Response to 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 thank Dr. Chhabra and Dr. Lazartigues for their thoughtful comments on the role of ACE type 2 (ACE2) in glycemic control (1). In *db/db* mice or in C57Bl/6J mice infused with angiotensin II, their group has shown that ACE2 can help protect against hyperglycemia by promoting pancreatic insulin secretion (2,3). We found that deficiency of ACE2 causes impaired insulin sensitivity of mice treated with angiotensin II infusion or a high-calorie diet (4). Thus, ACE2 appears to play a multifunctional role in maintaining glucose homeostasis by regulating both insulin secretion and insulin sensitivity.

The counterregulating action of ACE2 in the renin-angiotensin system is characterized by reduction of angiotensin II and production of angiotensin 1–7. The significance of reducing angiotensin II signaling in improvement of insulin sensitivity has been established by many studies including several clinical trials showing that angiotensin II type 1 receptor blockers (ARBs) and ACE inhibitors can reduce the risk of new-onset diabetes (5). One of the goals of our study was to determine whether production of angiotensin 1–7 by ACE2 could have additive effects on insulin sensitivity and glucose homeostasis. We found that compared with wild-type (WT) mice, ACE2 knockout (KO) mice exhibited exaggerated insulin resistance and glucose intolerance in response to angiotensin II infusion or a high-calorie diet. The metabolic effects of ACE2 ablation were abolished by administering an ARB in combination with angiotensin 1–7, but not by administering an ARB alone (4). Interestingly, ACE2 KO mice exhibited marked reduction of GLUT4 protein levels in skeletal muscle and adipose tissue, even when the mice were fed with a standard diet and had normal insulin sensitivity. The protein level of GLUT4 was regulated by angiotensin 1–7 in skeletal muscle, as GLUT4 and myocyte enhancer factor 2A (MEF2A), a gene important in GLUT4 mRNA transcription, were increased by angiotensin 1–7 in ACE2 KO mice and reduced by an angiotensin 1–7 inhibitor in WT mice. Consistent with our findings, Santos et al. (6) reported that GLUT4 protein was reduced in adipose tissue of Mas-deficient FVB/N mice that were insulin resistant.

The importance of ACE2-mediated angiotensin 1–7 production in maintaining glucose homeostasis is also supported by the work of Lazartigues and colleagues (2), which shows that improvement of glucose tolerance and insulin secretion by pancreatic ACE2 gene therapy in obese *db/db* mice was abolished by administration of an angiotensin 1–7 inhibitor. Thus, multiple lines of evidence indicate that angiotensin 1–7 production by ACE2 helps to maintain glucose homeostasis through mechanisms that involve more than just the simple counterregulation of angiotensin II signaling. Taken together, these findings could have implications for the development of anti-hyperglycemic therapies that work by activating the ACE2/angiotensin 1–7/Mas axis.

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REFERENCES

1. Chhabra KH, Lazartigues E. 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 (Letter). Diabetes 2013;62:e9. DOI: 10.2337/db13-0389
2. Bindom SM, Hans CP, Xia H, Boulares AH, Lazartigues E. Angiotensin I-converting enzyme type 2 (ACE2) gene therapy improves glycemic control in diabetic mice. Diabetes 2010;59:2540–2548
3. Chhabra KH, Xia H, Pedersen KB, Speth RC, Lazartigues E. Pancreatic angiotensin-converting enzyme 2 improves glycemia in angiotensin II-infused mice. Am J Physiol Endocrinol Metab 2013;304:E874–E884
4. Takeda M, Yamamoto K, Takemura Y, et al. Loss of ACE2 exaggerates high-calorie diet-induced insulin resistance by reduction of GLUT4 in mice. Diabetes 2013;62:223–233
5. Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. Mol Cell Endocrinol 2009;302:193–202
6. Santos SH, Fernandes LR, Mario EG, et al. Mas deficiency in FVB/N mice produces marked changes in lipid and glycemic metabolism. Diabetes 2008;57:340–347

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