Endocrine (2012) 42:1–2
DOI 10.1007/s12020-012-9713-0

EDITORIAL

Saturated free fatty acids: islet β cell "stressERs"

Raghavendra G. Mirmira

Published online: 1 June 2012

Diabetes mellitus is typically defined as a disorder characterized by hyperglycemia and an increased risk of macro- and micro-vascular diseases such as cardiovascular disease, retinopathy, and nephropathy. Indeed, a heavy emphasis has been placed on the occurrence of hyperglycemia as a defining feature of the disease, but to precisely what extent hyperglycemia itself, as opposed to concurrent dyslipidemia, contributes to the vascular complications of diabetes has remained a controversial topic. A common feature of both major types of diabetes (type 1 and type 2) is the absolute or relative deficiency of insulin secretion: in type 1 diabetes, immune cell invasion into the islet results in the rapid or gradual loss of β cells, whereas in type 2 diabetes β cells progressively fail to maintain insulin secretion in the face of insulin resistance and eventually undergo apoptosis. Indeed, the inherent susceptibility of β cells to dysfunction and death has been suggested as a contributing factor in the pathogenesis of both types of diabetes [1, 2]. Importantly, the absence of or resistance to insulin affects not only the ability to dispose of glucose and suppress hepatic glucose output, but also limits the expression of lipoprotein lipase on the capillary endothelial surface, thereby increasing circulating triglycerides and free fatty acids (FFAs). Speculation is increasing that chronic, elevated levels of FFAs—especially saturated FFAs such as palmitate—underlie not only the pathogenesis of vascular dysfunction in diabetes, but also contribute to a vicious cycle that impairs insulin secretion further through effects on the β cell.

Depending upon the context, FFAs have been shown to have both beneficial and detrimental effects on β cell function. Early studies showed that depletion of intra-islet FFA levels led to impairment of glucose-stimulated insulin secretion and restoration of FFA levels caused recovery, suggesting that intracellular FFAs may be important for the integrity of insulin secretion [3, 4]. These beneficial effects, mediated through FFA receptor 1 (GPR40) and FFA metabolism [4, 5], are thought to represent physiologic responses that reflect the need for lipid/metabolite homeostasis. However, chronic FFA exposure in vitro or in vivo or FFA exposure in the setting of concurrent hyperglycemia (glucolipotoxicity) has clearly detrimental effects on β cell function. The mechanisms by which FFAs, especially saturated FFAs such as palmitate, indirectly impair β cell function have been the subject of several recent studies. Studies of Nishimura, et al. [6] suggest that FFAs induce adipose tissue inflammation and enrich adipocyte secretion of pro-inflammatory cytokines such as IL-6 and TNF-α that, in turn, may promote β cell inflammation and apoptosis. A recent study by Eguchi et al. [7] indicates that palmitate also acts directly on the β cell to trigger inflammation via the TLR4/Myd88 pathway to cause release of chemokines that induce recruitment of pro-inflammatory M1-type macrophages into the islet. Taken together, these studies suggest that elevated saturated FFAs stimulate the production of pro-inflammatory cytokines by adipocytes and macrophages, a consequence of which is the deterioration of β cell insulin secretion.

Apart from the indirect role of adipocytes and macrophages, what is the evidence that FFAs directly impede β cell function? Elegant studies of Poitout and colleagues showed that palmitate impedes the nuclear localization of

R. G. Mirmira (✉)
Departments of Pediatrics, Medicine, and Cellular and Integrative Physiology and The Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, 635 Barnhill Drive, MS2031B, Indianapolis, IN 46202, USA
e-mail: rmirmira@iupui.edu

the master β cell transcription factor Pdx1 [8]. Recently, Alonso and colleagues showed that palmitate increases expression of the cell cycle inhibitors p16 and p18, leading to reduced β cell replication [9]. Finally, studies by Prentki and colleagues showed that in mice on a high saturated fat diet, defects in the cycling of glycerolipids and FFAs (owing to increased fatty acid oxidation) leads to decreased glucose-stimulated insulin secretion [10]. In this issue of Endocrine, Lin et al. [11] present findings that provide additional important insight into the intracellular signaling pathways triggered by FFAs. Using a well-established β cell line model, INS-1, the authors show that palmitate exposure results in the generation of reactive oxygen species (ROS), which appear to emanate from mitochondrial sources earlier than from cytosolic sources. The production of ROS is closely linked to protein misfolding in the endoplasmic reticulum (ER), leading to a phenomenon known as ER stress.

The relationship between ROS and ER stress is complex, and has been the subject of many studies and reviews in the literature (e.g., see [12]). The ER contains a highly oxidative environment that favors the formation of disulfide bonds for the folding of proteins. When incorrect disulfide bonds form, the bonds are reduced and correctly reoxidized in reactions-catalyzed ER oxidoreductases (typically, protein disulfide isomerase (PDI), and ER oxidoreduction 1 (Ero1) in eukaryotes). When protein load increases, the cycling of oxidoreductases increases, thereby generating ROS. Unless cleared by antioxidants, this increased ROS production initiates a vicious cycle that furthers aberrant disulfide bond formation and protein misfolding. Increased ROS input from whatever intra- or extracellular sources will further disrupt the balance of oxidation/reduction in the ER, thereby exacerbating protein misfolding and ER stress. Islet β cells have strikingly limited capacity to cope with oxidative stress, and given the central role of the ER in the production of secreted proteins such as insulin, are therefore especially prone to ER stress. Lin et al. [11] demonstrate not only the correlation between palmitate exposure and ER stress, but also show that inhibition of ROS formation by pretreatment with antioxidant drugs attenuates both the unfolded protein response and apoptosis. Lastly, the authors also identify the relationship between palmitate, c-Jun N-terminal kinase (JNK) signaling, and apoptosis. They show that palmitate activates JNK phosphorylation, but apparently via ER stress (rather than through oxidative stress). Reduction of either IRE-1α (ER stress cascade) or inhibition of JNK (using a specific inhibitor) mitigated palmitate-induced apoptosis. Thus, the authors show that palmitate appears to trigger apoptosis in part via oxidative stress leading to ER stress, and ultimately JNK activation.

The findings presented in Lin et al. [11] study, in the context of the published literature, provide insights that advance our understanding of the mechanisms by which saturated FFAs impair β cell function, particularly in the setting of elevated glucose levels. FFAs act via multiple, ultimately converging, pathways that include suppression of cellular proliferation, impairments in β cell gene transcription, alterations in glycerolipid/free fatty acid cycling, and elevations in ROS production. Short of hygienic measures of altering dietary habits, our elucidation of these mechanisms will provide the appropriate context upon which to base new therapies that will preserve β cell function.

References

1. T. Ogihara, R.G. Mirmira, An islet in distress: β cell failure in type 2 diabetes. J. Diabetes Investig. **1**, 123–133 (2010)
2. M.A. Atkinson, J.A. Bluestone, G.S. Eisenbarth, M. Hebrok, K.C. Herold, D. Accili, M. Pietropaolo, P.R. Arvan, M. von Herrath, D.S. Markel, C.J. Rhodes, How does type 1 diabetes develop? the notion of homicide or β-cell suicide revisited. Diabetes **60**, 1370–1379 (2011)
3. D.T. Stein, V. Esser, B.E. Stevenson, K.E. Lane, J.H. Whiteside, M.B. Daniels, S. Chen, J.D. McGarry, Essentiality of circulating fatty acids for glucose-stimulated insulin secretion in the fasted rat. J. Clin. Investig. **97**, 2728–2735 (1996)
4. T. Alquier, M.L. Peyot, M.G. Latour, M. Kebede, C.M. Sorensen, S. Gesta, C. Ronald Kahn, R.D. Smith, T.L. Jetton, T.O. Metz, M. Prentki, V. Poitout, Deletion of GPR40 impairs glucose-induced insulin secretion in vivo in mice without affecting intracellular fuel metabolism in islets. Diabetes **58**, 2607–2615 (2009)
5. C.J. Nolan, M. Prentki, The islet β cell: fuel responsive and vulnerable. Trends Endocrinol. Metab. **19**, 285–291 (2008)
6. S. Nishimura, I. Manabe, R. Nagai, Adipose tissue inflammation in obesity and metabolic syndrome. Discov. Med. **8**, 55–60 (2009)
7. K. Eguchi, I. Manabe, Y. Oishi-Tanaka, M. Ohsugi, N. Kono, F. Ogata, N. Yagi, U. Ohto, M. Kimoto, K. Miyake, K. Tobe, H. Arai, T. Kadowaki, R. Nagai, Saturated fatty acid and TLR signaling link β cell dysfunction and islet inflammation. Cell Metab. **15**, 518–533 (2012)
8. D.K. Hagman, M.G. Latour, S.K. Chakrabarti, G. Fontes, J. Amyot, C. Tremblay, M. Semache, J.A. Lausier, V. Roskens, R.G. Mirmira, T.L. Jetton, V. Poitout, Cyclical and alternating infusions of glucose and intralipid in rats inhibit insulin gene expression and Pdx-1 binding in islets. Diabetes **57**, 424–431 (2008)
9. J. Pascoe, D. Hollern, R. Stamateris, M. Abbasi, L.C. Romano, B. Zou, C.P. O'Donnell, A. Garcia-Ocaña, L.C. Alonso, Free fatty acids block glucose-induced β-cell proliferation in mice by inducing cell cycle inhibitors p16 and p18. Diabetes **61**, 632–641 (2012)
10. M.-L. Peyot, E. Pepin, J. Lamontagne, M.G. Latour, B. Zarrouki, R. Lussier, M. Pineda, T.L. Jetton, S.R.M. Madiraju, E. Joly, M. Prentki, β-cell failure in diet-induced obese mice stratified according to body weight gain: secretory dysfunction and altered islet lipid metabolism without steatosis or reduced beta-cell mass. Diabetes **59**, 2178–2187 (2010)
11. N. Lin, H. Chen, H. Zhang, X. Wan, Q. Su, Mitochondrial reactive oxygen species (ROS) inhibition ameliorates palmitate-induced INS-1 beta cell death. Endocrine (2012). doi:10.1007/s12020-012-9633-z
12. J.D. Malhotra, R.J. Kaufman, Endoplasmic reticulum stress and oxidative stress: A vicious cycle or a double-edged sword? Antioxid. Redox Signal **9**, 2277–2293 (2007)