Hypertension Research (2009) 32, 821–823
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COMMENTARY

Prevention of local lipotoxicity: a new renoprotective mechanism of peroxisome proliferator-activated receptor-α activation in hypertension and obesity?

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Hypertension Research (2009) **32,** 821–823; doi:10.1038/hr.2009.128; published online 14 August 2009

The renal complications of metabolic syndrome are attributed to multiple factors including insulin resistance, dyslipidemia, hypertension, activation of the renin–angiotensin system (RAS), oxidative stress and inflammation. There is growing evidence that excessive free fatty acids (FFAs) accompanied by triglyceride (TG) accumulation in multiple tissues, including pancreas, skeletal muscle, heart and liver, result in both acute and chronic cell dysfunction and injury.[1] In the kidney, an altered renal lipid metabolism (elevated TG and low levels of high-density lipoprotein cholesterol) may accelerate the progression to end-stage renal disease by enhancing lipotoxicity, oxidative stress and inflammation.[2–7] For example, experimental studies have shown that a high-fat diet leads to an altered balance between renal lipogenesis and lipolysis, subsequent renal lipid accumulation, macrophage infiltration, increased oxidative stress and renal injury, including glomerulosclerosis, interstitial fibrosis and albuminuria.[4,5] Furthermore, it has been suggested that FFAs bound to filtered albumin, rather than albumin itself, cause severe tubulointerstitial damage by promoting the transformation of tubule cells to a proinflammatory phenotype.[1,8–10]

In this issue of *Hypertension Research*, Shin *et al.*[11] have advanced our understanding of these relationships among local FAA accumulation, oxidative stress, inflammation and kidney damage in hypertension and obesity. They clearly demonstrated that an increase in intrarenal TG and FFA accumulation was associated with an enhancement of renal structural changes (glomerulosclerosis, inflammation and apoptosis) and functional changes (hypertension and sodium retention) in spontaneously hypertensive rats fed with a high-fat diet (SHR-HF). Importantly, they found that the renal changes in SHR-HF animals were correlated with an inability to upregulate the protein expression of peroxisome proliferator-activated receptor-α (PPARα) in the kidney. Fenofibrate, a PPARα ligand, restored the renal PPARα level, reduced lipid accumulation and attenuated renal inflammation and damage in this animal model of hypertension and obesity.[11] This study brings new evidence that pharmacological interventions aimed at improving lipid toxicity and inflammation may represent novel avenues to prevent and/or treat kidney diseases associated with metabolic syndrome.

As a member of the nuclear hormone receptor superfamily, PPARα regulates the transcription of an array of genes involved in cellular fatty acid utilization pathways including transport, esterification and oxidation.[12,13] Previous studies have shown that PPARα deficiency aggravates the severity of diabetic nephropathy through an increase in extracellular matrix formation and circulating FFA and TG concentration.[14] PPARα ligands could improve renal structure and function by decreasing glomerular hypertrophy and the mesangial matrix in animals with type 1 or type 2 diabetes.[14–16] In the report by Shin *et al.*,[11] an HF diet caused a renal depletion of PPARα parallel to an increase in intrarenal FFA and TG accumulation and renal injury in SHR animals. Treatment of SHR-HF rats with fenofibrate restored PPARα protein, reduced intrarenal FFA and TG and improved kidney structure and function. These findings imply that the renoprotective effects of fenofibrate are, at least in part, due to local PPARα activation in SHR-HF animals. This concept is also supported by previous reports that PPARα is highly expressed in the kidney and might be involved in the control of renal fatty acid β-oxidation.[17,18] However, the data generated by Shin *et al.*,[11] cannot distinguish between a direct pharmacological action of fenofibrate on kidney tissues from its substantial systemic effects, as fenofibrate treatment also improved plasma lipid metabolism, lowered body weight and blood pressure and increased insulin sensitivity in SHR-HF rats (Figure 1). Notably, beneficial effects of weight control have been clearly demonstrated by a recent report that systemic and renal alterations in mice on an HF diet were prevented by body weight control with the dietary restriction of feeding on an HF diet. The finding by Shin *et al.*[11] showed that fenofibrate treatment increased serum adiponectin, an anti-inflammatory and antidiabetic adipokine, in the SHR-HF group and also supports the fact that the anti-inflammatory effect of fenofibrate in the kidney could be secondary to systemic drug effects, apart from a decreased renal cell production of inflammatory mediators.

To date, the exact mechanisms by which fibrates exert their renoprotective effects in patients with hypertension and metabolic syndrome are not fully understood, although experimental studies have suggested a role of the cytochrome P450 pathway in the beneficial effect of PPARα activation.[19–22] Another

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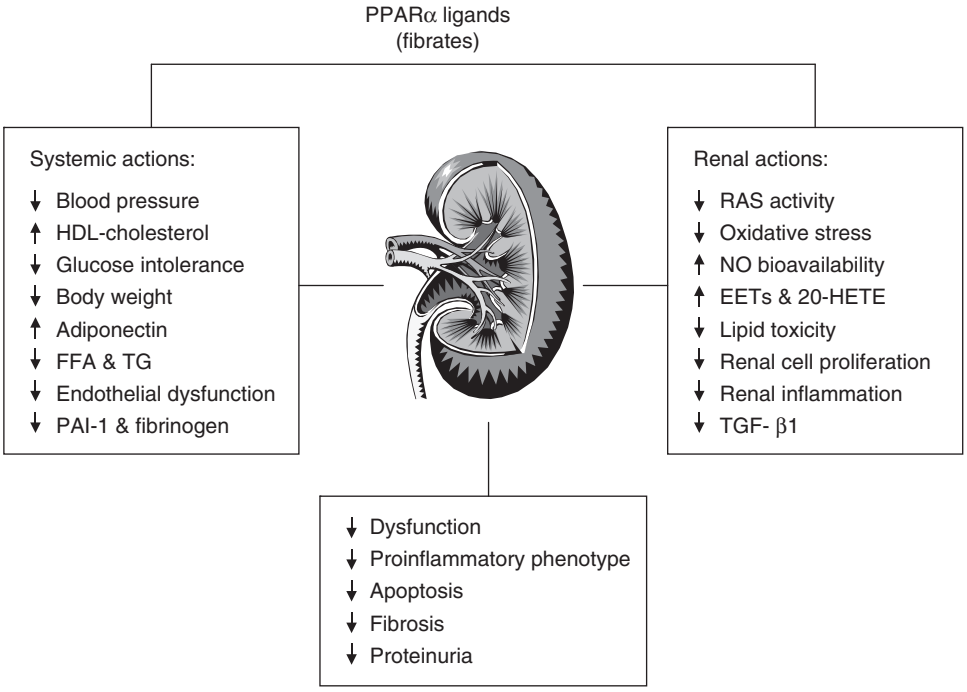

Figure 1 Systemic and renal actions of PPARα ligands possibly responsible for the improvement of renal structure and function. HDL-cholesterol, high-density lipoprotein cholesterol; FFA, free fatty acid; TG, triglyceride; PAI-1, plasminogen-activator inhibitor-1; NO, nitric oxide; EETs, epoxyeicosatrienoic acids; 20-HETE, 20-hydroxyeicosatetracnoic acid; TGF-β1, transforming growth factor-β1.

important finding of the study by Shin *et al.*[11] is that the PPARα content in kidney was negatively correlated with intrarenal angiotensin II concentrations.[11] They confirmed that renal RAS activity, not systemic, was significantly increased in hypertension and obesity, which was associated with an increase in oxidative stress and a reduction in nitric oxide bioavailability. These findings support the previous published hypothesis that activation of RAS contributes to early glomerular and tubulointerstitial injury, in part through the generation of reactive oxygen species.[3,23] Interestingly, the increase in renal RAS and oxidative stress was normalized by fenofibrate treatment, suggesting that amelioration of RAS and oxidative stress with fenofibrate could be a mechanism contributing to its renoprotective effects.

It is also worth pointing out that administration of fibrates to patients with mild-to-moderate renal insufficiency has been shown to be associated with a deterioration in renal function with uncertain mechanisms.[24] Thus, more care should be taken when prescribing fibrates to patients with a preexisting renal dysfunction.

ACKNOWLEDGEMENTS

This work was supported by the American Heart Association Scientist Development Grant, Satellite Healthcare Norman S Coplon Extramural Research Grant, NIH/NCRR Grant 5U54RR022814 and NIH/NCRR/RCMI Grant 5G12RR03034-23.

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