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DPP 4 (dipeptidylpeptidase-4) inhibitors: beyond glycemic control

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Abstract: *Type 2 diabetes is characterized by impaired insulin release from β-cell of pancreas and insulin resistance. Different classes of hypoglycemic drugs are available with different mechanism of action with nearly equipotent efficacy. GLP-1(glucagon like peptide-1) analogue and DPP 4 inhibitors are new developed molecules for the management of diabetes. They act via glucose dependent insulin release from β-cells as physiological manner. Here in this review we will discuss about the adventitous systemic effects of incretins and DPP 4 inhibitors beyond glycemic control.*

Key words: *DPP 4 inhibitors; GLP 1 analogues; incretins*

I. INTRODUCTION

DPP 4 (dipeptidyl peptidase-4) inhibitors are the recently developed and approved chemical for the treatment of the diabetes mellitus. They act mainly on pancreas via inhibition of degradation of the incretin hormones such as type 1 glucagon like peptide (GLP-1), and GIP. The Incretin hormones are release from the intestine in response to oral glucose ingestion and stimulate insulin release from β-cells of pancreas (so called incretin effect), and also suppress glucagon release from α-cells of pancreas. DPP-4 inhibitors are approved for the treatment in Type 2 diabetes either as monotherapy or as add-on therapy with other oral hypoglycemic agents like metformin. There are numerous DPP4 inhibitors; some are in various stages of clinical development. The first approved DPP4 was sitagliptin in 2006. Then vildagliptin, saxagliptin, alogliptine, linagliptine, anagliptin and teneligliptin were introduced.

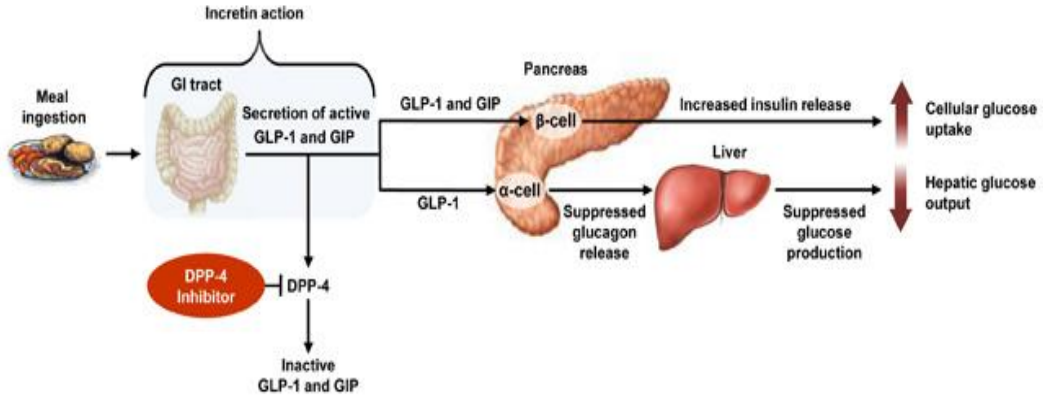
Table- Different DPP4 inhibitors with their pharmacokinetics

Drug	Sitagliptin	Vildagliptin	Linagliptin	saxagliptin	Alogliptin
blockade	competitive	Substrate blocker	competitive	competitive	Competitive
Dose(mg)	1×100/day	2×50/day	1×5/day	1×5/day	1×12.5-25/day
Excretion	80% unchanged in urine	Via urine, 21% unchanged	84% unchanged via faces, <6%urine	12-51% via urine	60-71% via urine, unchanged
Metabolism	Low	Liver	Low	Liver	Low
Renal insufficiency	Dose adjustment	Not recommended	No dose adjustment	Dose adjustment	Dose adjustment
Hepatic insufficiency	No dose adjustment	No dose adjustment but liver testing before administration	No dose adjustment	Dose adjustment in co-administration with CYP-enhancer/suppressors	No dose adjustment

Glycemic control

After meal, GLP-1 and GIP are secreted from the small intestine, but they are rapidly degraded by the enzyme DPP-4. Inhibition of DPP-4 prevents the degradation of GLP-1 and GIP and enhances glucose-stimulated insulin secretion (incretin action). GLP-1 and GIP act on the pancreatic β-cell to increase insulin release. GLP-1 also acts on the α-cell to suppress glucagon release and ultimately suppress hepatic glucose production. Together, the increased cellular glucose uptake and the decreased hepatic glucose output offer physiologic glucose control.

Figure 1 Mechanism of action of incretins and DPP 4 inhibitors



Beyond glycemic control

The growing incidence of type 2 diabetes mellitus (T2DM) leads to global public health crisis. The secondary complications associated with diabetes are frequent, severe, progressive and costly [1–3] cause significant burden of morbidity and mortality. They include diabetic nephropathy, coronary heart disease, stroke, peripheral arterial disease, neuropathy, as well as retinopathy. Despite reduction in the HbA1c the oral hypoglycemic drugs have little effect in term of protection from end organ damage. Although the safety profile of the recently introduced dipeptidyl peptidase-4 inhibitors(DPP-4 inhibitors) drugs has yet to be formally assessed, there is anticipation that they will offer benefits over existing therapies for example they don't cause fluid and water retention as with peroxisome proliferator-activated receptor (PPAR) alpha/gamma agonists.

GLP-1 receprtors are mainly expressed in the β-cells of pancreas. GLP-1 receptors are also expressed in various tissues like heart, kidney, CNS, lung, vascular endothelium, g.i. tract etc. Thus DPP 4 inhibitors also exert some effect on these systems.

Effects on Islet -cell Function

Type 2 diabetes is a progressive disease. As the UKPDS study demonstrate that b-cell function which was already loss up to 50% at the time of diagnosis [(4)], keep declining as the disease progress with worsening of glycemic control. Recent data from human autopsy studies confirm that β-cell mass is decreased in patients with type 2 diabetes[(5)].The main etiology behind this is increase β-cell apoptosis.

In clinical studies it was found that both incretins and DDP4 inhibitors shown to improve β-cell function. The effects of DPP-4 inhibition on β-cell function were studied by Xu and associates [(6)], who assessed the effect of sitagliptin on pancreatic β-cell function. They found that when sitagliptin is administered as in combination with metformin or as monotherapy, sitagliptin was not only associated with substantial reductions in postprandial glycemic excursions but also produced significant improvements in the static insulin resistence (ISR) and the average ISR over the average glucose concentrations. They concluded that sitagliptin improved b-cell function relative to placebo in both fasting and postprandial states in patients with type 2 diabetes. A similar study was done by Mari and associates [(7)] with vildagliptin, they found tha vildagliptin improves b-cell function in patients with diabetes by increasing the insulin secretory tone. Chang and colleagues [(8)] did a study with liraglutde and found that, In subjects with type 2 diabetes, liraglutide, in comparison with placebo, significantly increased insulin and C-peptide levels, the ISR area under the curve, and the slope of ISR versus plasma glucose, with values similar to those of nondiabetic control subjects. Thus liraglutide restored β-cell responsiveness to physiologic hyperglycemia in subjects with type 2 diabetes[(8)].

II. EFFECTS ON INSULIN SENSITIVITY

Type 2 diabetes characterized by impaired insulin secretion as well as by decrease insulin sensitivity. GLP-1 analogues associated with increased insulin action as well as sensitivity.

Effect on appetite, food intake and gastric emptying

It is well known that incretins and DPP4 inhibitors act via stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon secretion. However, some of their glycemic effects may also be mediated through their effects on gastric emptying, satiety, and food intake. Several studies have demonstrated that peripheral infusions of GLP-1 significantly enhance satiety and decrease food intake in lean healthy volunteers and obese nondiabetic and diabetic subjects [(9-11)].

III. CARDIOVASCULAR PROTECTION

Effect on Myocardial function

Heart failure, myocardial infarction, cardiac hypertrophy and coronary artery disease is often associated with diabetes and metabolic syndrome. As the DPP-4 enzyme is involved not only in the regulation of glucose but also several substrates (like BNP,brain natriuretic peptide; SDF-1, type 1 stromal derived factor; NPY, neuropeptide; PYY, peptide YY) known to have cardiovascular, renal and immune-modulating actions. Thus long-term DPP-4 inhibition may have clinical benefits and/or consequences including cardioprotective actions. Effects on contractility, blood pressure, cardiac output and cardioprotection appear to be independent of diabetes [12-19]. A few studies have been published on cardioprotective effect of GLP-1 analogues and DPP 4 inhibitors. In studies done on mice genetically lacking the DPP-4 receptors that were treated with sitagliptin, the investigators induced acute myocardial infarction by left anterior descending coronary artery ligation [20]. In these mice, an upregulation of cardio-protective genes and their protein products was shown. In another study in mice, it was shown that treatment with sitagliptin can reduce the infarct area and the protective effect of sitagliptin was protein kinase A dependent [21]. In diabetic patients who suffer from ischemic heart disease, it was demonstrated that treatment with sitagliptin improved their heart function and coronary artery perfusion, as observed in echo-debutamin tests [22].

IV. EFFECT ON BLOOD PRESSURE

The effect of DPP 4 inhibitors on blood pressure is contradictory. In diabetic rats, sitagliptin was associated with a significant normalization of blood pressure in diabetic rats with elevated blood pressure (versus non-diabetic rats)[23], whereas vildagliptin showed no influence on blood pressure in hypertensive fatty rats [24]. Recently, a study by Marney et al.[25], in metabolic syndrome patients, showed that during placebo and low-dose ACE inhibition (5 mg enalapril), sitagliptin lowered blood pressure. However, this trend was reversed during higher-dose acute ACE inhibition (10 mg enalapril). They hypothesized that the combination of sitagliptin and high-dose ACE inhibition causes activation of the sympathetic tone, hence attenuating blood pressure reduction. Marney et al. suggested that high levels of substance P, because of the double blockade of ACE and DPP-4, caused the activation of the sympathetic system.

V. ENDOTHELIAL FUNCTION

Endothelia dysfunction is an independent predictor for cardiovascular events in patients with type 2 diabetes. In some studies it was found that GLP-1 has some vasodilatory action and Sitagliptin significantly improved endothelial function and inflammatory state in patients with coronary artery disease and uncontrolled diabetes mellitus.

VI. LIPID METABOLISM

DPP 4 inhibitors found to decrease the postprandial surge in lipid levels. Matikainen et al.[26] in his study found that treatment with vildagliptin for 4 weeks improves postprandial plasma triglyceride and apolipoprotein B-48–containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal in drug-naive patients with type 2diabetes. Hsieh et al. [27] also suggested that DPP 4 inhibitors augment the level of GLP-1receptors thus reduce secretion of tryglycerol, cholesterol, and apolipoprotein B-40 from intestine. Anti-atherosclerotic effect has been found in some model by reducing media-intima ratio in carotid artery of rat in dose dependent manner.

VII. RENAL PROTECTION

Diabetes is the one of the most common cause of end stage renal disease (ESRD). And in patient with diabetes; hypertention and hyperglycemia are the major risk factor for the development of the ESRD. Thus slowing of progression and attenuation can be achieved by intensive effort to control hypertention and hyperglycemia. GLP-I reduce the glomerular hyperfiltration and it is diuretic and natriuretic in obese insulin resistant subjects. In one experimental model it was found that co-administration of linagliptin and the telmisartan, after only 11 weeks of treatment was associated with a marked reduction in albuminuria, an early predictor of diabetic nephropathy and cardiovascular morbidity[28]. Both plasma osteopontin (a marker of vascular calcification and fibrosis) and glomerulosclerosis (an indicator of morphologic changes in diabetic nephropathy) were significantly lower in linagliptin-treated subjects. Changes that could similarly be considered to be of potential clinical benefit were observed in proteinuria, albuminuria, urinary albumin/creatinine ratio, creatinine clearance, interstitial volume, glomerulosclerosis and glomerular basement membrane thickness. These effects appeared to be independent of blood glucose. Inhibitors of the DPP-4 enzyme have been shown to have a very good overall safety and tolerability profile, but for those excreted via the kidney dose adjustment is needed to avoid drug accumulation in patients with renal impairment. Linagliptin

is currently the only DPP-4 inhibitor that is not excreted via the kidney and does not need dose adjustment at any degree of declining kidney function.

VIII. NEURO-PROTECTION

It is well known that GLP-1 is not solely a gastrointestinal hormone and that it also has actions in other tissues including the central nervous system. In humans, in vitro GLP-1 receptor autoradiography[29] has revealed that the brain GLP-1 receptor mRNA is widely distributed throughout the cerebral cortex, hypothalamus (mainly ventromedial and arcuate nuclei), hippocampus, thalamus, caudate- putamen, and globus pallidum. In another study in humans, the most striking receptor expression was observed in the neurohypophysis, where the highest GLP-1 receptor density of all tissues was measured.[30] There is growing evidence that the ability of GLP-1 and the incretin hormones to affect gastric emptying, satiety, and food intake is mediated centrally. Inhibition of gastric emptying by GLP-1 is mediated by vagal afferents and leads to gastric distension[31]. This in turn leads to further activation of vagal afferents and signals from the stomach to the brain, which leads to a perception of fullness and satiety.[32]

Since GLP-1 and the GLP-1 receptor are expressed in most parts of the brain, it would be expected that GLP-1 agonism might have beneficial effects on brain physiology and function. This has been borne out in animal studies where centrally administrated GLP-1 has been shown to improve learning behavior and provide neuroprotection against toxin-induced apoptosis and seizures.[33,34] These effects raise the exciting possibility that GLP-1 and its analog could prove to be novel therapeutic agents for use in enhancing cognition and delaying/preventing degeneration in neurodegenerative diseases like Parkinson's disease and alzeimer disease.

IX. CONCLUSION

The incretin agents (GLP-1 receptor agonists and the DPP-4 inhibitors) belong to a unique class of antidiabetic agents. These agents have pleiotropic effects that extend beyond their known ability to lower glucose. These include effects to improve b-cell function and mediation of trophic effects on the b-cell (in animal and in vitro models); effects to reduce postprandial lipemia; effects to lower blood pressure; effects to improve myocardial contractility and endothelial function; and potential neuroprotective, neurotrophic, and bone resorptive effects (seen only in animal models). These beneficial effects of the incretins (if confirmed in long-term studies) have the potential to favorably influence the course of the disease process and its complications in patients with type 2 diabetes.

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