Comment on: Takeda et al. Loss of ACE2 Exaggerates High-Calorie Diet–Induced Insulin Resistance by Reduction of GLUT4 in Mice. Diabetes 2013;62:223–233

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We read with interest the recent article by Takeda et al. (1) suggesting a beneficial role of ACE type 2 (ACE2) in type 2 diabetes. We would like to share our recent observations (2) complementing this work. Takeda et al. showed that lack of ACE2 did not affect baseline glycemia, as reported previously (3), but promoted impaired glucose tolerance and insulin resistance when the mice were fed a hypercaloric diet. Surprisingly, this diet failed to increase fasting glucose, triglycerides, and blood pressure levels in all groups. Interestingly, the authors showed that when infused with angiotensin II (Ang-II) (100 ng/kg/min), only ACE2 knockout mice exhibited impaired glucose tolerance and insulin resistance. Similarly, we observed that a higher dose of Ang-II (200 ng/kg/min) led to the same results in C57Bl/6 wild-type mice and was associated with downregulation of ACE2 and upregulation of Ang-II type 1 receptors in the pancreas (2).

Takeda et al. (1) elegantly showed that the ACE2/angiotensin 1–7/Mas receptor signaling pathway is required to maintain normal insulin sensitivity in the presence of high Ang-II levels in liver and soleus muscle, extending our previous observations that ACE2 knockout mice have impaired levels of Mas receptors in the pancreas (4). Further, supporting the role of this compensatory axis, we previously reported that Mas receptor blockade prevented the beneficial effects of ACE2 gene therapy in reducing hyperglycemia in *db/db* mice (5). Moreover, we showed the benefits of maintaining physiological levels of ACE2 in the pancreas and the islets of Langerhans in order to counteract hyperglycemia in Ang-II–infused mice (2).

To unfold the mechanisms involved, Takeda et al. (1) demonstrated that regulation of myocyte enhancer factor 2A and GLUT4 expression by the ACE2/angiotensin 1–7/Mas receptor axis contribute to the improvement of insulin sensitivity. Adding to these, we observed that ACE2 improves β-cell function by counteracting Ang-II–mediated oxidative stress in the pancreas (2).

Altogether, the recent reports by Takeda et al. (1) and our group (2) support and extend previous observations (3–5) suggesting the therapeutic potential of ACE2 to control type 2 diabetes. Hence, strategies to restore ACE2 activity in diabetes need to be further investigated in order to utilize the beneficial effects of ACE2 in the regulation of glycemia.

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