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Opinion

Impact of Dietary Sugars on β-Cell Function

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Abstract: Regular consumption of dietary sugars can cause significant damage to the β-cells. Almost a century after the discovery of insulin, it has been suggested that the frequent consumption of certain carbohydrates can damage pancreatic β-cells, causing disturbances in the regulation of insulin secretion. Most noncommunicable diseases, such as diabetes, obesity, and hypertension have a common origin, metabolic dysfunction, which is partly due to β-cell malfunction. In this article, we believed that sugars can lead to an imbalance in cellular metabolism, causing insulin exocytosis to dangerously increase or decrease blood insulin concentrations. In this study, we describe the major mechanism of insulin secretion and discuss the effects of sugar on pancreatic β-cells. Although many environmental factors strongly influence β-cells, occidental diet, including excess sugar, has been found to be the predominant factor that kills or disrupts the functioning of the unique cells that produce, store, and secrete insulin.

Keywords: pancreatic β-cell; insulin; diet; type 2 diabetes; sugar consumption

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1. Introduction

The previous year marked 100 years since the discovery of insulin, a drug responsible for saving and mitigating the sufferings of millions diagnosed with diabetes mellitus (DM). DM is characterized by the dyshomeostasis of glucose metabolism, which leads to a chronic increase in blood glucose levels, primarily due to insulin secretion dysfunction and/or impaired insulin action in peripheral tissues [1,2]. Excessive consumption of added sugars, mainly fructose and sucrose, is highly correlated with DM, which can lead to insulin resistance, not only in adults [3] but also in children and young people [4].

The purpose of this opinion article is to highlight the current available literature on DM and discuss the impact of dietary sugars on pancreatic β-cells and diabetes development.

2. Endocrine Pancreas

Insulin is a hormone capable of decreasing blood glucose levels. It is produced, stored, and secreted by β-cells of the Langerhans islets in the pancreas. Each islet contains different types of endocrine cells. Insulin-secreting β-cells are the most abundant cell type (~80%) in the islets, followed by pancreatic α-cells (~15%) that secrete the hormone glucagon, and pancreatic δ-cells (5%) that secrete somatostatin, along with a small number of PP cells secreting pancreatic polypeptide. Endocrine cells account for <1% of the pancreatic tissue, while the rest are composed of exocrine cells, which produce digestive juices containing enzymes, such as proteases, lipases, and amylases; exocrine cells are responsible for degrading meal components, including carbohydrates, into the gut [5,6]. Functional pancreatic endocrine development occurs during gestation and continues until infancy. Specifically, β-cells can remodel or proliferate during the early postnatal period; however, the number

of these cells remains constant for the rest of life. Thus, destruction or malfunction of β-cells can lead to drastic metabolic dysfunction, causing DM [7].

3. β-Cells Burn Sugar to Provide Fuel to other Cells

Pancreatic β-cells can be considered metabolic sensors presenting a stimulus-secretion coupling with metabolism, including carbohydrate degradation. Glucose is the major hexose derived from carbohydrate-rich meals. Pancreatic β-cells capture glucose by specific transporters, such as glucose transport proteins (GLUT-2), located in the plasma membrane. Similar to other cells, β-cells degrade all six carbon atoms of glucose and convert the energy contained in their molecules into a small metabolite, adenosine triphosphate (ATP). Similar to neurons, β-cells are electrically excited. When depolarized, β-cells change their architecture and functions. Immediately after ATP production, β-cells are depolarized and a sequence of intracellular events occurs, culminating in the exocytosis of insulin in the blood. Specifically, by increasing the ATP/ADP ratio, ATP inhibits the activity of ATP-dependent potassium (K^+_{ATP}) channels, which drive K^+ ions into the extracellular medium via gradient straining. Subsequently, K^+ ions are trapped in the cytosol, which increases the positive cell charge. In this case, depolarization enhances the activity of certain calcium (Ca^{2+}) channels, thereby promoting the influx of Ca^{2+} from the extracellular medium. The free intracellular Ca^{2+} concentration increases and activates proteins that stimulate the cytoskeleton to transport insulin vesicles to the periphery of the cell membrane, leading to exocytosis. Together, these mechanisms are known as the "fuel hypothesis" that leads to insulin stimulus-secretion coupling, where nutrients act as a fuel to induce insulin secretion in pancreatic β-cells (Figure 1) [8].

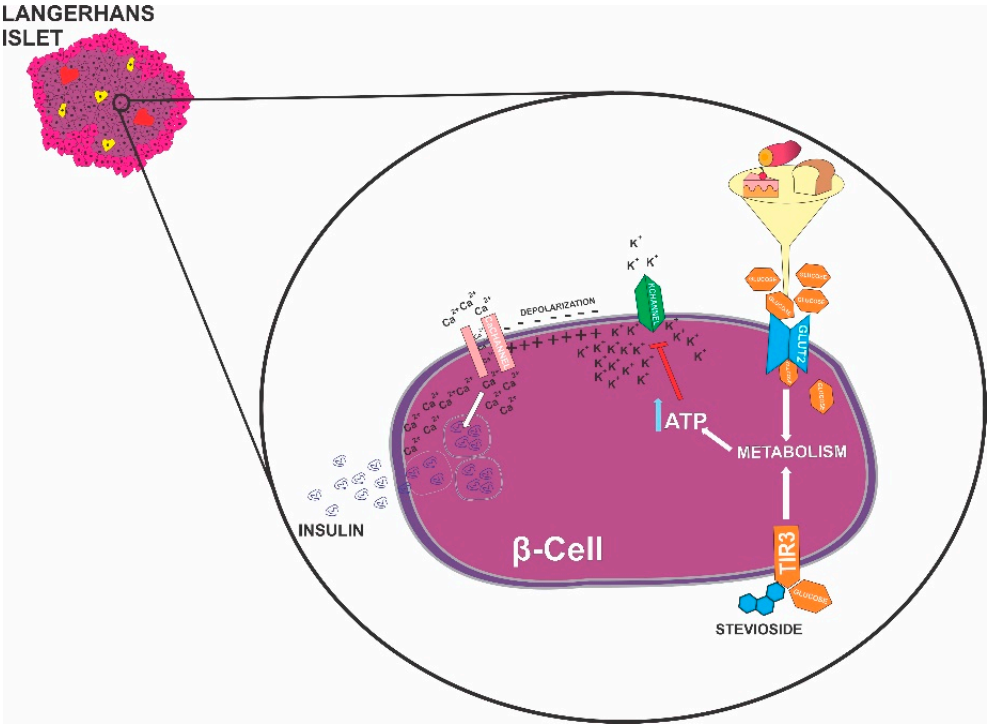

Figure 1. Glucose is transported to the β-cell mediated by the Glut2 membrane transporter. The intracellular metabolism of glucose induces changes in electrical activity, which culminate in an increase in the cytoplasmic Ca^{2+} concentration and exocytosis of insulin granules. The sweet taste receptor TIR3 is expressed in the pancreatic β-cells and is activated by various sugars, including sucrose, fructose, and glucose, and artificial sweeteners, such as stevioside, stimulating insulin secretion by increasing the metabolism of nutrients to produce ATP.

4. Great Conflict: Fuel Hypothesis vs. Glucose Receptor

In spite of the fuel insulin secretion-coupling, glucose stimulates insulin secretion in pancreatic β-cells, despite maintaining potassium-ATP channels under lowered activities, indicating an alternative pathway as a mechanism for glucose and other fuel metabolites to amplify their stimulation via ATP. This alternative mechanism can also be observed in neurotransmitters, such as acetylcholine, which bind to plasma membrane receptors and mediate an increase in intracellular Ca^{2+} levels and the ability of activated protein kinase C to increase the efficiency of Ca^{2+} in insulin exocytosis [8,9]. Therefore, glucose acts as the primary nutrient stimulating insulin secretion. Other nutrients, amino acids, and free fatty acids are capable of increasing insulin secretion, mostly through mechanisms involving the fuel hypothesis; however, the presence of glucose is required for them to be effective.

Numerous other hexoses and other monosaccharides, heptoses, pentoses, tetroses and trioses, aldoses or ketoses, or conjugated glucosamine can directly stimulate β-cells, coupling insulin secretion to energy transformation using carbohydrates as a nutrient; however, some of them, such as fructose and mannoheptulose, have demonstrated no or a weak capacity [10,11]. The fuel hypothesis was initially based on an artificial leucine, 2-amino-bicycle (2,2,1) heptane-2-carboxylic acid, which does not break down; however, it stimulates the metabolism of cells to produce ATP and induces insulin secretion [12].

Four decades of evidence collected through clinical and experimental trials support the idea of stimulus secretion-coupling for the metabolism of pancreatic β-cells. A recently proposed idea suggests that β-cells are equipped with receptors for glucose or nutrient secretagogues, such as monosaccharides, amino acids, and free fatty acids; however, these receptors have not yet been isolated. Despite this complex controversy, it has been shown to be a receptor for sweetness in the β-cell membranes.

5. β-Cells Sense Sweet, Bitter, Umami, and Salty Taste

Natural sweeteners, such as glucose and fructose, or artificial sweeteners with no caloric value, such as some fractions from *Stevia rabaudiana bertonni* leaves, sucralose extracted from sugar cane, aspartame from laboratory synthesis of amino acids, and cyclamate and saccharin obtained from petroleum, can bind to β-cell sweet taste receptors. The heterodimer comprises two members of the class C G protein-coupled receptor: type 1 taste receptor-2 (T1R2) and T1R3 (the dominant subunit expressed in pancreatic islets) [13–18]. Once sweeteners bind, they target a response to accelerate the degradation of stored nutrients, such as glucose, amino acids, and free fatty acids, to produce ATP and stimulate insulin granule exocytosis (Figure 1) [19].

6. Sugar Sources Potentially Transport Poisons or Medicines to β-Cells

The occidental diet is rich in glucose and fructose, which are the major sources of carbohydrates from different mono-and/or polysaccharides such as sucrose, starch, and sugar from other farinaceous foods. Most of these are processed by industries, eliminating other macro- and micro-compounds, fibers, and vitamins. High level daily consumption of carbohydrate sources can compromise the β-cells [20]. β-cells can be killed or become dysfunctional due to glucotoxicity, leading to type 2 diabetes (non-insulin-dependent) [21]. The impact of different sources of monosaccharides on β-cell function can be dependent on the amount consumed, carbohydrate source type, and environment. In some countries, there is a massive intake of fructose-rich corn syrup. This carbohydrate is captured less by β-cell, contrasting with hepatic cells. Most fructose metabolism occurs in the liver, and its excess causes hepatic dysfunction, which indirectly perturbs β-cell function through high glucose production and hepatic fat dysfunction [22]. Other sources of carbohydrates, such as manioca or sweet potato, and other vegetables and fruits rich in natural fiber, are less dangerous to β-cells [23]. Fibers stimulate intestinal contraction and increase intestinal transit, which reduces monosaccharide absorption, thus helping in glycemia attenuation [24,25]. One important effect of these sugar sources is the reduced insulin secretion from β-cells, which does not demand an increased amount of circulating insulin

to maintain low glycemia. Under these conditions, cells are protected from glucotoxicity. In contrast, diets with low fiber are associated with an increased risk of type 2 diabetes, which has been observed in women with a sedentary lifestyle and family history of diabetes [26].

Apart from fibers, fruits and artificial sweeteners also contain antioxidants, which can help protect β-cell function [27,28]. However, sugars with a high reducing capacity, such as ribose and fructose, can suppress insulin gene transcription and provoke oxidative stress-inducing apoptosis of β-cells [29].

7. Environment as Vectorial to β-Cell

Although we discuss β-cell function and focus on the mechanisms of insulin secretion stimulated by carbohydrates, it is important to consider the myriad of biological factors. Pre-and postprandial time durations have the potential to stimulate, potentiate, or inhibit insulin secretion processes. Any pancreatic β-cell dysfunction combined with high carbohydrate consumption can compromise entire metabolic regulation and provoke cardiometabolic diseases, such as obesity, diabetes, and hypertension [30].

The autonomic nervous system controls β-cell function. Under normal physiological situations of meal intake, the parasympathetic nervous system (PNS) potentiates glucose-insulin secretion coupling, whereas the sympathetic nervous system (SNS) inhibits it [31,32]. This is an equilibrium action; however, an imbalance may occur, as in obesity, where PNS is enhanced and SNS is decreased. Under these conditions β-cells oversecrete insulin, which causes fasting hyperinsulinemia, tissue insulin resistance, and high hepatic glucose production leading to excess blood glucose concentrations; thus, excessive carbohydrate consumption can aggravate metabolic dysfunction [33,34].

The central nervous system directly regulates insulin secretion. Recently, it was shown that the paraventricular hypothalamic nucleus (PVN), when stimulated immediately, suppresses the insulin secretion process via SNS neurons connected to β-cell; conversely, low blood glucose concentration is detected by the PVN, which allows rapid increase of glucose-induced insulin secretion. High sugar intake disrupts the central control of insulin secretion, causing cardiometabolic dysfunction [35,36].

Exercise is another important factor. Physical training improves the peripheral tissue insulin sensitivity, which reduces the demand for insulin secretion. Exercise also induces irisin from the muscle, which directly potentiates glucose-induced insulin secretion from β-cells; however, even physically trained individuals consuming calorie-dense diets can develop β-cell malfunction [37,38].

Additionally, overconsumption of fructose affects the gut microbiota. The gut microbiota consists of numerous gastrointestinal microorganisms. Diet, including the carbohydrate source and their quantities, can determine microbiota composition. High fructose consumption causes dysbiosis of the microbiota, which leads to increased gut barrier permeability, inflammation, and the progression of metabolic diseases [39].

Since the 18th century industrial revolution, the environment has changed considerably, ultimately compromising the health of human beings as well as that of animals and plants. Air, water, and food sources contain acids, heavy metals, plastics, and radiation, among many other poisons, that have the ability to disrupt metabolism, causing cardiometabolic dysfunction [40]. The β-cells are also a target for contaminants that combine with occidental diet increasing the risk of disrupting the insulin secretion process [41].

8. Conclusions and Future Perspectives

Considering that β-cells are a highly sensible target in many stressful situations, they exert their effects in a combined manner. Thus, it can be concluded that it is difficult to analyze the impact of different carbohydrate sources on pancreatic β-cells.

Given the delicate nature of β-cells as an "organ", numerous studies have suggested changes in the occidental diet to reduce the exposure of certain carbohydrates to the β-cells.

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