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STUDIES OF THE RENIN-ANGIOTENSIN SYSTEM IN MAN

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Summary

The thesis is introduced by a general review of the renin-angiotensin system and its physiological and pharmacological implications. In the second chapter the comparative merits of the Boucher and Skinner methods for determining plasma renin activity are considered and evaluated. The Skinner method is less time consuming, more economical and particularly applicable to handling large numbers of plasma samples. Some loss of sensitivity is incurred, however, by the exclusion of a concentrating step similar to that in the Boucher method. Both methods are equally effective in protecting human angiotensin from angiotensinase activity. Further evidence for the specificity of the angiotensin end product of Skinner plasma renin activity incubations was provided by the close parallel observed between samples assayed by bioassay and radioimmunoassay, using specific antibody to angiotensin II-amide. The bioassay can be considerably improved by the use of selectively angiotensin sensitive, nephrectomised rats. The degree of rat variation indicates the necessity of assaying in the same rat preparation all samples which are to be directly compared. In very large studies this is impracticable and may, to some extent, be overcome by repeated assay of random samples in several rats. The presence of an angiotensin-like pressor agent in a human stable plasma protein solution (SPPS), used clinically as a plasma volume

expander, is reported in the third chapter. The pressor agent exhibits a similar resistance to destruction by in vitro angiotensinase activity as human angiotensin. Levels of pressor activity, renin concentration, substrate and angiotensinase activity, during the manufacture of SPPS from pooled donor plasma, are examined and evidence is presented that the pressor agent is generated in donor plasma during transport at ambient temperature. The possible influence of this pressor agent on blood pressure and aldosterone secretion during infusion of SPPS at rates commonly employed, is discussed. In the fourth chapter the status of the renin-angiotensin system in congestive heart failure is re-evaluated. Plasma renin activity in eight patients, studied before the institution of therapy, was in the low normal range for healthy upright subjects on liberal sodium intake. In six patients studied during treatment with moderate dietary sodium restriction, digoxin and frusemide, renin activity increased in five from a pretreatment mean value of 353 ng/100 ml/3 hrs to 1168 ng/100 ml/3 hrs on the third treatment day. This response is similar to that seen in normal subjects following severe dietary sodium restriction and was also observed in one normal subject after moderate dietary sodium restriction and daily frusemide administration. In a subsequent study, described in the fifth chapter, the response of plasma renin activity to natriuretic agents, in regular clinical doses, and moderate dietary sodium restriction is examined in detail. These

studies indicate the transient response of the renin-angiotensin system under these conditions and emphasize the importance of the timing of blood sampling, in relation to the time of natriuretic administration and assumption of upright posture, if changes are to be detected. In the final chapter, the measurement of plasma renin activity in both renal veins in a group of 75 relatively unselected hypertensive patients is examined. No significant morbidity was associated with the collection of renal vein blood samples. In radiologically demonstrated renal arterial disease, significant renal vein renin ratios (high to low renal vein renin activity of 1.5 or greater) were observed in 63% of patients in whom both pyelography and angiography agreed as to the side of the lesion. This correlation was considerably less in radiologically apparent renal parenchymal disease. The not infrequent finding of significantly elevated renal vein renin activity in the absence of radiological abnormality is discussed. The determination of the ratio of high to low renal vein renin activity correctly predicted the outcome in nine out of 10 patients submitted to surgery, further indicating the usefulness of this procedure in ascertaining the functional significance of unilateral renal disease.

Significant Contributions of this Thesis

1. In terms of practicability, the Skinner method for determining plasma renin activity offers considerable advantages over the Boucher method. Both methods appear equally effective in protecting human angiotensin from angiotensinase activity. The importance of selective nephrectomised rats in achieving maximum sensitivity to angiotensin are reiterated in a critical evaluation of the rat bioassay technique. Additional evidence supporting angiotensin as the reaction product of the Skinner plasma renin activity method was provided by its ability to react in a radioimmunoassay, using antibody to angiotensin II-amide.
2. A pressor agent is described in a human stable plasma protein solution and evidence presented that it is angiotensin. It is present in sufficient concentration to influence blood pressure and aldosterone secretion when infused at rates commonly employed. The pressor agent resembles human angiotensin in its relative resistance to in vitro angiotensinase activity. Investigation of the stages of manufacture of stable plasma protein solution from donor plasma, indicate that the pressor agent is generated in donor plasma while at ambient temperature.

3. The low normal levels of plasma renin activity observed in untreated congestive heart failure, with a subsequent rise in the majority of patients during treatment, lends support to the view that hyperaldosteronism in this condition is a result of therapy and represents the physiological response of the renin-angiotensin system to sodium depletion.

4. The capacity of the renin-angiotensin system to respond to natriuretic agents, administered orally in clinical doses, in the presence of only moderate dietary sodium restriction is demonstrated. However, the timing of blood sampling in relation to the administration of the natriuretic agent and duration of upright posture, are important in the detection of these responses.

5. The estimation of plasma renin activity in both renal veins is a relatively simple, readily tolerated procedure which is of value in determining the functional significance of radiologically demonstrated unilateral renal disease in hypertensive patients, as indicated by the results of surgery. Significantly elevated renal vein renin activity occurs most frequently in patients with radiologically demonstrated reno-vascular disease when both angiography and pyelography agree as to the side of the lesion.