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# Insulinotropic action of monosaccharide esters: therapeutic perspectives

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Several monosaccharide esters were recently introduced as new tools in biomedical research. [1]. These esters seem to be able to cross the plasma membrane without requiring the intervention of a specific carrier system. They then undergo intracellular hydrolysis in esterase-catalysed reactions, so that their glucidic moiety becomes readily available for further metabolism or metabolic action [2, 3]. The major aim of this brief review is to draw attention to the possible use of some of these esters as new insulinotropic tools in the treatment of such diseases as Type II (non-insulin-dependent) diabetes mellitus, insulinoma or persistent hyperinsulinaemia in childhood. In the treatment of diabetes, they could be used in combination with other insulinotropic agents such as hypoglycaemic sulphonylureas [4–14], meglitinide analogues [15–24], imidazolidine [25–32] and guanidine [33–36] derivatives or glucagon-like peptide-1 [37–46].

## Experimental findings

Esters of metabolized hexoses, such as α-D-glucose pentaacetate or β-D-glucose pentaacetate, stimulate insulin release from islets incubated either in the absence of any exogenous nutrient or in the presence of such nutrient secretagogues as D-glucose and L-leucine [47] or, as shown in Figure 1, the dimethyl ester of succinic acid (SAD). Unexpectedly, however, some esters of non-metabolized hexoses, such as α-L-glucose pentaacetate and β-L-glucose pentaacetate also show positive insulinotropic action, the most obvious effect being in islets exposed to another nutrient secretagogue, e. g. L-leucine or the dimethyl ester of succinic acid (Fig. 1). Even more surprisingly, monosaccharide esters that inhibit D-glucose metabolism (such as D-mannoheptulose hexaacetate or 2-deoxy-D-glucose tetraacetate) and suppress D-glucose-stimulated insulin release [48, 49], were found to enhance the beta cell secretory response to non-glucidic nutrients, e. g. the dimethyl ester of succinic acid (Fig. 1). When tested in suitably low concentrations, the tetraacetate esters of 2-deoxy-D-glucose even enhance insulin release stimulated by D-glucose [49].

Detailed investigations on the metabolic fate of β-L-glucose pentaacetate in isolated pancreatic islets and its effects on variables such as protein biosynthesis, cyclic AMP formation, generation of inositol phosphates, intracellular pH, $^{86}Rb$ efflux and bioelectrical activity, $^{45}Ca$ net uptake and efflux, cytosolic $Ca^{2+}$ concentration and insulin release suggest that the esters of non-metabolized monosaccharides with positive insulinotropic action may directly interact with a receptor system, resulting in a decrease in $K^+$ conductance, plasma membrane depolarization and induction of electrical activity [50]. This model is thought to have analogies with the recognition of bitter compounds by taste buds [51]. Purified islet beta cells indeed contain the α-gustducin G-protein involved in this recognition process (unpublished observation).

The findings mentioned above also raise the idea that some monosaccharide esters, especially those of L-glucose, can be used as insulinotropic tools to stimulate insulin release in Type II diabetes. They are indeed likely to bypass those site-specific defects in D-glucose transport, phosphorylation and further metabolism currently held responsible for a preferential alteration of the diseased beta cell response to D-glucose in Type II diabetes [52].

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*Abbreviations*: GK rats, Goto-Kakizaki rats.

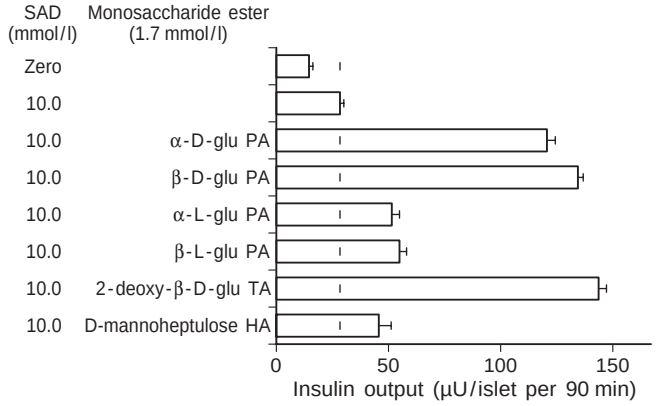


**Fig. 1.** Effects of α-D-glucose pentaacetate, β-D-glucose pentaacetate, α-L-glucose pentaacetate, β-L-glucose pentaacetate, 2-deoxy-β-D-glucose tetraacetate and D-mannoheptulose hexaacetate (all tested at 1.7 mmol/l concentration) upon insulin release evoked by 10.0 mmol/l succinic acid dimethyl ester (SAD) in pancreatic islets isolated from normal rats. Mean values (± SEM) refer to 24–216 individual determinations. The vertical dotted line indicates the mean secretory rate recorded in the sole presence of SAD ($n = 216$). glu = glucose, PA = pentaacetate, TA = tetraacetate, HA = hexaacetate

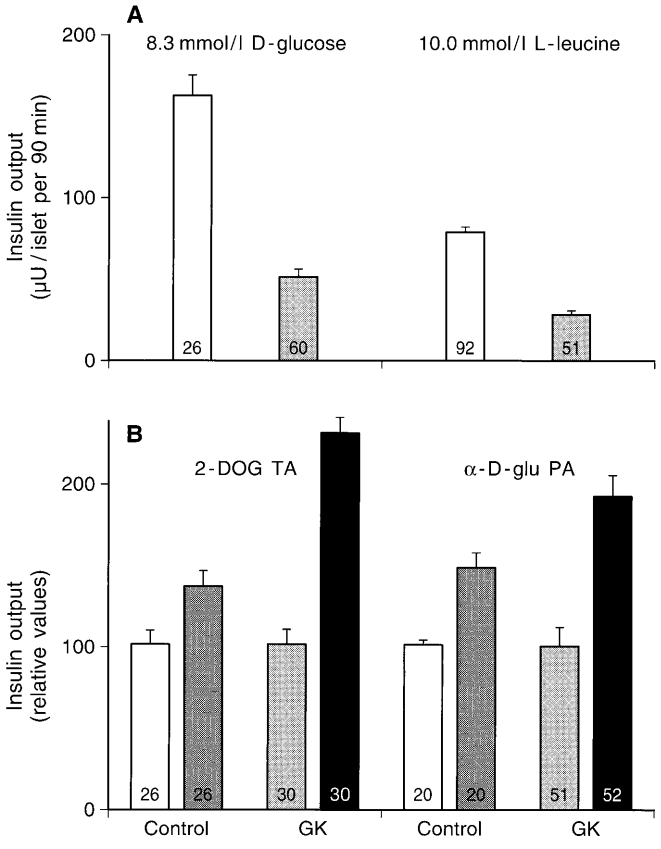


**Fig. 2.** **A** Absolute values for insulin release evoked by 8.3 mmol/l D-glucose (left) or 10.0 mmol/l L-leucine (right) in islets from either control (open columns) or GK (lightly shaded columns) rats. **B** Effects of 2-deoxy-D-glucose tetraacetate (1.7 mmol/l; darkly shaded or black columns) upon insulin release evoked by 8.3 mmol/l D-glucose (left) and of α-D-glucose pentaacetate (1.7 mmol/l; darkly shaded or black columns) upon insulin output caused by 10.0 mmol/l L-leucine (right) in islets from either control or GK rats, all results being expressed relative to the corresponding reference value found, within the same experiment, in the absence of the tested ester (open or lightly shaded columns). Mean values (± SEM) refer to the number of individual observations indicated at the bottom of each column. glu = glucose, DOG = deoxy-D-glucose, TA = tetraacetate, PA = pentaacetate

In light of such a proposal, the effects of several monosaccharide esters upon insulin secretion were compared in islets from either control rats or hereditarily diabetic Goto-Kakizaki rats (GK rats).

As illustrated in Figure 2 (upper panel), the rate of insulin release evoked by either 8.3 mmol/l D-glucose or 10.0 mmol/l L-leucine is much lower ($p < 0.001$) in islets from GK rats than in islets from control animals [53]. Relative to such a secretory rate, the enhancing action of 2-deoxy-D-glucose tetraacetate (1.7 mmol/l) upon glucose-stimulated insulin output and that of α-D-glucose pentaacetate (also 1.7 mmol/l) upon leucine-induced insulin release was more pronounced ($p < 0.025$ or less) in the diabetic animals than in the control rats (Fig. 2B). Likewise, in islets exposed to the dimethyl ester of succinic acid, the absolute value for insulin release is lower ($p < 0.001$) in GK rats than in control animals (Fig. 3A), but the relative magnitude of the enhancing action of either D-mannoheptulose hexaacetate or β-D-glucose pentaacetate (both 1.7 mmol/l) is higher ($p < 0.02$ or less) in GK rats than control animals (Fig. 3B).

Relative to the paired reference value recorded in the presence of the dimethyl ester of succinic acid (10.0 mmol/l) alone, the output of insulin found in islets exposed to both the succinic acid ester and α-L-glucose pentaacetate (1.7 mmol/l) was again higher in GK rats than in control animals, although such a difference failed to achieve statistical significance ($p < 0.11$). For β-L-glucose pentaacetate (also 1.7 mmol/l), the relative magnitude of enhancing action of the ester upon insulin release evoked by the dimethyl ester of succinic acid was even lower ($p < 0.001$) in GK rats than in control animals. In fact, the β-anomer of L-glucose pentaacetate failed to enhance significantly ($p < 0.3$) insulin output.

Inactivation of glycogen phosphorylase *a* by glucose could explain these findings [54]. It was indeed previously documented (i) that glycogen accumulates in the beta cell in situations of long-term hyperglycaemia [55], (ii) that D-glucose inactivates glycogen phosphorylase *a* in pancreatic islets as in liver [56], (iii) that such an enzymatic event coincides with a glucose-induced inhibition of glycogenolysis in glycogen-rich islets [57, 58], (iv) that the latter metabolic event may, in turn, result in a paradoxical inhibition of insulin release in response to a rise in D-glucose concentration [55, 59], (v) that the interaction of phosphorylase *a* with D-glucose shows α-stereospecificity [60], (vi) that, likewise, α-D-glucose seems

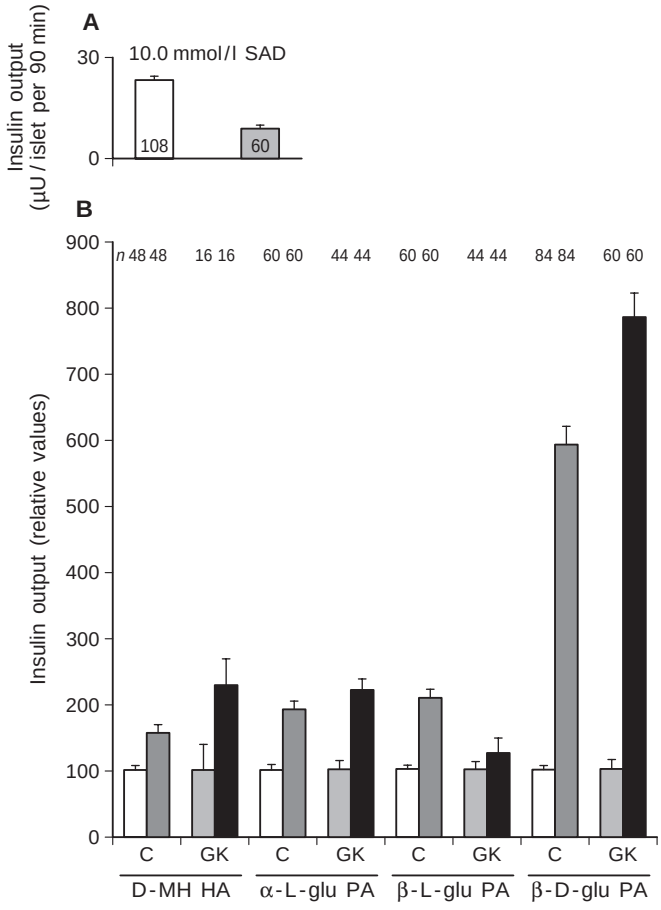


**Fig. 3.** **A** Absolute values for insulin release evoked by 10.0 mmol/l succinic acid dimethyl ester (SAD) in islets from either control (open columns) or GK (lightly shaded column) rats. **B** Effects of D-mannoheptulose hexaacetate, α-L-glucose pentaacetate, β-L-glucose pentaacetate and β-D-glucose pentaacetate (1.7 mmol/l; darkly shaded or black columns) upon insulin release caused by SAD in islets from either control (C) or GK rats all results being expressed relative to the corresponding reference value found, within the same experiments, in the sole presence of SAD. Mean values (± SEM) refer to number of individual determinations indicated at the bottom of each column (upper panel) or as *n* at the top of the lower panel. MH = mannoheptulose, HA = hexaacetate, PA = pentaacetate, glu = glucose

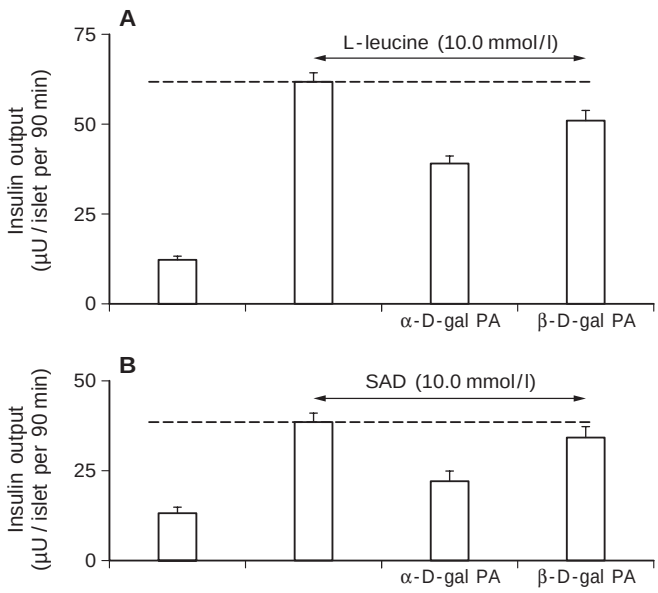


**Fig. 4.** Effects of α-D-galactose pentaacetate and β-D-galactose pentaacetate (1.7 mmol/l each) upon insulin release evoked by either 10.0 mmol/l L-leucine (**A**) or 10.0 mmol/l succinic acid dimethyl ester (SAD; **B**) in pancreatic islets isolated from normal rats. The first columns to the left illustrate the basal insulin output. Mean values (± SEM) refer to 30–60 individual determinations. gal = galactose, PA = pentaacetate

more efficient than β-D-glucose in suppressing glycogenolysis in glycogen-rich islets [55], and (vii) that, probably as a result, the anomeric specificity of the beta cell secretory response to D-glucose is disturbed in Type II diabetic subjects [61] and in animal models of Type II diabetes [62–65], the normal preference for α-D-glucose being attenuated, suppressed or even reversed as a function of the severity and duration of the hyperglycaemic state [66]. Because the conformation of β-L-glucopyranose resembles that of α-D-glucopyranose at the level of the $C_1$ hemiacetal group [67], the more pronounced insulinotropic action of α-L-glucose pentaacetate (as compared with β-L-glucose pentaacetate) in islets from GK rats might thus reflect the greater inactivation of glycogen phosphorylase *a* by the L-glucose β-anomer, which is produced by hydrolysis of its pentaacetate ester in the islet cells.

In conclusion, α-L-glucose pentaacetate can, therefore, be proposed as a novel insulinotropic tool in the treatment of Type II diabetes. This ester would offer the advantages of (i) bypassing the site-specific defects in D-glucose handling in the beta cell of diabetic patients, (ii) minimizing the inhibition of glycogenolysis otherwise attributable to interaction of β-L-glucose with phosphorylase *a* in the beta cell, and (iii) avoiding the stimulation of hepatic gluconeogenesis that may result from treatment with insulinotropic esters such as succinic acid dimethyl ester or D-glucose pentaacetate [68, 69]. This proposal is consistent with the recent observation that when normal rats were injected intravenously with no more pentaacetate ester of L-glucose than 8.8 nmol/g body weight, a sizeable increase in plasma insulin concentration was provoked within 2 min [70].

Note that the stimulation of insulin release by the polyacetate esters of monosaccharides cannot be attributed to the catabolism of their acetate moiety. Indeed, some esters that are as efficiently taken up and hydrolysed in pancreatic islets as α-D-glucose pentaacetate or β-L-glucose pentaacetate, e.g. β-D-galactose pentaacetate, have no positive insulinotropic action [47, 71].

Some of these esters may even inhibit nutrient-stimulated insulin release [72, 73]. This is illustrated

in Figure 4, which indicates that α-D-galactose pentaacetate inhibits insulin release evoked by either L-leucine or the dimethyl ester of succinic acid, whilst β-D-galactose pentaacetate inhibits less strongly – or even fails to noticeably affect – the secretory response to the non-glucidic nutrients. The pentaacetate ester of α-D-galactose (1.7 mmol/l) also inhibits D-glucose-stimulated insulin release [78].

The findings summarized in Figure 4 suggest that the receptor system mediating the beta cell functional response to the esters of non-metabolized or poorly metabolized monosaccharides could convey either a positive or negative message to the insulin-releasing effector machinery. These findings also led us to propose that the α-anomer of D-galactose pentaacetate could conceivably be used to prevent excessive insulin release in conditions such as persistent hyperinsulinaemia in childhood or insulinoma [72, 73].

The possible use of monosaccharide esters as insulinotropic agents is supported by recent findings documenting their insulinotropic action after intravenous injection into anaesthetized rats [70, 74, 75]. Monosaccharide esters may also be used to potentiate the beta cell secretory response to agents such as gliquidone or repaglinide [74]. They seem to have no undesirable side effects and have been used safely in human subjects (unpublished observation). New modalities for giving them orally might be required, however, to achieve a stimulation of insulin release comparable with that found after intravenous injection [74].

## Concluding remark

Recent studies have shown that monosaccharide esters represent new tools to interfere specifically with a given biochemical reaction in intact cells [76, 77] or for antitumoural therapy [78–81]. The information briefly reviewed here indicates that the introduction of these esters also allows the detection of a novel modality for (in)activation of the pancreatic islet beta cells and might lead, therefore, to the development of new agents for the treatment of hypoinsulinaemic or hyperinsulinaemic diseases.

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## References

1. Malaisse WJ (1998) Monosaccharide esters : new tools in biomedical research. Mol Gen Metab 65: 129–142
2. Malaisse WJ, Jijakli H, Kadiata MM, Sener A, Kirk O (1997) Stimulation of insulin release by α-D-glucose pentaacetate. Biochem Biophys Res Commun 231: 213–214
3. Sener A, Welsh N, Malaisse-Lagae F, Kadiata MM, Malaisse WJ (1998) Insulinotropic action of α-D-glucose pentaacetate : metabolic aspects. Mol Gen Metab 64: 135–147
4. Henquin JC, Meissner HP (1982) Opposite effects of tolbutamide and diazoxide on $^{86}$Rb fluxes and membrane potential in pancreatic B-cell. Biochem Pharmacol 31: 1407–1415
5. Meissner HP, Preissler M, Henquin JC (1980) Possible ionic mechanisms of the electrical activity induced by glucose and tolbutamide in pancreatic B-cells. In: Waldhäusl WK (ed) Diabetes. Excerpta Medica, Amsterdam, pp 166–171
6. Hellman B (1981) Tolbutamide-stimulation of $^{45}$Ca fluxes in microdissected pancreatic islets rich in B-cells. Mol Pharmacol 20: 83–88
7. Hellman B, Sehlin J, Täljedal IB (1971) The pancreatic β-cell recognition of insulin secretagogues. II. Site of action of tolbutamide. Biochem Biophys Res Commun 45: 1384–1388
8. Hellman B (1974) Factors affecting the uptake of glibenclamide in microdissected pancreatic islets rich in β-cells. Pharmacology 11: 257–267
9. Kaubish N, Hammer R, Wollheim C, Renold AE, Offord RE (1982) Specific receptors for sulfonylureas in brain and in a β-cell tumor of the rat. Biochem Pharmacol 31: 1171–1174
10. Deleers M, Malaisse WJ (1984) Binding of hypoglycaemic sulphonylureas to an artificial phospholipid bilayer. Diabetologia 26: 55–59
11. Sehlin J (1973) Evidence for specific binding of tolbutamide to the plasma membrane of the pancreatic B-cells. Acta Diabetol 5: 1052–1060
12. Täljedal IB (1974) Uptake of glibornuride by microdissected pancreatic islets. Horm Res 5: 211–216
13. Hellman B, Sehlin J, Täljedal IB (1973) The pancreatic B-cell recognition of insulin secretagogues. IV. Islet uptake of sulphonylurea. Diabetologia 9: 210–216
14. Loubatières A, Loubatières-Mariani MM (1974) Experimental study of the betacytotropic and betacytotrophic action of glisoxepide (Pro-Diaban). In: Schöffling K, Kroneberg G, Laudahn G (eds) Pro Diaban. F.K. Schattauer, Stuttgart, pp 53–63
15. Gromada J, Dissing S, Kofod H, Frøkjaer-Jensen J (1995) Effects of the hypoglycaemic drugs repaglinide and glibenclamide on ATP-sensitive potassium-channels and cytosolic calcium levels in βTC3 cells and pancreatic beta cells. Diabetologia 38: 1025–1032
16. Fuhlendorff J, Rorsman P, Kofod H et al. (1998) Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. Diabetes 47: 345–351
17. Ohnota H, Koizumi T, Tsutumi N, Kobayashi M, Inoue S, Sato F (1994) Novel rapid- and short-acting hypoglycemic agent, a calcium (2 S)-2-benzyl-3-(*cis*-hexahydro-2-isoindolinylcarbonyl)propionate (KAD-1229) that acts on the sulfonylurea receptor : comparison of effects between KAD-1229 and gliclazide. J Pharmacol Exp Ther 269: 489–495
18. Shinkai H, Nashikawa M, Sato Y (1989) Separation of a new antidiabetic agent, N-(*trans*-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, and its isomers by chiral high-performance liquid chromatography. J Liquid Chromatogr 12: 454–464
19. Sato Y, Nishikawa M, Shinkai H, Sukegawa E (1991) Possibility of ideal blood glucose control by a new oral hypoglycemic agent, N-[(*trans*-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine (A4166), and its stimulatory effect on insulin secretion in animals. Diabetes Res Clin Pract 12: 53–60

20. Kitahara Y, Akiyoshi M, Tsuchiya Y et al. (1998) Effect of A-4166 on postprandial hyperglycaemia in GK rats. Diabetologia 41[Suppl 1]A232
21. Geisen K, Hübner M, Hitzel V et al. (1978) Acylaminoalkyl-substituierte Benzol- und Phenylalkansäuren mit blutglukosesenkender Wirkung. Arzneimittelforschung 28: 1081–1083
22. Geisen K, Hitzel V, Ökomonopoulos R, Pünten J, Weyer R, Summ H-D (1985) Inhibition of $^3$H-glibenclamide binding to sulfonylurea receptors by oral antidiabetics. Arzneimittelforschung 35: 707–712
23. Puech R, Mantegheti M, Ribes G, Wollheim CB, Loubatières-Mariani MM (1985) Enhancement of insulin release and islet cell calcium content by an acyl-amino-alcyl benzoic derivative, HB 699. Horm Metab Res 17: 1–4
24. Sakamoto Y, Morimoto S, Mokuda O (1998) AY-4166 increases the sensitivity of insulin secretion to glucose in isolated rat pancreas. Diabetologia 41[Suppl 1]A232
25. Zaitsev SF, Efanov AM, Efanova IB et al. (1996) Imidazoline compounds stimulate insulin-release by inhibition of $K_{ATP}$ channels and interaction with the exocytotic machinery. Diabetes 45: 1610–1618
26. Efanova IB, Zaitsev SV, Brown G, Berggren P-O, Efendic S (1998) RX871 024 induces $Ca^{2+}$ mobilization from thapsigargin-sensitive stores in mouse pancreatic $\beta$-cells. Diabetes 47: 211–218
27. Schulz A, Hasselblatt A (1989) An insulin-releasing property of imidazoline derivatives is not limited to compounds that block alphaadrenoceptors. Naunyn-Schmiedebergs Arch Pharmacol 340: 321–327
28. Östenson CG, Cattaneo AG, Doxey JC, Efendic S (1989) Alphaadrenoceptors and insulin release from pancreatic islets of normal and diabetic rats. Am J Physiol 257: E439-E443
29. Chan SLF, Brown CA, Scarpello KE, Morgan NG (1994) The imidazoline site involved in control of insulin secretion : characteristics that distinguish it from $I_1$- and $I_2$-sites. Br J Pharmacol 112: 1065–1070
30. Jonas JC, Plant TD, Henquin JC (1992) Imidazoline antagonists of alpha-2-adrenoceptors increase insulin release in vitro by inhibiting ATP-sensitive $K^+$ channels in pancreatic beta-cells. Br J Pharmacol 107: 8–14
31. Chan SLF, Dunne MJ, Stillings MR, Morgan NG (1991) The alpha-2-adrenoceptor antagonist efaroxan modulates $K_{ATP}$ channels in insulin secreting cells. Eur J Pharmacol 204: 41–48
32. Chan SLF, Morgan NG (1990) Stimulation of insulin secretion by efaroxan may involve interaction with potassium channels. Eur J Pharmacol 176: 97–101
33. Byrom WD, Rotherman NE, Bratty JR (1994) Relationship between hypoglycaemic response and plasma concentrations of BTS 67 582 in healthy volunteers. Br J Clin Pharmacol 38: 433–439
34. Dickinson K, North TJ, Sills S et al.(1997) BTS 67 582 stimulates insulin secretion from perifused rat pancreatic islets. Eur J Pharmacol 339: 69–76
35. Jones RB, Dickinson K, Anthony DM, Marita AT, Kaul CL, Buckett WR (1997) Evaluation of BTS 67 582, a novel antidiabetic agent, in normal and diabetic rats. Br J Pharmacol 120: 1135–1143
36. Skillman CA, Raskin P (1997) A double-masked placebo-controlled trial assessing effects of various doses of BTS 67 582, a novel insulinotropic agent, on fasting hyperglycemia in NIDDM patients. Diabetes Care 20: 591–596
37. Göke R, Fehmann H-C, Göke B (1991) Glucagon-like peptide-1 (7–36)amide is a new incretin/enterogastrone candidate. Eur J Clin Invest 21: 135–144
38. Fehmann H-C, Habener JF (1992) Insulinotropic glucagon-like peptide-I (7–37)/(7–36)amide. A new incretin hormone. Trends Endocrinol Metab 3: 158–163
39. Ørskov C (1992) Glucagon-like peptide-1, a new hormone of the entero-insular axis. Diabetologia 35: 701–711
40. Thorens B, Waeber G (1993) Glucagon-like peptide-I and the control of insulin secretion in the normal state and in NIDDM. Diabetes 42: 1219–1225
41. Holst JJ (1994) Glucagonlike peptide 1 : a newly discovered gastro-intestinal hormone. Gastroenterology 107: 1848–1855
42. Mojsov S, Weir GC, Habener JF (1987) Insulinotropin: glucagon-like peptide 1 (7–37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. J Clin Invest 79: 616–619
43. Gutniak MK, Ørskov C, Holst JJ, Ahrén B, Efendic S (1992) Antidiabetogenic effect of glucagon-like peptide-1 (7–36) amide in normal subjects and patients with diabetes mellitus. New Engl J Med 326: 1316–1322
44. Weir GC, Mojsov S, Hendrick GK, Habener JF (1989) Glucagon-like peptide-1 (7–37) actions on endocrine pancreas. Diabetes 38: 338–342
45. Komatsu R, Matsuyama T, Namba M et al. (1989) Glucagonostatic and insulinotropic action of glucagonlike peptide 1-(7–36) amide. Diabetes 38: 902–905
46. Göke R, Wagner B, Fehmann HC, Göke B (1993) Glucose-dependency of the insulin stimulatory effect of glucagon-like peptide-1 (7–36) amide on the rat pancreas. Res Exp Med (Berl) 193: 97–103
47. Malaisse WJ, Sánchez-Soto C, Larrieta ME et al. (1997) Insulinotropic action of $\alpha$-D-glucose pentaacetate : functional aspects. Am J Physiol 273: E1090-E1101
48. Sener A, Kadiata MM, Olivares E, Malaisse WJ (1998) Comparison between the effects of D-mannoheptulose and its hexaacetate ester upon D-glucose metabolism and insulinotropic action in rat pancreatic islets. Diabetologia 41: 1109–1113
49. Malaisse WJ, Flores LE, Kadiata MM (1998) Dual effect of 2-deoxy-D-glucose tetraacetate upon glucose-induced insulin release. Biochem Mol Biol Int 45: 429–434
50. Malaisse WJ, Best LC, Herchuelz A et al. (1998) Insulinotropic action of $\beta$-L-glucose pentaacetate. Am J Physiol 275: E 993–E 1006
51. Malaisse WJ, Malaisse-Lagae F (1997) Bitter taste of monosaccharide pentaacetate esters. Biochem Mol Biol Int 43: 1367–1371
52. Malaisse WJ (1994) The beta-cell in non-insulin-dependent diabetes : giving light to the blind. Diabetologia 37[Suppl 2]S36–S42
53. Malaisse WJ, Laghmich A, Ladrière L, Kadiata MM, Sener A (1998) Insulinotropic action of the polyacetate esters of metabolized and non-metabolized monosaccharides in pancreatic islets from normal and diabetic rats. Res Commun Mol Pathol Pharmacol 99: 81–92
54. Malaisse WJ, Kadiata MM (1998) Insulinotropic action of the polyacetate esters of two non-nutrient monosaccharides in normal and diabetic rats. Int J Mol Med 2: 95–98
55. Marynissen G, Leclercq-Meyer V, Sener A, Malaisse WJ (1990) Perturbation of pancreatic islet function in glucose-infused rats. Metabolism 39: 87–95
56. Zhang T-M, Maggetto C, Malaisse WJ (1994) Hexose metabolism in pancreatic islets : glycogen synthase and glycogen phosphorylase activities. Biochem Med Metab Biol 51: 129–139
57. Malaisse WJ, Marynissen G, Sener A (1992) Possible role of glycogen accumulation in B-cell glucotoxicity. Metabolism 41: 814–819

58. Malaisse WJ, Maggetto C, Leclercq-Meyer V, Sener A (1993) Interference of glycogenolysis with glycolysis in pancreatic islets from glucose-infused rats. J Clin Invest 91: 432–436
59. Gomis R, Novials A, Coves MJ, Casamitjana R, Malaisse WJ (1989) Suppression by insulin treatment of glucose-induced inhibition of insulin release in non-insulin-dependent diabetes. Diabetes Res Clin Pract 6: 191–198
60. Bollen M, Malaisse-Lagae F, Malaisse WJ, Stalmans W (1990) The interaction of phosphorylase *a* with D-glucose displays α-stereospecificity. Biochim Biophys Acta 1038: 141–145
61. Rovira A, Garrotte FJ, Valverde I, Malaisse WJ (1987) Anomeric specificity of glucose-induced insulin release in normal and diabetic subjects. Diabetes Res 5: 119–124
62. Leclercq-Meyer V, Marchand J, Malaisse WJ (1987) Alteration of the insulin secretory response to D-glucose anomers in diabetic BB rats. Med Sci Res 15: 1535–1536
63. Leclercq-Meyer V, Marchand J, Malaisse WJ (1987) Anomeric specificity of the insulin and glucagon secretory response to D-glucose in lean and obese Zucker rats. Pancreas 2: 645–652
64. Leclercq-Meyer V, Marchand J, Malaisse WJ (1991) Attenuated anomeric difference of glucose-induced insulin release in the perfused pancreas of diazoxide-treated rats. Horm Metab Res 23: 257–261
65. Fichaux F, Marchand J, Yaylali B, Leclercq-Meyer V, Catala J, Malaisse WJ (1991) Altered anomeric specificity of glucose-induced insulin release in rabbits with duct-ligated pancreas. Int J Pancreatol 8: 151–167
66. Malaisse WJ (1991) The anomeric malaise : a manifestation of B-cell glucotoxicity. Horm Metab Res 23: 307–311
67. West ES, Todd WR, Mason HS, Van Bruggen JT (1996) Textbook of Biochemistry, 4th edn. MacMillan, New York, p 211
68. Malaisse WJ (1995) The esters of carboxylic nutrients as insulinotropic tools in non-insulin-dependent diabetes mellitus. Gen Pharmacol 26: 1133–1141
69. Zhang T-M, Sener A, Malaisse WJ (1994) Metabolic effects and fate of succinic acid methyl esters in rat hepatocytes. Arch Biochem Biophys 314: 186–192
70. García-Martínez JA, Cancelas J, Villanueva-Peñacarrillo ML, Valverde I, Malaisse WJ (1998) Insulinotropic action of β-L-glucose pentaacetate *in vivo*. Endocrinologia 45: 275
71. Vanhoutte C, Sener A, Malaisse WJ (1998) Hydrolysis of hexose pentaacetate esters in rat pancreatic islets. Biochim Biophys Acta 1405: 78–84
72. Kadiata MM, Malaisse WJ (1998) Opposite effects of D-glucose pentaacetate and D-galactose pentaacetate anomers on insulin release evoked by succinic acid dimethyl ester in rat pancreatic islets. Life Sci (in press)
73. Malaisse WJ, Kadiata MM (1998) Inhibition of insulin release by α-and β-D-galactose pentaacetate. Int J Mol Med 2: 331–332
74. García-Martínez JA, Ladrière L, Villanueva-Peñacarrillo ML, Valverde I, Malaisse WJ (1997) Insulinotropic action of α-D-glucose pentaacetate in vivo. Diabetes Nutr Metab 10: 198–202
75. García-Martínez JA, Cancelas J, Villanueva-Peñacarrillo ML, Valverde I, Malaisse WJ (1998) In vivo stimulation of insulin release by 2-deoxy-D-glucose tetraacetate. Med Sci Res (in press)
76. Malaisse WJ, Kadiata MM, Scruel O, Sener A (1998) Esterification of D-mannoheptulose confers to the heptose inhibitory action on D-glucose metabolism in parotid cells. Biochem Mol Biol Int 44: 625–633
77. Vanhoutte C, Kadiata MM, Sener A, Malaisse WJ (1997) Potentiation by its esterification of the inhibitory action of 2-deoxy-D-glucose on D-glucose metabolism and insulinotropic action. Biochem Mol Biol Int 43: 189–195
78. Malaisse WJ, Delvaux A, Rasschaert J, Kadiata MM (1998) Cytotoxic action of 2-deoxy-D-glucose tetraacetate in tumoral pancreatic islet cells. Cancer Lett 125: 45–49
79. Delvaux A, Kadiata MM, Malaisse WJ (1997) Cytotoxicity of 2-deoxy-D-glucose and its tetraacetate ester in tumoral cell lines. Oncol Res 4: 1295–1299
80. Reinhold U, Malaisse WJ (1998) Cytotoxic action of 2-deoxy-D-glucose tetraacetate upon human lymphocytes, fibroblasts and melanoma cells. Int J Mol Med 1: 427–430
81. Malaisse WJ, Delvaux A (1997) Cytostatic effect of 2-deoxy-D-glucose and its tetraacetate ester in transformed mouse fibroblasts. Med Sci Res 25: 727–728