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MINI REVIEW

Glucose-lowering action through targeting islet dysfunction in type 2 diabetes: Focus on dipeptidyl peptidase-4 inhibition

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ABSTRACT

Dipeptidyl peptidase-4 (DPP-4) inhibition is a glucose-lowering medication for type 2 diabetes. It works through stimulation of insulin secretion and inhibition of glucagon secretion in a glucose-dependent manner, resulting in lowered fasting and postprandial glycemia with low risk of hypoglycemia. As impaired insulin secretion and augmented glucagon secretion are key factors underlying hyperglycemia in type 2 diabetes, DPP-4 inhibition represents a therapy that targets the underlying mechanisms of the disease. If insufficient in monotherapy, it can preferably be used in combination with metformin, which targets insulin resistance, and also in combination with sodium–glucose cotransporter 2 inhibition, thiazolidinediones and insulin, which target other mechanisms. In individuals of East Asian origin, islet dysfunction is of particular importance for the development of type 2 diabetes. Consequently, it has been shown in several studies that DPP-4 is efficient in these populations. This mini-review highlights the islet mechanisms of DPP-4 inhibition, islet dysfunction as a key factor for hyperglycemia in type 2 diabetes and that, consequently, DPP-4 is of particular value in populations where islet dysfunction is central, such as in individuals of East Asian origin.

INTRODUCTION

Based on its ability to prevent the inactivation of the incretin hormone glucagon-like peptide-1 (GLP-1), dipeptidyl peptidase-4 (DPP-4) inhibition was explored as a target for glucose-lowering therapy of type 2 diabetes in the 1990s[1,2]. Mechanistic studies have shown that DPP-4 inhibition also prevents the inactivation of the incretin hormone, glucose-dependent insulinotropic polypeptide, and the combined effects of DPP-4 inhibition result in stimulation of insulin secretion and inhibition of glucagon secretion[3].

The first clinical studies showing a glucose-lowering action of DPP-4 inhibition in type 2 diabetes patients was published in 2002[4]. After subsequent development, DPP-4 inhibition was introduced into the clinical market in 2006, and has since been further developed and is now used in many countries[5,6]. Sitagliptin, linagliptin, vildagliptin, saxagliptin and alogliptin are the most commonly used DPP-4 inhibitors, but also others have been developed, particularly in Japan and South Korea, such as anagliptin, gemigliptin, evogliptin, teneligliptin, teleligliptin, gasogliptin and retagliptin[7].

There are several advantages of the use of DPP-4 inhibitors (Table 1). They are orally active and they reduce glycated hemoglobin (HbA1c) efficiently within the range of 0.5–1.0%[5,6]. They can be used in both monotherapy and in combination therapy with metformin, sodium–glucose cotransporter 2 inhibitors, thiazolidinediones and insulin[6,8-10]. They are also weight neutral and do not cause weight gain[6,11]. Furthermore, the risk for hypoglycemia is very low[12] and DPP-4 inhibitors can be used also in patients with renal impairment[13]. DPP-4 inhibitors are also effective in elderly patients[14]. DPP-4 inhibitors show no drug–drug interaction with other glucose-lowering medications or other commonly used pharmacotherapies in type 2 diabetes patients[6]. They are also safe and show good tolerability, with only a few adverse events reported – as evidenced by long experience, long-term large outcomes trials[6,11,15-19] and experience in the treatment of elderly patients[14] – except for an increased risk for hospitalization as a result of heart failure with saxagliptin[15]. There has been a discussion regarding signals for pancreatitis and pancreatic cancer, but long-term studies have not confirmed a definitive risk in this respect[20,21].

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Table 1 | Characteristics of dipeptidyl peptidase-4 inhibition

Orally active
Reduce HbA1c
Can be used in monotherapy
Can be used in combination with sulphonylureas, insulin, SGLT2-inhibitors and thiazolidinediones
Can be used in renal impairment
Can be used in elderly patients
Weight neutral, no weight gain
Very low risk of hypoglycemia
No drug-to drug interaction with medications commonly used in type 2 diabetes
Tolerable with low risk of adverse events
Safe in long-term treatment, including cardiovascular safety

SGLT2, sodium–glucose cotransporter 2.

MECHANISMS OF DPP-4 INHIBITION

The DPP-4 inhibitors differ in chemical structure, pharmacokinetics and metabolism, and they also have different mechanisms when they interact with the catalytic site of the DPP-4 enzyme[22,23]. Despite these differences, all DPP-4 inhibitors prevent the inactivation of GLP-1 and glucose-dependent insulinotropic polypeptide, thereby prolonging the increase in active forms of the two incretin hormones after meal ingestion. This results in stimulation of insulin secretion, as judged by increased insulin and C-peptide levels relative to glucose after oral glucose or mixed meal ingestion in individuals with type 2 diabetes[24-30]. This has also been observed in Japanese patients[31,32]. Furthermore, DPP-4 inhibitors also augment insulin secretion after intravenous glucose administration in humans[33-36]. What is also important is that the effect is glucose-dependent, which means that insulin secretion is stimulated when glucose levels are elevated, but that DPP-4 inhibition does not stimulate insulin secretion at low glucose levels[3]. This is explained by an increased glucose sensitivity in the β-cells, which has been shown with the DPP-4 inhibitors, vildagliptin[37] and sitagliptin[38]. This is mainly explained by the glucose-dependent mechanism of the insulin secretory effect of GLP-1, which was initially shown in *in vivo* model experiments in mice[39].

Another important effect of DPP-4 inhibition is inhibition of glucagon secretion. This was first shown in humans for vildagliptin after a mixed meal in individuals with type 2 diabetes[40], and was later confirmed for other DPP-4 inhibitors in white patients[3,41]. In Japanese patients, glucagon levels were slightly suppressed by DPP-4 inhibition after meal ingestion in two studies[42,43], but not significantly changed in another study[44], whereas in Chinese patients, a clear reduction in glucagon levels after meal ingestion was observed for DPP-4 inhibition[45]. These results might suggest that the increase in insulin secretion is more important than the reduction in glucagon in some populations, although this needs to be tested in further comparative studies. The glucagon-reducing effect of DPP-4 inhibition is most likely mediated by GLP-1, which already in 1992 was shown to inhibit glucagon secretion in individuals with type 2 diabetes[46]. More detailed studies on islet effects of DPP-4 inhibition exist, and they have been summarized and reviewed in more detail[3,47,48]. There are additional beneficial effects of DPP-4 inhibition on lipid metabolism, which was recently reviewed[3].

It was recently shown that the increase in insulin secretion and the inhibition of glucagon secretion by DPP-4 inhibitors persist throughout the day; that is, it occurs both after breakfast, lunch and dinner[49]. In fact, the reduction in postprandial glycemia, the increase in insulin secretion relative to glucose and the inhibition of glucagon secretion by three different DPP-4 inhibitors (vildagliptin, sitagliptin and saxagliptin) were similar after the three daily meals in individuals with metformin-treated type 2 diabetes.

ISLET DYSFUNCTION IN TYPE 2 DIABETES

As shown in Figure 1, key defects for the development of glucose dysregulation in type 2 diabetes is insufficient release of

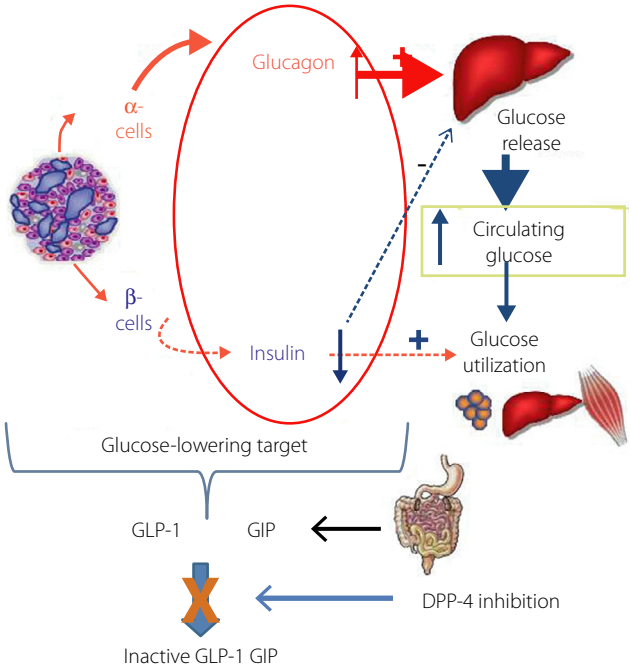

Figure 1 | Illustration of pathophysiology of type 2 diabetes showing enhanced glucagon release from the α-cells, which overstimulates hepatic glucose production, and impaired insulin secretion from islet β-cells, resulting in impaired stimulation of glucose utilization and less inhibition of liver glucose production – all this resulting in hyperglycemia. Dipeptidyl peptidase-4 (DPP-4) inhibition targets these changes by preventing the inactivation of the incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which are released from the gut, thereby increasing insulin secretion and inhibiting glucagon secretion, resulting in normalization of circulating glucose.

insulin from islet β-cells in association of exaggerated release of glucagon from islet α-cells. This conclusion has been possible to establish from the results of several clinical studies, showing defective insulin secretion[50-55] or inappropriately high glucagon secretion in type 2 diabetes[56-59]. The impaired insulin secretion results in inappropriately low circulating levels of insulin, leading to impaired stimulation of glucose utilization in peripheral tissues, and the inappropriately high glucagon levels result in exaggerated hepatic glucose production and release. These processes together raise circulating glucose. It has also been shown that these combined islet defects are present in individuals with impaired glucose tolerance; that is, before the onset of type 2 diabetes[60]. Furthermore, a long-term 12 year follow-up study in 49 white people with normal glucose tolerance showed that impaired insulin secretion and elevated glucagon secretion exist several years before the onset of impaired glucose tolerance[61]. Figure 2 shows these results. Insulin and glucagon secretion were evaluated using the glucose-dependent arginine stimulation test regularly for 12 years in individuals who had normal glucose tolerance at the start. By dividing the results into those who developed impaired glucose tolerance during the 12 year follow-up period and those who maintained normal glucose tolerance, it is evident that those developing impaired glucose tolerance had impaired insulin secretion and elevated glucagon secretion before the onset of diabetes.

When judging insulin secretion, it is important to relate the finding to insulin sensitivity, because insulin secretion is inversely upregulated in reduced insulin sensitivity, which is a relationship that has been described as a hyperbolic relationship[62,63]. When insulin secretion falls below the curve, it is insufficient for the prevailing insulin sensitivity, which results in glucose dysregulation[64]. Type 2 diabetes evolves when insulin secretion is high, but still insufficient to a reduced insulin sensitivity, which is illustrated as the blue dot in Figure 3, and which might be seen in individuals with obesity. Conversely, type 2 diabetes also evolves in high insulin sensitivity, if insulin secretion is lower than required, which is illustrated as the red dot. These two examples, therefore, show two different types of type 2 diabetes, which have therapeutic implications. A patient represented by the blue dot with combined insufficient insulin secretion and insulin resistance might be treated with agents that stimulate insulin secretion, such as DPP-4 inhibition or GLP-1 receptor agonists[65], in combination with agents that increase insulin sensitivity, such as metformin. In contrast, agents that stimulate insulin secretion might be sufficient in patients illustrated by the red dot. Both types of patients might, however, also be treated with agents that have other mechanisms, such as insulin or sodium–glucose cotransporter 2-inhibitors, as suggested previously[66].

DPP-4 INHIBITION TARGETS ISLET DYSFUNCTION

The islet focus of the mechanism of action of DPP-4 inhibitors and the critical role of islet dysfunction for the development of type 2 diabetes would make DPP-4 inhibitors appropriate for individuals with the greatest reduction in islet function. Hypothetically this would be particularly so in individuals with high insulin sensitivity; that is, patients illustrated by the red dot in Figure 3. This would imply that DPP-4 inhibition would be particularly powerful in patients with low body mass index (BMI) compared with high BMI, as BMI correlates inversely with insulin sensitivity, and, consequently, that DPP-4 inhibitors would be less efficient in individuals with high insulin

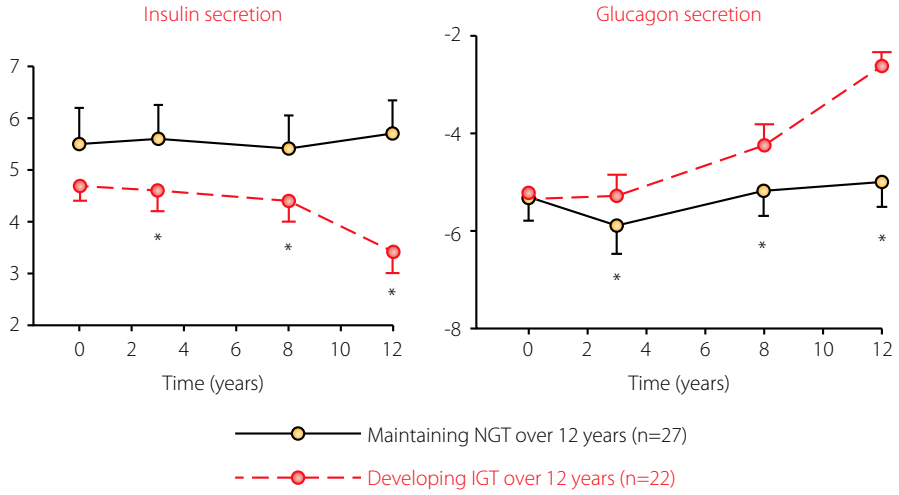

Figure 2 | Insulin secretion and glucagon secretion, as obtained from the glucose-dependent arginine-stimulation test at baseline, and after 3, 8 and 12 years in a cohort of women who had normal glucose tolerance at baseline and either maintained normal glucose tolerance (NGT; $n = 27$) or developed impaired glucose tolerance (IGT; $n = 22$) during the 12 year follow-up period. Means ± standard deviations are shown. Asterisks indicate the probability level of random difference between the two groups of $P < 0.05$. Original data reported in Ahrén[61].

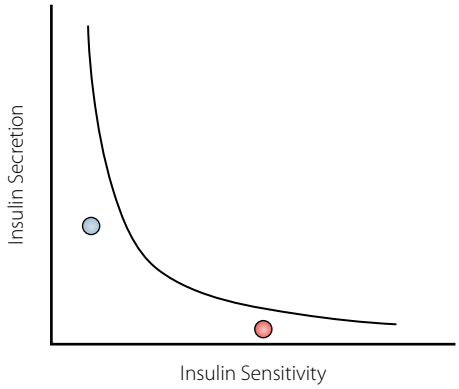

Figure 3 | Schematic illustration of the inverse hyperbolic relationship between insulin sensitivity and insulin secretion in normal individuals with two patterns of pathophysiology of type 2 diabetes. The blue dot represents a patient with insulin resistance and insufficient increase in insulin secretion, whereas the red dot represents a patient with high insulin sensitivity and with low, and therefore insufficient insulin secretion.

resistance. Such hypotheses are important for the examination of the discussion of precision medicine. This hypothesis was supported by the results of a 6-month study showing that DPP-4 inhibition was less active in reducing HbA1c in individuals with high insulin resistance, as estimated by indirect markers, whereas there was no association with markers of insulin secretion[67]. However, studies aiming at predicting changes in HbA1c by DPP-4 inhibitors using BMI have in general been inconclusive, as although some studies have reported an association between BMI and less response to DPP-4 inhibition[67], most studies have reported no such influence[68-71]. A problem in the interpretation of these studies is, however, that the most powerful predictor is baseline HbA1c, which might mask any independent prediction by BMI. Hence, baseline HbA1c has been shown to predict 34% of change in HbA1c in one meta-analysis consisting of 98 randomized clinical trials with various DPP-4 inhibitors in more than 24,000 patients[70]. Similarly, in five randomized clinical trials with vildagliptin, 36% of change in HbA1c was attributed to baseline HbA1c[71], and a pooled analysis of three trials with linagliptin showed similarly that BMI did not predict the change in HbA1c[72]. Therefore, whereas insulin resistance might be a factor in reducing the efficacy of DPP-4 inhibitors, this is not translated to clinical markers, such as BMI, and is therefore of less clinical importance.

TARGETING ISLET DYSFUNCTION AND TYPE 2 DIABETES IN EAST ASIA

Several studies have presented results that are consistent with a view that type 2 diabetes in East Asia is relatively more dependent on insufficient insulin secretion relative to insulin resistance or hyperglucagonemia when compared with white individuals[73]. This has been demonstrated by showing a lower insulin response to oral and intravenous glucose in East Asian than in white patients[74-76], and that a progressive reduction in insulin secretion relative to insulin resistance is the critical key factor for the development of type 2 diabetes in Korean individuals[77,78].

It has also recently been proposed that the dietary intake of macronutrients is of relevance for the glucose-lowering action of DPP-4 inhibition. Thus, it was shown that the HbA1c lowering action of DPP-4 inhibition was higher in individuals who consumed less saturated fat[79]. This might be related to the action of glucose-dependent insulinotropic polypeptide, which after high-fat intake facilitates energy storage in adipocytes[80]. This might contribute to the explanation that DPP-4 inhibition is more efficient in populations with a lower intake of saturated fats as east Asians.

The importance of islet dysfunction for the development of type 2 diabetes in East Asian people suggests that DPP-4 inhibition will be an effective glucose-lowering therapy in this population. This is supported by several studies in East Asian individuals[81-84]. It has also been shown, which is of particular interest, that the glucose-lowering efficacy of DPP-4 inhibition seems to be greater in East Asian people than in white people, as has been reviewed by meta-analyses[85-87]. In a meta-analysis of 55 studies, HbA1c was reduced by 1.01% in Asian individuals versus 0.74% in non-Asian individuals, which was a significant difference. Also, the fasting plasma glucose-lowering efficacy was higher with DPP-4 inhibition in the Asian individuals[85]. In another meta-analysis, a reduction in HbA1c by DPP-4 inhibition was 0.65% in non-Japanese individuals in 55 studies versus by 1.67% in Japanese individuals in seven studies[86]. Similarly, a meta-analysis of 93 studies showed a reduction in HbA1c by 0.62% in non-Japanese individuals versus 0.86% in Japanese individuals[87]. This was also shown in a meta-analysis of studies using GLP-1 receptor agonists[88]. Hence, although no direct head-to-head study exists comparing the efficacy of DPP-4 inhibition in East Asian versus white individuals, there is a clear and significant trend that the efficacy is greater in East Asian individuals.

CONCLUSION

There is a firm basis that DPP-4 inhibition is an efficient and safe glucose-lowering therapy for type 2 diabetes that is orally effective and associated with a low risk of hypoglycemia, weight gain or other adverse events. There is also a large amount of data, both clinical and experimental, showing that improvement of islet function is a key mechanism behind the glucose-lowering action of DPP-4 inhibition, both related to an increase in insulin secretion and inhibition of glucagon secretion. Furthermore, there are experimental and clinical bases for a conclusion that islet dysfunction is a more important key factor for the development of type 2 diabetes in individuals from East Asia than in white individuals. Therefore, DPP-4 inhibition is an important alternative for glucose-lowering medication in

East Asia, and clinical experience with efficacy and durability supports this.

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DISCLOSURE

The author has throughout the years been consulting for and/or lecturing for Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi and Takeda, which all are companies producing DPP-4 inhibitors or GLP-1 receptor agonists.

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