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Effects of S 21403 on hormone secretion from isolated rat pancreas at different glucose concentrations

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Abstract

We investigated the in vitro effects of therapeutical concentrations of S 21403 (a succinic acid derivative also known as KAD 1229 and mitiglinide) on insulin and glucagon secretion during a metabolic stimulus (glucose rising from 5 to 8.33 mM) or at a stable 2.22 mM glucose using the isolated perfused rat pancreas model, and we compared them with the patterns of repaglinide and glibenclamide. Control perfusions were also performed. During 8.33 mM glucose, insulin release peaked to 339.12 ± 22.87 μU/ml in controls. S 21403 enhanced insulin release (first peak 413.02 ± 14.90 μU/ml; $P<0.03$ vs. controls, $P=$ ns vs. repaglinide, $P<0.005$ vs. glibenclamide). Repaglinide increased glucose-induced first peak secretion to 409.33 ± 20.05 μU/ml within the eighth minute ($P<0.05$ vs. controls, $P<0.01$ vs. glibenclamide). Glibenclamide did not affect the first phase of glucose-induced insulin release (peak of 338.41 ± 29.79 μU/ml) but potentiated and delayed the second phase. No drug affected glucagon release. In conclusion, S 21403 induces a faster, more physiological pattern of insulin release than the other drugs we tested.

Keywords: S 21403; Repaglinide; Glibenclamide; Pancreas, isolated, rat; Insulin release; Glucagon release

1. Introduction

The normal pancreatic insulin response to glucose shows a biphasic profile, i.e. a rapid, transitory peak of hormone secretion within the first 10 min, followed by a second phase of release lasting for as long as the glycaemic stimulus. Typical of type 2 diabetes is the loss of the first phase of insulin secretion and a reduced, delayed second phase of insulin-secretory profile so that a global B-cell dysfunction develops (Bruce et al., 1988; Luzi and De Fronzo, 1989; Mitrakou et al., 1990; DeFronzo et al., 1992).

Hypoglycemic sulfonylureas are usually prescribed, since they stimulate insulin secretion in normal subjects and in diabetic patients. However, some sulfonylureas, e.g. glibenclamide, induce delayed monophasic insulin secretion and others, e.g. gliclazide, although inducing biphasic hormone release, do not stimulate an early secretory peak as fast as glucose (Groop, 1992; DeFronzo, 1999), so that in clinical practice, administration should generally precede meals by 20–30 min (Groop, 1992; DeFronzo, 1999).

Recently, new non-sulfonylurea insulin-stimulatory hypoglycaemic agents have been developed (Malaisse, 1995, 1999; Perfetti et al., 1998; DeFronzo, 1999) In vitro and in vivo studies indicate that these non-sulfonylurea oral insulin secretagogues induce a biphasic insulin release more rapid in onset and shorter in residual effects than sulfonylureas (Ohnota et al., 1995a,b; Mark and Grell, 1997; Kinukawa et al., 1996; Ladrière et al., 1997; Damsbo et al., 1999). Thus, these drugs, which can be taken immediately before each meal, restrict their insulin-stimulatory effect to the absorptive state, thus leading to the new concept of "prandial glucose regulation" (Owens, 1998; Damsbo et al., 1999; Editorial, 1999).

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Furthermore, the rapid-acting oral insulin secretagogues seem relatively ineffective in stimulating insulin release when glucose concentration is low but appear to exert a strong insulin-releasing activity as glycaemic levels rise (Bakkali-Nadi et al., 1994; Mark and Grell, 1997; Fuhlendorf et al., 1998).

Repaglinide, to date the most extensively studied rapid-acting oral insulin secretagogue, is used in many countries (Bakkali-Nadi et al., 1994; Ladrière et al., 1997; Owens, 1998; Damsbo et al., 1999). S 21403 (also identified as KAD 1229 and mitiglinide), a succinic acid derivative, is another interesting rapid-acting oral insulin secretagogue currently under development worldwide (Editorial, 1999).

In this study, we investigated the insulin-secretory profiles induced by S 21403 in the same in vitro model we successfully used in the past to study sulfonylurea compounds (Gregorio et al., 1992, 1994, 1996). As ambient glucose concentrations seem to exert a strong influence on the B-cell-releasing activity induced by rapid-acting oral insulin secretagogues, we evaluated insulin-stimulatory effects at stable 2.22 mM glucose (which is in the range of the glycaemic drops during hypoglycaemic episodes caused by antidiabetic treatments) and during a glucose increase from 5 to 8.33 mM (which is similar to the glycaemic rise after a light meal). We also compared the insulin-secretory profiles with the physiological hormone response produced by the same moderate glycaemic stimulus alone (increase of glucose levels from 5 to 8.33 mM).

Moreover, we confronted the amounts and kinetics of insulin released by S 21403, by repaglinide (as the first rapid-acting oral insulin secretagogue) and by glibenclamide (as the standard reference second-generation sulfonylurea).

The effects of sulfonylureas on A-cell function are still unclear (Kadowaki et al., 1983; Ostenson et al., 1986; Gregorio et al., 1992), and similarly, the effects of rapid-acting oral insulin secretagogues on pancreatic glucagon secretion are conflicting, since stimulatory, inhibitory or no effects have all been observed (Ohnota et al., 1995a,b; Kinukawa et al., 1996; Leclercq-Meyer et al., 1997). Therefore, we also investigated the effects of S 21403, repaglinide and glibenclamide on pancreatic glucagon secretion.

As we aimed at evaluating the "therapeutical" nontoxic effects, we infused concentrations of all three drugs in the range of circulating plasma levels found in humans during treatment (Ikegami et al., 1986; Oliver et al., 1997; Hatorp et al., 1998; Patat et al., 2000).

2. Materials and methods

2.1. Animals and perfusion system

Male Sprague-Dawley rats kept in an animal research laboratory at a stable 16–18 °C temperature with natural daylight and fed ad libitum on standard laboratory chow were used. The European Community guidelines for the use of experimental animals were followed. The study was approved by the Hospital Ethics Committee.

Animals weighing 200–250 g were anaesthetized after an overnight fast with pentobarbital (60 mg/kg b.w., i.p.) and each pancreas was isolated and perfused using a modified Sussman's method described elsewhere (Gregorio et al., 1992, 1994, 1996). Briefly, the aorta was cannulated and the pancreas removed with the exclusion of the duodenum. The pancreas was placed in a perfusion chamber at 37 °C and perfused with Krebs–Ringer-Bicarbonate buffer (pH 7.4, 4% albumin, 95% O_2 and 5% CO_2, flow rate 2.5 ml/min, perfusion pressure 30 mm Hg). The perfusion buffer also contained a mixture of natural amino acids at the same concentrations and proportions found in normal rat serum (Gregorio et al., 1992, 1994, 1996).

Table 1
AUC of the different phases of insulin-secretory response to a 8.33 mM glucose stimulus alone (controls) or combined with the three different insulin-stimulatory agents we tested

Perfusion time (min)	0–20	21–28	29–40	41–60
Release phases	Basal condition (5 mM/glucose)	Insulin-secretory agent perfusion plus 8.33 mM glucose		Residual effects (5 mM/glucose)
		First phase	Second phase	
S 21403	439.15 ± 44.97	3142.81 ± 135.04[a]	2929.73 ± 123.75[b]	935.30 ± 31.18[c]
Repaglinide	447.64 ± 36.72	3028.23 ± 136.39[d]	2815.03 ± 160.57[e]	2256.00 ± 106.67[f]
Glibenclamide	411.68 ± 36.74	2552.87 ± 103.41	2889.80 ± 202.31[g]	4476.78 ± 325.82[h]
Controls	415.86 ± 28.94	2530.67 ± 201.65	2038.27 ± 160.88	793.78 ± 29.91

Insulin concentrations (μU/ml) are given as mean ± S.E.
[a] $P<0.01$ vs. glibenclamide and vs. controls.
[b] $P<0.001$ vs. controls.
[c] $P<0.001$ vs. repaglinide and $P<0.0005$ vs. glibenclamide.
[d] $P<0.04$ vs. glibenclamide and $P<0.03$ vs. controls.
[e] $P<0.01$ vs. controls.
[f] $P<0.001$ vs. glibenclamide and vs. controls.
[g] $P<0.001$ vs. controls.
[h] $P<0.001$ vs. controls.

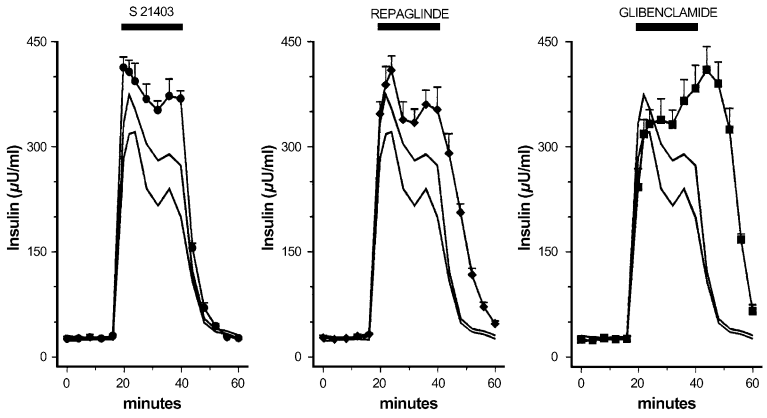

Fig.1. Insulin released by S 21403 (left panel, solid circles), repaglinide (central panel, solid diamonds) and glibenclamide (right panel, solid squares) perfusions during a moderate rise—from 5 to 8.33 mM—in glucose concentrations. The range of insulin release in response to the metabolic glucose stimulus in control perfusion (without any insulin-secretory agent) is also indicated (white area) in all the panels.

Basal glucose, the glycaemic stimulus, S 21403, repaglinide and glibenclamide perfusion were all added to the perfusion buffer through another pump, via a "T" pipe-fitting, (flow rate 0.1 ml/min) at appropriate concentrations. Venous effluent was collected at 4-min intervals (reduced to 2 min at the start of the stimuli with the insulin-secretory agents and/or glucose) into refrigerated tubes containing aprotinin (Trasylol, Bayer, West Germany), 500 U/ml, as proteolytic inhibitor. Samples were frozen immediately at − 70 °C and stored until assay.

2.2. Compounds and experimental design

S 21403 and repaglinide were both kindly supplied by the Institut de Recherches Internationales Servier, (Courbevoie, France), and glibenclamide was purchased from Sigma (St. Louis, MO, USA).

Fresh solutions were prepared in 1N NaOH at final "therapeutical" concentrations of 1.5 mg/l for S 21403 (Patat et al., 2000), 30 μg/l for repaglinide (Oliver et al., 1997; Hatorp et al., 1998) and 50 μg/l for glibenclamide (Ikegami et al., 1986). Doses are expressed as anhydrous free acids.

Before starting each experiment, an equilibration phase of 15 min was allowed to elapse to permit the basal state to stabilize after surgical handling.

The insulin-secretory agents were infused for 20 min:

- during a moderate rise—from 5 to 8.33 mM—in glucose levels after a 20-min basal perfusion with 5 mM glucose. The metabolic stimulus overlapped with the perfusion of each insulin-secretory agents. In this group of experiments, control perfusions with the 8.33 mM glucose stimulus, but without insulin-secretory agents, were also performed.
- in the presence of a stable 2.22 mM glucose concentration. Perfusions were started after 20 min of basal state to provide a reference value before the insulin-secretory agent was added.

Sampling continued for 20 min after the perfusion of each insulin-secretory agent was stopped in order to evaluate the residual effects on A- and B-cell hormone release.

Sets of six experiments were carried out for each group of perfusions.

Table 2
AUC of the different phases of insulin-secretory response to the three different insulin-stimulatory agents we tested in the presence of a low 2.22 mM glucose concentration

Perfusion time (min)	0–20	21–28	29–40	41–60
Release phases	Basal condition	Insulin-secretory agent perfusion		Residual effects
		First phase	Second phase	
S 21403	216.18 ± 12.18	575.60 ± 28.18[a]	537.86 ± 21.49	324.83 ± 12.42[b]
Repaglinide	210.31 ± 5.54	566.78 ± 44.87[c]	611.81 ± 38.04	818.93 ± 41.77[d]
Glibenclamide	198.43 ± 9.22	252.72 ± 13.76[a]	543.89 ± 29.91[b]	1260.94 ± 68.67[c]

Insulin concentrations (μU/ml) are given as mean ± S.E.
[a] $P < 0.0001$ vs. glibenclamide.
[b] $P < 0.0001$ vs. glibenclamide.
[c] $P < 0.001$ vs. glibenclamide.
[d] $P < 0.0005$ vs glibenclamide.

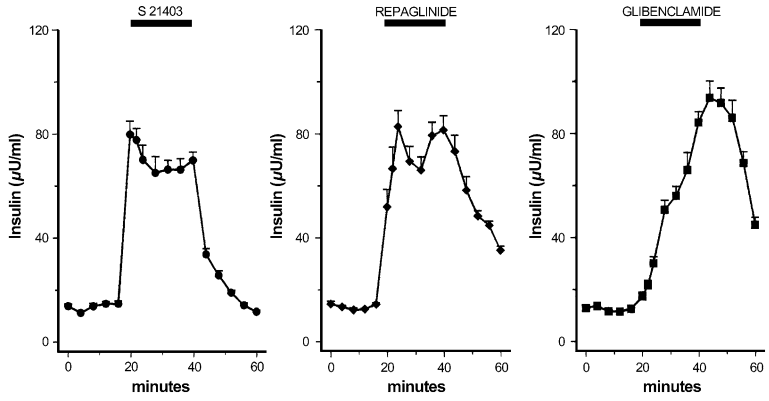

Fig. 2. Insulin released by S 21403 (left panel, solid circles), repaglinide (central panel, solid diamonds) and glibenclamide (right panel, solid squares) perfusion during a stable 2.22 mM glucose.

2.3. Analytical determinations and statistics

Immunoreactive insulin and glucagon were determined by radioimmunoassay as previously described by our group elsewhere (Gregorio et al., 1992, 1994, 1996). Each hormone determination was performed in a single assay to eliminate interassay variability. The within-assay coefficient of variation was less than 3% for insulin and 5% for glucagon.

Peaks of insulin release induced by glucose and/or drugs were compared by the one-way analysis of variance.

Trapezoidal areas under the curve of insulin and glucagon release for each insulin-secretory agents were calculated. Areas for insulin secretion were evaluated at the times 0–20, 21–28, 29–40 and 41–60 min of perfusion and areas for glucagon secretion at 0–20, 21–40 and 41–60 min of perfusion.

The Shapiro–Wilk's test was performed to verify normal distribution of the areas.

The effects of drugs on glucagon and insulin were evaluated separately by analysis of variance for repeated measures.

A level of 5% was chosen to assess the statistical significance.

The statistical package SAS was used for data compilation and processing.

3. Results

3.1. Insulin secretion

Increasing glucose from 5 to 8.33 mM in control perfusions produced the typical biphasic insulin release with a first-phase peak value of 339.12 ± 22.87 μU/ml within the fourth minute followed by a second-phase peak value of 264.51 ± 24.68 μU/ml within the 40th minute. After the end of the metabolic stimulus, insulin secretion quickly returned to basal levels within 8 min (Table 1, Fig. 1).

All the insulin-secretory agents we tested strongly stimulated the B-cell hormone release but induced rather different kinetic patterns (Table 1).

After adding S 21403 to the metabolic stimulus, the first-phase peak of glucose-induced insulin release increased to 413.02 ± 14.90 μU/ml ($P < 0.03$ vs. controls, P = ns vs. repaglinide, $P < 0.005$ vs. glibenclamide) and occurred at the second minute. The second peak of hormone release was also potentiated to 372.16 ± 24.12 μU/ml ($P < 0.02$ vs. controls, P = ns vs. repaglinide and vs. glibenclamide). In the residual effect assessment period, insulin secretion returned to the basal level 8 min after the combined glucose + S 21403 stimulus was stopped (Fig. 1).

Repaglinide enhanced the first peak of glucose-induced insulin release to 409.33 ± 20.05 μU/ml within the eighth minute ($P < 0.05$ vs. controls, $P < 0.01$ vs. glibenclamide). It also potentiated the second phase of hormone release to a peak of 360.17 ± 20.32 μU/ml ($P < 0.02$ vs. controls, P = ns vs. glibenclamide) at the end of the drug perfusion. In the residual effect assessment period, insulin release returned to baseline only 20 min after the combined glucose + repaglinide perfusion was interrupted (Fig. 1).

With glibenclamide perfusion, the first phase of glucose-induced insulin release overlapped with the controls with a

Table 3
AUC of the different phases of glucagon-secretory response to a 8.33 mM glucose stimulus alone (controls) or combined with the perfusion of the three different insulin-stimulatory agents we tested

Perfusion time (min)	0–20	21–40	41–60
Release phases	Basal condition (5 mM/glucose)	Insulin-secretory agent perfusion plus 8.33 mM glucose	Residual effects (5 mM/glucose)
S 21403	1382.13 ± 41.50	807.36 ± 20.98	1344.83 ± 20.12
Repaglinide	1415.21 ± 78.16	809.78 ± 35.21	1353.21 ± 31.67
Glibenclamide	1409.25 ± 69.77	832.87 ± 23.94	1290.08 ± 35.91
Controls	1396.41 ± 40.37	850.43 ± 29.89	1881.32 ± 21.98

Glucagon concentrations (pg/ml) are given as mean ± S.E.
No significant difference was observed among groups.

peak value of 338.41 ± 29.79 μU/ml (P = ns vs. controls). The second phase of insulin secretion was strongly potentiated but delayed. The peak of 409.50 ± 33.28 μU/ml ($P < 0.002$ vs. controls) was reached 4 min after the beginning of the second phase; at the end of the residual effect assessment period, basal levels had still not been reached (Fig. 1).

At a stable environmental 2.22 mM glucose level, the hormone-stimulatory effect of all the insulin-secretory agents tested was low (Table 2). The reduction was most marked for the rapid-acting oral insulin secretagogues. However, the hormone-secretory profile showed the same kinetic patterns we observed during the 8.33 mM glucose stimulus.

S 21403 produced the sharpest rise in insulin secretion with a first peak of 79.72 ± 4.41 μU/ml within the second minute of the drug perfusion (P = ns vs. repaglinide). It dropped to a minimum of 65.06 ± 6.24 μU/ml before rising again to 69.83 ± 3.21 μU/ml at the 20th minute (P = ns vs. repaglinide, $P < 0.02$ vs. glibenclamide) and then quickly returning to basal levels (Fig. 2).

With repaglinide, insulin release reached the first-phase peak of 81.71 ± 6.18 within the eighth minute, dropped to 65.98 ± 5.02 μU/ml and rose again at the 20th minute to 80.36 ± 5.54 μU/ml (P = ns vs. glibenclamide). At the end of the drug perfusion, it approached basal values (Fig. 2).

Glibenclamide did not elicit fast insulin release but again produced a monophasic, delayed hormone secretion that reached its peak of 93.62 ± 6.46 μU/ml 4 min after the sulfonylurea perfusion was stopped. At the end of the residual effect assessment period, it was still far above the basal levels (Fig. 2).

3.2. Glucagon secretion

Basal glucagon-secretory concentrations were closely and inversely related to environmental glucose levels. A rise in the glucose concentration from 5 to 8.33 mM in the control perfusion caused significant suppression of glucagon release (Table 3).

None of the insulin-secretory agents we tested influenced the 8.33 mM glucose inhibitory action on glucagon secretion (Table 3) or affected A-cell hormone secretion in the presence of the 2.22 mM surrounding glucose level (Table 4).

Table 4
AUC of the different phases of glucagon-secretory response to the three different insulin-stimulatory agents we tested in the presence of a low 2.22 mM glucose concentration

Perfusion time (min)	0–20	21–40	41–60
Release phases	Basal condition	Insulin-secretory agent perfusion	Residual effects
S 21403	2706.78 ± 118.79	3369.46 ± 137.39	2697.15 ± 111.40
Repaglinide	2630.86 ± 96.23	3308.31 ± 127.55	2628.41 ± 105.74
Glibenclamide	2617.28 ± 76.77	3255.81 ± 121.68	2586.28 ± 123.34

Glucagon concentrations (pg/ml) are given as mean ± S.E.
No significant difference was observed among groups.

4. Discussion

This study confirms our previous findings showing glibenclamide produces a slow, sustained insulin release that reaches its stimulatory peak rather late (Gregorio et al., 1992, 1994). When glibenclamide was infused together with the metabolic stimulus, it potentiated but delayed the second phase of insulin secretion leaving the first unaffected. The maximum of insulin release was reached after the sulfonylurea perfusion was stopped. When infused at the 2.22 mM surrounding glucose level, glibenclamide induced a monophasic and long-lasting insulin release.

Interestingly, the two rapid-acting oral insulin secretagogues we tested behaved rather differently, since they always stimulated biphasic insulin secretion. When infused with the metabolic stimulus, each increased the first and the second phases of glucose-induced insulin secretion and, when infused at the 2.22 mM environmental glucose, they still produced a biphasic hormone release of weak amplitude.

Although gliclazide and glimepiride induce biphasic insulin secretion under different glucose concentrations in the same experimental model we used in this study (Gregorio et al., 1992, 1994), with the rapid-acting oral insulin secretagogues, the increase and decrease in the pancreatic hormone release are faster.

Different rapid-acting oral insulin secretagogues, however, seem to have different insulin-stimulatory effects (Malaisse, 1999). Our results indicate S 21403 induces an insulin-secretory profile which is more rapid in onset and decreases faster to pre-stimulatory levels than repaglinide, whatever the surrounding glucose levels. This confirms previous findings showing the repaglinide-induced peak in insulin release is followed by a relatively slow decrease (Jijakli et al., 1996; Leclercq-Meyer et al., 1997), whereas S 21403 produces a rapid, and rapidly reversible, hormone secretion (Malaisse and Sato, 1995; Ohnota et al., 1995b; Kinukawa et al., 1996).

Using the isolated, perfused rat pancreas model Kinukawa et al. reported S 21403 induces different insulin secretion kinetics as glucose conditions vary. At a stable 5.6 mM glucose level, S 21403 significantly stimulated both the first and the second phase of insulin release. However, as the basal 5.6 mM glucose level was reduced to the 2.8 mM concentration, only the first phase of hormone secretion was stimulated by S 21403. On the other hand, as the basal 5.6 mM glucose perfusion increased to the 16.7 mM concentration, S 21403 increased only the second phase of the glucose-induced insulin secretion (Kinukawa et al., 1996).

The discrepancies between these results and ours are hard to explain, but some differences in the experimental model may account for them: the duodenum was not excluded from the pancreas as in our model; their animals did not fast

overnight like ours; their perfusion buffer did not contain physiological concentrations of amino acids such as in our experiments; they evaluated S 21403 after a drop from normal basal glucose values to hypoglycaemic conditions, while we used a stable low glucose level; they tested the drug under a maximally stimulatory condition and not at a moderate glucose stimulation as in our study (Kinukawa et al., 1996).

One property common to all insulin-secretory agents is the reduction in the B-cell-stimulatory efficacy as surrounding glucose falls, and this may act as a self-regulatory mechanism limiting the risk of hypoglycaemic events during treatments with oral antidiabetic agents (Gregorio et al., 1994).

Our data show this effect is much more marked with rapid-acting oral insulin secretagogues than with glibenclamide. Bearing in mind our observations in the same experimental model with various sulfonylureas, the reduction in the insulin-stimulatory effect with rapid-acting oral insulin secretagogues at low glucose levels seems more pronounced than with these other compounds (Gregorio et al., 1992, 1994, 1996). Of all the sulfonylurea and rapid-acting oral insulin secretagogues, S 21403 seems to stimulate pancreatic insulin production very little when the glucose concentration drops.

With regard to the effects on A-cell activity, none of the insulin-secretory agents tested affected glucagon secretion at 2.22 mM glucose condition and none influenced the 8.33 mM glucose-induced suppression of glucagon release.

Other in vivo and in vitro studies observed sulfonylureas had no effect on glucagon secretion (Gregorio et al., 1992). However, some claimed sulfonylureas inhibited A-cell function, both under normal (Ostenson et al., 1986) and low (Kadowaki et al., 1983) glucose concentrations, and others described a stimulatory effect under normal and high glucose conditions (Kadowaki et al., 1983).

Similarly, several studies have reported rapid-acting oral insulin secretagogues exert no effect on glucagon secretion (Ohnota et al., 1995a; Leclercq-Meyer et al., 1997). However, some have described S 21403 slightly inhibits the hypoglycaemic-induced rise in glucagon secretion (Kinukawa et al., 1996), and others have reported a slight stimulatory effect on stable 5.55 mM glucose (Ohnota et al., 1995b).

Once again we believe that differences in the experimental conditions might account for these discrepancies.

In conclusion, as the metabolic stimulation of B-cell activity is blunted in type 2 diabetic patients and the first phase of insulin release is lost, the kinetics of the S 21403-induced insulin release seem appropriate to improve the impaired insulin response to glucose and to restore the sharp hormone secretion.

Needless to say, data from animal models, especially healthy animals, cannot be extrapolated directly to human beings and particularly not to type 2 diabetic patients with real possible B-cell dysfunction. However, if in vivo clinical studies confirm our result that S 21403 induces a more physiological insulin-secretory profile than other insulin-secretory agents, it might improve post-meal glycaemic control and at the same time reduce the risk of post-absorptive hypoglycaemic events.

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