COMMENTARY

And in the end—Telmisartan directly binds to PPAR γ

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Angiotensin type 1-receptor blockers (ARBs) are widely used for the treatment of hypertension and hypertension-related end-organ damage. In 2004, a subgroup of ARBs was identified as partial agonists of peroxisome proliferator-activated receptor γ (PPAR γ) with selective PPAR γ -modulating properties.^{1–3} In contrast to the glitazones, which are full agonists, PPAR γ -activating ARBs selectively recruited nuclear cofactors, resulting in *in vivo* insulin sensitization in the absence of weight gain in obese insulin-resistant mice.² Of the ARBs, telmisartan was shown to be the most potent PPAR γ agonist.³ On the basis of these *in vitro* results, together with data from animal experiments, numerous clinical studies investigated the metabolic actions of telmisartan in various patient populations.⁴ The key finding from these ‘small’ studies was that telmisartan was not consistently better than comparators, such as other ARBs, ACE-inhibitors, or calcium antagonists, at improving insulin and glucose metabolism in patients with metabolic syndrome or diabetes.⁴

In 2008, most researchers and clinicians in the field of hypertension and cardiovascular prevention were expecting that the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) would provide the ultimate answer to whether the PPAR γ -activating properties of telmisartan translate into a clinical benefit.⁵ ONTARGET compared the ARB telmisartan and the ACE inhibitor ramipril in 25 620 high-risk patients over the age of 55 years who had vascular disease (coronary, peripheral, or cerebrovascular) or diabetes with end-organ damage. The trial was developed to

explore whether telmisartan is as effective as ramipril at preventing the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure.⁵ One of the secondary endpoints of ONTARGET was the incidence of diabetes. Diabetes was diagnosed in 366 patients (6.7%) in the ramipril group and 399 patients (7.5%) treated with telmisartan, thereby indicating no significant difference between the groups and demonstrating that telmisartan was as effective as ramipril at preventing diabetes. One of the main conclusions drawn from these results was that telmisartan’s PPAR γ -activating properties did not translate into a stronger anti-diabetic action than that of ramipril, and therefore that the activation of PPAR γ by telmisartan has no clinical relevance—an alternative conclusion was that telmisartan does not activate PPAR γ in humans. One explanation for the findings might be the low dose of telmisartan that was used in ONTARGET: this 80 mg per day dose might not have led to a sufficient plasma concentration of the drug to activate PPAR γ and thus to have anti-diabetic effects. Along these lines, we recently showed that a higher dose of telmisartan (160 mg per day) results in a stronger induction of PPAR γ -target genes in human monocytes than lower telmisartan doses, indicating that higher doses of telmisartan are required to activate PPAR γ .⁶ Thus, there seems to be evidence that telmisartan, in higher doses, can activate PPAR γ in humans.

In parallel to the clinical studies conducted with telmisartan, multiple preclinical studies were performed to further characterize the mechanism of telmisartan’s PPAR γ -activating potential. On the basis of these data, it was still unclear whether telmisartan directly binds to the ligand-binding domain (LBD) of PPAR γ and acts as a ‘classical’ PPAR γ ligand.

In the present issue of this journal, Amano *et al.*⁷ answered this question for the first time. Using crystallographic analysis, they showed, in an elegant study, that telmisartan binds to the PPAR γ LBD, forming a ternary complex with a PPAR γ cofactor, SRC-1. As a partial agonist, the binding mode of telmisartan differed from the binding of rosiglitazone, which is a full agonist.⁸ More interestingly, telmisartan exhibited an unexpected binding mode that differed from the mode predicted by previous modelling studies. The binding of telmisartan involved a suboptimal hydrogen-bonding network around helix 12 of the PPAR γ LBD, affecting coactivator binding. These data help to understand the unique binding profile of telmisartan to the PPAR γ LBD and provide the final proof that this ARB directly binds to PPAR γ . Furthermore, these results may provide a molecular and pharmacological platform for the development of new telmisartan-like partial agonists or selective modulators of PPAR γ with an improved efficacy and risk profile.⁹

CONFLICT OF INTEREST

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