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Review Article

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Antidiabetic Drugs: Mechanisms and Their Effects

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Abstract

Diabetes mellitus (DM) is the most common metabolic diseases which affects various organs of the human body due to defects in carbohydrate, protein and fat metabolism. They are certain class of drugs available to maintain optimal glycemic level for the management of DM. Among them sulfonylurea, biguanides, thiazolidinediones, inhibitors of carbohydrate hydrolyser's (α-amylase and α-glucosidase) and DPP-IV are effective against several pathways of glucose metabolism including insulin secretion, glucose uptake by target tissues and delayed nutrient absorption. In this review, We have discussed the mechanism of action, efficacy and side effects of α-amylase, α-glucosidase and DPP-IV inhibitors in the management of DM.

Keywords: Antidiabetic Drugs; A-Amylase And A-Glucosidase And DPP-IV

Introduction

Metabolism in the living system is concerned with managing the material and energy resources within cells involving complex molecules like carbohydrates, lipids and proteins as chief substrates. After a normal meal, the transient increase in plasma glucose, amino acids, triglycerides and chylomicrons is responsible for insulin secretion from pancreatic islet cells, thus enhancing the synthesis of triacylglycerols, glycogen and protein. During this period, virtually all tissues use glucose. Problems with glucose and carbohydrate metabolism are quite rare in cultures adhering to a primitive diet, low in refined foods, starches and sugars. Although hereditary predispositions, viral and bacterial diseases of the pancreas and auto antibodies to pancreatic islets do contribute to the secondary complication of obesity and are most significant risk factors. In this review, we have discuss the mechanisms of action and effects of antidiabetic drugs for the management of Diabetic mellitus.

Carbohydrates hydrolyzing inhibitor

The Postprandial hyperglycemia (PPHG) is a major factor for development of DM and also a prominent factor for the development of diabetes associated complications such as micro and macro vascular complications [1]. Therefore, therapies targeting the reduction of PPHG are one of the major clinical approaches for the control of DM [2]. In the normal digestive process, the dietary carbohydrates breakdown into polysaccharides and disaccharides with the help of α-amylase secreted from saliva and finally they are converted to monosaccharides by α-glucosidase found in the brush borders of the small intestine [3]. Therefore, by inhibiting these enzymes (α-amylase and α-glucosidase) eventually delay the carbohydrate digestion rate and glucose absorption, which consequently suppress the PPHG. At present, several synthetic α-amylase and α-glucosidase (acarbose and miglitol) inhibitors are available for the management of DM. Despite of their effectiveness, 20% of patients are affected with several adverse side effects such as flatulence, diarrhea, abdominal discomfort and bloating [4].

Dipeptidyl peptidase-IV (DPP-IV) inhibitors

The Dipeptidyl peptidase-IV (DPP-IV) inhibitors are another class of oral medications which has beneficial effect on glucose regulation by enhancing the production incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon - like peptide-1 (GLP-1) [5]. During normal metabolic condition these incretin hormones (GIP and GLP-1) regulates insulin secretion and glycogenesis by promoting α and β cell function [6] and it also regulates the level of gastric emptying and gastric acid secretion to re-

duce the postprandial glucose level [7]. These hormones (GIP and GLP-1) have minimal life of about 1 - 2 minutes and are degraded by a membrane bound enzyme called DPP-IV [8]. Therefore, administration of DPP-IV inhibitors will prolong the life of incretin hormones and also improves the glucose tolerance in diabetic individuals by enhancing the insulinotropic effects of incretins (GIP and GLP-1) [9]. The major side effects caused due to DPP-IV inhibitors are weight loss, gastrointestinal problems and nausea [10].

Antidiabetic action and mechanisms

Reduction of blood glucose can also be achieved by various other diverse mechanisms. Among them, skeletal tissue is a major organ for glucose uptake and removal [11]. Glucose uptake through skeletal muscles can be achieved through two diverse mechanisms. Phosphatidylinositol-3 kinase (PI3-K) and Akt are one of the major activators for GLUT4 which promotes the translocation of glucose from intracellular pool to plasma membrane [12]. Further antidiabetic mechanism involves to certain secondary complication conditions such as oxidative stress, hypoxia, heart shock, and ischemia, when 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK) activate and accelerates the glucose uptake and fatty acid oxidation by regulating key metabolic enzymes [13]. The major drugs for the activation of skeletal muscle AMPK is metformin and thiazolidinediones, therefore they can stimulate skeletal muscle glucose uptake and maintain blood glucose level for the control of diabetes [14]. Inhibition of protein tyrosine phosphatase 1B (PTP 1B) is another curative approach for the management of DM, which is localized on the cytoplasmic surface of the endoplasmic reticulum in muscle, fat and liver tissues [15]. The search for novel natural compounds that can inhibit PTP 1B and enhance glucose uptake through skeletal muscle will also be an efficient method for preventing insulin resistance and type-II DM.

Conclusion

In modern medicine no satisfactorily effective therapy is available to cure Diabetes Mellitus. It is apparent that due to the side effects of currently used drugs, there is a need for finding safe natural anti diabetic bioactive compounds which can be taken for long treatment period with minimal side effects.

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