Improvement of renal hemodynamics during hypertension-induced chronic renal disease: role of EGF receptor antagonism

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Helle F, Jouzel C, Chadjichristos C, Placier S, Flamant M, Guerrot D, François H, Dussaule JC, Chatziantoniou C. Improvement of renal hemodynamics during hypertension-induced chronic renal disease; role of EGF receptor antagonism. Am J Physiol Renal Physiol 297: F191–F199, 2009. First published May 6, 2009; doi:10.1152/ajprenal.00015.2009.—The present study investigated mechanisms of regression of renal disease after severe proteinuria by focusing on the interaction among EGF receptors, renal hemodynamics, and structural lesions. The nitric oxide (NO) inhibitor Nω-nitro-ω-arginine-methyl ester (L-NAME) was administered chronically in Sprague-Dawley rats. When proteinuria exceeded 2 g/mmol creatinine, animals were divided into three groups for an experimental period of therapy of 2 wk: in one group, L-NAME was removed to allow reactivation of endogenous NO synthesis; in the two other groups, L-NAME removal was combined with EGF or angiotensin receptor type 1 (AT1) antagonism. L-NAME removal partially reduced mean arterial pressure and proteinuria and increased renal blood flow (RBF), but not microvascular hypertrophy. Progression of structural damage was stopped, but not reversed. The administration of an EGF receptor antagonist did not have an additional effect on lowering blood pressure or on renal inflammation but did normalize RBF and afferent arteriole hypertrophy; the administration of an AT1 antagonist normalized all measured functional and structural parameters. Staining with a specific marker of endothelial integrity indicated loss of functional endothelial cells in the L-NAME removal group; in contrast, in the animals treated with an EGF or AT1 receptor antagonist, functional endothelial cells reappeared at levels equal to control animals. In addition, afferent arterioles freshly isolated from the L-NAME removal group showed an exaggerated constrictor response to endothelin; this response was blunted in the vessels isolated from the EGF or AT1 receptor antagonist groups. The EGF receptor is an important mediator of endothelial dysfunction and contributes to the decline of RBF in the chronic kidney disease induced by NO deficiency. The EGF receptor antagonist-induced improvement of RBF is important but not sufficient for a complete reversal of renal disease, because it has little effect on renal inflammation. To achieve full recovery, it is necessary to apply AT1 receptor antagonism.

angiotensin; fibrosis; proteinuria; regression

RENOAL CHRONIC DISEASE IS A complex degenerative process involving hemodynamic alterations, endothelial dysfunction, inflammation, protein leaking, alterations in extracellular matrix assembly, and changes in renal structure that ultimately lead to the decline of renal function. Since the solutions existing to date are replacement strategies such as dialysis and transplantation, an important challenge for public health is to stop the decline of renal function and, if possible, to achieve regression of renal fibrosis and restoration of renal structure.

In previous studies investigating the mechanisms of progression of renal disease during nitric oxide (NO) deficiency [Nω-nitro-ω-arginine-methyl ester (L-NAME) model], we have observed that angiotensin receptor type 1 (AT1) antagonism reversed renal fibrosis and restored renal structure independently of systemic hemodynamics (5), and that NO inhibition increased, whereas arrest of L-NAME administration decreased, the activation of the collagen I gene in transgenic mice (6, 24). Again, expression of collagen I was independent of systemic hemodynamics. Other investigators have also observed arrest or reversal of renal disease independently of blood pressure in experimental models (2, 22). In other studies, we found that inhibition of the EGF receptor prevented the development of renal failure independently of variations of blood pressure (12). In additional studies, we observed that transactivation of the EGF receptor mediated the hemodynamic and fibrogenic affects of endothelin (10, 12). However, the curative efficiency of EGF receptor antagonism, the role of renal hemodynamics, and its interaction with the regression of renal inflammatory or structural lesions were not addressed in these studies. In addition, the above-mentioned regression studies did not consider the degree of proteinuria before the start of therapy.

The present study was designed to address the above concerns. Therapy was introduced when animals reached a severe degree of proteinuria, and renal blood flow (RBF) was measured in addition to structural and functional parameters. Our findings indicate that EGF receptor antagonism plays an important role in the improvement of renal hemodynamics but is less efficient in alleviating renal inflammatory lesions.

METHODS

Animal treatment. Male Sprague-Dawley rats, weighing 250 g, were maintained on a normal-salt diet and had free access to chow and tap water. NO synthesis was inhibited by L-NAME (orally, 30 mg·kg⁻¹·day⁻¹). We have previously found that this dose produced a gradual elevation of blood pressure accompanied by the progression of renal disease (5). When proteinuria exceeded 2 g/mmol creatinine (between 4 and 6 wk), a group of animals was killed to allow estimations of renal hemodynamics and morphological parameters just before the beginning of therapy (L-NAME group, n = 14). The remaining animals were divided into three subgroups for an additional experimental period of 2 wk: in the first subgroup, L-NAME was removed from the drinking water to allow reactivation of endogenous NO synthesis (removal group, n = 20); in the second and third subgroups, L-NAME removal was accompanied by the administration of an AT1 receptor antagonist (losartan, orally 30 mg·kg⁻¹·day⁻¹, Merck Sharp and Dohme-Chibret, removal+losartan group, n = 18) or an EGF receptor antagonist.
antagonist (gefitinib, orally 50 mg·kg⁻¹·day⁻¹, AstraZeneca, removal + gefitinib group, n = 20). The doses of the drugs were based on pilot experiments and previously published studies (5). Control animals were killed at 4, 6, and 8 wk. Since control animals gave similar results for all measured parameters, pooled data are presented (control group, n = 16). Because of the extra preparation time and use of anesthesia during RBF measurements, separate animals were used for preparation of ex vivo afferent arteriole contractility measurements and assessment of microvascular hypertrophy, totaling five in each group. All protocols and treatments were performed with the approval of the French government ethics committee.

**Systolic blood pressure.** Systolic blood pressure was measured by the tail-cuff method as previously described (5). To avoid variations in blood pressure due to day cycle, all measurements were carried out between 9 and 11 AM. Eight measurements from each rat were taken at 2-min intervals, and a mean value was determined.

**Renal hemodynamics.** After anesthesia by pentobarbital sodium (50–60 mg/kg body wt ip, Nembutal, Abbott, Chicago, IL), animals were placed on a servo-controlled table kept at 37°C and the trachea was cannulated to facilitate respiration. The left femoral artery was catheterized for measurement of arterial pressure, and a femoral venous catheter was used for infusion of volume replacement. An ultrasound transit-time flow probe (1RB, Transonic, Ithaca, NY) was placed around the left renal artery. Bovine serum albumin (4.75 g/dl) was infused initially at 50 ml/min with a streptavidin secondary antibody (Histofine Kit Solution), primary antibody, sections were washed in PBS and incubated for 30 min with a polyclonal acid solution at 98°C for 30 min, and incubated first with a polyclonal CD68 antibody recognizing macrophages/monocytes (Serotec, Oxford, UK), and then incubated at room temperature with a second antibody from Envision kit (Dako, Carpinteria, CA). Staining was revealed by applying AEC (Dako), counterstained with hematoxylin QS (Vector, Burlingame, CA), and finalized with Permanent Aqueous Mounting Media (Innovex). Quantification of CD3- and CD68-positive cells was performed using Olympus analysis software.

**Immunohistochemistry for CD3 and CD68.** Four-micrometer-thick sections of paraffin-embedded kidneys were dewaxed, heated in citric acid solution at 98°C for 30 min, and incubated first with a polyclonal goat anti-rat CD3 antibody recognizing lymphocytes (Santa Cruz Biotechnology, Santa Cruz, CA) or a monoclonal mouse anti-rat CD68 antibody recognizing macrophages/monocytes (Serotec, Oxford, UK), respectively, and then incubated at room temperature with a second antibody from Envision kit (Dako, Carpinteria, CA). Staining was revealed by applying AEC (Dako), counterstained with hematoxylin Q5 (Vector, Burlingame, CA), and finalized with Permanent Aqueous Mounting Media (Innovex). Quantification of CD3- and CD68-positive cells was performed using Olympus analysis software.

**Results**

Partial improvement of renal hemodynamics and function following arrest of l-NAME administration. In agreement with previous results, NO inhibition was accompanied by a gradual increase in mean arterial pressure, reaching 190–200 mmHg after 3 wk. Mean arterial pressure remained at this level until the beginning of therapy (Fig. 1). Abnormal proteinuria (>0.5 g/mmol creatinine) was detected as early as 1 wk after l-NAME administration and progressed to >2 g/mmol creatinine.
after 4–6 wk. Pilot experiments showed that when proteinuria exceeded 3 g/mmol creatinine, animals were vanishing, rapidly showing symptoms of malignant hypertension and/or stroke. In contrast, when proteinuria was <2 g/mmol creatinine, the degree of renal lesions was not very pronounced. For these reasons, the end point for L-NAME treatment was set to values of proteinuria exceeding 2 g/mmol creatinine. At the therapy starting point, RBF was profoundly decreased and concentration of plasma creatinine was increased (Fig. 1).

To test whether renal disease is a reversible process when animals showed such a high degree of proteinuria, L-NAME was removed from the drinking water. It has been previously shown that this manipulation reactivates endogenous NO synthesis and is accompanied by a decrease in collagen I gene activation (2, 13, 25). Two weeks after L-NAME removal, mean arterial pressure was reduced, but not normalized (160 ± 9 mmHg, P < 0.01 vs. L-NAME; P < 0.05 vs. control, Fig. 1). In addition, L-NAME removal reduced, without normalizing, proteinuria and partially improved RBF (P < 0.01 vs. L-NAME; P < 0.05 vs. control, Fig. 1).

**Effect of combining L-NAME removal with AT1 receptor antagonism on renal hemodynamics and function.** The rationale of these experiments was based on our previous findings that the renin-angiotensin system is activated during prolonged inhibition of NO synthesis and is a major mediator of the activation of collagen I synthesis and the development of renal fibrosis (3, 5, 6).

The addition of an AT1 receptor antagonist further reduced mean arterial pressure to control values, decreased proteinuria to almost normal levels (P = 0.22 vs. control, P < 0.05 vs. removal of L-NAME), and normalized RBF (Fig. 1). These data indicate that ANG II continued to be active (for at least 2 wk) after withdrawal of L-NAME.

**Effect of combining L-NAME removal with EGF receptor antagonism.** For insights into the role of the EGF receptor, we tested the association of L-NAME removal to EGF receptor
antagonism. This choice was based on previous studies in which we found that blockade of the EGF receptor prevented rats from developing renal fibrosis (6) and because other investigators demonstrated that the EGF receptor is transactivated by ANG II in angiotensin-induced hypertensive nephropathy (20).

The addition of an EGF receptor antagonist did not have an additive effect on the reduction of blood pressure observed after removal of l-NAME alone; blood pressure remained increased in this group of animals compared with control or the removal + losartan groups ($P > 0.3$ vs. removal; $P < 0.01$ vs. control or removal + losartan group, Fig. 1). In contrast, RBF was increased and reached values similar to control or to the removal + losartan groups (Fig. 1).

**Impairment and recovery of renal morphology.** The above-mentioned functional and hemodynamic changes were associated with important structural alterations (Fig. 2). Confirming previous results, semiquantitative estimation of renal morphological parameters showed that l-NAME treatment was accompanied by glomerular ischemia ($1.16 \pm 0.20$), glomerulosclerosis ($0.85 \pm 0.21$), vascular necrosis ($1.28 \pm 0.30$), and inflammation (Fig. 3) ($P < 0.01$ for these 4 parameters). Mixed results were obtained with the evaluation of morphological parameters after the arrest of l-NAME: vascular necrosis almost disappeared ($0.20 \pm 0.10$), whereas glomerular ischemia ($0.95 \pm 0.19$), glomerulosclerosis ($1.08 \pm 0.30$), and inflammation (Fig. 3) remained similar to the l-NAME group. The addition of the EGF receptor antagonist gefitinib improved glomerular ischemia ($0.16 \pm 0.10$, $P < 0.01$ vs. l-NAME), glomerulosclerosis ($0.42 \pm 0.14$, $P < 0.05$ vs. l-NAME), and vascular necrosis ($0.10 \pm 0.05$, $P < 0.01$ vs. l-NAME) but had little effect on cellular infiltration (Fig. 3). To better characterize cell infiltrates, experiments were performed with antibodies specific to macrophages (CD68-positive cells) and lymphocytes (CD3-positive cells). As shown in Fig. 3 (middle and left), the abnormal presence of macrophages and lymphocytes persisted during gefitinib treatment despite the improvement in RBF.

The inflammatory index and CD3 and CD68 staining were significantly decreased only in animals treated with the AT1 receptor antagonist (no statistical difference vs. control group; $P < 0.05$ vs. removal of l-NAME, Fig. 3), indicating that this therapeutic approach produced an additional protective effect that attained an almost complete reversal of renal disease despite the extensive proteinuria at the beginning of the treatment.

![Fig. 2. Representative examples of extracellular matrix (Masson’s trichrome) in control animals (A), rats treated with l-NAME (B), and rats in which l-NAME was removed without (C) and with addition of losartan (D) or gefitinib (E). Note the extracellular matrix accumulation and the inflammatory cell infiltration during chronic inhibition of NO (B); inflammation persisted after removal of l-NAME (C), whereas all types of lesions clearly regressed when removal of l-NAME was combined with losartan administration (D); in contrast in the gefitinib group (E), the inflammatory lesions persisted.](http://ajprenal.physiology.org/;98334-4)
Impairment and recovery of endothelial integrity. The clear peritubular staining of RECA-1 in control animals (Fig. 4A) became negligible in the L-NAME group (Fig. 4B) and was not improved substantially after removal of L-NAME (Fig. 4C). In contrast, it reappeared in normal levels after losartan or gefitinib treatment (Fig. 4D and E).

Ex vivo contractility of freshly isolated afferent arterioles. To test whether the applied treatments altered differently the function and contractile properties of renal resistance vessels, contractility to endothelin-1 was measured in freshly isolated afferent arterioles (1–2 afferent arterioles from each kidney in 5 animals from all groups, Fig. 5). ANG II administration was not considered suitable for this purpose, because a group of animals was chronically treated with an AT1 antagonist and in preliminary experiments we found that vessels from this group were not responding to ANG II. In addition, we have previously observed that the major pathological mechanism leading to renal disease in the L-NAME model is an ANG II-induced activation of endothelin within renal resistance vessels (3, 4, 29). In preliminary dose-response experiments, we observed that afferent arterioles from control animals did not contract to $10^{-9}$ M endothelin-1, and thus we considered that contractility at this concentration would signify an abnormal sensitivity to endothelin-1. Indeed, vessels isolated from the L-NAME group gradually contracted at $10^{-9}$ M endothelin-1: 8, 13, 25, and 38% decrease in lumen diameter at 40 s, and 2, 4, and 6 min, respectively (Fig. 5). In vessels isolated from the removal group, the contractile response to endothelin-1 remained abnormal. This contrasted with responses of vessels from losartan- or gefitinib-treated animals, which were similar to control.
(Fig. 5). Statistical differences were the same whether results are expressed as absolute change or percentile change from baseline.

Afferent arteriole vessel wall thickness. As a measure of microvascular hypertrophy, vessel wall thickness was analyzed in isolated afferent arterioles ex vivo. The afferent arteriole vessel wall and media/lumen ratio was significantly increased in arterioles from L-NAME and removal groups (Fig. 6). In contrast, RECA-1 staining was restored in glomeruli and peritubular capillaries (arrows) after losartan (D) or gefitinib (E) administration. F: quantification of functional endothelium in controls (open bar) and rats treated with L-NAME (black bar); results from animals in which L-NAME was removed without or with addition of losartan or gefitinib for 2 additional wk are depicted by light gray, darker grey, and darkest gray bar, respectively. Values are means ± SE; n = 16, 14, 20, 18, and 20 for control, L-NAME, removal, removal + losartan, and removal + gefitinib groups, respectively. *P < 0.01 vs. control. #P < 0.01 vs. L-NAME. §P < 0.01 vs. removal.

DISCUSSION

In the present study, we investigated mechanisms of the regression of renal disease by focusing on the relationship between renal hemodynamics and structural and functional alterations. A partial regression was achieved by correcting the cause of the pathology (inhibition of NO synthesis). A novel finding is that an improvement of renal hemodynamics is associated with EGF receptor antagonism and is under the control of local vasoactive systems operating independently of their systemic effects. Interestingly, this beneficial effect does not apply to inflammation. To achieve a complete recovery of renal structure, the involvement of ANG II receptor antagonism is necessary.

Alterations in endothelial function and in the activity of NO play a major role in vascular remodeling. NO is an important inhibitor of vascular smooth muscle cell growth and extracellular matrix synthesis in vitro and in vivo (15), whereas chronic inhibition of NO synthesis is accompanied by renal vascular fibrosis (1, 32). Conversely, removal of L-NAME from the drinking water normalized collagen I gene expression in transgenic mice harboring the luciferase gene under the control of the promoter of collagen I-chain α2 gene (24). However, mice are resistant compared with rats in developing proteinuria or
Even if L-NAME administration was prolonged up to 30 wk, no proteinuria or important alterations in renal structure were observed (24). For this reason, we used rats as an experimental model in the present study, and we waited until the appearance of considerable proteinuria (>2 g/mmol creatinine) before removing L-NAME. The major observation from this part of the study is that correction of the cause certainly improved but was not sufficient to completely restore renal hemodynamics, structure, and function, which remained below normal values. This partial improvement could be due to the systemic vasodilatory action of NO. For instance, glomerular ischemia or afferent arteriole hyper trophy remained abnormal, reflecting the incomplete improvement in RBF. Similarly, removal of L-NAME was inefficient against renal inflammation, as the measured inflammatory indexes remained abnormally high. Furthermore, staining with the RECA-1 antibody, a marker of rat endothelial cells, demonstrated severe endothelial dysfunction during L-NAME treatment, which did not improve unless rats were treated with losartan or gefitinib.

Fig. 5. Endothelin-1-induced vasocontraction expressed either as absolute (top) or as % of baseline (bottom) changes in the diameter of afferent arterioles freshly isolated from kidneys of control and rats treated with L-NAME during 4–6 wk. Results from animals in which L-NAME was removed after 4–6 wk without or with losartan for 2 additional wk are also shown. Endothelin-1 concentration was 10^{-9} M. Values are means ± SE; n = 11, 17, 14, 13, and 12 afferent arterioles from 5 animals in control, L-NAME, removal, removal + losartan, and removal + gefitinib groups, respectively. *P < 0.05 vs. control.

Fig. 6. Vessel wall thickness and media/lumen ratio in the afferent arterioles were increased in animals from the L-NAME (black bars) and removal groups (gray bars) compared with controls (open bars). In losartan (darker gray bars) and gefitinib (darkest gray bars)-treated animals, however, microvascular hypertrophy was completely regressed; n = 20, 20, 25, 17 and 28 afferent arterioles from 5 animals in control, L-NAME, removal, removal + losartan, and removal + gefitinib groups, respectively. *P < 0.05 and **P < 0.01 vs. control. #P < 0.01 vs. L-NAME. §P < 0.01 vs. removal.

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Fig. 5. Endothelin-1-induced vasocontraction expressed either as absolute (top) or as % of baseline (bottom) changes in the diameter of afferent arterioles freshly isolated from kidneys of control and rats treated with L-NAME during 4–6 wk. Results from animals in which L-NAME was removed after 4–6 wk without or with losartan for 2 additional wk are also shown. Endothelin-1 concentration was 10^{-9} M. Values are means ± SE; n = 11, 17, 14, 13, and 12 afferent arterioles from 5 animals in control, L-NAME, removal, removal + losartan, and removal + gefitinib groups, respectively. *P < 0.05 vs. control.

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These observations imply that other vasoactive and/or profibrotic systems are still operating after \( l \)-NAME removal.

One possible candidate is endothelin, which is known to be activated in conditions of NO inhibition. Indeed, in previous studies we found that inhibition of NO synthesis was accompanied by increased expression of endothelin, which in turn activates the collagen I gene (6, 29). In other studies, however, we demonstrated that the activation of endothelin during NO inhibition was due to ANG II and that the progression of renal fibrosis in the \( l \)-NAME model was controlled by the interaction between NO and the renin-angiotensin system (3, 9). In agreement with this hypothesis, other investigators found that the intrarenal renin-angiotensin system is activated during NO inhibition (14). In addition, we have observed that endothelin transactivated the EGF receptor and the MAPK pathway to stimulate the collagen I gene and to induce fibrosis (12). Based on these previous observations, we postulated that an additional EGF and/or AT1 receptor blockade could be an appropriate supplementary therapy. The fact that a combination of \( l \)-NAME removal with EGF or AT1 antagonism fully restored renal hemodynamics, and reversed most of renal lesions, clearly indicates that both therapies can be used to achieve regression of renal disease, at least in this model. The AT1 receptor antagonism, however, appeared to be a better treatment because of its efficiency on renal inflammatory lesions.

The mechanism(s) by which blockade of angiotensin receptor contributes to reversal of renal disease is probably multiple. We have previously shown that ANG II antagonism can regress renal fibrosis by inhibiting the de novo synthesis of the extracellular matrix (due to the blockade of TGF-\( \beta \) action) associated with increased matrix degradation (due to metalloproteinase activity), both mechanisms acting independently of systemic hemodynamics (5). In the present study, we report additional mechanisms: improvement in renal hemodynamics, suppression of inflammation, and regression of microvascular hypertrophy. The information obtained from the histological and the afferent arteriole contractility experiments (an ex vivo setting in which circulating factors are not implied) supports the notion that the improvement in renal hemodynamics during AT1 antagonism was due to local mechanisms improving the structure of renal resistance vessels. It is interesting to note that changes in the endothelial phenotype may increase vascular resistance, since animals displaying low or absent RECA-1 staining (\( l \)-NAME and removal groups) also showed exaggerated vascular reactivity to endothelin-\( \text{I} \). We have previously showed that ANG II activates endothelin during \( l \)-NAME treatment (5). The action of endothelin under normal conditions can be considered as complicated, mediating constriction (through ET1) or relaxation (through ET2) depending on the cell population. Both receptor subtypes are expressed on renal vessels (31), and depending on the conditions, ET2 either antagonizes endothelin-\( \text{I} \) action through NO and NO-independent mechanisms (19) or mediates a part of the endothelin-\( \text{I} \)-induced decrease in RBF (18, 28). Our previous findings clearly indicated that both receptor subtypes are involved in collagen I gene activation and renal fibrosis during chronic inhibition of NO synthesis (5, 6, 29).

An exaggerated local action of ANG II can also explain the effectiveness of AT1 antagonism against renal inflammation. Indeed, in previous studies we have observed that the renin-angiotensin system was activated in the renal cortex after 4–6 wk of \( l \)-NAME, because of an upregulation of angiotensin-converting enzyme activity (30), and several investigators have described the proinflammatory action of ANG II in renal vessels and glomeruli (26, 27). In agreement with these observations, we have found an important influx of inflammatory cells in renal cortical tissue after chronic infusion of ANG II or in transgenic mice expressing high levels of renin (10, 17).

Growth factors and their receptors have been proposed to mediate ANG II-induced alterations of renal structure and hemodynamics. For instance, the PDGF family has been recently involved in the profibrotic action of ANG II in chronic renal disease (8, 11). Regarding renal vascular contractility and hemodynamics, it was demonstrated that the angiotensin-induced-calcium influx in afferent arterioles was partly mediated through activation of the EGF receptor (7), and it has been proposed that the EGF receptor mediates contraction in arteries from DOCA-salt but not normotensive rats (23). Mice overexpressing a dominant negative isoform of the EGF receptor were protected from renal lesions during chronic ANG II infusion, and a similar protection was also observed in mice lacking TGF-\( \alpha \), an endogenous ligand of the EGF receptor (20). Moreover, we have observed that the EGF receptor was activated within glomeruli concomitantly with the development of glomerulosclerosis in the NO deficiency model and that use of an EGF receptor antagonist in a preventive way cancelled the activation of collagen I gene expression and protected kidneys against development of renal fibrosis (10, 12). In the present study, we show that the antagonism of the EGF receptor can have curative effects with regard to renal hemodynamics and microvascular hypertrophy. However, blockade of the EGF receptor did not reverse the inflammatory action of ANG II, indicating that the effect of ANG II on renal hemodynamics is distinct from that on inflammation. In this regard, we have demonstrated recently that the discoidin domain receptor 1 (DDR1), a tyrosine-kinase collagen receptor, is a major mediator of ANG II-induced renal inflammation (10). In agreement with this hypothesis, DDR1 expression is induced in renal vessels after chronic inhibition of NO, whereas mice lacking DDR1 are protected against \( l \)-NAME-induced renal inflammation (data not shown).

In conclusion, the present study investigated the reversal of renal disease by starting therapy after reaching a substantial degree of proteinuria. Correction of the cause partially improved renal hemodynamics and incompletely reversed renal structural lesions. Renal hemodynamics and microvascular hypertrophy, but not renal inflammation, were restored when correction of the cause was combined with EGF receptor antagonism. Reversal of renal disease was obtained only when correction of the cause was combined with angiotensin blockade. These results provide novel insights into the mechanisms of progression and/or regression of chronic renal disease and suggest that improvement of renal hemodynamics and reversal of inflammation are important targets to achieve therapy.

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