The inhibition of the renin-angiotensin axis with the angiotensin II (ATII) receptor blockers, such as losartan, candesartan, and valsartan, has been demonstrated, similar to angiotensin-converting enzyme inhibitors, to reduce mortality in patients with arterial hypertension, chronic congestive heart failure, and acute myocardial infarction.1

Initially, the ATII receptor antagonist losartan helped to demonstrate new classes of ATII receptors and substantially expanded our knowledge about the cardiovascular effects of the renin-angiotensin-aldosterone system and its effector peptide ATII. Researchers dealing with this compound soon revealed that, beyond its antihypertensive effects attributed to blockade of the ATII receptor type 1 (AT1R), losartan has antiaggregatory and anti-inflammatory actions that are potentially independent of the hypotensive actions. In this regard, it is important to note that losartan is a prodrug. In vivo cytochrome P450-mediated oxidation leads to the formation of the metabolite EXP3174 with an ∼40-fold higher capacity to bind the AT1R. Another metabolite, EXP3179, has a striking structural homology to the cyclooxygenase inhibitor indomethacin and abolishes cyclooxygenase-2–mediated formation of thromboxane and prostaglandin-F2α. Additional beneficial effects include stimulation of endothelial NO synthase, suppression of tumor necrosis factor-α–induced apoptosis, and agonistic action on peroxisome proliferator–activated receptor-γ.

Vascular function, especially in the setting of arterial hypertension, is influenced by the balance between NO and superoxide. One of the most important vascular superoxide sources is NADPH oxidase, an enzyme that was initially characterized in inflammatory cells and later demonstrated to also exist in vascular cells. The important question, whether superoxide produced by the vascular NADPH oxidase of the NADPH oxidase of inflammatory cells contributes more to endothelial function, remains unsolved. A study by Guzik et al2 revealed that T-cell deficiency in RAG1−/− mice leads to reduced inflammation within the vasculature, markedly improved endothelial function, and reduced oxidative stress, as well as NADPH oxidase activity, in the setting of ATII hypertension. Because the phagocytic NADPH oxidase has been demonstrated to be overactivated in hypertension, a phenomenon which accompanies endothelial dysfunction in this setting, a reduction in phagocytic NADPH oxidase may represent a therapeutic goal.

Protein kinase C (PKC) is an important activator of NADPH oxidase in inflammatory as well as vascular cells; PKC mediates the phosphorylation of p47phox and rac1, thereby initiating translocation of these regulatory proteins from the cytosol to the membrane and leading to the assembly and activation of the membrane-bound functional multimer NADPH oxidase (Figure). In animal models of hypertension (as well as diabetes mellitus4), PKC inhibitors ameliorated endothelial dysfunction and vascular reactive oxygen species formation and lowered blood pressure in vivo.5,6

It is noteworthy that, in 1996, the release of matrix metalloproteinases (MMPs) was identified as a consequence of macrophage-derived reactive oxygen species, and it has been linked to plaque instability and an increased risk of plaque rupture.7 In 2007, Zalba et al8 identified the colocalization of NADPH oxidase and MMP-9 in plaques of atherosclerotic patients.

Building on these results, Fortuño et al9 present novel data in their article published in this issue of Hypertension showing that the losartan metabolite EXP3179 blocks PKCα and PKCβ activation and thereby prevents NADPH oxidase–dependent release of MMP-9 in isolated human phorbol-ester-stimulated phagocytes. Even more exciting, patients with arterial hypertension treated with losartan show less phagocytic NADPH oxidase activity and lower MMP-9 plasma levels than untreated hypertensive controls or patients treated with other ATII receptor blockers or angiotensin-converting enzyme inhibitors. Despite these intriguing findings and the logical order of the different observations in the current study, several questions need to be addressed in the future, as described below.

First, a causal relationship between PKC inhibition by EXP3179 and its purported effects, decreased NADPH oxidase activation and MMP-9 secretion, remains to be established. One important question would be whether inhibition or genetic ablation of PKC isoforms might neutralize the observed effects of EXP3179 on NADPH oxidase activation or MMP-9 secretion.

Second, the proposed pathway consisting of PKC → NADPH oxidase activation → MMP-9 secretion will be also inhibited by losartan in cells that express the AT1R, because the AT1R is known to be a proximal part of this signaling cascade (see Figure). Therefore, the effects of EXP3179 might be of particular interest in cells lacking the AT1R or in the case of AT1R-independent PKC activation, because

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Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.109.136218

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AT1R blockade itself will prevent the majority of the undesired effects of vascular PKC activation.

Third, the current work focuses its attention on phagocytic cells as mediators of vascular disease, although EXP3179 was also able to inhibit endothelial NADPH oxidase activity but at much higher concentrations. However, the overall contribution of phagocytic versus vascular NADPH oxidase–derived reactive oxygen species on vascular pathology is not clear, and, furthermore, it might vary depending on the underlying pathology.

Fourth, it will be difficult to determine the different contributions of the vascular protective effects of the major metabolites EXP3174 and EXP3179, because in vivo application of losartan will always result in the formation of both metabolites.

Studies using EXP3179 and EXP3174 alone or in comparison with the prodrug losartan may help to clarify this issue. However, scepticism about pleiotropic effects of losartan independent of the ATII receptor blockade is indicated. Until today, there has been no evidence from clinical trials indicating effects of ATII receptor blockers beyond ATII receptor antagonism in patients with hypertension, heart failure, myocardial infarction, or diabetes mellitus.

Taken together, the results of the present study clearly demonstrate an inhibition of the phagocytic but also vascular NADPH oxidase by the losartan metabolite EXP3179, an effect that appears to depend on a PKC-dependent mechanism. The simultaneous reduction in MMP-9 formation may lead to an inhibition of matrix degeneration and, therefore, may contribute to stabilize atherosclerotic plaques in patients with hypertension and other cardiovascular diseases.

Acknowledgment

We thank Thilo Weckmüller for expert graphic assistance.

Disclosures

None.
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Protein Kinase C-Inhibiting Properties of the Losartan Metabolite EXP3179 Make the Difference
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Hypertension. 2009;54:707-709; originally published online August 17, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.136218

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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