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DIPEPTIDYL PEPTIDASE-IV INHIBITORS-A NOVEL CLASS OF ANTIHYPERGLYCEMIC DRUGS: CHEMICAL AND PHARMACOLOGICAL PROFILE-A REVIEW

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ABSTRACT

The incretin effect is based on the understanding that oral glucose has a greater stimulatory effect on insulin secretion than that of intravenous glucose. Glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) are incretin hormones which account for higher insulin response after oral versus intravenous administration of glucose. The dipeptidyl peptidase-IV inhibitors are a new class of antihyperglycemic agents which were developed for the treatment of type-2 diabetes by rational drug design, based on an understanding of the underlying mechanism of action and knowledge of the structure of the target enzyme. Although they differ in terms of their chemistry, they are all small molecules which are orally available. Many new drugs are currently in development for the treatment of diabetes, including products with a new mechanism of action such as dipeptidyl peptidase-IV inhibitors.

KEYWORDS: Incretin, GLP-1, GIP, DPP-4, Type-2 diabetes.

1. INTRODUCTION

Diabetes Mellitus is a chronic disorder which is characterized by four metabolic disorders: impaired insulin action, obesity, insulin secretory dysfunction and increased endogenous glucose output.[1] It is the most common endocrine disorder, affecting as many as 200 million people worldwide, with the number estimated to grow to 366 million or more by 2030 affecting both developed and developing countries alike. Type 2 diabetes is the world's fifth leading cause of death according to the World Health Organization.[2] India can be truly called the diabetes capital of the world with reference to the Diabetes Atlas 2009 published by the International Diabetes Federation which estimated diabetic population in India to be around 50.8 million, which is expected to rise to 87 million by 2030.[3] All forms of diabetes have been managed since insulin became available in 1921, and type-2 diabetes may be controlled with medications. Apart from insulin, few other drugs which can be administered orally are also used widely. Commonly known as Oral Hypoglycemic Drugs, they are classified in to different types according to their mode of action. Few major classes of oral hypoglycemic agents extensively used are: insulin secretagogues like sulfonylureas, Sensitizers like biguanides, thiazolidinedione and glucoside inhibitors.[4] Each drug class works on different mechanism of actions, which are briefly presented in Table-1. Insulin secretagogues or sulfonylureas increase the pancreatic insulin secretion by acting on the receptors present in islet cells of pancreas.[5, 6] Meglitinide also act as sulfonylureas, but the binding site is different. They close the K+ channels and open Ca^{2+} channels in the pancreatic beta cells and enhance the insulin production. Biguanides target hepatic insulin resistance, thereby reducing hepatic glucose output and increasing the uptake of glucose by the periphery, including skeletal muscles, enhancing the binding of insulin to its receptors and stimulating insulin mediated glucose disposal.[7, 8]

The principle of using DPP-4 inhibitors as therapy of T2DM is now firmly established, and numerous inhibitors are in varying stages of clinical development, with four already approved: sitagliptin in 2006, vildagliptin in 2007 and more recently, saxagliptin in 2009 and alogliptin in 2010 (presently only in Japan).[9, 10] The purpose of this article is to review briefly the leading compounds in the DPP-4 inhibitor class with chemical and pharmacological profile with special emphasis on any features which may help to distinguish between them.