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## A New Therapy of Type 2 Diabetes: DPP-4 Inhibitors

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### 1. Introduction

Type 2 diabetes is a progressive disease which is significantly spreading all over the world. It is characterized by developing insulin resistance, impairment of the pancreatic beta cells and an impaired suppression of glucagon production of the pancreatic alpha cells (Figure 1) (DeFronzo 2009). When choosing a therapy for it, several aspects should be taken into consideration, e.g. is a patient obese or has he/she a normal body weight; is he/she elderly;

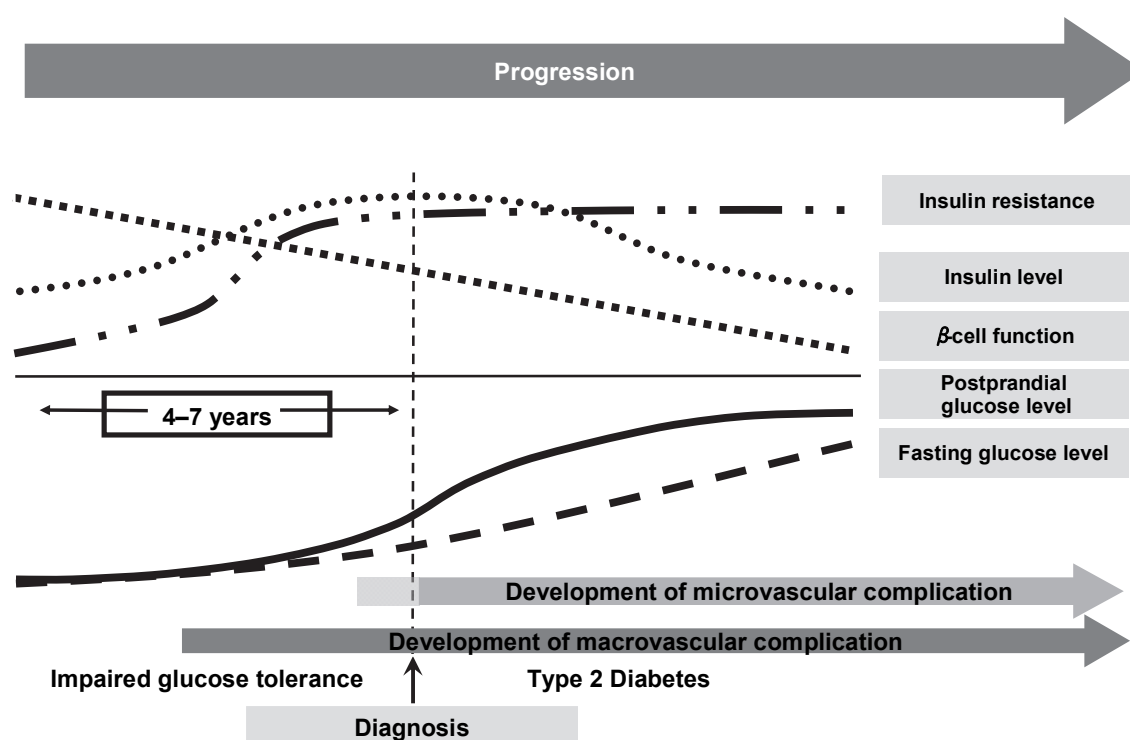


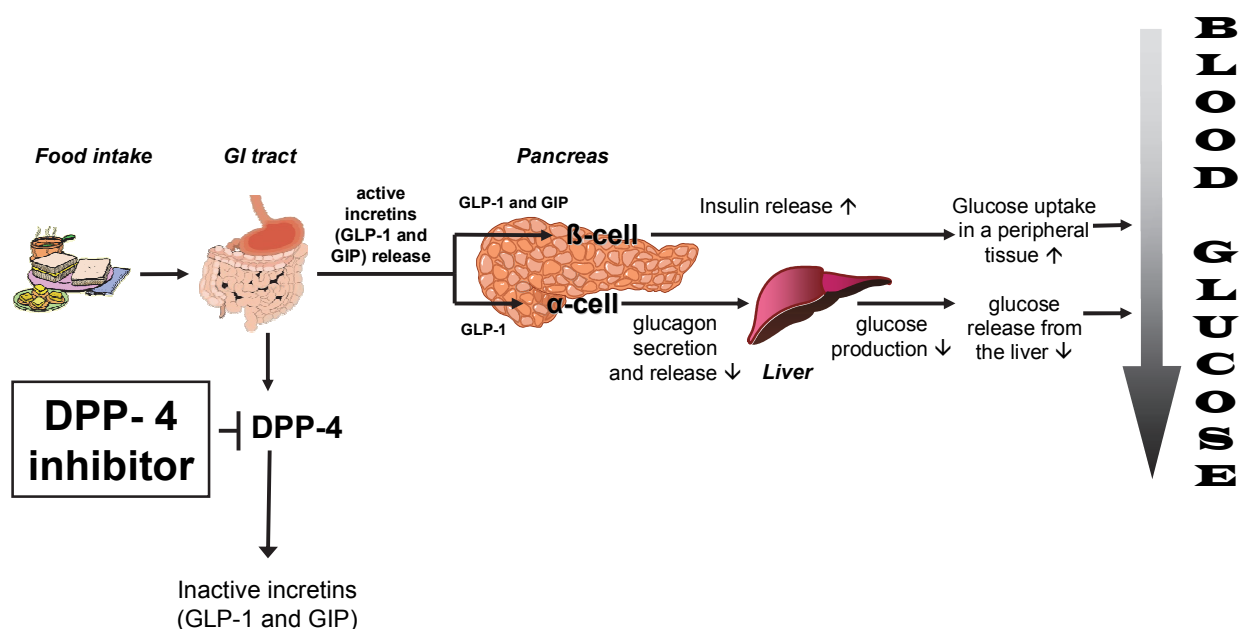
Fig. 1. Type 2 diabetes features

how long has his/her diabetes been known; were there any side effects caused by his/her previous antidiabetic medication, and are there any complications present (e.g. nephropathy). A good glycemic control reduces the rates of diabetes-associated microvascular and possibly macrovascular complications. Reduction of the associated risk

factors, including those related to excessive weight, high blood pressure and dyslipidemia are also necessary to meaningfully decrease cardiovascular risk. Agents that can improve glycemia with weight neutrality could offer an additional benefit to overweight patients with type 2 diabetes. Many new drugs are currently in development for the treatment of diabetes, including products with a new mechanism of action such as dipeptidyl peptidase-4 (DPP-4) inhibitors.

## 2. Mechanisms of DPP-4 inhibitor action

Up to now the treatment of type 2 diabetes has been limited primarily to elevation of insulin production, increase of insulin sensitivity, reduction of glucose absorption and replacement of insulin. In the recent years, however, DPP-4 inhibitors (gliptins) emerged. These belong to a novel group of medicines which exert their action by increasing incretin levels (Drucker, Sherman et al. 2010). Incretins include glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which are produced in the intestine and contribute to the physiological regulation of glucose homeostasis (Thornberry and Gallwitz 2009) (Figure 2). Active endogenous GLP-1 and GIP concentrations increase two- to threefold following a meal. Active GLP-1 and GIP increase the production and release of insulin by pancreatic beta cells. Approximately 60% of the postprandial insulin release is promoted by these two hormones. In addition, GLP-1 also reduces the secretion of glucagon by pancreatic alpha cells, resulting in a decreased hepatic glucose production. These effects are glucose-dependent; GLP-1 stimulates insulin secretion and reduces glucagon production only at a higher blood glucose level. However, the effects of GLP-1 and GIP last only for a few minutes as they are inactivated due to DPP-4 (Thornberry and Gallwitz 2009).



DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1;

Fig. 2. Mechanisms of DPP-4 inhibitor action.

The promising therapeutic potential of GLP-1 as a pharmacological tool for treating type 2 diabetes has been discovered in the 1990s. By inhibiting DPP-4, the gliptins increase insulin production and release as well as reduce glucagon levels in a glucose-dependent way, resulting in a decrease of fasting and postprandial glycemia, as well as HbA1c levels (Nauck, Vilsboll et al. 2009). Further, it has the ability to restore the blunted first phase insulin secretion in type 2 diabetes. Also in this respect, their mechanism of action differs from that of the sulfonylureas which stimulate insulin secretion also at low levels of blood glucose and may lead to hypoglycemia.

Fix combinations of sitagliptin and then vildagliptin with metformin have also been launched; these affect pathogenic factors of type 2 diabetes at more target points: they reduce the extent of insulin resistance, regulate insulin secretion in a glucose-dependent way, reduce glucagon secretion and also decrease hepatic glucose production (Nauck, Vilsboll et al. 2009). Their effects are additive, levels of active GLP-1 are increased not only by DPP-4 inhibitors but by metformin as well (Cho and Kieffer 2011).

### 3. Clinical and experimental evidence with the DPP-4 inhibitors

The oral antidiabetic drugs (OADs) used before the emergence of DPP-4 inhibitors may cause significant side effects including e.g. gastrointestinal symptoms, weight gain, cardiac heart failure, myocardial infarction, bone fractures and hypoglycemia and they do not reverse the progressive decline in beta cell function. Among others this led to the development of newer OADs, the DPP-4 inhibitors.

As a first step, according to the consensus statement of the European Diabetes Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), in patients with no metabolic upset, lifestyle changes and metformin are recommended (Nathan, Buse et al. 2009). If no sufficient metabolic control can be attained by this way (HbA1c > 7%), or the patient should not receive metformin (it is not tolerated or it is contraindicated), addition of an oral antidiabetic of second choice is recommended. Although DPP-4 inhibitors are mentioned as second-line drugs among the less validated therapies, this seems to have to be changed due to the increasing amount of study results published in relation to them.

The use of sitagliptin, the first oral DPP-4 inhibitor was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2006 and in 2007 respectively (Gerich 2010). Sitagliptin can be given in monotherapy or in combination with metformin, sulfonylurea, thiazolidinediones, or as a triple combination with metformin and sulfonylurea or metformin and thiazolidinediones both in the USA and Europe. In the recent years a fix combination of sitagliptin/metformin has also been available. Concomitant administration of sitagliptin with insulin has been approved by FDA and EMA in 2010.

Saxagliptin can be used in combination with other OADs (metformin, sulfonylurea, thiazolidinediones) both in the USA and in Europe in 2007 (Gerich 2010).

Marketing of vildagliptin was not approved by the FDA due to dermal lesions and renal impairment observed in animal studies. In Europe, based on the approval of EMA in 2008, vildagliptin can be given with metformin, sulfonylurea or thiazolidinediones. A fix combination of vildagliptin/metformin has also been marketed.

#### 3.1 Clinical efficacy

As far the results have shown no difference between DPP-4 inhibitors in the reduction of HbA1c values. Both in monotherapy and in combination (with metformin, sulfonylurea,

thiazolidinediones, or insulin) they effectively reduce HbA1c levels (by 0.6% to 1.1%) (Ahrén 2011). This effect has proven to be dependent of diabetes duration and baseline HbA1c values as well. Greater reductions in HbA1c are seen in subjects with higher baseline levels and they are more effective in patients with shorter diabetes duration (< 3 years). A survey summarized the results of 18 publications and 3 presentations where elderly ( $\geq 65$  years) patients with type 2 diabetes received DPP-4 inhibitor (sitagliptin, saxagliptin, vildagliptin, or alogliptin) treatment in monotherapy or in combination (metformin, gliclazide, glibenclamide, thiazolidinediones or insulin) (Schwartz 2010). No significant difference was found in the HbA1c level reducing effect of DPP-4 therapy in elderly and in younger patients.

Although the DPP-4 inhibitors differ from each other in several aspects, it is not known yet whether this means any substantial difference in their e.g. long-term efficacy (Table 1).

| Inhibitor    | Metabolism  | Elimination route                                | Dosing   | DPP-4 selectivity | DPP-4 inhibition*              |
|--------------|---|--|----------|-------------------|--------------------------------|
| Sitagliptin  | not appreciably metabolized   | renal (~ 80% unchanged as parent)                | 100mg qd | high              | max ~ 97%; > 80% 24 h postdose |
| Saxagliptin  | hepatically metabolized to active metabolite (via P <sub>450</sub> 3A4/5) | renal (12-29% as parent, 21-52% as metabolite)   | 5mg qd   | moderate          | max ~ 80%; ~ 70% 24 h postdose |
| Vildagliptin | hydrolyzed to inactive metabolite (P <sub>450</sub> enzyme independent)   | renal (22% as parent, 55% as primary metabolite) | 50mg bid | moderate          | max ~ 95%; > 80% 12 h postdose |

Table 1. Characteristics of DPP-4 inhibitors.

### 3.2 Hypoglycemia

Intensive glucose control increases the risk of developing hypoglycemia. In the Diabetes Control and Complications Trial (DCCT) the rate of severe hypoglycemia was 65% and 35% in the arms of intensive and conventional insulin therapy respectively (Keen 1994; The Diabetes Control and Complications Trial Research Group 1997). In the UK Diabetes Prospective Study the episodes of major hypoglycemia occurred in 0.7%, 1.4% and 1.8% in the groups receiving conventional, glibenclamide and insulin treatment respectively (Gore, McGuire 2009). Some epidemiological studies and minor prospective studies found that hypoglycemia increased cardiovascular risk (Desouza, Bolli et al. 2010). Its occurrence and a severe, even fatal outcome are not rare in patients with type 2 diabetes, primarily during the administration of insulin therapy and use of medicines which stimulate insulin secretion (sulfonylurea). Far from enough importance seems to have been attributed to hypoglycemia in the practice, although it increases the risk of accidents in certain situations, it impairs cognitive function, it may cause hemorrhage at the fundus and in the vitreous body, but it may also play a role in the development of tachycardia, hypertension and arrhythmia (Desouza, Bolli et al. 2010). Therefore it represents a not negligible risk for morbidity and mortality.

Hypoglycemia is a potential side effect of OAD, primarily sulfonylurea, therapy. As compared to metformin, sulfonylurea therapy represents an approximately threefold risk. In

contrast, there has been a very low occurrence of hypoglycemia, nearly identical with that of placebo, during DPP-4 inhibitor monotherapy or its combination with metformin or thiazolidinedione (Blonde 2009). No differences were found in the risk of developing hypoglycemia between each DPP-4 inhibitor treatments (Tahrani, Piya et al. 2010) (Table 2).

| DPP - 4 inhibitors | Study   | Any hypoglycemia                              |
|--------------------|---|---|
|                    |   | (number)<br>investigational drug / comparator |
| Sitagliptin        | Scott, R., Loeys, T. et al. (2008)              | 1/1   |
|                    | Scott, R., Wu, M. et al. (2007)                 | 12/21   |
|                    | Goldstein, B. J., Feinglos, M. N. et al. (2007) | 1/1   |
|                    | Charbonnel, B., Karasik, A. et al. (2006)       | 6/5   |
| Saxagliptin        | Rosenstock, J., Sankoh, S. et al. (2008)        | 0/0   |
| Vildagliptin       | Schweizer, A., Couturier, A. et al. (2007)      | 2/1   |
|                    | Bolli, G., Dotta, F. et al. (2008)              | 1/0   |
|                    | Bosi, E., Camisasca, R. P. et al. (2007)        | 1/1   |
|                    | Rosenstock, J., Baron, M. A. et al. (2007)      | 1/0   |

Table 2. Occurrence of hypoglycemia during DPP-4 therapy.

While the DPP-4 inhibitors and the GLP-1 increase insulin production in a glucose-dependent way, in contrast with them the sulfonylureas exert their effect via the ATP-dependent potassium channel, even at low levels of blood glucose, and therefore they make patients susceptible to hypoglycemia. Thus the incidence of hypoglycemia increases when DPP-4 inhibitors are combined with sulfonylurea. This has also been demonstrated in a metaanalysis of studies with a great number of subjects (n=10246), where sitagliptin monotherapy or its combination (with metformin, pioglitazone, sulfonylurea, sulfonylurea + metformin or metformin + rosiglitazone) was compared with placebo or other OAD (metformin, pioglitazone, sulfonylurea, sulfonylurea + metformin or metformin + rosiglitazone) treatment in patients with type 2 diabetes (Williams-Herman, Engel et al. 2010). A lower incidence of hypoglycemia (5.2%) was found in the group of sitagliptin therapy as compared to the control group (12.1%) that could be attributed primarily to sulfonylurea therapy.

### 3.3 Body weight

There is no increase of body weight during treatment with DPP-4 inhibitors, and even a reduction of it is possible during a combined therapy with metformin (Monami, Iacomelli et al. 2010).

The safety and tolerability of sitagliptin was investigated in patients with type 2 diabetes, who were on a stable dose of metformin for at least 8 weeks and were randomised in double-blind manner to receive either sitagliptin 100mg q.d. (n= 588) or glipizide 5mg/day (up-titrated, to a maximum dose of 20mg/day, based upon prespecified glycemic criteria) (n= 584) (Seck, Nauck et al. 2010). The analysis showed that the addition of sitagliptin to ongoing metformin monotherapy was associated with weight loss (-1.6 kg) compared with weight gain (+ 0.7 kg) with glipizide. In addition patients treated with sitagliptin compared with those treated with glipizide had a lower incidence of hypoglycemia (5% vs 34%).

The body weight neutral effect of DPP-4 inhibitors may prevail through several mechanisms which include the following (Foley and Jordan 2010):

- After a meal that is rich in fat, DPP-4 inhibitor treatment reduces the level of chylomicron apoB-48 and so it hinders intestinal triglyceride absorption.
- Postprandial catecholamine (norepinephrine) levels increase upon the administration of DPP-4 inhibitors, resulting in an increased lipolysis in the adipose tissue and fatty acid oxidation in the musculature.

### 3.4 Cardiovascular effects

Although it summarized the results of studies with non-cardiovascular endpoints, a metaanalysis investigating the safety of sitagliptin (100mg/day) showed no substantial differences as compared to the control group in relation to coronary artery disease (0.2 vs. 0.4 event per 100 patient-years), myocardial ischemia (0.0 vs. 0.2 event per 100 patient-years) and acute myocardial infarction (0.1 vs. 0.2 event per 100 patient-years) respectively (Williams-Herman, Engel et al. 2010).

A post hoc metaanalysis of saxagliptin's effect on major cardiovascular events (CV death, non-fatal MI, non-fatal stroke) showed no increase of CV risk in the treated patients (Wolf, Friedrich et al. 2009).

Recently, a large outcome trial with sitagliptin (A randomized placebo controlled clinical Trial to Evaluate Cardiovascular Outcomes after treatment with Sitagliptin in patients with type 2 diabetes mellitus and inadequate glycaemic control on mono or dual combination oral antihyperglycaemic therapy, TECOS) and with saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus, SAVOR-TIMI 53) has been started.

GLP-1 receptors can be found in cardiac muscle cells and vascular endothelial cells as well (Nauck and Smith 2009; Nikolaidis, Mankad et al. 2004). The beneficial effect of GLP-1 has been demonstrated also in coronary ischemia and left ventricular failure both in animal experiments and in human studies (Nikolaidis, Mankad et al. 2004; Bose, Mocanu et al. 2005; Nikolaidis, Elahi et al. 2004). In rats, myocardial necrosis developed in a smaller area when they received GLP-1 infusion (Bose, Mocanu et al. 2005). Following intravenous infusion of GLP-1, less wall motion disorder and better left ventricular function developed in patients with and without type 2 diabetes who had undergone angioplasty after acute myocardial infarction (Nikolaidis, Mankad et al. 2004).

Based on these, a beneficial effect of DPP-4 inhibitors on cardiovascular disease may be presumed, however further long-term clinical studies with a high number of patients are required for an exact elucidation.

### 3.5 Other side effects and potential for drug-drug interactions

Based on the results so far, DPP-4 inhibitors seem to have no group-specific side effects (Nauck and Smith 2009; Hollander and Kushner 2010). An occurrence of slightly increased upper respiratory symptoms was not confirmed by a metaanalysis investigating the safety of sitagliptin therapy on a high number of subjects (29 placebo-controlled and 11 active comparison studies) (Williams-Herman, Round et al. 2008). Also a similar result was obtained in a study investigating the safety of vildagliptin (Ligueros-Saylan, Schweizer et al. 2010).

DPP-4 inhibitors are eliminated mostly through the kidneys, so that the question has emerged whether they can be used in patients with impaired renal function (Table 1). The results so far show that sitagliptin was tolerated well also in patients with mild, moderate and severe renal failure (including those on dialysis) (Bergman, Cote et al. 2007). Currently DPP-4 inhibitors are approved in patients with mild renal impairment (creatinine clearance [ $C_{Cr}$ ]  $\geq 50$  mL/min) both in Europe and in the USA. However, in patients with moderately ( $C_{Cr} \geq 30$  to  $< 50$  mL/min) and severely ( $C_{Cr} < 30$  mL/min) impaired renal function / end stage renal disease (ESRD) in Europe it is not approved, while in the USA sitagliptin and saxagliptin can be given in a reduced dose (Deacon 2011).

In patients with mild and moderate liver disease, of the DPP-4 inhibitors solely sitagliptin has been approved with no restrictions. Monitoring of transaminase levels is required before and during saxagliptin therapy (Deacon 2011). If transaminase levels exceed three times the upper limit of normal, the therapy should be discontinued. At present, vildagliptin should not be given to patients with mild to moderate hepatic impairment. Neither DPP-4 inhibitor is approved in patients with severely impaired hepatic function.

Results show that DPP-4 inhibitors cause no more interactions with other OADs (metformin, pioglitazone, glyburide) or simvastatin. Only saxagliptin is metabolized via the CYP3A4/5 system; therefore a reduction of saxagliptin dose (2.5mg qd) is recommended when it is administered concomitantly with a strong CYP3A4/5 inhibitor (e.g. ketoconazole) (Table 1).

### 3.6 $\beta$ -cell function

Typically, islet function has already declined by approximately 50% by the time patients are diagnosed with type 2 diabetes mellitus (Wajchenberg 2007). Reduced pancreatic beta cell mass, largely because of accelerated apoptosis, seems to account for, at least in part, the impaired islet cell function (Butler, Janson et al. 2003). In vitro, neither sulfonylureas, nor metformin protect beta cell from apoptosis (Maedler, Carr et al. 2005; Kefas, Cai et al. 2004).

Studies in diabetic animals showed beneficial effects of GLP-1 on pancreatic beta cells (Farilla, Hui et al. 2002; Mu, Petrov et al. 2009; Gallwitz and Häring 2010) (Figure 3). GLP-1 stimulates beta cell proliferation and differentiation while it hinders beta cell apoptosis both in vitro and in animal studies. DPP-4 inhibitors increased the number of insulin-positive beta-cells in islets and the beta to alpha cell ratio in different diabetic animals was normalized.

The effects of sitagliptin vs. sulfonylurea therapy were compared in mice with type 2 diabetes (Mu, Petrov et al. 2009). Sitagliptin treatment was found to have repaired the amount of beta and alpha cells and also alpha/beta cell rate to a significantly greater degree as compared to glipizide therapy. The effect of sitagliptin therapy (50mg/day) on beta cell function in patients with type 2 diabetes (n=28) taking metformin was analyzed in a double-



blind randomized placebo-controlled study (Brazg, Xu et al. 2007). Beta cell function was determined with the 'C-peptide minimal model' by measuring blood glucose and C-peptide levels for 5 hours after a standardized breakfast. Sitagliptin therapy was found to have significantly improved beta cell function in comparison to the placebo group. In addition sitagliptin and vildagliptin significantly improved HOMA-B value and it also reduced the proinsulin/insulin rate.

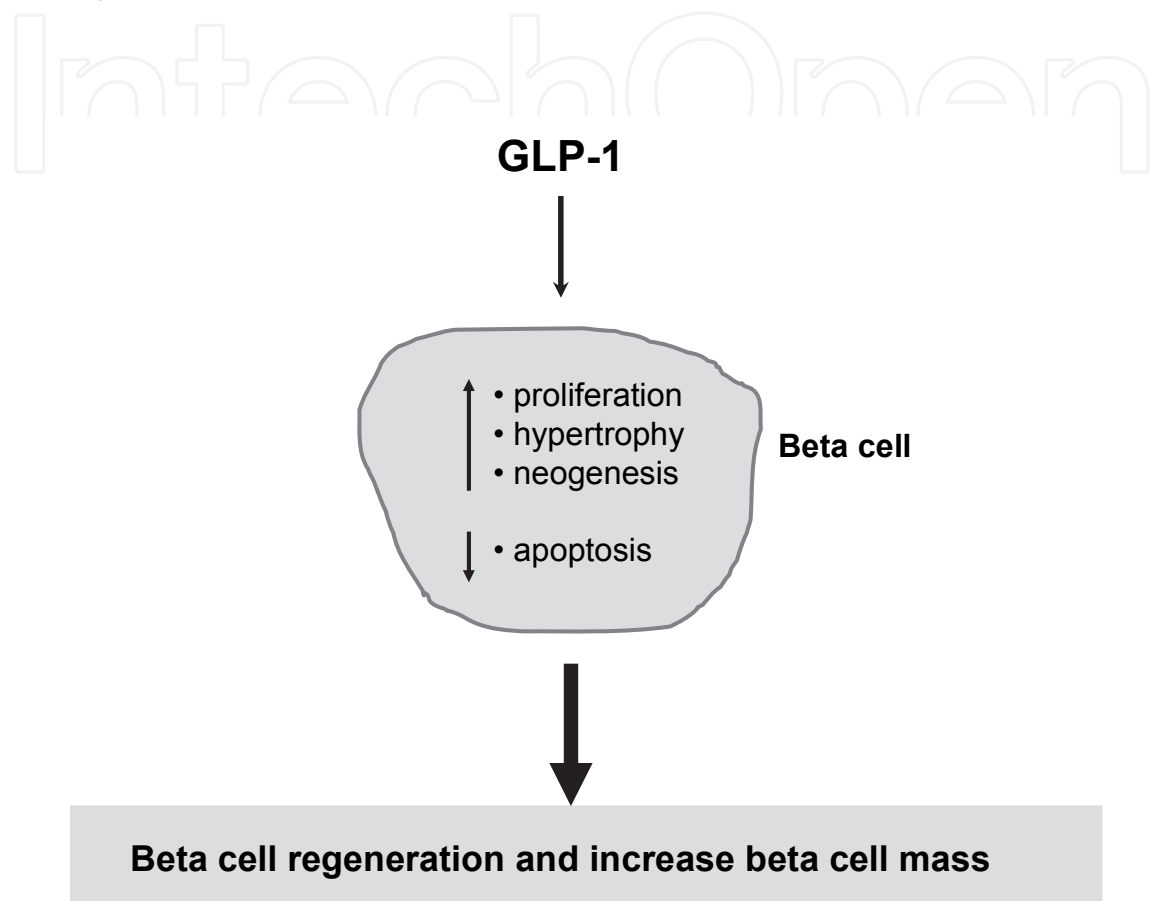


Fig. 3. Effects of GLP-1 on beta cell.

Thus, DPP-4 therapy can delay or prevent the progression of type 2 diabetes, but further studies are required in order to obtain a more exact knowledge relating to its effect on beta cells, as well as its mechanism of action.

#### 4. Conclusion

Large intervention studies demonstrated that antihyperglycemic therapy with treatment goals aiming at normoglycemia can reduce the risk or the progression of microvascular as well as macrovascular risk.

Sulfonylureas, glinides and insulin therapy are associated with an increased risk for hypoglycemia and are also associated with weight gain. The novel incretin based therapies with DPP-4 inhibitors, both in monotherapy and in combination therapy, can effectively reduce fasting and postprandial blood glucose levels and also HbA1c value. When administered concomitantly with metformin, their GLP-1-increasing effects are additive.

Based on studies and clinical experience so far, they can be tolerated very well, and they cause no increase of body weight, hypoglycemia and gastrointestinal side effects and the potential, based on animal and in vitro studies, for preservation or enhancement of beta cell function. Their administration is particularly beneficial in overweight patients who represent the majority of patients with type 2 diabetes, as well as in elderly patients and in diabetics who are susceptible to hypoglycemia. At present, there seems to be little to distinguish between the different inhibitors in terms of their efficacy as antidiabetic agents and their safety. Long-term accumulated clinical experience will reveal whether compound-related characteristics lead to any clinically relevant differences. In the future further gliptins (alogliptin, linagliptin, denagliptin) may be marketed, with which Phase III studies are in progress or the results have already been published.

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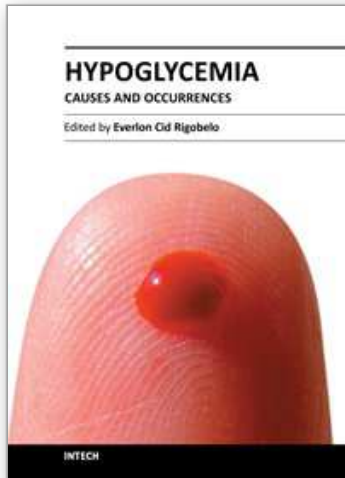
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## **Hypoglycemia - Causes and Occurrences**

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Glucose is an essential metabolic substrate of all mammalian cells being the major carbohydrate presented to the cell for energy production and also many other anabolic requirements. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the glucose serum concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. This book provides an abundance of information for all who need them in order to help many people worldwide.

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