

Short Communication

Polyamine catabolism via spermine oxidase in the pathogenesis and treatment of hyperglycemia and diabetes mellitus—A short discussion

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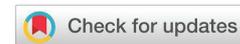
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Abstract

Diabetes mellitus can be described as chronic, endocrine dysfunction of pathophysiological regulation related to glucose and insulin. Hyperglycemia is the most common and intensely related complication of this dysfunction and has countless methods of pathogenicity. Hyperglycemia has the ability to exacerbate a degenerative positive feedback loop within critical tissues. Considering the fact that pancreatic hormonal regulation has played an increasingly considerable role in serum glucose homeostasis, here we begin a discussion into the implication of polyamine catabolism as a pathway with a mechanism that would contribute considerably to the necrosis and dysfunction of islet cells in the pancreas. The pathogenicity of this mechanism focuses on how the sustained increase in free radical production by hyperglycemic induction extenuates several complications in diabetes mellitus. The oxidation of spermine to spermidine produces hydrogen peroxide, as well as 3-aminopropanol (which spontaneously converts to acrolein) and spermidine (the precursor for the substrate of this reaction). This increase in reactive oxygen species exhibits the ability to inhibit autophagy and apoptosis as well as stimulate fat necrosis within the cells of the pancreas. Considering the islet cells of the pancreas play an extremely important role in glucose homeostasis, small changes in concentrations of these ROS are able to eliminate large regulatory factors while going undetected in the analysis of disease processes and therapeutics.

Background

According to the 2020 National Diabetes Statistics Report, upwards of 34 million Americans have Diabetes Mellitus. This disease is widely understood to be either an increased measure of pancreatic islet cell dysfunction, reduced hormone sensitivity across receptors of varying cell types, or a combination of both. More notably, upwards of 88 million Americans were estimated to have “pre-diabetes”, a condition with noted fasting plasma glucose levels above that of a normal range but not high enough to warrant a pharmacologic approach to treatment [1]. Several Prominent guidelines for the treatment of diabetes mellitus notate the drug Metformin, to be the first line treatment, followed by Glucagon-like-peptide 1 receptor agonists and Sodium-glucose linked transport protein inhibitors. With the exception of metformin, the mechanisms of these drug classes are explicitly understood with SGLT-2 inhibitors being the simplest approach. SGLT-2 inhibitors

utilize somewhat of a brute-force approach to the treatment of diabetes by focusing on increasing the excretion of glucose via inhibition of glucose reuptake in the proximal convoluted tubule. Conversely, the mechanisms of Metformin and GLP-1 RA's are more complex and possess the keys to controlling metabolic glucose regulation.

Revolutionary approaches towards the treatment of diabetes have been noted to include much greater emphasis placed on hormonal regulation, specifically with GLP-1 receptor agonists leading the way. There is also a new drug under development, tirzepatide, that is in stage 3 and has been displaying superiority over the top drugs in the aforementioned class. Tirzepatide is yet another synthetic hormone analog that has displayed strong agonist activity at both the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. The SURPASS trials that have been conducted display an increased marker of homeostasis and regulation (superior HbA1C lowering and body



mass) achieved by this novel therapy [2]. Conversely, metformin has a seemingly positive connotation amongst clinicians but not much about its mechanisms of action are well understood within these communities. Beyond suppressing hepatic glucose production and increasing glucose uptake in muscle tissues, what should be considered the most notable aspect of the therapeutic utility of metformin is its anti-oxidative and anti-inflammatory effects. The inhibition of inflammatory cytokines such as nuclear factor κ B (NF κ B) via AMP-activated protein kinase (AMPK)-dependent and independent pathways is how metformin gains its merit as somewhat of a miracle drug and largely contributes to its utilization outside of type 2 diabetes [3,4]. Spermine Oxidase is a highly inducible enzyme and its expression is up-regulated by these inflammatory cytokines as well as several other intracellular factors. Furthermore, the increased production of ROS that would be observed would be followed closely by enhanced recruitment of other respective inflammatory cytokines.

Discussion

The dysregulation of polyamine metabolism has been extensively observed in neurodegenerative diseases and it is understood that the excess production of reactive oxygen species and reactive aldehydes contributes heavily to the necrosis and degeneration of cells [2]. Endogenously, 3-aminopropanal is spontaneously converted to 2-aminopropanal (acrolein) which has been demonstrated to induce necrotic and apoptotic cell death [5]. Acrolein is also a carcinogen found in cigarette smoke associated with several chronic inflammatory diseases in addition to cancers. The molecular polarity of acrolein allows it to travel across membranes by passive diffusion which leads to adverse interactions with important biomolecular targets such as adduction to DNA and amino acids and cross-linking of proteins. The main pathway for the elimination of acrolein is conjugation with glutathione (GSH) and with a decrease in anti-oxidant concentrations, intracellular concentrations of ROS subsequently increase.

The aforementioned processes are relevant and can be extrapolated and examined in relation to other tissues and organ systems because of their presence and inherent ability to produce the same cytotoxic and carcinogenic effects. With respect to diabetes mellitus, the tissues of greatest concern are those within the central nervous system followed closely by those within the endocrine pancreas. Despite Acinar cells making up nearly 98% of all pancreatic cells, Islet cells, while low in cell count, are extremely important in serum glucose regulation. This is due to their excretion of metabolic regulatory hormones primarily in charge of the utilization and storage of glucose. The endocrine pancreas is prioritized here because it is exceptionally sensitive to changes in intracellular concentrations of reactive oxygen species. Moreover, beta-islet cells, responsible for insulin production and secretion, have been shown to have the highest concentration of polyamines of all five islet cell types. With increased concentrations of ROS, the physiologic levels of tissue expression seen with spermine oxidase potentially provided an opportunity to play a much larger role in islet cell damage and decreased hormone

secretion. Lastly, pharmacologic inhibition of spermine oxidase has been shown to ameliorate inflammatory disease processes therefore further research should be conducted into the potential to prevent oxidative damage to islet cells, thereby decreasing chronic inflammation and enhancing glycemic control via improvement of pancreatic hormone regulation [6-8].

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