Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that heterodimerize with the retinoid X receptor and modulate functions of many target genes. Three PPARs, α, β/δ, and γ, have been demonstrated. PPARα is involved in fatty acid oxidation and expressed in liver, kidney, and skeletal muscle; PPARβ/δ is ubiquitous and regulates lipid metabolism; and PPARγ plays a role in fat cell differentiation, lipid storage, and insulin sensitivity.1 PPARs are present in cardiovascular tissues, including the endothelium, smooth muscle cells, macrophages, and the heart.2–4 Fibates (hypolipemic agents) and fatty acids activate PPARα, and thiazolidinediones or glitazones (antidiabetic drugs) stimulate PPARγ.5 However, the endogenous ligands of PPARs remain unknown.

PPARα and PPARγ have increasingly been demonstrated to exert cardiovascular protective effects, independent of their metabolic actions.3,4 Whereas metabolic effects of PPARs are mediated by activation of a PPAR-responsive element present in the promoter region of different genes, the cardiovascular protective actions may result from anti-inflammatory and antioxidant actions mediated by transrepression of proinflammatory and pro-oxidant genes. PPAR activators lowered blood pressure, induced favorable effects on the heart, and corrected vascular structure and endothelial dysfunction in several rodent models of hypertension, including genetic models,6 angiotensin II,7–9 and endothelin-1 (ET-1)–dependent hypertension.10 These effects were associated with antioxidant, anti-inflammatory, antiproliferative, antihypertrophic, and antifibrotic effects.10 Different studies have demonstrated as well that activation of PPARγ exerts antiatherosclerotic actions.12 PPARα, through its effect to lower triglycerides as well as its anti-inflammatory action, also prevents progression of atherosclerosis.13 We3,4 and others have proposed that activators of PPARs may become therapeutic agents useful in the prevention of cardiovascular disease beyond their effects on carbohydrate and lipid metabolism.

In this issue of Hypertension, Williams et al14 demonstrate that the PPARα activator clofibrate reduced blood pressure in salt-dependent hypertension during endothelin B (ETβ) receptor blockade. ETα receptors have been demonstrated to exert a natriuretic function along different nephron segments in vitro and in vivo in rodents. Gene knockout of the ETα receptor with rescue of extrarenal ETα receptors results in blood pressure elevation in mice,15 presumably the result, at least in part, of decreased natriuresis, although the hypertension has also been attributed to increased circulating ET-1 impacting on ETα receptors.16 Interestingly, in humans, the natriuretic effect of ETβ receptors appears to be minor.17 ETα receptor-induced natriuresis is, in part, mediated by inhibition of the sodium epithelial channel. The mechanisms whereby ETα receptors signal to the epithelial channel appear to include cylooxygenase activation and prostaglandin E2 formation. In addition, in vitro and in vivo studies suggest that cytochrome P450 4A (CYP4A) activation and 20-HETE may be mediators of ETα-induced natriuresis.18 Recently, increased production of 20-HETE in the kidney was shown to participate in the blood pressure–lowering effects of fenofibrate, another PPARα activator, in angiotensin II–induced hypertension in mice.19 Williams et al20 extend these observations by demonstrating that PPARα regulates the activation of CYP4A and generation of 20-HETE. This results in an increased natriuresis that counteracts the ETα receptor antagonist-induced anti-natriuresis. In this model of sodium-dependent hypertension, the natriuretic effect of 20-HETE lowers blood pressure. Interestingly, 20-HETE has seemingly opposed actions to induce natriuresis20 and cause vasoconstriction.21 In the present paradigm, the natriuretic effect is the predominant one. PPARα activation thus lowers blood pressure in this model by enhancing an ET-1–mediated action. In another model of salt-sensitive hypertension, the deoxycorticosterone acetate–salt rat, PPARα activation reduced prepro–ET-1 expression in the vasculature and contributed to cardiovascular protection, albeit without a major degree of blood pressure lowering.10 This underlines the dual actions of ET-1 through renal (natriuretic) and vascular ETα (constrictor) and ETβ receptors (smooth muscle constrictor and endothelial dilator) and those of 20-HETE (natriuretic and constrictor actions). It also underlines that PPAR activators that exert cardiovascular and renal protective actions via their metabolic effects do so also through their pleiotropic effects at different levels. A caveat that should be noted is that some of these effects present in rodents may not occur in humans, as mentioned for ETα-induced natriuresis17 or for PPARα-induced blood pressure lowering, which has not been observed with fibrates.

In summary, by different mechanisms, PPAR activators (α in this and other studies and γ in other reports) are able to exert cardiovascular and renal protective actions. With the
advent of the new dual PPARα/γ agonists, there is promise that cardiovascular and renal protection may be achieved in a variety of cardiovascular conditions. The mechanisms for these cardiorenal protective actions, as demonstrated in part by the work of Williams et al., are only starting to be revealed.

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