body. Hence, cells highly dependent on mitochondrial oxidative phosphorylation require the greatest degree of metabolic flexibility to maintain ATP generation. However, ultimately, despite many backstops, these highly-metabolic tissues are susceptible to changes in fuel and oxygen uptake, manufacture, and delivery. There is clear evidence that the factor PGC1∝ is linked to cellular resilience and likely to metabolic flexibility. PGC-1∝ stimulates mitochondrial biogenesis and metabolically polarises cells to a more-oxidative and less-glycolytic phenotype. Not surprisingly, PGC-1∝ is being considered as a pharmacological target in the treatment of obesity and type 2 diabetes [9].

In the paper by Tran *et al.* there is accumulation of FAs in kidneys damaged by ischaemia, which is exacerbated with PGC1∝ knockout and reversed by restoring cellular NAD concentrations [2]. Although the authors suggest that the accumulation of kidney free FAs is pathological, some studies suggest a contrasting argument. One such study also demonstrates reduced expression of key enzymes and regulators of fatty acid oxidation (FAO) and higher intracellular lipid deposition with kidney injury [10]. However, in that study, despite significant kidney fat accumulation (triglyceride and long-chain FAs), this was not found to be causally associated with pathology. Instead, defective FAO and ATP depletion were found to be the mediators of kidney injury. Making this even more interesting is the clinical success of high-fat and high-ketone based diets in the treatment of mitochondrial diseases and other metabolic disorders, which also suggests that sustaining ATP generation is an important endpoint for organ protection. Hence strategies which force cells to alter their energy source warrant further investigation for the treatment of metabolic disorders.

Mitochondria are truly fascinating organelles, and their dysfunction is likely central to many diseases. My advice? Get out the biochemistry textbooks and dive into the complexities of cellular energy production. Our lives may depend on it.

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Forum

Glucagon-Like Peptide-1 Receptor Agonists: Beta-Cell Protection or Exhaustion?

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Glucagon-like peptide (GLP)-1 receptor agonists enhance insulin secretion and may improve pancreatic islet cell function. However, GLP-1 receptor (GLP-1R) agonist treatment may have more complex, and sometimes deleterious, effects on beta cells. We discuss the concepts of beta cell protection versus exhaustion for different GLP-1R agonists based on recent data.

Beta Cell Dysfunction in Type 2 Diabetes Mellitus: Target for Treatment

While obesity may induce insulin resistance, type 2 diabetes mellitus (T2DM) is ultimately caused by failure of the insulin-producing beta cells to accommodate increased demand. Moreover, the continuous decline in beta cell function determines the natural course of the disease, characterized by increasing need for glucose-lowering therapies and finally insulin replacement therapy in many patients. The progressive decline in beta cell function is accompanied by a loss of mass, likely due to increased apoptosis. Several beta cell stresses, along with genetic susceptibility, contribute to the decline in beta cell function and mass. These include chronically elevated levels of glucose (glucotoxicity) and nonesterified fatty acids (lipotoxicity), which may affect beta cell function and survival by inducing endoplasmic reticulum (ER) stress, oxidative stress, and mitochondrial dysfunction. Additionally, aggregation of the beta cell peptide islet amyloid polypeptide (IAPP) to form amyloid plaques has been linked to beta cell dysfunction in human islets, in both T2DM and following transplantation. Finally, a low-grade inflammatory response, with influx and activation of proinflammatory macrophages, occurs in T2DM islets, which may ultimately drive beta cell death and/or dysfunction [1]. Thus, the search for interventions that improve beta cell function by mitigating the processes indicated above is justified.

The Concept of Beta Cell Rest

In humans, beta cell function is assessed by measuring insulin secretion after an intravenous or oral glucose challenge,

corrected for insulin sensitivity. Indeed, most studies investigating the protective properties of certain therapies on the beta cell have focused on insulin secretion. However, it is debatable whether enhanced insulin secretion *per se* reflects improved beta cell health, especially in the long term. Illustrative in this respect are the sulfonylurea class of drugs. Sulfonylureas drive insulin secretion by depolarizing the beta cell plasma membrane, independently of blood glucose levels and without addressing pathological processes ongoing in beta cells. Although the secreted insulin has a temporary beneficial effect on glycemic control, sulfonylureas may increase the deterioration of beta cell function and glycemic control, as demonstrated in ADOPT (A Diabetes Outcome Progression Trial) [2].

If driving insulin secretion over the long term leads to deterioration of beta cell function, then beta cell rest would be beneficial. Indeed, in a recent study, exposure of beta cells from obese mice characterized by the depletion of insulin granules to normal glucose concentrations restored morphology and insulin secretion [3]. In patients with either T1DM or T2DM, short-term treatment with diazoxide (which inhibits insulin release by hyperpolarizing the beta cell membrane), is associated with improved beta cell function after treatment cessation. Compared with the normalization of glycemia using oral agents, short-term intensive insulin treatment in patients with recent-onset T2DM improved beta cell function, and drug-free remission was achieved in 46% of patients after 1 year, suggesting a benefit of beta cell rest [4]. Finally, insulin sensitizers, such as the thiazolidinedione rosiglitazone [2], have beneficial long-term beta cell effects by decreasing insulin demand, although thiazolidinediones may also have direct beneficial effects on the beta cell.

GLP-1R Agonists: Beta Cell Protection…?

GLP-1R agonists, analogs of the gut hormone GLP-1, are used for the treatment of T2DM. Native GLP-1 lowers blood glucose levels by affecting beta cell (glucose-dependent stimulation of insulin production and secretion) and alpha cell (inhibition of glucagon release) function. Additionally, GLP-1 has extrapancreatic effects, including reduction of gastric emptying and intestinal glucose uptake, suppression of hepatic glucose production, and promotion of satiety resulting in reduced food intake and weight loss [5]. The beneficial effects of GLP-1 on beta cell function have been followed with great interest, since GLP-1 has been shown to improve beta cell function and survival *in vitro* and in several rodent models of diabetes. Thus, GLP-1 reduces glucose- and fatty acid-induced ER stress, protects against the detrimental effects of IAPP, and decreases the expression of proinflammatory cytokines. Collectively, these actions reduce beta cell apoptosis, which may explain the GLP-1-induced increment in beta cell mass and sustained improvement in glucose homeostasis lasting several weeks after cessation of GLP-1 therapy observed in rodent studies [6].

…Or Beta Cell Exhaustion?

The situation may be different in humans. Although GLP-1R agonists improve beta cell function in patients with T2DM for up to 1 year, no substantial persistent improvement was seen following therapy withdrawal [7]. A limitation of current human studies has been the short duration of treatment. Trials such as ADOPT have shown the importance of prolonged follow-up, because the short- and long-term effects of glucose-lowering therapies may vary widely with respect to beta cell function and glycemic control [2]. Although a few GLP-1R agonist trials assessing glycemic control have had extended follow-up, these were open-label extension studies of Phase III trials, which are uncontrolled and unblinded by design and which allow use of other glucose-lowering medication during the protocol. Moreover, they carry a large risk of selection bias: the patients who benefited most during the original trial are likely to continue in follow-up studies.

A recent study aimed to address this gap in our knowledge. Abdulreda *et al.* treated immunodeficient, streptozotocin-induced diabetic nude mice that received a human islet transplant in the intraocular space with the long-acting GLP-1R agonist liraglutide, for 250 days [8]. Not surprisingly, compared with vehicle, liraglutide reduced the time required for the islet graft to restore normoglycemia; but remarkably, during follow-up, liraglutide induced progressive deterioration in glycemia due to impaired insulin secretion. This study has, for the first time, assessed the chronic *in vivo* effects of a GLP-1R agonist on human pancreatic islets and the findings raise the possibility that treatment with GLP-1R agonists has deleterious long-term effects on the beta cell.

Still, the results from this transplant study should be interpreted with caution. Human beta cells may respond differently to GLP-1R treatment in an immunocompromised mouse with chemically induced diabetes compared with their native environment. Also, human beta cells likely become dysfunctional following the stress of islet isolation and transplantation, may lack complete perfusion and innervation following transplant, and may be more prone to inflammation and amyloid formation. It should also be noted that the liraglutide dose given was higher than what is administered to patients with T2DM. Finally, given that no histological or other data were reported that might identify the cause of the liraglutide-induced beta cell defect, insight into the mechanism(s) by which long-term liraglutide treatment may induce beta cell dysfunction was limited.

Short-Acting versus Long-Acting GLP-1R Agonists

This study raises several questions that need to be addressed. First, the mechanism by which long-term liraglutide treatment may induce human islet dysfunction needs to be understood. Prolonged stimulation of insulin secretion could lead to beta cell ER stress, as has been suggested to