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THERAPY WITH GLP-1 AGONISTS AND DIPEPTIDYL-PEPTIDASE IV INHIBITORS IN TYPE 2 DIABETES MELLITUS

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Abstract

Since type 2 diabetes is increasing and most patients do not reach their therapeutic goals, novel treatment options are needed. The novel therapeutic options for type 2 diabetes mellitus (Type 2 DM); respectively those based on the action of the incretin hormone glucagon-like peptide-1 (GLP-1) were introduced in practice in 2005. Incretin therapies consist in two classes: the injectable GLP-1 receptor agonists only acting on the GLP-1 receptor and dipeptidyl-peptidase inhibitors (DPP-4 inhibitors) as oral medications which increase endogenous GLP-1 and other hormone levels by inhibiting their degradation. In Type 2 DM therapy, incretin-based therapies are attractive and frequently used due to their action and safety profile. Insulin secretion stimulation and glucagon secretion inhibition by the above-mentioned drugs occur in a glucose-dependent manner. However, incretinbased therapies have no risk for hypoglycemias. This review gives data of the mechanism of action of these substances and clinical information.

key words: *DPP-4 inhibitor, GLP-1 agonists, Incretins, Type 2 diabetes mellitus.*

Type 2 DM and the need for further treatment options

Type 2 DM incidence and prevalence are increasing highly in the world, especially in the countries with lifestyles with less physical activity and high caloric nutrition. The prevalence rates are expected to more than double within the next 20 years. Estimates expect 440 million type 2 diabetic people by 2030 (International Diabetes Federation 2009).

In addition, type 2 DM changes its prevalence by affecting increasingly younger parts of the population, with higher incidence rates in children and adolescents [1].

Much of the population with Type 2 DM also suffer from ineffective treatment and don't reach the therapeutic goals. In addition, further important treatment goals such as body weight reduction or the prevention of hypoglycemia are seldom accomplished. Insufficient metabolic control in Type 2 DM is associated with microvascular and macrovascular complications. The cardio-vascular mortality risk is increased and 75% of patients with Type 2 DM die from cardiovascular events. The microvascular and

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macrovascular complication risk can be decreased by an improved metabolic control [2].

The treatment regimes with sulfonylureas or meglitinides are associated with an elevated incidence of hypoglycemic events or with an unwanted weight gain. Glitazones are also associated with weight gain, heart failure and fractures. Exogenous insulin therapy causes weight gain and increases the risk for hypoglycemic episodes [3].

Current available options of therapy do not address the problem of islet-cell dysfunction. Both sulfonylureas and glinides stimulate insulin secretion from the β cells, metformin and glitazones act on insulin resistance and α-glucosidase inhibitors delay the digestion of carbohydrates. The progressive loss of islet function that occurs in Type 2 DM is not ameliorated by any of the current therapeutic options [4].

Because insulin resistance is constant in the course of Type 2 DM, islet function declines continuously over time and progression of Type 2 DM is characterised by a loss of islet function. Hyperglycaemia, free fatty acids, cytokines and toxic metabolic products may lead to a loss of β-cell function and β-cell mass in the islets. The α cells in the islet develop additionally a disorder of glucagon secretion. In healthy subjects, glucagon secretion is suppressed under hyperglycaemic conditions, whereas in Type 2 DM glucagon secretion is elevated, leading to excessive glucose production by the liver [5].

Incretin hormones and incretin-based therapies

The incretin hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) are secreted after a meal by the endocrine K- and L-cells of the intestinal mucosa and stimulate insulin secretion.

The physiological and pharmacological actions of the GLP-1 were used to develop two novel drug classes for Type 2 DM treatment: the GLP-1 receptor agonists and the dipeptidyl-peptidase IV inhibitors (DPP-4 inhibitors). GLP-1 and GIP contribute to approximately 60% of the insulin secretion postprandially and are responsible for the incretin effect. This effect describes the phenomenon that orally ingested glucose leads to a much larger insulin response than an isoglycemic intravenous glucose load. One important reason for the diminished incretin effect in Type 2 DM is that GIP does not act as an insulinotropic hormone under chronic hyperglycemia for reasons that are not completely understood yet. GLP-1, on the other hand, is able to stimulate insulin secretion under hyperglycemic conditions in Type 2 DM [6]. However, hyperglycemia acutely reduces the postprandial levels of GIP and GLP-1, probably through slowing gastric emptying. Therefore, the reduced incretin hormone concentrations in some patients with Type 2 DM may be a consequence rather than a cause of Type 2 DM.

Exogenous GLP-1 administration by subcutaneous or intravenous injection leads to supraphysiological GLP-1 plasma concentrations and restores the incretin effect with an adequate insulin response under hyperglycemic conditions [6].

GLP-1 shows numerous physiological actions in various tissues and a broad therapeutic potential (Fig. 1). GLP-1 stimulates insulin secretion of the beta cells and additionally inhibits glucagon secretion from the alpha cells in a strictly glucose-dependent manner and leads to a

normalization of glycemia in the fasting or the postprandial state. Under hypoglycemic conditions, the regulation by glucagon is not affected and insulin secretion is not stimulated. Therefore, GLP-1 is not able to elicit hypoglycemia by itself [6].

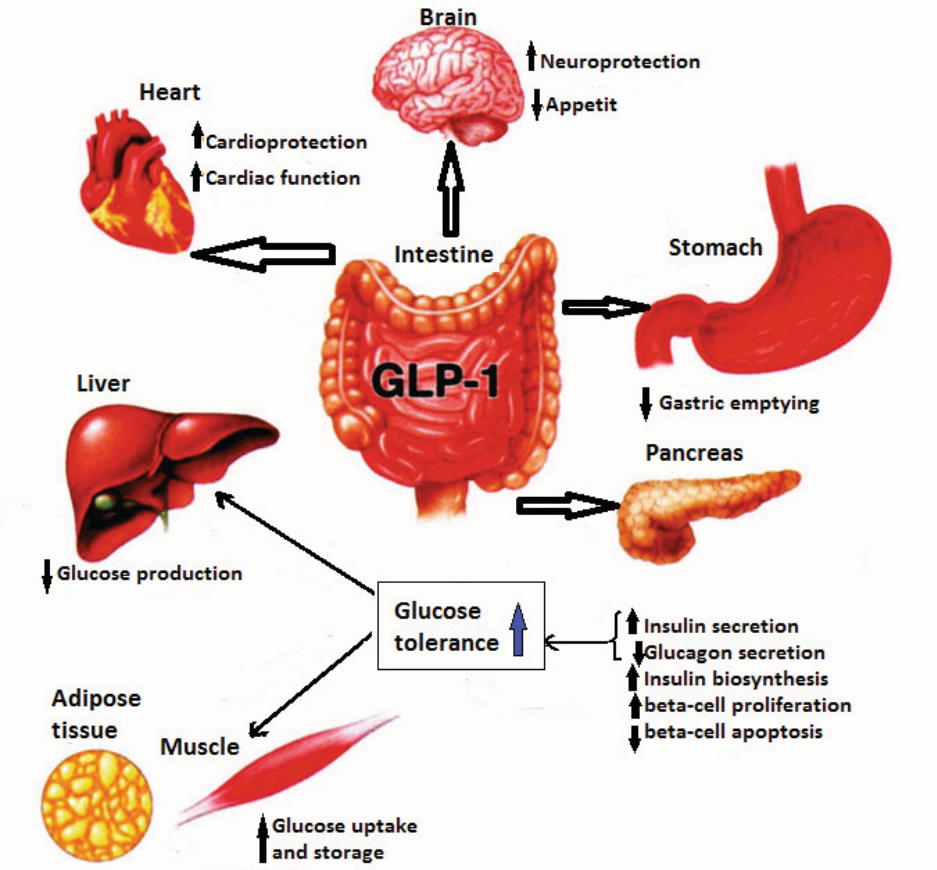


Fig. 1. Multiple physiological effects of GLP-1 (adapted from Drucker and Nauck 2006).

GLP-1 binds to its receptor on hypothalamic neurons, where it is also found as a neurotransmitter and stimulates satiety by direct action and these explain that long-term treatment with GLP-1 receptor agonists leads to weight loss [6].

Additionally, GLP-1 stimulates β-cell formation from precursor cells and also inhibits their apoptosis, leading to an increase in β-cell mass and to an improvement in β-cell function [7].

Studies in different rodent species and studies in isolated human islets showed beneficial long-term actions of GLP-1: insulin synthesis is stimulated and beta-cell mass is increased [6, 8]. Long-term study data from clinical studies in type 2 DM with a sufficient observation time are still not available. Recent studies additionally revealed that pharmacological application of GLP-1 or GLP-1 receptor agonists improved cardio-vascular parameters (reduction of systolic blood pressure, beneficial effects on myocardial ischemia in animal models and positive effects on left ventricular function in heart failure) and these promising effects may have important clinical implications for Type 2 DM therapy with GLP-1 receptor agonists [9].

The enzyme dipeptidyl-peptidase IV (DPP-4) has a greater affinity to GLP-1 than other peptides, including GIP. DPP-4 cleaves

and inactivates GLP-1 within a few minutes [6, 7]. Subcutaneous injections of GLP-1 also do not result in a sufficiently high and long-lasting elevation of GLP-1 concentrations to use native GLP-1 as a practical therapeutic agent in type 2 DM. An animal study in rodents demonstrated that DPP-4 expression in the intestine and the kidneys is also dependent on metabolic factors and is increased by high-fat feeding and type 2 DM [10]. In order to utilize GLP-1 action for type 2 DM therapy, two options are presently available [6]:

– GLP-1 receptor agonists as injectable compounds,
– Dipeptidyl-peptidase IV (DPP-4) inhibitors as orally active substances.

GLP-1 receptor agonists

Exenatide (Byetta, Amylin, Bydureon) was the first GLP-1 receptor agonist approved for the treatment of type 2 diabetes. Exenatide has a 53% amino acid sequence similarity to human GLP-1 and is a strong GLP-1 receptor agonist.

It is available as prefilled injection pens that provide either 5 or 10 micrograms of exenatide per each dose. In type 2 DM treatment, it is injected subcutaneously twice daily and has a half-life of approximately 3.5 h, sufficient plasma concentrations are reached within at least 4–6 h [4].

Bydureon is a medicine that contains the active substance exenatide. It is available as a powder and solvent to be made up into a prolonged-release suspension for injection that provides 2 mg of exenatide. Bydureon is given as one subcutaneous injection once a week on the same day each week in the abdomen, thigh or back of the upper arm.

According to the European Medicines Agency (EMA), exenatide can be used with metformin, sulphonylureas, thiazolidine-diones, metformin and a sulphonylurea, or metformin and a thiazolidinedione in patients who do not achieve the therapeutic goals on oral medication.

Exenatide reduced the HbA1c by 0.8–1.1% in various clinical studies. The HbA1c reduction was sustained and remained constant over a period of 3 years in one study. Comparative clinical studies show that the efficacy of exenatide on glycemic parameters is comparable to that of a newly implemented insulin therapy [13, 14, 15].

In addition, exenatide therapy also induced weight loss in patients with type 2 DM. In clinical studies, a significant body weight loss (1.5–3.0 kg) was documented after 30 weeks. This effect continued and led to a further weight loss of 5.3 kg after 3 years [15].

Under treatment with exenatide, beta-cell function also improved and the proinsulin/ insulin ratio changed in a favourable way. Additionally, the first phase of insulin secretion, which is lost already in the early stages of type 2 DM, is restored under treatment with exenatide [15]. Exenatide itself has no intrinsic risk for causing hypoglycemias. Severe hypoglycemic events were only observed in exenatide-treated patients who had a combined therapy with a sulfonylurea. The hypoglycemic episodes were caused by the sulfonylurea and it is suggested to reduce the sulfonylurea dose when starting exenatide treatment as additional therapy [14, 15].

The most frequent adverse effects associated with exenatide therapy were fullness and nausea. These adverse effects were less pronounced when the exenatide dose

was titrated from a small dose to the full dose at the beginning of treatment. Dose titration is therefore recommended with exenatide starting with a dose of 5 μg twice daily and an increase to 10 μg twice daily after 4 weeks. Generally, nausea is mild to moderate and occurred in the first weeks of treatment ceasing with time [15].

According to the warning by the FDA, exenatide should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease.

Liraglutide (Victoza), the long-acting human GLP-1 analogue is available in pre-filled pens (6 mg/ml), in Europe and the USA [16]. According to the EMA, Victoza is administered by the patient once a day by subcutaneous injection in the abdomen, thigh or upper arm. It is given independent of meals and preferably at the same time each day. The starting dose of Victoza is 0.6 mg. After at least one week, the dose is increased to 1.2 mg. In some patients, the dose can be further increased to 1.8 mg one week later to achieve better control of blood glucose.

In clinical studies in approximately 4200 patients with Type 2 DM receiving liraglutide, it is efficacious and safe in all stages of Type 2 DM, in monotherapy, as well as in combination with either one or more oral antidiabetic agents [17].

In a 2-year study on newly diagnosed type 2 diabetic patients, liraglutide in monotherapy led to a sustained and stable HbA1c reduction of 0.9% or 1.1% in a dose of 1.2 mg or 1.8 mg once daily, respectively [17]. Liraglutide therapy also caused a significant weight loss comparable to that previously observed in studies with exenatide. The weight loss was accompanied by a more pronounced loss in visceral fat than subcutaneous fat. Additionally, systolic blood pressure was lowered by 2–6 mmHg in the patients treated with liraglutide. This effect was independent from the weight loss, since the reduction of blood pressure was already observed early on in therapy, when weight loss had not occurred yet [17].

In a study, directly comparing the clinical efficacy and safety of exenatide and liraglutide, liraglutide proved advantageous with regard to lowering the glycemic parameters HbA1c, fasting glucose and improving the homeostasis model assessment of beta-cell function (HOMA-B) [16].

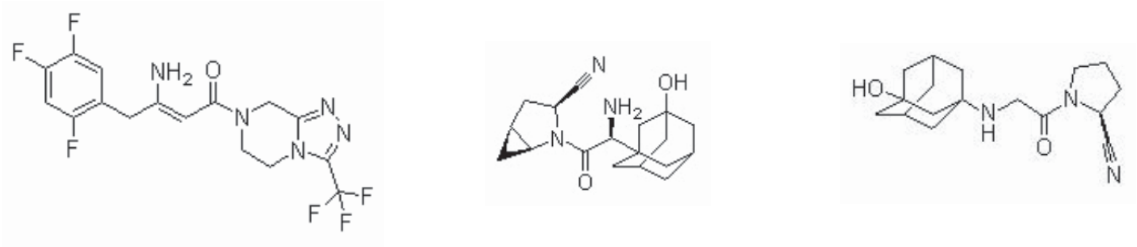
DPP-4 inhibitors

DPP-4 inhibitors are orally active and they are well tolerated. After once- or twice-daily dosing they inhibit DPP-4 effectively and lead to a postprandial elevation of endogenous GLP-1 concentrations to the 2- to 3-fold of the normal physiological levels after a meal.

The presently available compounds are Sitagliptin (Januvia), Vildagliptin (Jalra, Galvus), and Saxagliptin (Onglyza) (Fig. 2).

DPP-4 inhibitors are approved in combination with metformin, a sulfonylurea or a glitazone or a combination of metformin and a sulfonylurea.

Sitagliptin is the first DPP-4 inhibitor with a wider indication that also includes insulin therapy as well as monotherapy (general monotherapy indication USA only, mono-therapy indication in Europe for patients with metformin contraindications or intolerance) [18]. There are fixed dose combinations for both sitagliptin and vildagliptin with metformin (sitagliptin plus metformin: Janumet, vildagliptin plus metformin: Eucreas).



Saxagliptin Vildagliptin Sitagliptin

Fig. 2. Structural formulas of the DPP-4 inhibitors sitagliptin, saxaglitpin and vildagliptin.

Long-term studies investigating cardiovascular outcomes and a possible positive influence on disease progression of Type 2 DM are ongoing with the DPP-4 inhibitors.

Sitagliptin

The first DPP-4 inhibitor is available as 25 mg, 50 mg and 100 mg tablets.

In monotherapy, as well as in combined therapy, sitagliptin lowers HbA1c by 0.6–1.1% compared to placebo in a standard dose of 100 mg once daily [18]. It also reduces fasting plasma glucose and postprandial glucose significantly. Sitagliptin was weight neutral in all clinical studies [18, 19]. As additional treatment to an existing metformin therapy, sitagliptin lowered the HbA1c by 0.7%. Hypoglycemia incidence observed under sitagliptin was comparable to that under placebo [20].

The most common side effects of sitagliptin were unspecific, like headache, arthritis, nasopharyngitis, respiratory or urinary tract infections and rarely skin reactions [20].

The elimination of sitagliptin is mainly renal (75% in the urine as unchanged drug), with a half-time of 12–14 h [21]. Sitagliptin was also generally well tolerated and effective in patients with impaired renal function. In patients with impaired renal function, a dose of 25 mg/day was chosen for patients with a creatinine clearance under 30 ml/min or end-stage renal disease and a dose of 50 mg/day was given to patients with a creatinine clearance between 30 and 50 ml/min [22].

Vildagliptin

Vildagliptin, second available compound of the DPP-4 inhibitors, is given 50 mg twice daily. In clinical studies testing vildaglitpin in monotherapy or in combined therapies with metformin, glimepiride, pioglitazone or insulin, vildagliptin decreased the HbA1c by approximately 0.5–1% [14, 19]. As an additional therapy to metformin, it decreased the HbA1c by 0.65–1.1% [19]. Vildagliptin has a good safety and tolerability profile and its most common adverse effects are unspecific (flue-like symptoms, headache, dizziness and rarely liver enzyme elevations during the therapy initiation). The incidence of hypoglycemia is also comparable to placebo and like the other DPP-4 inhibitors, vildagliptin is also weight neutral.

Saxagliptin

Saxagliptin was approved in 2009 and it was shown to reduce fasting plasma glucose and postprandial glucose significantly and also HbA1c (0.7–0.9%, baseline 7.9%) in a dose dependent manner. According to the EMA, the recommended Onglyza dose is 5 mg once

daily as add-on combined therapy with metformin, a thiazolidinedione or a sulphonylurea. The pharmacokinetics (PK) of saxagliptin has been investigated in 30 PK studies with 497 subjects exposed to saxagliptin doses up to 400 mg.

As additional medication to a therapy with metformin or a glitazone, saxagliptin also led to significant metabolic improvements comparable to other DPP-4 inhibitors [23, 24]. Saxagliptin also did not cause hypoglycemias, was well tolerated and was weight neutral just as the other available DPP-4 inhibitors [25].

Conclusions

The therapeutic principle of GLP-1 with multiple modes of action, in addition to its glucose-normalising effect, adds a completely novel and attractive perspective to diabetes therapy. The inhibition of glucagon secretion and the improvement of β-cell function are important needs, unmet in Type 2 DM therapy.

DPP-4 inhibitors are oral agents that do not exclusively act via pharmacological concentrations of GLP-1-like activity, but increase endogenous levels of GIP and other peptide hormones possibly involved in maintaining of the metabolic control in physiological range.

The DPP-4 inhibitors sitagliptin, vildagliptin and saxagliptin are approved in many countries for an oral combined therapy, when therapeutic goals are not reached with a lifestyle intervention and metformin monotherapy. Sitagliptin and vildagliptin have been shown to be effective, well tolerated and safe in clinical studies over a two-year time period.

If the effects of DPP-4 inhibitors observed on β-cell mass and function in pre-clinical studies are also applied to human studies, DPP-4 inhibitors could eventually be used in pre-diabetic stages and the early stages of diabetes to slow or prevent the progression of Type 2 DM.

Future clinical studies need to demonstrate the cardiovascular benefits of these drugs.

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