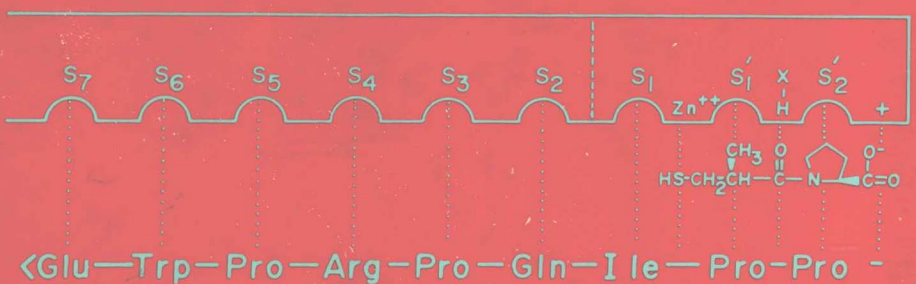
Angiotensin Converting Enzyme Inhibitors

Mechanisms of Action and Clinical Implications



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Mechanisms of Action and Clinical Implications

Edited by
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The Squibb Institute for Medical Research
Princeton, New Jersey

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Introduction

This volume is a compilation of the papers and discussions presented at a meeting in Philadelphia, PA, USA, on May 8–9, 1980. It represents an interdisciplinary interaction of biochemists, physiologists, pharmacologists and clinicians, all of whom have been active in studying the effects of angiotensin converting enzyme (ACE) inhibitors.

Because of the complexities of drug discovery we live with today, breakthroughs representing new types of pharmacological agents are very rare. However, we have a unique opportunity in this volume to explore the implications of a completely new class of agents. The questions raised are obviously numerous. Can these agents help explain the role of the hormone angiotensin in both normal function and pathological conditions? Do these agents work only by lowering effective levels of angiotensin or are there other mechanisms involved? Do ACE inhibitors represent an improved method of treating diseases such as hypertension or congestive heart failure? Is this therapy only symptomatic or can it actually reverse pathological causative factors? These questions are very complex and will probably require decades of research to answer. The text of this volume, though, begins to address these and other questions that the discovery of selective ACE inhibitors has raised.

The first section of this book presents an interesting history of the decade of research that went into finding and proving the merit of ACE inhibitors. It also describes the unique molecular design studies at The Squibb Institute for Medical Research that resulted in the synthesis of captopril, the first orally effective ACE inhibitor. It also includes an excellent, in-depth review of the effects of these agents on various hypertensive animal models. The remaining papers in Section I and throughout Section II address themselves to the possible site and mechanism of action of these new compounds.

Section III describes research studies in animals and man on the effects of angiotensin and ACE inhibitors on hemodynamics and fluid balance. We also find preliminary data on the effect of decreasing the levels of angiotensin in diseases other than hypertension. The papers in Section IV address themselves to the treatment of various types of hypertension with ACE inhibitors.

Each section is followed by discussion between the authors and members of the symposium audience, which numbered over 300 people. This volume closes with a paper by Dr. John Laragh, The A. N. Richards Memorial Lecturer, entitled "The Renin System in Hypertension: A Research Journey," and an excellent symposium summary and overview by Dr. Franz Gross.

My colleagues and I at The Squibb Institute for Medical Research are very proud of being able to provide the scientific and medical communities with a new way to study the renin angiotensin system and possibly a new method to treat cardiovascular diseases. The importance of the information these compounds have generated and the ideas coming from this volume are made more relevant by a letter to the editor in *The Journal of the American Medical Association* (*JAMA*, April 25, 1980, Vol. 243, p. 1631, No. 16) appearing just two weeks before this symposium and entitled "Angiotensin and Hypertension". The first paragraph reads: "I think the time has come when the cliché, 'the mechanisms and cause of essential hypertension are unknown,' can justifiably be altered to, 'it is highly probable that the core of the mechanism of essential, renovascular, and malignant hypertension is angiotensin.' The evidence from blocking the converting enzyme and from peptide blocking agents all but conclusively shows that when angiotensin is unable to function, blood pressure returns to normal or near normal, especially if salt has been depleted." The author was Dr. Irving Page, and although he might be accused of being somewhat biased since he was one of the discoverers of angiotensin, I do believe the results described in this book partially support him. With the availability, in some countries, of the first marketed ACE inhibitor, captopril,* occurring while this book is being printed, the research community may soon be able to make the evidence conclusive and vindicate Dr. Page's belief in the crucial role of angiotensin in the pathogenesis of hypertension.

Finally, I would like to thank the many people who helped make the symposium and this volume possible:

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Dr. *Morton E. Goldberg*, who originated the idea of this symposium, who served as its Co-Chairman and did such a wonderful job of arranging the facilities and serving as liaison with the Society.

*Capoten®, E. R. Squibb & Sons, Inc.

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August, 1980

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Contents

SECTION I

Development: Central and Autonomic Effects

Joseph P. Buckley, *Chairperson*

Angiotensin Converting Enzyme Inhibitors: Evolution of a New Class of Antihypertensive Drugs

David W. Cushman, Hong Son Cheung, Emily F. Sabo and Miguel A. Ondetti
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INTRODUCTION

The history of the development of antihypertensive drugs that act by inhibiting angiotensin converting enzyme is inextricably linked to the prevailing level of understanding of the structural and catalytic properties of this unusual peptidase. The action of most drugs is initiated by specific attachment to a macromolecular "receptor," the chemical constitution of which is usually unknown. For converting enzyme inhibitors, the drug receptor is the active site of the enzyme, a limited but readily accessible portion of the protein structure that is responsible for specific binding of peptide substrates and for hydrolytic cleavage of the proper peptide bond. Specific binding to the active site of angiotensin converting enzyme has been the guiding principle behind the development of teprotide and captopril, potent competitive inhibitors of this enzyme that have found clinical use as antihypertensive drugs. Development of captopril, in particular, was highly dependent on a general understanding of the chemical nature of the active site of angiotensin converting enzyme, one result of almost three decades of study of its properties.

PROPERTIES OF ANGIOTENSIN CONVERTING ENZYME

In 1954, Skeggs and coworkers found that angiotensin, the pressor product of renin action known then as hypertensin or angiotonin, existed in two forms that were separable by countercurrent distribution. The product obtained from incubations of renin with its plasma substrate in the presence of chloride was named angiotensin II, that obtained in the absence of such a monoanion was called angiotensin I. That angiotensin I lacked direct vasoconstrictor action was demonstrated by studies in artificially perfused kidney (Skeggs et al., 1956) and on the isolated aortic strip (Helmer, 1957). The enzyme responsible for conversion of the inactive angiotensin I to the vasoconstrictor angiotensin II in the presence of chloride ion was partially purified from horse plasma by Skeggs et al. (1956), and given the name angiotensin converting enzyme (originally hypertensin converting enzyme). This enzyme appeared to contain a tightly bound functional metal ion, since it was inhibited by metal-chelating agents such as EDTA, but lost no activity upon dialysis. When the sequences of angiotensins I and II were determined, it was apparent that the converting enzyme hydrolyzed the carboxyl-terminal dipeptide His-Leu from the decapeptide angiotensin I to liberate the

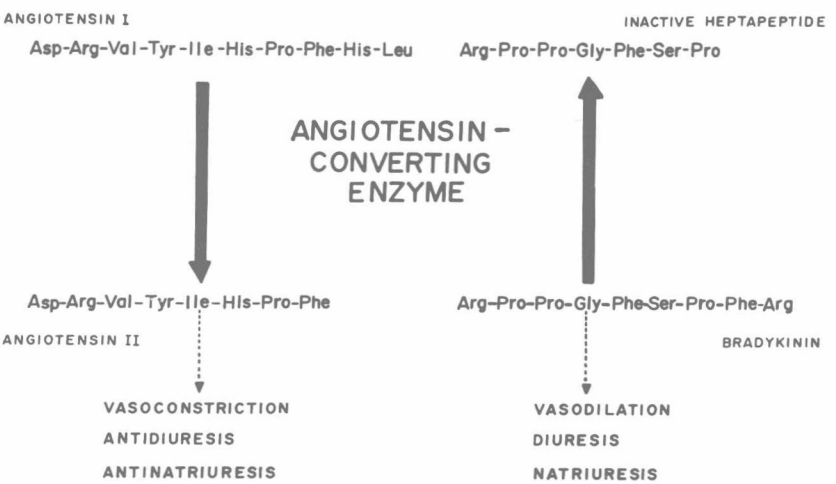

Fig. 1. Two reactions catalyzed by angiotensin converting enzyme (kininase II) that have potential importance in blood pressure regulation. Reprinted with permission from *Enzyme Inhibitors as Drugs*, Merton Sandler, editor, 1980, p. 232. Copyright by The Macmillan Press, Ltd., London.