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DRUGS AFFECTING THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

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Drugs Affecting the Renin-Angiotensin-Aldosterone System

Use of Angiotensin Inhibitors

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In STOKES and EDWARDS: Drugs Affecting the Renin-Angiotensin-Aldosterone System. Use of Angiotensin Inhibitors
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Introduction

This volume contains a collection of recent work on the use of angiotensin inhibitors in the diagnosis of human hypertension, and in analysing the pathophysiology of certain experimental situations, such as sodium depletion, high output heart failure, acute renal failure or renal-clip hypertension.

Theoretically, the actions of angiotension could be inhibited by preventing its binding to receptors, by interfering at any stage in its production from renin substrate or by interfering with the production or actions of its target hormones, the most important of which is aldosterone. Numerous potential modes of inhibition exist. Interference with the production of renin substrate from the liver or of renin from the kidneys, competitive inhibition of renin or of the enzyme which converts the decapeptide angiotensin I to angiotensin II, and antagonists or antibodies to the effector angiotensins 'II' (the octapeptide) and 'III' (the heptapeptide) have all been described, as have inhibitors of aldosterone biosynthesis and action.

The book does not attempt to deal in a sequential way with the entire subject of inhibition of the renin-angiotensin system. Some topics which are adequately reviewed elsewhere, such as the blockade of renin release and the role of aldosterone antagonists, are not mentioned, while others, namely competitive inhibition of renin and inhibition of converting enzyme, are each the subject of a single special chapter. The principle thrust of this presentation is to explore the practical application of angiotensin analogues, which have proved the most specific type of angiotensin inhib-

itor yet devised for clinical use. The analogue which has had the widest use is the octapeptide saralasin ('P113' – Norwich Pharmacal Company) in which sarcosine has been substituted for aspartic acid at the N-terminal end of the angiotensin II molecule and alanine for phenylalanine at the C-terminal end. The abbreviated chemical nomenclature we have used for this peptide is Sar^1-Ala^8-angiotensin II. Other analogues discussed are Sar^1-Ile^8-angiotensin II and Sar^1-Thr^8-angiotensin II.

The contributing authors, all of whom have been prominent in recent developments in this field, were originally invited to present their papers at the Fifth Kanematsu Conference on the Kidney. This conference, which was held at Sydney Hospital in February 1976 as a satellite of the Fourth Meeting of the International Society of Hypertension, had as its topic *The Use of Angiotensin Inhibitors in Clinical Diagnosis*. The introductory reviews in section I were contributed by Prof. J. O. DAVIS, who delivered the 1975 Volhard Lecture of the International Society of Hypertension on the subject of blocking agents and the renin-angiotensin system, and by Prof. EDGAR HABER, whose studies with the nonapeptide converting enzyme inhibitor in normal subjects have paved the way for understanding the role of the renin-angiotensin system in the adjustments to posture and sodium depletion in man. Both these authors graciously submitted manuscripts even though they were unable to come to Australia for the Conference. Sections II and III, covering experimental and clinical research, respectively, contain the 16 papers which were read at the Conference, together with the transcripts of the discussion periods which followed each pair of papers.

In the task of organising the Fifth Kanematsu Conference and editing the papers and transcripts, we have had unstinting support and much practical help from the members of the Cardio-Renal Unit, Sydney Hospital. We owe a particular debt of gratitude to Mr. IAN THORNELL, Dr. HELEN OATES and Miss JUDY GAIN.

G. S. STOKES
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Section II: Studies in Experimental Animals

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Prog. biochem. Pharmacol., vol. 12, pp. 1–15 (Karger, Basel 1976)

Angiotensin II Blockade and the Functions of the Renin-Angiotensin System

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Introduction

In 1960–62, a large body of evidence accumulated to show that the renin-angiotensin system is a primary controller of aldosterone secretion [1]. Most of the early evidence came from studies in dogs and man and attempts to extend these findings to other species, especially the rat, failed to show a clear-cut relationship. Also, many of the observations were made during sodium depletion, which is a potent stimulus for aldosterone secretion. BLAIR-WEST *et al.* [2] have done extensive studies on the mechanisms controlling aldosterone secretion during sodium depletion in sheep and reported that factors other than the renin-angiotensin system, ACTH and plasma electrolyte concentrations are involved. The present report includes extensive studies of the mechanisms controlling adrenal steroid secretion, during sodium depletion in the dog

and rat, and during thoracic caval constriction in the dog, by use of angiotensin II blockade. In addition, data are presented on the role of the renin-angiotensin system in experimental high output failure and in experimental renovascular hypertension.

Effects of an Angiotensin II Antagonist on Aldosterone Secretion in the Dog

The angiotensin II analogue which has been used most extensively and most successfully for angiotensin II blockade is 1-sarcosine-8-alanine angiotensin II. Since most of the controversy in the past has centered around the control mechanisms for aldosterone secretion during sodium depletion, our most extensive studies have been directed at this specific problem by use of Sar^1-Ala^8-angiotensin II. However, even before blocking agents were available, the effects of bilateral nephrectomy were studied in sodium-depleted hypophysectomized dogs [3]. Aldosterone secretion fell to very low levels following nephrectomy and corticosterone production which was very low as a result of hypophysectomy fell further after nephrectomy (fig. 1). The experiments were conducted in hypophysectomized dogs to prevent a high level of ACTH secondary to laparotomy from obscuring a possible fall in aldosterone secretion after removal of the kidneys. When the problem of the control of aldosterone secretion during sodium depletion was reinvestigated recently by use of the angiotensin II antagonist, Sar^1-Ala^8-angiotensin II [4], aldosterone secretion fell to levels indistinguishable from zero in 5 of 7 dogs (table I); in these studies, dexamethasone was given to depress ACTH release. Interesting incidental findings were the striking increase in plasma renin activity (PRA) and the decrease in arterial pressure. As suggested elsewhere [5], it seems likely that the increase in PRA resulted from interruption of the negative feedback of angiotensin II on the JG cells and from the fall in arterial pressure. The studies were conducted in anaesthetized dogs with a chronic indwelling catheter for collection of adrenal venous blood and for direct measurement of the rate of aldosterone secretion.

In recent unpublished observations, this experiment was repeated with measurements of the concentration of plasma aldosterone by radioimmunoassay in conscious sodium-depleted dogs. Sar^1-Ala^8-angiotensin II was given for prolonged periods up to 210 min. A striking fall to the extent of 73–92% in the plasma aldosterone level occurred and

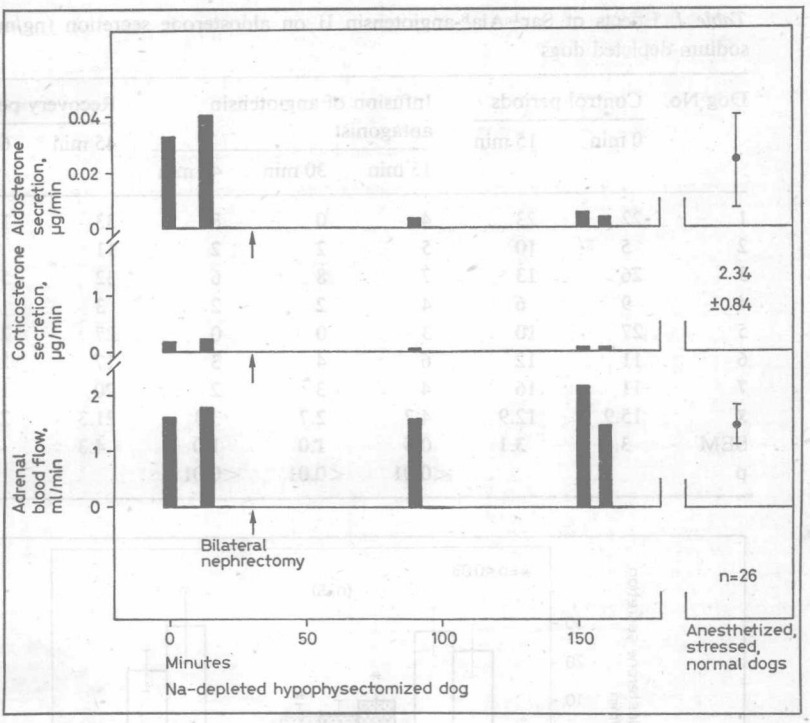

Fig. 1. Effects of bilateral nephrectomy in sodium-depleted hypophysectomized dogs. For comparison, data are presented for anesthetized, stressed, normal dogs. Reprinted with permission of the *Journal of Clinical Investigation* [3].

was sustained in 2 of the 3 dogs throughout the period of infusion of the angiotensin II antagonist. In the third animal, plasma aldosterone decreased initially and then increased from this very low level during the last hour of analogue infusion. Under these circumstances, the presence of an increased plasma level of angiotensin II might have produced a decrease in the efficacy of Sar^1-Ala^8-angiotensin II in the maintenance of a low plasma level of aldosterone; an increase in PRA did occur in all 3 animals. The expected progressive fall in arterial pressure also occurred. Conscious normal dogs studied similarly failed to show a change in either PRA or in arterial pressure.

The observations during sodium-depletion were extended to another experimental model in the dog, namely chronic constriction of the thoracic inferior vena cava. The results in this model have important clinical

Table I. Effects of Sar[1]-Ala[8]-angiotensin II on aldosterone secretion (ng/min) in sodium-depleted dogs

Dog No.	Control periods		Infusion of angiotensin antagonist			Recovery periods	
	0 min	15 min	15 min	30 min	45 min	45 min	60 min
1	22	23	4	0	8	33	19
2	5	10	5	2	2	11	–
3	26	13	7	8	6	32	57
4	9	6	4	2	2	3	2
5	27	10	3	0	0	27	27
6	11	12	6	4	3	17	13
7	11	16	4	3	2	20	19
$\bar{x}$	15.9	12.9	4.7	2.7	3.3	21.3	22.8
SEM	3.4	3.1	0.5	1.0	1.0	4.3	7.6
p			<0.01	<0.01	<0.01		

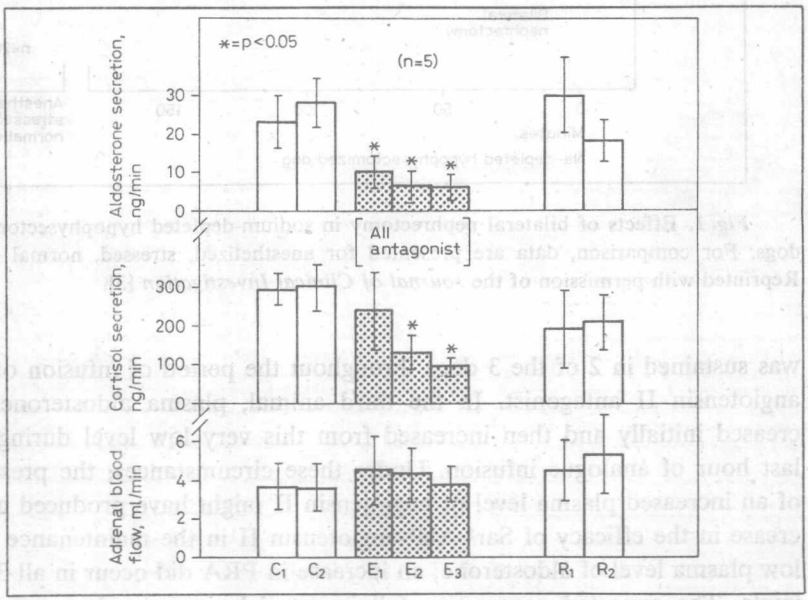

Fig. 2. Effects of intravenous infusion of the angiotensin II antagonist, Sar[1]-Ala[8]-angiotensin II on steroid secretion in dogs with chronic thoracic inferior vena caval constriction. The abreviations C_1, C_2 are for control periods and R_1, R_2 are for recovery periods. The three experimental periods, E_1, E_2, and E_3, are for measurements made at 15, 30, and 45 min of infusion of the angiotensin II antagonist. Reprinted with permission of *Science* [4].