

# ACE2 and Diabetes: ACE of ACEs?

Daniel Batlle,<sup>1</sup> Maria Jose Soler,<sup>2</sup> and Minghao Ye<sup>1</sup>

**T**he mechanisms involved in the development of diabetes and its complications are complex, with a long list of potential derangements on different pathways (1,2). In this commentary, we discuss angiotensin converting enzyme 2 (ACE2) as a potential participant in the development of both islet  $\beta$ -cell insufficiency early on and in the development of nephropathy later.

ACE has long been recognized as the key enzyme within the renin-angiotensin system (RAS) mainly by cleaving angiotensin (Ang I) to form Ang II, which is the main active peptide within the system. ACE2, a homologue of ACE, is a monocarboxypeptidase that preferentially removes carboxy-terminal amino acids from various substrates, including Ang II, Ang I, and apelin (3–6). ACE2 cleaves Ang II to form Ang-(1-7) with a high catalytic efficiency, suggesting an important role in preventing Ang II accumulation, while enhancing Ang-(1-7) formation (7) (Fig. 1). Other mammalian homologues of ACE, such as collectrin and, more recently, ACE3, have also been described (8). ACE2, however, is the only known homologue of ACE with enzymatic activity (3–5).

In the kidney, ACE2 colocalizes with ACE on the apical surface area of the proximal tubules and is also localized in the glomerulus (9). In the pancreas, ACE2 was found to be localized to acini and islets following a similar distribution to that of ACE (10). In rodent models of diabetes, pharmacological inhibition of ACE2 (9,11) and genetic ablation (12) have both been shown to worsen albuminuria and the associated glomerular lesions. Moreover, decreased glomerular expression of ACE2 has been described in rodent models of diabetes (9) and in human kidney biopsies from patients with diabetic nephropathy (13). Accordingly, ACE2 has been proposed as a target for therapies aimed at increasing the activity of this enzyme as a way to treat diabetic kidney disease (9,14) (Fig. 1).

In ACE2 deficient mice, alterations in glucose tolerance and reduced first-phase insulin secretion have been described, suggesting a potential role of ACE2 in the development of diabetes (15). Collectrin, another homologue of ACE, has also been shown to be expressed in  $\beta$ -cells of the pancreas, and although its function is unknown, it could also be implicated in insulin secretion and  $\beta$ -cell proliferation (16). Much like in the kidney, the pancreas expresses

key components of a local angiotensin peptide generating system as described by Chappell et al. (17) almost 2 decades ago. These authors found Ang II to be the predominant angiotensin peptide in the pancreas, with lower levels of Ang-(1-7) and low to nondetectable levels of Ang I. The effects of Ang II in the pancreas could be counterbalanced by Ang-(1-7), as it has been proposed to do in the kidneys and other tissues (18). The levels of both peptides in the pancreas were several-fold higher than those observed in the plasma (17). Carlsson et al. (19) later found that Ang II can delay insulin secretion and reduces blood flow in the islets of Langerhans in a dose-dependent manner. Consistent with this effect of Ang II, blockade of RAS with either ACE inhibitors or Ang II receptor antagonists increases islet blood flow (19). Moreover, these agents have been shown to attenuate pancreatic inflammation and fibrosis (20). Also of note is the finding of Tikellis et al. (10) that RAS blockade in the Zucker diabetic fatty (ZDF) rat not only reduced islet fibrosis, but also improved structural parameters in association with improvement in first-phase insulin secretion. These findings are particularly relevant given clinical evidence that RAS blockade may be associated with reduced incidence of new-onset type 2 diabetes (21). Although recent trials have called these results into question (22), there are ongoing studies specifically designed to demonstrate that blockade of the RAS helps prevent the development of type 2 diabetes.

In the October issue of *Diabetes*, Bindom et al. (23) report studies examining ACE2 gene therapy in the *db/db* model of type 2 diabetes. ACE2 gene therapy targeting the islet cells through the use of adenoviral vectors increased pancreatic ACE2 expression and activity in both *db/db* and *db/m* mice, with a peak occurring 7 days after infection. Prior to gene therapy at 8 weeks of age, pancreatic ACE2 was increased in the *db/db* mice. This finding is consistent with a previous report by Tikellis et al. (10) in the ZDF rat model of type 2 diabetes in which ACE as well as AT<sub>1</sub> receptor expression was increased. It is likely that the increase in ACE2 was an adaptive effort to counter ACE overactivity. ACE2 gene therapy in the *db/db* mice resulted in improved fasting blood glucose levels and glucose tolerance (23). An increase in first-phase insulin secretion and  $\beta$ -cell proliferation, as well as a reduction in  $\beta$ -cell apoptosis when compared with *db/db* mice receiving control adenoviral infection were also observed (23).

Unlike at 8 weeks of age, at 16 weeks of age *db/db* mice showed a decrease in pancreatic ACE2 mRNA expression. Also of note, 16-week-old *db/db* mice had much more severe diabetes than the younger group, as indicated by higher levels of fasting glucose, and they benefited much less from ACE2 gene therapy, showing no improvement in glucose tolerance, first-phase insulin secretion,  $\beta$ -cell proliferation, or apoptosis (23). Possibly, by 16 weeks of age it is too late to intervene with ACE2 therapies because significant  $\beta$ -cell failure may not be readily reversible. It will be of interest to study whether increasing ACE2

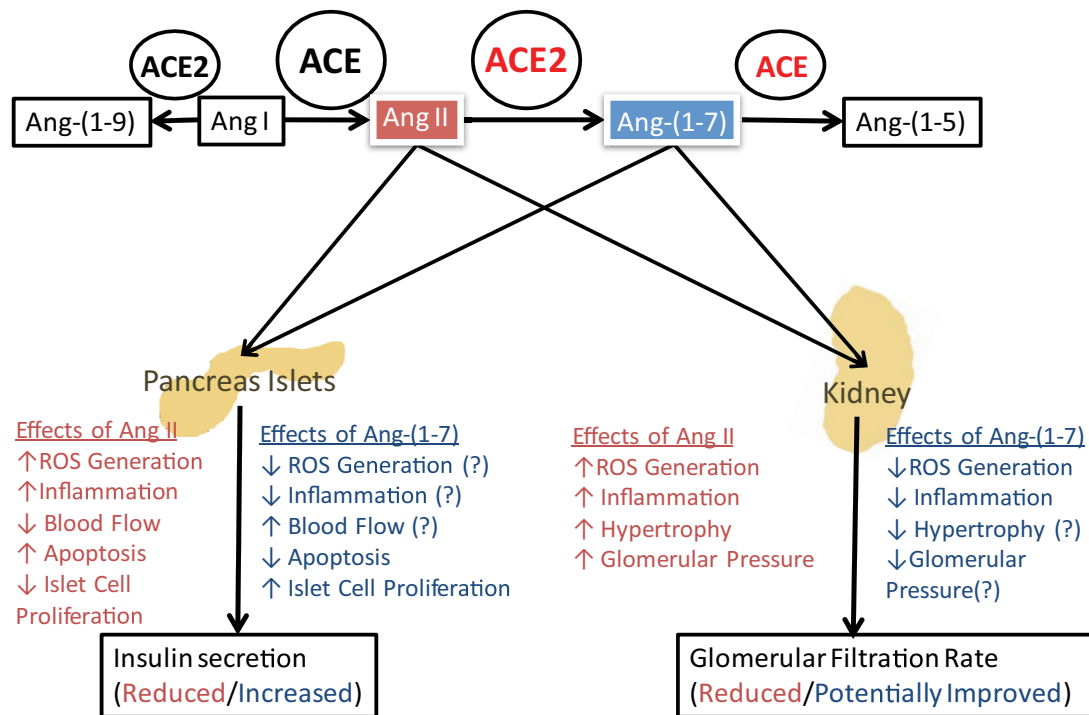
From the <sup>1</sup>Division of Nephrology and Hypertension, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, Illinois; and the <sup>2</sup>Nephrology Department, Hospital del Mar, Fundacio IMIM, Parc de Salut Mar, Barcelona, Spain.

Corresponding author: Daniel Batlle, d-batlle@northwestern.edu.

DOI: 10.2337/db10-1205

© 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

**See accompanying original article, published in *Diabetes* 2010;59:2540–2548.**



**FIG. 1.** Potential therapeutic role of ACE2 amplification in diabetes, both at the level of the pancreatic islets and at that of the kidney. ACE2 amplification leads to reduced Ang II overactivity and increased Ang-(1-7) activity. Please note that the actions of ACE2 on angiotensin peptides are just the opposite of those of ACE, which promotes Ang II formation while increasing Ang-(1-7) degradation. In general, the effects of Ang-(1-7) (blue) are less well documented (as reflected by the question marks) than those of Ang II (red). It is possible that the benefits of ACE2 amplification result largely from reduced ACE2 overactivity and not so much from increased Ang-(1-7) activity, but that needs to be further studied. There are also potential effects of Ang-(1-7) on insulin sensitivity (not shown).

activity early on can improve insulin secretion in models of type 1 diabetes such as the NOD mice and therefore help prevent or delay the onset of the disease.

How could ACE and its homologues be involved in the development of diabetes? The most obvious possibility is that ACE and ACE2, by regulating the levels of Ang II and/or Ang-(1-7) in pancreatic islets, are involved in the control of insulin secretion to the extent that blood flow is influenced by local levels of angiotensin peptides as noted above. Other effects of these peptides relevant to insulin secretion in islet cells are listed in the figure. Similar actions of these peptides at the kidney level may determine the fate of the decline in glomerular filtration rate at later phases of diabetes. It should be noted that, unlike insulin secretion, insulin sensitivity did not improve after ACE2 gene therapy in the *db/db* model at either 8 or 16 weeks of age (23). This lack of effect is somewhat unexpected because ACE2 overexpression should increase Ang-(1-7) levels, as recently shown after recombinant ACE2 protein administration (7). Ang-(1-7) has been shown to increase insulin sensitivity (24), and moreover, mice with genetic ablation of the Mas receptor, on which Ang-(1-7) acts, develop features of metabolic syndrome, including hyperinsulinemia and impaired glucose tolerance (25). The finding that  $\beta$ -cell function improvement by ACE2 overexpression was attenuated when a Mas-receptor blocker was given, suggests, at least in part, mediation by Ang-(1-7) (23).

In summary, ACE2 may play a pivotal role in diabetes: in the pancreas, a relative deficiency of ACE2 as the disease progresses may contribute to decreased insulin secretion, whereas in the kidney glomerulus it may foster proteinuria, as a result of both impaired degradation of Ang II and the attendant Ang II accumulation locally. The findings of

Bindom et al. (23) that ACE2 overexpression by means of adenoviral gene delivery can improve pancreatic islet  $\beta$ -cell function in *db/db* mice are exciting and are in keeping with an important role of ACE2 as a therapeutic target for diabetic kidney disease and several other conditions in which overactivity of Ang II is undesirable. ACE2, by fostering the degradation of Ang II and the formation of Ang-(1-7), may have beneficial effects on both the kidney and pancreas (Fig. 1). ACE2 truly seems to be the “good” ACE, and therapies aimed at amplifying its activity should be explored in the prevention and treatment of diabetes and its complications.

#### ACKNOWLEDGMENTS

D.B. has active grant support from the National Institute of Diabetes and Digestive Kidney Diseases (Grant 1R01DK080089–01A2) and the Juvenile Diabetes Research Foundation. M.J.S. has grant support from Fondo de Investigación Sanitaria Instituto Carlos III, Spain. D.B. has a pending patent application entitled “Methods for achieving a protective ACE2 expression level to treat kidney disease and hypertension.”

No potential conflicts of interest relevant to this article were reported.

We thank Mirza Khan of Northwestern University for help in the preparation of this commentary.

#### REFERENCES

1. Leahy JL. Mary, Mary, quite contrary, how do your  $\beta$ -cells fail? *Diabetes* 2008;57:2563–2564
2. Luo X, Herold KC, Miller SD. Immunotherapy of type 1 diabetes: where are we and where should we be going? *Immunity* 2010;32:488–499
3. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. A

- novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. *Circ Res* 2000;87:E1–E9
4. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveira-dos-Santos AJ, da Costa J, Zhang L, Pei Y, Scholey J, Ferrario CM, Manoukian AS, Chappell MC, Backx PH, Yagil Y, Penninger JM. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature* 2002;417:822–828
  5. Turner AJ, Hooper NM. The angiotensin-converting enzyme gene family: genomics and pharmacology. *Trends Pharmacol Sci* 2002;23:177–183
  6. Kalea AZ, Battle D. Apelin and ACE2 in cardiovascular disease. *Curr Opin Investig Drugs* 2010;11:273–282
  7. Wysocki J, Ye M, Rodriguez E, González-Pacheco FR, Barrios C, Evora K, Schuster M, Loibner H, Brosnihan KB, Ferrario CM, Penninger JM, Battle D. Targeting the degradation of angiotensin II with recombinant angiotensin-converting enzyme 2: prevention of angiotensin II-dependent hypertension. *Hypertension* 2010;55:90–98
  8. Battle D, Soler MJ, Wysocki J. New aspects of the renin-angiotensin system: angiotensin-converting enzyme 2: a potential target for treatment of hypertension and diabetic nephropathy. *Current Opinion in Nephrology and Hypertension* 2008;17:250–257
  9. Ye M, Wysocki J, William J, Soler MJ, Cokic I, Battle D. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. *J Am Soc Nephrol* 2006;17:3067–3075
  10. Tikellis C, Wookey PJ, Candido R, Andrikopoulos S, Thomas MC, Cooper ME. Improved islet morphology after blockade of the renin-angiotensin system in the ZDF rat. *Diabetes* 2004;53:989–997
  11. Soler MJ, Wysocki J, Ye M, Lloveras J, Kanwar Y, Battle D. ACE2 inhibition worsens glomerular injury in association with increased ACE expression in streptozotocin-induced diabetic mice. *Kidney Int* 2007;72:614–623
  12. Wong DW, Oudit GY, Reich H, Kassiri Z, Zhou J, Liu QC, Backx PH, Penninger JM, Herzenberg AM, Scholey JW. Loss of angiotensin-converting enzyme-2 (ACE2) accelerates diabetic kidney injury. *Am J Pathol* 2007;171:438–451
  13. Reich HN, Oudit GY, Penninger JM, Scholey JW, Herzenberg AM. Decreased glomerular and tubular expression of ACE2 in patients with type 2 diabetes and kidney disease. *Kidney Int* 2008;74:1610–1616
  14. Oudit GY, Liu GC, Zhong J, Basu R, Chow FL, Zhou J, Loibner H, Janzek E, Schuster M, Penninger JM, Herzenberg AM, Kassiri Z, Scholey JW. Human recombinant ACE2 reduces the progression of diabetic nephropathy. *Diabetes* 2010;59:529–538
  15. Niu MJ, Yang JK, Lin SS, Ji XJ, Guo LM. Loss of angiotensin-converting enzyme 2 leads to impaired glucose homeostasis in mice. *Endocrine* 2008;34:56–61
  16. Akpinar P, Kuwajima S, Krützfeldt J, Stoffel M. Tmem27: a cleaved and shed plasma membrane protein that stimulates pancreatic beta cell proliferation. *Cell Metabolism* 2005;2:385–397
  17. Chappell MC, Millsted A, Diz DI, Brosnihan KB, Ferrario CM. Evidence for an intrinsic angiotensin system in the canine pancreas. *J Hypertens* 1991;9:751–759
  18. Ferrario CM, Trask AJ, Jessup JA. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1–7) in regulation of cardiovascular function. *Am J Physiol Heart Circ Physiol* 2005;289:H2281–H2290
  19. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. *Diabetologia* 1998;41:127–133
  20. Kuno A, Yamada T, Masuda K, Ogawa K, Sogawa M, Nakamura S, Nakazawa T, Ohara H, Nomura T, Joh T, Shirai T, Itoh M. Angiotensin-converting enzyme inhibitor attenuates pancreatic inflammation and fibrosis in male Wistar Bonn/Kobori rats. *Gastroenterology* 2003;124:1010–1019
  21. Cooper ME, Tikellis C, Thomas MC. Preventing diabetes in patients with hypertension: one more reason to block the renin-angiotensin system. *J Hypertens Suppl* 2006;24:S57–S63
  22. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW, PROFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008;359:1225–1237
  23. 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
  24. Giani JF, Mayer MA, Muñoz MC, Silberman EA, Höcht C, Taira CA, Gironacci MM, Turyn D, Dominici FP. Chronic infusion of angiotensin-(1–7) improves insulin resistance and hypertension induced by a high-fructose diet in rats. *Am J Physiol Endocrinol Metab* 2009;296:E262–E271
  25. Santos SH, Fernandes LR, Mario EG, Ferreira AV, Pôrto LC, Alvarez-Leite JL, Botion LM, Bader M, Alenina N, Santos RA. Mas deficiency in FVB/N mice produces marked changes in lipid and glycemic metabolism. *Diabetes* 2008;57:340–347