Commentary

MOLECULAR METABOLISM

Chewing the fat for better insulin secretion

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Defective insulin secretion in the presence of insulin resistance is the cause of hyperglycemia in type 2 diabetes [1]. In addition, the UK Prospective Diabetes Study estimated that, at diagnosis, beta cell function is reduced by 50% in patients with type 2 diabetes. Of particular concern is that following diagnosis, beta cell function continues to decline as glycemic control worsens with disease progression [2]. Therefore therapeutic interventions that protect and promote insulin secretion will lead to better glycemic management and prevent the morbidity and mortality associated with diabetic complications. Current drugs (biguanides, sulfonylureas, GLP-1 agonists, DPP4 and SGLT2 inhibitors and insulin) do not provide the durability required to prevent diabetic complications because they do not adequately support and prevent the decline in beta cell function. Therefore understanding how insulin is secreted will not only enhance our knowledge of this critically important process but also will provide us with the information required to develop effective and more durable therapeutic interventions that can lead to better diabetes management.

It is well accepted that glucose is the most important nutrient stimulus for insulin secretion. Yet, while the mechanism by which this occurs has been well studied, it is not completely understood. In brief, glucose is transported into the beta cell via GLUT2 and phosphorylated by glucokinase (proposed as the "glucose-sensor" for secretion) and enters the TCA cycle to generate ATP. The rise in ATP/ADP ratio is responsible for plasma membrane depolarization, which allows calcium influx into the cell that assists in the exocytosis of secretory granules containing insulin. Insulin is secreted in two distinct phases, an early sharp rise called first phase and a later sustained phase referred to as second phase. This however does not account for the multiple other signals (e.g. NADPH, glutamate) that are generated by metabolism that contribute to this process or indeed other nutrient stimuli (eg amino acids, fatty acids) that are critical for attaining the full response and likely contribute to both phases of insulin secretion.

Prentki and colleagues have been at the forefront of research to understand how fat can signal to augment glucose-mediated insulin secretion [3]. In this pursuit, they have developed the glucose-fatty acid cycle, which in simple terms argues that the increase in glucose metabolism and the subsequent increase in malonyl-CoA inhibits fat oxidation and increases fatty acid esterification that provides the signals (triglycerides (TG), diacylglycerol (DAG)) for insulin secretion [4]. At the same time, there is an increase in islet lipolysis that can also contribute secretion signals. One of the ways that the Prentki group demonstrated this was by assessing islet glucose/fat metabolism in the Zucker Fatty (ZF) rat that despite being obese and insulin resistant hypersecretes insulin to maintain normal fasting glucose levels [5]. This increased secretory response to glucose plus fatty acid of the ZF islet is associated with increased esterification, lipolysis and TG and DAG levels. Indeed inhibition of lipolysis using orlistat significantly reduced glucose-stimulated insulin secretion from the ZF islet. While the identity of these signaling molecules has not been clear, studies using gene-knockout mouse models of adipose triglyceride lipase (which converts TG to DAG) and hormone sensitive lipase (which converts DAG to monoacylglycerol (MAG)) were both characterized with reduced glucose-stimulated insulin secretion. Thus, the signal must be downstream of DAG.

In a seminal study, the Prentki group showed that, indeed, the fatty acid signaling molecule that augments glucose-mediated insulin secretion is 1-MAG [6]. Taking advantage of a recently identified lipase called α/β-hydrolase domain-containing 6 (ABHD6 — which is highly expressed in islet βeta cells) and using genetic and chemical knockdown strategies, Zhao and colleagues showed higher 1-MAG levels causing increased glucose-stimulated insulin secretion. Indeed, they showed that 1-MAG is a better binding partner to the vesicle exocytosis molecule Munc13-1 than DAG. Thus, this study very eloquently showed that the fatty acid signal that augments glucose-mediated insulin secretion is 1-MAG and that this occurs (at least in part) via interaction with Munc13-1 at granule exocytosis level.

What more do we need to know about ABHD6, MAG and insulin secretion? In this issue, Zhao et al. [7] provide further details using inducible islet beta-cell specific ABHD6 knockout mouse islets and show increased secretion in response to a range of secretagogues, including palmitate/oleate, amino acids, KCl and diazoxide, ketoisocaproate, GLP-1 and carbachol. This increased insulin secretory response is independent of effects on cytosolic calcium, glucose utilization and oxidation and fat oxidation. These responses are expected, given the high affinity of MAG with Munc13-1 [6], which acts at the distal step of the granule exocytosis process.

Of particular note, in the present study, Zhao and colleagues showed that the absence of ABHD6 specifically enhanced second- but not first-phase insulin secretion [7]. This is interesting and at odds with the study these authors published last year. In that article, they suggested that MAG enhanced both phases of secretion [6]. The discrepancy could be due to a difference in methodology. In the previous article, the authors used islets from Munc13-1 heterozygous knockout mice and assessed cell membrane capacitance in the absence or presence of

This commentary refers to "α/β-hydrolase domain-6 and saturated long chain monoacylglycerol regulate insulin secretion promoted by both fuel and non-fuel stimuli by Zhao et al.", http://dx.doi.org/10.1016/j.molmet.2015.09.012.

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Received October 12, 2015 • Accepted October 13, 2015 • Available online 21 October 2015

http://dx.doi.org/10.1016/j.molmet.2015.10.003

added MAG. In the present study, they used islets from beta cell specific ABHD6 knockout mice and assessed secretion using islet perfusion. Whether this also reflects the discrepancy in the literature about Munc13-1 and its effect on insulin secretion is not clear. These authors have previously published that Munc13-1 affected both phases of insulin secretion [8,9], while the study by Kang and colleagues showed that second phase secretion was specifically decreased in Munc13-1 deleted islets [10]. Again, differences in methodology and whether one or both alleles of Munc13-1 were deleted could explain the discrepancy in the results. It is generally accepted that fatty acids potentiate second phase insulin secretion [11,12] and the current study by Zhao and colleagues certainly supports this thesis.

This is an exciting time in understanding how fat regulates insulin secretion and indeed in islet beta cell (dys) function as a whole. As stated earlier, knowing how insulin secretion is regulated will provide us with better targets for the development of therapies that can effectively improve beta cell function and provide effective management for the individual with diabetes. The recent work by the Prentki group has made a significant contribution to this understanding and we look forward to further delineating the mechanism(s) by which MAG leads to enhanced second phase insulin response.

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