Acta Diabetol (2005) 42:S26–S32
DOI 10.1007/s00592-005-0178-y

U. Kintscher • T. Unger

Vascular protection in diabetes: a pharmacological view of angiotensin II type 1 receptor blockers

Abstract Vascular protection is key to reducing the morbidity associated with diabetes. Angiotensin II is known to exert a variety of deleterious effects on the vasculature, and this is likely to be a major explanation of the protective benefits observed with blockade of the renin–angiotensin–aldosterone system (RAAS). Intriguingly, RAAS blockade also appears to reduce the onset of new diabetes, which points to a fundamental effect on metabolism. Recent developments have thrown new light onto the mechanism of these effects. The importance of unopposed stimulation of the angiotensin II type 2 (AT_2) receptor in vascular protection is recognised, and recent studies have revealed that some angiotensin II type 1 (AT_1) receptor blockers (ARBs) show partial peroxisome proliferator-activated receptor-gamma (PPARγ) agonistic activity *in vitro*, an effect that is at least partly due to direct interaction with PPARγ itself. There is a clear order of potency among the ARBs, with telmisartan the most potent and the only ARB to show an effect at physiologically achievable plasma concentrations. Adiponectin, an adipokine closely involved with glucose sensitisation, is also modulated by the relative activation of AT_1 and AT_2 receptors. Such effects would suggest that important benefits may result from the use of ARBs in clinical practice, although confirmation of the clinical relevance will depend upon the results of numerous ongoing studies.

Key words Peroxisome proliferator-activated receptor-gamma • Adiponectin • Angiotensin type 2 receptor • Telmisartan • Vascular disease • Diabetes mellitus

U. Kintscher • T. Unger (✉)
Center for Cardiovascular Research (CCR)
Institut für Pharmakologie und Toxikologie
Charité Campus Mitte, Charité - Universitätsmedizin Berlin
Hessische Str. 3–4, 10115 Berlin, Germany
E-mail: thomas.unger@charite.de

Introduction

Diabetes is associated with numerous micro- and macrovascular sequelae that result from hyperglycaemia, dyslipidaemia and other metabolic disturbances. Control of these metabolic factors, particularly tight glucose control, and reducing hypertension to optimal levels are fundamental to providing vascular protection in patients with diabetes [1]. Because many patients with diabetes will require one or more antihypertensive drugs to achieve goal blood pressure, there has been a great deal of interest in the secondary effects of different drug classes on vascular health and the metabolic abnormalities that foster vascular disease in diabetes.

This review will examine recent evidence for the vascular protective effect of one of the newest antihypertensive classes, the angiotensin II receptor blockers (ARBs), and consider the potential clinical consequences.

Role of angiotensin II in vascular damage

Angiotensin II, acting through the angiotensin II type 1 (AT_1) receptor, exerts a wide variety of pathological effects [2]. Blockade of this receptor, which is widely distributed in tissues including blood vessels, can reduce blood pressure as well as having beneficial effects on pathophysiological processes. Examples abound and include such wide-ranging effects as inhibition of atherogenesis [3], reduction of fibrinogenesis [4], and improvement of vascular compliance [5] and endothelial function [6].

In adults, the type 2 (AT_2) receptor is expressed at very much lower levels than the AT_1 receptor and, in consequence, has been less well studied. However, in numerous studies, it has been shown to act in opposition to many of the effects mediated by the AT_1 receptor: for example, exerting a variety of growth-inhibitory effects in contrast to the pathological effects mediated by the AT_1 [7]. It has become increasingly clear in recent years that many of the physiological benefits of ARBs are mediated by altering the delicate balance of activation of these two receptors [8].

One provocative hypothesis is that activation of the AT_2 receptor may be responsible for the cerebroprotective effects of ARBs and diuretics [9]. In patients with heart failure, ARBs may enhance vasodilation partly by AT_2 receptor-mediated upregulation of endothelial nitric oxide synthase [10], whereas AT_1 activation increases oxidative stress in the microvasculature by activating NADPH oxidase [11, 12]. Consequently, activation of the AT_2 receptor is partly responsible for the blood-pressure lowering effects of ARBs [13].

The kidney is a sensitive marker of vascular health, and angiotensin II is a central mediator of the changes in glomerular haemodynamics that lead to progressive renal injury [14]. Although 90–95% of AT receptors in the kidney are AT_1 [15], the balance between AT_1 and AT_2 plays a critical role in the pathogenesis of renal disease [16]. Clinical trials of ARBs with renal outcomes are, therefore, a potent marker of the effects of these agents on the microvasculature.

The PRogramme for Irbesartan Mortality and morbidity Evaluations (PRIME), the MicroAlbuminuria Reduction with VALsartan (MARVAL) and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial (RENAAL) [17] are major comparative clinical studies of ARBs that are of particular significance due to the similarity of their patient populations and of their results. The PRIME programme comprised two studies: IRbesartan MicroalbuminuriA in type 2 diabetes (IRMA 2) [18] and the Irbesartan Diabetic Nephropathy Trial (IDNT) [19]. IRMA 2 investigated irbesartan 150 mg or 300 mg in 590 type 2 diabetics with microalbuminuria and found significant reductions in microalbuminuria compared with placebo [18]. MARVAL, which was performed in a similar patient population, showed the superiority of valsartan over amlodipine [20]. Both RENAAL and IDNT, which recruited hypertensive type 2 diabetics with macroalbuminuria [17, 19], demonstrated a significant reduction in the composite endpoint of a doubling in serum creatinine, end-stage renal disease or death with ARB treatment compared with placebo, with IDNT also bringing about a significant reduction (p=0.006) compared with the active comparator amlodipine. This is especially important clinically, as it strongly suggests a vascular protective effect of ARBs independent of the lowering of blood pressure.

Effect of ARBs on insulin sensitivity

It is clear from the evidence already discussed that ARBs can exert vascular protection via a combination of AT_1 receptor blockade and AT_2 receptor activation. However, in recent clinical trials, ARBs have been shown to reduce risk of new-onset diabetes compared with several other antihypertensive classes, a finding that has attracted considerable interest. The seminal observation, a 25% relative reduction in risk in the onset of diabetes with losartan compared with atenolol in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial [21], was variously attributed to a decreased absolute risk with losartan, or an increased risk with atenolol. Recently, however, the VAlsartan Long-term Use Evaluation (VALUE) trial showed a significant reduction in new-onset diabetes with valsartan compared with the metabolically neutral amlodipine, despite the fact that other endpoints were similar in the two groups [22].

Augmenting the clinical data are the findings from animal models, which show that high doses of ARBs may improve insulin sensitivity. In obese Zucker rats given irbesartan 50 mg/kg for 21 days, insulin-mediated glucose uptake into skeletal muscle was significantly increased (p<0.05), along with increased expression of glucose transporter-4 and improvements in glucose tolerance [23]. A similar result was obtained when olmesartan was administered as a 0.01% drinking solution for 21 days: insulin sensitivity was significantly increased and plasma triglycerides were significantly reduced [24].

These and similar results prompted research groups on both sides of the Atlantic to investigate the potential for a pleiotropic effect of ARBs on insulin sensitivity and have stimulated comparison with another new pharmacological class, the peroxisome proliferator-activated receptor-gamma (PPARγ) agonists. Clinically, the defining characteristic of PPARγ agonists is their ability to reduce insulin resistance [25], and they also markedly

improve the lipid profile of diabetics [26]. The mechanism of this effect is uncertain, but it appears likely that adipogenesis and remodelling of white adipose tissue are important.

PPARγ agonists and vascular protection

PPARγ is also expressed by all cells in the vasculature [27] and appears to be a vascular protective factor with wide-ranging effects. In the endothelium, it acts to inhibit CXC cytokines, adhesion molecule expression and endothelin expression [28–30], as well as stimulating nitric oxide production. It has antiproliferative effects on smooth muscle cells [31] and inhibits monocyte activation as well as migration [32, 33]. As a result, PPARγ agonists have potent anti-atherogenic effects [34, 35]. In addition to their current use as a second-line agent in type 2 diabetes, PPARγ agonists have also been proposed for a variety of other clinical indications, including autoimmune and other inflammatory diseases [36].

The pathway for PPARγ activation is complex and allows for interaction with many modulating factors that play a role in its multifaceted, tissue-specific effects. PPARγ is a nuclear receptor and so requires a ligand able to diffuse across the cell membrane. When activated, it forms a heterodimer with the retinoid X receptor (RXR), creating a complex that includes a variety of tissue-specific cofactors [25]. The activated complex binds to DNA and induces transcription of target genes via PPAR-responsive elements (PPRE) (Fig. 1). A variety of endogenous ligands have been identified, mostly prostanoids [37], and several synthetic ligands have been developed, most notably the thiazolidinediones.

Do some ARBs act as partial PPARγ agonists?

Recently, two papers have been published with the first evidence that certain ARBs appear to possess PPARγ agonist activity [38, 39]. Although differing somewhat in the detail of the experimental approach, both teams came to similar, remarkable conclusions regarding the efficacy and potency of different ARBs on *in vitro* tests of PPARγ agonist activity. The following is a brief overview of the experimental overview and results described by Schupp et al. [39].

Initial interest was provoked by a classic test of 3T3-L1 adipocyte differentiation, which is stimulated by both telmisartan and irbesartan. PPARγ agonists are known to stimulate adipocyte differentiation, and it has been hypothesised that failure of adipocyte differentiation is a cause of type 2 diabetes [40]. Real-time PCR-based analysis of the adipogenic marker gene adipose protein 2 (*aP2*), which is also a target for PPARγ, provides a sensitive, quantitative surrogate-assay for adipogenesis and allows a comparison of the dose dependency of drug effects. Using this assay, it was shown that eprosartan had no significant adipogenic effects, and that losartan only stimulated adipogenesis at high concentrations (100 μmol/l). Irbesartan in concentrations of ≥1 μmol/l was effective, but only telmisartan was able to stimulate adipogenesis at a dose of 0.1 μmol/l.

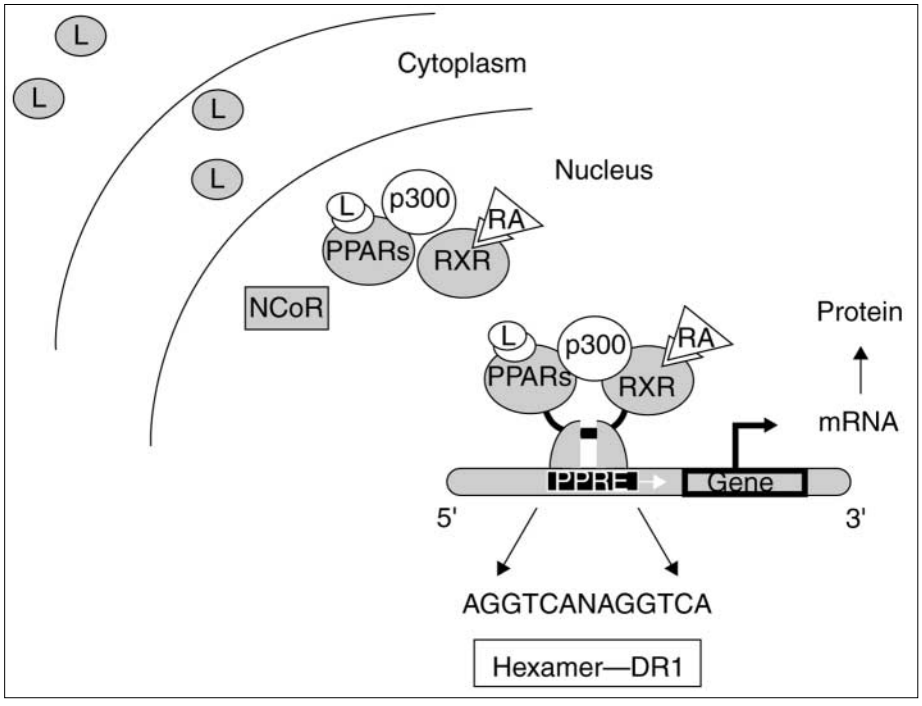

Fig. 1 Mechanism of action of PPARγ agonists. *L*, ligand; *RXR*, retinoid X receptor; *NcoR*, nuclear receptor corepressor; *RA*, retinoic acid; *PPRE*, PPAR-responsive element; *NcoR*, nuclear receptor corepressor

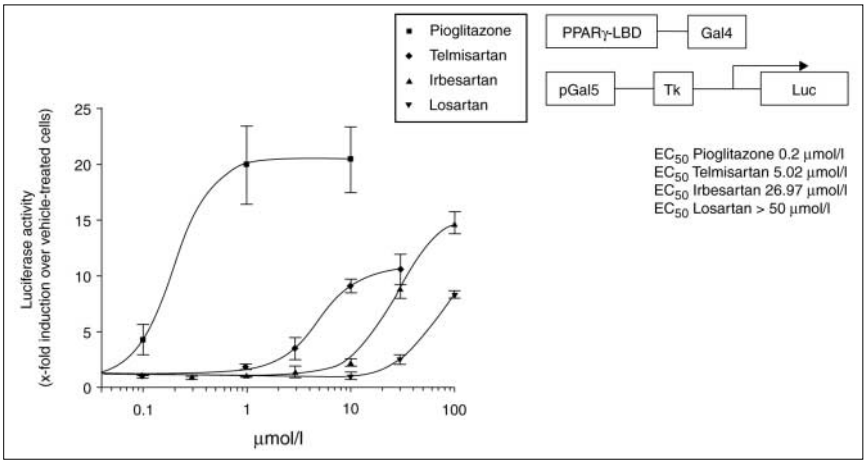

Fig. 2 Dose–response agonism of PPARγ by a full agonist (pioglitazone) and three ARBs that act as partial agonists with differing potency (order of potency: telmisartan> irbesartan>losartan).With permission from [39]

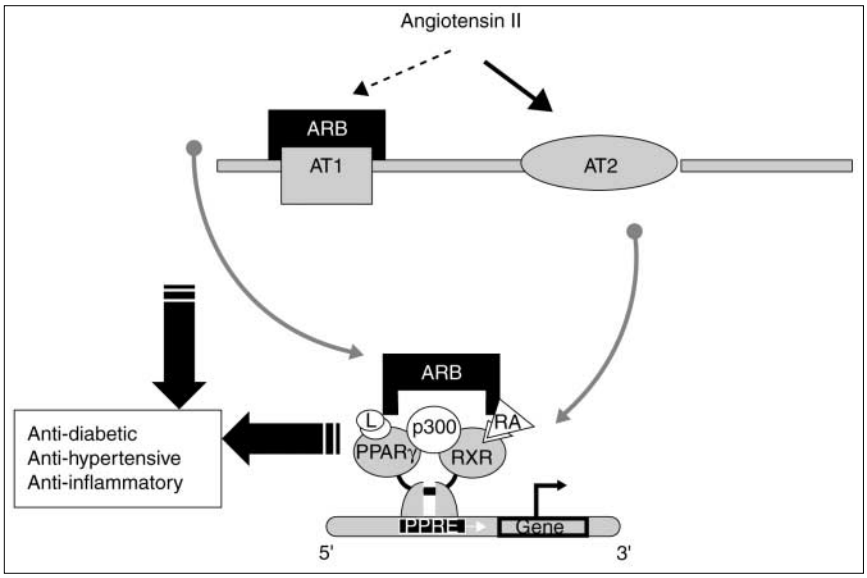

Fig. 3 Summary of potential mechanisms whereby angiotensin II receptor blockers (ARBs) interact with peroxisome proliferator-activated receptor-gamma (PPARγ), either directly (by crossing the cell membrane and activating the PPARγ-retinoid X receptor [RxR] complex) or indirectly (by allowing activation of the angiotensin type 2 [AT_2] receptor unopposed by type 1 [AT_1]-receptor activation). *PPRE*, PPAR-response elements

To exclude the possibility that these observations were a direct effect of PPARγ activation or an indirect effect of blocking the AT_1 receptor, PPARγ2 and RXRα were over-expressed in an AT_1 receptor-deficient cell model (PC12W cells). In this model, both telmisartan and irbesartan (and the thiazolidinedione pioglitazone, which is a full PPARγ agonist) were able to stimulate PPARγ activation. A remaining possible explanation is that the observed results are a consequence of AT_2 receptor activation in the absence of AT_1 receptor activation. Such a phenomenon is suggested by the finding that expression of PPARγ can be stimulated by AT_2 receptor activation in PC12W cells [41]. However, the differentiation of mouse fibroblasts lacking the AT_2 receptor is stimulated by telmisartan, irbesartan and pioglitazone, which suggests that the effect is at least partly mediated by a non-AT_2 receptor process (Schupp M, Unger T, Kintscher U, unpublished data). The direct interaction of ARBs with the PPARγ was tested using a luciferase reporter (Fig. 2). The PPARγ agonist pioglitazone yields a strong signal in this assay. The ARBs, in contrast, act as partial agonists, with concentration-dependent activation of the reporter and a clear order of potency, measured as the concentration that provides half-maximal activation (EC_{50}) (telmisartan EC_{50}=5.02 µmol/l; irbesartan EC_{50}=26.97 µmol/l; and losartan EC_{50}>50 µmol/l). This order of potency reflects that observed in the adipocyte differentiation assay described above.

Thus, telmisartan is the only ARB to show activation of PPARγ at concentrations achievable in the plasma with normal oral dosing. Various explanations may be proposed for the relative potency of ARBs at the PPARγ receptor (Fig. 3). In particular, it is notable that the order of potency mirrors lipophilicity and so it may be that a pharmacological limiting factor is diffusion across the cell membrane to the nuclear compartment. The maximal response may depend on structure–activity relationships, as suggested by the fact that eprosartan, which shows no activity in these assays, is the only ARB to lack a biphenyl element.

Adiponectin and the renin–angiotensin–aldosterone system

Adiponectin, an adipokine first identified in the mid-1990s [42], has a number of tissue effects. The most important is insulin sensitisation [43, 44], but it also stimulates nitric oxide release from the vascular endothelium [45] and reduces NF-kappaB signalling [46]. *In vivo*, globular adiponectin has been shown to protect ob/ob mice from diabetes and apolipoprotein E-deficient mice from atherosclerosis [43].

In an *in vitro* assay, angiotensin II at a concentration of 5 nM has been shown to stimulate adiponectin production in 3T3 adipocytes [47]. As this effect can be stimulated by ARBs and blocked by PD 123319, it appears that activation of the AT_1 and of the AT_2 receptors have opposing effects on adiponectin production. However, ARB-mediated adiponectin upregulation started beyond the concentration needed for AT1R blockade, implicating additional AT_1-independent mechanisms of adiponectin regulation. The clinical significance of this effect was demonstrated by a study of 12 insulin-resistant and 18 non-insulin-resistant hypertensive patients, 16 of whom were given either temocapril 4 mg or candesartan 16 mg for 2 weeks [48]. Both treatments significantly reduced adiponectin levels, although the magnitude of the effect in the candesartan group (+30%) was double that in the temocapril group (+15%).

Conclusions

Evidence from clinical trials that blockade of the renin-angiotensin–aldosterone system (RAAS) has direct vascular protective effects continues to mount. The data from large trials provide only limited information on the mechanism of this effect, the elucidation of which depends on laboratory studies and on small clinical trials designed to investigate potential metabolic and pathophysiological changes.

Already, numerous avenues for further study have been identified that could potentially separate agents that block the RAAS from other antihypertensive drugs, and differentiate ARBs and angiotensin-converting enzyme inhibitors. Some of these are well established in principle, such as the effects of AT_1 and AT_2 receptor activation, but require further investigation as to the precise physiological manifestation and clinical relevance. The potential for PPARγ agonism is a new concept that could have far-reaching implications for the way ARBs are used across a broad spectrum of patients, as the co-morbidity of hypertension with metabolic disorders is already high and likely to increase with increasing levels of over-nutrition. Of the ARBs, telmisartan is the only one to stimulate PPARγ at therapeutically relevant concentrations, as has also been shown by Benson et al. [38]. Likewise, the effects of ARBs on adiponectin are of interest, but require much more investigation. There is a likelihood that the effects of ARBs on adiponectin and PPARγ are connected, as there is crosstalk between the two systems [49, 50]. There are numerous other adipokines and related metabolic markers that may also be modulated by ARBs. These pleiotropic actions, which appear comparable to those of the glitazones, may contribute to their insulin-sensitising and antidiabetogenic effects. Further study is required to explore more fully the impact of ARBs on the metabolic profile of patients at risk of cardiovascular disease and elucidate whether differences between the ARBs that are apparent in laboratory studies translate into clinically meaningful effects.

Such clinical studies will require comparative clinical trials using intermediate endpoints of vascular disease, such as the Programme of Research tO show Telmisartan End-organ proteCTION (PROTECTION), a suite of clinical trials with renal, vascular and blood pressure endpoints [51]. Clinical trials comparing ARBs and ACE inhibitors will be particularly important for testing some of the hypotheses outlined above. The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) is the largest such trial underway, having recruited 31 396 patients at risk of cardiovascular disease [52]. ONTARGET, which is due to be completed in 2007, will provide definitive evidence on the clinical significance of the pleiotropic effects of the ARB telmisartan.

References

1. American Diabetes Association (2004) American Diabetes Association: clinical practice recommendations 2004. Diabetes Care 27[Suppl 1]:S1–S143
2. Chung O, Unger T (1999) Angiotensin II receptor blockade and end-organ protection. Am J Hypertens 12[2 Pt 1]:S150–S156
3. Strawn WB, Chappell MC, Dean RH, Kivlighn S, Ferrario CM (2000) Inhibition of early atherogenesis by losartan in monkeys with diet-induced hypercholesterolemia. Circulation 101:1586–1593
4. Makris TK, Stavroulakis GA, Krespi PG, Hatzizacharias AN, Triposkiadis FK, Tsoukala CG, Votteas VV, Kyriakidis MK (2000) Fibrinolytic/hemostatic variables in arterial hypertension: response to treatment with irbesartan or atenolol. Am J Hypertens 13:783–788
5. Resnick LM, Lester MH (2002) Differential effects of antihypertensive drug therapy on arterial compliance. Am J Hypertens 15:1096–1100
6. Bragulat E, Larrousse M, Coca A, de la Sierra A (2003) Effect of long-term irbesartan treatment on endothelium-dependent vasodilation in essential hypertensive patients. Br J Biomed Sci 60:191–196

7. Siragy HM (2000) The role of the AT_2 receptor in hypertension. Am J Hypertens 13[6 Pt 2]:62S–67S
8. Kaschina E, Unger T (2003) Angiotensin AT_1/AT_2 receptors: regulation, signalling and function. Blood Press 12:70–88
9. Fournier A, Messerli FH, Achard JM, Fernandez L (2004) Cerebroprotection mediated by angiotensin II: a hypothesis supported by recent randomized clinical trials. J Am Coll Cardiol 43:1343–1347
10. Thai H, Wollmuth J, Goldman S, Gaballa M (2003) Angiotensin subtype 1 receptor (AT_1) blockade improves vasorelaxation in heart failure by up-regulation of endothelial nitric-oxide synthase via activation of the AT_2 receptor. J Pharmacol Exp Ther 307:1171–1178
11. Sohn HY, Raff U, Hoffmann A, Gloe T, Heermeier K, Galle J, Pohl U (2000) Differential role of angiotensin II receptor subtypes on endothelial superoxide formation. Br J Pharmacol 131:667–672
12. Zhang C, Hein TW, Wang W, Kuo L (2003) Divergent roles of angiotensin II AT_1 and AT_2 receptors in modulating coronary microvascular function. Circ Res 92:322–329
13. Carey RM, Jin XH, Siragy HM (2001) Role of the angiotensin AT_2 receptor in blood pressure regulation and therapeutic implications. Am J Hypertens 14[6 Pt 2]:S98–S102
14. Brewster UC, Perazella MA (2004) The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. Am J Med 116:263–272
15. Chung O, Unger T (1998) Unopposed stimulation of the angiotensin AT2 receptor in the kidney. Nephrol Dial Transplant 13:537–540
16. Siragy HM (2004) AT_1 and AT_2 receptor in the kidney: role in health and disease. Semin Nephrol 24:93–100
17. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, for the RENAAL Study Investigators (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861–869
18. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P, for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345:870–878
19. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I, for the Collaborative Study Group (2001) Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851–860
20. Viberti G, Wheeldon NM (2002) Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 106:672–678
21. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, for the LIFE study group (2002) Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 359:995–1003
22. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 363:2022–2031
23. Henriksen EJ, Jacob S, Kinnick TR, Teachey MK, Krekler M (2001) Selective angiotensin II receptor antagonism reduces insulin resistance in obese Zucker rats. Hypertension 38:884–890
24. Okada K, Hirano T, Ran J, Adachi M (2004) Olmesartan medoxomil, an angiotensin II receptor blocker ameliorates insulin resistance and decreases triglyceride production in fructose-fed rats. Hypertens Res 27:293–299
25. Picard F, Auwerx J (2002) PPAR(gamma) and glucose homeostasis. Annu Rev Nutr 22:167–197
26. Boyle PJ, King AB, Olansky L, Marchetti A, Lau H, Magar R, Martin J (2002) Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus: a retrospective review of randomly selected medical records. Clin Ther 24:378–396
27. Hsueh WA, Law RE (2001) PPARgamma and atherosclerosis: effects on cell growth and movement. Arterioscler Thromb Vasc Biol 21:1891–1895
28. Marx N, Mach F, Sauty A, Leung JH, Sarafi MN, Ransohoff RM, Libby P, Plutzky J, Luster AD (2000) Peroxisome proliferator-activated receptor-gamma activators inhibit IFN-gamma-induced expression of the T cell-active CXC chemokines IP-10, Mig, and I-TAC in human endothelial cells. J Immunol 164:6503–6508
29. Jackson SM, Parhami F, Xi XP, Berliner JA, Hsueh WA, Law RE, Demer LL (1999) Peroxisome proliferator-activated receptor activators target human endothelial cells to inhibit leukocyte–endothelial cell interaction. Arterioscler Thromb Vasc Biol 19:2094–2104
30. Delerive P, Martin-Nizard F, Chinetti G, Trottein F, Fruchart JC, Najib J, Duriez P, Staels B (1999) Peroxisome proliferator-activated receptor activators inhibit thrombin-induced endothelin-1 production in human vascular endothelial cells by inhibiting the activator protein-1 signaling pathway. Circ Res 85:394–402
31. Law RE, Meehan WP, Xi XP, Graf K, Wuthrich DA, Coats W, Faxon D, Hsueh WA (1996) Troglitazone inhibits vascular smooth muscle cell growth and intimal hyperplasia. J Clin Invest 98:1897–1905
32. Ricote M, Huang JT, Welch JS, Glass CK (1999) The peroxisome proliferator-activated receptor (PPARgamma) as a regulator of monocyte/macrophage function. J Leukoc Biol 66:733–739
33. Kintscher U, Goetze S, Wakino S, Kim S, Nagpal S, Chandraratna RA, Graf K, Fleck E, Hsueh WA, Law RE (2000) Peroxisome proliferator-activated receptor and retinoid X receptor ligands inhibit monocyte chemotactic protein-1-directed migration of monocytes. Eur J Pharmacol 401:259–270
34. Li AC, Brown KK, Silvestre MJ, Willson TM, Palinski W, Glass CK (2000) Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice. J Clin Invest 106:523–531

35. Collins AR, Meehan WP, Kintscher U, Jackson S, Wakino S, Noh G, Palinski W, Hsueh WA, Law RE (2001) Troglitazone inhibits formation of early atherosclerotic lesions in diabetic and nondiabetic low density lipoprotein receptor-deficient mice. Arterioscler Thromb Vasc Biol 21:365–371
36. Pershadsingh HA (2004) Peroxisome proliferator-activated receptor-gamma: therapeutic target for diseases beyond diabetes: quo vadis? Expert Opin Investig Drugs 13:215–228
37. Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, Lehmann JM (1997) Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. Proc Natl Acad Sci USA 94:4318–4323
38. Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW (2004) Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ-modulating activity. Hypertension 43:993–1002
39. Schupp M, Janke J, Clasen R, Unger T, Kintscher U (2004) Angiotensin type 1 receptor blockers induce peroxisome proliferators-activated receptor-γ activity. Circulation 109:2054–2057
40. Danforth E Jr (2000) Failure of adipocyte differentiation causes type II diabetes mellitus? Nat Genet 26:13
41. Zhao Y, Unger, Kintscher U (2003) Angiotensin II induces PPARgamma in PC12 cells via AT2 receptor activation [abstract]. Hypertension 42:389
42. Stefan N, Stumvoll M (2002) Adiponectin – its role in metabolism and beyond. Horm Metab Res 34:469–474
43. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T (2001) The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 7:941–946
44. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y (2002) Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 8:731–737
45. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ (2003) Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem 278:45021–45026
46. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y (2000) Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation 102:1296–1301
47. Clasen R, Sprang C, Schupp M, Unger T, Kintscher U (2003) Angiotensin type 1 receptor antagonism induces adiponectin expression in adipocytes. Hypertension 42:634
48. Furuhashi M, Ura N, Higashiura K, Murakami H, Tanaka M, Moniwa N, Yoshida D, Shimamoto K (2003) Blockade of the renin–angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension 42:76–81
49. Iwaki M, Matsuda M, Maeda N, Funahashi T, Matsuzawa Y, Makishima M, Shimomura I (2003) Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. Diabetes 52:1655–1663
50. Chinetti G, Zawadski C, Fruchart JC, Staels B (2004) Expression of adiponectin receptors in human macrophages and regulation by agonists of the nuclear receptors PPARalpha, PPARgamma, and LXR. Biochem Biophys Res Commun 314:151–158
51. Weber M (2003) The telmisartan Programme of Research tO show Telmisartan End-organ proteCTION (PROTECTION) programme. J Hypertens 21[Suppl 6]:S37–S46
52. Teo K, Yusuf S, Anderson C, Mookadam F, Ramos B, Hilbrich L, Pogue J, Schumacher H, The ONTARGET/TRANSCEND Investigators (2004) Rationale, design and baseline characteristics of two large, simple randomized trials evaluation telmisartan, ramipril and their combination in high-risk patients: the ONTARGET/TRANSCEND trials. Am Heart J 148:52–61