Acceptance of the notion that physiologically specific interruption of the renin-angiotensin-aldosterone system (RAAS) is of considerable therapeutic benefit in the treatment of hypertension and congestive heart failure has generated great interest in the search for novel pharmacological inhibitors. The RAAS is expressed at the whole body, organ/tissue and cellular level through the action of the octapeptide angiotensin II (Ang II), the primary effector molecule of the RAAS. The availability of selective, potent, orally active and long-acting nonpeptide Ang II type 1 (AT₁) receptor antagonists provided the opportunity to obtain the benefits of selectively blocking the RAAS at the level of the AT₁ receptor that mediates most, if not all, of the important actions of Ang II, and avoid the nonspecificity of the Ang I converting enzyme (ACE) inhibitors. Losartan was the first, but by no means remained the only nonpeptide AT₁ receptor antagonist. Numerous other “sartans” have emerged in the past several years and successfully completed clinical development. With the exception of Eprosartan, all others, i.e. Candesartan, Irbesartan, Sarpisartan, Tasosartan, Telmisartan, Valsartan and Zolasartan, are based on modifications of Losartan's prototypic chemical structure. AT₁ receptor antagonists represent the newest addition to the arsenal of cardiovascular therapeutics. The predominant role of the AT₁ receptor in mediating the pathophysiological role of Ang II underlies the effectiveness of this novel class of agents to lower arterial blood pressure, reduce pre- and afterload, inhibit sympathetic nervous system activity and prevent cardiovascular hypertrophy and cardiac failure induced by inappropriate control of the RAAS. *(Hypertens Res 1999; 22: 147-153)*

**Key Words:** renin-angiotensin-aldosterone system, angiotensin II, angiotensin II receptors, AT₁ receptors, AT₁ receptor antagonists

The renin-angiotensin-aldosterone system (RAAS) has emerged from an academically interesting, but obscure, regulatory mechanism to an important hormone pathway know to play a pivotal role in the regulation of blood pressure and fluid and electrolyte homeostasis *(1)*. Activation of the RAAS is critically involved in the development and maintenance of hypertension and congestive heart failure. The octapeptide angiotensin II (Ang II) is the primary mediator of the RAAS. Its actions are mediated by specific surface receptors on the various target organs. The most specific and direct way to inhibit the RAAS is by antagonism of the effector hormone Ang II at the level of its target receptors. In theory, Ang II receptor antagonists would be able to completely and selectively inhibit the RAAS independently of the source of Ang II.

Even before the appearance of Ang I converting enzyme (ACE) inhibitors, pharmacological inhibition of the RAAS was achieved in 1971 with saralasin, the first specific peptide antagonist of Ang II *(2)*. Although saralasin reduced arterial pressure in hypertensive patients with high circulating plasma renin activity *(3)*, its therapeutic potential remained limited, since due to its peptidic nature it has a very short plasma half-life, is not orally bioavailable and still possesses significant Ang II-like agonistic properties. Nonetheless, saralasin showed that the principle of interfering with Ang II at the level of its receptor had therapeutic potential.

Despite considerable efforts, there had been little progress in the development of nonpeptide Ang II receptor antagonists until the publication of two patents granted in 1982 to Furukawa and colleagues at Takeda Chemical Industries *(4, 5)*. They disclosed a series of small-molecule imidazole analogues (see below) possessing Ang II antagonistic properties. Additional studies showed that although the potency of these nonpeptide molecules was very moderate, the oral bioavailability very limited and the duration of action very short, they behaved as selective and competitive Ang II receptor antagonists without agonistic properties *(6)*. These low-molecular-weight imidazole compounds were adopted as leads for further optimization. Structural modification provided important chemical features that led
to increasingly more potent and eventually orally active nonpeptide Ang II receptor antagonists. These activities culminated into the discovery of losartan (7), the first clinically useful nonpeptide Ang II receptor antagonist, followed by eprosartan (8). Numerous other “sartans” were subsequently created based on modifications of losartan’s prototypic chemical structure (9).

Losartan and nonpeptide spinacine-derived compounds, such as PD 123,177 and PD 123,319 along with peptides, such as CGP 42112A, have firmly established the concept of Ang II receptor heterogeneity and have provided critical probes for the isolation and cloning of the two receptors for Ang II characterized in mammals, including man. According to current nomenclature, losartan represents the prototype antagonist of the Ang II type 1 (AT₁) receptor family (further subtypes of rat and mouse AT₁ receptors are designated AT₁A and AT₁B), and does not possess significant affinity for the so-called AT₂ receptor for which PD 123,177, PD 123,319 and CGP 42112A exhibit high and selective affinity (10). Virtually, if not all of the known actions of Ang II could be blocked by losartan, emphasizing the major role of the AT₁ receptor subtype in mediating the patho (physiological) actions of this hormone (11). It also clearly explains why most of the pharmaceutical effort has been focused on developing nonpeptide AT₁ receptor-selective antagonists.

As indicated above, the origin of the current potent nonpeptide AT₁ receptor antagonists, of which losartan is the prototype, can be traced back to the Takeda series of 1-benzylimidazole-5-acetic acid derivatives, such as S-8307 (CV2947) and S-8308 (CV2961) (Fig. 1) (4, 5). Losartan (7) and eprosartan (8) were derived from this benzylimidazole series using two different molecular models of puta-

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**Fig. 1.** Structural modifications of the initial lead compounds, S-8307 (CV2947) and S-8308 (CV2961) which led to the successful discovery of the nonpeptide AT₁ receptor antagonists losartan and eprosartan.
tive active conformations of Ang II to align the Takeda derivatives with the C-terminal region of Ang II. The first modeling strategy gave rise to EXP 6155 (Fig. 1) which showed a 10-fold increase in binding affinity. From this starting point a series of phthalamic acids and related compounds were synthesized with progressively higher affinity for the AT1 receptor. EXP 6803 exemplified this approach which produced another 10-fold enhancement in binding affinity.

However, all the compounds were virtually devoid of oral activity, until the amide linker was replaced with a single bond, which resulted in EXP 7711. This biphenyl derivative had only slightly less affinity for the AT1 receptor than EXP 6803, but represented a breakthrough to orally active congeners. To further improve the oral activity and duration of action of these biphenyl compounds, a number of acidic groups were systematically evaluated as bioisosteric replacements for the carboxylic acid group. This effort culminated in the identification of the AT1-selective antagonist, losartan, in which a tetrazole moiety substitutes for this carboxylic acid functionality (Fig. 1).

In many animal species as well as in man, losartan is metabolized to E3174, the imidazole-5-carboxylic acid, resulting from oxidation of the imidazole 5-hydroxymethyl group. Like losartan, E3174 is a selective AT1 receptor antagonist, but is appreciably more potent and possesses a much longer duration of action (12). Like losartan, E3174 has served as a template for the development of many other AT1 receptor antagonists.

A different modeling approach assisted in the synthesis of eprosartan (8) which is representative of one of the few AT1 receptor antagonists designed
independently from the Takeda benzylimidazoles and not from losartan. A combination of molecular modeling and knowledge of the structure-activity relationship for Ang II-like peptides resulted in a 15-fold enhancement in binding affinity by chain extension at the imidazole-5-position via a trans-5-acrylic acid group followed by addition of an α-benzyl group which appeared to better mimic the Phe₈ side chain in Ang II. Replacement of this α-benzyl group with a 2-thienylmethyl moiety followed by replacement of the 2-chlorobenzyl group with a 4-carboxylbenzyl group to better mimic the phenolic moiety of Tyr₄ resulted in eprosartan (Fig. 1). Eprosartan is a potent, AT₁-selective antagonist.

Losartan (E3174) was the first, but by no means remained the only potent, selective, orally active and clinically useful nonpeptide AT₁ receptor antagonist. Numerous other antagonists have successfully completed clinical development and have been (will be) approved and marketed for the treatment of hypertension and some for congestive heart failure. The number of products within this class will undoubtedly further increase.

Valsartan (Fig. 2) represents a nonheterocyclic AT₁ receptor selective antagonist in which the imidazole of losartan is replaced with an acylated amino acid. This antagonist is a diacidic compound, like E3174 (13).

A number of additional antagonist designs have replaced the substituted imidazole found in losartan with various five-membered ring heterocycles. The potent AT₁ receptor antagonist irbesartan (Fig. 2) incorporates an imidazolinone ring in which a carbonyl group functions as a hydrogen bond acceptor in place of the hydroxymethyl group of losartan (14).

Potent antagonists have been obtained by joining substituents at the imidazole C₄ and C₅ positions to yield ring-fused imidazoles. The benzimidazole, candesartan cilexetil (Fig. 2), is an ester carbonate prodrug which is rapidly converted in vivo to the corresponding 7-carboxylic acid candesartan (15).

Potent antagonists have also been obtained by replacing the imidazole of losartan with six-membered ring and fused six-membered ring heterocycles. An example is the AT₁ receptor antagonist tasosartan (Fig. 2) (16). The enol metabolite, enoltasosartan, is responsible for the long pharmacodynamic action of the drug (17).

Telmisartan (Fig. 2) incorporates a carboxylic acid as the biphenyl acidic group. Unlike the case in other series of antagonists, the biphenylcarboxylic acid telmisartan was more potent than its tetrazole analog. Telmisartan is a potent, selective AT₁ receptor antagonist (18).

In zolasartan (Fig. 2), the “spacer” phenyl ring of E3174 is replaced by a bromobenzofuran. The presence of the 3-bromo substituent is essential for high AT₁ receptor affinity exhibited by this series of compounds. Zolasartan is a potent, selective AT₁ receptor antagonist possessing long-lasting antihypertensive effects in laboratory animals (19).

In saprisartan (Fig. 2), the imidazolecarboxylic acid of zolasartan was replaced by a neutral imidazole-5-carboxamide in order to enhance oral bioavailability. This strategy was combined with the replacement of the tetrazole with a triflamic. Saprisartan has high affinity for the AT₁ receptor and its oral bioavailability in animals and man exceeds that of zolasartan (20).

Table 1 lists the affinity of the various AT₁ receptor antagonists for the AT₁ receptor determined by radioligand binding displacement experiments. The

<table>
<thead>
<tr>
<th>AT₁ Receptor Antagonist</th>
<th>AT₁ Receptor Affinity</th>
<th>Mode of AT₁ Receptor Antagonism</th>
<th>AT₁ Receptor Off-Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan cilexetil</td>
<td>280</td>
<td>Noncompetitive</td>
<td>Slow</td>
</tr>
<tr>
<td>Candesartan</td>
<td>1</td>
<td>Noncompetitive</td>
<td>N/A⁺</td>
</tr>
<tr>
<td>Saprisartan</td>
<td>3</td>
<td>Noncompetitive</td>
<td>Slow</td>
</tr>
<tr>
<td>Zolasartan</td>
<td>5</td>
<td>Noncompetitive</td>
<td>Slow</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>10</td>
<td>Noncompetitive</td>
<td>Slow</td>
</tr>
<tr>
<td>Valsartan</td>
<td>10</td>
<td>Competitive</td>
<td>N/A⁺</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>20</td>
<td>Competitive</td>
<td>N/A⁺</td>
</tr>
<tr>
<td>Enoltasosartan</td>
<td>N/A⁺</td>
<td>Competitive</td>
<td>Fast</td>
</tr>
<tr>
<td>Losartan</td>
<td>50</td>
<td>Noncompetitive</td>
<td>Slow</td>
</tr>
<tr>
<td>E3174</td>
<td>10</td>
<td>Competitive</td>
<td>Fast</td>
</tr>
</tbody>
</table>

⁺N/A, not available.
binding affinity is reported as an average value of several published independent measurements using membrane preparations from different tissues. All values are expressed relative to the most potent antagonist (affinity = 1). Candesartan and saprisartan possess the highest affinity for the AT1 receptor followed by zolasartan and irbesartan, the affinity of which is 3- and 5-fold less, respectively. Valsartan, telmisartan and E3174 (the active metabolite of losartan) show comparable affinities that are 10-fold less than those of candesartan and saprisartan. Losartan's affinity for the AT1 receptor is approximately 5 times less than that of E3174, whereas the concentration of eprosartan has to be 100-fold higher than that of candesartan and saprisartan. Losartan's affinity for the AT1 receptor is approximately 5 times less than that of E3174, whereas the concentration of eprosartan has to be 100-fold higher than that of candesartan and saprisartan. Finally, the prodrug candesartan cilexetil has a very moderate AT1 receptor binding affinity.

Effects of AT1 receptor antagonists on the dose/concentration-response curves of Ang II have been characterized as either surmountable or competitive (i.e., the antagonist produces a dose/concentration-dependent, parallel shift to the right of the dose/concentration-response curve of Ang II without a change of the maximally attainable response) or insurmountable or noncompetitive (i.e., the antagonist produces a dose/concentration-dependent, non-parallel shift to the right of the dose/concentration-response curve of Ang II accompanied by a progressive dose/concentration-dependent decrease of the maximally attainable response) (21). Vasopressor responses in vivo and vasoconstrictor effects in vitro to Ang II have been studied to document this distinction. Accordingly, losartan, tasosartan and eprosartan have been classified as competitive AT1 receptor antagonists, whereas candesartan, saprisartan, zolasartan, irbesartan, valsartan, telmisartan and E3174 behave as noncompetitive antagonists (Table 1). In order for true surmountable antagonism to occur it is assumed that complete equilibrium between agonist, antagonist and receptor is established in the interval between addition of the agonist and development of the response in the tissue which is usually less than 1 min (22). The most common mechanism of insurmountable antagonism is irreversible, covalent binding of the antagonist with the receptor. The receptor number is effectively reduced to the point where the receptor reserve is exhausted and a full agonist response can no longer be obtained. However, there are kinetic conditions under which antagonists that do/can not chemically react with the receptor protein produce insurmountable antagonism (see 23). This is observed for antagonists that slowly dissociate from the receptor and therefore the agonist cannot reach equilibrium with the antagonist/receptor complex under the time constraints of the experiment. The more rapid the antagonist can adjust to the presence of the agonist the more surmountable (competitive) the antagonism becomes. It is very likely that slow dissociation kinetics from the AT1 receptor of AT1 receptor antagonists underlie insurmountable antagonism. As Table 1 shows, all noncompetitive AT1 receptor antagonists have a slow off-rate from the AT1 receptor protein. In addition, in radioligand binding displacement assays in which much more time is allowed to approach equilibrium than feasible in functional studies, all AT1 receptor antagonists show (close to) competitive antagonism of Ang II binding.

The mode of AT1 receptor antagonism (competitive vs. noncompetitive) most probably does not play a role in defining the antihypertensive effect of the antagonists. Under those circumstances the antagonist has ample time (hours!) to reach equilibrium. It is therefore very unlikely that noncompetitive AT1 receptor antagonists are more efficacious antihypertensive agents than competitive antagonists. The extensive preclinical experience with AT1 receptor antagonists clearly documents similar antihypertensive/hypotensive efficacies (11). However,
the slow off-rate from the AT₁ receptor exhibited by several antagonists may extend the time of occupancy of the receptor protein and lengthen the duration of the antagonism. Table 2 summarizes some characteristics of AT₁ receptor antagonists currently available. Interestingly, eprosartan is dosed twice daily and represents the only antagonist that is competitive/disassociate fast from the AT₁ receptor and does not produce an active (noncompetitive) metabolite.

An appreciation of the full scope of the (patho)physiological effects of Ang II (endocrine, paracrine and autocrine) has been made possible by the discovery and design of specific, potent, long-acting and orally active nonpeptide AT₁ receptor antagonists discussed above. For the first time, agents have become available to more specifically dissect and more completely block the actions of Ang II, without the limitations of the earlier peptide Ang II receptor antagonists and the nonspecificity of the ACE inhibitors. They offer a more complete blockade of the RAAS by also antagonizing the actions of Ang II produced by non-ACE dependent pathways. Virtually all of the well known actions of Ang II are inhibited by AT₁ receptor antagonists, emphasizing the pivotal role of this distinct receptor subtype in mediating an activated RAAS. The extensive preclinical experience with AT₁ receptor antagonists to date suggests that they produce comparable inhibition of the RAAS to that obtained by ACE and renin inhibitors (II). In numerous models of experimental and genetic hypertension, AT₁ receptor antagonists are effective antihypertensive agents with similar efficacy to that produced by ACE and renin inhibitors. This new class of agents also markedly reduces or prevents cardiovascular hypertrophy/remodeling. In animal models of renal disease, AT₁ receptor antagonists significantly decrease proteinuria, protect against diabetic glomerulopathy and increase survival in stroke-prone SH rats. In several models of heart failure, AT₁ receptor antagonists have shown beneficial effects in lowering intracardial pressures, preventing or blunting hypertrophy/remodeling and fibrosis of the heart as well as increase in heart failure post myocardial infarction.

AT₁ receptor antagonists represent the newest addition to the armamentarium of cardiovascular drugs for the treatment of hypertension and congestive heart failure. It is beyond the scope of this review to discuss the clinical pharmacology of this new class of agents. Suffice to say that losartan, being the first member of this class has been most extensively studied. Reviews on the therapeutic usage of AT₁ receptor antagonists have recently been published with a special focus on losartan (25, 26). The quality of the therapeutic effect and the excellent tolerability of this class of drugs is expected to enhance patient compliance compared to other commonly used antihypertensives. The place of AT₁ receptor antagonists in therapy will ultimately depend in large part on health economic factors and the availability of positive end-point data from several large trials that are currently ongoing with these agents. AT₁ receptor antagonists represent a new milestone in the development of cardiovascular therapeutics and add another dimension to the arsenal of drugs manipulating the RAAS.

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