Antidiabetic mechanisms of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists: beyond the renin–angiotensin system

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Several lines of evidence suggest that angiotensin-converting enzyme (ACE) inhibitors and some angiotensin II receptor blockers (ARBs) may improve insulin sensitivity and decrease the risk for type 2 diabetes. It is widely assumed that the potential antidiabetic properties of these agents are largely mediated by their ability to interfere with the adverse metabolic effects of angiotensin II. However, recent studies suggest that ACE inhibitors might improve glucose metabolism primarily through effects on kinin–nitric oxide pathways. In addition, one ARB in particular, telmisartan, has been found to effectively activate the peroxisome proliferator activated receptor gamma (PPARγ), a well-known target for insulin-sensitizing, antidiabetic drugs. Thus, the beneficial metabolic effects of some ACE inhibitors and ARBs may go well beyond their effects on the renin–angiotensin system. Moreover, the identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ modulating ability suggests new opportunities for developing third-generation ARBs and PPARγ activators, with enhanced potential for treating hypertension, diabetes and the metabolic syndrome. *J Hypertens* 22:2253–2261 © 2004 Lippincott Williams & Wilkins.

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Introduction

Growing concern about the increasing prevalence of the metabolic syndrome and type 2 diabetes has generated substantial interest in the metabolic effects of antihypertensive drugs [1–4]. Historically, most of the focus has been on disturbances in carbohydrate and lipid metabolism associated with diuretics and beta-blockers. However, the results of several large-scale clinical trials have recently begun to shift attention to the possibility that some of the newer antihypertensive agents may not only cause fewer metabolic side-effects than diuretics and beta-blockers, but may also decrease the overall risk for type 2 diabetes [5–10]. Given the morbidity and mortality associated with type 2 diabetes and hypertension, the availability of drugs that have antidiabetic as well as antihypertensive properties could be of considerable clinical value.

Antidiabetic effects of interrupting the renin–angiotensin system

In vitro experiments and studies in animals and in humans have suggested a possible relationship between the renin–angiotensin system and the pathogenesis of insulin resistance. For example, recent studies have suggested that angiotensin II (AII) may promote impaired glucose metabolism through its effects on insulin signaling pathways, tissue blood flow, oxidative stress, sympathetic activity and adipogenesis [11–25]. Thus, pharmacologic interruption of the renin–angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) might improve glucose metabolism by interfering with AII generation or AII receptor activation (Table 1). These observations have begun to motivate clinical trials designed to investigate whether drugs that interrupt the RAS can ward off the development of type 2 diabetes. Indeed, given some of the evidence accumulated to date, it is possible that pharmacologic interruption of the RAS may someday prove capable of improving insulin sensitivity and decreasing the risk for diabetes. However, this review focuses on the alternative notion that ACE inhibitors and ARBs differ in their capacity to affect insulin sensitivity, and that interruption of the RAS may not be the sole, or even central,

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Table 1 Potential antidiabetic mechanisms of interrupting the renin–angiotensin system

Both ACE inhibitors and ARBs may interfere with adverse effects of angiotensin II on:
Insulin signaling
Tissue blood flow
Oxidative stress
Sympathetic activity
Adipogenesis

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

mechanism that mediates the apparent antidiabetic properties of some of these drugs. The metabolic effects of molecules that interrupt the renin–angiotensin system may differ both between and within various drug classes and it is conceivable that some of these agents may improve insulin sensitivity and decrease the risk for diabetes much more effectively than others.

Antidiabetic effects and mechanisms of converting enzyme inhibition

Recent studies in experimental animal models and in small- and large-scale clinical trials have suggested that ACE inhibitors may have the capacity to increase insulin sensitivity and/or decrease the risk of type 2 diabetes [5–7,24,26–33]. Although the data are not conclusive, the results of these studies have been sufficiently interesting to motivate the design of prospective, placebo-controlled randomized trials to investigate the ability of ACE inhibitors to decrease the incidence of new-onset type 2 diabetes as a primary end-point [4,34]. For example, in the placebo-controlled DREAM study, investigators will determine if the ACE inhibitor ramipril, the thiazolidinedione rosiglitazone, or both drugs in combination can delay or prevent the development of type 2 diabetes (T2DM) in subjects with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). Enrollment was completed in 2003, with over 5000 patients (4531 with IGT and 738 with IFG) who will be followed for at least 3 years to determine the occurrence of new-onset T2DM or all-cause mortality as primary outcomes [35].

As noted, ACE inhibitors might improve insulin sensitivity by interfering with AII generation, thereby limiting adverse effects of AII on glucose metabolism (Table 1). However, recent studies have suggested that the antidiabetic properties of ACE inhibitors may be largely mediated through increases in bradykinin levels, nitric oxide and the GLUT4 glucose transporter (Table 2) [24,26–31,36,37]. For example, metabolic studies in animals lacking bradykinin B2 receptors and in animals treated with both an ACE inhibitor and a bradykinin antagonist strongly suggest that the insulin-sensitizing effects of ACE inhibitors involve more than just reductions in angiotensin II levels [24,28,36,37]. Increases in bradykinin levels stemming from converting enzyme inhibition may improve glucose metabolism by affecting insulin signaling pathways, nitric oxide production and translocation of GLUT4 [24,28–30]. A potential role for bradykinin in the insulin-sensitizing actions of converting enzyme inhibition is further suggested by the inconsistent effects of angiotensin II receptor blockade on glucose metabolism [8,24,26,31,38].

Table 2 Antidiabetic mechanisms of ACE inhibitors and particular ARBs that may go beyond their effects on the renin–angiotensin system

ACE inhibitors may enhance glucose metabolism by:
Activating bradykinin/nitric oxide pathways
Particular ARBs (e.g. telmisartan) may improve glucose and lipid metabolism by:
Activating PPARγ

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; PPARγ, peroxisome proliferator activated receptor gamma.

Antidiabetic effects and mechanisms of angiotensin II receptor blockade

To the extent that the antidiabetic effects of ACE inhibitors are secondary to interference with angiotensin II-dependent mechanisms that promote insulin resistance (Table 1), one might expect ARBs to be similarly as effective as ACE inhibitors, if not more effective, in improving insulin resistance and preventing type 2 diabetes (Table 1). In a small, single-blind, placebo-controlled study using the euglycemic hyperinsulinemic clamp technique in hypertensive patients, Paolisso *et al.* [15] reported that losartan-induced increases in whole-body glucose disposal were correlated with losartan-induced increases in femoral artery blood flow. However, few head-to-head comparisons have been made of the insulin-sensitizing effects of ACE inhibitors versus ARBs and, to date, no large-scale clinical trials have compared the ability of ACE inhibitors and ARBs to decrease the risk for diabetes. In several randomized, blinded, placebo-controlled studies that have been performed with the euglycemic hyperinsulinemic clamp technique, different ACE inhibitors have been found to improve insulin sensitivity, whereas the ARB losartan has been found to have comparatively little or no effect on insulin action [24,39–41]. Some investigators have also suggested that the inhibitory effects of AII on insulin-signaling pathways may not be mediated by either type 1 or type 2 angiotensin II receptors and that another type of angiotensin receptor may be involved [13]. If so, this could further explain why ACE inhibitors might be more effective in improving insulin sensitivity than at least some ARBs.

Clinical trials using ARBs have provided some indirect support for the possibility that angiotensin II receptor blockade *per se* may improve insulin sensitivity and decrease the incidence of type 2 diabetes. In the LIFE trial, the incidence of new-onset type 2 diabetes was reported to be significantly lower in hypertensive subjects treated with losartan than in those treated with

atenolol, suggesting potential antidiabetic effects of angiotensin receptor blockade [8]. However, it should be noted that the LIFE trial did not include a placebo control. Given the known diabetogenic effects of beta-adrenergic blockers, it is possible that the lower incidence of new-onset diabetes in the losartan arm of the trial was related to a pro-diabetic effect of atenolol, rather than an anti-diabetic effect of angiotensin receptor blockade. In the recent VALUE trial, the incidence of new-onset type 2 diabetes was observed to be lower in hypertensive subjects treated with valsartan than in those treated with amlodipine [10]. As in the LIFE trial, a placebo control could not be included in the VALUE trial. Thus, while the VALUE trial indicates that the risk for developing new-onset type 2 diabetes is either lower or delayed in patients treated with valsartan than in those treated with amlodipine, it does not establish that angiotensin receptor blockade *per se* reduces or delays the onset of type 2 diabetes. However, it is generally believed that calcium-channel antagonists such as amlodipine are metabolically neutral. If this is correct, the lower incidence of new-onset diabetes in the valsartan-treated subjects might well be reflecting an antidiabetic effect of angiotensin II receptor blockade.

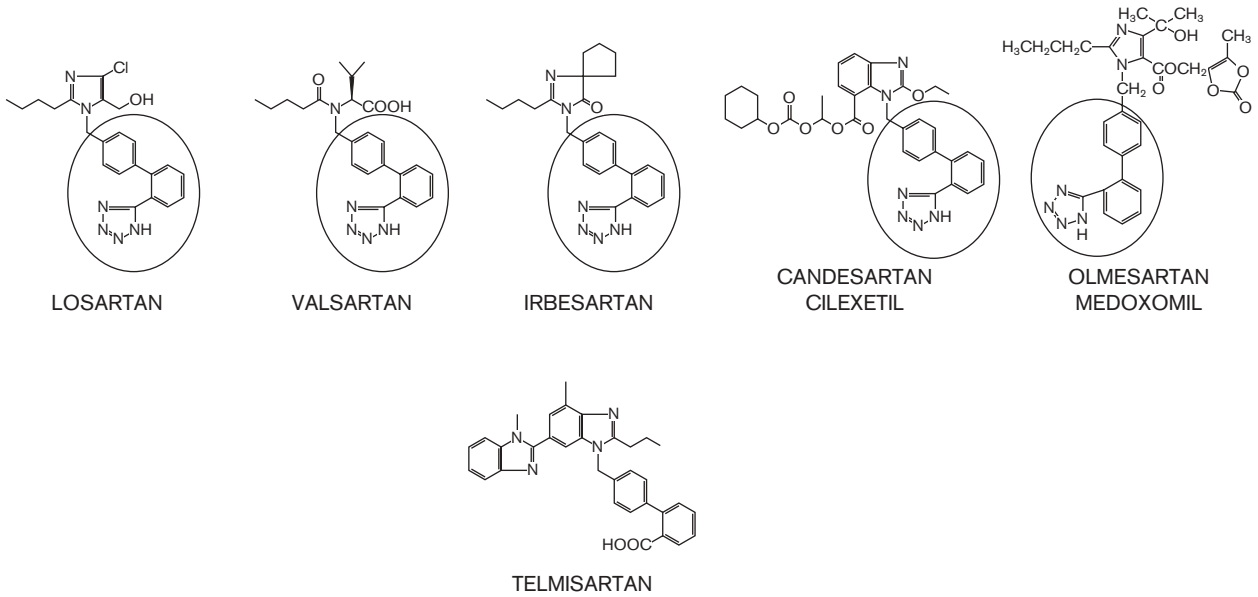
In contrast to the LIFE and VALUE trials, the CHARM Preserved, CHARM Alternative, CHARM Added, and SCOPE trials included placebo controls [9,42–44]. These placebo-controlled trials directly tested whether angiotensin receptor blockade could decrease the risk for new-onset diabetes as a pre-specified endpoint. In the CHARM Preserved trial, the incidence of new-onset type 2 diabetes was significantly lower in subjects given candesartan than in those given placebo [9]. However, in the other placebo-controlled trials, including CHARM Alternative [42], CHARM Added [43] and SCOPE [44], there was no significant difference in the incidence of new-onset diabetes in subjects given candesartan compared to controls. In the ALPINE [45] and CROSS [38] studies, in which the effects of candesartan on glucose and lipid metabolism were directly investigated, the administration of candesartan had no effect on serum levels of insulin, glucose or triglycerides. Although candesartan treatment appeared to improve an indirect estimate of insulin action in the CROSS study [38], it failed to show any effect on the HOMA index of insulin resistance in the ALPINE study [45]. In summary, several clinical trials have suggested that angiotensin receptor blockade might exert protective effects on glucose metabolism. However, most of the placebo-controlled trials (all performed with candesartan) have failed to show an antidiabetic effect of angiotensin receptor blockade. The results of studies designed to directly investigate the metabolic effects of candesartan have also failed to show any beneficial effects of angiotensin receptor blockade on glucose, insulin or triglyceride levels.

Despite data suggesting that candesartan is metabolically neutral, the metabolic effects of ARBs could vary, and some ARBs might have greater effects on glucose and lipid metabolism than others. Thus, the results of ongoing, placebo-controlled clinical trials designed to investigate the metabolic effects of other ARBs will be of considerable interest in this regard. For example, in the ONTARGET trial, subjects at increased risk for cardiovascular events, including many subjects at increased risk for diabetes, will be randomized to receive either telmisartan, ramipril or a combination of telmisartan and ramipril [46,47]. In the companion TRANSCEND trial, subjects that are intolerant of ACE inhibitors but are otherwise similar to those enrolled in ONTARGET will be randomized to placebo or telmisartan [46,47]. Reduction in the incidence of new-onset type 2 diabetes will be a secondary endpoint in both of these trials. Taken together, the ONTARGET and TRANSCEND trials are of considerable interest because this program not only includes a placebo control, but also head-to-head comparisons of the antidiabetic effects of an ARB, an ACE inhibitor, and the combination of both an ARB and an ACE inhibitor. The ONTARGET trial finalized recruitment of 25 260 subjects in May of 2003 and the TRANSCEND trial finalized recruitment of 5926 subjects in April of 2004. Because these studies are 'event driven', there is no fixed timeline but the expectation is that results will be available in 2007. The NAVIGATOR trial is investigating whether the oral antidiabetic agent nateglinide or the ARB valsartan can prevent diabetes as a primary endpoint in individuals with impaired glucose tolerance who are at high risk for cardiovascular events [48]. This randomized, double-blind, placebo-controlled trial involves over 7000 subjects, and the diabetes end-point will be assessed 3 years after the last trial participant is enrolled.

Do some ARBs have antidiabetic effects that are independent of RAS blockade?

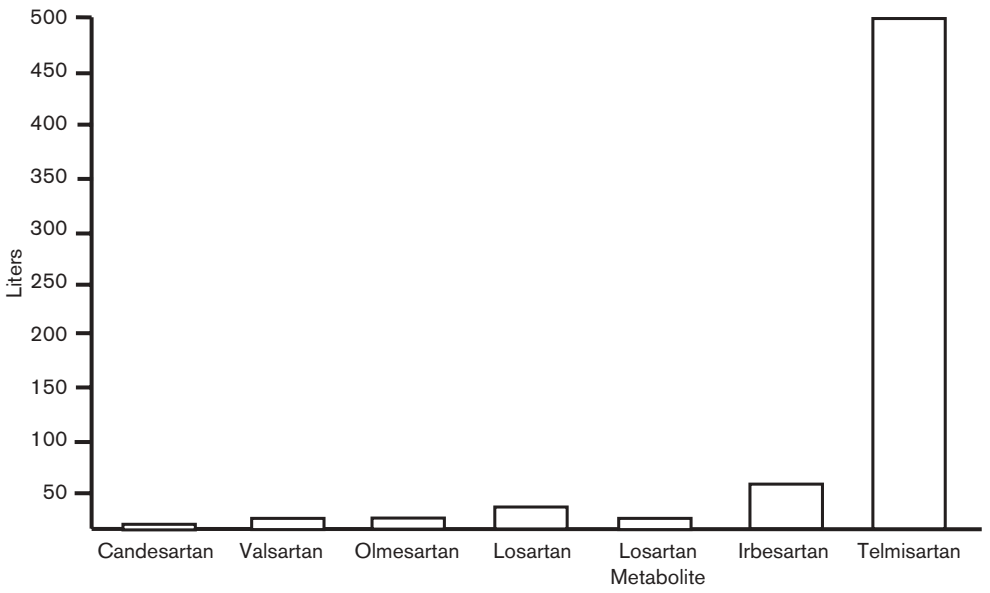
Most studies investigating the metabolic effects of angiotensin II receptor blockade have focused on the use of losartan, or other ARBs, such as candesartan, that bear a close structural resemblance to losartan. It should be noted, however, that one ARB in particular, telmisartan, appears to be structurally quite distinct from all other angiotensin II antagonists in clinical use today. Most of the commonly used ARBs are structurally similar to losartan and are biphenyl tetrazole derivatives (Fig. 1). In contrast, telmisartan is a highly lipid soluble, non-tetrazole derivative, with a single carboxylic acid group instead of the large tetrazole ring. A graphic example of the unique chemical nature of telmisartan is illustrated by its extraordinarily high volume of distribution relative to other commonly used ARBs (Fig. 2). The only other non-tetrazole ARB, eprosartan (not shown), includes carboxylic acid groups

Fig. 1



Chemical structures of the most widely used angiotensin receptor blockers (ARBs), illustrating the unique nature of telmisartan. The circle encloses the biphenyl tetrazole moiety that is common to losartan and its related ARBs.

Fig. 2



Volumes of distribution of the most widely used angiotensin receptor blockers (ARBs), including the active metabolite of losartan. Telmisartan has a much greater volume of distribution than other ARBs.

at both ends of the molecule and it is less lipid soluble than telmisartan. Thus, although some studies with ARBs such as losartan and candesartan suggest that angiotensin receptor blockade may have limited effects on insulin sensitivity or glucose and lipid levels [39–45], they do not speak to the potential metabolic effects of structurally distinct ARBs such as telmisartan.

The tacit assumption that underlies the interpretation of most studies involving ARBs is that these molecules

interact only with the angiotensin II receptor and, therefore, that most, if not all, of their biologic properties are secondary to AII receptor blockade. However, this assumption appears to be incorrect, as we have found that telmisartan has unique chemical properties that may enable it to target insulin resistance and diabetes therapeutically at the molecular level through mechanisms that are unrelated to blockade of the renin–angiotensin system (Table 2) [49,50].

Identification of telmisartan as a structurally unique ARB with selective PPARγ modulating ability

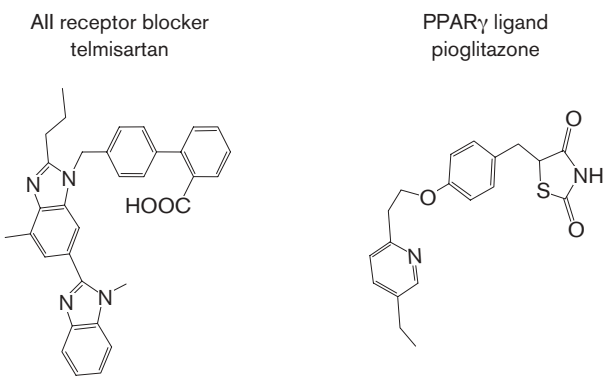
Recently, we [49,50] reported that telmisartan bears an interesting structural resemblance to the insulin sensitizer pioglitazone, a thiazolidinedione ligand of the peroxisome proliferator activated receptor gamma (PPARγ) approved for the treatment of type 2 diabetes (Fig. 3). PPARγ is a member of the nuclear hormone receptor superfamily and functions as a transcription factor that regulates the expression of multiple genes involved in carbohydrate and lipid metabolism and inflammation [51–56]. While PPARγ is principally expressed in adipose tissue, it can be found in a variety of cells, including vascular smooth muscle cells, endothelial cells and monocytes. In addition to improving insulin sensitivity, PPARγ activators can ameliorate multiple pathogenetic determinants of atherosclerosis (Table 3) [51–59]. Thus, intense interest exists in the potential use of thiazolidinediones and other PPARγ activators for prevention and treatment of coronary vascular disease, as well as for the prevention and treatment of diabetes [51–59]. These observations, together with reports that mutations in PPARγ are associated with severe insulin resistance and dyslipidemia [60], have clearly established PPARγ as a valuable target for the development of antidiabetic and anti-atherosclerotic drugs. Large-scale clinical trials designed to investigate prospectively the cardioprotective effects of PPARγ activators are currently under way [35,61]. Although the first clinically approved thiazoldinedione ligand of PPARγ (troglitazone) was withdrawn from the market because of hepatotoxicity, this does not appear to be a class effect, because liver toxicity has not been an issue with other PPARγ activators, such as pioglitazone or rosiglitazone [62].

Table 3 Potential anti-atherosclerotic mechanisms of PPARγ activators

Increase insulin sensitivity
Decrease fatty acid and triglyceride levels
Increase reverse cholesterol transport and HDL levels
Increase buoyancy of LDL particles
Decrease inflammation
Decrease oxidative stress
Decrease blood pressure
Decrease vascular smooth muscle cell proliferation and migration

PPARγ, peroxisome proliferator activated receptor gamma; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Fig. 3

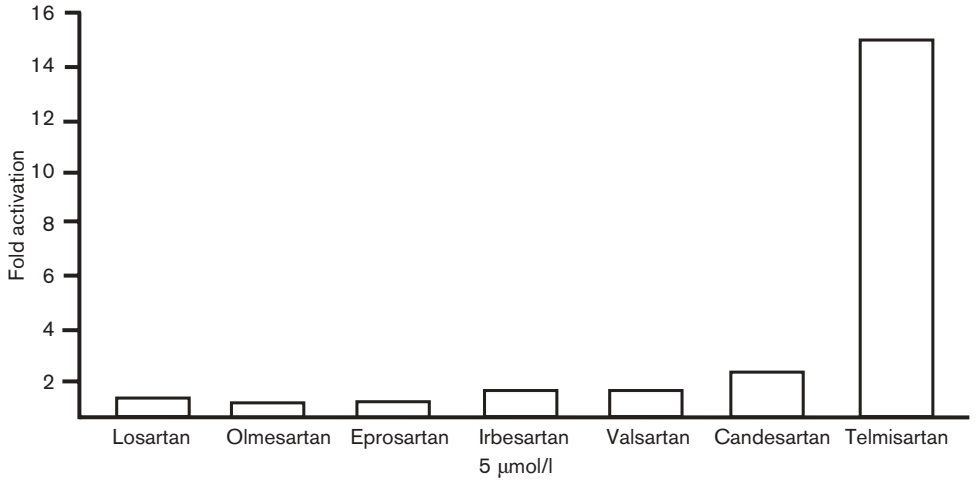


Comparison of the chemical structures of telmisartan and the peroxisome proliferator activated receptor gamma (PPARγ) ligand, pioglitazone. AII, angiotensin II.

Benson and colleagues [49,50] have demonstrated that telmisartan can function as a partial agonist of PPARγ, influence the expression of PPARγ target genes involved in carbohydrate and lipid metabolism, and reduce glucose, insulin and triglyceride levels in rats fed a high-fat, high-carbohydrate diet. None of the other clinically approved ARBs appears to activate PPARγ when tested at maximal concentrations that might be achieved in plasma with conventional oral dosing (Fig. 4) (T. Kurtz, unpublished observations) [49,50]. When tested at relatively high concentrations (10 μmol/l or above), irbesartan appears to have some potential to activate PPARγ, although it is unclear whether its effects on PPARγ will be achievable with normal oral dosing [49,50]. Recently, Schupp *et al.* [63] have confirmed that telmisartan can act as a PPARγ agonist when tested at therapeutically relevant concentrations, and that relatively high concentrations of irbesartan can also activate PPARγ. The ability of telmisartan and irbesartan to activate PPARγ appears to be independent of AII receptor blockade, as Schupp *et al.* [63] have further noted that these molecules can activate PPARγ in cells that lack AII type 1 receptors.

By virtue of its unique ability to activate PPARγ at reasonable concentrations, telmisartan may have a greater potential than other ARBs to improve the disturbances in carbohydrate and lipid metabolism that often accompany hypertension as part of the metabolic syndrome, type 2 diabetes or both. Consistent with this possibility, a case study and a small-scale clinical trial were recently reported, in which telmisartan improved biochemical features of the metabolic syndrome and diabetes whereas valsartan and eprosartan did not

Fig. 4

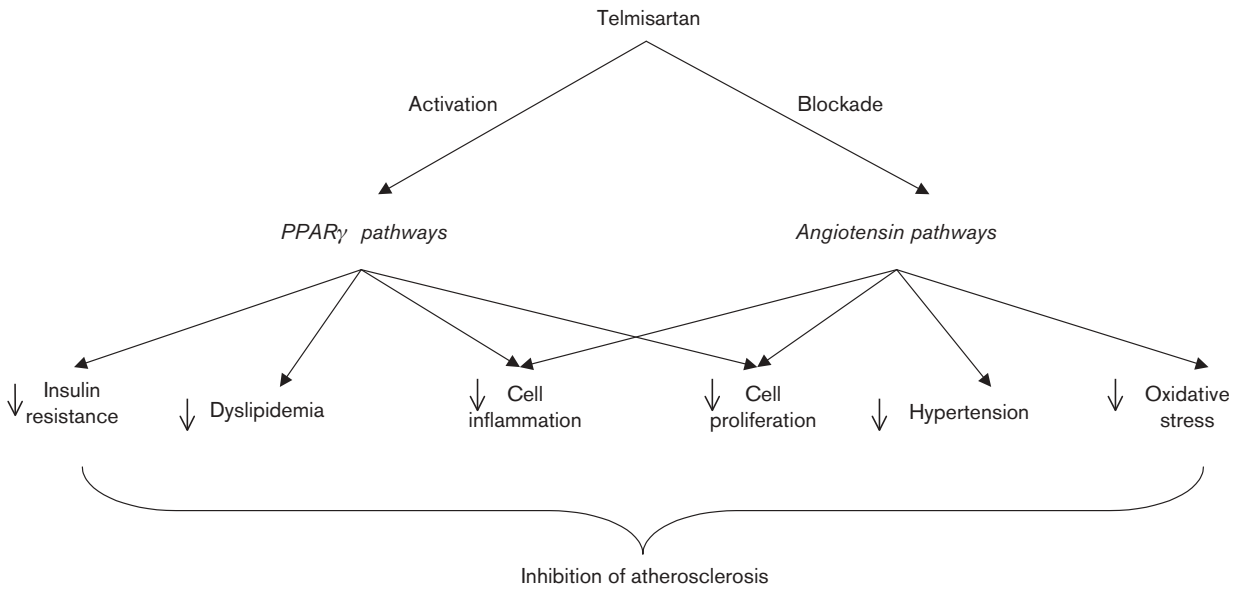


Comparison of the ability of different angiotensin receptor blockers (ARBs) to activate peroxisome proliferator activated receptor gamma (PPARγ) in a cell-based transient transfection assay when tested at a concentration of 5 μmol/l. Telmisartan is the only ARB that clearly activates PPARγ when tested at concentrations between 1 and 5 μmol/l.

[64,65]. However, systematic clinical trials such as ONTARGET and TRANSCEND will be required to help determine the extent to which the ability of telmisartan to selectively modulate PPARγ affords metabolic benefits beyond its effects on the renin–angiotensin system [46,47,66].

Many of the mechanisms involved in the pathogenesis of atherosclerosis can be modulated by PPARγ, angiotensin II or both (Fig. 5) [25,57,59]. Theoretically, multifunctional compounds such as telmisartan, which simultaneously activate PPARγ and block the angiotensin II type 1 receptor, should be particularly effective in preventing atherosclerotic cardiovascular disease in patients with hypertension or diabetes (Fig. 5). Moreover, activation of PPARγ has been reported to de-

Fig. 5



Potential influence of telmisartan on pathways that are likely primarily to mediate the anti-atherosclerotic effects of peroxisome proliferator activated receptor gamma (PPARγ) activation and angiotensin II receptor blockade.

crease expression of the angiotensin II type 1 receptor gene and inhibit the effects of angiotensin II on intracellular signaling pathways [67–69]. These PPARγ-related actions could further contribute to the ability of telmisartan to interfere with the adverse cardiovascular effects of angiotensin II.

It should be emphasized that telmisartan belongs to a category of molecules known as selective PPAR gamma modulators (SPPARMs) [70,71]. The SPPARMs differ from conventional PPARγ activators such as rosiglitazone and pioglitazone in a number of important respects. Rosiglitazone, pioglitazone and other conventional PPARγ activators typically function as full agonists of the receptor and affect the expression of a very broad range of genes, whereas SPPARMs, such as telmisartan, function as partial agonists, with more restricted effects on gene expression [50,71]. SPPARMs influence the expression of some, but not all, of the same target genes regulated by conventional PPARγ activators [50,71]. The overlapping, yet differential, effects on gene expression of SPPARMs versus conventional PPAR ligands may mediate some of the similarities and differences in their biologic effects. For example, in rodent models of insulin resistance and obesity induced by administration of high fat, high carbohydrate diets, both conventional PPARγ activators and SPPARMs can improve carbohydrate and lipid metabolism [50,71]. However, in these models the conventional PPARγ activators also promote weight gain and accumulation of body fat, whereas SPPARMs such as telmisartan and nTZDpa (an experimental Merck compound) do not. In fact, both telmisartan and nTZDpa appear to attenuate diet-induced increases in weight gain and body fat independent of effects on energy intake (T. Kurtz, unpublished observations) [50,71].

The precise mechanisms that mediate the ability of SPPARMs such as telmisartan to attenuate diet-induced increases in body weight and body fat remain to be determined. However, it is possible that some of these molecules may be affecting energy balance by influencing the expression of genes involved in fatty acid metabolism [50,71]. It should also be noted that some of the weight gain associated with administration of conventional PPARγ activators is likely caused by renal salt and water retention occurring secondary to reflex activation of the renin–angiotensin–aldosterone system [72]. Thus, SPPARMs such as telmisartan, which also have the ability to block angiotensin II receptors, should be much less likely to cause fluid retention and edema than conventional PPARγ ligands. Given that patients with hypertension and diabetes are already at increased risk for myocardial dysfunction, the availability of insulin-sensitizing PPARγ activators that do not promote fluid retention and edema would be of considerable clinical value.

Conclusions

Tantalizing experimental and clinical evidence suggests that at least some drugs that interrupt the renin–angiotensin system may improve glucose and lipid metabolism and decrease the risk for type 2 diabetes. Although some of the antidiabetic properties of ACE inhibitors and ARBs might be mediated by their ability to interfere with adverse effects of angiotensin II on carbohydrate and lipid metabolism, it is also possible that the beneficial metabolic effects of ACE inhibitors and certain ARBs go well beyond just simple interruption of the renin–angiotensin system. Studies with bradykinin receptor knockout mice and with bradykinin antagonists indicate that ACE inhibitors might improve glucose metabolism through effects on kinin–nitric oxide pathways. In addition, one ARB in particular, telmisartan, has been found to effectively activate PPARγ, a well-known target for insulin-sensitizing, antidiabetic drugs. Thus, it is possible that ARBs will show significant differences in their metabolic actions. The identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ-modulating ability suggests new opportunities for developing third-generation ARBs and PPARγ activators, with enhanced potential for treating hypertension, diabetes and the metabolic syndrome. The results of ongoing and future clinical trials should help to answer whether recent experimental findings on the antidiabetic potential of certain ACE inhibitors and ARBs, including telmisartan, will ultimately prove relevant to clinical practice.

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