I

n 2002, my colleagues and I suggested that blockade of the renin–angiotensin system may prevent diabetes by promoting adipogenesis, thereby allowing redistribution of fat from dangerous visceral and ectopic fat deposits to less-dangerous subcutaneous depots. This hypothesis was based on our observation that angiotensin II inhibits human preadipocyte differentiation. We subsequently demonstrated increased activity of the renin–angiotensin system in obesity and suggested, therefore, that renin-angiotensin blockade should be the treatment of choice in obesity-related hypertension.

In 2004, Benson et al reported the novel observation that the highly lipophilic angiotensin receptor blocker (ARB) telmisartan may directly stimulate the peroxisome proliferator-activated receptor γ (PPARγ), a key inducer of adipocyte differentiation. Although this property has since been also reported for irbesartan and a losartan metabolite, there is no doubt that telmisartan by 1 order of magnitude is the most powerful stimulator of PPARγ activity among the ARBs. Because thiazolidinediones, a class of even more potent PPARγ agonists (“glitazones”), are widely used as insulin sensitizers in the treatment of type 2 diabetes mellitus and promote both adipocyte proliferation and fat redistribution, the report that telmisartan may have similar glitazone-like properties led to widespread and enthusiastic speculations regarding the possible metabolic benefits of this compound. Without doubt, such a “eumetabolic” property of an antihypertensive drug would be of considerable interest, given that there is increasing evidence implicating mitochondrial dysfunction as a key player in the development of obesity, insulin resistance, and type 2 diabetes mellitus associated with sedentariness and aging. Thus, for example, the PPARγ coactivator 1α, a key determinant of adaptive thermogenesis, the regulated production of heat by burning calories in adipose tissue and skeletal muscle by stimulating the generation of mitochondria and oxidative phosphorylation, has been found to be expressed at lower levels in the healthy relatives of people with insulin resistance and diabetes. Indeed, a host of factors and pathways that can potentially affect thermogenesis and mitochondrial function have been suggested to play an important role in the pathogenesis of obesity, insulin resistance, and the metabolic syndrome. These include the steroid receptor coactivator family, the nuclear receptors PPARβ/δ, thyroid hormone receptors, estrogen-related receptors, protein kinase A, calcium/calmodulin-dependent protein kinase IV, p38 mitogen-activated protein kinase, and cyclin-dependent kinase 9 (reviewed in Reference 13). It is, therefore, not surprising that increasing mitochondrial activity has been suggested as a potential target to prevent and treat obesity and the metabolic syndrome. Physical activity and dietary restriction, the cornerstones of clinical management of the metabolic syndrome, are already known to enhance mitochondrial activity. The suggestion that telmisartan may similarly increased mitochondrial activity clearly deserves further exploration, particularly if the present findings can be confirmed in humans.

Unfortunately, there remains a dearth of information on the metabolic effects of telmisartan or other ARBs from human studies. In fact, the PPARγ activating effect of telmisartan has yet to be demonstrated in human cells, a matter of
substantial interest because there are important differences in the function of the adipocyte tissue renin-angiotensin system between rodents and humans. Thus, for example, the angiotensin II type 2 receptor, which is highly expressed on murine adipocytes and has been shown to mediate some of the proadipogenic effects of angiotensin II in murine cell lines, is virtually absent in humans. Currently, apart from the well-documented ability of angiotensin blockade in general to reduce the incidence of type 2 diabetes mellitus, the possible adipocyte-tissue effects, that may explain why blockade of the renin-angiotensin system prevents diabetes (Table).

Whether or not the PPARγ modulating effects of telmisartan discovered by Sugimoto et al will translate into greater cardiovascular and metabolic protection with this agent will certainly be the focus of much speculation until conclusive answers from clinical trials become available. A study on the effect of telmisartan on intramyocellular lipids, liver fat, and adipocyte cell size in individuals with abdominal obesity is currently underway (http://www.ClinicalTrials.gov, identifier: NCT00147264), as is a large outcome trial with this compound (ONTARGET). In the meantime, studies like the one by Sugimoto et al will continue to foster the discussions on the potential benefits of renin-angiotensin blockade in individuals with abdominal obesity and the metabolic syndrome.

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**References**

Telmisartan: The ACE of ARBs?
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