



# Pharmacological aspects of candesartan, an effective AT<sub>1</sub>-receptor blocker

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## KEYWORDS

AT<sub>1</sub>-receptor blockers;  
Angiotensin II;  
Candesartan;  
EXP-3174;  
Losartan;  
*In vitro* studies

Blockade of the angiotensin type-1 (AT<sub>1</sub>) receptor represents a rational therapeutic strategy in cardiovascular disease since it inhibits AT<sub>1</sub>-receptor-mediated vasoconstriction, cardiovascular remodelling, and vascular inflammation, while preserving AT<sub>2</sub>-receptor-mediated vasodilatation and antiproliferative effects. The AT<sub>1</sub>-receptor blockers currently available bind selectively to the AT<sub>1</sub> receptor, but there are marked differences in their affinity for the receptor and their duration of binding. Of the existing agents, candesartan has the highest affinity for the AT<sub>1</sub> receptor and has a long duration of binding. Furthermore, candesartan markedly decreases the maximal response to angiotensin II and thus acts as an insurmountable inhibitor; agents such as irbesartan and EXP-3174 (the active metabolite of losartan) can also reduce the maximal response to angiotensin II, although to a lesser extent. In contrast, agents such as losartan act as surmountable inhibitors. These pharmacological differences are reflected in clinically relevant differences regarding the duration of antihypertensive action between agents. In the decade since the introduction of the first AT<sub>1</sub>-receptor blocker, the therapeutic role of these agents has expanded beyond hypertension to include conditions such as heart failure and diabetic nephropathy. This expanded role reflects the emerging evidence for additional benefits at target organ level that appear to be independent of blood pressure control.

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## Introduction

Blockade of the angiotensin type-1 (AT<sub>1</sub>) receptor represents a rational therapeutic strategy in hypertension and heart failure since this approach results in inhibition of a variety of deleterious processes mediated by AT<sub>1</sub> receptors, including vasoconstriction, vascular inflammation, cardiovascular remodelling, fibrosis and proteinuria<sup>1,2</sup>. Furthermore, since circulating concentrations of angiotensin II increase during treatment with AT<sub>1</sub>-receptor blockers, selective blockade of AT<sub>1</sub> receptors would be expected to result in hyperstimulation of AT<sub>2</sub> receptors,

thereby enhancing AT<sub>2</sub>-mediated vasodilatation and antiproliferative effects<sup>3</sup>. AT<sub>1</sub>-receptor blockade also offers potential advantages over angiotensin-converting-enzyme (ACE) inhibitors since it inhibits the effects of angiotensin II produced by both ACE and ACE-independent pathways, and avoids the increases in kinin levels seen with ACE inhibitors that are believed to be related to side effects such as cough and angio-oedema.

Since the introduction of the first AT<sub>1</sub>-receptor blocker, losartan, in 1994, a number of others have entered clinical practice, including candesartan, irbesartan, valsartan, telmisartan, eprosartan and olmesartan. With the exception of eprosartan, all of these are based on a biphenyl ring structure; several, including losartan, candesartan and irbesartan, have a biphenyltetrazole structure that appears to be favourable for binding to the AT<sub>1</sub> receptor. Candesartan and olmesartan are formed by first-pass metabolism of oral prodrugs (candesartan

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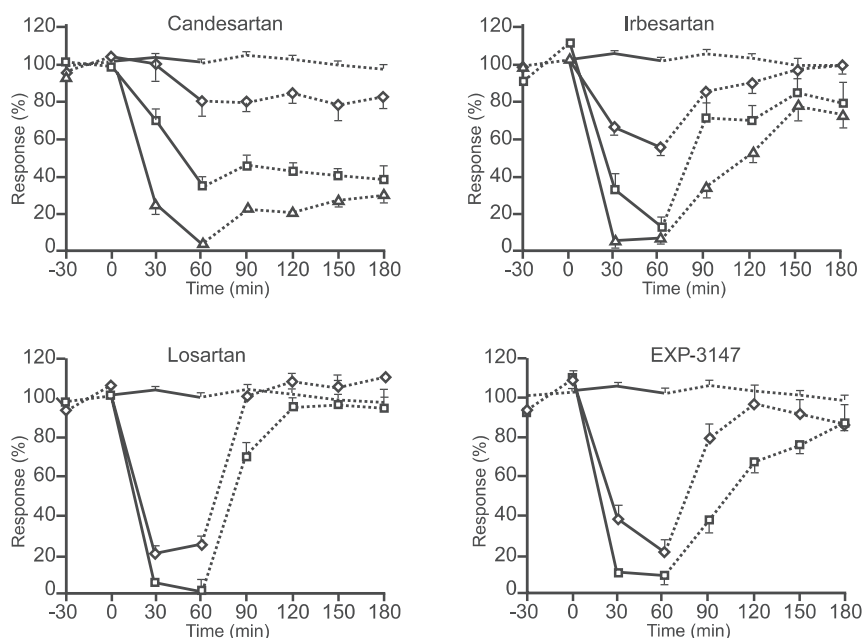


Fig. 1. Duration of blockade of the vascular contractile response to angiotensin II 3 nmol/L, in isolated rat portal vein preparations. Portal vein was incubated for 1 hour (solid lines) with vehicle (no symbol), losartan 30 nmol/L ( $\diamond$ ) or 100 nmol/L ( $\square$ ), EXP-3174 1 nmol/L ( $\diamond$ ) or 100 nmol/L ( $\square$ ), irbesartan 1 nmol/L ( $\diamond$ ), 3 nmol/L ( $\square$ ) or 50 nmol/L ( $\triangle$ ), or candesartan 0.1 nmol/L ( $\diamond$ ), 0.3 nmol/L ( $\square$ ) or 1 nmol/L ( $\triangle$ ), before washing with drug-free Krebs buffer (dashed lines). Results are presented as means  $\pm$  SEM,  $n=8-15$  for AT<sub>1</sub>-receptor blockers,  $n=80$  for vehicle. Reproduced from Morsing et al. 1999<sup>8</sup> with the permission of Lippincott, Williams & Wilkins.

cilexetil and olmesartan medoxomil), while losartan is partly converted in the liver to a more active metabolite EXP-3174; the other compounds are active in their own right.

Each of the available AT<sub>1</sub>-receptor blockers binds selectively to the AT<sub>1</sub> receptor, producing more complete inhibition of the renin-angiotensin system than can be achieved with ACE inhibitors. There are, however, marked differences between the available agents in terms of their binding characteristics at the AT<sub>1</sub> receptor. Clinically, the AT<sub>1</sub>-receptor blockers produce effective and well-tolerated reductions in blood pressure. Moreover, increasing evidence suggests that they also exert protective effects in target organs such as the left ventricle, kidney and brain, while the recent results of the CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) programme show that candesartan significantly reduces mortality and morbidity associated with congestive heart failure<sup>4</sup>.

### Binding characteristics of the AT<sub>1</sub>-receptor blockers at the AT<sub>1</sub> receptor

In studies using isolated blood vessels from laboratory animals, AT<sub>1</sub>-receptor blockers bind to the AT<sub>1</sub> receptor with high affinity and selectivity, but the affinities of the different agents vary by several orders of magnitude. For example, the affinity of candesartan for the receptor is approximately 80 times higher than that of losartan and 10 times higher than that of EXP-3174<sup>5,6</sup>. Indeed, among the currently available agents, candesartan has the highest relative receptor affinity, followed

by irbesartan, valsartan/EXP-3174/telmisartan, losartan and eprosartan<sup>7</sup>.

The duration of binding of different AT<sub>1</sub>-receptor blockers to the receptor also varies widely. Wash-out studies in isolated blood vessels have shown that candesartan dissociates from the receptor significantly more slowly than some other AT<sub>1</sub>-receptor blockers (Fig. 1)<sup>8,9</sup>. Similarly, in a study in Chinese hamster ovary (CHO) cells expressing the human AT<sub>1</sub> receptor, [<sup>3</sup>H]-labelled candesartan was not readily displaced from the receptor by subsequent exposure of the cells to losartan; moreover, the duration of inhibition of angiotensin-II-induced inositol phosphate accumulation was longer with candesartan than with losartan, EXP-3174 or irbesartan<sup>10</sup>. The mean dissociation half-lives of AT<sub>1</sub>-receptor blockers in this study ranged from 5.2 minutes for losartan to 152 minutes for candesartan<sup>10</sup>.

Another important difference between AT<sub>1</sub>-receptor antagonists is in the nature of angiotensin-II antagonism produced at the receptor. When angiotensin-II-sensitive tissue is preincubated with AT<sub>1</sub>-receptor blockers, some agents, such as losartan, shift the angiotensin II dose-response curve to the right but do not affect the maximal response; this form of inhibition is referred to as *surmountable* inhibition since it can be overcome by increasing concentrations of angiotensin II (Fig. 2)<sup>11-13</sup>. In contrast, candesartan and olmesartan reduce the maximal response to angiotensin II, and can almost completely abolish the response; this inhibition cannot be overcome by increasing concentrations of angiotensin II and hence is described as *insurmountable* inhibition<sup>11,12</sup>. Some of the other AT<sub>1</sub>-receptor blockers,

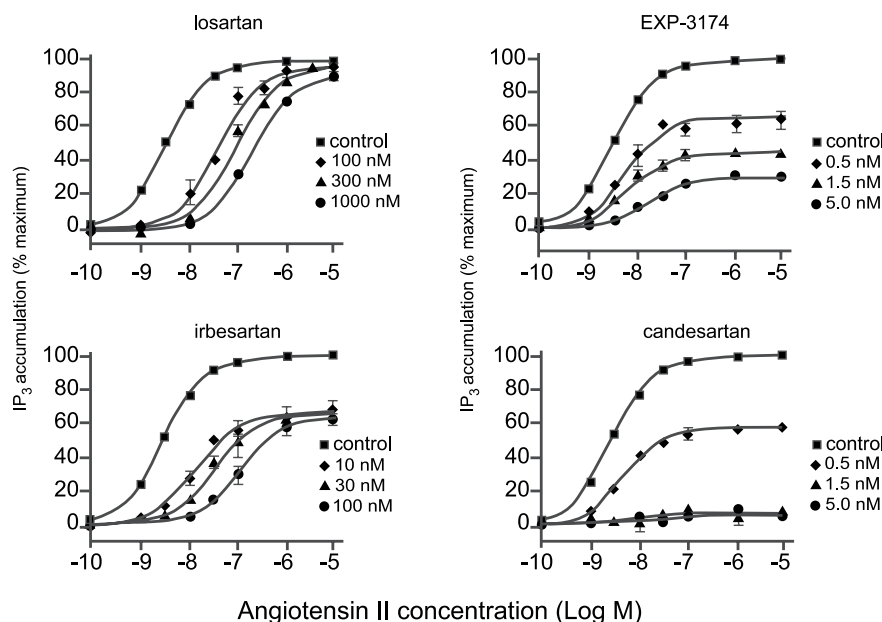


Fig. 2. Concentration-response curves for angiotensin-induced inositol phosphate production in CHO-AT<sub>1</sub> cells after pre-incubation for 30 minutes with AT<sub>1</sub>-receptor blockers at the concentrations shown<sup>13</sup>. Reproduced with permission from Vanderheyden et al. 1999<sup>13</sup>.

such as irbesartan, telmisartan, valsartan and EXP-3174, also reduce the maximal response to angiotensin II, but can only partially suppress the response. Surmountable inhibition results from fast and reversible binding of the antagonist to the receptor, whereas fully insurmountable inhibition, as with candesartan, is related to slow dissociation of the receptor-antagonist complex<sup>12</sup>.

These differences in the antagonist properties of different AT<sub>1</sub>-receptor blockers have been demonstrated in several studies with isolated blood-vessel preparations or CHO cells expressing human AT<sub>1</sub>-receptors<sup>8,13</sup>. For example, in experiments in rabbit aortic strips, all sartans shifted the dose-response curve to the right. However, candesartan produced complete inhibition of the contractile response to angiotensin II at a concentration of 1 nmol/L, whereas irbesartan and EXP-3174 produced less marked inhibition, and losartan had no effect on the maximal response at concentrations of up to 100 nmol/L<sup>8</sup>. In other studies, reversal of the inhibitory effect of candesartan in CHO cells was slower than with irbesartan or EXP-3174, while the effect of losartan was almost instantaneously reversible, suggesting that insurmountable antagonism is related to prolonged binding of the antagonist to the receptor<sup>13</sup>.

The potent AT<sub>1</sub>-receptor blockade produced by candesartan and EXP-3174 appears to be related to the presence of two negatively charged groups, a carboxyl group and a tetrazole moiety: the less potent precursors of these molecules, candesartan cilexetil and losartan, possess only the tetrazole moiety<sup>12</sup>. Other potent AT<sub>1</sub>-receptor blockers also appear to be diacidic molecules<sup>12</sup>. Experiments with candesartan analogues suggest that appropriate alignment of the carboxyl groups is a prerequisite for tight and prolonged binding, and hence for insurmountable antagonism<sup>5,12</sup>.

## Clinical profiles of AT<sub>1</sub>-receptor blockers

The AT<sub>1</sub>-receptor blockers offer a favourable clinical profile, including effective blood-pressure reduction, good tolerability and increasing evidence of protection against target-organ damage. However, the differences in pharmacological properties between the available agents are reflected in certain differences in clinical properties.

### Antihypertensive efficacy

Each of the available AT<sub>1</sub>-receptor blockers has proven antihypertensive efficacy. However, there are marked differences between them in the maximal antihypertensive effect<sup>14</sup>, and in the duration of action. In one randomized study, for example, hypertensive patients received candesartan cilexetil 8-16 mg, losartan 50-100 mg, or placebo for 8 weeks; ambulatory blood pressure was measured for 36 hours after dosing and clinic blood pressure was measured 24 and 48 hours after the last dose<sup>15</sup>. Candesartan produced significantly greater reductions in ambulatory blood pressures than losartan, which were sustained for at least 36 hours after dosing (Fig. 3). In contrast, in losartan-treated patients blood pressure had returned almost to baseline levels at 36 hours after dosing (Fig. 3). Moreover, significant reductions in both systolic and diastolic clinic blood pressures were seen 48 hours after the last dose of candesartan, whereas blood pressures in losartan-treated patients were not significantly different from baseline levels. Indeed, blood pressures in candesartan-treated patients 48 hours after the last dose were comparable with those seen in losartan-treated patients 24 hours after dosing.

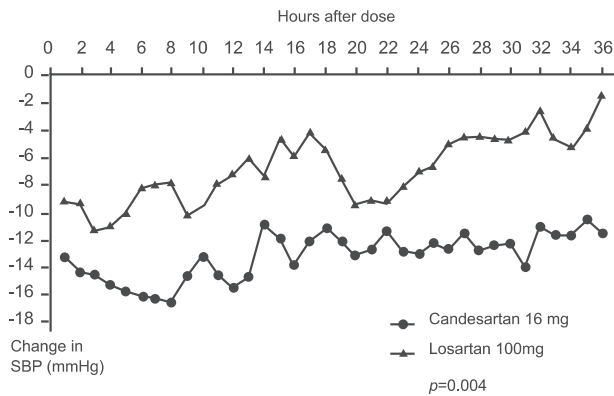


Fig. 3. Mean change from baseline in systolic ambulatory blood pressure 0-36 hours after dosing in 268 antihypertensive patients treated with candesartan cilexetil 16 mg or losartan 100 mg. Reproduced from Lacourcière and Asmar 1999<sup>15</sup>, copyright 1999, with the permission of American Journal of Hypertension Ltd.

### Tolerability and safety

For most classes of drugs, an increase in dose is associated with both increased efficacy and a decrease in tolerability, and hence the optimal therapeutic window lies in the middle of the dosing range. In contrast, for AT<sub>1</sub>-receptor blockers, placebo-like tolerability is maintained across the dosing range. Thus, the dose can be increased if necessary to achieve blood-pressure control and organ protection without a loss of tolerability. There is currently no evidence that the available AT<sub>1</sub>-receptor blockers differ significantly in tolerability<sup>16,17</sup>.

### Target-organ protection

Evidence is accumulating from both laboratory and clinical studies that AT<sub>1</sub>-receptor blockers offer protection against target-organ damage, and that these effects are not related to blood-pressure reductions alone. In one study, for example, stroke-prone spontaneously hypertensive rats were treated for 10 weeks with candesartan cilexetil 0.1, 1 or 10 mg/kg, or enalapril maleate 10 mg/kg<sup>18</sup>. Control animals developed severe hypertension, which was associated with neurological signs of stroke and an increase in urinary protein excretion. Treatment with candesartan 1 or 10 mg/kg significantly reduced blood pressure, stroke, left-ventricular weight, and urinary protein excretion, compared with control animals. With the lowest dose of candesartan, significant decreases in stroke incidence and urinary protein excretion were seen in the absence of changes in blood pressure.

The protective effects of AT<sub>1</sub>-receptor blockers against stroke may be due to inhibition of the central effects of angiotensin II, resulting in improved vascular function, and to direct neuroprotective effects such as decreased sensitivity to ischaemia. Evidence for inhibition of the central effects of angiotensin II comes from a study in which conscious rats received oral doses of candesartan cilexetil 0.1, 1, 10 or 30 mg/kg; drinking responses, pressor responses and vasopressin release were measured after administration of angiotensin II into

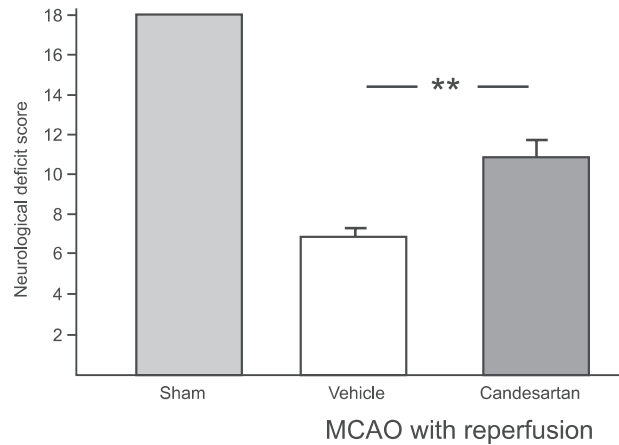


Fig. 4. Neurological outcome in rats subjected to middle cerebral artery occlusion, followed by reperfusion, after pretreatment for 5 days with candesartan 0.1 mg/kg s.c., or vehicle. Neurological deficit was scored according to the system of Garcia et al.<sup>19</sup>. For each of six tests, severe impairment is graded 0-1, while no observable deficit is graded 3. Thus, the maximum score (least neurological deficit) is 18. \*\* $P < 0.001$ . Reproduced from Groth et al. 2003<sup>20</sup> with the permission of Lippincott, Williams & Wilkins.

the cerebral ventricles 0.5, 2, 4 and 24 hours after dosing<sup>21</sup>. Candesartan treatment produced dose- and time-dependent reductions in all of the central responses to angiotensin II, which were sustained for 24 hours with the highest dose.

Evidence for neuroprotective effects of AT<sub>1</sub>-receptor blockers comes from a study in which focal cerebral ischaemia was induced in normotensive rats by occlusion of the middle cerebral artery followed by reperfusion<sup>20</sup>. Neurological deficits, infarct volume and brain oedema were assessed 24 hours after the induction of ischaemia<sup>19</sup>. Acute pretreatment with candesartan 0.1 or 0.3 mg/kg produced dose-dependent reductions in arterial blood pressure but had no effect on outcome after cerebral ischaemia. In contrast, treatment with candesartan 0.1 mg/kg twice daily for 5 days prior to the induction of ischaemia resulted in significant improvements in neurological deficits (Fig. 4) and infarct volume (Fig. 5), compared with vehicle-treated animals. Cerebral oedema was also significantly reduced in candesartan-treated animals, compared

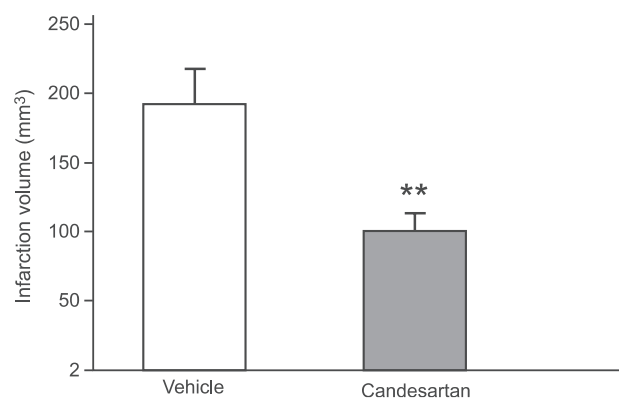


Fig. 5. Effect of pre-treatment with candesartan 0.1 mg/kg s.c. on infarct volume in rats subjected to middle cerebral artery occlusion, followed by reperfusion. \*\* $P < 0.001$ . Reproduced from Groth et al. 2003<sup>20</sup> with the permission of Lippincott, Williams & Wilkins.

with the control group. Such studies suggest that AT<sub>1</sub>-receptor blockade in the brain and cerebrovascular circulation attenuates the reduction in blood flow during brain ischaemia, reduces the volume of neuronal injury, and improves neurological outcome<sup>22</sup>. These effects can be abolished by AT<sub>2</sub>-receptor blockade<sup>22</sup>, suggesting that activation of AT<sub>2</sub> receptors following AT<sub>1</sub>-receptor blockade may induce neuroregeneration or induce apoptosis in severely ischaemic tissue, both of which are important in the recovery from stroke<sup>23</sup>. Other potential neuroprotective effects of AT<sub>1</sub>-receptor blockers, such as decreasing inflammation and increasing neuronal regeneration, are currently under investigation.

### Reduction in morbidity and mortality

Evidence from several large outcome trials suggests that the beneficial effects of AT<sub>1</sub>-receptor blockers against target-organ damage translates into reductions in mortality and morbidity from cardiovascular disease. For example, the results of the Study of Cognition and Prognosis in the Elderly (SCOPE) with candesartan<sup>24</sup> and the Losartan Intervention For Endpoint reduction in hypertension (LIFE)<sup>25</sup> study suggest that treatment with an AT<sub>1</sub>-receptor blocker can reduce the risk of major cardiovascular events by 11-15%, and that of stroke by 24-26%, compared with control therapy; furthermore, the incidence of new-onset diabetes mellitus was also reduced, by 20-25%, in these studies. Furthermore, among patients in the SCOPE Study with some cognitive impairment at baseline, as measured by the Mini-Mental State Examination (MMSE), the decline in cognitive function during the study was significantly lower in the candesartan group than in the placebo group.

The CHARM Programme has shown significant reductions in cardiovascular mortality and morbidity in patients with congestive heart failure treated with candesartan, compared with placebo-treated patients<sup>4</sup>. The CHARM results are described in detail in other papers in this supplement.

### Conclusions

In the decade since the introduction of the first AT<sub>1</sub>-receptor blocker, the therapeutic role of these agents has expanded beyond hypertension to include conditions such as heart failure and diabetic nephropathy. This expanded role reflects both the effective blood-pressure control and outstanding tolerability offered by AT<sub>1</sub>-receptor blockers, and the emerging evidence for additional benefits at target-organ level that are independent of blood-pressure control. Pharmacological studies have highlighted the differences among AT<sub>1</sub>-receptor blockers, and confirmed the tight receptor binding and long-acting properties of candesartan.

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