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Diabetes: a Disease with No Cure and Effective Treatment

Abstract

Diabetes is a highly complex disease. Despite many different pharmacological alternatives to treat diabetes, they simply slow the illness's progression. Once installed, it becomes a pathology that cannot be cured. Its significant growth worldwide makes it challenging for governments to manage the high costs of treating people suffering from diabetes. Many research investigations are carried out, and prominent pharmaceutical corporations emphasize the creation of novel medicines. The present lifestyles, diets, and sedentary behavior of the population have exacerbated the disease. Diabetes must find new approaches for new studies and methodologies focusing on the pathometabolic signaling and early manifestations of hyperglycemia.

Keywords: diabetes mellitus, insulin receptor, hyperglycemia, metabolic signaling

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Introduction

Diabetes mellitus is a chronic multifactorial disease with metabolic, inflammatory, and energetic imbalance components. It is a disease that affects millions worldwide and has spread like wildfire.[1] The development of this disease is mainly predisposed to diet and a sedentary lifestyle. Type 1 diabetes is a autoimmune disease while Type 2 is associated with isulin resistance due to molecular alteration in the insulin receptor. The insulin receptor (IR), receptor is a tyrosine kinases, a transmembrane receptor that is activated by insulin, IGF-I (insulin-like growth factor) and IGF-II**.** Tyrosine residue phosphorylation is a requirement for the activation of insulin receptors. It is known that the phosphorylation of serine residues rather than tyrosine delays the transport of glucose, leading to insulin resistance, which has been associated with obesity, high blood sugar, activation of nuclear factor-kB kinase (IKkB) inhibitors, and protein kinase C (PKC).[2]

The prevalence of diabetes has increased significantly despite the development of new drugs and improvements in treatment. At this point, the key objective of the new medications for diabetes treatment is to regulate blood glucose levels and to treat its complications. The current clinical tools are insufficient to promote a cure for diabetes. Apart from the patient's suffering, the government also bears a significant financial burden. The absence of a cure for diabetes highlights the need to investigate novel research methods.

The role of hyperglycemia

It seems that hyperglycemia is simply a trigger for the onset of diabetes. So once path metabolic signaling is activated, controlling diabetes complications becomes difficult. The control of blood hyperglycemia only slows the development of disease complications but cannot stop them, including nephropathy, neuropathy, retinopathy, and cardiopathy.[1] Diabetes is a complex disease that activates many metabolic signaling pathways, resulting in a network signaling that is still unknown. The pathology itself predominates the lipid pathway as the one more effective metabolic pathway over the carbohydrate metabolism for energy production. It leads to the formation of harmful substances, which damage the organs and aggravate the pathology, exacerbating diabetic complications. Furthermore, high glucose levels can lead to substrate stress, which can cause sugar and protein molecules to react and form AGEs (advanced glycation end products). AGEs have been shown to have significant pro-inflammatory properties. Several types of AGEs interact with respective receptors and activate pro-inflammatory signaling to generate cytokines. In an attempt to control diabetic complications in animals, soluble AGE receptors (RAGE) have been used to block the AGE-RAGE interaction on the cell surface. However, hyperglycemia and glycated hemoglobin (HbA1c) are the most commonly used biomarkers for diabetes. High blood glucose levels trigger the onset of the disease, and HbA1c is a robust biomarker for long-term glycemic control. However, it appears that hyperglycemia just functions as a trigger for an array of metabolic processes that result in a pathological scenario that leads to vascular and neurological damage and establishes a root cause of diabetes complications.

The role of metabolic signaling

Besides the physical consequences of induced hyperglycemia on cell membranes, several metabolic signaling pathways are activated, forming a network that can communicate, altering cellular reactivity. Diabetes has highly complex signaling, and different metabolic processes interact with one another. We can summarize this complexity in an overview. After hyperglycemia-induced activation, phospholipase C, IP3 generation, PI3-K formation, diacylglycerol, PKC activation, AMP-activated protein kinase (AMPK) pathway, and cyclic AMP production from ATP are all activated besides ROS generation, NFk-B activation, and AGE-mediated activation of NRLP3 and Toll-like receptors are proinflammatory pathways.[3,4] Even though it is quite complicated, one or more of them contain points that, if activated or inhibited, could act as therapeutic targets for treating the pathology. It is important to remember that despite the pharmaceutical industry's efforts and the work of thousands of scientists researching new medications and treatments for diabetes globally, there is currently no effective cure or therapy for preventing the onset of diabetes hyperglycemia-induced and controlling its complications. Despite the fact that many products and drugs have been submitted for patent registration, most of them have not been put through any clinical or experimental testing. Some of them include: Ruboxistaurin,

PKC-412 (staurosporine, a PKC inhibitor), PKC-412A (N-benzyl-staurosporineas, a PKC inhibitor), Pyrazolopyrimidines, GKT137831, GLX351322 GYY4137, (EXP3179; and LY2109761, a selective inhibitor of TGF-1/Smad2 are drugs already tested or in trial.[5] They all aim to act as protective for renopathy, retinopathy, neuropathy, as VEGF and VEGF receptor inhibitors, for reducing vasculopathy and oxidative stress and modulating diabetes complications consequences. At this point, some questions need to be answered. What is the main challenge? Is our current strategy appropriate? Would a focus primarily on controlling hyperglycemia be sufficient to control the disease? How could be controlled the inflammatory vascular process? In fact, diabetes is a metabolic, energetic, and inflammatory disease, with vascular and neural aggression where its complications occur and must be controlled.

Comments and opinion

The importance of both glycemic control and signaling pathways research must be particularly emphasized. Nevertheless, there are specific challenges that may arise in this context. Multiple and different metabolic pathways have been identified and the signaling involved in diabetes is well investigated. However, most of them focalize the activation of the insulin receptor signaling or the biochemical alteration in it t leading to insulin resistance. Despite the great focus on the signaling study of insulin receptor activation, there aren't many reports exploring the direct effects of hyperglycemia on the general metabolic signaling network in diabetes. It's possible that hyperglycemia, itself, triggers the signaling network an imbalance in several metabolic routes, leading the cell to a pathologic state due to that imbalanced. Thus, hyperglycemia could interfere not only with the insulin receptor signaling, but also with several other routes inside the metabolic network. Additional study is required to clarify the complete effect of hyperglycemia on the metabolic network to identify a potential treatment target. The description of the principal routes, nonetheless, is unclear, and potential treatment targets cannot be proposed, yet. How do we identify the most important signaling, and how do we distinguish them? Is hyperglycemia just the onset of diabetes? Is there any possibility of doing anything following the hyperglycemic trigger? The diagnosis of diabetes is currently based on the measurement of blood sugar levels and glycated hemoglobin (HbA1c). In addition to these established biomarkers, there is no utilization of novel metabolic signaling molecules within clinical practice, which might be linked to substrate stress or the metabolic alterations induced by hyperglycemia. There is no predictive test available. Thus, only the symptoms and complications are taken care of, and recommendations for altering one's lifestyle have a limited impact on preventing the disease from progressing. Therefore, it is reasonable to suggest that a reliable biomarker is required to be discovered that could be used to define the onset of diabetes, when the metabolic adaptation to hyperglycemia occurs, and when the metabolic shift has taken place from a reversible to an irreversible state. Therefore, it is fundamental to discuss novel perspectives and learn more about metabolic networks in diabetes.

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Conflicts of interest

Authors declare that there is no conflict of interest exists.

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