A short note on pathogenesis of chronic hyperglycemia

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Introduction

Type 2 diabetes is commonly bulimia. It is caused by insulin resistance and impaired insulin secretion. These are mainly induced gradually by hyperglycemia combined with other factors such as obesity, aging, genetic predisposition and lack of exercise. Sustained binge eating leads to consistently high blood sugar levels that are toxic to the macrovasculature and microvasculature, an effect known as glycotoxicity.[1] Oxidative stress is thought to contribute to the pathogenesis of glucose toxicity during the onset of diabetes and diabetic complications, but reductive stress due to excess NADH produced by hyperglycemia has received less attention.

Normal blood glucose levels below 100 mg/dL are tightly maintained, controlled, and achieved by the rate of glucose uptake by all tissues and the rate of glucose synthesis by the liver and kidneys. Approximately 75% of total glucose in the body is used by insulin-insensitive tissues such as brain, red blood cells, liver and intestines, and the remainder by insulin-sensitive tissues such as muscle.[2] A rapid rise in blood sugar after a meal stimulates insulin secretion, resulting in a temporary increase in blood insulin levels known as hyperinsulinemia.

Description

Increased blood levels of both glucose and insulin co-ordinately inhibit glucose production by the liver and promote glucose uptake by insulin-insensitive tissues. Therefore, euglycemia is tightly maintained. This is highly dependent not only on adequate insulin secretion from β-cells after food stimulation, but also on insulin action in the liver and peripheral tissues.

Electrons from the aerobic breakdown of glucose are primarily stored in NADH for oxygen reduction and ATP generation. NADH is therefore a reducing compound and excessive amounts can cause reductive stress.[3] NADH overproduction or NAD+ deficiency induces an accumulation of NADH, causing an imbalance between NADH and NAD+, creating a condition known as pseudohypoxia. Oxygen is not consumed efficiently. This leads to metabolic stress or metabolic syndrome common in diabetes. It should be noted that the accumulation of GSH and NADPH, which are closely related to NADH metabolism, can also cause reductive stress. Thus, as mitochondrial complex I is the key enzyme responsible for NADH recycling, dysfunction of complex I may induce NADH accumulation and reductive stress, which may lead to insulin release by β-cells may be related to inhibition of the glycolytic pathway breaks down approximately 80%-90% of the body's glucose, while the pentose-phosphate pathway consumes the remaining 10%-20% under physiological conditions. In hyperglycemic conditions, more glucose flows through the glycolytic pathway, producing more pyruvate and acetyl-CoA, producing more NADH causes electron pressure on the mitochondrial electron transport chain.[4] This is especially true for hepatocytes and pancreatic β-cells, as glucokinase (hexokinase D) is a supply-dependent enzyme and this enzyme is not inhibited by glucose-6-phosphate (G6P). Therefore, the more glucose there is, the more G6P is produced and broken down by glycolysis and the Krebs cycle to produce more NADH.

Conclusion

Persistent hyperglycemia is highly toxic. It not only induces insulin resistance, but also impairs insulin secretion by pancreatic β-cells. Over time, hyperglycemia adversely affects the macrovasculature and microvasculature. Hyperglycemia causes overproduction of acetyl-CoA, which feeds into the Krebs cycle and generates excess NADH, thus subjecting the mitochondrial electron transport chain to strong electron pressure. Thus, oxidation of overproduced NADH by mitochondria would inevitably lead to the production of more superoxide and thus more ROS, which could attack and inactivate GAPDH. This causes the accumulation of glycolytic metabolites upstream of glyceraldehyde-3-phosphate, activating alternative glucose disposal pathways, all associated with ROS production, and increasing levels of oxidative stress.

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Received: *01 November 2022, Manuscript No. ajdm-22-81288;* ***Editor assigned:*** *03 November 2022, Pre QC No ajdm-22-81288 (PQ);* ***Reviewed:*** *17 November 2022, QC No ajdm-22-81288;* ***Revised:*** *22 November 2022, Manuscript No. ajdm-22-81288 (R);* ***Published:*** *29 November 2022*

Acknowledgement

None

Conflict of interest

The author has nothing to disclose and also state no conflict of interest in the submission of this manuscript.

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