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SYMPATHETIC CONTROL OF RENIN RELEASE

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INTRODUCTION

The pressor activity of kidney extracts was described before the turn of the century (1). However, it was Goldblatt's (2) observation on the hypertensive effect of renal ischemia that kindled interest in the mechanism of the pressor action of renin, leading ultimately to its elucidation in the laboratories of I. H. Page and E. Braun-Menéndez. Using the current nomenclature (3, 4) the events are as follows: renin substrate (angiotensinogen), a plasma α-2-globulin, formed in the liver, is cleaved by the hydrolytic action of renin. Angiotensin (1–10) decapeptide (angiotensin I) is formed, and subsequently transformed to angiotensin (1–8) octapeptide (angiotensin II) by the action of peptidylpeptidase (converting enzyme, kininase II), an enzyme that removes the 9–10 dipeptide. The biological effects of angiotensin II go beyond its commonly recognized effects as a vasoconstrictor and a stimulus to the glomerulosa cells of the adrenal cortex (5). The octapeptide as well as the decapeptide may be degraded by a group of peptidases. One of the possible products is believed to have biological activity, i.e. angiotensin (2–8) heptapeptide (angiotensin III).

Disenchantment followed the initial enthusiasm for the potential role of renin in the pathogenesis of hypertension (6). Nevertheless, 25 years after Goldblatt's observation, the role of the renin-angiotensin system in the regulation of the secretion of aldosterone was established (7–10) and interest in the factors that regulate renin release was rekindled. More recently a role for the renin-angiotensin-aldosterone system in the pathogenesis of hypertension has been widely accepted though not fully understood.

Renin is synthetized, stored, and released by juxtaglomerular granular cells (JG cells) of the vascular component of the juxtaglomerular apparatus (JGA). The mechanisms that control the synthesis and release of renin by

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the JG cells are referred to as intrarenal, when the signal for the release is perceived by a structure within the kidney (vascular receptor, macula densa), or as extrarenal when the signal is perceived or initiated outside the kidney and the message conveyed by the autonomic nervous system or by plasma borne substances. The multiplicity of control factors, some of which may affect the JG cells directly as well as through the intrarenal receptors, introduces an element of complexity in the design and interpretation of experiments. Moreover, it is hardly conceivable that under physiological conditions renin release is controlled by one mechanism without the simultaneous participation of the others. The mechanisms that regulate the release of renin by the kidney were frequently reviewed during the past decade (11–15). Keeton & Campbell (16) have recently compiled the most extensive review of the subject, covering the literature through 1979.

Studies on the innervation of the JGAs in the rat overwhelmingly support its adrenergic nature (17). There is not enough evidence in support of a role of the parasympathetic outflow in the control of renin release. The effects of acetylcholine on renin release appear to be indirect, through alterations perceived by other regulatory mechanisms (16).

The role of the sympathetic nervous system in the control of renin release has been studied in vivo in unanesthetized and anesthetized animals as well as in the isolated perfused kidney, kidney slices, glomeruli, or concentrates of JG cells. Much of the progress in the understanding of the sympathetic nervous system is related to the development of pharmacological agents, agonists and antagonists of catecholamines, the majority of which have been employed in studies on the control of renin release. The use of radioligand binding techniques for the identification and quantification of adrenergic receptors (18) has not been applied to JG cells. Unfortunately the multiplicity of structures that receive adrenergic innervation within the kidneys is a deterrent to any such attempts. It will be necessary to wait for the development of adequate procedures to separate JG cells from tubular cells and other vascular cells before definitive identification and characterization of adrenergic receptors in JG cells become possible.

METHODS OF STUDY

Experiments In Vivo

The two main end-points used to detect changes in the release of renin by the kidney are: (*a*) a change in the level of renin in plasma or serum, or (*b*) a change in the output of renin by the kidney, calculated as the product of renal plasma flow and the difference in renin levels between renal venous and arterial plasma. Some authors have made semi-quantitative estimates of renin release by collecting blood from the vena cava next to a renal vein (19) or above and below the renal veins (20).

The use of systemic plasma levels presumes that the half-time of renin is not altered by the experimental condition studied. A half-time of 2 hours or less has been reported for the slower phase of the two exponential components of the disappearance curves in nephrectomized animals (21–24) and somewhat longer in nephrectomized humans (23, 25). The kidney, however, appears to remove renin from the circulation (26) at a rate that may be modified experimentally (27, 28). However, in acute experiments in which changes in plasma renin activity are monitored over short periods, the impact of changes in metabolism or excretion of renin are probably irrelevant. To increase plasma renin activity by 50% in 30 minutes in the dog without a change in the rate of renin release, its metabolism should become less than one tenth of control (29).

The assumption that the experimental procedure will not affect the rate of uptake of circulating renin by the kidney is also made when Fick's equation is used to estimate renal renin release. Likewise it is assumed that there are no significant changes in the proportion of released renin being delivered to the general circulation via the renal lymphatics. It has been documented in several species that the lymphatics drain renin from the kidney (27, 30, 31). Indeed micropuncture studies support the concept that all renin is released by the JG cells to the interstitium and that the uptake of renin by plasma occurs at a point beyond the efferent arteriole (32, 33). Renin concentration in renal lymph is higher than in renal venous plasma, and follows its changes closely (34, 35). However, on account of the slow flow of renal lymph, the fraction of renin released to the circulation by this route is quite small. The data of Gan & Lockett (31) in the cat indicate that no more than 5% of the renin released by the kidney reaches the systemic circulation via the lymphatics. A potentially more important pitfall in the use of Fick's equation to measure renal renin release by the cat kidney stems from the unique disposition of the renal venous drainage in this laboratory animal (36), a factor that is often overlooked. Since there is a difference in the concentration of renin in subcapsular and deep renal venous plasma of the cat kidney (24), and adequate mixture of blood from both sources in the common renal vein is unlikely (36), to measure common renal venous minus arterial renin concentration difference may be misleading. This consideration gains relevance if there are differences in the relative contribution of superficial and deep JGAs to renin release in response to the stimulus studied (37). Renal losses of water are reflected in the concentration of solutes in the renal vein. The potential for error, albeit small, that this artifact entails in the application of the Fick formula to the kidney increases with high or variable urine flows. Results may be corrected by the incorporation of urine flow rate to the calculation (38) or by normalizing renin concentration in arterial and venous blood by the corresponding plasma protein concentration (24).

The plasma levels of renin are expressed by the rate of formation of angiotensin I in the presence of inhibitors of converting enzyme and angiotensinases. Radioimmunoassay has become the standard laboratory procedure to measure angiotensin I. However, the conditions under which the reaction of renin and renin substrate proceed are far from standard. Any differences in the conditions for the generation of angiotensin I in the course of the analysis must be considered when comparing or even interpreting experimental results. The term plasma or serum renin activity (PRA or SRA) is reserved for measurements in which only endogenous renin substrate is available for renin to hydrolyze. This amount of substrate is usually insufficient to assure zero order kinetics (39). This is a disadvantage in chronic studies during the course of which the experimental procedure may modify the plasma levels of renin substrate as well as those of renin itself. Even in acute experiments the use of PRA or SRA might fail to reveal significant changes in the renal venous minus arterial renin levels (40). Plasma or serum renin concentration (PRC or SRC) designates measurements in which the sample is complemented with an excess of renin substrate. Although higher yields of angiotensin I are obtained, the usual techniques need not secure zero order kinetics in these reactions (39). Moreover, for purposes of comparison the source of substrate, whether homologous or heterologous (39), as well as other conditions such as the pH of incubation, should be considered. The procedure used to inactivate endogenous substrate in PRC determinations, as well as certain inhibitors of the degradation of angiotensin I used to measure either PRA or PRC, may result in the activation in vitro of enzymatically inactive renin that circulates in the plasma of some species. This is a potential source of error in estimating the release of active renin (41).

Attempts to infer the direction and intensity of changes in the rate of renin release from the renal content have been made since the early studies on granularity of the JG cells in different forms of hypertension (42). Within a certain range, renal renin content in the dog was found to correlate with the rate of renin release both in vivo and in vitro (43). The content of renin of the JGAs has been measured in outer and inner cortex of the rat under various conditions in an effort to explore regional differential responses (44–46). However, there are reports that suggest that changes in total (47) or regional (37) renin release need not be followed by proportional changes in renal renin, or that the latter may actually change in the opposite direction (48).

An inverse relation between sodium balance and the content and rate of renin release of the kidney has been repeatedly confirmed since Gross & Sulser (49) reported that the pressor activity of kidney extracts decreased in salt loaded steroid treated rats. This inverse relation is best illustrated by

plotting PRA versus urinary sodium excretion (an expression of sodium intake) as proposed by Laragh's laboratory (50).

Effective doses of anesthetics stimulate renin release and modify the intensity of the response of JGAs to other stimuli. With few exceptions PRA or PRC have been found to rise in response to all types of general anesthetics in adult humans and laboratory animals. The mechanisms responsible for the mobilization of renin during anesthesia may vary and have not been defined for all agents. With pentobarbital the rise in peripheral plasma renin is maximal during induction (51–55), whereas PRA and PRC remain elevated for the duration of the anesthesia with diethyl ether (51, 55) or urethane (55, 56). Beta-adrenergic blockade suppresses the renin response during anesthesia with diethyl ether (58), urethane (55, 56), and ketamine (59). The effect of pentobarbital is not suppressed by propranolol in dogs (60–62) or rats (55), and is seen in adrenomedullectomized rats after neonatal sympathectomy with 5-hydroxy-dopamine (55). Some investigators observed a rise in PRA in response to pentobarbital (57) or halothane, enflurane, or ketamine (63) only in salt restricted animals. In newborn piglets PRC increased with halothane but not with pentobarbital anesthesia. Whether this response depends on the species or the maturity of the animals remains to be established (64).

Experiments in the Isolated Perfused Kidney

Isolation of an organ with preservation of its vascular channels may facilitate the study of its function. Unfortunately the isolated mammalian kidney does not maintain all of its functional characteristics when its natural vascular and nervous routes are interrupted. Nevertheless, several preparations of isolated perfused kidneys (65–67) have been used successfully to approach several aspects of the regulation of renin release. The main differences among these preparations are: (*a*) the nature of the perfusate, i.e. whether it does or does not contain red blood cells (66, 67); (*b*) the relation of the perfused organ to a donor animal, i.e. whether the circuit of perfusion is completely isolated (66, 67) or there is a direct or indirect connection of the circulation of the kidney to the circulation of a donor animal (65); and (*c*) whether the perfusate does (66, 67) or does not (68) recirculate through the kidney.

Control of the perfusion pressure, flow rate, and composition of the perfusate plus severance of the renal nerves allows a close definition of the conditions affecting renin release. Nevertheless the functional changes that the isolated perfused kidney undergoes might affect the input from the macula densa to the JGAs. Of particular concern in this connection is that microsampling of the early distal convolution shows tubular fluid concentrations of sodium in the isolated kidney perfused with cell-free medium

(69) that are twice as high as those reported for the kidney in situ (70, 71). It is possible that at this rate of sodium loss, changes are not perceived by the macula densa, or that this receptor is nonfunctional in the preparation. Varying the sodium concentration of the perfusate, Fray (72) obtained a ninefold change in sodium excretion rate without a significant change in renin release. The isolated kidney perfused with cell-free medium has a low vascular resistance with a high flow rate, which permits an adequate oxygen supply. However, a high rate of medullary flow is probably responsible in part for the inability of the perfused kidney to concentrate urine. Glomerular filtration rate is lower than normal. It increases with the perfusion pressure and falls with higher concentrations of oncotic materials in the perfusate. Among the oncotic materials used, fraction V bovine albumin is claimed to be more desirable than the synthetic polymers (73). The suspension of red cells in the perfusate is reported to decrease the flow rate and increase glomerular filtration rate and overall absolute tubular reabsorption of sodium. Nevertheless, the fractional rejection of sodium remains elevated (68). It has not been determined whether the presence of red cells in the perfusate modifies the derangements in segmental fractional solute reabsorption in the isolated kidney.

Experiments In Vitro

Several preparations have been used to study factors that control renin release in vitro to exclude extrarenal, vascular, and tubular influences on the JGAs.

Long after the introduction of renal cortical slices to study renal transport of organic anions (74, 75), essentially the same technique was introduced to measure renin release in vitro (76–78). Release of renin by the slices appears to be a specific process: Renin is released to the bathing medium at a faster rate than soluble protein or alkaline phosphatase (79). The rate of renin release is independent of tissue content of renin (79), except when the kidney content of renin is chronically depressed (80). The presence of glucose in the medium is required (78) for the release of renin. The latter is also reversibly affected by temperature (81). During the process of incubation the slices remain viable, as evidenced by their oxygen consumption (82), and maintain their renin content (83) or even increase it in response to catecholamines (82). Finally, the system responds to the addition of hormones to the bathing medium: Aldosterone (79) and angiotensin II (84) are inhibitory whereas norepinephrine (85) stimulates the release of renin. The rate of renin release by slices of kidney cortex is influenced by the sodium balance of the animals previous to their preparation: slices from sodium deficient animals release renin at a faster rate (86–88), and the rate can be depressed by placing the animals on a high-salt diet (89). If the rate

of release is expressed as a fraction of the tissue content of renin no difference is detected in the unstimulated state (86). However, there is a marked increase in the rate of renin release by the slices from sodium deficient rats in response to norepinephrine added to the bath (88).

Unfortunately there is considerable disparity in the results reported (90). The basal rate of renin release by rat kidney slices may vary between laboratories by a factor of ten (81, 89). Several differences of procedure may contribute to such variability. The thickness of the slice may affect the local concentrations of the components of the medium as they diffuse to the JGAs, as well as the relative contribution to the total renin released by passive leakage through the cut edges. Cho & Malvin (90) report that the half-life of renin in the bath is only 15 minutes if a gas mixture is bubbled through the medium, whereas there is no loss of renin from the medium if the gas is layered above it. In agreement with an earlier report (78) Morris et al (91) found the rate of renin release from rat kidney slices incubated in McCoy's medium to be 50% higher than in a medium with one third its glucose concentration. Weinberger et al (85) added ascorbic acid to delay the degradation of catecholamines in the alkaline medium. It has since been reported (88) that catecholamine breakdown proceeds over 1 hour of incubation in a medium with 1% ascorbic acid at one third the rate observed in the absence of this additive. Finally, the proportion of superficial and deep cortical layers in the slices may determine variations in the measured rate of renin release. Both the content (92) and the rate of release (24) of renin is higher in superficial than deep renal cortex. Baumbach & Skøtt (93) have recently reported seasonal variations in a series of observations on renin release by isolated rat glomeruli; in the course of 5 years summer appeared as the high responsive period.

Several laboratories have successfully measured renin release from concentrates of glomeruli obtained by centrifugation of a collagenase digest of cortex (94–96), by mechanically separating the glomeruli by graded sieving followed by centrifugation (97) or by passage of the suspension through a length of glass tubing between the poles of an electromagnet when the kidney had been previously perfused with a suspension of magnetic oxide particles (98). Khayat et al (99) have recently pointed out that renin release by such preparations may be affected by the length of afferent arteriole that remains attached to the glomerulus. In addition, there may be problems derived from uneven exposure of the granular cells to the bathing medium. They report success with a technique of suspension of JG cells in tissue culture medium. If the claim (99) that large volumes of viable cells can be prepared at one time is substantiated, this technique may prove to be an asset for those interested in testing physiological and pharmacological factors that may affect renin release in vitro.

EXPERIMENTAL EVIDENCE

Experiments In Vivo

The concept that the sympathetic nervous system directly influences the mobilization of renin by the JG cells is supported by anatomical, physiological, and pharmacological studies.

Barajas (17) has recently reviewed the fluorescent histochemical and electron microscopical evidence of adrenergic innervation of the JGAs. This anatomical relationship is the basis for claims of a direct influence of the sympathetic nervous system on the mobilization of renin.

Early experiments showed an increase in renin release following electrical stimulation of the renal nerves (100–102). However these studies did not discriminate between a direct and an indirect effect on renin release inasmuch as a simultaneous fall in renal blood flow and glomerual filtration rate might have determined the change in renin release by the activation of the vascular receptor or the macula densa (101). It has since been established that the renal sympathetic nerves may affect the distal tubular load independently of changes in glomerular filtration rate through stimulation of proximal tubular reabsorption of sodium (103, 104). The issue of a direct action of sympathetic nerves on the JG cells was addressed by Johnson et al (105) by combining the use of papaverine, to block a vasoconstrictive response, with the electrical stimulation of the distal end of renal nerves in the nonfiltering kidney preparation (106) where changing signals from the macula densa are excluded. In these conditions in which variations in the input from intrarenal receptors is suppressed they observed a rise in renin release in response to stimulation of the renal nerves. LaGrange et al (107) obtained an increase in the release of renin by the kidney without measurable changes in glomerular filtration rate of renal plasma flow by selecting the amplitude, frequency, and intensity of the stimuli to the renal nerves. Nevertheless, in these experiments the macula densa cannot be excluded as a mediator of the increase in renin release on account of a drop in urinary sodium excretion observed during the period of nerve stimulation. Taher et al (108) were able to obtain an increase in renin release by stimulating the renal nerves without altering glomerular filtration rate, renal blood flow, or urinary sodium output. They used parameters of nerve stimulation similar to those of LaGrange et al (107). The frequency of stimulation was 0.33 Hz, which seems to be the threshold for renin release in the dog with this procedure (107, 109). Together these observations on the effect of direct stimulation of the renal nerves support the idea that the rise in renin release following hemorrhage (106, 110), hypoglycemia (111), or pharmacological increase in vascular capacitance (112, 113) is due to the increase in sympathetic outflow elicited by these maneuvers. Thames & DiBona (109) observed that stimulation of the renal nerves with an even lower frequency

(0.25 Hz), which in itself had no effect on renin secretion rate, renal blood flow, or urinary sodium excretion, greatly augments the release of renin in response to aortic constriction and furosemide administration. These observations support the concept that renal sympathetic outflow may modulate the intensity of renin mobilization in response to stimuli that affect the JG cells predominantly through signals from the intrarenal receptors (107, 114–118). The effect of the renal nerves on the JGAs has also been studied by comparing renin release from both kidneys after unilateral renal denervation. After one or two weeks, the denervated kidney of the dog releases significantly less renin to the circulation in the anesthetized (119) or awake animal (118). Such difference is not consistently found after acute unilateral renal denervation in the dog (108, 109, 120), and in the cat the same laboratory does not observe it regularly (116, 121, 122). There is no difference in renal perfusion after chronic unilateral renal denervation in the dog (119) to account for the difference in renin release. However, this might be related to the fall in renin content (43) that is observed after chronic denervation (123, 124). The lack of regular results in the cat may be related to the procedure used to sample renal venous blood (116, 121, 122). The dual venous drainage and regional differences in the rate of renin release by the cat kidney (37) were not considered in these experiments. Regardless of the basal rate of renin release, the denervated kidney releases renin at a lower rate than the contralateral organ in response to a variety of stimuli (116, 118, 121, 124, 125), a fact that supports the concept of the modulatory influence of the sympathetic nervous system on renin mobilization. It is of interest, though, that in the absence of a normally innervated kidney, the denervated organ releases renin at a normal rate in response to lowered perfusion pressure (124, 126) or sodium depletion (127, 128).

Several laboratories have demonstrated an increase (129–133) or a decrease (134) in renin mobilization during electrical stimulation of the brainstem and diencephalon. These effects were abolished by renal denervation (130, 132–134). Hemodynamic changes have been observed to occur independently or in a direction opposite to that anticipated were they to be the mediators in the stimulation of renin release (130, 132). Unfortunately urinary sodium was not monitored in these studies. It is of interest that Passo et al (131) required the addition of phenoxybenzamine, a drug that was ineffective by itself, to maximize the inhibitory action of propranolol on the increased renin release following the stimulation of the medulla oblongata. Had sympathetically stimulated increases in proximal tubular reabsorption of electrolytes influenced renin release through the macula densa, such effect would be cancelled by phenoxybenzamine (103). The effect of severance of the connections between brain and sympathetic outflow has been studied in rats and man. Rats fail to respond to hemorrhage with an increase in plasma renin within 2 hours of a spinal cord transection.

However, 24 hours after the transection the rise in plasma renin following hemorrhage was higher than that of controls (135). Mathias et al (136) found that 45° head up tilting of tetraplegic patients produced a substantial fall in blood pressure without changes in plasma norepinephrine or epinephrine. Plasma renin activity rose beyond its already high basal level. Propranolol failed to affect plasma renin activity in the tetraplegics in supine or head up positions. A variety of psychosocial stimuli result from an increase in renin release in several species studied [for references see (14, 16)]. The effect of these conditions after renal denervation has not been studied, and they have been seldom tested after adrenergic blockade. Propranolol pretreatment reduced by 50% the increase in plasma renin activity of rats exposed to an open field (137), and entirely prevented the rise observed during exposure of baboons to high ambient temperature (138), or of rats to intermittent electrical shock (139). In the latter case phentolamine administration was also tested and found to potentiate the increase in plasma renin activity (139). These observations on the influences of psychosocial stimuli on renin release underscore the importance of handling procedures in the sampling of blood for plasma renin determinations (58, 140).

The receptors and afferent pathways that affect the sympathetic outflow to the kidneys have received considerable attention during the past decade. Their possible participation in the control of renin release has been carefully reviewed in recent years (15, 16, 141–144). In addition to the tonic restraining influence of the arterial baroreceptors, there is tonic control of the sympathetic outflow by impulses that originate in low pressure cardiopulmonary receptors and are conveyed to the central system by the vagi. The renal nerves share in the general withdrawal of sympathetic outflow that follows stimulation of these receptors.

Initial studies on the effects of carotid sinus receptors on renin release produced conflicting results. It has since become apparent that input from the cardiopulmonary receptors may simultaneously affect sympathetic outflow, and that input from the intrarenal receptors may simultaneously affect the JG cells, so that withdrawal of the restraining influences of the carotid sinuses may not elicit the expected increase in renin release unless the other factors that affect it are kept constant. Cunningham et al (145) found that plasma renin activity of anesthetized salt-deprived dogs increased within 5 minutes of bilateral carotid artery occlusion, provided the aortic pressure was kept constant. Jarecki et al (146) failed to obtain an increase in renin release following a reduction of the pressure in the vascularly isolated carotid sinuses in seven of ten anesthetized dogs despite maintenance of a constant renal arterial pressure. However, after the input from cardiopulmonary receptors was suppressed by cervical vagotomy, nine of the ten dogs responded to carotid sinus hypotension with an increase in renin release.

This effect was inhibited when arterial pressure was allowed to rise, and abolished by renal denervation. Rocchini & Barger (147) studied conscious uninephrectomized dogs with vagi intact fed normal or low sodium diets. Renal perfusion pressure was kept constant by inflation of a silastic rubber cuff placed around the origin of the renal artery. They observed no change in renin activity following bilateral carotid artery occlusion if renal pressure was allowed to rise. However, if renal pressure was kept constant, occlusion of both carotid arteries for 20 minutes was followed by a significant rise in plasma renin activity. The magnitude of the rise was proportional to the basal level of plasma renin activity in both groups of dogs, with a much higher absolute rise in the salt restricted animals. Ammons et al (19) also found that the relative increase in plasma renin release in response to low carotid sinus pressure was not affected by sodium restriction. They conducted their experiments in anesthetized vagotomized cats whose renal blood flow was kept constant. Propranolol prevented the rise in renin release following hypotension of the carotid sinuses. A similar effect of β-adrenergic blockade was observed in anesthetized, vagotomized dogs whose renal pressure was kept constant during carotid sinus hypotension (148). In the latter studies the possible mediation of an intrarenal receptor in the response of JG cells to carotid sinus hypotension was suggested by the abolition of this response in the ipsilateral kidney during the infusion of phenoxybenzamine to one renal artery. Mark et al (149) studied healthy humans subjected to lower body negative pressure. At levels of –40 mmHg that produce a drop in central venous and arterial pulse pressures, they observed forearm vasoconstriction, tachycardia, and increased plasma renin activity. Under these conditions the restraining input of high pressure arterial receptors and low pressure cardiopulmonary receptors is suppressed.

Evidence in support of the participation of low pressure cardiopulmonary receptors in the regulation of renin release has accumulated over the years (15, 16, 141–143). Provided there are functional vagal afferents and arterial blood pressure or renal blood flow remains unchanged, renin release has been found to increase in response to: modest hemorrhage (15, 150), passive head up tilting (118, 121, 122), and decreases in right atrial pressure (151, 152). Likewise, renin release in dogs is inhibited by: elevation of left atrial-pulmonary pressure in salt restricted animals (153), mechanical stretch of the right atrial wall (154), or the stimulation of receptors in the territory of the left coronary artery by cryptenamine (155). Interruption of vagal afferent pathways prevents the renin response to these stimuli (122, 153, 154) and in basal experimental conditions (156, 157) results in an increase in renin release, suggesting that vagal afferents from the cardiopulmonary region convey a tonic inhibitory influence on renin release. The renal sympathetic nerves are thought to be the efferent limb, since the effects are not seen in denervated kidneys (118, 152, 153, 156). Moreover, since pro-

pranolol prevents the rise in renin release after a nonhypotensive hemorrhage (15, 150), a decrease in right artrial pressure in the supine position (152), passive head up tilting (122) or bilateral cervical vagotomy (157), the effect probably depends on direct adrenergic stimulation of the JG cells. An alternative explanation was set forth by Schrier et al (158) who found that in dogs undergoing a water diuresis bilateral cervical vagotomy was followed by an increase in urinary concentration and a fall in the rate of renin secretion. Vagotomy did not affect these values in hypophysectomized animals. Exogenous vasopressin administered to hypophysectomized dogs had the same effect on urinary concentration and renin secretion rate as bilateral vagotomy had in normal dogs. In addition exogenous vasopressin caused a significant rise in arterial blood pressure, that was not seen in the vagotomized dogs.

Thames et al (10) have studied the interaction of the high and low pressure receptors in the regulation of renin release. They summarized their conclusions as follows (20): (*a*) cardiopulmonary receptors with vagal afferents exert a tonic inhibition of renin secretion in the presence of normally functioning carotid baroreceptors; (*b*) cardiopulmonary receptors can respond to a decrease in blood volume to which arterial baroreceptors are insensitive; and (*c*) when free to exert their normal buffering influence, carotid baroreceptors can markedly or totally inhibit the release of renin which results from complete interruption of afferent vagal traffic from cardiopulmonary receptors. Fisher & Malvin (120) have recently concluded that the cardiopulmonary receptor-vagal afferent-renal sympathetic efferent pathway is not the only mechanism involved in the control of renin release in response to expansion of the circulatory volume. Renin release was suppressed by volume expansion after bilateral cervical vagotomy. In uninephrectomized animals the remaining denervated kidney responded to volume expansion with a suppressed renin release. The participation of low pressure cardiopulmonary receptors in the regulation of renin release in humans is also controversial (149, 152). It is possible that these receptors exhibit a reduced sensitivity in primates as a successful adaptation to the erect posture, the assumption of which in itself probably exposes the right chambers of the heart to greater changes in pressure than a modest hemorrhage (159).

The influence of increased sympathetic activity on renin release is not mediated exclusively by impulses conveyed by the renal nerves. The participation of the adrenal medulla was clearly demonstrated by Otsuka et al (29) who used insulin to induce hypoglycemia and stimulate the sympathetic system in anesthetized dogs. The increase in plasma renin activity was not prevented by bilateral renal denervation, but was markedly reduced by unilateral adrenalectomy and denervation of the contralateral gland. Although a majority of authors believe that circulating catecholamines stimu-

late renin release by direct β-receptor mediated action on JC cells, there is evidence that the intravenous administration of isoproterenol (160), norepinephrine (161), and epinephrine (161, 162) to anesthetized (160) and conscious (161, 162) dogs stimulates renin release at plasma concentrations that are ineffective when attained by direct infusion in the renal artery. Propranolol prevents this effect, (160, 161) suggesting that is is also β-receptor mediated. Johnson et al concluded that this extrarenal action of catecholamines on plasma renin is not mediated by the renal nerves, changes in perfusion pressure, hematocrit, or the plasma concentration of potassium or prostaglandins (162) The multitude of studies on the effects of exogenous catecholamines on renin release has been recently reviewed by Keeton & Campbell (16).

Efforts to characterize the adrenergic receptors that mediate the stimulation of JG cells by norepinephrine liberated at nerve endings or circulating catecholamines have relied on pharmacological studies of the effects of α- and β- receptor agonists and antagonists. After initial reports that propranolol blocks the increase in renin mobilization during stimulation of the brainstem (131) or hypoglycemia (111), experiments in the nonfiltering kidney (163) gave credence to the concept of a direct β-receptor mediated effect on the JG cells. Morphological support for this concept derived from the observation of fluorescent aggregates of 9-amino-acridin propranolol in the vascular poles of rat glomeruli, a phenomenon prevented by *l*- but not by *d*-propranolol (163a). Several attempts have been made to further characterize JG cells β-adrenoceptors within the frame of their subdivision into β_1 (cardiac) or β_2 (bronchial and vascular). Not all the evidence is consistent. Part of the differences may derive from the legitimacy of the assumptions as to the relative selectivity of agonists and antagonists (164) and part may be due to species differences. Keeton & Campbell (16) concluded that while in rats, dogs, and humans the evidence presented by several laboratories suggests that adrenergic stimulation of renin release appears to be mediated by β_1-receptors, experiments in the conscious rabbit (165) and the anesthetized cat (166) identify such receptors as of the β_2 type. Using direct stimulation of the renal nerves in the dog, at low frequencies that do not modify renal blood flow or sodium excretion (167) or increased only to the point that produced a 5% reduction in renal blood flow (168), the stimulation of renin release appears mediated by β_1-adrenoceptors, since it was completely blocked by *d,l*-propranolol and metoprolol (168) or atenolol (167), but was not affected by butoxamine (167). In the cat Johns & Singer (166) found that a cardioselective adrenoceptor blocker was only 20% as effective as *d,l*-propranolol in inhibiting the increase in renin release obtained with high frequency nerve stimulation and thus concluded that the adrenoceptors mediating the renin effect were different from those in the heart. However, these experiments may be interpreted otherwise in the light

of the observations of Kopp et al (168) who found that *d*-propranolol did not affect the increase in renin release following low frequency stimulation of the renal nerves, but did reduce the renin response obtained with a frequency of stimulation that reduced blood flow by half and was only one sixth that used by Johns & Singer (166). Thus, probably an important part of the *d,l*-propranolol effect measured in the latter studies was due to "membrane stabilizing" properties of *d*-propranolol (168).

Several types of evidence suggest that α-adrenergic receptors may also participate in the neural regulation of renin release. Unfortunately in this case the evidence is often contradictory, probably because the intensity and direction of the effects may vary with physiological agents tested. In fact α-adrenergic stimulation may lead to an increase in the release of renin through its effects on the vascular receptor or the electrolyte load of the macula densa. However an inhibitory component in the action of norepinephrine is suggested by evidence in vitro and the observation of an increase in renin release subsequent to α-adrenergic blockade in some experiments in vivo (14). The most convincing evidence in vivo in support of the concept of α-adrenergic mediated inhibitory influence on renin release is found in experiments in the conscious rat (169, 170, 171). Pettinger et al (169) found clonidine, an α-adrenoceptor agonist, to decrease basal, diuretic, and sympathetic nervous system mediated renin release. This effect was not prevented by cholinergic, ganglionic, or peripheral sympathetic neuronal blockade, but was suppressed by the α-adrenergic blockers phenoxybenzamine and phentolamine. For an unexplained reason the latter drug produced complete suppression only in salt-restricted animals. The intrarenal nature of this effect was further supported by the depression of renin release obtained with analogs of clonidine that do not cross the blood-brain barrier (172, 173). Meyer et al (170) studied the effect on renin release of isoproterenol and other drugs administered by the tail vein to conscious rats kept in restraining cages. They found that the stimulatory effect of isoproterenol on renin release was enhanced by ganglionic blockade, administration of guanethidine or reserpine, or by α-receptor blockade with phenoxybenzamine. The effect of isoproterenol was also enhanced by unilateral renal denervation after contralateral nephrectomy. The conclusion that endogenously released catecholamines were responsible for this α-receptor mediated inhibitory effect was further strengthened by the observation of the interaction of tyramine and isoproterenol in this preparation (171). Whereas in small doses tyramine increased the renin response to isoproterenol, a dose-related inhibition of this effect was attained at higher doses. Phenoxybenzamine prevented the suppressive action of tyramine on isoproterenol induced renin release, which was not apparent in rats with chronically denervated kidneys. The authors concluded that the catecholamines released at nerve endings within the kidneys could inhibit renin

release by an α-receptor mediated action. Not all investigators report findings consistent with this concept. In man α-adrenergic blockers normalized catecholamine enhanced renin release in patients with pheochromocytoma (174) and interfered with the renin response to a variety of stimuli in normal men (175). On the other hand a sympathetic discharge stimulated by inhalation of amyl nitrites increased renin release only after the administration of phentolamine (176).

Alpha-adrenergic agonists might inhibit renin release either by a direct α_1-receptor mediated action on the JG cells, or through inhibition of norepinephrine release at neuronal endings by activation of presynaptic α_2-receptors (14).

Experiments in the Isolated Perfused Kidney

Addition of isoproterenol to the perfusion medium, with or without red blood cells, results in an increase in renin release by the isolated kidney of rat (68, 177) and rabbit (178), without simultaneous changes in perfusion pressure or renal vascular resistance. This effect is blocked by *d,l*-propranolol (68, 177, 178), but is not affected by phenoxybenzamine (177). These observations support the concept of a direct β-adrenoceptor mediated stimulation of renin release by catecholamines. Nakane et al (179) could not characterize these receptors as to their subtype in the isolated rat kidney. They found a dose dependent increase in renin release in response to a nonselective or a β_2-selective agonist, and the response to either of them was suppressed by a nonselective or a β_1-selective antagonist.

A case in support of the concept of an α-receptor mediated inhibitory influences on JG cells has been presented by Vandongen et al (180–182). Phenylephrine prevented the renin response to isoproterenol, except in the presence of α-adrenergic blockade with phenoxybenzamine. The possible role of vasoconstriction, which was suppressed by phenoxybenzamine, was ruled out by abolishing it with dihydralazine, a drug that did not interfere with the inhibitory effect of phenylephrine on isoproterenol induced renin release (182). Clonidine lowered the basal rate of renin release by the isolated perfused rat kidney, without suppressing its increase in response to isoproterenol (181). Low concentrations of norepinephrine stimulated renin release (183), but at higher concentrations this effect could only be seen after α-adrenergic blockade with phenoxybenzamine (180). In both cases propranolol blocked the increase in renin release. Fray (72) reported opposite effects of α-adrenergic agonists in the isolated perfused rat kidney. Renin release by the preparation increased after addition of phenylephrine or methoxamine. This effect was interpreted as due to the renal vasoconstrictor action of the drugs, since it was suppressed by increasing the perfusion pressure or preventing vasoconstriction with papaverine.

Since Vandongen & Peart (184) reported that lowering the calcium concentration of the perfusion medium altered the basal rate of renin release of the isolated kidney and the intensity of its responses to medium-borne substances, other laboratories have addressed this problem. Perfusion of the kidney with a calcium-free medium enhanced renin secretion (184–186) and was found to increase the effectiveness of isoproterenol in stimulating renin release (186). Beta-adrenergic stimulation of renin release is coincident with an increase in ^{45}Ca efflux from prelabeled isolated kidneys (185). Lanthanum, a blocker of net calcium efflux, prevents the stimulation of renin release by catecholamines (187), whereas verapamil, which blocks inward movement of calcium in other secretory cells, was found to attenuate norepinephrine induced vasoconstriction (188) as well as the vasoconstriction produced by increasing calcium concentration in the medium (189), maneuvers that inhibited renin release (188, 189). Verapamil did not inhibit renin release stimulated by isoproterenol (188). It is conceivable that factors that raise cytoplasmic calcium are inhibitory and those that lower it are stimulatory of renin release. Fray (190) suggests that the stimulus-secretion coupling process for renin secretion may be exactly opposite to that in other secretory systems. He further hypothesizes (186) that β-adrenergic mediated stimulation of renin release depends on calcium extrusion through a series of events that depend on the integrity of the Na-K pump and end with Na-Ca exchange (186, 189). The attenuation of the stimulatory effect of catecholamines on renin release by the isolated kidney perfused with high concentrations of calcium or low concentrations of sodium (186) and its complete suppression by ouabain or low potassium in the medium (189) support this concept.

Experiments In Vitro

Conclusive evidence for a direct, β-adrenoceptor mediated stimulation of renin release by catecholamines has been obtained by several investigators using preparations in vitro where changes in hemodynamic conditions, electrolyte load to the macula densa, and sympathetic tone or concentration of plasma borne substances are excluded. Isoproterenol stimulates renin release by rat kidney slices (81, 84, 85, 191) and glomeruli (97, 192). This effect is prevented by *dl*- or *l*-propranolol (85, 191) but is not affected by *d*-propranolol (85). Attempts to characterize the β-adrenoceptors of JG cells as to their subtypes have given conflicting results in rat kidney slices (191, 193).

Reports on the effects of catecholamines with α- and β-receptor affinities are somewhat variable. Stimulation of renin release was reported in slices from rat (82, 85, 194) and human (84) kidneys, cortical cell suspensions of rat (94) and cat (95) kidneys, and isolated rat glomeruli (97, 192). This

increased renin release is suppressed by propranolol (81, 82, 85, 195) and persists in the presence of the α-adrenoceptor blocker phentolamine (85). Nevertheless, there is a possible role for α-adrenoceptors as mediators of a direct action of catecholamines on renin release by JG cells. In fact, at concentrations of 10^{-5}M, norepinephrine (81, 195) and epinephrine (81) inhibit renin release from rat kidney slices, and this effect was reversed by phenoxybenzamine (81) or phentolamine (195). Another laboratory (82) found that both α-receptor blockers potentiated the stimulation of renin release by norepinephrine. In a later publication this laboratory (91) reported that norepinephrine and epinephrine caused a dose related inhibition of renin release at concentrations of 10^{-6} to 10^{-3} M, and that this effect was completely reversed by phentolamine. It is of interest that in the latter study the authors carefully discarded the outermost slice from each side of the kidney, thus working only with the inner layers of the cortex. The other authors that reported α-receptor mediated inhibition of renin release always studied deep cortex, since they sliced the kidneys transversally (81, 195). It is conceivable that α-adrenoceptors in JG cells effectively mediate inhibitory influences on renin release, but that in JGAs as in other territories (196) α-adrenoceptors distribute regionally, clustering in the deeper layers of the cortex. Alternatively, the effect may be α_2-receptor mediated, as has been postulated to explain similar effects observed in vivo (14). That sympathetic neurone endings are viable structures in kidney slices is suggested by the observation that tyramine stimulated renin release by rat kidney slices, an effect blocked by propranolol and cocaine, but not phentolamine (197).

The concept that β-adrenergic agonists stimulate renin secretion by activation of adenylcyclase is supported by several observations in vitro. Renin release by a dog renal cell suspension was increased by the addition of cyclic AMP to the medium (97). Theophylline, an inhibitor of phosphodiesterase, with no effect by itself, potentiates catecholamine stimulation of renin release by rat kidney slices (82), which is actually accompanied by an increase in the cyclic AMP content of the slices (88). Surprisingly, papaverine, a potent inhibitor of phosphodiesterase, was reported to block the stimulating effect of catecholamines on renin release by rat kidney slices (198). However, since papaverine produced a dose dependent inhibition of basal renin release in this preparation, there may be some degree of specificity to its effect (198). In fact there may be species specificity since in dog kidney slices papaverine increased renin release and tissue content of cyclic AMP (199). These facts deserve to be considered in the interpretation of experiments in which papaverine is used to suppress the influence of the vascular receptor on renin release.

Lately several laboratories have investigated the effects of calcium on renin release by rat (93, 200) or cat (201) glomeruli and rat kidney slices

(202). Although there is agreement on the basic observation that, as seen in the isolated perfused kidney, lowering the calcium concentration of the medium increases basal renin release, there still is disagreement as to the significance of this and parallel observations. Both vanadate (203) and ouabain (203, 204), inhibitors of Na-K activated adenosine triphosphatase (Na-K-ATPase), antagonized basal and isoproterenol-stimulated renin secretion. The inhibitory effect of ouabain was potentiated by lowering the extracellular potassium concentration, which by itself also lowered the rate of renin release when calcium concentration in the medium was lowered below 10^{-8} M. The authors suggested that as a result of the Na-K-ATPase inhibition intracellular concentration increased leading to an increase in sodium calcium exchange and thus to intracellular concentrations of calcium that inhibit renin release. However, this series of events requires a minimum extracellular calcium concentration to proceed (204).

SUMMARY

Sympathetic outflow influences the renal release of renin through modifications of the tonic activity of the renal nerves and the plasma concentration of catecholamines. These influences may initiate changes in the rate of renin secretion or modulate the response initiated by another of the mechanisms that control renin release. Beta-adrenoceptor mediated stimulation of renin release has been demonstrated in vivo, in the isolated perfused kidney and in preparations in vitro. Likewise an array of evidence has accumulated pointing to the existence of α-adrenoceptor mediated inhibition of renin release. However, the cellular location, the physiological significance, and even the existence of these α-adrenoceptors is still disputed.

Receptors sensitive to alterations in the vascular volume have been identified in areas of low and high pressure of the circulation. There is evidence that input from both types of receptors may cancel each other, and that to demonstrate experimentally the effects on renin release of the low pressure cardiopulmonary receptors it is necessary to avoid changes in the input from the high pressure arterial receptors, and vice versa. Again there are dissenting voices that disclaim a tonic inhibitory effect of cardiopulmonary receptor initiated impulses on renin release.

The majority of the pharmacological evidence identifies the β-adrenoceptors in JG cells as of the β_1-subtype. However, some species may make exception to this generalization. As in other tissues, β-adrenoceptor mediated influences appear to relate to activation of adenylcyclase in the cell membrane. Considerable interest in the role of calcium in the process of activation of renin release has met with some unexpected, though consistent, experimental findings.

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