Imeglimin - A New Oral Anti-Diabetic that Targets the Three Key Defects of Type 2 Diabetes

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Abstract

Study background: The objective of this collated research paper is to highlight the anti-diabetic effects and mode of action of imeglimin, the first in a new tetrahydrotiazine-containing class of oral anti-diabetic agents: the glimens. Imeglimin acts on both insulin resistant organs (liver and muscle) and pancreatic β-cells (insulin secretion in response to glucose and protection against apoptosis).

Methods: The aim of the investigations reported here is to present data on the mode of action of imeglimin and its anti-diabetic effects, demonstrating that it represents a promising treatment for type 2 diabetes by acting on the three key pathological defects of the disease, namely excessive hepatic glucose production, impaired peripheral glucose uptake by skeletal muscle, and insufficient insulin secretion.

Results: Imeglimin significantly lowered fasting plasma glucose concentrations in a dose-dependent manner in STZ rats. HbA1c was significantly reduced (P<0.01) by imeglimin (6.2%) compared with controls (9.83%). At a 150 mg kg⁻¹ dose, imeglimin significantly improved glucose tolerance compared with controls (AUC₀–₁₅₀ mmol·L⁻¹·h⁻¹ respectively). With regards to its mode of action, imeglimin significantly decreased the rate of hepatic gluconeogenesis, stimulated muscle glucose uptake, induced a potentiation of glucose-dependent insulin secretion, and decreased β-cell apoptosis.

Conclusion: Our investigations found that imeglimin uniquely targets the three key defects of type 2 diabetes. It could provide more durable, sustained glycemic control than currently achieved with oral anti-diabetics and has the potential to be used at any stage in the disease continuum. Imeglimin’s potential for combination with other oral anti-diabetics is also under investigation.

Keywords: Imeglimin; Glimin; Novel oral anti-diabetic; Type 2 diabetes; Type 2 diabetes pharmacological treatment; Three defects type 2 diabetes; Pre-clinical findings

Introduction

Imeglimin is the first of a new class of drugs – the glimens – and is being developed for the treatment of type 2 diabetes. Imeglimin is a tetrahydrotiazine compound with a chemical name of (6R)-(+-)-4-dimethylamino-2-imino-6-methyl-1,2,5,6-tetrahydro-1,3,5-triazine hydrochloride. The aim of developing imeglimin was to provide a safe and well-tolerated drug with unique pharmacological properties that can effectively treat the underlying metabolic defects in patients with type 2 diabetes mellitus. Indeed, imeglimin has already achieved its clinical proof of concept in an extensive Phase I/II programme [1]. In addition, because imeglimin appears to have a different mechanism of action to other oral anti-diabetic compounds, it may be suitable for safe and effective combination with other drugs routinely used for treating type 2 diabetes and its common co-morbidities.

The primary pathophysiological defects of type 2 diabetes include: excessive hepatic glucose production, impaired peripheral glucose uptake by insulin-sensitive tissues, and insufficient insulin secretion/ increased β-cell apoptosis [2,3]. Type 2 diabetes is a progressive disease and deterioration of glycaemic control is partly due to a gradual loss of β-cell function and mass [4,5,6]. Currently, pharmacological agents for treating type 2 diabetes comprise drugs acting on insulin-resistant organs or on the pancreas. Thus, these agents target one or two, but not all three key defects of type 2 diabetes and help achieve glycaemic targets in the short-to-medium term; however, loss of glycaemic control also occurs in the long term [7]. Cross-sectional data suggest that around 56% of patients with type 2 diabetes have a HbA₁c ≤ 7.0% [8]. However, with increasing duration of diabetes, glycaemic control continues to deteriorate and it requires the addition of increasingly complex insulin-containing regimens to maintain 50% of the patients at HbA₁c ≤ 7.0% [9]. Metformin is currently the first-line pharmacological treatment for type 2 diabetes together with lifestyle intervention, recommended by the American Diabetes Association and the European Association for the Study of Diabetes [10]. However, an annual failure rate of 17% for metformin therapy has been reported, although this was reduced to 12% in patients who initiated metformin therapy within 3 months of type 2 diabetes diagnosis [11]. In addition to deterioration in glycaemic control, existing treatments also have limitations either because of side effects, especially weight gain, hypoglycaemia, cardiovascular disorders or contraindications limiting their use [12].

Newer classes of agents are being developed with novel mechanisms.
Diabetes was induced by soleus and gastrocnemius muscle: 20 n19

Citation: contained Dulbecco medium (DME) only, and subsequent sets of

period, the cells were cultured for 16–18 h. One set of wells (Wistar rats using the method of Seglen [43 x85].

Hepatic glucose production time 0 and 30 min post oral glucose load and the incremental change

the insulinogenic index (∆I/∆G) was calculated. This was defined as using genetic type 2 diabetic GK rats. An OGTT was performed and

imeglimin (50, 100 or 150 mg·kg

60, 120, and 180 min afterwards.

was performed on rats after 8 weeks of treatment, with a 2 g·kg

metformin (50 mg·kg

saline solution) to Wistar rats. Several groups of diabetic rats received either oral imeglimin (25, 50, or 100 mg·kg

oral metformin (50 mg·kg

35 days), with a further group serving as a placebo control. Blood samples were collected after 35 days in rats

fasted for 16 h for fasting plasma glucose and HbA1c measurements. Results are expressed as the mean and standard error of the mean

(150 mCi·mmol

m) rats were treated with various doses of imeglimin (0.125–

Goto-Kakizaki rats: The effect of chronic administration of oral imeglimin (25, 75, or 150 mg·kg

bid) for 8 weeks was investigated using male genetic type 2 diabetic Goto-Kakizaki (GK) rats. An OGTT was performed on rats after 8 weeks of treatment, with a 2 g·kg

body weight glucose load administered 2 h after the last administration of the

Blood samples were collected at the time of the glucose load and

60, 120, and 180 min afterwards.

In another experiment, the effect of chronic administration of oral imeglimin (50, 100 or 200 mg·kg

bid) for 16 days was investigated using genetic type 2 diabetic GK rats. An OGTT was performed and

and the insulinogetic index (AI/AG) was calculated. This was defined as the ratio of the incremental change (AI) in plasma insulin between
time 0 and 30 min post oral glucose load and the incremental change (AG) in plasma glucose between time 0 and 30 min after the glucose

load. Statistical analysis was performed using ANOVA followed by a Bonferroni/Dunnnett protected least-significant differences post hoc test.

Hepatic glucose production

Isolated hepatocytes: Hepatocytes were isolated from male Wistar rats using the method of Seglen [18]. After a 4 h-attachment

period, the cells were cultured for 16–18 h. One set of wells (n = 5)

contained Dulbecco medium (DME) only, and subsequent sets of wells contained AMPc (50 µmol·L

and imeglimin at either 0.125, 0.25, 0.5, 1.0, or 1.5 mmol·L

(n = 5 for each concentration). At the end of the culture period, the medium was removed and replaced by Krebs buffer supplemented with lactate/ pyruvate (10 mM/1mM respectively) gluconeogenic precursor for 3 additional h. The concentrations of AMPc/Dex and imeglimin

remained as previously described. After the three-h incubation period, the amount of glucose in the medium was measured. Imeglimin

activity was expressed as percentage inhibition of glucose production. Dunnnett’s t-test was used to analyse differences between imeglimin

and the control group.

Liver slices: Precision-cut liver slices were prepared from 48-h-fasted male rats aged 10–12 weeks and were incubated for 4 h in oxygenated Krebs-Henseleit medium with 2-13C-labeled lactate (5 mmol·L

in the absence or presence of imeglimin. Addition of perchloric acid was used to terminate the incubations. Consumption of these substrates

and product accumulation was measured enzymatically and utilization/ production rates were calculated as the difference between the amount of substrate or product present before and after incubation. Results are presented as means and standard error of the means (SEMs) and were

analysed using Student’s t-test.

Muscle glucose uptake

In vitro H-2Kb muscle cell line: H-2Kb cells were derived from heterozygous H-2Kb transgenic mice and were seeded in plates coated

with matrigel. Cells were cultured at 33°C for 4 days under permissive conditions [19], and then switched to non-permissive culture conditions at 37°C in the absence of interferon-γ. The cells were then incubated for 4 h in Dulbecco’s Modified Eagle’s Medium containing 1 g·L

of glucose and various concentrations of imeglimin (0.125–

2.0 mmol·L

pyruvate (10 mM/1mM respectively) gluconeogenic precursor for

was removed and replaced by Krebs buffer supplemented with lactate/

pyruvate (10 mM/1mM respectively) gluconeogenic precursor for

3 additional h. The concentrations of AMPc/Dex and imeglimin

remained as previously described. After the three-h incubation period, the amount of glucose in the medium was measured. Imeglimin

activity was expressed as percentage inhibition of glucose production. Dunnnett’s t-test was used to analyse differences between imeglimin

and the control group.

Pancreatic glucose-dependent insulin secretion

Perfused pancreas: Pancreatic insulin secretion was also investigated using the perfused pancreas model. Male Wistar rats were

made diabetic by administration of STZ (100 mg·kg

intravenously) at birth (NOSTZ). Isolation and perfusion of the pancreas was performed on animals at 10–17 weeks old using a modification of the Sussman technique [20,21]. Krebs Ringer Bicarbonate (KRB) buffer pH 7.4
was continuously oxygenated (O₂:CO₂: 95:5). D-glucose (16.5 mM, final concentration) or L-arginine (19 mM, final concentration) were administered through a side-arm syringe. The bolus of 19 mM arginine was performed at the end of the experiment to assess the integrity of the pancreata.

Four groups were assessed: controls (n = 5) and imeglimin at 50µmol·L⁻¹ (n = 5), 100 µmol·L⁻¹ (n = 4), and 250 µmol·L⁻¹ (n = 4). Following a 20-min equilibration period, pancreata were perfused for 35 min with KRB alone (control group) or imeglimin. Glucose was added (final concentration 16.5 mmol·L⁻¹) to both control (KRB) and imeglimin pancreata, and the tissues were perfused for a further 20 min. The insulin secretion rate was calculated by multiplying the insulin concentration by the flow rate and expressed as µU·min⁻¹. The effect of imeglimin on peak insulin response to glucose was analysed using ANOVA followed by a Student-Newman-Keuls test.

**Hyperglycaemic clamp:** The effects of imeglimin (200 mg·kg⁻¹) on insulin secretion were investigated using the hyperglycaemic clamp method in anaesthetized female non-diabetic Wistar rats (n = 7) and NOSTZ Wistar rats (n = 12). Imeglimin was compared against the insulin secretagogue repaglinide (0.1 mg·kg⁻¹; n = 7) for the non-diabetic Wistar rats and n = 11 for the NOSTZ Wistar rats respectively, the incretin enhancer sitagliptin (3 mg·kg⁻¹; n = 8 and n = 11 respectively), and controls (n = 7 and n = 9 respectively). Sitagliptin was chosen as a comparator because it is the first oral glucos-dependent insulin secretagogue in the incretin class. Animals received their allotted treatment following a 1-h fast. A tracheotomy was performed on the anaesthetized animals and blood sampling was undertaken using a carotid artery catheter. A saphene vein was isolated and catheterized for glucose infusions. Fifty-five min post-treatment (T0), a blood sample was collected to assess basal levels of insulin and glucose. Thirty min later, glucose was infused to maintain plasma glucose at 2 distinct levels: 9.5 mmol·L⁻¹ (first-stage hyperglycaemia) and 12.5 mmol·L⁻¹ (second-stage hyperglycaemia) for the Wistar rats; and 19.5 mmol·L⁻¹ (first-stage hyperglycaemia) and 24.7±1.7 mmol·L⁻¹ (second-stage hyperglycaemia) for the NOSTZ rats. Blood was collected from the carotid artery at 0 min (T0); 50, 55, and 60 min (for first-stage hyperglycaemia); and 80, 85, and 90 min (for second-stage hyperglycaemia). Blood insulin and glucose levels were subsequently measured, with insulin concentrations expressed as pmol·L⁻¹. Statistical analyses were performed using ANOVA and Dunnett’s t-test.

**Cell death**

Pancreatic β-cell apoptosis: Male Wistar rat islets were cultured in a cytokine cocktail that mimicked inflammatory stress in diabetes. Islet cells were isolated using collagenase and cultured in Roswell Park Memorial Institute (RPMI) 1640 medium incorporating penicillin (100 U·mL⁻¹), streptomycin, (100 µg·mL⁻¹), and gentamycin (100 µg·mL⁻¹). Cells were incubated at 37°C in a humidified atmosphere of 95% air/5% CO₂.

For glucose-induced cell death, cells were incubated for 72 h in complete RPMI 1640 medium supplemented with 19 mmol·L⁻¹ D-glucose (final concentration 30 mmol·L⁻¹). Osmotic control was performed by supplementing RPMI 1640 medium with mannitol (19 mmol·L⁻¹). Before exposure to 30 mmol·L⁻¹ glucose, cells were incubated in the presence or absence of imeglimin (100µmol·L⁻¹) for 24 h.

Apoptosis analyses were performed using a double-stain system with FluoProbes 488 conjugated with Annexin V (Interchim) and propidium iodide (Sigma Aldrich). INS-1 cells were detached by trypsinization, washed by centrifugation, and incubated with 100L µl from a stock) was added. The suspension was immediately analysed using a FACS CALibur flow cytometer (Becton Dickinson Biosciences) equipped with a 15-mW argon ion laser tuned to 488 nm and Cell Quest Pro software (Becton Dickinson Biosciences). Data were presented as a function of fluorescence intensity on FL-1 (530 nm/30 nm band-pass filter) (Annexin V) and propidium iodine channels (585–542 nm band-pass filter). Normal healthy cells were both Annexin V/propidium iodine negative. Results were presented as means (SEM) and statistical analysis of any differences was analysed using Student’s t-test.

**Results**

**Anti-diabetic effects in experimental diabetes**

**STZ diabetic rats:** After 35 days, imeglimin treatment significantly lowered fasting plasma glucose concentrations in a dose-dependent manner.
When compared with control STZ rats (9.83%), fasting HbA1c (% after 36 days of treatment and 2 h after the last drug administration were investigated as described in Methods. Results are means and SEM for n = 10 (**P<0.01 compared with control).

Imeglimin caused a dose-dependent inhibition of hepatic glucose production compared to that of metformin (6.78%) (**P<0.01) at doses from 0.25–1.5 mmol·L\(^{-1}\)) in isolated rat hepatocytes. The strong inhibitory effect was concentration dependent, with percentage inhibitions of 9% (0.25 mmol·L\(^{-1}\)), 34% (0.5 mmol·L\(^{-1}\)), 68% (1 mmol·L\(^{-1}\)), and 80% (1.5 mmol·L\(^{-1}\)). At the higher doses, this effect was comparable to that of metformin (data not shown).

Inhibition of hepatic glucose production

Isolated hepatocytes: Imeglimin (0.25–1.5 mmol·L\(^{-1}\)) decreased the levels of hepatic gluconeogenesis induced by cAMP/Dex with lactate/pyruvate as precursors (Figure 5) in isolated rat hepatocytes. The strong inhibitory effect was concentration dependent, with percentage inhibitions of 9% (0.25 mmol·L\(^{-1}\)), 34% (0.5 mmol·L\(^{-1}\)), 68% (1 mmol·L\(^{-1}\)), and 80% (1.5 mmol·L\(^{-1}\)). At the higher doses, this effect was comparable to that of metformin (data not shown).

Liver slices: As shown in Figure 6, imeglimin caused a dose-dependent inhibition of gluconeogenesis in liver slices from 48 h fasted non-diabetic ZDF rats as described in Methods. Results are the mean values of five wells each. Imeglimin significantly inhibited glucose production (**P<0.01) at doses from 0.25–1.5 mmol·L\(^{-1}\) when compared with controls.
dependent inhibition of 14C-glucose production in liver slices from 48-h-fasted non-diabetic ZDF rats following 4 h acute treatment. Decreases in 14C-glucose production were 14% (2.5 mmol·L⁻¹), 48% (5 mmol·L⁻¹) and 84% (10 mmol·L⁻¹).

Stimulation of skeletal muscle glucose uptake

In vitro H-2Kb muscle cell line: Imeglimin significantly stimulated glucose uptake (P<0.001) by in vitro H-2Kb muscle cells in a dose-dependent manner (from 0.5 to 2.0 mmol·L⁻¹) (Figure 7). A maximum stimulation of glucose uptake by 3.3-fold was observed at the highest dose (2.0 mmol·L⁻¹) of imeglimin.

In vivo soleus and gastrocnemius muscle: Muscle glucose uptake by soleus and gastrocnemius in vivo was reduced in STZ rats compared with controls under basal conditions (P<0.01). Following 45 days of treatment with imeglimin, glucose uptake was significantly increased (P<0.01) by the lowest dose of imeglimin (25 mg·kg⁻¹) and was restored to normal levels by the two higher doses of the drug (50 and 100 mg·kg⁻¹) (P<0.05 and P<0.01 respectively) (Figure 8). Stimulation of glucose-dependent insulin secretion

Perfused pancreas: Imeglimin (0.05, 0.1, or 0.25 mmol·L⁻¹) had no effect on insulin secretion in the absence of glucose, but in the presence of glucose (16.5 mmol·L⁻¹) it induced a strong potentiation of first-phase glucose-induced insulin secretion (Figure 9). First-phase insulin secretion is markedly diminished in this particular model of diabetes. The response to imeglimin did not appear to be dose-dependent, although this may have been due to the variability in response observed at the 0.05 mmol·L⁻¹ concentration.
Figure 11: The effects of imeglimin (0.1 mmol-L\(^{-1}\) or 1 mmol-L\(^{-1}\)) on protection of rat pancreatic β cells against apoptosis were investigated as described in Methods. Values are mean (SEM) of n = 4 in each group. Imeglimin provided significant protection against apoptosis in the presence of cytokines controls: § P<0.05 and §§§ P<0.001 for between group comparisons as indicated on the graph; *** P<0.001 compared with control plus cytokines; #### P<0.001 compared with control minus cytokines.

Figure 12: The effects of imeglimin (0.1 mmol-L\(^{-1}\)) on protection of rat INS-1 cells against glucose-induced cell death was investigated as described in Methods. Values are mean (SEM) of n = 4 in each group.

Hyperglycaemic clamp: In the non-diabetic Wistar rats, imeglimin increased insulin secretion by 25% at the highest level of hyperglycaemia (12.5 mmol-L\(^{-1}\)) when compared to controls. This increase was equal to that of sitagliptin (25%) and more prominent than that of repaglinide (11%) (Figure 10a). No imeglimin-related increases in insulin secretion were observed at basal glycaemic levels (T0) or at the (relatively low) first stage of hyperglycaemia (glycaemia: 9.5 mmol-L\(^{-1}\)). In the diabetic N0STZ rats, imeglimin increased insulin secretion versus controls at all glycaemic levels, evoking a 48% increase at T0 (glycaemia: 10.8 mmol-L\(^{-1}\)); a 62% increase at the first stage of hyperglycaemia (glycaemia: 19.5 mmol-L\(^{-1}\)); and a 68% increase at the second stage of hyperglycaemia (glycaemia: 24.7 mmol-L\(^{-1}\)). At first-stage hyperglycaemia, and second-stage hyperglycaemia, these increases were comparatively greater than those evoked by either sitagliptin (34%, and 39% respectively) or repaglinide (8%, and 37% respectively) (Figure 10b).

Protection against cell death

β-cell apoptosis: In the absence of cytokines, imeglimin (0.1 mmol-L\(^{-1}\)) appeared to have a protective effect on basal apoptosis: 10% less apoptosis than untreated islets. Exenatide (10 mmol-L\(^{-1}\)) produced a 16% decrease in cell death. Conversely, a 17% increase in apoptosis was noted with cyclosporin A. The cytokine cocktail caused a 12% increase in cell death. This was completely abrogated in the presence of imeglimin, with 37% less apoptosis at the lower concentration and 25% less at the higher concentration (Figure 11). It is noteworthy that both concentrations of imeglimin abolished the pro-apoptotic effect of the cytokines. This may be explained by the cytokines’ sequential bimodal effect on β cells (stimulatory then suppressive) which is directly dependent on cytokine dose, duration of exposure, and ambient glucose concentration [22]. Exenatide also decreased apoptosis by 29%, whereas cyclosporin A resulted in an 8% increase in apoptosis over and above that caused by cytokines. The protective effect of imeglimin was 49% greater than that achieved by exenatide.

Protection of INS-1 cells from cell death: As shown in Figure 12, cell viability was dramatically affected by 30 mmol-L\(^{-1}\) glucose, whereas previous experiments have shown that osmotic change (exposure to mannitol 19 mmol-L\(^{-1}\)) does not affect the viability of INS-1 cells (data not shown). Importantly, imeglimin (0.1 mmol-L\(^{-1}\)) had a significant protective effect on glucose-induced toxicity.

Discussion

Imeglimin is the first in a new glimin class of anti-diabetic drugs and is currently being developed for the treatment of type 2 diabetes. Management of type 2 diabetes emphasizes glycaemic control in terms of HbA\(_1c\) (lowering fasting and post-prandial blood glucose concentrations); there is an ongoing need for new agents which have sustained efficacy and excellent safety. Early studies showed that imeglimin is as effective as metformin in regulating glycaemic control [1]. This paper strengthens these findings by investigating other effects of imeglimin, including peripheral skeletal glucose uptake and insulin secretion.

Most of the anti-diabetic compounds currently available act either on peripheral organs to control hepatic glucose production and/or muscle glucose uptake or on β-cell failure to improve insulin secretion and/or exert β-cell protection. But none of these compounds is able to target all defects. We report here that imeglimin is an innovative compound able to regulate multiple targets, including insulin resistant organs as well as β-cell failure.

Imeglimin was tested in two animal models of type 2 diabetes, the STZ and the GK rat models. An improvement comparable to metformin was observed on all glycaemic parameters: fasting plasma glucose, post absorptive plasma glucose, HbA\(_1c\), and glucose tolerance. These effects were observed after 5 and 8 weeks of treatment in STZ and GK rats, respectively. Skeletal muscle is the major tissue for insulin-mediated glucose disposal, accounting for approximately 75% of insulin-stimulated glucose uptake in the body as a whole [23]. Decreased uptake of glucose by muscle (peripheral insulin resistance) is an important factor resulting in hyperglycaemia in type 2 diabetes. The in vitro increase in glucose uptake observed with imeglimin in the muscle cell line has been confirmed in vivo with a complete restoration of glucose consumption in two types of muscles (soleus and gastrocnemius) after 45 days of treatment in STZ rats. Moreover, preliminary data from an acute euglycaemic hyperinsulinaemic clamp performed in GK rats suggested that imeglimin shows some anti-hyperglycaemic properties at the dose of 100 mg·kg\(^{-1}\)·h\(^{-1}\) in basal conditions associated with an increased glucose utilization rate (data not shown).

Overcoming the excessive hepatic glucose production observed in type 2 diabetes is also an important therapeutic aspect of glycaemic control as it participates in the control of both fasting and post-prandial plasma glucose. Imeglimin demonstrates dose-dependent decrease in hepatic glucose production in primary hepatocytes from...
Wistar rats in the absence of insulin. Inhibition of hepatic glucose production was also confirmed in liver slices of lean 48-h fasted rats after a 4 h acute treatment using isotopic method (13C-glucose). This effect is correlated with a decrease in the gene transcription of two important enzymes controlling gluconeogenesis and glycogenolysis, namely phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), in H4IIE cells (data not shown).

Progression of type 2 diabetes is caused by insufficient insulin secretion, usually in the context of resistance of peripheral tissues to the action of the hormone, and is characterized by progressive deterioration of β-cell function over time [24], which occurs very early in the course of the disease. Associated with the reduced β-cell function (50% of normal level at the time of diagnosis), a reduction in β-cell mass is also observed (reduction of 60% at necropsy), involving both increased apoptosis and reduced proliferation of pre-existing β cells [25]. Among the factors contributing to overall β-cell failure are hypersecretion of insulin secondary to insulin resistance and/or insulin secretory drugs, glucotoxicity, lipotoxicity and glucolipotoxicity.

Imeglimin addresses β-cell failure by targeting both β-cell function and survival. Its effects on insulin secretion have been well documented in isolated perfused pancreas of NOSTZ rats and confirmed in hyperglycaemic clamps performed in Wistar and NOSTZ rats, and also during OGTT performed in GK rats (AI/AG at 30 min). The glucose-dependency of insulin secretion observed with imeglimin provides clear advantages in terms of safety regarding the risk of hypoglycaemia. In the clamp experiments, the effect was comparable to the effect observed with the DPP-IV inhibitor sitagliptin in the Wistar rat and higher in the NOSTZ rat. Sitagliptin has been shown to induce glucose-dependent insulin secretion through an incretin effect, by increasing GLP-1 half-life and subsequently GLP-1 concentration. Although the mechanism of action of imeglimin on insulin secretion has not yet been fully elucidated, it is reasonable to assume that it is distinct from DPP-IV inhibitors, thereby leading to a potential additive effect. Whether this hypothesis is correct needs to be further investigated.

The effects of imeglimin on β-cell function are associated with a significant protective effect on cells in vitro which have been submitted to various acute stresses. Experiments have been conducted in two types of β cells, isolated rat islets and the rat insulinoma cell line INS-1. The β-cell preparations have been submitted to two different stresses: a cocktail of cytokines and a high glucose concentration. Both are relevant types of β cells, isolated rat islets and the rat insulinoma cell line INS-1. The β-cell preparations have been submitted to two different stresses: a cocktail of cytokines and a high glucose concentration. Both are relevant types of β cells, isolated rat islets and the rat insulinoma cell line INS-1.

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