The Role of Renin Substrate in Hypertension

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SUMMARY A positive correlation between blood pressure and renin substrate concentration is found in a wide variety of conditions in human beings and in animal experiments. The evidence concerning this relationship is reviewed and the exceptions are discussed. The frequent positive correlation between renin substrate and elevated blood pressure suggests that increased renin substrate concentration may be a causal factor in hypertension. (Hypertension 5: 353-362, 1983)

KEY WORDS • angiotensinogen • renin substrate • blood pressure • liver disease • estrogens • captopril • pregnancy

RECENTLY, Gardes et al.1 reported that intravascular injections of antiserum to renin substrate cause a prompt fall of blood pressure in rats. This suggests that renin substrate may play a role in maintenance of normal blood pressure. Numerous other studies have indicated a possible relation between elevated renin substrate and elevated blood pressure. A review of the literature concerning the relation of plasma renin substrate concentration and the level of blood pressure reveals a frequent positive correlation between these two entities. The results of my review are presented here according to the following outline:

1. Role of the liver in hypertension
   A. Clinical observations of liver disease
   B. Experimental injury to the liver

2. Hypertension in high plasma renin substrate states
   A. Pregnancy
   B. Women taking oral contraceptives or estrogens
   C. Patients with Cushing’s syndrome and patients treated with glucocorticoids
   D. Men given di-ethylstilbestrol (DES)

3. Hypertension with associated elevation of plasma renin substrate
   A. Essential hypertension
   B. Malignant hypertension
   C. Experimental and spontaneous hypertension

4. Low blood pressure or low vascular resistance associated with low plasma renin substrate
   A. Cirrhosis of the liver
   B. Bartter’s syndrome
   C. Adrenal insufficiency

5. Effect of therapy on plasma renin substrate

Role of the Liver in Hypertension
Clinical Observations of Liver Disease
Since the beginning of this century, various clinical investigators have noted that a low blood pressure is characteristic of cirrhosis of the liver,2 that low blood pressures occur in acute infectious hepatitis,3 and that hypertensive patients may have an acute as well as prolonged fall in blood pressure following an attack of acute infectious hepatitis.4 Raaschou,5 a Danish physician, in 1954 summarized this early work and presented the results of his own study of a series of 102 women autopsied after dying of chronic hepatitis (subchronic yellow atrophy of the liver). These were compared with a control group of 93 women of similar age who died from diseases unrelated to the liver. He used three criteria of arterial hypertension: 1) incidence of cerebral hemorrhage; 2) evidence of cardiac hypertrophy; and 3) known elevations of blood pressure. Based on these criteria, he found that the frequency of arterial hypertension is considerably lower in patients with severe hepatic disease than in patients without liver disease. He hypothesized that severe impairment of liver func-
tion prevents arterial hypertension or can eliminate already existing hypertension.

In the United States, the leading investigator of the relationship between liver disease and blood pressure has been Hubert F. Loyke. He published a series of studies beginning in 1955 with a report on blood pressure in over 500 patients with cirrhosis of the liver. The age distribution of this group was broad, with an average of about 55 years. Of these patients, only 60 had diastolic blood pressures over 90 mm Hg (based on blood pressure measurement at the time of hospital admission). Of the 60, in 14 cases there was coexisting renal disease and in 13 cases there was some kind of distressing or painful stimulus at the time of admission. Eliminating these cases left 33 patients (out of 470) with coexistent hypertension and cirrhosis, or 7% of the population studied. This is definitely less than would be expected in a similar group of otherwise normal individuals without liver disease, but Loyke did not include a group of noncirrhotic hospital patients as controls. He made three additional important observations: 1) in the cirrhotic patients as a group there was no progressive rise in blood pressure with age, the mean value remaining close to 134/80; 2) in a few patients with preexisting hypertension, there was a fall in blood pressure, often to normal, as the liver failure progressed; and 3) in these cases there was a "reversal" of the plasma albumin:globulin ratio coincident with the deterioration of liver function. Loyke published the results of subsequent clinical studies, which are described in the following section.

Experimental Injury to the Liver

The earliest reports of remission of hypertension produced by experimental liver damage are those of Page et al. and Davis et al. Page et al., as early as 1941, reported that oral administration of a mixture of alcohol and carbon tetrachloride to five renal hypertensive dogs sometimes caused a fall in arterial blood pressure (data are presented only for three dogs, two of whom showed a fall from hypertensive to normoten- sive levels). They also showed that these dogs had a reduction in plasma renin substrate concentration as judged by the rather crude means of measurement, which was the only one available to them at this early date. Davis and coworkers in 1949 and 1951 showed that partial occlusion of the portal vein in renal hypertensive dogs resulted in a significant fall in blood pressure. They did not measure renin substrate. In 1953 Raaschou and Trautner reported that obstruction of the common bile duct in dogs with hypertension due to bilateral constriction of the renal arteries reduced arterial pressure to, or nearly to, normal levels. They found, as Davis had previously reported, that some degree of hepatic injury was necessary for remission of hypertension to occur. They did not measure renin substrate.

In 1966, Schwartz et al. showed that the operation of "portacaval transposition" (end-to-end portacaval anastomosis combined with above kidney end-to-end cava portal shunt) reversed or prevented hypertension due to renal artery constriction in dogs. In 1969, Schwartz et al. reported that the same operation prevented or corrected hypertension in dogs subjected to unilateral radiation nephritis. Renin substrate was not measured in either experiment.

Recently, there has been a revival of interest in the effect of portacaval anastomosis (not transposition) on blood pressure in experimental animals. In 1976, Edwards et al. found that this operation significantly lowered blood pressure in normotensive rats on a special high fat diet. Edwards et al. did measure renin substrate concentration and found a significant 30% decrease. Furthermore, the fall in blood pressure and the decrease in renin substrate were significantly corre- lated.

Other than the early experiments of Page, the first use of hepatotoxic chemical agents to assess their effect on experimental hypertension was carried out by Loyke and coworkers. In 1960, Loyke et al. reported that semweekly subcutaneous injections of carbon tetrachloride, CCl₄, into renal hypertensive rats resulted in a marked fall of blood pressure. In subsequent years, Loyke continued his investigation of the effect of chlorinated hydrocarbons on hypertension in rats and found that methylene chloride, CH₂Cl₂, and chloroform, CHCl₃, as well as carbon tetrachloride, were effective blood pressure lowering agents, even in mildly hepatoxic doses. Loyke also investigated the possible mechanism of the blood pressure lowering action of liver damage. In one of these studies plasma renin substrate was measured and no decrease was found. In experiments done some 7 years later, however, Loyke reported a marked decrease in renin substrate concentration in renal hypertensive rats in which blood pressures were lowered by biweekly subcutaneous injections of chloroform, CHCl₃.

More recently Douglas et al. reported that methylene chloride injected daily for 5 days into spontaneous hypertensive rats resulted in a significant fall in blood pressure. They measured plasma renin activity and found it slightly but not statistically significantly reduced in the treated hypertensive rats. They did not measure renin substrate concentration.

From the preceding reports one may conclude that experimental damage to the liver, by a variety of means, is able to reduce or eliminate several types of experimental hypertension. The mechanism of this action remains to be elucidated; the hypothesis that a fall in renin substrate level is responsible is supported by some, but not all, of the available evidence.
Hypertension in High Plasma Renin Substrate States

It is well known that, in several different clinical and natural conditions, human beings with elevated levels of renin substrate show a tendency toward or actually do have hypertension. It is equally well known that, in most of these conditions, the majority of people with elevated renin substrate do not have high blood pressure. If some explanation for this lack of correlation were available, it would help to clarify the relationship between renin substrate and arterial pressure. The following are specific examples of the positive correlation between high renin substrate and high blood pressure and an attempt to explain the frequent observation that high renin substrate levels may coexist with normal blood pressure.

Pregnancy

In most women, blood pressure goes down during pregnancy, usually with some tendency to return to prepregnancy levels during the third trimester. However, in a significant proportion of pregnancies, the blood pressure rises to hypertensive levels during the third trimester. Chesley has emphasized the importance of distinguishing between true preeclampsia and other forms of gestational hypertension. Preeclampsia has several distinguishing characteristics: it occurs primarily in nulliparas; it involves proteinuria and a characteristic glomerular lesion; and apparently has a familial or genetic basis. Gestational hypertension other than preeclampsia may be, according to Chesley: 1) latent hypertension revealed by pregnancy; 2) chronic glomerulonephritis or other renal disease; or 3) essential hypertension or renal hypertension which has abated during the first part of pregnancy but which reappears during the last part. In general there is, in early pregnancy, a tendency toward lowering of blood pressure and, in late pregnancy, a tendency toward elevation of blood pressure.

What is the basis of the decrease in blood pressure during early or midpregnancy? There is no conclusive answer but there is considerable evidence to support two or three possible mechanisms. One is estrogen-induced vasodilation. During pregnancy there is a decreased vascular resistance and corresponding increased blood flow in various parts of the body, including hands and feet, uterus, kidneys, and skin. There is also a vasodilation and increased distensibility of veins. This widespread vascular relaxation may be due to the action of the increased levels of estrogens that occur during pregnancy. Estrogens have been shown, when administered to animals or humans, to cause prompt vasodilator effects on vessels of the limbs, nasal mucosa, ears, and uterus. There is some evidence that progesterone may have a similar vasodilator influence but it appears that estrogens are more potent in this action.

A diminished responsiveness to the pressor effect of angiotensin is another important vascular alteration during human pregnancy. It has been shown by several investigators that, during normal human pregnancy, a greater amount of angiotensin II is required to produce the same rise in blood pressure, as compared to nonpregnant women. This diminished responsiveness may be specific for angiotensin, although there are conflicting reports as to responsiveness to vasopressin and to norepinephrine in nonpregnant vs pregnant women.

Chesley and Gant et al. made the important observation that women with pregnancy-induced hypertension do not have the usual pregnancy-associated refractoriness to the pressor effect of angiotensin. Furthermore, Gant et al. showed that this change actually precedes the development of hypertension. After the development of reduced responsiveness to angiotensin in early pregnancy, sensitivity to angiotensin gradually increases, starting about the 22nd week of pregnancy and reaches or surpasses the nonpregnant level of sensitivity during the last 1 or 2 months of pregnancy, at which time hypertension may occur. Everett et al. have recently investigated the mechanism of the loss of sensitivity to angiotensin in pregnant women and have found that it apparently involves prostaglandins, since indomethacin or aspirin (prostaglandin-synthetase inhibitors) restore sensitivity to the nonpregnant level. They also found that a metabolite of progesterone (5α-dihydroprogesterone), but not progesterone itself, restores vascular refractoriness to angiotensin in women with mild pregnancy-induced hypertension. In addition, they reported that theophylline (an inhibitor of the enzyme phosphodiesterase) has a similar effect in such women. Their tentative conclusion is that the mechanism of refractoriness to angiotensin in normal pregnant women involves a localized prostaglandin or prostaglandin-like action mediated by cyclic nucleotides and that progesterone or one of its metabolites influences the synthesis or catabolism of locally produced prostaglandins.

Thus, there appear to be two basic mechanisms underlying vasodilation and lowered blood pressure during pregnancy, one mediated by estrogens and possibly representing a direct effect of estrogens on blood vessels, the other mediated by progesterone acting indirectly by affecting prostaglandin synthesis at the vascular level.

What about the mechanism underlying the increase of blood pressure in late pregnancy? An increased concentration of renin substrate might be expected to promote vasoconstriction and to elevate blood pressure. All pregnant women have a substantial and progressive increase in renin substrate concentration during pregnancy, the highest levels occurring during the third trimester. Presumably, during normotensive pregnancy the vasodilator mechanisms just described adequately compensate for the vasoconstrictor influence of renin substrate, especially during early pregnancy. In particular, reduced responsiveness to angiotensin would diminish the vasoconstrictor effect of increased angiotensin levels resulting from increased renin substrate. However, if this refractoriness is progressively
diminished, as occurs in some pregnant women, and as the concentration of renin substrate progressively increases, there will be a greater and greater tendency to vasoconstriction and elevation of blood pressure. In late pregnancy, if both influences (increased sensitivity and increased concentration) are sufficiently exaggerated, frank hypertension would be expected to occur.

The evidence supporting a role for renin substrate in gestational hypertension may be summarized as follows: 1) in pregnancy renin substrate increases and in some pregnant women hypertension develops; 2) the highest levels of renin substrate occur late in pregnancy, which is also when hypertension, if it occurs at all, will be present; 3) hypertension is more likely to occur in women who regain sensitivity to angiotensin, which would make them more responsive to the vasoconstrictor action of renin substrate; and 4) the fact that most women have high levels of renin substrate during pregnancy but do not become hypertensive can be accounted for by the presence of potent vasodilator influences throughout pregnancy, presumably resulting from increased plasma levels of estrogens and progesterone.

Women Taking Oral Contraceptives or Estrogens

The relationship between blood pressure and renin substrate concentration in women taking oral contraceptives is quite similar to that in pregnancy, although there are some important differences. Only a small percentage of women who take estrogen-containing oral contraceptives develop a significant degree of hypertension, although most of them, according to Fisch, et al., have some small elevation of both systolic and diastolic blood pressure. However, all women who take such oral contraceptives do have elevated levels of renin substrate. The question again arises: Why do some women become hypertensive, while most do not?

There has been some speculation about this question, mostly centered about what happens to renin concentration in these women when renin substrate concentration rises. Skinner et al. showed, in 1969, that in normal women taking oral contraceptives, renin substrate concentration increases and renin concentration decreases. They also found increased renin substrate levels in six hypertensive women taking oral contraceptives (average for hypertensives, 4.77 μg/ml; average for normotensives, 3.4 μg/ml). They proposed that "suppressed renin secretion is a normal response to elevated substrate and that inadequate suppression might account for the hypertensive effect of oral contraceptives."

In 1970, Saruta et al. supported this hypothesis in a more extensive study. They gave oral contraceptives to 56 initially normotensive women for a period of 18 to 30 weeks. During this period 10 of these women developed mild to moderate hypertension. Plasma renin activity, plasma renin concentration, and renin substrate concentration were measured. Comparisons were made between the group that remained normotensive and the group that became hypertensive. Higher concentrations of renin substrate were found in the hypertensive group, but the difference was statistically significant only at the 6-week interval. However, plasma renin concentration was statistically and consistently different in the two groups, being higher than the control (pretreatment) value in the hypertensive group and slightly lower than the control value in the normotensive group. Thus, Saruta et al. not only did not find a decrease in renin concentration in the women who became hypertensive, but found an actual increase.

However, this result is contrary to that found by other investigators. Beckerhoff, et al., in 1972, reported just the opposite result; in women who were hypertensive while taking oral contraceptives, plasma renin concentration was not only reduced (compared to the normal mean value) but was reduced to a lower value than that found in normotensive women taking oral contraceptives. Thus, hypertension in these women could not be due to a failure of suppression of renin. The reason for the discrepancy between the results of Saruta et al. and those of Beckerhoff et al. is not clear. There were significant differences in the technique used to measure renin concentration. A more likely explanation is that in the study reported by Saruta et al., the women were taking oral contraceptives for a shorter time (values measured at approximately 4-week intervals from the start of oral contraceptive therapy up to 18 to 30 weeks) whereas in the Beckerhoff study "the onset of hypertension was first noted between 3 and 36 months after the medication was started," and, presumably, the study was begun some months after hypertension was established in these patients. Further support for this notion is given by Saruta et al., who added some results of more prolonged study to their paper and stated: "With continuation of oral contraceptives through 52 weeks, renin substrate remains elevated and constant, whereas renin activity and concentration tend to decrease an average of 20% in both women who remain normotensive and in those who become hypertensive."

It has also been shown that estrogen use by postmenopausal women is associated with a significantly increased occurrence of hypertension. Pfeffer found that the incidence of hypertension is 1.6 to 2 times greater in women who take estrogens than in women of the same age who do not. Almost half (47%) of the women below age 70 in his study who used estrogens were hypertensive, while of the comparable group who did not take estrogens, some 29% were hypertensive. In the age group 70–79 years, the corresponding figures were 39% hypertension in estrogen users and 19% in nonusers.

Surprisingly, there is very little published data on renin substrate levels in women taking estrogens for other than contraceptive purposes. In 1971, Crane et al. reported increased plasma renin substrate levels in a few women with hypertension due to taking conjugated estrogens (Premarin). We found a high level in one such patient tested in my laboratory. When she stopped taking estrogens, her blood pressure returned to normal. Crane and Harris found that conjugated estrogens...
estrogens (1.25 mg daily) caused a significant progressive rise in renin substrate concentration in 10 women of premenopausal age (21 to 49 yrs) and also in 10 women of postmenopausal age (42–64 yrs).

In summary, young women who take estrogen-containing oral contraceptives and older women who take estrogens for relief of postmenopausal symptoms have an increased incidence of hypertension. They also have, without exception, increased plasma levels of renin substrate. Whether the latter is the cause of the former remains to be proven. Since the increase in renin substrate due to estrogen intake is universal and the elevated blood pressure is exceptional, it remains to be explained why all of the estrogen-treated women do not become hypertensive or, conversely, what is special about the women who do. A possible clue to the latter is the finding by Ahluwalia et al.\(^5\) that hypertensive users of oral contraceptives have significantly higher plasma estrogen levels than normotensive users of the same medication. Apparently in some women the metabolism of estrogens is different from that of most other women and, presumably, the ones who attain the highest plasma concentration of estrogens are the ones who are likely to develop hypertension.

### Patients with Cushing’s Syndrome and Patients Treated with Glucocorticoids

Krakoff\(^5\) has shown that in patients with Cushing’s syndrome and in patients given large doses of glucocorticoids there is a significant increase in the concentration of renin substrate in the plasma. It is well known that in both conditions there is a high incidence of hypertension. Krakoff et al.\(^5\) have suggested that the elevated levels of plasma renin substrate may play a role in the pathogenesis of hypertension in these conditions.

### Men Given Diethylstilbestrol (DES)

The use of DES for treatment of prostatic cancer in men has been shown to be a beneficial procedure in that it reduces morbidity and mortality due to the cancer itself. However, in a large controlled study involving over 2000 patients, a comparison of patients given placebos with those receiving 5 mg of DES daily showed that the mortality rate was higher in the DES-treated group.\(^5\) Although deaths from prostatic cancer were reduced, the number of deaths from other causes, especially heart failure and cerebrovascular accident, increased disproportionately, so that the overall mortality was greater, not less, in the treated group. In a subsequent study\(^5\) it was shown that smaller doses of DES caused fewer cardiovascular deaths, while still permitting some reduction of mortality due to the prostatic cancer. As a result of these findings, the approved therapy with DES is now limited to 1 mg daily.

Surprisingly, in the studies cited above, the status of blood pressure in the patients was not reported. Only a brief reference to blood pressure levels in DES-treated patients has been published by Byar.\(^5\) It is possible that some or all of the increased mortality in the DES-treated patients may be related to increased arterial pressure, although other possible pathogenetic mechanisms, such as an increased tendency to thrombosis, are not excluded. By analogy, the finding by Pfeffer\(^5\) seems very relevant, that the increased incidence of stroke in older women taking estrogens could be entirely related to their increased blood pressure.

Do men given DES for treatment of prostatic cancer have elevated levels of renin substrate? In male rats given DES, renin substrate levels are elevated.\(^5\) In women given DES, renin substrate levels are elevated,\(^5\) and in men given other estrogens, renin substrate levels are elevated.\(^5\) For some reason (as far as I know) no study has been published showing that men given DES have elevated levels of renin substrate. Yet, in fact, they do, as we have found in some preliminary experiments in my laboratory (Gordon DB et al., unpublished data).

More studies are obviously needed, but it appears likely from the available evidence that: 1) men given DES have an increased incidence of hypertension; 2) that this may contribute to the increased mortality found in such men; and 3) that increased levels of renin substrate, if sought, will be found.

### Hypertension with Associated Elevation of Plasma Renin Substrate

In the preceding section, evidence was considered that indicates that in various situations in which renin substrate levels are increased, hypertension is also present, not invariably, but in a greater or lesser proportion of the population involved. In this section, the evidence will be examined concerning renin substrate concentration in a few situations in which, by definition, all the individuals concerned have elevated blood pressure, namely, essential hypertension and malignant hypertension in humans and experimental and spontaneous hypertension in animals.

### Essential Hypertension

Walker et al.,\(^5\) showed that in a large group of individuals with essential hypertension, or with normal blood pressure, there is a good correlation between blood pressure level and renin substrate concentration. This must mean that those with essential hypertension have, on the average, higher levels of renin substrate than those with normal blood pressure and, in fact, in another paper Walker et al.\(^5\) reported that those subjects who had diastolic blood pressures greater than 90 mm Hg did have a significantly higher plasma renin substrate concentration than those subjects with blood pressures below 90. However, other studies, while concurring that there is a somewhat higher level of renin substrate in patients with essential hypertension, reported a within-group variability so large that the difference was not statistically significant.\(^5\) An exception is the result reported by Gould and Green\(^5\) who found a modest, but highly significant difference in
renin substrate concentration in males with essential hypertension compared to normotensive males. In our own studies of renin substrate in men with essential hypertension (Gordon DB et al., unpublished data) we found some with the same concentration as normotensive men and others with considerable increases, reaching two times the mean value of normotensives in some cases. Essential hypertensive patients can be subdivided into two categories, those with normal or slightly above normal levels of renin substrate and those with elevated levels. This concept, it seems to me, is a reasonable one and might have heuristic value. In those patients with significantly elevated levels of renin substrate, say 1500 to 2000 ng/ml, the elevated renin substrate together with adequate vascular responsiveness may be the cause of the hypertension.

Malignant Hypertension

Since Helmer's report in 1964, all investigators have found that the majority of patients with malignant hypertension have elevated levels of plasma renin substrate. Most such patients also have very high levels of plasma renin activity and plasma renin concentration. The two groups (high renin and high substrate) may not, in fact probably do not, completely coincide. It is likely that renin, in high concentration in plasma, consumes renin substrate at such a high rate that the concentration of renin substrate in plasma is diminished, in spite of a high rate of production by the liver. Schultze and Oelkers have published evidence to support this concept. They found in one patient with severe malignant renovascular hypertension that, before antihypertensive therapy, plasma renin activity was extremely high (149 ng/ml/hr) while plasma renin substrate was below their normal range. After a few days' treatment with methyldopa, plasma renin activity had fallen considerably (to 48 ng/ml/hr) but was still far above the normal range, and plasma renin substrate had increased significantly. Subsequent removal of the ischemic kidney resulted in a prompt fall of plasma renin activity and of blood pressure, followed by a much slower, modest rise of plasma renin substrate.

There are two conflicting effects of plasma renin on plasma renin substrate concentration. On the one hand, as described above, increased renin concentration reduces renin substrate concentration because of more rapid conversion to angiotensin I. On the other hand, as has been shown by several investigators, increased levels of renin and of angiotensin stimulate the production of renin substrate by the liver. Rosset et al. found that there is usually an inverse relationship between plasma renin activity and plasma renin substrate in normal humans, but that in malignant hypertension this relationship does not hold; both plasma renin activity and the renin substrate may be greatly elevated.

Experimental and Spontaneous Hypertension

Surprisingly little work has been done in this area. Some investigators have found an increased level of plasma renin substrate in rats with spontaneous hypertension while others have not. In rats with hypertension due to constriction of one renal artery (one clip, two kidney) elevated plasma renin substrate has also been reported. Many years ago Kohlstaedt et al. reported an increase in renin substrate in the plasma of dogs with experimental renal hypertension, but this result was dismissed as some kind of artifact by Braun-Menendez et al. who found no change in dogs with chronic experimental renal hypertension and without renal insufficiency.

Low Blood Pressure or Low Vascular Resistance Associated with Low Plasma Renin Substrate

Cirrhosis of the Liver

As previously described, in patients with severe cirrhosis of the liver there is usually no elevation of blood pressure, in spite of a significantly increased concentration of plasma renin. There may be a normal blood pressure with decreased peripheral vascular resistance and increased cardiac output or there may be a frank lowering of blood pressure. Evidently a potent vasodilator influence exists in cirrhosis. There is also a moderate to severe diminution of plasma renin substrate concentration, depending on the degree of impairment of hepatic function. The lowered renin substrate concentration may be the cause of the widespread vasodilation. Since, in severe cirrhosis, there are many abnormalities of plasma components, there may be vasodilator effects due to other chemical or hormonal changes. Nevertheless, cirrhosis of the liver, especially in its severe stages, is a good example of a correlation between decreased renin substrate concentration and decreased vascular resistance.

Bartter's Syndrome

Bartter's syndrome is a complex syndrome characterized by low to normal blood pressure, decreased sensitivity to angiotensin, increased plasma levels of renin and aldosterone, and excessive excretion of potassium by the kidneys resulting in hypokalemia and weakness. It is, as is liver cirrhosis, one of those clinical entities in which high plasma renin activity and normal blood pressure coexist. We have measured renin substrate in three women and two men with Bartter's syndrome (Gordon DB et al., unpublished data). The three women had normal levels of renin substrate but the two men had clearly decreased concentrations. Tree has reported very low values of plasma renin substrate in two children who either had Bartter's syndrome or some condition closely resembling it, including hypotension, hypokalemia, and extremely high plasma renin levels.

Adrenal Insufficiency

In adrenal insufficiency, both clinical, as in Addison's disease, and experimental, as in animals subject-
ed to bilateral adrenalectomy, there are many disturbances of normal physiological function, including a tendency to abnormally low blood pressure. The latter is primarily due to renal loss of sodium and the consequent depletion of salt and water from the body with dehydration and hypovolemia. However, other effects of lack of adrenal cortical hormones on the cardiovascular system are probably involved, and some part of these may be due to a decrease in plasma renin substrate concentration.

In adrenalectomized animals and in human beings with severe adrenal insufficiency, i.e., with Addison’s disease, there is a profound decrease in the concentration of renin substrate in plasma. The degree of diminution of plasma renin substrate has been shown to be proportional to the degree of reduction of plasma cortisol in untreated Addisonian patients. At the same time that renin substrate is reduced, renin concentration is greatly increased, but blood pressure is not elevated and is usually below normal. Stockigt et al. noted that their most severely hypotensive Addisonian patient was the one who had the lowest concentration of renin substrate and the highest concentration of renin. The low renin substrate may be responsible, at least in part, for the low blood pressure in adrenal insufficiency.

Effect of Therapy on Plasma Renin Substrate

If the concentration of renin substrate in plasma is an important determinant of blood pressure level, it is reasonable to suppose that some therapeutic agents that are effective in lowering blood pressure in hypertensive patients may lower the concentration of renin substrate. This possibility has not been extensively investigated. Two of the most widely used therapeutic modalities for treating high blood pressure in humans are restriction of sodium intake and the use of sodium-depleting diuretic agents. Rosset and coworkers have shown that in normal men salt depletion by restriction of sodium in the diet results in a decrease in plasma renin substrate and also an increase in plasma renin activity. Similar observations have been made in salt-depleted rats, although not all investigators have found such a decrease. Rosset and Veyrat found that, with certain notable exceptions such as malignant hypertension, there is in general an inverse relationship between plasma renin activity and renin substrate in normal humans and in some pathological conditions, too. Because increased renin concentration will increase the rate of utilization of renin substrate, one would expect plasma renin substrate to be decreased whenever plasma renin concentration is increased, that is, unless the rate of renin substrate production by the liver increases enough to balance or overbalance the increased utilization. The fact that angiotensin II stimulates synthesis and release of renin substrate by the liver complicates this relationship, since any increase of plasma renin concentration would be expected to provoke both increased destruction and increased production of renin substrate. Herrmann et al. have admirably clarified this situation by showing that a large increase in angiotensin II concentration in plasma (produced by a continuous intravenous infusion) does result in a significant increase in renin substrate output by rat liver slices, whereas a modest increase, such as occurs in sodium-deficient rats, does not result in any increase in renin substrate output. In such salt-deficient rats, increased utilization is not balanced by increased output, and renin substrate concentration in plasma falls.

With this information in mind, one can presume that antihypertensive diuretics that provoke an increase in plasma renin activity or plasma renin concentration would also cause some reduction in plasma renin substrate concentration. Actual measurements of plasma renin substrate are needed to verify this presumption. In fact, most antihypertensive diuretics, such as the thiazides, do cause an increase in plasma renin activity and renin concentration.

Whether other antihypertensive drugs that are not diuretics may have some more direct action on the liver and cause a lowering of plasma renin substrate largely remains to be investigated. There is one antihypertensive drug, captopril, which, while presumably not acting directly on the liver, does have a significant effect on plasma renin substrate.

Captopril (2 D-methyl-3 mercapto propanoyl-L-proline) is an inhibitor of converting enzyme. It can be given orally, and in adequate doses it prevents the conversion of angiotensin I to angiotensin II and thus blocks the vasoconstrictor action of the renin-angiotensin system. The mechanism of the blood pressure lowering action of captopril was originally attributed to this specific blocking action. This was supported by the findings that its blood pressure lowering effect in human beings is proportional to the level of plasma renin activity prior to drug therapy and that the rise in plasma renin activity induced by the drug is also proportional to the extent of the fall in blood pressure.

However, while this mechanism of action is generally accepted, considerable controversy has arisen about the possibility that captopril may have some other action that also tends to lower blood pressure. Captopril, while most effective in high renin states, also is effective in lowering blood pressure in essential hypertension and even, in some circumstances, in nephrectomized dogs, rats, and human beings. On the other hand, it usually does not lower blood pressure in anephric human beings, nephrectomized rats, or rabbits. Antonaccio and Asaad have recently summarized this controversial topic.

Another interesting observation is that captopril plus hydrochlorothiazide may be more effective in lowering blood pressure in spontaneous hypertensive rats and in hypertensive humans than captopril alone, in spite of the fact that captopril alone completely blocks the conversion of angiotensin I to angiotensin II. In the experiments on rats, Chan et al. showed that the greater hypotensive effect of hydrochlorothiazide plus...
captopril could not be attributed to loss of electrolytes and water since it was equally pronounced in rats with ligated ureters and, presumably, nonfiltering kidneys. The clue to explaining this otherwise puzzling observation is the fact that the two drugs together cause a greater increase in plasma renin level than either one acting alone. According to the discussion presented above, this would make the combination of two drugs more effective in lowering plasma renin substrate concentration. The question is — Does it?

Rasmussen et al. have reported that this is precisely what occurs. They studied nine patients with severe or malignant hypertension whose blood pressure was not adequately controlled by a combination of antihypertensive drugs. After stopping the previous therapy, they began therapy with captopril in increasing doses up to 450 mg daily, then added hydrochlorothiazide (100 mg/day), and after at least a month added propranolol as a third antihypertensive agent. Plasma concentrations of renin, renin substrate, angiotensin I and angiotensin II, as well as plasma renin activity, were measured. They found that captopril alone caused a significant decrease in plasma renin substrate (from a mean value of 2151 ng/ml to 1693 ng/ml) and that captopril plus hydrochlorothiazide caused a greater decrease (to 990 ng/ml). Correspondingly, plasma renin concentration rose somewhat with captopril alone but much more with both drugs together. Addition of propranolol to the other two agents partially reversed these changes; plasma renin concentration decreased somewhat and plasma renin substrate increased accordingly.

These results strongly support the concept, described above, that increases in plasma renin concentration will tend to reduce plasma renin substrate concentration. Whether the fall in plasma renin substrate is responsible for the fall in blood pressure is unproven.

Conclusions

The evidence presented shows that in a wide variety of circumstances there is a positive correlation between arterial blood pressure and the concentration of renin substrate in plasma. When renin substrate rises, blood pressure goes up; when renin substrate falls or is brought down, blood pressure also goes down. There are several obvious exceptions but usually some reasonably acceptable explanation can be found. The bulk of the evidence supports the hypothesis that renin substrate may play an important role in hypertension, and that high renin substrate levels, together with adequate vascular responsiveness, may be a cause of elevated blood pressure. The strength of the hypothesis rests on the wide range of circumstances in which it seems to apply. Its weakness is in the lack of a uniformly positive correlation. Probably the main value of the hypothesis rests on the fact that it is straightforward and easily testable. It is to be hoped that its consideration will lead to additional experiments on the role of renin substrate in hypertension.

Addendum

Since submission of this manuscript, a paper by Tewksbury DA and Dart RA entitled “High Molecular Weight Angiotensinogen Levels in Hypertensive Pregnant Women” was published in Hypertension 4: 729, 1982. They reported that a high molecular weight fraction of angiotensinogen (renin substrate) is present in higher concentrations in hypertensive than in normotensive pregnant women. This study provides a significant new approach to the question of the relationship of renin substrate to high blood pressure in pregnancy.

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The role of renin substrate in hypertension.
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