulus in a variety of situations. It should be recognized, however, that many stimuli such as pain, fright, or exercise might be capable of initiating reflexes leading to alteration of renin release.

It is clear that the control of renin release is considerably more complicated than originally visualized. On the one hand, there exists a wholly intrarenal mechanism, be it baroreceptor or macula densa (or both), capable of altering renin release. On the other hand, there exist more complex reflex control pathways that may predominate under usual physiological conditions. Generally, these two mechanisms probably work additively or synergistically. However, the dual effects of natriuretic drugs demonstrate that they can operate, at least in part, in opposing directions. As regards the intrarenal mechanism, it seems to this reviewer that a considerable body of evidence is consistent with the concept of a macula densa receptor but cannot be explained by the baroreceptor theory as presently postulated. Yet, despite the ability of the macula densa hypothesis to explain most (but not all) of the present data, there certainly exists no conclusive evidence to rule out the possibility that a baroreceptor also exists. The need at this time is for experiments that will provide critical differentiation between the two theories and a more precise delineation of functional characteristics. It is my hope that the theoretical
analysis described in this review will stimulate such experiments. It is obvious that our recent realization of the importance of reflex pathways controlling renin release has opened new and fertile areas for future research. Of particular importance will be the elucidation of the functional and anatomical relationships between the reflex pathways and the intrarenal mechanism. The "X hormone" of Fig. 1 is, at present, based only on indirect evidence from experiments on acute and chronic sodium deprivation; the evidence is suggestive enough to warrant further investigation. Another area that has been neglected concerns the possibility that changes in distribution of the renal blood flow might be important in controlling renin release.

In conclusion, it seems likely that the juxtaglomerular apparatus may well be a site for integration of several diverse inputs.

ADDENDUM

A recent micropuncture study by J. H. Dirks, W. J. Cirkensa, and R. W. Berliner (J. Clin. Invest. 45: 1875-1885, 1966) demonstrates that various potent diuretics, including mercurials, actually produce increased proximal fractional sodium reabsorption, despite continued presence of the diuresis, when salt depletion is allowed to occur in dogs. These experiments, therefore, raise a critical question as to whether macula densa sodium load is really increased or perhaps even decreased during natriuretic-induced acute salt depletion. If the latter, then the experiments described above in Acute Sodium Depletion by Natriuretic Drugs would be explainable in terms of the macula densa hypothesis. This is by no means certain, however, since inhibition of loop sodium transport might still produce enhanced macula densa sodium load despite a reduced delivery from the proximal tubule. Measurements of total early distal sodium load will be critical.

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