Angiotensin

Overview: The actions of angiotensin II (Ang II) are mediated by AT_1 and AT_2 receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors; see De Gasparo *et al*., 2000), which have around 30% sequence similarity. AT_1 receptors are predominantly coupled to $G_{q/11}$. Most species express a single *AT1* gene, but two related *AT1A* and *AT1B* receptor genes are expressed in rodents. The AT_2 receptor counteracts several of the growth responses initiated by the AT_1 receptors. The AT_2 receptor is much less abundant than the AT_1 receptor in adult tissues and is up-regulated in pathological conditions. Endogenous ligands are Ang II and Ang III, while Ang I is weakly active in some systems.

Nomenclature	AT_1	AT_2
Ensembl ID	ENSG00000144891	ENSG00000180772
Principal transduction	$G_{q/11}$	Tyr & Ser/Thr phosphatases
Selective agonists	L162313	[p-NH_2-Phe^6]-Ang II, CGP42112
Selective antagonists	EXP3174, eprosartan, valsartan, irbesartan, losartan	PD123319, PD123177
Probes	[^{3}H]-A81988, [^{3}H]-L158809, [^{3}H]-eprosartan, [^{3}H]-losartan, [^{125}I]-EXP985	[^{125}I]-CGP42112

There is also evidence for an AT_4 receptor that specifically binds Ang IV and is located in the brain and kidney. An additional putative endogenous ligand for the AT_4 receptor has been described (LVV-hemorphin, a globin decapeptide) (Moeller *et al*., 1997). The AT_1 and bradykinin B2 receptors have been proposed to form a heterodimeric complex (AbdAlla *et al*., 2000). The antagonist activity of CGP42112 has also been reported (Lokuta *et al*., 1995). Novel AT_1 receptor antagonists bearing substituted 4-phenylquinoline moieties have recently been designed and synthesized. The best of these compounds bind to AT_1 receptors with nanomolar affinity and are slightly more potent than losartan in functional studies (Cappelli *et al*., 2004).

Abbreviations: A81988, 2(*N*-*n*-propyl-*N*-[{2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl}methyl]amino)pyridine-3-carboxylate; **CGP42112A**, nicotinic acid-Tyr-(*N*-benzoylcarbonyl-Arg)-Lys-His-Pro-Ile-OH; **eprosartan**, (E)-α-([2-butyl-1-{(4-carboxyphenyl)methyl}-1*H*-imidazol-5-yl]methylene)-2-thiophenepropanoate; **EXP3174**, *n*-butyl-4-chloro-1-([2′-{1*H*-tetrazol-5yl}biphenyl-4-yl]methyl)imidazole-5-carboxylate; **EXP985**, *N*-(2-[4-hydroxy-3-iodophenyl]ethyl)-4-chloro-2-propyl-1-([2′-{1*H*-tetrazol-5yl}biphenyl-4-yl]methyl)imidazole-5-carboxamide; **losartan**, 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole, also known as Dup 753; **irbesartan**, 2-butyl-3-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one; **L158809**, 5,7-dimethyl-2-ethyl-3-(2-[1*H*-tetrazol-5yl]biphenyl-4-yl)imidazo[4,5-*b*]pyridine; **L162313**, 5,7-dimethyl-2-ethyl-3-[[4-[2(*n*-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl] imidazo[4,5,6]pyridine; **PD123177**, 1-(4-amino-3-methylphenyl)methyl-3-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **PD123319**, (*S*)-1-(4-[dimethylamino]-3-methylphenyl)methyl-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*] pyridine-6-carboxylate; **valsartan**, *N*-(1-oxopentyl)-*N*-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine

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