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The pancreas: Bandmaster of glucose homeostasis

Nathalie Jouvet[a,b], Jennifer L. Estall[a,b,c,*]

[a] Institut de Recherches Cliniques de Montreal (IRCM), Montreal, Quebec, Canada
[b] Department of Experimental Medicine, McGill University, Montreal, Quebec, Canada
[c] Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada

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ABSTRACT

The pancreas is a centralized organ vital for whole body metabolic control. Recent advances in the field of metabolism have reinforced its importance for orchestrating endocrine hormone secretion in response to several nutrients including glucose, lipids and amino acids, in addition to hormones and inflammatory signals. Cell types within the pancreas, in particular the insulin-producing β cells, control nutrient breakdown and energy production and are essential to maintain not only efficient hormone secretion, but also cell integrity, survival, and the ability to sense and adapt to changing metabolic environments. The present review highlights recent research advances on how glucolipotoxicity, mitochondrial dysfunction, and systemic inflammation affects pancreatic metabolism, and how new technologies and more advanced research models are improving our ability to study this organ system. Taken together, careful characterization and understanding of the importance of nutrient metabolism within this important, yet complex organ, will help us to better understand pathologies intimately associated with the pancreas and possibly discover new and more effective therapeutic strategies.

1. Introduction

Nutrient metabolism in pancreatic cells is not only essential for providing energy for the cell like in most cells, but also serves as a mechanism to sense and react to circulating levels of macronutrients, putting pancreatic metabolism central to regulation of whole body energy homeostasis. Efficient energy metabolism in pancreatic endocrine cells of the islet is required to permit secretion of many hormones, mainly insulin and glucagon, that regulate glucose and lipid utilization throughout the body. Dysfunction of this metabolic framework causes major problems, the most prominent being type-2 diabetes, and its prevalence has been dangerously increasing over the past few decades. According to the World Health Organization (WHO), the number of diabetic patients is four times higher in 2014 than it was in the eighties. In addition to problems with islet cell function, recent work focusing on nonalcoholic fatty pancreas disease (NAFPD) indicates that accumulation of fat within the pancreas as a whole (possibly due to inefficient lipid metabolism) also disrupts insulin secretion and may contribute to or even initiate metabolic diseases. Additionally, research has identified that disruption of pancreatic metabolism is often consequent to pathology in other organs, such as inflammation in liver or adipose tissue or disruptions in the gut microbiome, adding another level of complexity to metabolic disease development that has only begun to be appreciated.

Recent advances in the field of pancreas biology and its roles in metabolic disease are reviewed below, with specific emphasis on metabolism, mitochondrial dysfunction, glucolipotoxicity and novel pathways that may show promise for new therapeutic approaches. We also draw attention to on-going challenges in the β-cell and pancreatic research fields, particularly the need for field-wide consensus on methodology and the best research models (both cell and animal).

2. The pancreas and its hormones

The pancreas is located behind the stomach and connected to the liver, the spleen and the small intestine. The main functions of the pancreas are to produce exocrine enzymes to aid digestion and endocrine hormones to regulate blood glucose. The exocrine function of the pancreas represents around 98% of the pancreatic mass and is comprised of acinar cells responsible for synthesis, storage and secretion of digestive enzymes (e.g. pancreatic lipase and amylase, phospholipase, nucleases) into the duodenum [1]. The endocrine function of the pancreas, representing about 2% of its total mass, is made up of the islets of Langerhans that contain 5 distinct cell types; α- β- δ- ε- and γ (PP) cells. The main population, β cells, secrete amylin, C-peptide and insulin, while α-cells secrete glucagon. The small proportion of δ-cells and ε-cells secrete somatostatin and ghrelin, respectively. Finally, PP cells produce pancreatic polypeptide that acts

* Correspondence to: Molecular Mechanisms of Diabetes, Institut de Recherches Cliniques de Montreal, 110 avenue des Pins Ouest, Montreal, Quebec, Canada H2W 1R7.

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locally within the pancreas to autoregulate endocrine function and regulate gastrointestinal secretion [2].

Insulin and glucagon are the predominant hormones secreted by the pancreas and their interplay has a pivotal role in the regulation of glucose homeostasis. β cells secrete insulin in response to high blood glucose, such that occurs after ingestion of a meal and absorption of nutrients. Insulin is then released in the blood stream and binds to its receptor found on most tissues, but particularly high in liver, muscle and fat cells to facilitate glucose uptake and storage.

3. Normal pancreatic metabolic balance

β cells are the principal glucose sensors of the pancreas and their presence and function are absolutely required for proper glucose balance within the whole body. In a healthy individual, glucose enters β cells through facilitated diffusion via the glucose transporter (GLUT2). Following glucose uptake, the rate-limiting glucokinase enzyme generates glucose-6-phosphate, which is metabolized during glycolysis to generate pyruvate, NADH and ATP. In the mitochondria, pyruvate and NADH fuel the production of cytosolic ATP via the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Elegant work over multiple decades demonstrates that in the β-cell, this increase in ATP/ADP ratio causes closure of K_{ATP} channels and depolarization of the cellular membrane, opening voltage-gated calcium channels to increase intracellular Ca^{2+}, promoting fusion of insulin granules with the plasma membrane for hormone release into the circulation [3]. Essentially, mitochondrial metabolism is absolutely vital for efficient glucose stimulated insulin secretion (GSIS), a theory clearly supported by studies in cell and mouse models following chemical [4] or genetic disruption [5,6] of mitochondrial function in islets. These studies continue to be refined and expanded to convincingly demonstrate the importance of nutrient metabolism for β-cell function. For example, dynamin-related protein 1 (DRP1) deficiency in β cells (which limits mitochondrial fission) prevents glucose-stimulated insulin secretion not through impaired oxidative phosphorylation, but rather limiting substrate availability to mitochondria. GSIS is rescued in these islets by the simple addition of pyruvate, revealing for the first time that mitochondrial dynamics can impact metabolic pathways outside of the mitochondria, including glycolysis [7]. Additionally, rodent/human mitochondrial metabolism was recently shown to be important for amplifying insulin exocytosis in response to high glucose via sentrin/SUMO-specific protease-1 (SENP1). NADPH produced by mitochondrial export of citrate/isocitrate and engagement with cytosolic isocitrate dehydrogenase acts on glutathione/glutaredoxin reduction, increasing activity of SENP1 in the secretory granules, transducing the redox signal for insulin secretion [8].

β cells also respond to other macronutrients such as other monosaccharides, amino acids, free fatty acids (FFA), as well as hormones and neurotransmitters. Although fructose (a simple sugar from fruit/corn used extensively as a caloric source and sweetener in many processed foods) is mainly metabolized in liver, it was recently discovered that mouse and human β cells could secrete insulin in response to fructose following interaction with the sweet taste receptor T1R2 on the β-cell surface [9]. Amino acids are also essential nutrients with both positive and negative effects on β-cell insulin secretion depending on the time, concentration and type of amino acid. Indeed, L-glutamine, one of the most abundant amino acids in the blood, cannot induce insulin secretion alone, but enhances insulin secretion when combined with L-leucine [10,11]. Inversely, the non-protein amino acid homocysteine has inhibitory effects on insulin secretion [12]. FFAs modulate insulin secretion in β cells through three distinct metabolic signalling mechanisms. Following entry into β cells, FFA are converted into FA-CoA by acyl-CoA synthase (ACS) and either 1) enter the glycerolipid/FFA cycling (lipogenesis and lipolysis) or 2) get oxidized to acetyl-CoA and enter Krebs cycle [13]. In addition to facilitating ATP production, metabolites generated in these reactions can independently influence insulin secretion through other parallel mechanisms. These include the production of monoacylglycerol (MAG) that directly induces insulin granule exocytosis through binding and activation of the vesicle priming protein Munc13-1 [14]. Of note, recent advances have identified the mammalian glycerol-3-phosphate (Gro3P) phosphatase (G3PP), an enzyme which directly hydrolyses Gro3P into glycerol, revealing a new pathway and potential target involved in β-cell metabolic regulation, particularly in response to glucolipotoxic stress [15]. Finally, 3) long-chain FFAs directly activate G-protein coupled receptor 40 (GPR40), abundant on β cells, to increase insulin secretion [16], a mechanism to potentiate the insulin response to glucose when circulating fatty acids are high (e.g. such as in multiple pathologies including cardiovascular disease, diabetes and fatty liver). While GPR40 knockout mice have reduced insulin secretion in response to glucose, FFAs and other metabolites [17], altered receptor signalling may not be a driving force in the pathogenesis of diabetes, as knockout mice are not protected from glucose intolerance or insulin resistance when compared to controls following challenge with high fat/sugar diets [18,19].

Mitochondrial metabolism of glucose and other substrates is thought to be essential for efficient insulin secretion. This theory can be challenged or supported by studies showing redundancy of multiple steps, depending on your viewpoint. For example, El Azzouny et al. recently illustrated that pharmacological or shRNA inhibition of ATP citrate lyase (*Acyl*), an enzyme responsible for conversion of citrate to short chain acyl-CoA during lipid metabolism, has no effect on glucose flux to fatty acids in culture β cells. They explain that following knockdown of this pathway, pyruvate is instead metabolized into acetoacetate, which also leads to production of short chain acyl-CoA [20]. These data illustrate that without thorough metabolic analysis, one should be wary to discount the importance of nutrient metabolism to β-cell function and/or metabolic disease in general following knockdown of single enzymes.

In addition to nutrient responses, circulating hormones also regulate β-cell metabolism. Examples of non-pancreas-derived hormones important for glucose homeostasis are the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both hormones are released from the intestine in response to food intake and activate their corresponding G-protein-coupled receptors (GLP-1R or GIPR) on β cells. While it is widely known that GLP-1 and GIP stimulate insulin secretion only when glucose is high [21,22], there is little data on whether this is due to direct effects on nutrient metabolism in β cells. There is, however, accumulating evidence that GLP-1 and related peptides have beneficial effects on mitochondrial metabolism, biogenesis and reactive oxygen species (ROS) generation in cardiac, liver and neuronal cells [23–25]. Nonetheless, GLP-1 treatment increases mitochondrial biogenesis and function in cultured rat β cells [26] and its anti-apoptotic properties may be via preservation of mitochondrial oxidative capacity [27,28]. Given the currently limited, but encouraging, evidence linking beneficial effects of some approved drugs to improved mitochondrial function, a renewed focus on β-cell metabolic pathways could be promising to protect / preserve β-cell function and mass. However, therapeutics specifically targeting β-cell nutrient metabolism are just starting to be realized.

4. When pancreatic metabolic balance is disturbed

Currently, sedentary lifestyle and western diets are major contributors to obesity and insulin resistance, which are intimately linked to the metabolic syndrome. Pancreatic β cells are primary nutrient-sensors in our bodies. In response to chronically higher-than-normal levels of circulating nutrients (i.e. like found in a pre-diabetic state), β cells increase in mass to compensate for higher insulin requirements, but the inherent slow rate of cell proliferation and regeneration in this highly differentiated cell population is often not enough to fully