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FOREWORD

The design and synthesis of angiotensin II (Ang II) antagonists has become an extraordinary focus of effort in the pharmaceutical industry, with over thirty companies actively involved in this area. Although effective peptide antagonists of Ang II have been known since the early 1970's, only during the past several years have potent, nonpeptidic antagonists, devoid of agonist activity, been reported. These new antagonists, the subject of this Symposium-in-Print, offer potential advantages over the angiotensin-converting enzyme (ACE) inhibitors as selective blockers of the renin-angiotensin system. Several potent, non-peptidic antagonists, including losartan, have shown efficacy in animal models of hypertension and in man, and are hoped to enjoy clinical and commercial success in the treatment of hypertension and congestive heart failure. This Symposium-in-Print comprises thirty-six manuscripts representing work from eighteen research groups.

Many of the antagonists currently in development were derived from a series of benzyl-substituted imidazoles first reported by Takeda.[1] The development of losartan (DuPont Merck)[2] and SK&F-108,556 (SmithKline Beecham)[3] from the Takeda lead has been reviewed. Since the publication of losartan in 1989, many related antagonist designs have been reported.[4] It is a tribute to the collective creativity of medicinal chemists working in this area, that successful antagonist designs have been derived from a diverse range of chemical structures. The results of this extraordinary effort are amply reflected in the manuscripts in this Symposium-in-Print. Interestingly, two reports of novel AT_1-selective antagonist series not derived from the Takeda structures appear in this Symposium-in-Print. It is possible that these novel antagonist series will yield in vivo candidates with unique in vivo profiles.

Losartan and related antagonists are now known to bind selectively to a subtype of Ang II receptors referred to as AT_1 which appears to mediate the actions of Ang II to increase blood pressure. Ang II antagonists which bind to a second Ang II receptor subtype, designated AT_2, have been reported by several groups, and a manuscript revealing a novel heterocyclic series with high affinity for AT_2 the receptor appears in this Symposium-in-Print. Although the structure and function of the AT_2 receptor have not yet been established, its widespread occurrence and specific tissue locations suggest that it may play important physiological roles.[5] Recent progress in pharmacological evaluation of AT_2-selective antagonists and in the cloning of this receptor should help clarify potential utilities for AT_2-selective antagonists or agonists.[6]

Elevated levels of Ang II have been observed in man during AT_1 receptor blockade with losartan.[7] Since activation of unblocked AT_2 receptors could result in as-yet unidentified in vivo responses, the simultaneous blockade of Ang II binding to both AT_1 and AT_2 receptors with a non-selective or "balanced" antagonist has become of interest. Progress in this area is demonstrated by three manuscripts in this Symposium-in-Print.

Several nonpeptidic AT_1-selective antagonists are now undergoing clinical evaluation for the treatment of hypertension. It will be interesting to learn what advantages these antagonists may show relative to ACE inhibitors.

Current work to characterize additional Ang II receptor subtypes and to define their roles will continue to enliven this important area for many years to come. It is hoped that the manuscripts in this Symposium-in-Print will contribute to the interest in this area. We gratefully acknowledge those who contributed manuscripts or served as reviewers.

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