HIGHLIGHT ADVISORS

ERIK DE CLERCQ

KATHOLIEKE UNIVERSITEIT
LEUVEN, BELGIUM

RODERICK FLOWER

WILLIAM HARVEY RESEARCH
INSTITUTE, QMW, LONDON, UK

YOSHIMI FUJITA

CLINICAL PROTEOME CENTER,
TOKYO MEDICAL UNIVERSITY

F. PETER GUENGERICH

VANDERBILT UNIVERSITY
NASHVILLE, TN, USA

FRANZ HEFTI

RINAT NEUROSCIENCE
CORPORATION, PALO ALTO,
CA, USA

JOAN HELLER BROWN

UNIVERSITY OF CALIFORNIA
SAN DIEGO, CA, USA

MADS KROGSGAARD THOMSEN

NOVO NORDISK, BAGSVAERD,
DENMARK

HUGO KUBINYI

UNIVERSITY OF HEIDELBERG,
GERMANY

ROBERT LANGER

MASSACHUSETTS INSTITUTE
OF TECHNOLOGY
CAMBRIDGE, MA, USA

JULIO LICINIO

UNIVERSITY OF CALIFORNIA
LOS ANGELES, CA, USA

CHRISTOPHER LIPINSKI

PFIZER GLOBAL RESEARCH
AND DEVELOPMENT, GROTON,
CT, USA

LESLIE MEYER-LEON

IP LEGAL STRATEGIES GROUP,
CAPE COD, MA, USA

TOMI SAWYER

ARIAD PHARMACEUTICALS,
CAMBRIDGE, MA, USA

JANET WOODCOCK

CENTER FOR DRUG
EVALUATION AND RESEARCH,
WASHINGTON, MD, USA

METABOLIC SYNDROME

Two for the price of one

A widely prescribed antihypertensive drug has been shown to exert an antidiabetic effect by activating peroxisome proliferator-activated receptor- γ (PPAR- γ).

A study by Theodore Kurtz, Harrihar Pershadsingh, Mitchell Avery and colleagues, published in *Hypertension*, was prompted by three observations. First, clinical trials have shown that treating hypertensive patients with some antagonists of the angiotensin II type I receptor (ARBs) can reduce their risk of developing type 2 diabetes. Second, the blood pressure of diabetics treated with drugs that activate PPAR- γ — a transcriptional regulator of glucose and lipid metabolism — is often moderately reduced. When they also noted a structural resemblance between the ARB telmisartan and the PPAR- γ ligand pioglitazone, the authors set out to test the hypothesis that some molecules can modulate both angiotensin receptors and PPAR- γ .

Different ARBs were tested for their capacity to activate the expression of a reporter gene conjugated to murine PPAR- γ in cultured monkey fibroblasts. At physiological concentrations, only telmisartan induced a substantial response. With an EC₅₀ of 4.5 μ M, the authors classified telmisartan as a moderately potent, partial PPAR- γ agonist, by comparison to full agonists such as pioglitazone.

Telmisartan-mediated agonism induced several responses that characteristically result from PPAR- γ activation. These included *in vitro*

differentiation of adipocytes, and selective modulation of the expression of genes involved in carbohydrate and lipid metabolism. In rats fed fat- and carbohydrate-enriched chow, daily administration of 5 mg per kg telmisartan for five weeks reduced serum levels of glucose, insulin and triglycerides. These changes correlated with a 10% attenuation of weight gain.

Does the bifunctionality of telmisartan arise through it acting on the two receptor types in series or in parallel? This question was addressed in a separate study by Ulrich Kintscher's team. They used cells that lack angiotensin II type I receptors to show that PPAR- γ -dependent adipocyte differentiation occurs independently of angiotensin receptor blockade. Their brief communication in *Circulation* also shows that the activation of PPAR- γ by telmisartan is mediated solely through its ligand-binding domain.

Docking studies by Kurtz *et al.* revealed that telmisartan interacts with a region of the ligand-binding domain similar to that occupied by other partial agonists. The telmisartan-PPAR- γ complex is probably stabilized by strong hydrophobic interactions with helices H3 and H7, and by the formation of a hydrogen bond with serine 342.

So, it is clear that telmisartan acts on both angiotensin receptors and PPAR- γ , and could therefore be a first line of defence against the metabolic syndrome that commonly presages

cardiovascular disease and type 2 diabetes. This new work might stimulate the design of the next generation of ARBs that are even more potent activators of PPAR- γ . It could also form the basis for the development of new antidiabetic PPAR- γ ligands that are less likely to induce fluid retention and oedema — side effects of existing treatments caused by reflex activation of the renin-angiotensin system.

Suzanne Farley

References and links

ORIGINAL RESEARCH PAPERS Benson, S. C. *et al.* Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR γ -modulating activity. *Hypertension* **43**, 993–1002 (2004) | Schupp, M. *et al.* Angiotensin type I receptor blockers induce peroxisome proliferator-activated receptor- γ activity. *Circulation* **109**, 2054–2057 (2004)

FURTHER READING Zaman, M. A., Oparil, S. & Calhoun, D. A. Drugs targeting the renin-angiotensin-aldosterone system. *Nature Rev. Drug Discov.* **1**, 621–636 (2002)