Report of the U.S.-Japan Seminar on Control of Renin Secretion

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A Seminar on the control of renin secretion sponsored by the Japan-U.S.A. Cooperative Science Program was held in the Miyako Hotel in Kyoto, Japan, on October 28–31, 1969. The meeting was organized by Dr. Kenjiro Yamamoto of the Department of Pharmacology, Osaka City University Medical School, Osaka, Japan, and by Dr. Arthur, J. Vander of the Department of Physiology, University of Michigan, Ann Arbor, Michigan, U.S.A. The participants at the Seminar were welcomed by Mr. Kiyoshi Okano, Executive Director of the Japan Society for the Promotion of Science and by Dr. Richard Ries of the National Science Foundation. The Japan-U.S.A. Cooperative Science Program was initiated in 1961 to foster the exchange of ideas between scientists of the United States and Japan.

The meeting aimed at clarifying the mechanisms involved in the control of renin secretion. The relative roles of catecholamines and other physiological agents and intrarenal versus extrarenal sensing mechanisms in the regulation of renin secretion were emphasized.

The first session was devoted to catecholamines, vasoactive agents and to neural control of renin secretion. Dr. Franklin D. Nash (Indianapolis) discussed the effects of catecholamines on renin release in the opening paper. He described experiments in which norepinephrine was administered either directly into the renal artery or systemically to stimulate renin release. When the norepinephrine infusion was given intravenously, renin release occurred during the fall in arterial pressure which followed termination of the infusion. Infusion of norepinephrine into the renal artery stimulated renin release, but renal arterial infusion of angiotensin, which produced similar hemodynamic effects, was not associated with renin release. Catecholamine-induced renin release was blocked by renal arterial infusion of hypertonic saline without changes in systemic plasma sodium concentration.

Dr. Hisakazu Yasuda (Tokyo) discussed the effect of norepinephrine, isoproterenol and adrenergic blockers on renin release. He and his associates stimulated renin release with infusions of norepinephrine and isoproterenol. Dibenamine blocked the hemodynamic changes of norepinephrine but did not blunt the renin release response. Beta blockade (propranolol) prevented the renin release response to isoproterenol but not to norepinephrine. A discussion on the effects of alpha and beta adrenergic blockade as well as renal denervation on renin secretion followed. It was the consensus that norepinephrine, isoproterenol, epinephrine, and central nervous system stimulation all increase renin release. Alpha blockade either had no effect on the renin release response to these agents or caused partial inhibition.

Dr. Masaru Maebashi (Sendai) reported a patient with pheochromocytoma.

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which compressed the renal artery in whom increased peripheral plasma renin activity was noted; the renin activity returned to normal following surgery. He reported a correlation between renin activity and the norepinephrine-epinephrine ratio in patients with pheochromocytoma. Dr. Vander remarked that most patients with pheochromocytoma do not have elevated renin activity. During the same session, Dr. William F. Ganong (San Francisco) reported the effects of hypoglycemia and brain stem stimulation on renin secretion. Hypoglycemia consistently resulted in elevated plasma renin activity as well as plasma catecholamines. When insulin plus glucose was given, no change in renin activity occurred, and the response was not blocked by renal denervation. Dr. Ganong concluded that the mediation of hypoglycemia-induced renin secretion is via catecholamines. Adrenal denervation prevents this response. Alpha blockers, such as phenoxybenzamine, had no effect on the renin elevation induced by hypoglycemia, but beta blockade with propranolol inhibited the renin response. Dr. Ganong also noted that others have postulated that reduced plasma potassium concentration such as that produced by insulin stimulates renin release. Since the results of preliminary experiments suggest that it is possible to block the hemodynamic effects of catecholamines with pharmacological agents without blocking renin secretion and to block renin release, but not the hemodynamic changes by beta adrenergic blocking agents, it seems unlikely that changes in renal blood flow mediate this response. The possibility of redistribution of the intrarenal blood flow still needs to be considered. The actual receptor involved in stimulation is unclear since the results observed by different investigators with beta blocking agents are somewhat at variance.

Dr. Yoshihiro Kaneko (Tokyo) reported that sodium nitroprusside administration in hypertensive patients causes renin release. Ganglion blocking agents partially inhibit this response. Since the relation of renin secretion to sodium excretion is maintained after ganglion blockade, he suggested that the renin releasing mechanism related to sodium excretion may be independent of innervation.

Dr. Yoshinori Nara (Niigata) reported a patient with hyperthyroidism in whom peripheral plasma renin activity was increased. Patients with hyperthyroidism have an exaggerated renin release response to postural change, and hypothyroid patients show a blunted response.

Dr. Teruo Omae (Kyoshu) discussed the response of the ischemic kidney to angiotensin administration. Angiotensin delivered to the kidney after aortic constriction increases renin activity. However, the observations of various members of the group suggested that the angiotensin effect on renin activity may be quite variable depending upon the experimental situation and that in the animal without renal vascular disease there clearly was no stimulatory effect on renin release.

Dr. Vander discussed the effects of adenosine on the kidney and noted that adenosine causes an immediate transient reduction in renal blood flow with a prompt return of renal blood flow to control levels. Glomerular filtration rate and sodium excretion are reduced as well as renin secretion. He postulated that increased concentrations of adenosine and AMP may result in reduced renin release.

Dr. Carlos Ayers (Charlottesville) discussed his work on renin secretion in renal vascular hypertension and the effect of vasoactive agents on renin release in this experimental situation. Dr. Ayers noted that reserpine, trimethaphen and hydralazine, all decrease blood pressure and stimulate renin release. Dopamine also resulted in increased renin activity. These effects were potentiated by low
sodium diet.

Dr. M. Donald Blaufox (New York) reported on peripheral plasma renin activity in Parkinson’s disease. Patients with Parkinson’s disease have peripheral plasma renin activity in the low normal range on either high or low salt diets. However, there is a markedly exaggerated postural response both in the control patients and those receiving therapy. These data are at variance with a previous study from another group.

The second session was devoted to electrolytes, blood volume, and diuretics. This session began with a paper by Masaru Maebashi (Sendai). Dr. Maebashi reported that administration of Aldactone to patients results in a reduction in serum sodium with an increase in plasma potassium and an increase in plasma renin activity. No correlation was found between plasma renin activity and the concentration of the plasma sodium. Treatment of diabetes insipidus lends to a decrease in plasma renin activity. The stimulus to renin in these conditions may be hypovolemia or tubular sodium delivery rather than plasma sodium concentration. The administration of potassium chloride tends to decrease the plasma renin activity in patients with renal vascular hypertension but not in normal subjects or patients with primary aldosteronism. Thiazides increase plasma renin activity but when administered with potassium chloride lead to a reduction in plasma renin activity. Dr. Vander noted that potassium given directly into the renal artery without any chance of aldosterone effect leads to a reduction in plasma renin and an increase in sodium concentration with no change in renal dynamics.

Dr. Masashi Imai (Tokyo) discussed renin activity in childhood and infancy. Plasma renin activity and plasma osmolality tend to be increased after water deprivation in patients with diabetes insipidus. The increase in plasma renin activity is inversely related to the change in body weight. Plasma renin activity is also increased in patients with severe diarrhea irrespective of plasma sodium concentration. He suggested that elevation of renin activity in children is related to plasma volume and not to sodium concentration. Dr. Imai’s paper was followed by a paper by Dr. Nash who discussed tubular sodium load in relation to renin release. He reported that partial occlusion of the renal artery in the dog results in an increase in renin release only if there is a concomitant decrease in fractional sodium excretion. Furthermore, if sodium is infused into the renal artery, this increase in renin release can be inhibited. A variety of experiments were reported which suggested an inverse relationship between the filtered sodium load and renin release. During ureteral pressure elevation with sustained urine flow, a linear correlation was demonstrated between ureteral pressure and renin release. This relationship is disrupted by renal arterial infusion of sodium. Since there is an inverse relationship between the filtered sodium load and renin release ($r=0.84$, $p<0.001$), it was concluded that renin release by the canine kidney is controlled by a tubular natriostat rather than by a vascular barostat.

The final paper in this session was given by Dr. Vander who discussed the mechanism of the effects of Furosemide on renin secretion in anesthetized dogs. Dr. Vander reported that renin activity is stimulated by administration of Furosemide. He went on to introduce a modification of his theory of action of the macula densa in the regulation of renin activity. He suggested that the regulation of renin is determined not only by the total sodium load delivered to the macula densa area but also by the reabsorptive capacity of the macula densa cells. Agents which
affect sodium load may also affect reabsorptive capacity. In a situation such as the administration of Furosemide he hypothesized that Furosemide increases sodium load to the macula densa which theoretically would inhibit renin release. However, the depression of reabsorptive capacity is so great that the transport of sodium across the macula densa cells is reduced and, therefore, renin release is stimulated rather than inhibited. This theory was expanded to explain the effects on renin secretion noted in states such as thiazide administration, reductions in perfusion pressure, and their various combinations with or without salt loading. For each case if the major effect was either a reduction in sodium delivery to the macula densa or a reduction in macula densa transport capacity, which would exceed and nullify any increase in sodium delivery, the result would be increase in renin release.

The third session was devoted to renal hemodynamics and intrarenal mechanisms. Dr. Omae discussed the effects of hydralazine on renin release in rats made hypertensive by partial renal infarction. Renal pressor activity was determined by grafting the kidney from the experimental animal into a bilaterally nephrectomized rat. The development of hypertension following segmental renal infarction in the rat was accompanied by a lower pressor activity in the infarcted kidney than in the intact control kidney. Although hydralazine abolished the hypertension subsequent to segmental renal infarction, it did not cause any measurable change in the pressor activity of either the infarcted kidney or the intact control kidney.

Dr. Yoshihiro Kaneko (Tokyo) proposed a mechanism for the increase in renin release which occurs when hydralazine is administered intravenously to subjects with benign essential hypertension. Renin release correlated positively with the increase in heart rate \(r=0.67, p<0.001\) but not with any other hemodynamic factor or with sodium excretion. Renin release increased only when hydralazine was administered intravenously and not when it was infused into the renal artery. Dr. Kaneko suggested that the renin release which follows systemic hydralazine administration is due to increased sympathetic discharge stimulated reflexly by the peripheral hemodynamic effects of the drug.

Dr. Hirofumi Sokabe (Tokyo) discussed the control of renin secretion in lower vertebrates and outlined the evolution of the juxtaglomerular apparatus, the site of renin secretion. Juxtaglomerular cells appear first in teleosts; the macula densa, and polkissen are found only in mammals. Based upon his studies of the relationships between osmoregulation and renin in the Japanese eel and of renin release in hydrated and dehydrated states in the bullfrog, he proposed two different mechanisms for the control of renin secretion; a combined feed forward-feedback system in mammals and a feed forward system in the lower classes.

Dr. Blaufox reported on the relationships between the intrarenal distribution of blood flow, sodium balance, and renin secretion in patients with benign essential hypertension. Cortical blood flow was higher in those patients on high sodium diet than in those on low sodium diet. A direct relationship was found between the logarithm of the 24 hour urinary sodium excretion and cortical blood flow \(r=0.54, p<0.05\). Changes in corticomedullary flow were inversely related to changes in cortical flow. Reduced sodium intake was associated with reduced cortical flow, increased corticomedullary flow, decreased urinary sodium excretion, and increased renal venous renin activity. Dr. Blaufox, interpreted the data as being compatible with a sodium-conserving mechanism playing a role in the control of renin release and in the regulation of the intrarenal distribution of blood flow.
Dr. Yamamoto discussed the relationships between plasma sodium, glomerular filtration rate, and renin secretion in the dog. He studied these variables in the autoperfused canine kidney in situ and also during perfusion using a heart-lung machine. In both situations he found renin release to be inversely related to glomerular filtration rate \( r = -0.849, \ p < 0.01, \) and \( r = -0.728, \ p < 0.01 \) whether the decrease in filtration rate was caused by either vasodilation or vasoconstriction. It was pointed out that in these experiments, as well as in the others presented in this session, increases in renin release were accompanied by decreases in tubular sodium delivery and so could all be used in support of the macula densa hypothesis, i.e., renin release is under the control of an intrarenal, sodium-sensitive mechanism.

A variety of subjects were presented at the last session. Dr. Blaufox discussed the effects of antihypertensive therapy on peripheral plasma renin activity in patients with benign essential hypertension. He stated that patients receiving antihypertensive therapy may present unusual or abnormal responses to postural changes or alteration in sodium intake. He concluded that interpretations of the results of a single determination of peripheral plasma renin activity in this group of patients may be misleading if they have been taking antihypertensive medication.

Dr. Kaneko reported the results of studies of hepatic inactivation of renin in patients with the nephrotic syndrome. He concluded that the elevation in circulating renin levels in these patients may be due, in part, to a decrease in the rate of hepatic inactivation rather than to an increase in the absolute rate of renin secretion by the kidney.

Dr. Andrew M. Michelakis (Nashville) discussed his studies on the in vitro production of renin. He used isolated renal cells in suspension to study the effects in vitro of agents which have been shown to alter the rate of renin release in vivo. He suggested that agents which stimulate renin release (e.g., catecholamines) or which inhibit renin release (e.g., sodium, angiotensin) in the intact animal may exert their effects, at least in part, through direct chemical actions on the renal cells and that cyclic AMP may play a role as an intracellular mediator of the renin stimulating action of catecholamines.

Dr. Yamamoto discussed his studies of the release of renin from incubated canine renal cortical slices. The rate of renin release into the medium paralleled the rates for succinic dehydrogenase, acid phosphatase, glucose-6-phosphatase, and total protein, indicating that renin release from incubated canine renal cortical slices occurred by a passive process.

In summary of the conference, it appears that although there are still many questions to be answered, many of the discrepancies which appear in the literature can be attributed to differences between the methods used and experimental subjects employed by different laboratories. The effects on renin release of many physiological maneuvers appear to be explained by the macula densa hypothesis, that renin secretory activity is controlled by an intrarenal, but extravascular, sodium-sensitive mechanism and that the stimulus is a function of sodium movement into the macula densa cells or across them into the interstitium surrounding the contiguous juxtaglomerular cells. However, it is also apparent that the macula densa hypothesis cannot explain the effects of all physiological maneuvers nor those of most pharmacological agents. At present, we must accept the probability that there are extrarenal inputs to the juxtaglomerular cells which can influence, and at times possibly override, the macula densa mechanism. The definitive experiments will involve direct
studies of single juxtaglomerular complexes, an endeavor which is not technically feasible at present.