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Viewpoint

Pancreatic β-cell: the beauty of being plastic

Ernest Adeghate

Email: eadeghate@uaeu.ac.ae

Type 2 diabetes mellitus (T2DM) is a chronic endocrine disorder affecting more than 240 million people worldwide. The prevalence of T2DM continues to rise in many parts of the world, partly because a lot of people are enslaved to a sedentary lifestyle and inappropriate diet. Genetic factors also play a role in whether an individual develops T2DM or not. A strong interaction between genetic and environmental factors in the development of T2DM has been reported (Adeghate *et al.* 2006). Irrespective of which factor is to be blamed, the key molecule in the pathogenesis of T2DM is insulin. It is a major hormone of the endocrine pancreas that plays an important role in the metabolism of carbohydrate, but also has a say in how protein and fat are utilized.

Optimal insulin secretion and action are crucial to the maintenance of normoglycaemia. In the absence of intact and adequate insulin, an individual is condemned to developing T2DM. What, then, is the driving force behind the secretion and effective insulin molecule? The pancreatic β-cell of the islets of Langerhans must be viable and in sufficient numbers and mass to be able to produce intact insulin in adequate quantities. An ideal pancreatic β-cell that will not put an individual in danger of developing T2DM must also be smart enough to adapt to the variations in the level of blood glucose in a timely and calibrated manner. It must also be able to maintain normoglycaemia during a variety of endeavours ranging from intense physical activity to fasting. The plasticity of insulin release in different metabolic conditions has been examined largely in small animal models (Del Zotto *et al.* 2004; Alonso *et al.* 2007). However, the mechanism by which insulin plasticity is executed is complex and has been poorly understood.

The article by Gartford *et al.* (2012) in the May issue of *Experimental Physiology* used sheep, a large-animal model, to examine the mechanisms of insulin plasticity. This is the first time that a large-animal model, with a semblance of human size, has been used to investigate how pancreatic β-cell plasticity is achieved. Gatford *et al.* (2012) provide compelling evidence that the sheep model adapted to 16 days of continuous, moderate hyperglycaemia by increasing glucose and arginine-induced insulin release rather than initiating an increase in pancreatic cell mass. Their findings were supported by techniques such as steady-state infusion, immunofluorescence (for β-cell mass) and radioimmunoassay (for insulin). Insulin sensitivity, blood glucose level, glucose tolerance, body composition and growth of several organs were also determined. This novel observation contradicts previous reports, where large and significant increases in pancreatic β-cell mass were observed after rodent models were challenged with hyperglycaemia (Alonso et *al.* 2007).

The article by Gatford *et al.* (2012) shows that pancreatic β-cells are smarter than previously thought, because they respond to chronic glucose challenge by working more efficiently rather than initiating an increase in number. This appears to make sense, because it is physiologically easier for the body to handle variations in function than accumulated cell mass. What would the islet do with the extra pancreatic β-cells when the individual is fasting or exposed to low glucose levels?

More importantly, Gatford *et al.* (2012) showed, for the first time, that insulin sensitivity was not altered in the course of chronic glucose challenge. This is in sharp contrast to reports on rodent models, where a significant decrease in insulin sensitivity was observed after a glucose load (Topp *et al.* 2004).

This is a change in paradigm in the way the plasticity of the pancreatic β-cell is viewed. The conclusion of the study has a wider ramification, because plasticity has also been observed in other cell types. It is well known that neurons can adapt to different environmental conditions and produce novel transmitters if and when challenged by a new *millieu*.

What could be the way forward in further exploring the mechanism(s) by which pancreatic β-cells adapt to changes in the level of blood glucose? The limit of the plasticity of pancreatic β-cells will also be of interest in future studies. For example, how would the β-cell respond in an environment of constant and severe hyperglycaemia, ageing and many other epigenetic and environmental factors? A look at a different animal model may also be helpful in the search for a better understanding of the plasticity of pancreatic β-cells. The sheep is a ruminant and may therefore, not experience the wide variations in blood glucose concentrations seen in humans, because of a constant and trickle supply of energy substrates from the gastrointestinal tract. The use of pig might be a preferred model because they are omnivores, have a similar size and eat sporadically like humans.

The study by Gatford *et al.* (2012) shows that further research into the mechanism of pancreatic β-cell plasticity will probably focus more on the functional aspect of insulin release and its effect on target cells rather than on an increase in cell mass. Transcriptomic, proteomic and/or peptidomic approaches that examine the nature and function of genes expressed and of proteins/peptides released by pancreatic β-cells after exposure to chronic hyperglycaemia may be used to address the molecular basis of the issues raised in this valuable sheep model.

References

Adeghate E, Schattner P & Dunn E (2006). An update on the etiology and epidemiology of diabetes mellitus. *Ann N Y Acad Sci* **1084**, 1–29.

Alonso LC, Yokoe T, Zhang P, Scott DK, Kim SK, O'Donnell CP & Garcia-Ocaña A (2007). Glucose infusion in mice: a new model to induce β-cell replication. *Diabetes* **56**, 1792–1801.

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Del Zotto H, Borelli MI, Flores L, García ME, Gómez Dumm CL, Chicco A, Lombardo YB & Gagliardino JJ (2004). Islet neogenesis: an apparent key component of long-term pancreas adaptation to increased insulin demand. *J Endocrinol* **183**, 321–330.

Gatford KL, De Blasio MJ, How TA, Harland ML, Summers-Pearce BL & Owens JA (2012). Testing the plasticity of insulin secretion and β-cell function *in vivo*: responses to chronic hyperglycaemia in the sheep. *Exp Physiol* **97**, 663–675.

Topp BG, McArthur MD & Finegood DT (2004). Metabolic adaptations to chronic glucose infusion in rats. *Diabetologia* **47**, 1602–1610.