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DPP-4 Inhibitors as Antidiabetic Agents

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Type 2 diabetes is reaching epidemic proportions worldwide, with an estimated 140 million people suffering from it and current projections suggest that this figure is set to increase to 300 million by 2025. Type 2 insulin resistant diabetes mellitus accounts for 90-95% of all diabetes. Diabetes is characterized by impaired insulin secretion from pancreatic β-cells, insulin resistance or both. Moreover, insulin resistance syndrome is responsible for the excess of cardiovascular disease. Majority of type-2 diabetic patients can be treated with agents that reduce hepatic glucose production (glucagon antagonist), reduce glucose absorption from gastro intestinal track GIT, stimulate β-cell functions (insulin secretagogues) or with agents that enhance the tissue sensitivity of the patients towards insulin (insulin sensitizes). Older antidiabetic agents such as sulfonylureas, and insulin are more effective than lifestyle modification in reducing microvascular complications of type-2 diabetes, but overall do not reduce cardiovascular risk. Metformin or thiazolidinedione used in type-2 diabetes also reduce cardiovascular risk. The drugs presently used to treat type-2 diabetes include α-glucosidase inhibitors, insulin sensitizers, insulin secretagogues and K_{ATP} channel blockers. However, almost half of type-2 diabetic subjects lose their response to these agents over a period of time and thereby require insulin therapy. Problem with current treatment necessitates new therapies to treat type-2 diabetes. In this regard glucagon like peptide 1 (GLP-1) agonist which promote glucose dependent insulin secretion in the pancreas and glucagon receptor antagonist, which inhibit hepatic glucose production by inhibiting glycogenolysis and gluconeogenesis, were found to be therapeutically potential. But native or synthetic GLP-1 peptidase are rapidly metabolized (they have very short half life) by proteolytic enzymers, such as dipeptidyl peptidase 4 (DPP-4) into inactive metabolite, thereby limiting the use of GLP-1 as a drug. Thus because of multiple benefits of GLP-1 augmentation, DPP-4 inhibition has been recognized as a mechanistic approach of potential value in the treatment of type-2 diabetes. Various aspects of DPP-4 inhibitors as antidiabetic agents will be discussed.