Although currently available angiotensin II type 1 (AT₁) receptor blockers (ARBs) share a common mechanism of action, blocking AT₁ receptors, their receptor binding kinetics and biological actions are not identical. Two ARBs, namely losartan and candesartan cilexetil, are prodrugs that are converted to active drugs in vivo. After oral administration, losartan undergoes the first-pass metabolism in the liver and is converted into EXP3174, whose affinity to the AT₁ receptor is 10 times higher than that of losartan. It should be noted that losartan is not a typical prodrug because it has significant ARB activity and only 14% of the administered dose is converted to EXP3174. This indicates that pharmacological effects of losartan are mediated not only by losartan itself but also by EXP3174 and possibly other metabolites as well.

There is growing evidence to suggest that losartan has AT₁ receptor–independent actions primarily related to antiinflammatory and antiaggregatory mechanisms (Table). These actions have been speculated to be independent of the AT₁ receptor blockade primarily because these properties are not shared by other ARBs, such as candesartan and valsartan, or by angiotensin-converting enzyme inhibitors. Furthermore, losartan blocks vasoconstriction and platelet aggregation induced by the thromboxane A₂ (TXA₂) analog, U46619, and displaces ligand binding to the TXA₂ receptor, suggesting that losartan can act as a dual-receptor antagonist. Interestingly, EXP3174 and irbesartan, another ARB, both of which have the imidazole moiety of biphenyl tetrazole in their structure similar to losartan, interact with the TXA₂ receptor. Thus, the chemical structure appears to determine the AT₁ receptor–independent actions of the ARBs. However, because stimulation of the AT₁ receptor alone is also able to stimulate inflammation and thrombosis through up-regulation of inflammatory cytokines and prostaglandins (PGs), the significance of such AT₁ receptor–independent actions of losartan over its AT₁ receptor antagonism has been difficult to prove.

In this issue of Circulation Research, Krämer et al⁶ have shown that EXP3179, another metabolite of losartan, possesses antiinflammatory and antiaggregatory properties, despite the fact that it does not interfere with ligand binding to the AT₁ receptor. After a single oral dose of 100 mg losartan in patients, inhibition of PGF₂α production was observed over 6 to 8 hours in vivo. By that time, a significant amount of EXP3179 has been produced through the hepatic circulation.

Although EXP3179 is structurally similar to indomethacin, a conventional nonsteroidal antiinflammatory drug and an inhibitor of both cyclooxygenase (COX)-1 and COX-2, the precise mechanism of its antiinflammatory and antiaggregatory actions remains to be elucidated. Inhibition of PGF₂α synthesis reflects that EXP3179 works as a COX inhibitor. Like other antiinflammatory agents, however, EXP3179 may also exert its action through COX inhibition-independent effects (reviewed in Tegeder et al⁷). Many nonsteroidal antiinflammatory drugs inhibit transcription factors, such as NF-κB, AP-1, or CCAAT enhancer-binding proteins (C/EBPs), thereby negatively regulating transcription of proinflammatory genes, including cytokines and cell adhesion molecules. Indomethacin may exert its antiinflammatory activities through activation of peroxisome proliferator-activated receptor γ. These antiinflammatory agents also affect activities of various protein kinases, including IkB kinase β, mitogen-activated protein kinases, Cdk, and Src. EXP3179 may share these mechanisms, thereby negatively regulating mRNA expression of COX-2 and ICAM-1, important mediators of inflammation (Figure). EXP3179 may also act as a receptor antagonist for TXA₂ receptors to prevent U46619-induced platelet aggregation.

Stimulation of the AT₁ receptor causes both activation of phospholipase A₂ and upregulation of COX-2 in vascular smooth muscle cells, which in turn mediate production of eicosanoids, including PGE₂ and TXA₂, and cell proliferation. Thus, losartan should block cellular responses mediated by PGs through multiple mechanisms in vivo: AT₁ receptor blockade by losartan and EXP3174, suppression of COX-2 expression by EXP3179, and blockade of TXA₂ receptor by all 3 compounds. In this regard, losartan may be effective in treating atherosclerosis, where both the local renin-angiotensin system and the inflammatory process are stimulated.

Myocardial COX-2 expression is upregulated in failing hearts as well as after myocardial infarction. Increased production of PGs, including PGE₂ and PGF₂α, stimulates cardiac hypertrophy, whereas selective inhibition of COX-2 prevents myocardial infiltration of inflammatory cells after myocardial infarction. By contrast, COX-2 prevents cardiac myocyte apoptosis and mediates the late phase of ischemic preconditioning. Thus, whether or not downregulation of COX-2 by EXP3179 is salutary in treatment of patients with coronary artery diseases or heart failure remains to be elucidated. Although treatment of heart failure patients with losartan did not show survival advantage over...


### AT₁ Receptor–Independent Actions of Losartan

<table>
<thead>
<tr>
<th>Physiological pathways inhibited</th>
<th>Antiinflammatory and antiaggregatory action of EXP3179[a]</th>
<th>Inhibition of prostaglandin production[^24]</th>
<th>Production of NO[^25]</th>
<th>Receptor targets</th>
</tr>
</thead>
</table>

Losartan exhibits antiinflammatory and antiaggregatory actions through multiple mechanisms. PKC indicates protein kinase C; PPAR, peroxisome proliferator–activated receptor; and ROS, reactive oxygen species. Some kinases, such as p38-MAPK and JNK, may be activated.

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inhibit the metabolism of losartan in the liver P450 pathway at multiple stages. Second, losartan and EXP3174 also work as TXA2 receptor antagonists. The potency of antiaggregatory and antiinflammatory actions of EXP3179 should be compared with that of losartan and EXP3174. Third, recent evidence suggests that COX-2 is not entirely inducible, and its constitutive expression in vascular endothelium may critically regulate the generation of prostacyclin, which is a vasodilator and inhibitor of platelet aggregation. In this regard, how EXP3179 affects production of prostacyclin needs to be determined. Finally, it will be interesting to determine the crucial chemical structure that confers antiinflammatory actions to EXP3179.

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### References


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