Nomenclature for Angiotensin Receptors

A Report of the Nomenclature Committee of the Council for High Blood Pressure Research

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The peptide hormone angiotensin II is produced by the sequential processing of the prohormone angiotensinogen by renin and angiotensin I converting enzyme. Angiotensin II, by interacting with cell-surface receptors, produces many diverse physiological effects. Over the last 3 decades, studies with peptide analogues of angiotensin II have provided important clues to the presence of angiotensin receptor subtypes. Recently, however, definitive evidence for the presence of angiotensin II receptor subtypes has been based on binding site analyses using the two series of nonpeptide angiotensin receptor antagonists: 1) the biphenylimidazoles typified by DuP 753,1 and 2) the tetrahydroimidazopyridines typified by PD 1231771 or structural analogues.2,3 The development of a markedly modified analogue of angiotensin II, CGP 42112A,4 has also been instrumental in providing evidence for the presence of angiotensin receptor subtypes. In the several publications that have resulted from the use of these antagonists, each group of investigators has proposed its own subclassification of the angiotensin receptor, which has led to some confusion. With the sole object of clarifying this issue, a nomenclature committee was established in 1990 by the American Heart Association Council for High Blood Pressure Research. The committee’s specific task was to make recommendations and provide guidelines for creating the nomenclature for angiotensin receptor subtypes. The committee met in Baltimore, Md., in September 1990.

The committee agreed that the format of the proposal should be based on the recently published “Receptor Nomenclature Supplement” in TIPS.5 Table 1 summarizes the proposed classification. In choosing an abbreviation for the angiotensin receptor, we decided AT (angiotensin) would be more appropriate than Ang (the standard abbreviation for angiotensin peptides) because using the former would avoid confusion with angiotensin II and its fragments, which have varying degrees of biological activity. The subclassification of AT receptors were denoted as subscript 1, 2, 3, and so on. Selective antagonists displaying differences in potency of at least two orders of magnitude were used to subclassify AT receptors as AT1 and AT2. The prototypical antagonist of the AT1 receptor is DuP 753. The prototypical antagonists of the AT2 receptor are CGP 42112A, PD 123177, and PD 123319. At present we realize that the classification of the AT2 as a receptor must be tentative until a function or a physiological response can be attributed to this angiotensin II binding site. Additionally, the designation of the ligands CGP 42112A, PD 123177, and PD 123319 as antagonists is tentative since a physiological response has not as yet been attributed to this angiotensin II binding site. If, on the basis of results with selective agonists or antagonists, convincing evidence can be presented that angiotensin II receptor subtypes exist, then a subclassification of these receptors can be proposed. At present we are aware of two angiotensin II receptor subtypes: one with high affinity for CGP 42112A, PD 123177, and PD 123319; the other with high affinity for DuP 753. Both subtypes are present in cardiac tissue, and both respond to angiotensin II by protein and gene expression. The presence of angiotensin receptor subtypes has been confirmed in a variety of tissues, including the lung, kidney, brain, and heart. The presence of angiotensin receptor subtypes has been confirmed in a variety of tissues, including the lung, kidney, brain, and heart. The presence of angiotensin receptor subtypes has been confirmed in a variety of tissues, including the lung, kidney, brain, and heart. The presence of angiotensin receptor subtypes has been confirmed in a variety of tissues, including the lung, kidney, brain, and heart.

Table 1. Angiotensin Receptors

<table>
<thead>
<tr>
<th>Proposed nomenclature*</th>
<th>AT1</th>
<th>AT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous names</td>
<td>AII-1; AII-B; AIIa</td>
<td>AII-2; AII-A; AIIb</td>
</tr>
<tr>
<td>Potency order</td>
<td>Angiotensin II &gt; angiotensin III</td>
<td>Angiotensin II = angiotensin III</td>
</tr>
<tr>
<td>Selective antagonists†</td>
<td>DuP 753</td>
<td>PD 123177; PD 123319; CGP 42112A</td>
</tr>
<tr>
<td>Effector pathways</td>
<td>IP/DP</td>
<td>cAMP ↓</td>
</tr>
<tr>
<td>Endogenous ligands</td>
<td>Angiotensin II, angiotensin III. Other fragments of angiotensin II may show selectivity among receptor subtypes. Other receptor/binding sites: A soluble angiotensin binding protein, isolated from the liver and other tissues, displays high affinity for CGP 42112A but not PD 123319 or DuP 753; this binding protein may represent a subtype of the AT2 receptor.</td>
<td></td>
</tr>
</tbody>
</table>

*If angiotensin receptor subtypes can be further subdivided based on selective agonists or antagonists, we propose that AT1 and AT2 be subdivided as follows: AT1a, AT1b, AT2a, AT2b, and so on.
†Chemical names: DuP 753: 2-n-butyl-4-chloro-5-(hydroxymethyl)-1-[2'- (1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole; PD 123177: 1-[(4-amino-3-methylphenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid; PD 123319: (5S)-1-[(4-(di-methylamino)-3-methylphenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid; CGP 42112A: nicotinyl-Tyr-(Nβ-benzoyloxycarbonyl-Arg)Lys-His-Pro-Ile-OH.

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presented for the further subdivision of the AT₁ or AT₂ receptor, we recommend that the subscripts A, B, C, and so on be used (e.g., AT₁₁). Finally, we recommend that 1) the AT₁ notation replace the previous terminology (e.g., the type 1 angiotensin II receptor,¹,² the type B angiotensin II receptor,⁴ and the angiotensin II₆ receptor⁶), and that 2) the AT₂ notation replace the previous terminology (e.g., the type 2 angiotensin II receptor,¹,² the type A angiotensin II receptor,⁴ and the angiotensin II₆ receptor⁶).

References


Key Words • nomenclature • angiotensin II • angiotensin receptors
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