

GPR40: Good Cop, Bad Cop?

Thierry Alquier and Vincent Poitout

Since its deorphanization in 2003 (1,2), the fatty acid receptor GPR40 (FFAR1/FFA1) has drawn considerable attention as a potential therapeutic target for type 2 diabetes. Because fatty acids acutely amplify insulin secretion only in the presence of glucose, the discovery of a “drugable” cell surface receptor whose activation glucose-dependently enhances insulin release generated much interest in the pharmaceutical industry. The study by Nagasumi et al. (3) in this issue of *Diabetes* provides support for the notion that activation of GPR40 improves glucose tolerance and may thereby be beneficial for the treatment of type 2 diabetes.

GPR40 is a G protein-coupled receptor highly expressed in β -cells and activated by long-chain fatty acids (1,2). Loss of function of GPR40 via small interfering RNA (2,4–6), antisense oligonucleotides (7), pharmacological inhibition (8), or gene deletion (9,10) has shown that GPR40 mediates, at least in part, fatty acid potentiation of glucose-induced insulin secretion. Although the role of GPR40 in the acute effects of fatty acid is relatively well established, its potential contribution to chronic deleterious effects of fatty acids on β -cell function has remained controversial. This question has important implications because a potential contribution of GPR40 to β -cell dysfunction would preclude the development of GPR40 agonists as therapeutic agents. Nagasumi et al. (3) generated a transgenic mouse overexpressing the human GPR40 gene under the mouse insulin II promoter (hGPR40 transgenic mice). GPR40 overexpression did not affect the metabolic status of the animals under fed conditions, but it was associated with lower fasting blood glucose. hGPR40 transgenic mice showed markedly improved oral glucose tolerance and insulin secretion without changes in insulin tolerance. These results contradict those of Steneberg et al. (9), who reported that GPR40 knockout mice were protected from high-fat diet-induced insulin resistance and glucose intolerance and that overexpression of GPR40 under the pancreatic and duodenal homeobox factor 1 (PDX-1) promoter led to impaired insulin secretion and diabetes. These authors concluded that excessive activation of GPR40, either by high-fat diet or overexpression of the receptor, is detrimental to β -cell function (9). Similar findings were obtained by another group using a different knockout strain (11). In contrast, subsequent studies also using whole-body knockout found

that GPR40 deletion did not protect mice from high-fat diet-induced glucose intolerance (12,13). This conclusion was further supported by the observation that small-molecule GPR40 agonists improved glucose tolerance in mice with high-fat diet-induced obesity (14).

Why such extreme discrepancies? We see three possible reasons for the differences in phenotypes of transgenic mice between the study of Steneberg et al. (9) and that of Nagasumi et al. (3). First, the levels of overexpression of the receptor were different: 20- to 100-fold in Steneberg et al. (9) versus 10-fold in Nagasumi et al. (3). Second, the PDX-1 promoter used by Steneberg et al. (9) also drives expression in non- β -cells, whereas expression of the mouse insulin II promoter is essentially restricted to β -cells. However, it has not been conclusively ruled out that these promoters also have activity in the hypothalamus, which could influence the transgenic phenotype. Finally, it is conceivable that transgenic expression during embryonic development under the PDX-1 promoter might have affected islet morphogenesis. Indeed, the transgenic line in the Steneberg et al. (9) study showed disorganized islet architecture and decreased insulin content (9), whereas Nagasumi et al. (3) did not observe changes in islet morphology or β -cell mass. Less clear to us are the reasons for the differences in the responses to high-fat diet among different GPR40 knockout lines reported in the literature, although we suspect the genetic background to be a critical variable.

Nagasumi et al. (3) further showed that GPR40 overexpression prevents the development of hyperglycemia in high-fat diet-fed hGPR40 transgenic mice. Expression of the transgene in the diabetic KK background resulted in improved insulin secretion and glucose tolerance without changes in body weight. These findings raise three important points. First, overexpression of GPR40 is sufficient to restore insulin secretion in a diabetic model. Second, it does not appear to induce lipotoxicity. This is consistent with our previous observation, that islets from GPR40 knockout mice are not protected from fatty acid inhibition of insulin secretion after prolonged exposure (10), and with that of Tan et al. (14), who showed that culture of islets in the presence of a GPR40 agonist does not impair insulin secretion. Third, the data from Nagasumi et al. (3) support a role for GPR40 in the mechanisms of β -cell compensation for insulin resistance. Consistent with our observation that GPR40 knockout mice on a high-fat diet develop fasting hyperglycemia sooner than their wild-type littermates (12), Nagasumi et al. (3) now demonstrate that overexpression of the receptor enables β -cells to more effectively compensate for insulin resistance. This has important implications for our understanding of the pathogenesis of β -cell failure (Fig. 1). Based on their observations, Steneberg et al. (9) suggested that chronic fatty acid-induced hyperinsulinemia induces insulin resistance, which is prevented by GPR40 deletion (Fig. 1A). In contrast, the results of Nagasumi et al. (3) and others (12–14) support the notion that fatty acid-induced hyperinsulinemia represents a mechanism by which the β -cell compensates for insulin resistance and that this ability is compromised by

From the Montreal Diabetes Research Center, Research Center of the University of Montreal Hospital Center (CRCHUM), and Department of Medicine, University of Montreal, Montreal, Quebec, Canada.

Corresponding author: Vincent Poitout, vincent.poitout@umontreal.ca.

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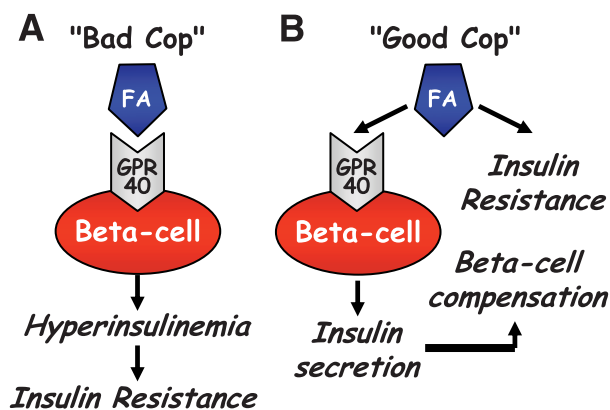


FIG. 1. Two alternative hypotheses on the mechanisms behind lipid-induced insulin resistance and β -cell compensation. **A:** According to Steneberg et al. (9), the GPR40-mediated increase in insulin secretion in response to high-fat diet causes insulin resistance. **B:** In contrast, previous reports (12,13,15) and the findings of Nagasumi et al. (3) suggest that the lipid-induced GPR40-mediated increase in insulin secretion contributes to β -cell compensatory response. FA, fatty acid.

GPR40 deletion (Fig. 1B). Importantly, this concept is supported by the observation that a loss-of-function mutation of the GPR40 gene in humans is associated with altered insulin secretion (15). Although the validity of therapeutic approaches consisting of enhancing insulin secretion in type 2 diabetes is a matter of debate (16), we believe that most available evidence, including the study discussed herein (3), favors the view that GPR40-mediated fatty acid induction of insulin secretion is part of the β -cell compensatory response.

In conclusion, the study by Nagasumi et al. (3) supports the concept that activation of GPR40 might be a suitable therapeutic strategy to improve insulin secretion and glucose tolerance in type 2 diabetes. Clearly, several questions remain to be answered before GPR40 agonists further progress down the path of drug development. First, prolonged activation of the receptor may lead to down-regulation and loss of potency. Second, the mechanisms of action of GPR40 remain to be fully characterized. Third, GPR40 expression has been detected in non- β -cells, e.g., ileum (1,2), monocytes (1), pancreatic α -cells (17), some areas of the brain (1,18), entero-endocrine cells (19), and osteoclasts (20), and its function in these tissues is essentially unknown. Finally, the potential contribution of other long-chain fatty acid receptors expressed in the β -cell remains to be examined.

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REFERENCES

1. Briscoe CP, Tadayyon M, Andrews JL, Benson WG, Chambers JK, Eilert MM, Ellis C, Elshourbagy NA, Goetz AS, Minnick DT, Murdock PR, Sauls

- HR Jr, Shabon U, Spinage LD, Strum JC, Szekeres PG, Tan KB, Way JM, Ignar DM, Wilson S, Muir AL. The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. *J Biol Chem* 2003;278:11303–11311
2. Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y, Uejima H, Tanaka H, Maruyama M, Satoh R, Okubo S, Kizawa H, Komatsu H, Matsumura F, Noguchi Y, Shinohara T, Hinuma S, Fujisawa Y, Fujino M. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* 2003;422:173–176
3. Nagasumi K, Esaki R, Iwachidow K, Yasuhara Y, Ogi K, Tanaka H, Nakata M, Yano T, Shimakawa K, Taketomi S, Takeuchi K, Odaka H, Kaisho Y: Overexpression of GPR40 in pancreatic β -cells augments glucose-stimulated insulin secretion and improves glucose tolerance in normal and diabetic mice. *Diabetes* 2009;58:1067–1076
4. Shapero H, Shachar S, Sekler I, Hershinkel M, Walker MD. Role of GPR40 in fatty acid action on the beta cell line INS-1E. *Biochem Biophys Res Commun* 2005;335:97–104
5. Itoh Y, Hinuma S. GPR40, a free fatty acid receptor on pancreatic beta cells, regulates insulin secretion. *Hepatology* 2005;33:171–173
6. Schnell S, Schaefer M, Schöfl C. Free fatty acids increase cytosolic free calcium and stimulate insulin secretion from beta-cells through activation of GPR40. *Mol Cell Endocrinol* 2007;263:173–180
7. Salehi A, Flodgren E, Nilsson NE, Jimenez-Felstrom J, Miyazaki J, Owman C, Olde B. Free fatty acid receptor 1 (FFA1R/GPR40) and its involvement in fatty-acid-stimulated insulin secretion. *Cell Tissue Res* 2005;322:207–215
8. Briscoe CP, Peat AJ, McKeown SC, Corbett DF, Goetz AS, Littleton TR, McCoy DC, Kenakin TP, Andrews JL, Ammala C, Fornwald JA, Ignar DM, Jenkinson S. Pharmacological regulation of insulin secretion in MIN6 cells through the fatty acid receptor GPR40: identification of agonist and antagonist small molecules. *Br J Pharmacol* 2006;148:619–628
9. Steneberg P, Rubins N, Bartoov-Shifman R, Walker MD, Edlund H. The FFA receptor GPR40 links hyperinsulinemia, hepatic steatosis, and impaired glucose homeostasis in mouse. *Cell Metab* 2005;1:245–258
10. Latour MG, Alquier T, Oseid E, Tremblay C, Jetton TL, Luo J, Lin DC, Poitout V. GPR40 is necessary but not sufficient for fatty acid stimulation of insulin secretion in vivo. *Diabetes* 2007;56:1087–1094
11. Brownlie R, Mayers RM, Pierce JA, Marley AE, Smith DM. The long-chain fatty acid receptor, GPR40, and glucolipotoxicity: investigations using GPR40-knockout mice. *Biochem Soc Trans* 2008;36:950–954
12. Kebede M, Alquier T, Latour MG, Semache M, Tremblay C, Poitout V. The fatty acid receptor GPR40 plays a role in insulin secretion in vivo after high-fat feeding. *Diabetes* 2008;57:2432–2437
13. Lan H, Hoos LM, Liu L, Tetzloff G, Hu W, Abbondanzo SJ, Vassileva G, Gustafson EL, Hedrick JA, Davis HR. Lack of FFAR1/GPR40 does not protect mice from high-fat diet-induced metabolic disease. *Diabetes* 2008;57:2999–3006
14. Tan CP, Feng Y, Zhou YP, Eiermann GJ, Petrov A, Zhou C, Lin S, Salituro G, Meinke P, Mosley R, Akiyama TE, Einstein M, Kumar S, Berger JP, Mills SG, Thornberry NA, Yang L, Howard AD. Selective small-molecule agonists of G protein-coupled receptor 40 promote glucose-dependent insulin secretion and reduce blood glucose in mice. *Diabetes* 2008;57:2211–2219
15. Vettor R, Granzotto M, De Stefani D, Trevisan E, Rossato M, Farina MG, Milan G, Pilon C, Nigro A, Federspil G, Vigneri R, Vitiello L, Rizzuto R, Baratta R, Frittitta L. Loss-of-function mutation of the GPR40 gene associates with abnormal stimulated insulin secretion by acting on intracellular calcium mobilization. *J Clin Endocrinol Metab* 2008;93:3541–3550
16. Aston-Mourning K, Proietto J, Morahan G, Andrikopoulos S. Too much of a good thing: why it is bad to stimulate the beta cell to secrete insulin. *Diabetologia* 2008;51:540–545
17. Flodgren E, Olde B, Meidute-Abaraviciene S, Winzell MS, Ahren B, Salehi A. GPR40 is expressed in glucagon producing cells and affects glucagon secretion. *Biochem Biophys Res Commun* 2007;354:240–245
18. Ma D, Lu L, Boneva NB, Warashina S, Kaplamadzhiev DB, Mori Y, Nakaya MA, Kikuchi M, Tonchev AB, Okano H, Yamashita T. Expression of free fatty acid receptor GPR40 in the neurogenic niche of adult monkey hippocampus. *Hippocampus* 2008;18:326–333
19. Edfalk S, Steneberg P, Edlund H. Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. *Diabetes* 2008;57:2280–2287
20. Cornish J, MacGibbon A, Lin JM, Watson M, Callon KE, Tong PC, Dunford JE, van der Does Y, Williams GA, Grey AB, Naot D, Reid IR. Modulation of osteoclastogenesis by fatty acids. *Endocrinology* 2008;149:5688–5695