1° CORSO NAZIONALE DI AGGIORNAMENTO

Associazione Medici Endocrinologi

I PER[CORSI]AME

ROMA

9__11 NOVEMBRE 2012

Percorso 7

DIABETE (2)
Quale farmaco per il Diabete 2: efficacia vs farmaco-economia

GLP 1 Agonisti & DPP IV inibitori

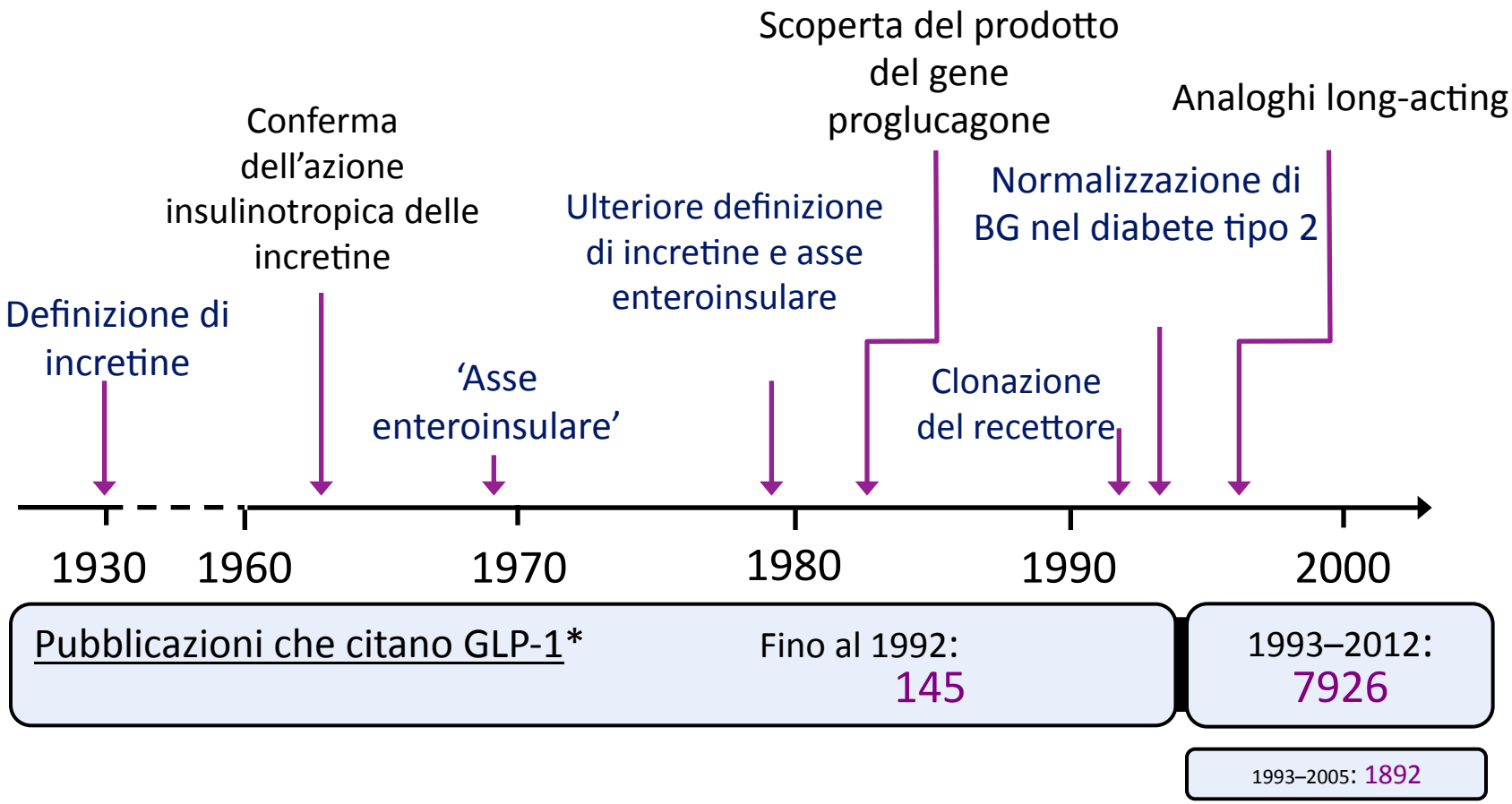
Silvio Settembrini

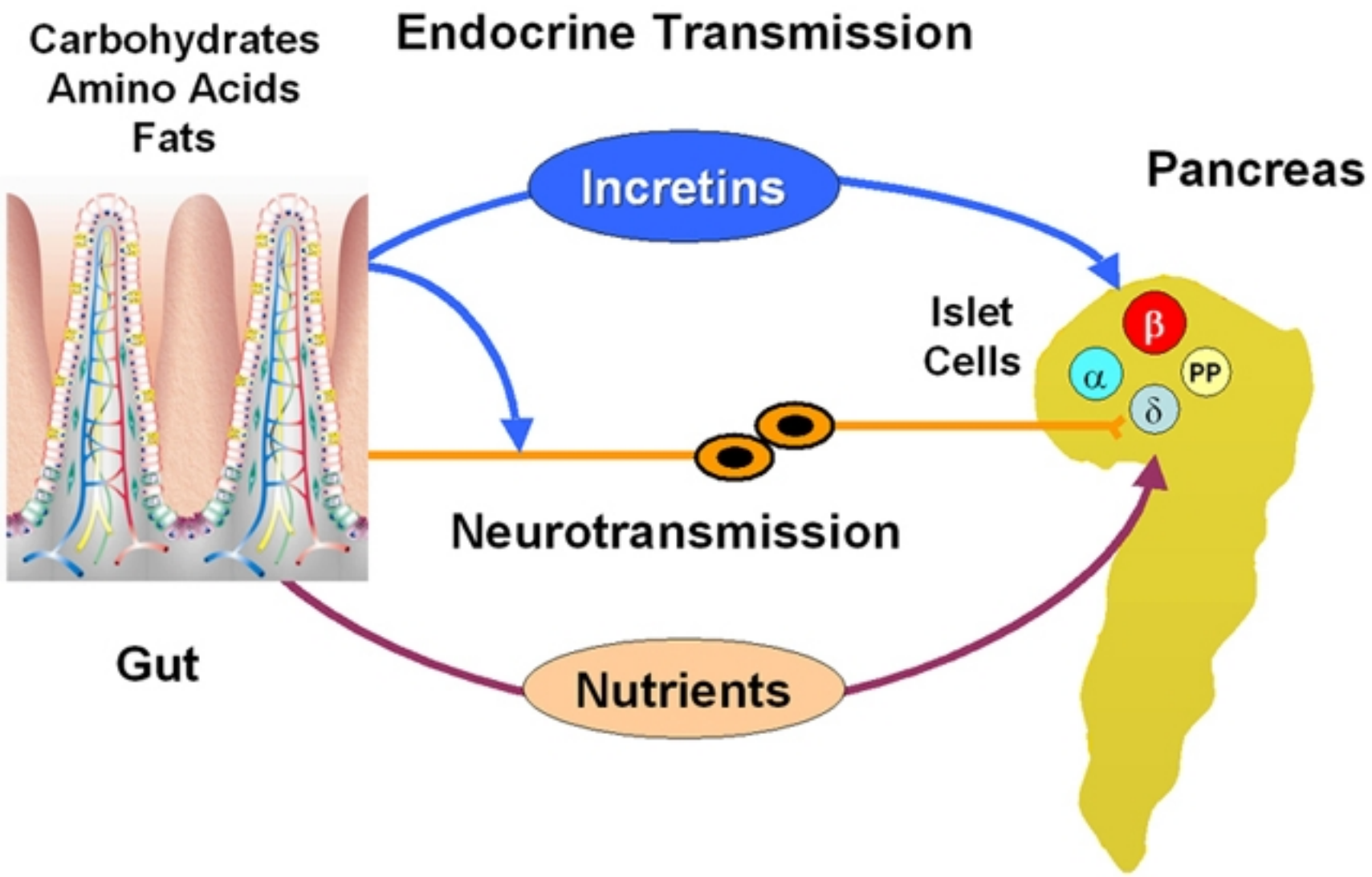
ASL Napoli 1

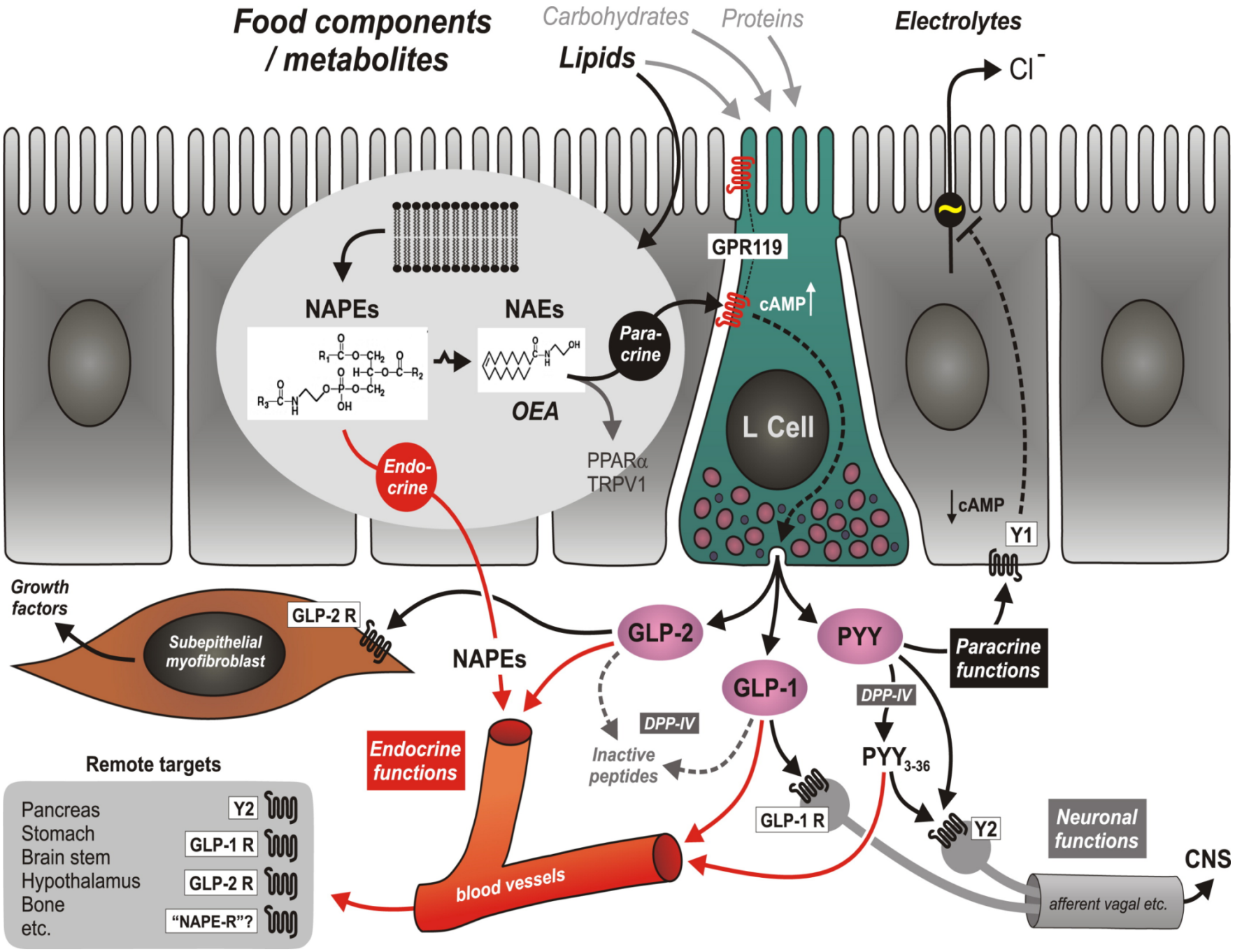
Servizio di Endocrinologia, Diabetologia e Malattie Metaboliche - DSB 26

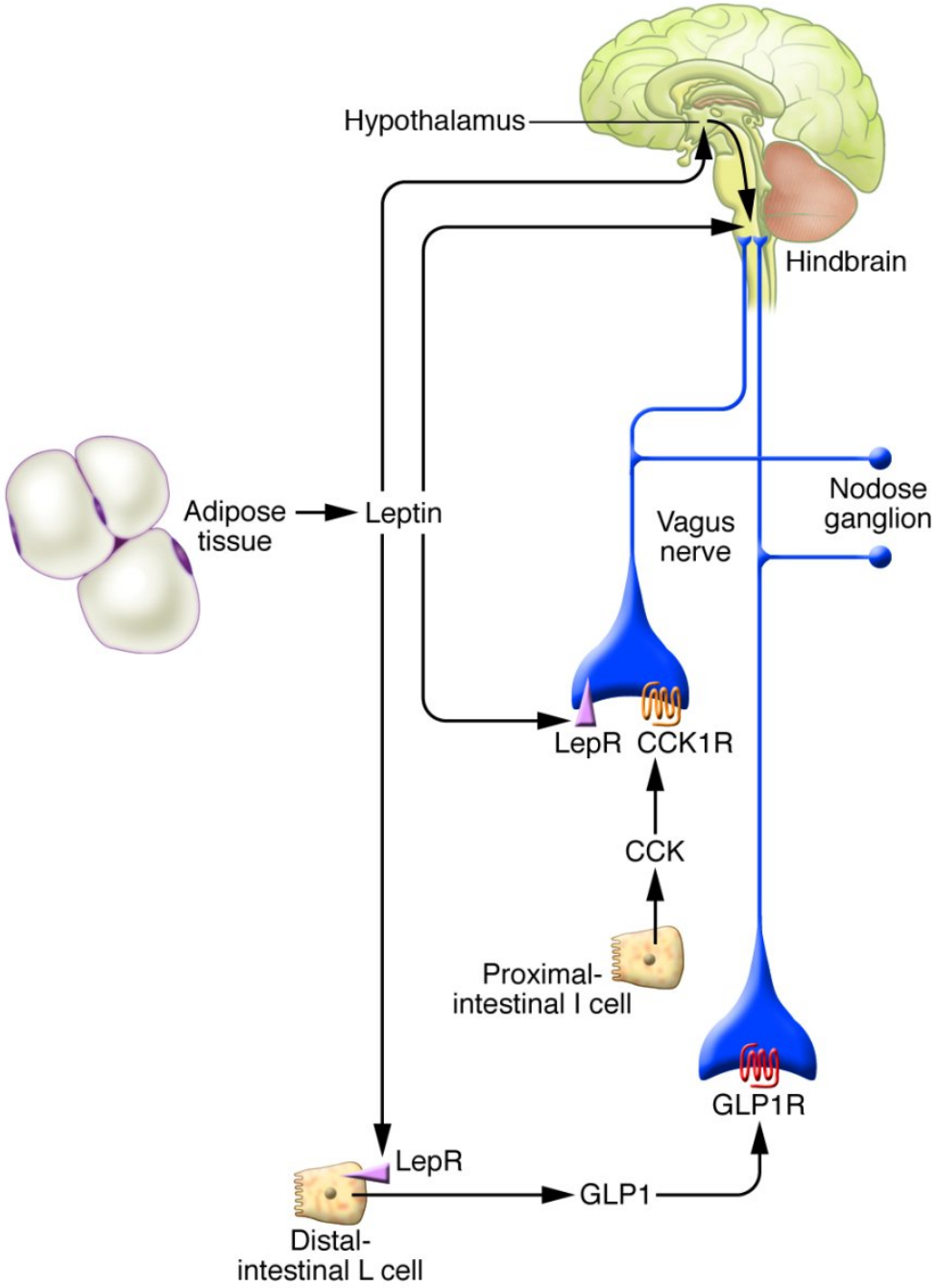
Unità di Nefro-Endocrinologia e Diabetologia - Ospedale dei Pellegrini – Napoli

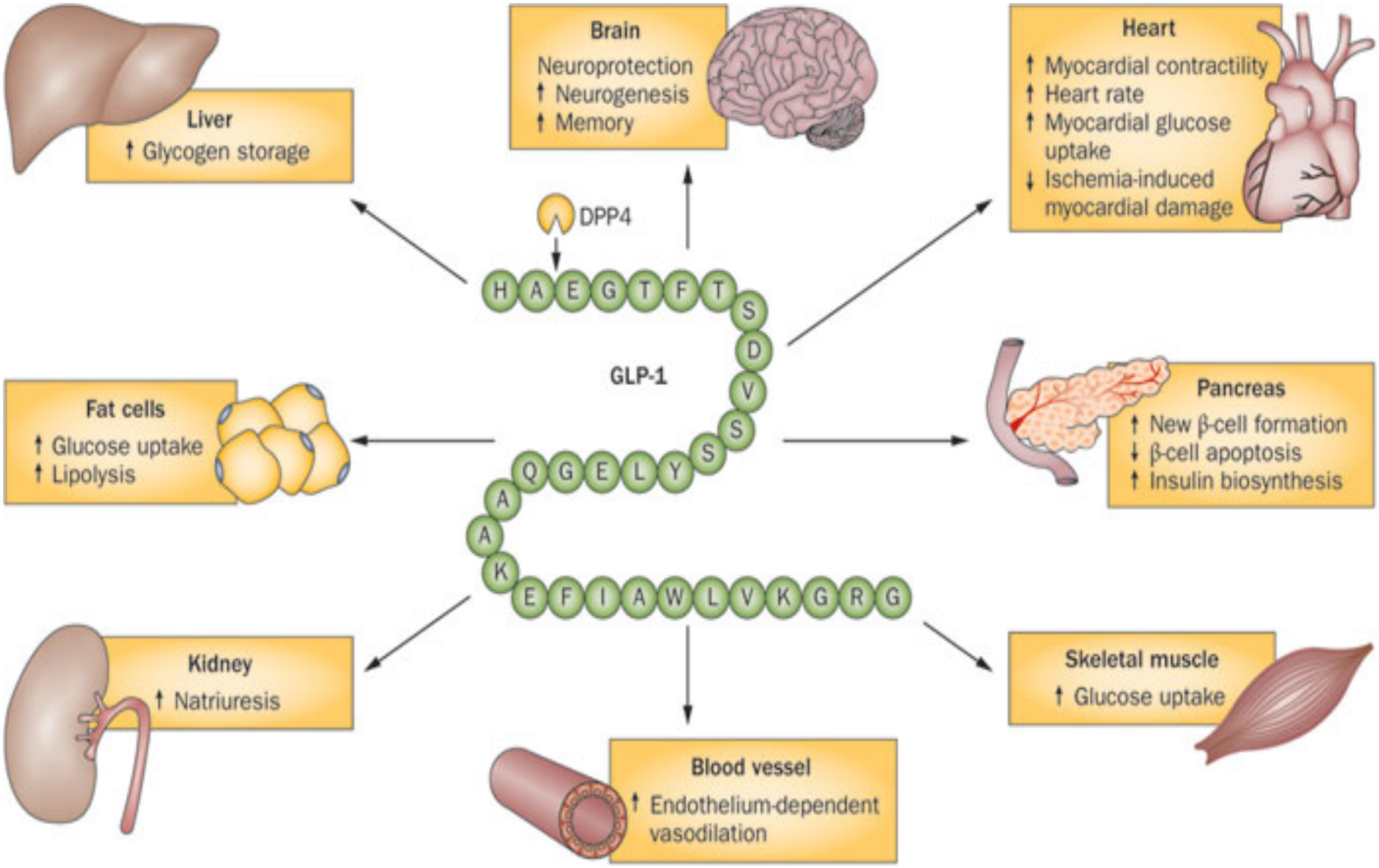
Storia del GLP-1

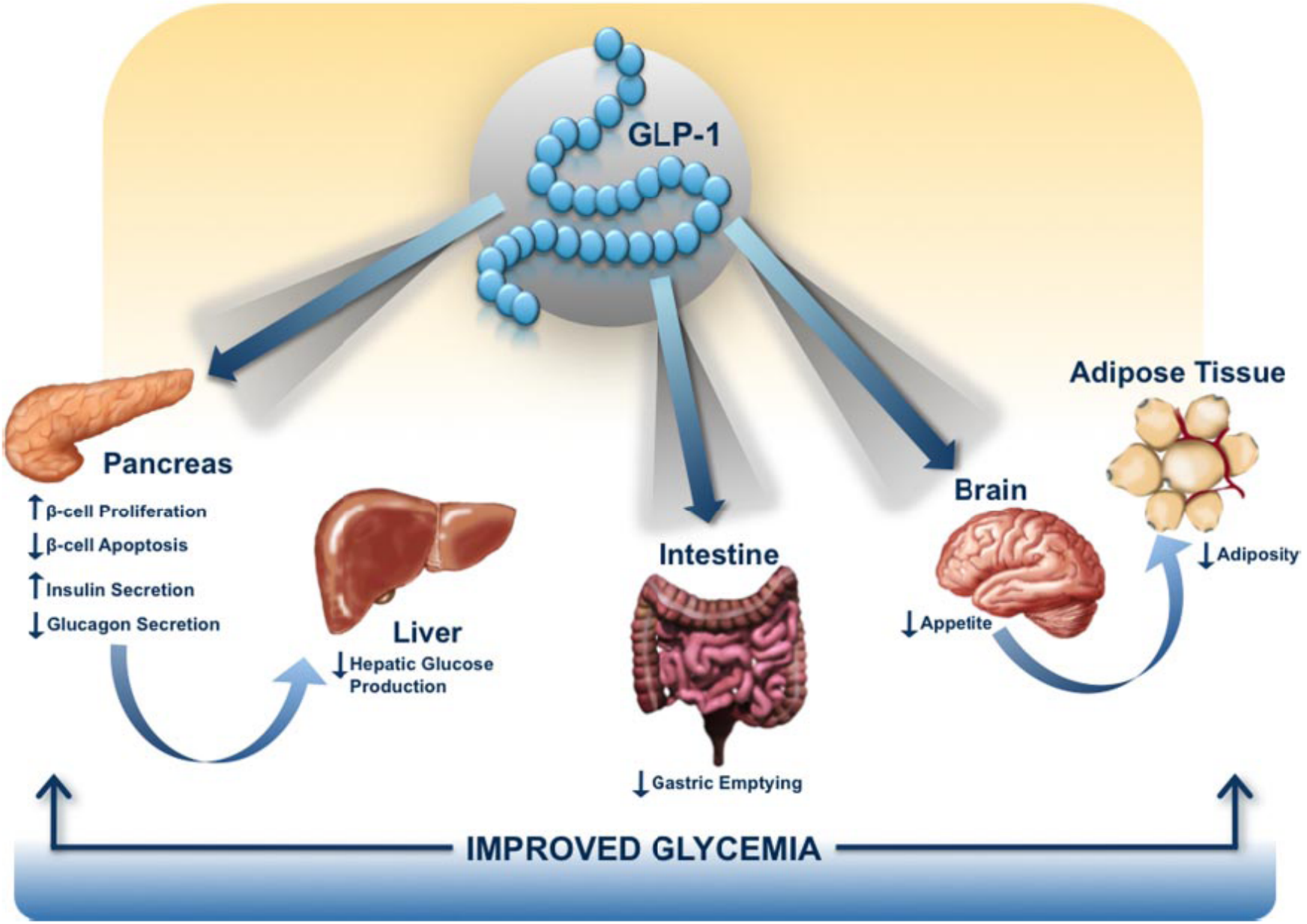



Carbohydrates
Amino Acids
Fats
Endocrine Transmission
Incretins
Pancreas
Islet
Cells
β
α
PP
δ
Neurotransmission
Gut
Nutrients


Food components / metabolites
Carbohydrates
Proteins
Lipids
Electrolytes
Cl⁻
GPR119
cAMP
NAPEs
NAEs
OEA
Para-crine
Endo-crine
PPARα
TRPV1
L Cell
cAMP
Y1
Growth factors
Subepithelial myofibroblast
GLP-2 R
GLP-2
PYY
Paracrine functions
NAPEs
GLP-1
DPP-IV
DPP-IV
Endocrine functions
Inactive peptides
PYY3-36
GLP-1 R
Y2
Neuronal functions
CNS
blood vessels
afferent vagal etc.
Remote targets
Pancreas
Stomach
Brain stem
Hypothalamus
Bone
etc.
Y2
GLP-1 R
GLP-2 R
"NAPE-R"?


Hypothalamus
Hindbrain
Adipose tissue
Leptin
Vagus nerve
Nodose ganglion
LepR
CCK1R
CCK
Proximal-intestinal I cell
GLP1R
LepR
GLP1
Distal-intestinal L cell


Liver
↑ Glycogen storage
Brain
Neuroprotection
↑ Neurogenesis
↑ Memory
Heart
↑ Myocardial contractility
↑ Heart rate
↑ Myocardial glucose uptake
↓ Ischemia-induced myocardial damage
DPP4
H A E G T F T S D V S S Q G E L Y A A K E F I A W L V K G R G
GLP-1
Fat cells
↑ Glucose uptake
↑ Lipolysis
Pancreas
↑ New β-cell formation
↓ β-cell apoptosis
↑ Insulin biosynthesis
Kidney
↑ Natriuresis
Skeletal muscle
↑ Glucose uptake
Blood vessel
↑ Endothelium-dependent vasodilation


GLP-1
Pancreas
↑ β-cell Proliferation
↓ β-cell Apoptosis
↑ Insulin Secretion
↓ Glucagon Secretion
Liver
↓ Hepatic Glucose Production
Intestine
↓ Gastric Emptying
Brain
↓ Appetite
Adipose Tissue
↓ Adiposity
IMPROVED GLYCEMIA

Insulin secretion

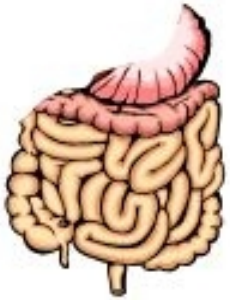
↑ Sulfonyureas
↑ Meglitinides
↑ Incretins

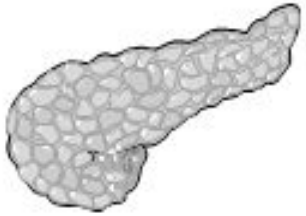
Glucagon secretion

↓ Incretins
↓ Amylin

GI

Incretins
α glucosidase inhibitors
Amylin
Bile acid sequestrant

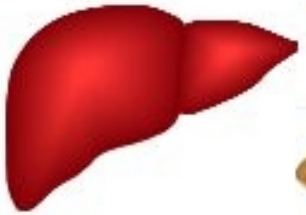




Appetite control

Incretins
Amylin

Hyperglycemia



Hepatic glucose output

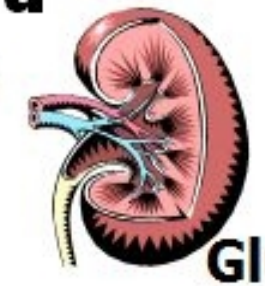
↓ Metformin
↓ Thiazolidinediones

Lipotoxicity

Thiazolidinediones
Salicylates

Glucose uptake and utilization

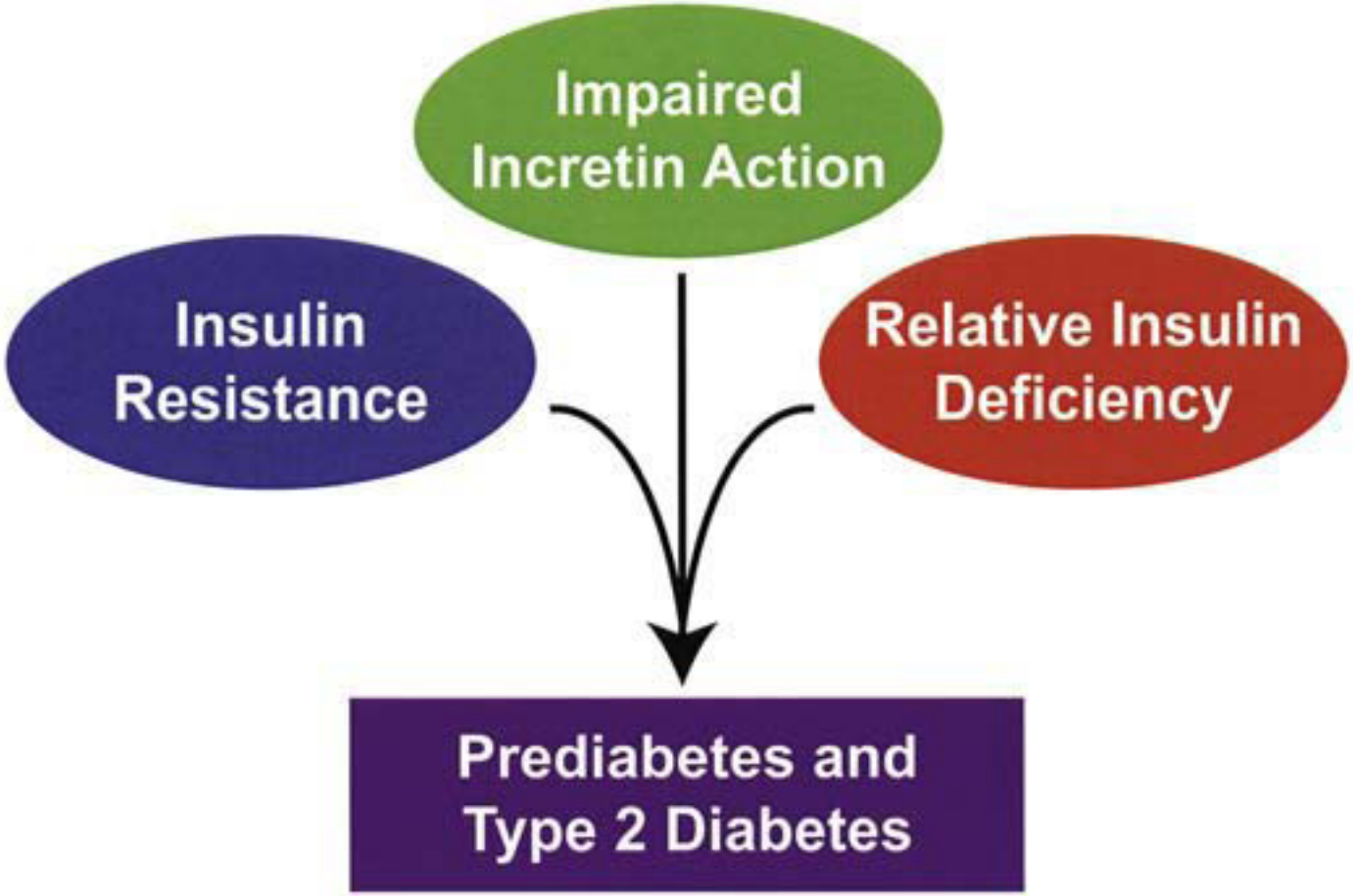
↑ Thiazolidinediones
↑ Metformin



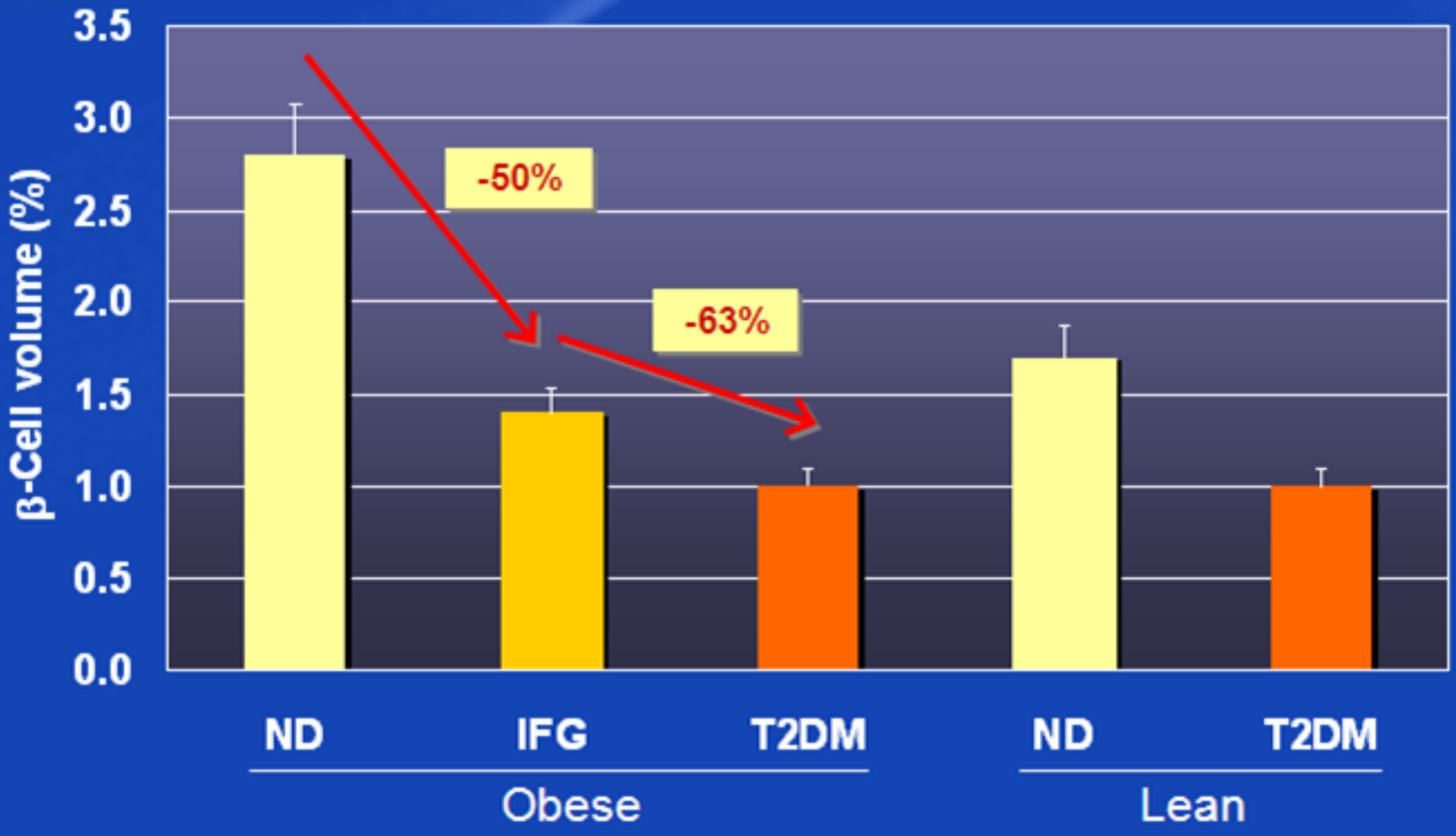
Glucose reabsorption

↓SGLT2 inhibitors

Redefining Pathophysiology of Type 2 Diabetes



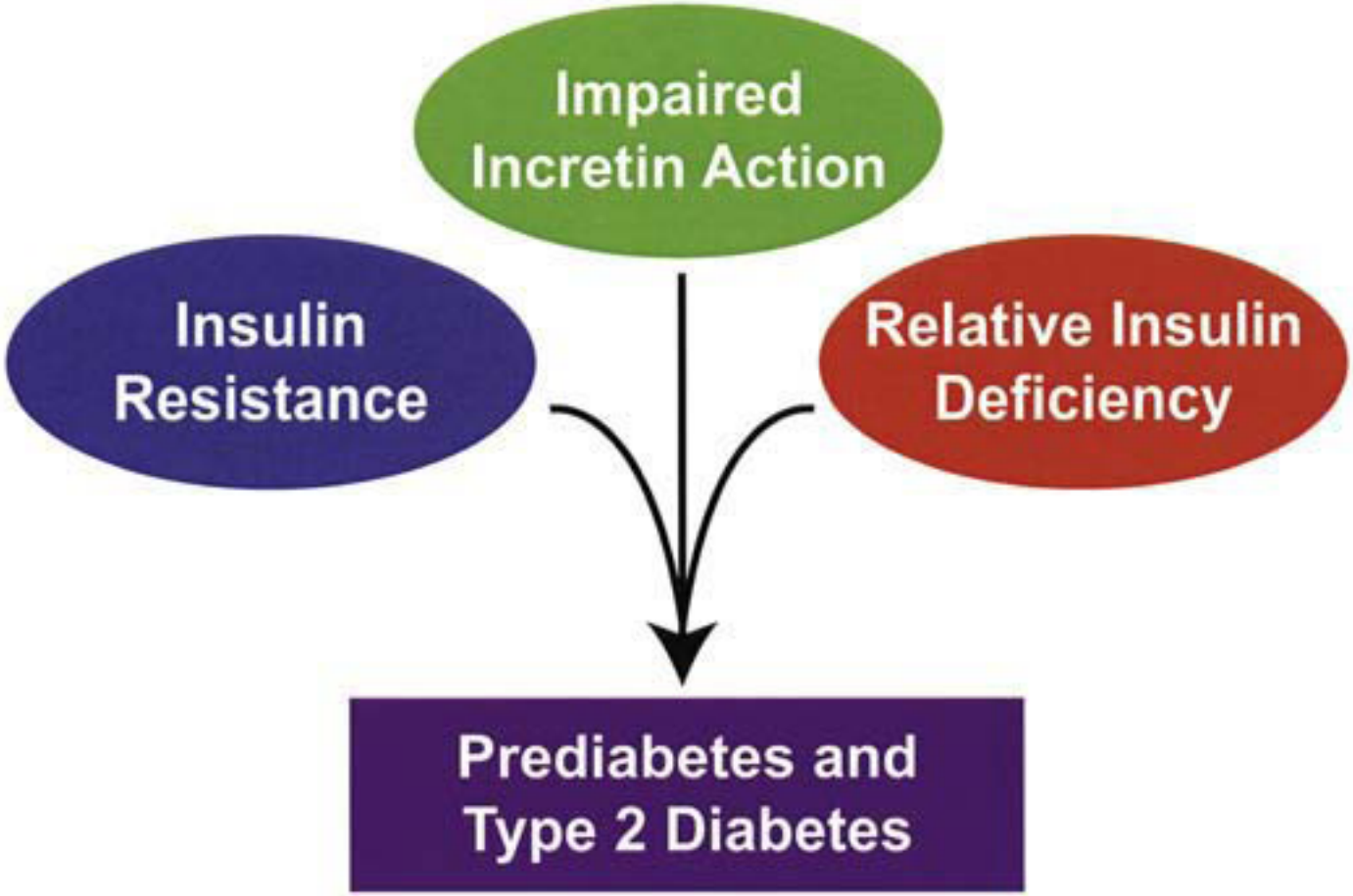
β-Cell mass in Type 2 diabetes

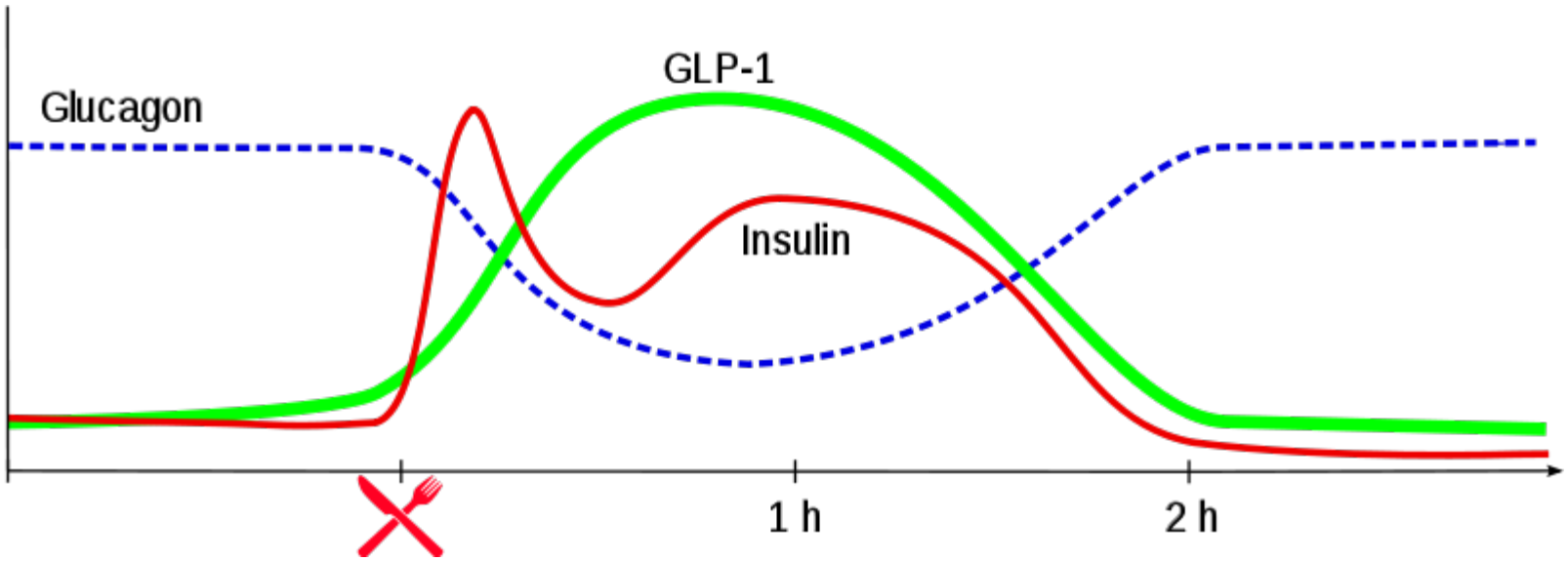


ND=non-diabetic; IFG=impaired fasting glucose; T2DM=Type 2 diabetes mellitus

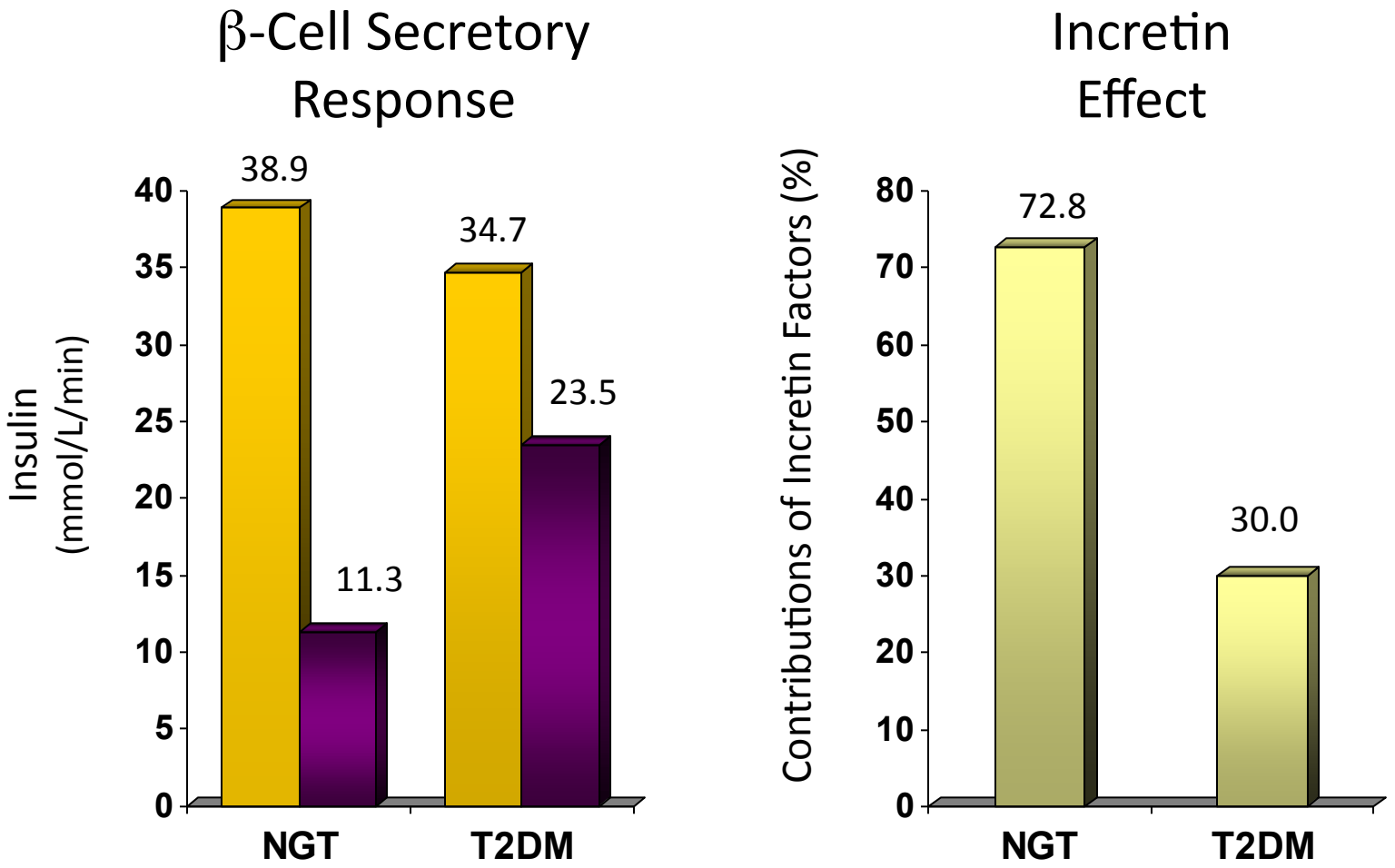
Butler et al. *Diabetes*. 2003

Redefining Pathophysiology of Type 2 Diabetes




Glucagon
GLP-1
Insulin
1 h
2 h

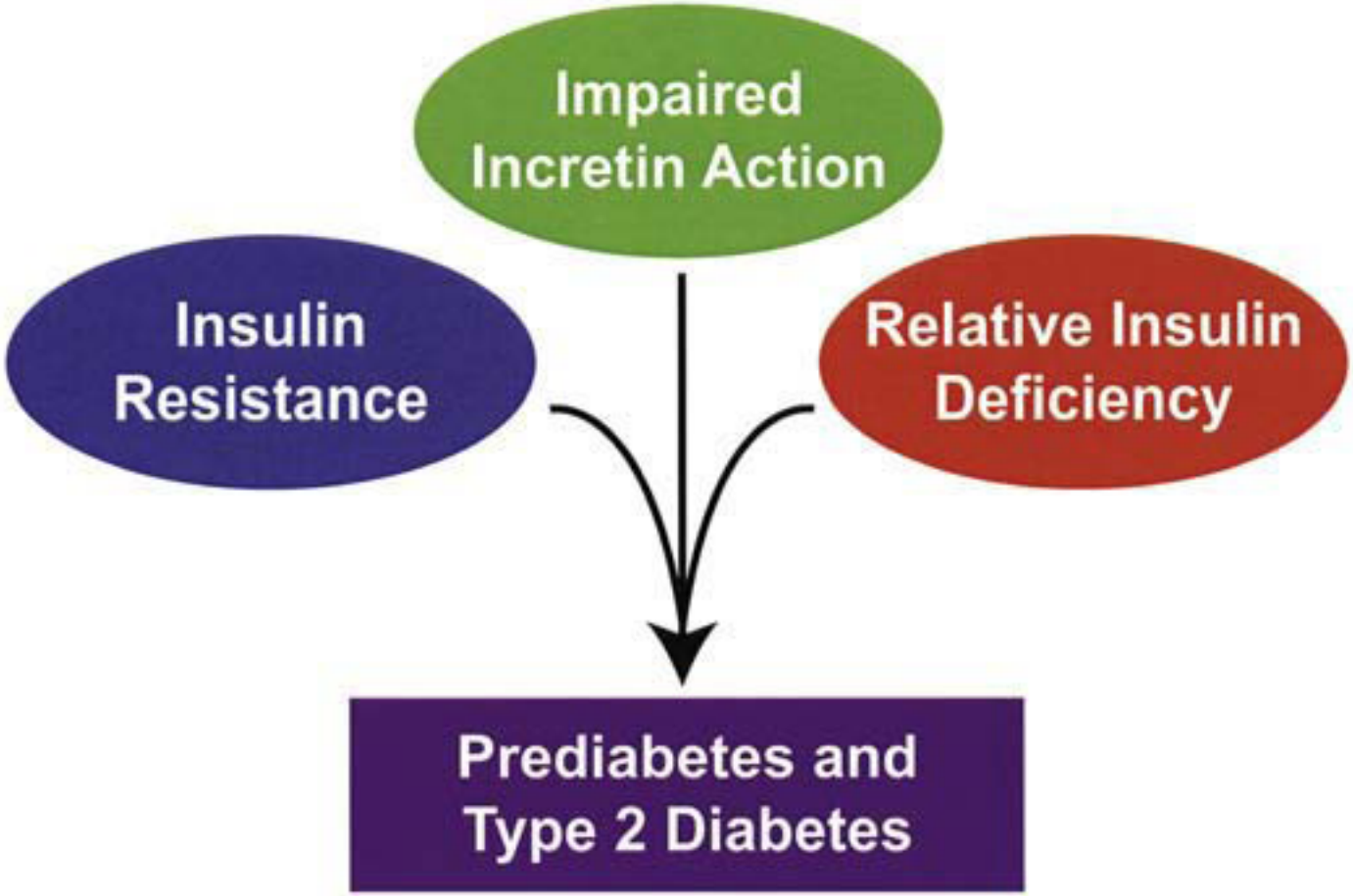
The Incretin Effect Is Reduced in T2DM Compared With NGT

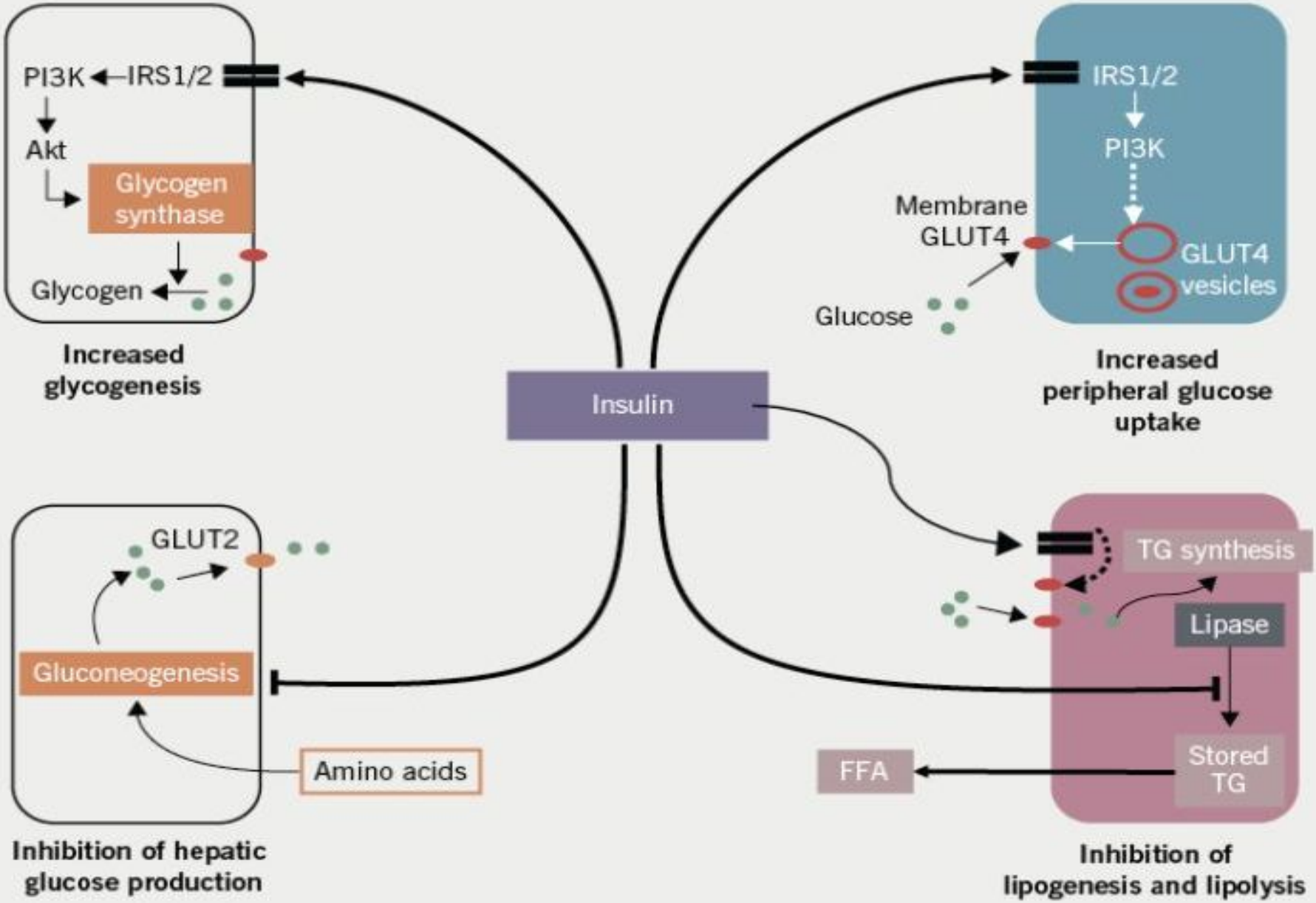


NGT=normal glucose tolerance

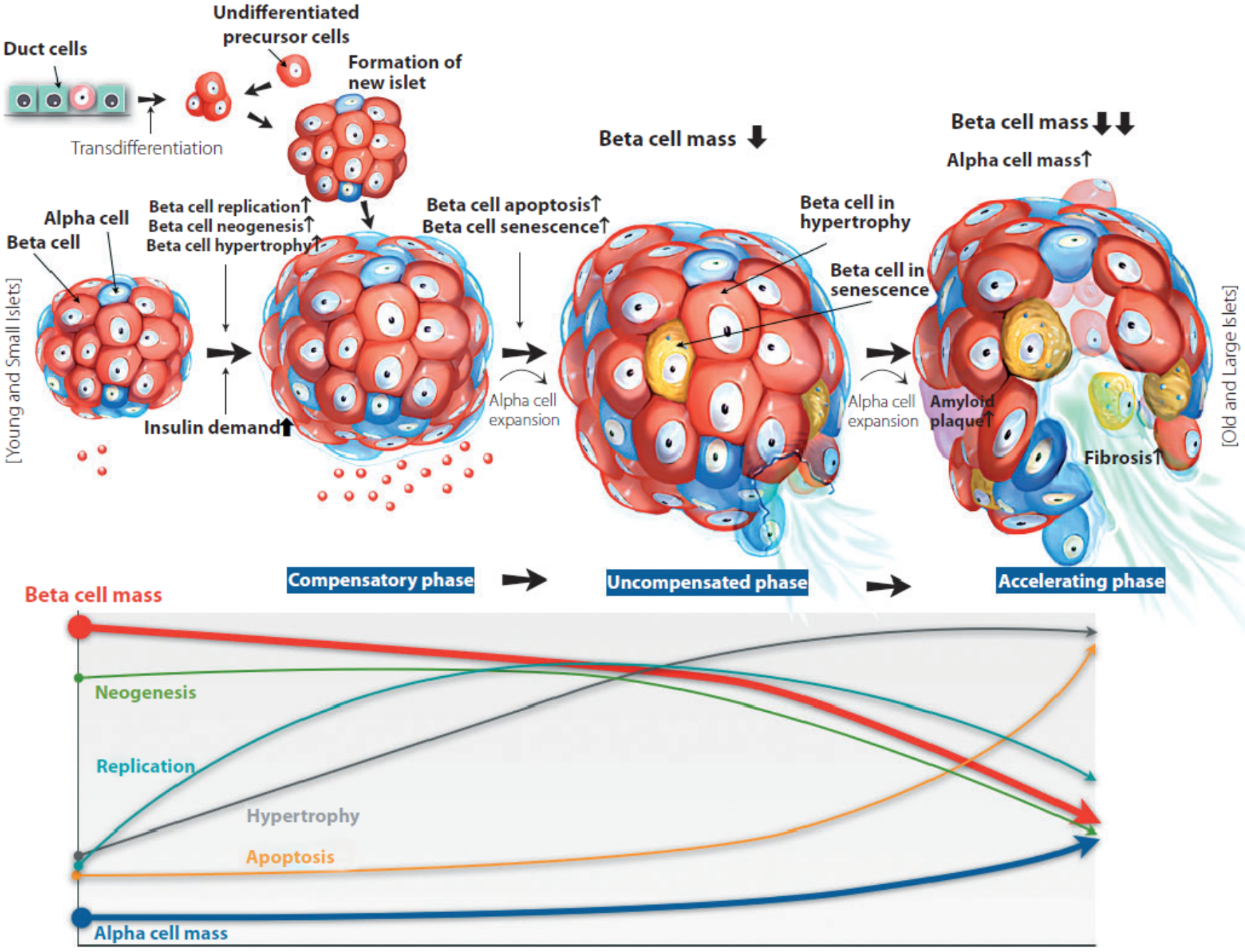
Nauck. *Diabetologia.* 1986;29:46.

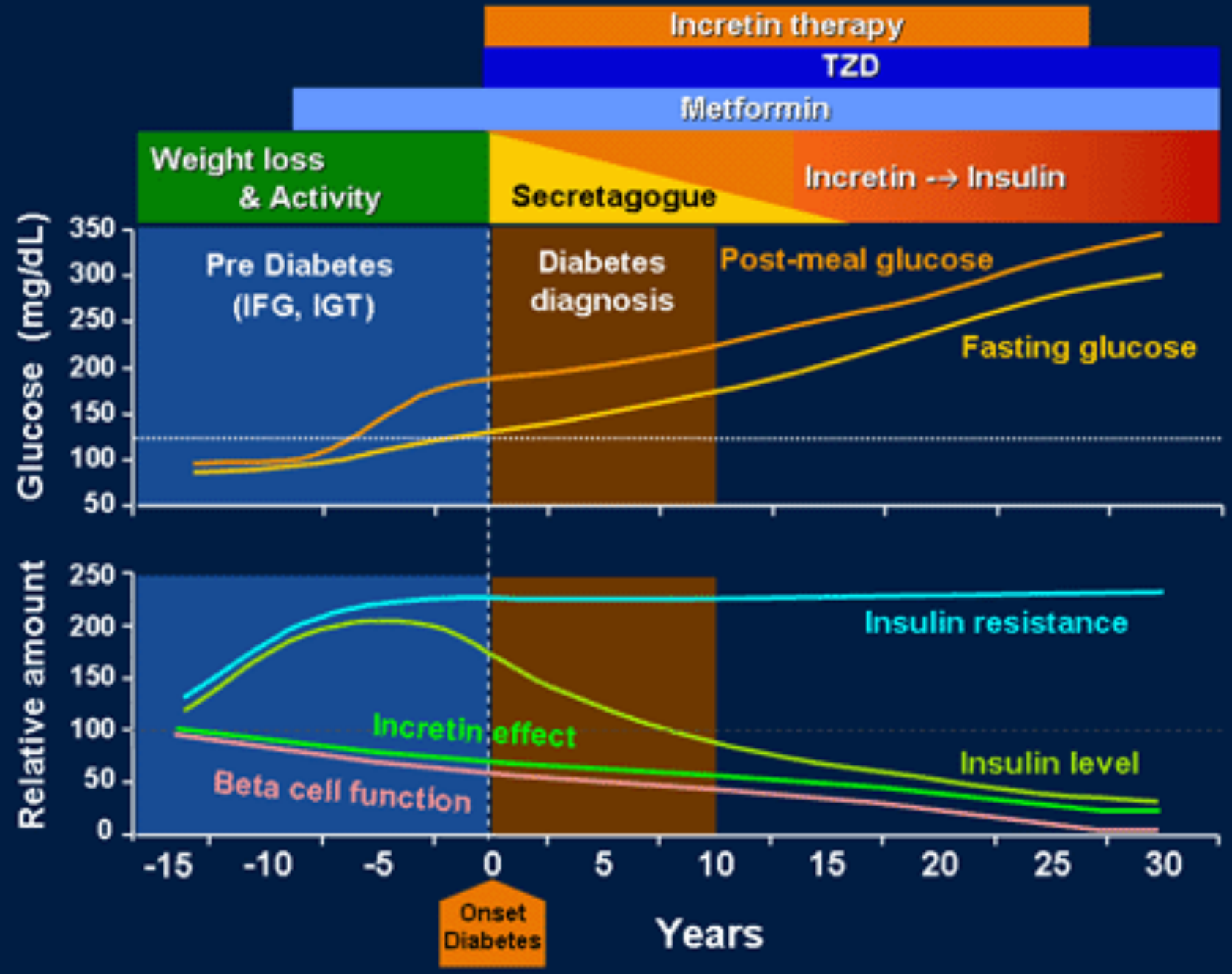
Redefining Pathophysiology of Type 2 Diabetes



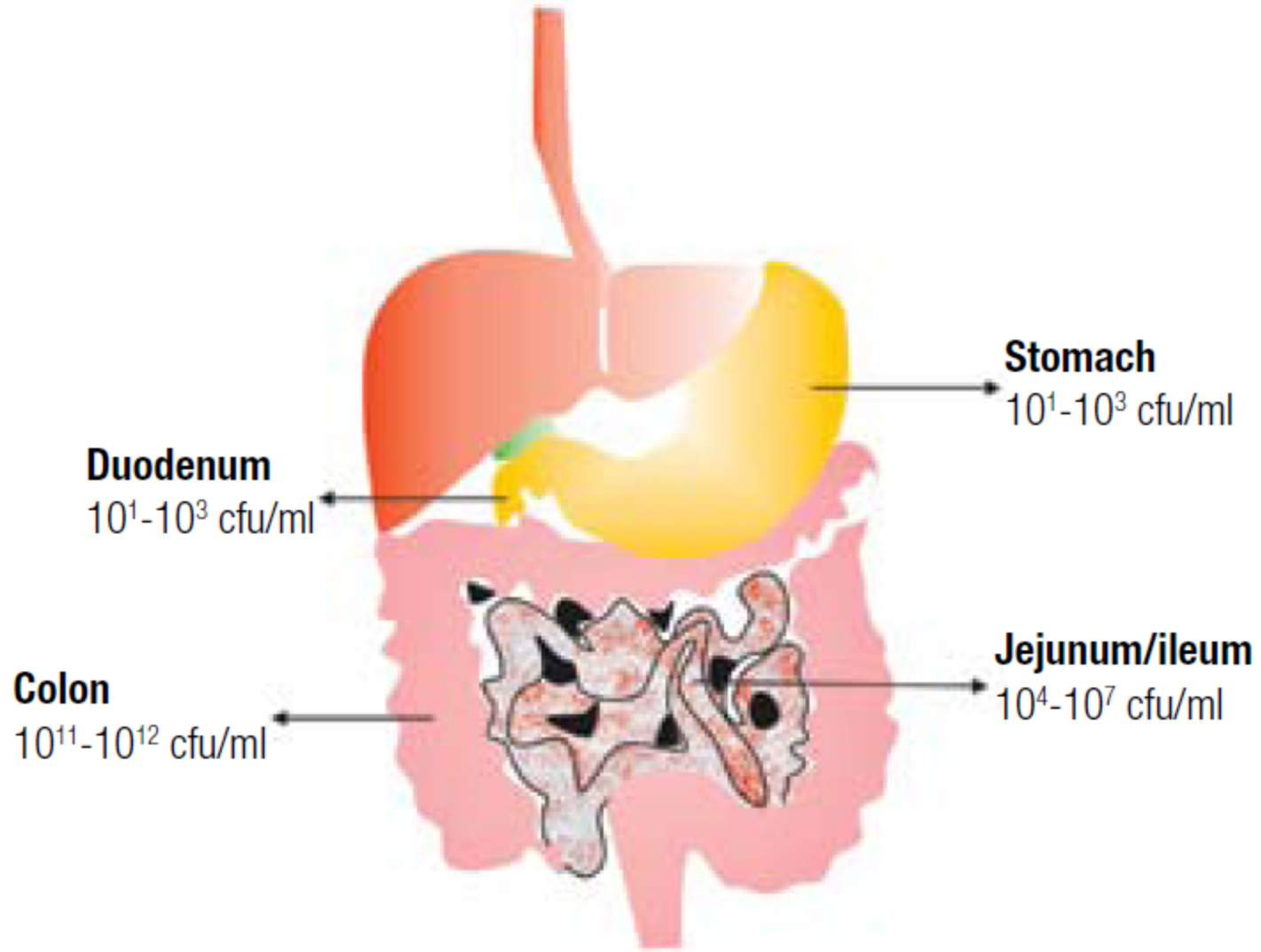


Key: FFA = free fatty acid; GLUT2 = glucose transporter 2; GLUT4 = glucose transporter 4; IRS1/2 = insulin receptor substrate-1/2; PI3K = phosphoinositide 3-kinase; TG = triglyceride


Duct cells
Undifferentiated precursor cells
Formation of new islet
Transdifferentiation
Beta cell mass ⬇
Beta cell mass ⬇⬇
Alpha cell mass↑
Alpha cell
Beta cell
Beta cell replication↑
Beta cell neogenesis↑
Beta cell hypertrophy↑
Beta cell apoptosis↑
Beta cell senescence↑
Beta cell in hypertrophy
Beta cell in senescence
[Young and Small Islets]
Insulin demand⬆
Alpha cell expansion
Alpha cell expansion
Amyloid plaque↑
Fibrosis↑
[Old and Large Islets]
Compensatory phase
Uncompensated phase
Accelerating phase
Beta cell mass
Neogenesis
Replication
Hypertrophy
Apoptosis
Alpha cell mass

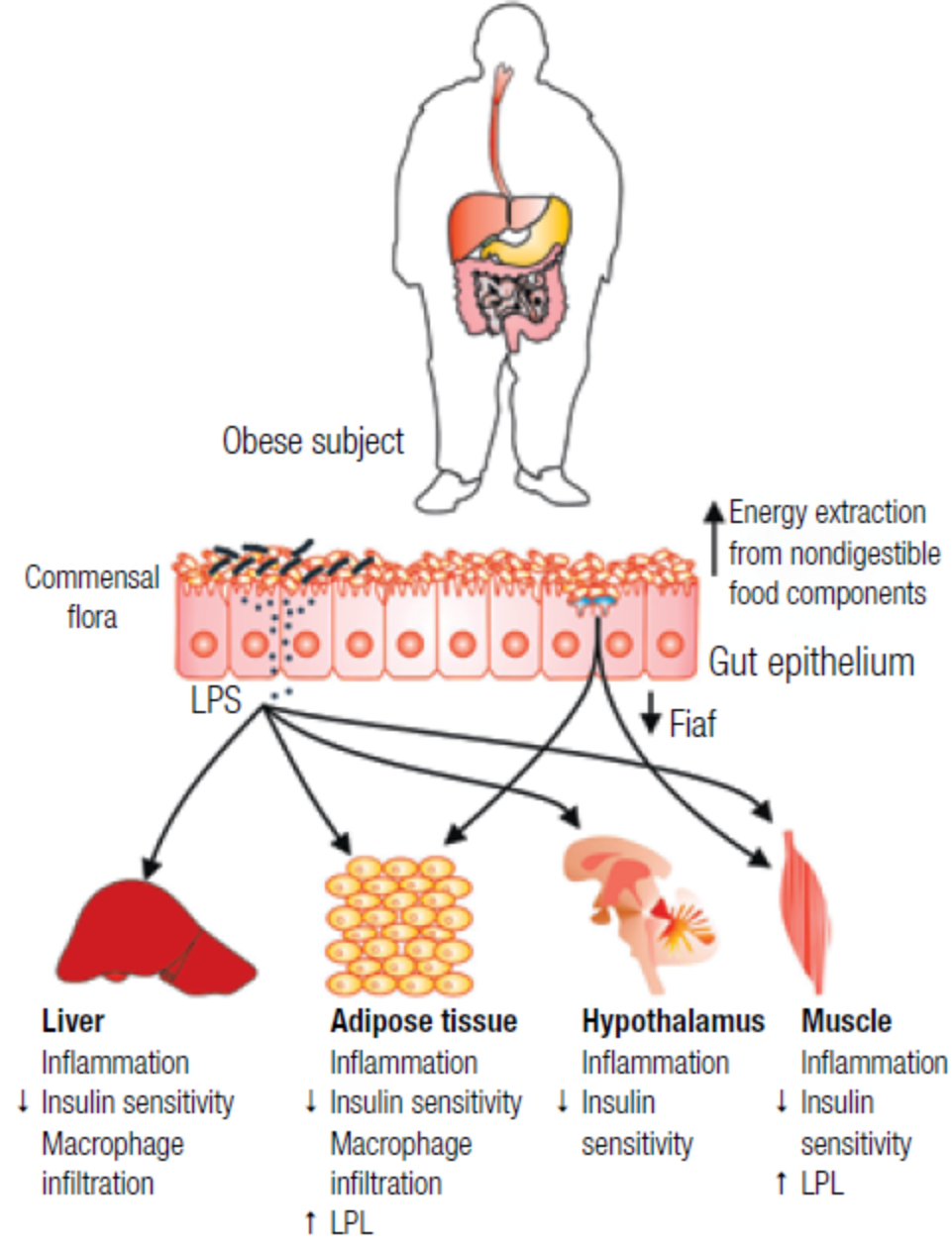


Kendall DM, Cuddihy RM, Bergenstal RM. *Am J Med.* In press.



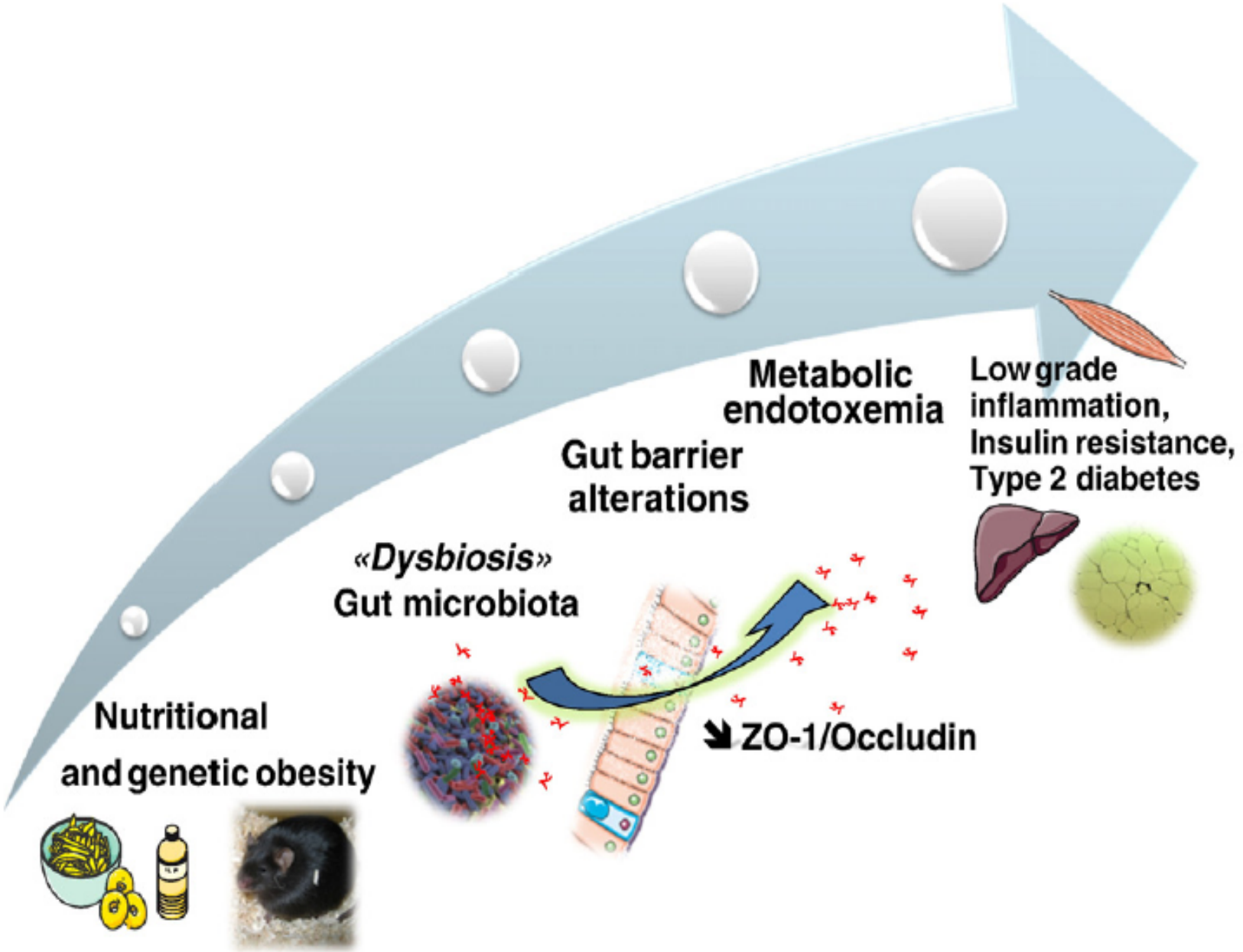
cfu = colony-forming unit.

Relative concentrations of bacteria at various locations within the gut.



Fiaf = fasting-induced adipose factor; LPL = lipoprotein lipase; LPS = lipopolysaccharide.

Schematic view of the possible mechanisms linking gut flora to obesity


Nutritional
and genetic obesity
«Dysbiosis»
Gut microbiota
Gut barrier
alterations
↘ ZO-1/Occludin
Metabolic
endotoxemia
Low grade
inflammation,
Insulin resistance,
Type 2 diabetes

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Chronic administration of ezetimibe increases active glucagon-like peptide-1 and improves glycemic control and pancreatic beta cell mass in a rat model of type 2 diabetes

Soo Jin Yang [a], Jung Mook Choi [a], Lisa Kim [a], Byung-Joon Kim [b], Jin Hee Sohn [c], Won Jun Kim [d], Se Eun Park [d], Eun Jung Rhee [d], Won Young Lee [d], Ki Won Oh [d], Sung Woo Park [d], Sun Woo Kim [d], Cheol-Young Park [d,*]

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Glucagon-like peptide-1
Glycemic control
Pancreatic beta cell
Type 2 diabetes

ABSTRACT

Ezetimibe is a cholesterol-lowering agent targeting Niemann-Pick C1-like 1, an intestinal cholesterol transporter. Inhibition of intestinal cholesterol absorption with ezetimibe may ameliorate several metabolic disorders including hepatic steatosis and insulin resistance. In this study, we investigated whether chronic ezetimibe treatment improves glycemic control and pancreatic beta cell mass, and alters levels of glucagon-like peptide-1 (GLP-1), an incretin hormone involved in glucose homeostasis. Male LETO and OLETF rats were treated with vehicle or ezetimibe (10 mg kg^{-1} day^{-1}) for 20 weeks via stomach gavage. OLETF rats were diabetic with hyperglycemia and significant decreases in pancreatic size and beta cell mass compared with LETO lean controls. Chronic treatment of OLETF rats with ezetimibe improved glycemic control during oral glucose tolerance test compared with OLETF controls. Moreover, ezetimibe treatment rescued the reduced pancreatic size and beta cell mass in OLETF rats. Interestingly, ezetimibe significantly decreased serum dipeptidyl peptidase-4 activity and increased serum active GLP-1 in OLETF rats without altering serum total GLP-1. These findings demonstrated that chronic administration of ezetimibe improves glycemic control and pancreatic beta cell mass, and increases serum active GLP-1 levels, suggesting possible involvement of GLP-1 in the ezetimibe-mediated beneficial effects on glycemic control.

GLP-1 HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

DPP 4

Exenatide HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS

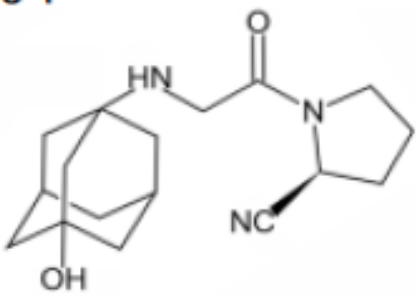
Liraglutide HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG

E

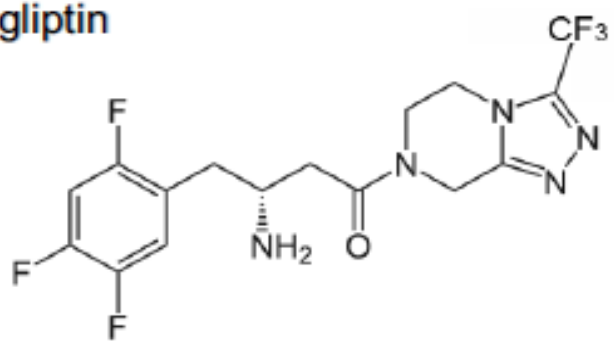
C-16 fatty acid derivative via a glutamoyl spacer

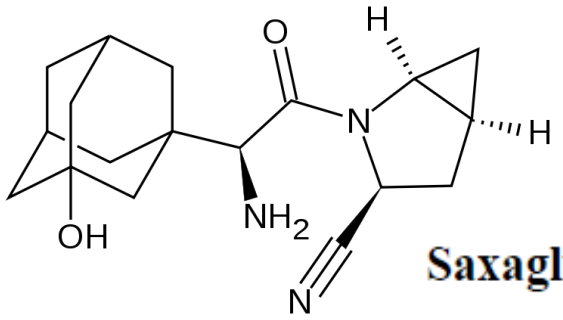
Albumin

Vildagliptin



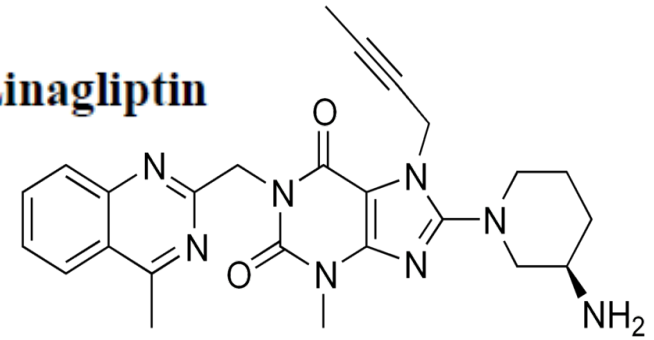
Sitagliptin





Saxagliptin

Linagliptin



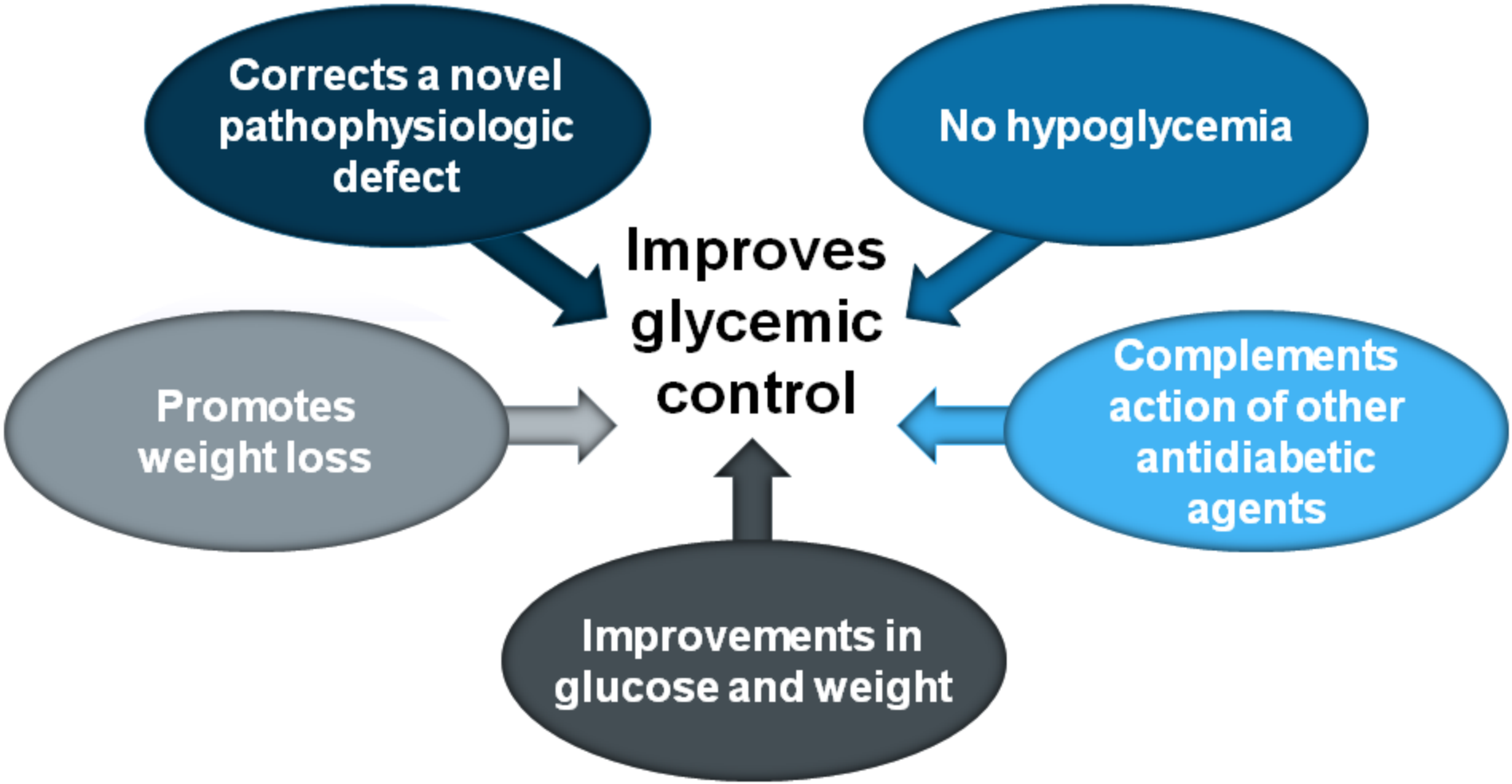
Nuovi obiettivi per un trattamento ottimale

- **L'approccio terapeutico ideale dovrebbe soddisfare tutti i seguenti aspetti:**

- efficacia clinica a lungo termine
- basso rischio di ipoglicemie
- preservazione della funzionalità beta cellulare
- effetto neutrale o di riduzione sul peso corporeo
- effetto protettivo sul rischio cardiovascolare
- buon profilo di sicurezza e tollerabilità
- regime di trattamento semplice e flessibile

UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352: 837-53
Kahn SE, et al. for the ADOPT Study Group. N Engl J Med 2006; 35: 2427-43

Individualizing Therapy: Factors to Consider



DeFronzo RA. *Diabetes*. 2009;58:773-795.

Summary of the Clinical Effects of Glucagon-like Peptide–1 (GLP-1) Receptor Agonists and Dipeptidyl Peptidase–4 (DPP-4) Inhibitors.

DPP-4 Inhibitors (sitagliptin, alogliptin, saxaglitpin, vildagliptin)	GLP-1 Receptor Agonists (exenatide, liraglutide, taspoglutide)
• HbA_{1c} reduction 0.5–1.0% • Weight neutral • Oral administration • No significant GI side effects • Low rates of hypoglycemia • Improved meal-related insulin secretion, reduced glucagon release • Can reduce dose and use in renal insufficiency	• HbA_{1c} reduction 0.6–1.5% • Significant and sustained weight loss generally observed • Injected therapy (once daily, twice daily, once weekly) • GI side effects most common (nausea, diarrhea particularly with initiation) • Low rates of hypoglycemia • Multiple mechanisms of action — ↑ Insulin secretion, ↓ glucagon release — Reduced food intake, slowing of gastric emptying — Weight loss

GI = gastrointestinal; HbA_{1c} = hemoglobin A_{1c}; ↑ = increased; ↓ = decreased.

Registro farmaci antidiabetici sottoposti a monitoraggio

Rapporto farmaci incretino-mimetici e DPP-4 inibitori

AIFA

Agenzia Italiana del Farmaco

Registro farmaci antidiabetici sottoposti a monitoraggio

Rapporto farmaci incretino-mimetici e DPP-4 inibitori

Gennaio 2011

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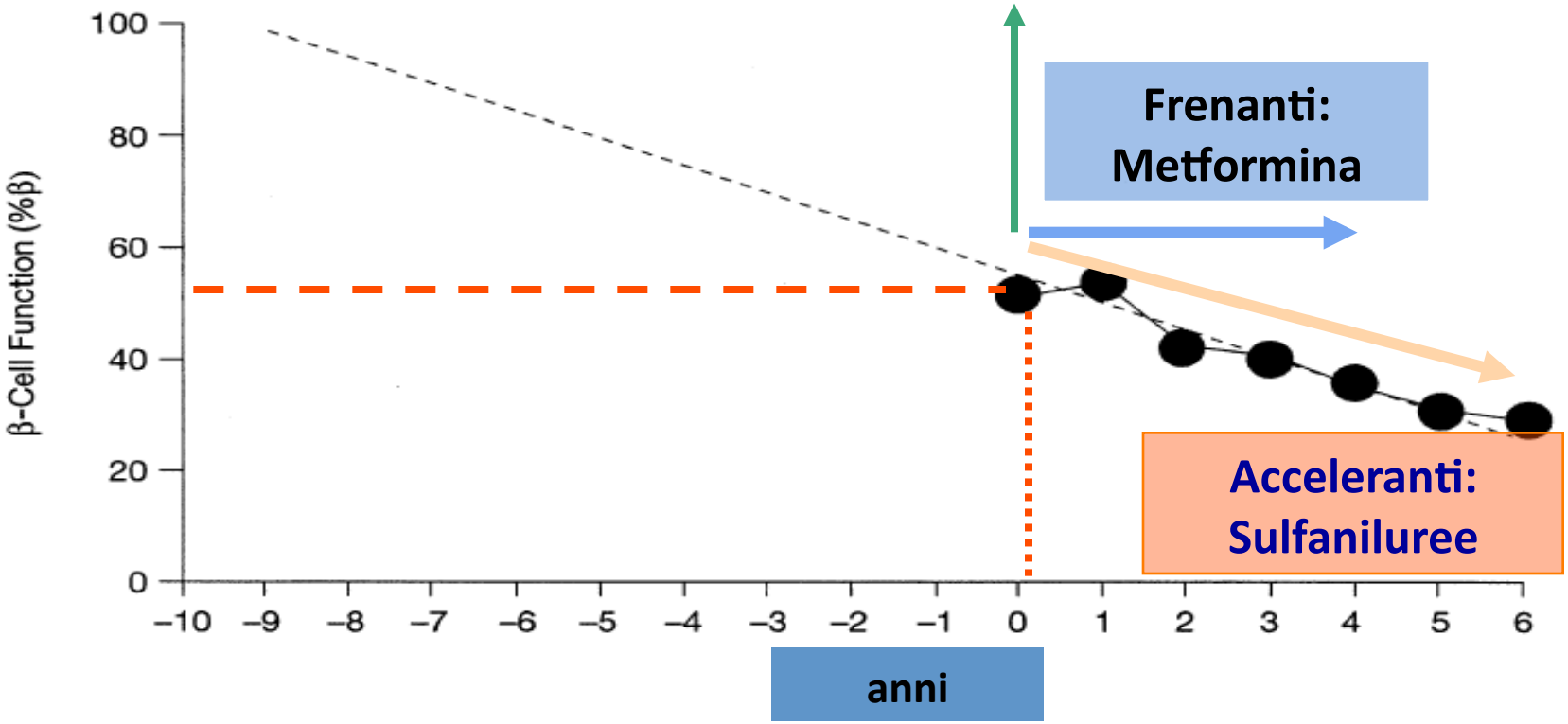
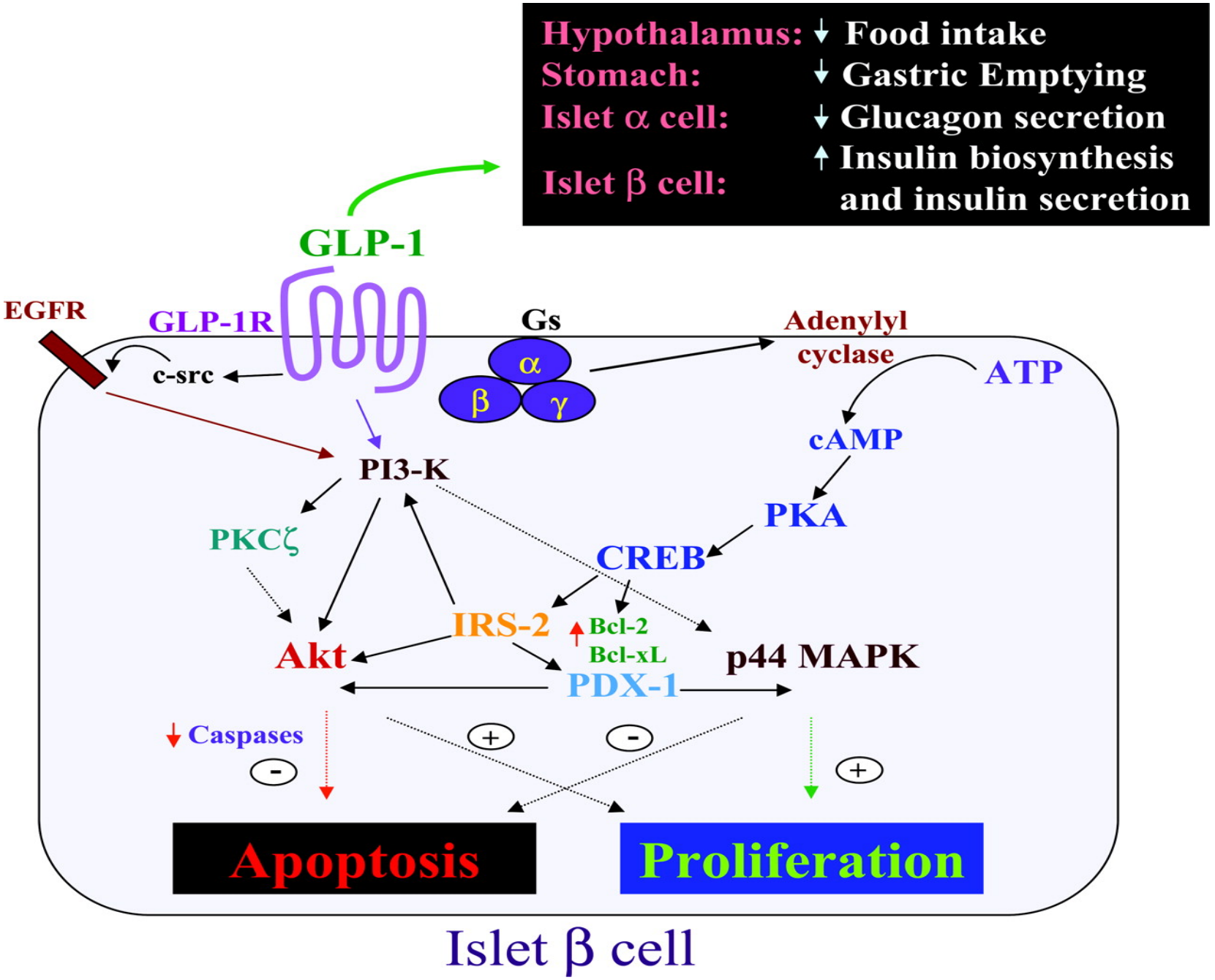
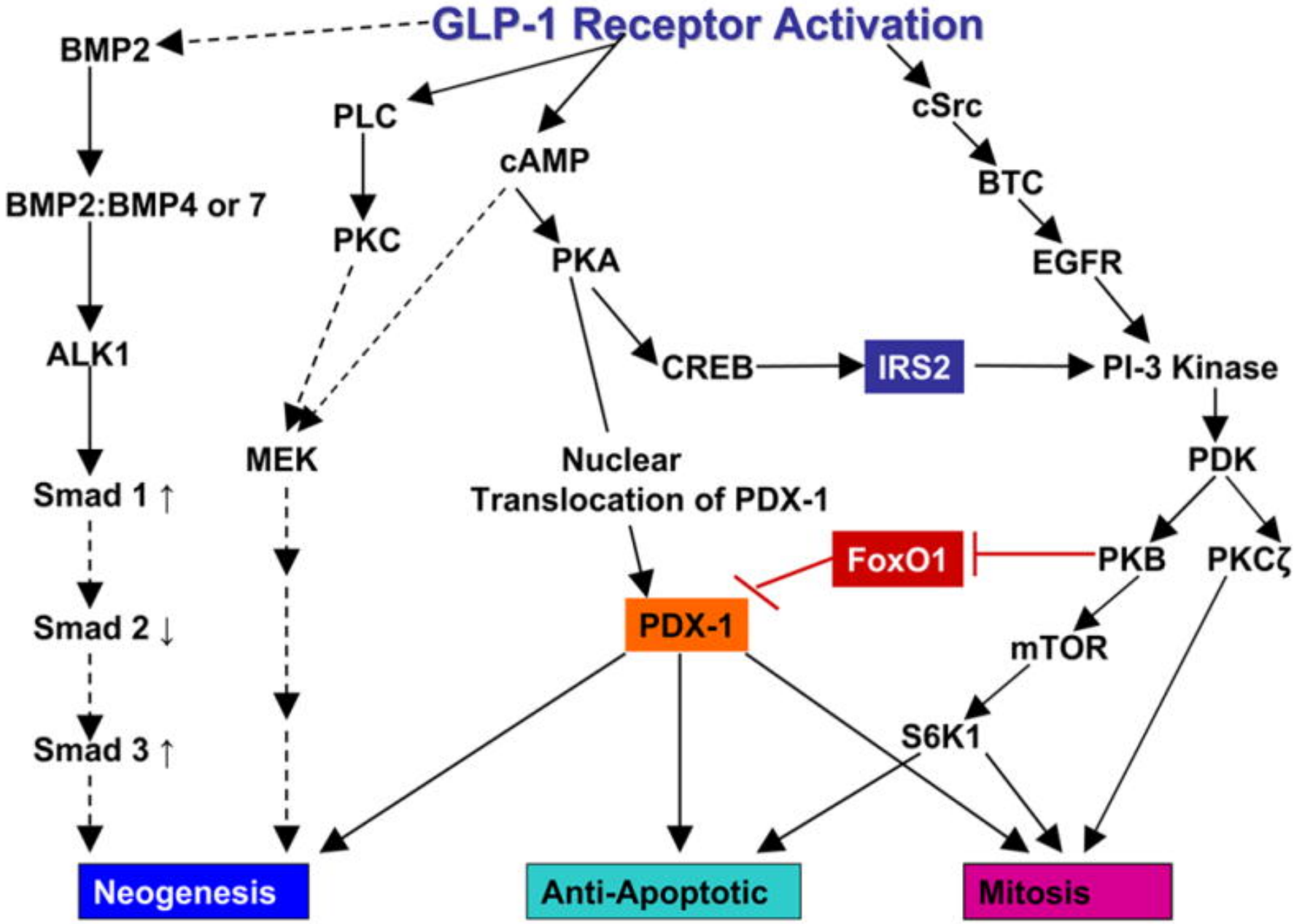
I&C Forum: A. Pezzi, L. Martuzzi

Storia naturale dell'esaurimento della funzionalità delle beta cellule pancreatiche in pazienti con diabete di Tipo 2

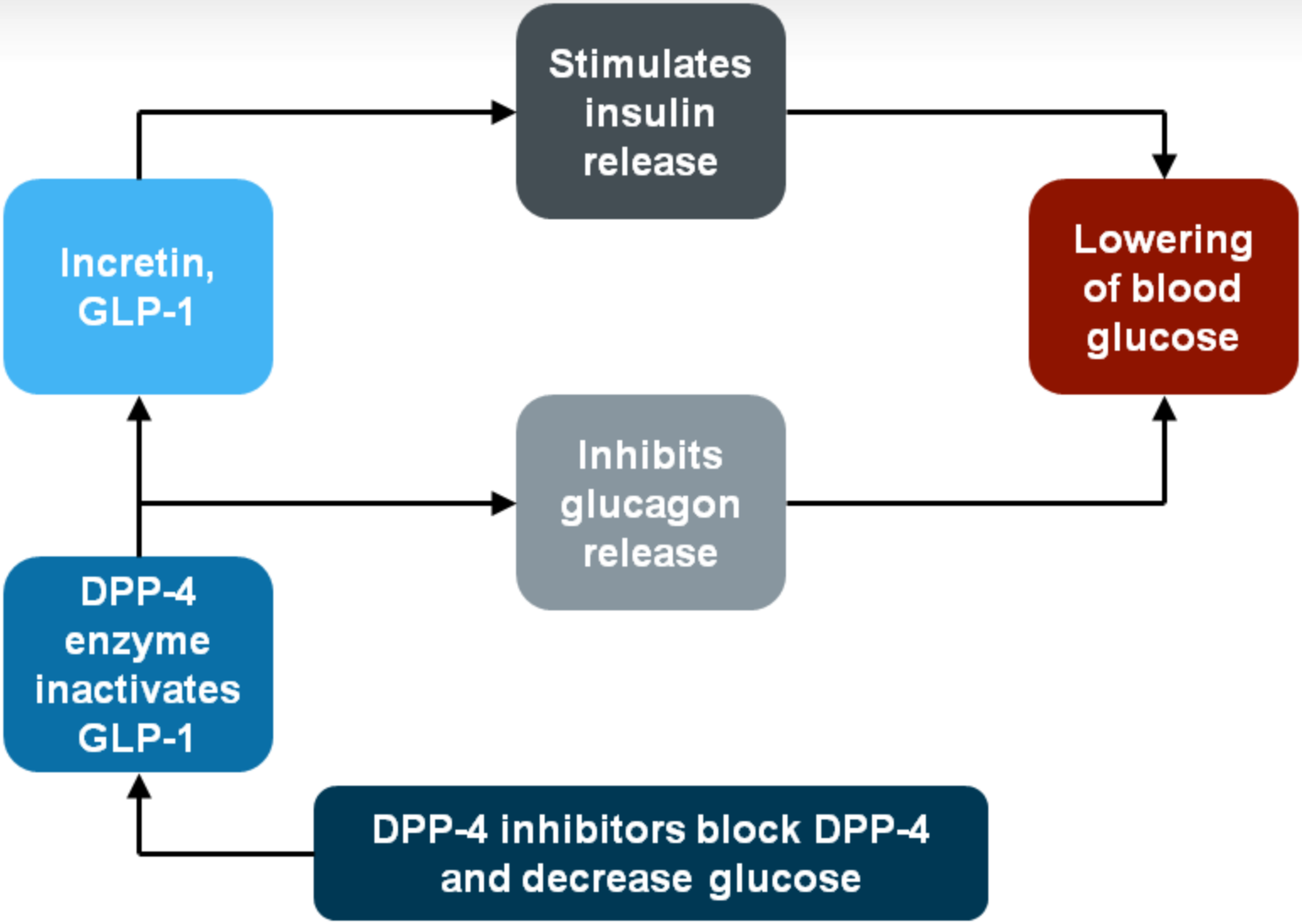
Stop dell'apoptosi / Rigeneranti:
Incretine Glitazoni




Hypothalamus: ↓ Food intake
Stomach: ↓ Gastric Emptying
Islet α cell: ↓ Glucagon secretion
Islet β cell: ↑ Insulin biosynthesis and insulin secretion
GLP-1
EGFR
GLP-1R
Gs
Adenylyl cyclase
ATP
c-src
α
β
γ
cAMP
PI3-K
PKA
PKCζ
CREB
IRS-2
Bcl-2
Bcl-xL
Akt
p44 MAPK
PDX-1
↓ Caspases
+
-
-
+
Apoptosis
Proliferation
Islet β cell


GLP-1 Receptor Activation
BMP2
BMP2:BMP4 or 7
ALK1
Smad 1 ↑
Smad 2 ↓
Smad 3 ↑
PLC
PKC
cAMP
PKA
MEK
CREB
IRS2
Nuclear
Translocation of PDX-1
PDX-1
cSrc
BTC
EGFR
PI-3 Kinase
PDK
FoxO1
PKB
PKCζ
mTOR
S6K1
Neogenesis
Anti-Apoptotic
Mitosis

Effect of DPP-4 Inhibitors



White JR. *Clin Diab*. 2008;26:53-57.

Effetti degli inibitori della DPP-4 in pazienti con DM2

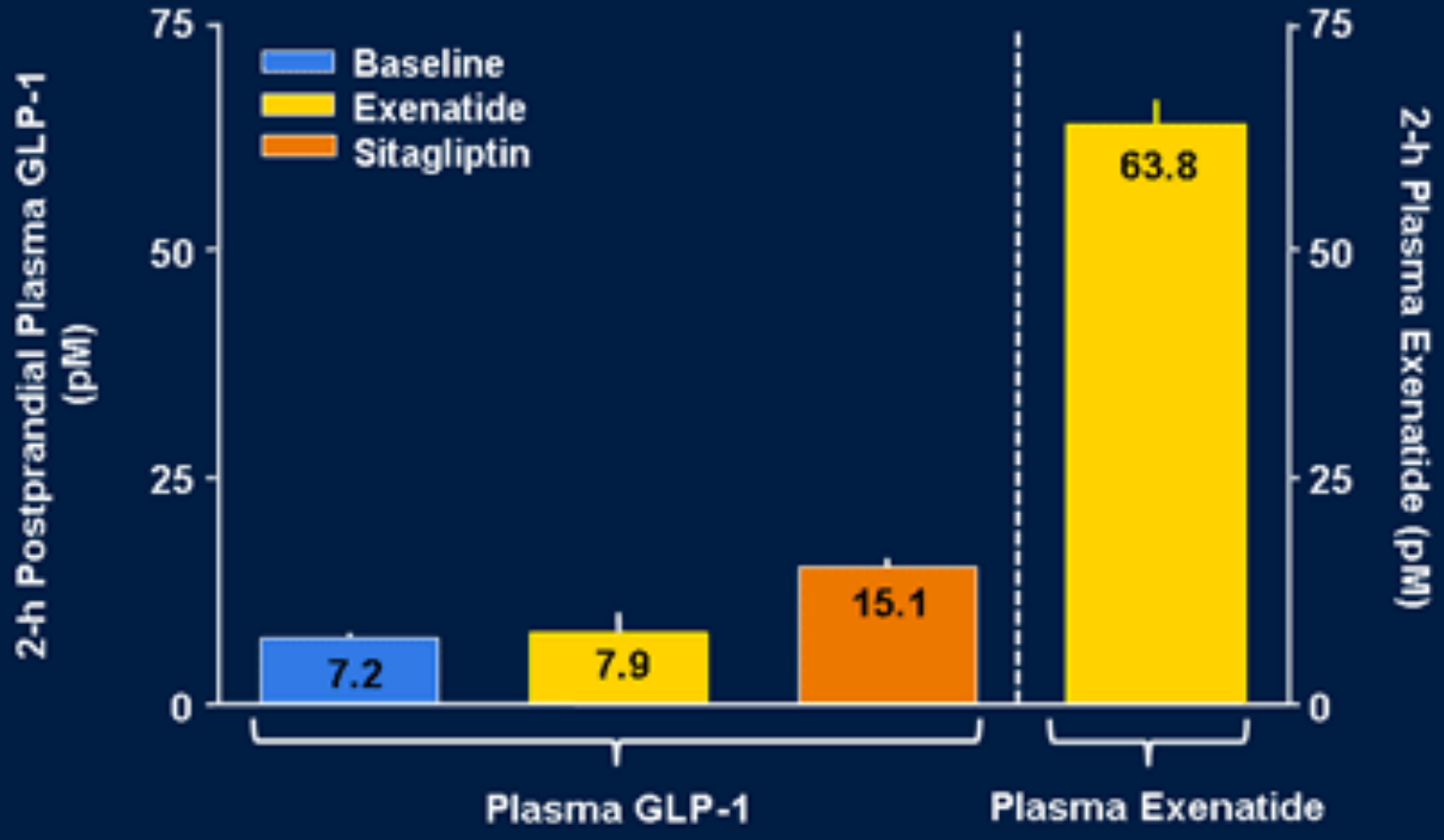
Inibitori della DPP-4

- Prevengono la degradazione del GLP-1 [1,2]
- Migliorano la secrezione insulinica [1,2]
- Riducono i livelli di glucagone [1,2]
- Riducono la glicemia post-prandiale [2,3]
- Riducono la glicemia a digiuno [4,5]
- Riducono l'HbA1c [4,5]

- Non ritardano lo svuotamento gastrico [2]
- Sono neutri sul peso [5,6]

1. Herman GA, et al. J Clin Endocrinol Metab. 2006; 91:4612-4619; 2. Vella A, et al. Diabetes. 2007;56:1475-1480; 3. Aschner P, et al. Diabetes Care. 2006;29:2632-2637; 4. Pi-Sunyer FX, et al. Diabetes Res Clin Pract. 2007;76:132-138; 5. Zerilli T and Pyon EY. Clin Ther. 2007;29(12): 2614-2634; 6. Bolli G, et al. Diabetes Obes Metab. 2008;10:82-90.

Postprandial Plasma Levels of Exenatide Exceeded Physiologic Levels of GLP-1



Patients with T2DM; Evaluable population, n=61 for all treatment groups; Mean ± SE
2-week post-treatment concentration data

DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24(10):2943-2952.

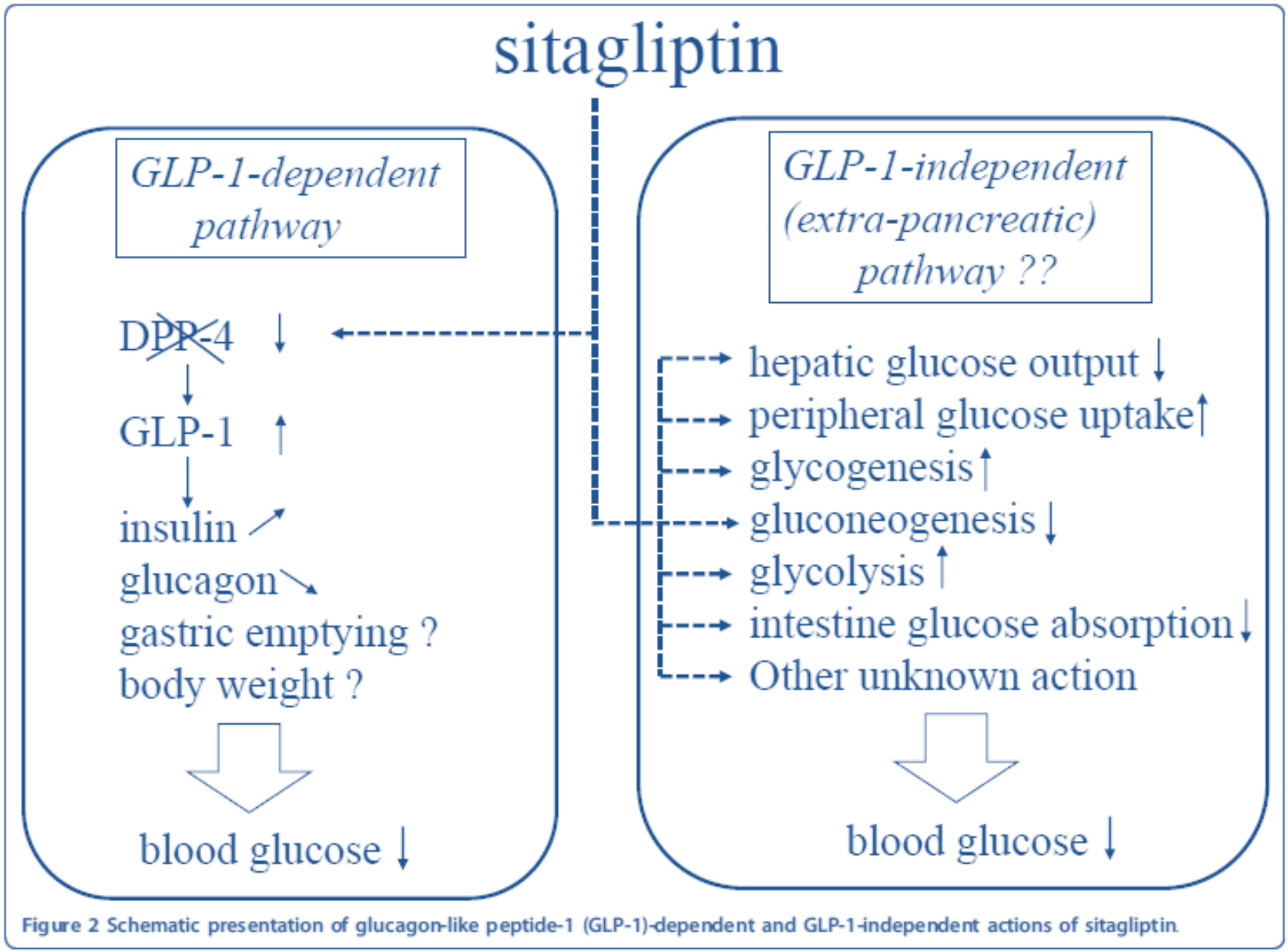


Figure 2 Schematic presentation of glucagon-like peptide-1 (GLP-1)-dependent and GLP-1-independent actions of sitagliptin.

GLP-1 mimetici

- exenatide

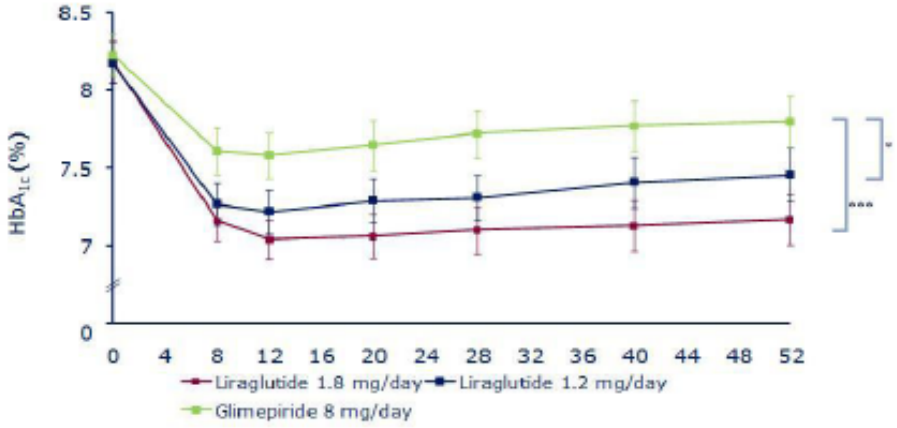
GLP-1 analoghi

- liraglutide

Sono farmaci efficaci a lungo?

Sono farmaci efficaci a lungo?

HbA_{1c} change over 52 weeks: all subjects

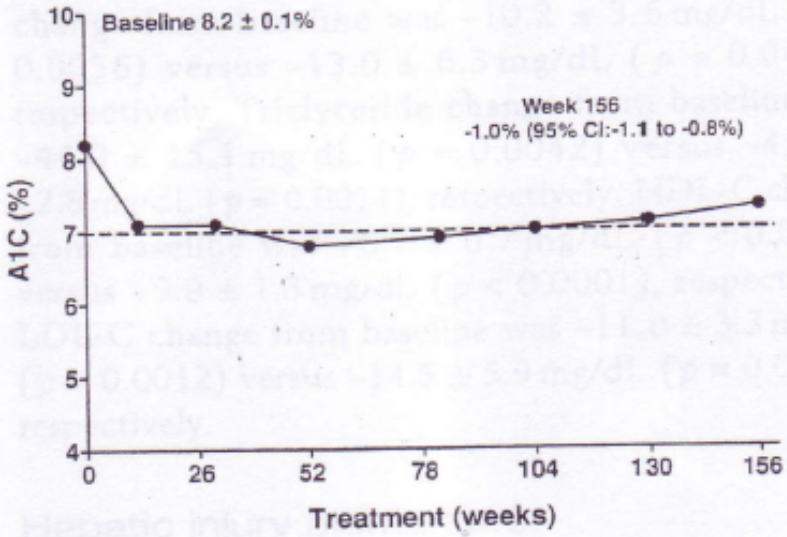


P-values relate to estimated treatment difference for changes from baseline: *p<0.05; ***p<0.0001

Garber et al. Lancet 2009;373(9662):473–81 (LEAD-3)

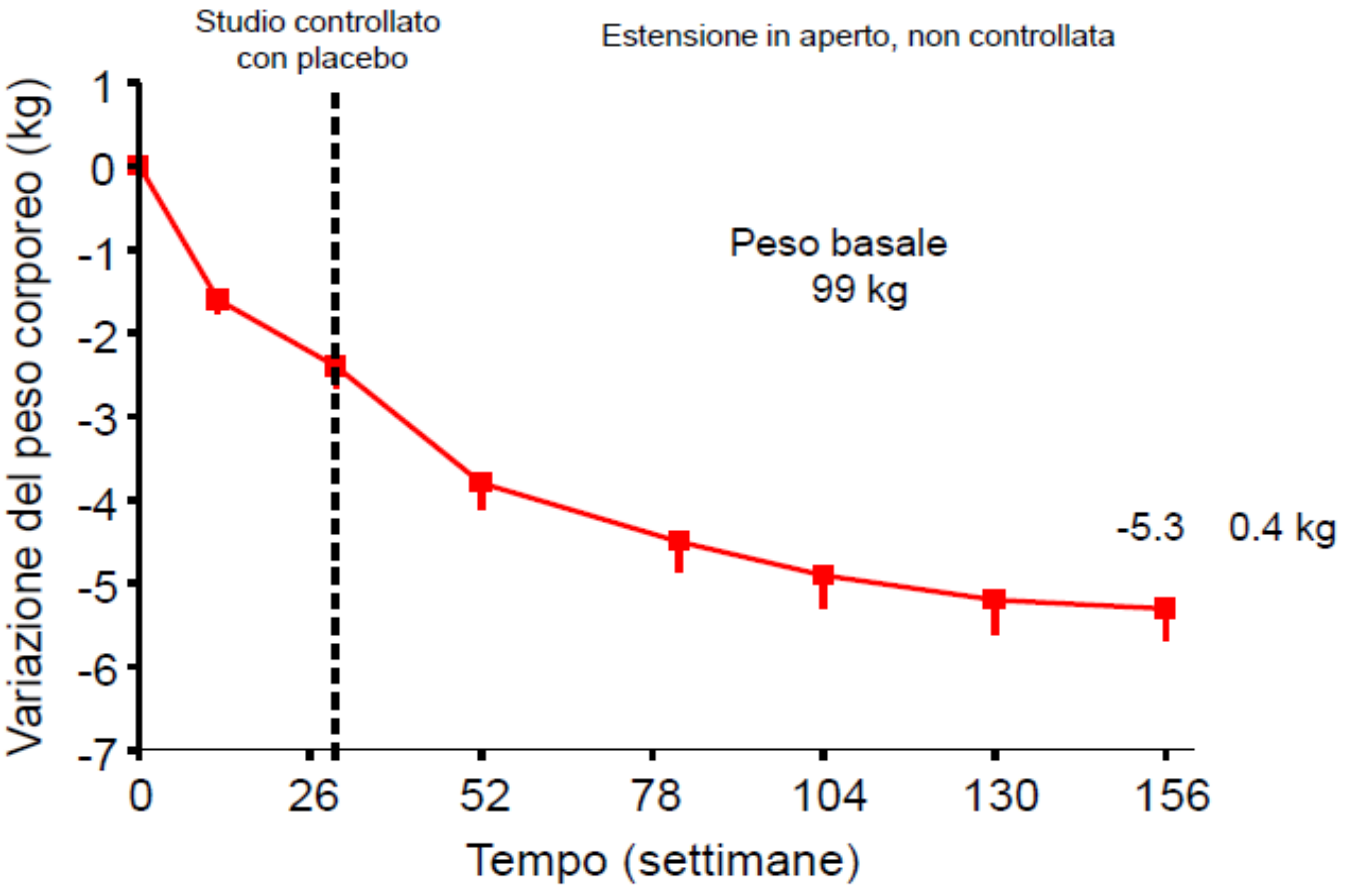
Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years*

David C. Klonoff[a], John B. Buse[b], Loretta L. Nielsen[c], Xuesong Guan[c], Christopher L. Bowlus[d], John H. Holcombe[e], Matthew E. Wintle[c] and David G. Maggs[c]



Curr Med Opin 2008

Exenatide riduce progressivamente il peso a 3 anni



No diet and exercise regimen was provided
N = 217; Mean (- SE); P<0.0001 from baseline to 3 years and between 30 weeks and 3 years
Buse et al. ADA 2007; Klonoff et al, Curr Med Res Opinion 2008, 275-286

Registro Farmaci Antidiabetici sottoposti a Monitoraggio

Report a due anni

Dati aggiornati al 15 Febbraio 2010

exenatide

N. schede di follow-up: 34765 di cui 3974 (11.4%) ad un anno (+/- 60 gg)

Caratteristiche basali	Pazienti	Media (Min-Max)		Scarto	Variazione	Mediana	
		Visita	FUP	(Fup-Visita)	%	Visita	FUP
Peso	3974	96.6 (45 - 198)	91.7 (44 - 210	-4.9	-5.0	95	90
BMI	3974	35.4 (18.7 - 76.9)	33.6 (18.3 - 72.9	-1.8	-5.1	34.6	32.8

BMJ

BMJ 2012;344:d7771 doi: 10.1136/bmj.d7771 (Published 10 January 2012)

RESEARCH

Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials

Tina Vilsbøll *associate professor and chief consultant endocrinologist*, Mikkel Christensen *specialist registrar*, Anders E Junker *registrar*, Filip K Knop *associate professor and specialist registrar*, Lise Lotte Gluud *consultant hepatologist*

Diabetes Research Division, Department of Internal Medicine F, Gentofte Hospital, University of Copenhagen, DK-2900 Hellerup, Denmark

BMJ

BMJ 2012;344:d7771 doi: 10.1136/bmj.d7771 (Published 10 January 2012)

RESEARCH

Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials

What is already known on this topic

- Improved glycaemic control is associated with increased body weight
- Agonists to the glucagon-like peptide-1 receptor (GLP-1R) enhance glucose homoeostasis and suppress food intake and appetite

What this study adds

- Treatment with clinically relevant doses of GLP-1R agonists for at least 20 weeks leads to weight loss in obese or overweight patients with or without type 2 diabetes mellitus in spite of an improved metabolic regulation
- The effect of GLP-1R agonists could be more pronounced in patients without diabetes
- GLP-1R agonists also reduce systolic and diastolic blood pressure and total cholesterol

BMC
Endocrine Disorders

RESEARCH ARTICLE Open Access

Glucagon-like peptide analogues for type 2 diabetes mellitus: systematic review and meta-analysis

Deepson S Shyangdan*, Pamela L Royle, Christine Clar, Pawana Sharma, Norman R Waugh

Abstract

Background: Glucagon-like peptide (GLP-1) analogues are a new class of drugs used in the treatment of type 2 diabetes. They are given by injection, and regulate glucose levels by stimulating glucose-dependent insulin secretion and biosynthesis, suppressing glucagon secretion, and delaying gastric emptying and promoting satiety. This systematic review aims to provide evidence on the clinical effectiveness of the GLP-1 agonists in patients not achieving satisfactory glycaemic control with one or more oral glucose lowering drugs.

Methods: MEDLINE, EMBASE, the Cochrane Library and Web of Science were searched to find the relevant papers. We identified 28 randomised controlled trials comparing GLP-1 analogues with placebo, other glucose-lowering agents, or another GLP-1 analogue, in patients with type 2 diabetes with inadequate control on a single oral agent, or on dual therapy. Primary outcomes included HbA1c, weight change and adverse events.

Results: Studies were mostly of short duration, usually 26 weeks. All GLP-1 agonists reduced HbA1c by about 1% compared to placebo. Exenatide twice daily and insulin gave similar reductions in HbA1c, but exenatide 2 mg once weekly and liraglutide 1.8 mg daily reduced it by 0.20% and 0.30% respectively more than glargine. Liraglutide 1.2 mg daily reduced HbA1c by 0.34% more than sitagliptin 100 mg daily. Exenatide and liraglutide gave similar improvements in HbA1c to sulphonylureas. Exenatide 2 mg weekly and liraglutide 1.8 mg daily reduced HbA1c by more than exenatide 10 μg twice daily and sitagliptin 100 mg daily. Exenatide 2 mg weekly reduced HbA1c by 0.3% more than pioglitazone 45 mg daily.
Exenatide and liraglutide resulted in greater weight loss (from 2.3 to 5.5 kg) than active comparators. This was not due simply to nausea. Hypoglycaemia was uncommon, except when combined with a sulphonylurea. The commonest adverse events with all GLP-1 agonists were initial nausea and vomiting. The GLP-1 agonists have some effect on beta-cell function, but this is not sustained after the drug is stopped.

Conclusions: GLP-1 agonists are effective in improving glycaemic control and promoting weight loss.

original article

Diabetes, Obesity and Metabolism 14: 67–76, 2012.

Effect of initial combination therapy with sitagliptin and metformin on β-cell function in patients with type 2 diabetes

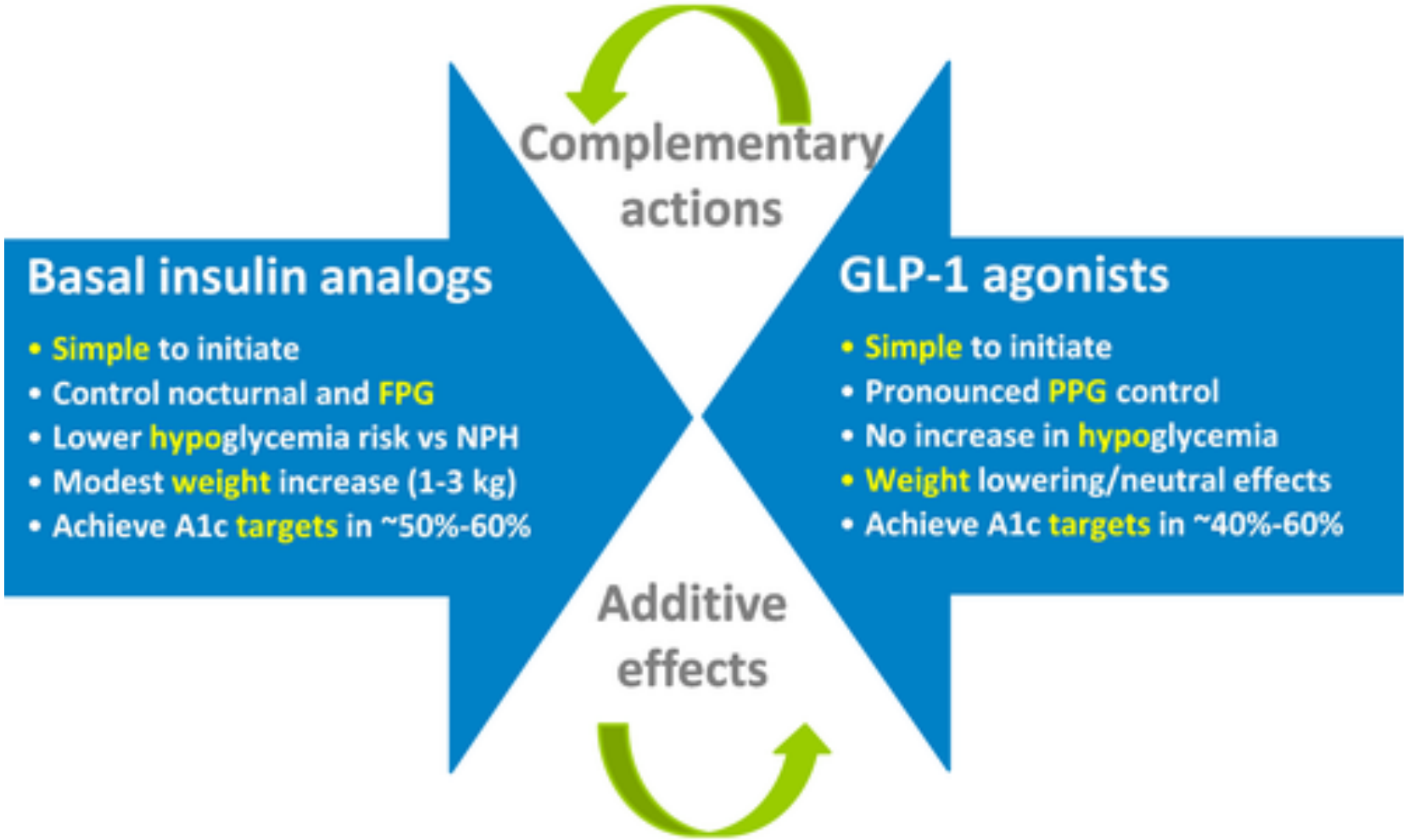
D. Williams-Herman, L. Xu, R. Teng, G. T. Golm, J. Johnson, M. J. Davies, K. D. Kaufman & B. J. Goldstein

Department of Clinical Research, Merck Sharp & Dohme Corp., Rahway, NJ, USA

ORIGINAL ARTICLE

In summary, the initial combination of sitagliptin and metformin enhanced the responsiveness of pancreatic β-cells to glucose in both the fasting and postprandial states at 24 weeks in patients with type 2 diabetes. The improvement in β-cell function appeared to be maintained over the 2-year treatment period.

Rationale for Combination Therapy: Basal Insulin and a GLP-1 Agonist



GLP-1 agonists with > 24 hour duration seem to be associated with:

- Greater HbA1c lowering
- Greater FPG lowering
- Lesser PPG lowering
- Larger Increase in fasting insulin
- Larger decrease in fasting glucagon
- Equivalent weight loss
- Decreased effect on gastric emptying
- Less nausea (except taspoglutide)
- Less associated hypoglycemia
- Larger increase in heart rate

Illustrates some differences between the once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist and exenatide BID.

Diabetes, Obesity and Metabolism 12: 167–177, 2010.

Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes

ORIGINAL ARTICLE

T. Vilsbøll[1], J. Rosenstock[2], H. Yki-Järvinen[3], W. T. Cefalu[4], Y. Chen[5], E. Luo[5], B. Musser[5], P. J. Andryuk[5], Y. Ling[5], K. D. Kaufman[5], J. M. Amatruda[5], S. S. Engel[5] & L. Katz[5]

[1] *Diabetes Research Division, Department of Internal Medicine F, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark*
[2] *Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX, USA*
[3] *University of Helsinki, HUCH, Helsinki, Finland*
[4] *Louisiana State University Health Science Center and Pennington Biomedical Research Center, Baton Rouge and New Orleans, LA, USA*
[5] *Merck Research Laboratories, Rahway, NJ, USA*

Objective: To evaluate the efficacy and tolerability of sitagliptin when added to insulin therapy alone or in combination with metformin in patients with type 2 diabetes.

Methods: After a 2 week placebo run-in period, eligible patients inadequately controlled on long-acting, intermediate-acting or premixed insulin (HbA1c ≥7.5% and ≤11%), were randomised 1:1 to the addition of once-daily sitagliptin 100 mg or matching placebo over a 24-week study period. The study capped the proportion of randomised patients on insulin plus metformin at 75%. Further, the study capped the proportion of randomised patients on premixed insulin at 25%. The metformin dose and the insulin dose were to remain stable throughout the study. The primary endpoint was HbA1c change from baseline at week 24.

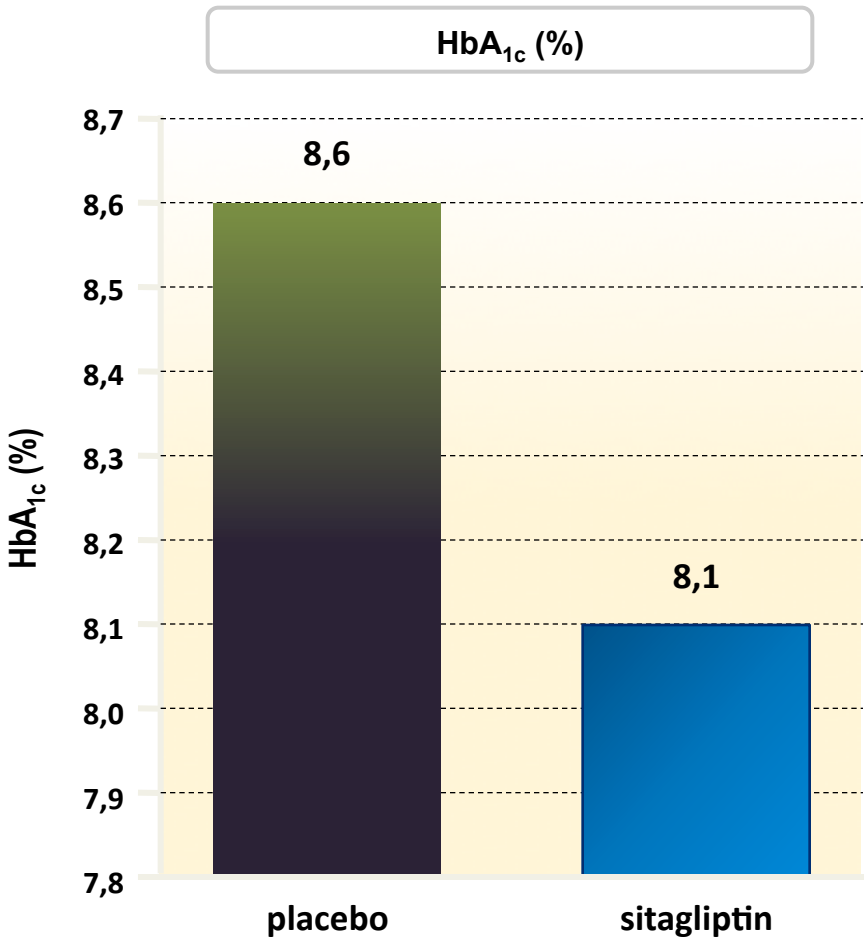
Results: Mean baseline characteristics were similar between the sitagliptin (n = 322) and placebo (n = 319) groups, including HbA1c (8.7 vs. 8.6%), diabetes duration (13 vs. 12 years), body mass index (31.4 vs. 31.4 kg/m^2), and total daily insulin dose (51 vs. 52 IU), respectively. At 24 weeks, the addition of sitagliptin significantly ($p < 0.001$) reduced HbA1c by 0.6% compared with placebo (0.0%). A greater proportion of patients achieved an HbA1c level <7% while randomised to sitagliptin as compared with placebo (13 vs. 5% respectively; $p < 0.001$). Similar HbA1c reductions were observed in the patient strata defined by insulin type (long-acting and intermediate-acting insulins or premixed insulins) and by baseline metformin treatment. The addition of sitagliptin significantly ($p < 0.001$) reduced fasting plasma glucose by 15.0 mg/dl (0.8 mmol/l) and 2-h postmeal glucose by 36.1 mg/dl (2.0 mmol/l) relative to placebo. A higher incidence of adverse experiences was reported with sitagliptin (52%) compared with placebo (43%), due mainly to the increased incidence of hypoglycaemia (sitagliptin, 16% vs. placebo, 8%). The number of hypoglycaemic events meeting the protocol-specified criteria for severity was low with sitagliptin (n = 2) and placebo (n = 1). No significant change from baseline in body weight was observed in either group.

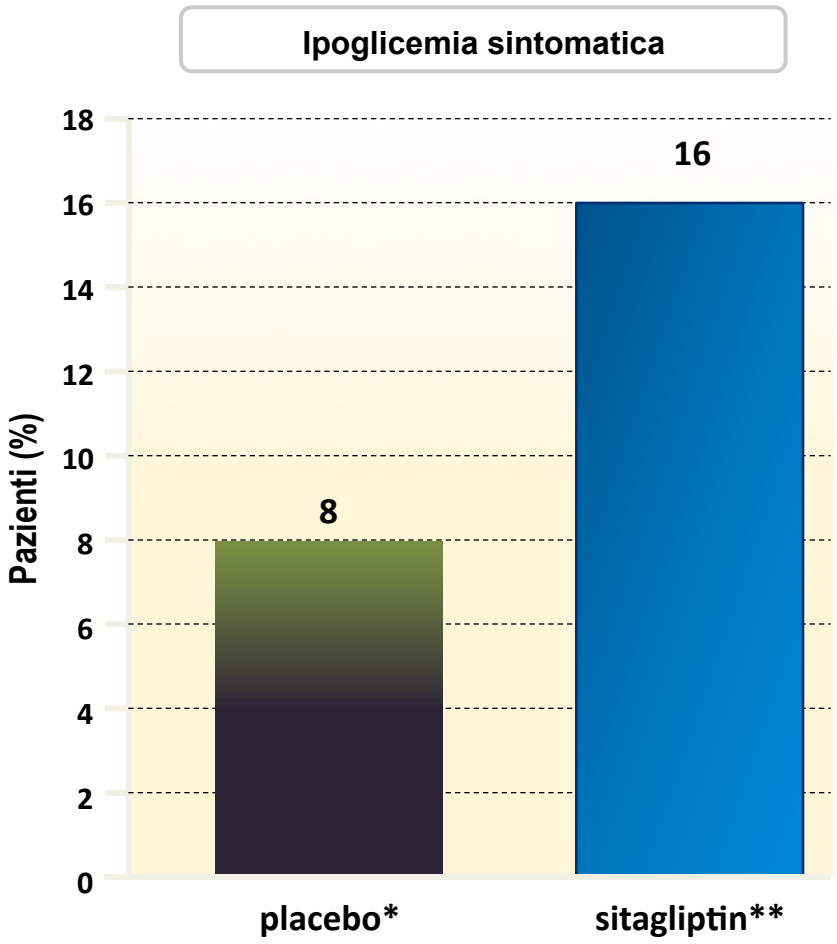
Conclusion: In this 24-week study, the addition of sitagliptin to ongoing, stable-dose insulin therapy with or without concomitant metformin improved glycaemic control and was generally well tolerated in patients with type 2 diabetes.

Keywords: sitagliptin, dipeptidyl peptidase-4 inhibitor, DPP-4 inhibitor, insulin, type 2 diabetes

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

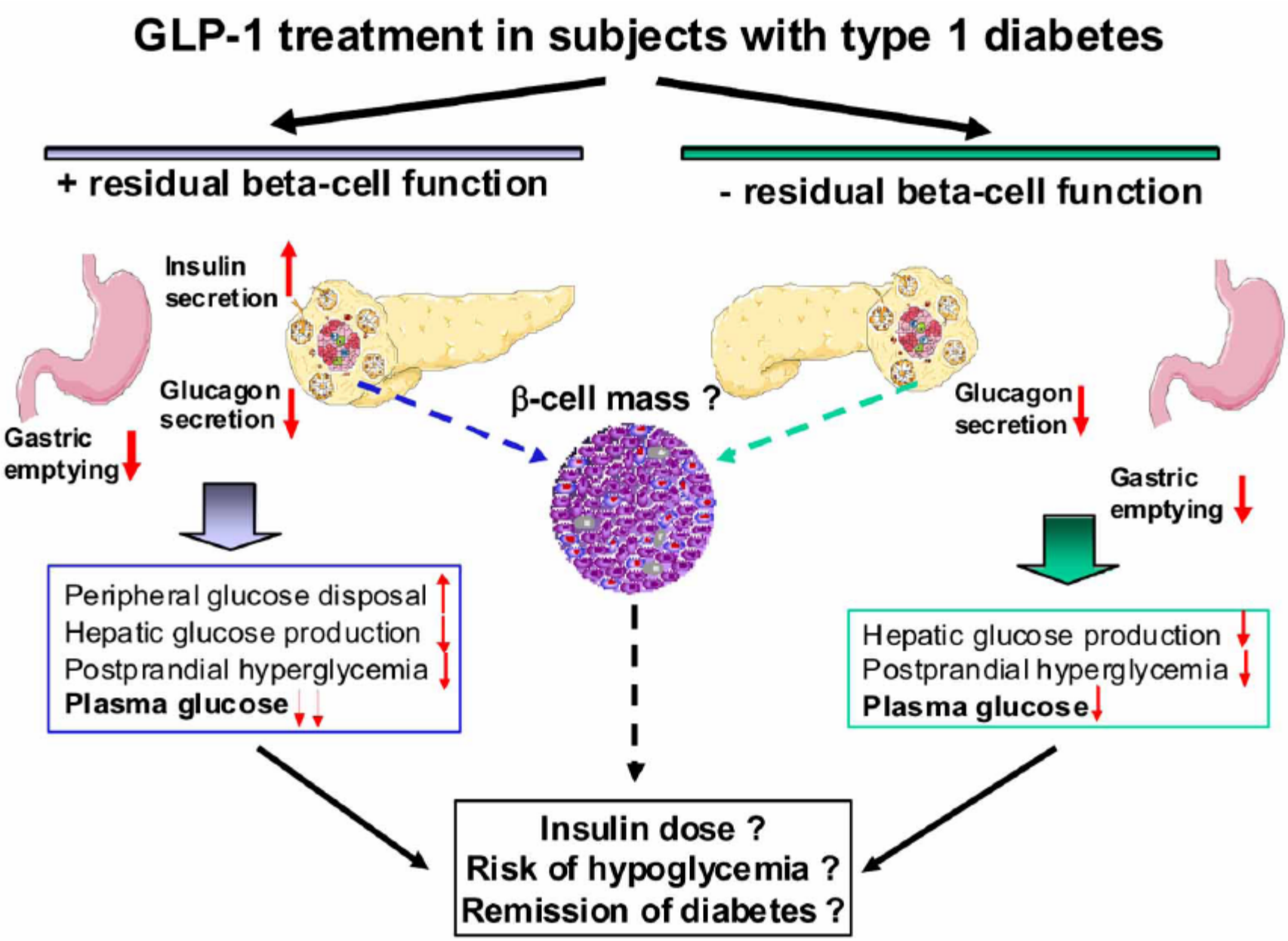
Sitagliptin 100 mg once daily in add-on a insulina (~50 UI/die) con o senza metformina



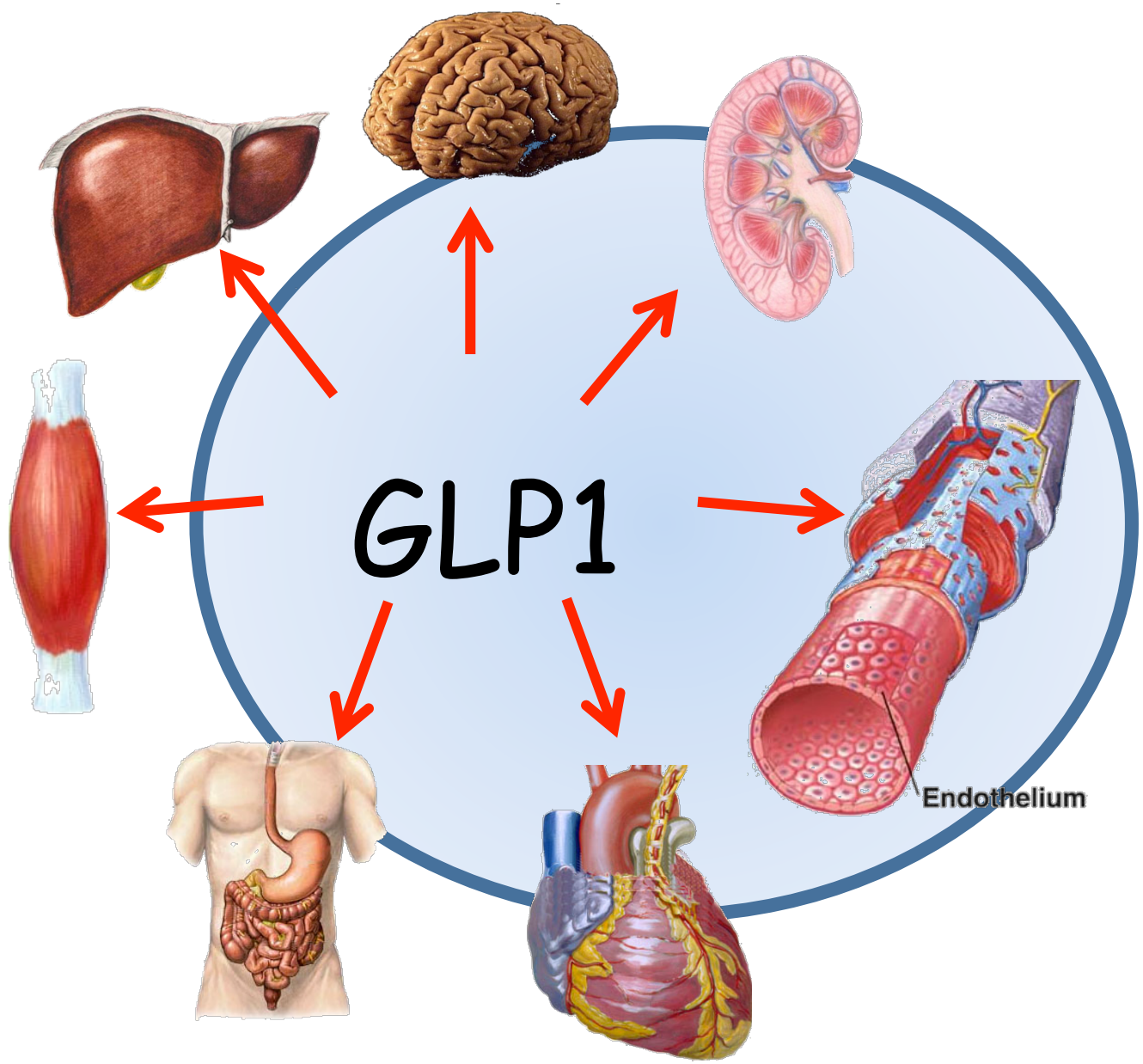


*1 episodio di ipoglicemia severa nel gruppo placebo
**2 episodi di ipoglicemia severa nel gruppo sitagliptin

Vilsbøll T et al. Diabetes Obes Metab 2010;12:167–177


GLP-1 treatment in subjects with type 1 diabetes
+ residual beta-cell function
- residual beta-cell function
Insulin secretion
Glucagon secretion
Gastric emptying
β-cell mass ?
Glucagon secretion
Gastric emptying
Peripheral glucose disposal
Hepatic glucose production
Postprandial hyperglycemia
Plasma glucose
Hepatic glucose production
Postprandial hyperglycemia
Plasma glucose
Insulin dose ?
Risk of hypoglycemia ?
Remission of diabetes ?

Tessuti che esprimono il recettore del GLP-1



Glucagon-Like Peptide 1—A Cardiologic Dimension

Marek Treiman*, Mikkel Elvekjær,
Thomas Engstrøm, and Jan Skov Jensen

Recent experimental data suggest glucagon-like peptide 1 (GLP-1) and its analogs to have direct effects on the cardiovascular system, in addition to their classic glucoregulatory actions. These direct effects may be cardioprotective, contractility augmenting, and vasorelaxant. A few preliminary clinical trials appear to support a mechanical function improvement after GLP-1 administration to patients with a weakened left ventricle. Based on animal studies, diminished lethal injury to the postischemic reperfused myocardium appears to be a particularly promising prospect, awaiting to be tested in clinical settings. (Trends Cardiovasc Med 2010;20:8–12)

Table 2. Proposed pathogenic mechanisms for glucagon-like peptide (GLP)-1 cardioprotection.

Pathogenic mechanisms
Achievement of fasting and postprandial euglycaemia
Increased myocardial glucose uptake
Activation of cAMP and concomitant PIK-3 and PKA antiapoptotic pathways
Activation of Akt
Activation of antioxidant gene HO-1
Nrf2 gene expression (through HO-1)
Activation of PPAR-β and -δ
Suppression of GSK-3β
Inhibition of caspase-3
GLP-1R-independent pathway role of GLP-1(9-39)
Beneficial effects on endothelium
Increased activity of NO.
NO-independent vasodilation through GLP-1
Inhibition of monocyte/macrophage accumulation
Anti-inflammatory effects
Inhibition of atherosclerosis

Table 3. Glucagon-like peptide (GLP)-1 and atherosclerosis.

Related tissues	Proposed mechanisms
Endothelium	Expression of GLP-1 receptors NO-dependent action Upregulation of NOS Inhibition of AGE receptor gene expression Inhibition of expression of TNF-α, VCAM-1 and PAI-1
Vascular smooth muscle cells	Expression of GLP-1 receptors Increased flow-mediated vasodilation
Macrophages	Expression of GLP-1 receptors Inhibition of macrophage accumulation through cAMP/PKA pathways
Monocytes	Expression of GLP-1 receptors

frontiers in
ENDOCRINOLOGY

MINI REVIEW ARTICLE
published: 07 September 2012
doi: 10.3389/fendo.2012.00112

Incretin hormones as immunomodulators of atherosclerosis

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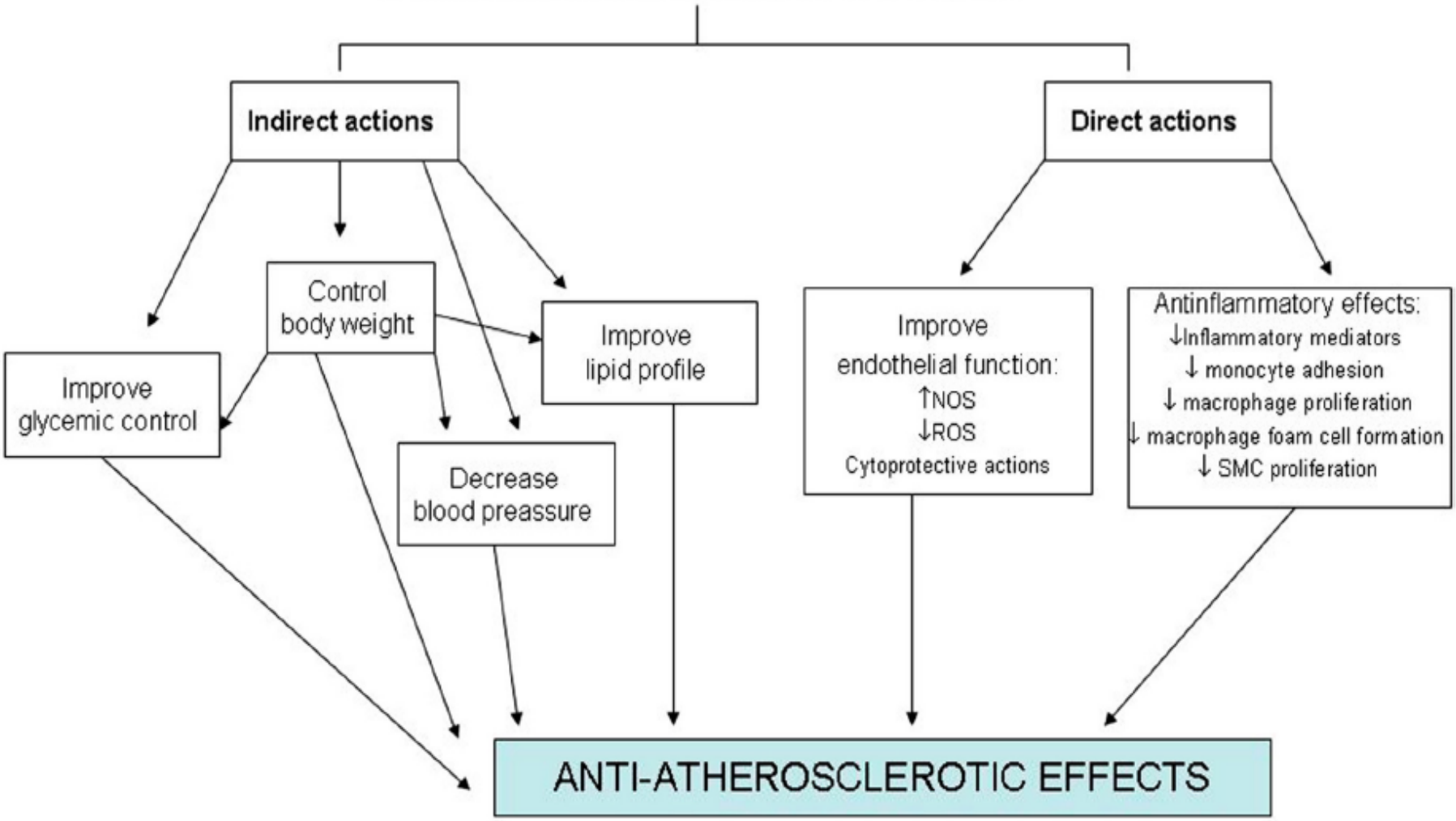
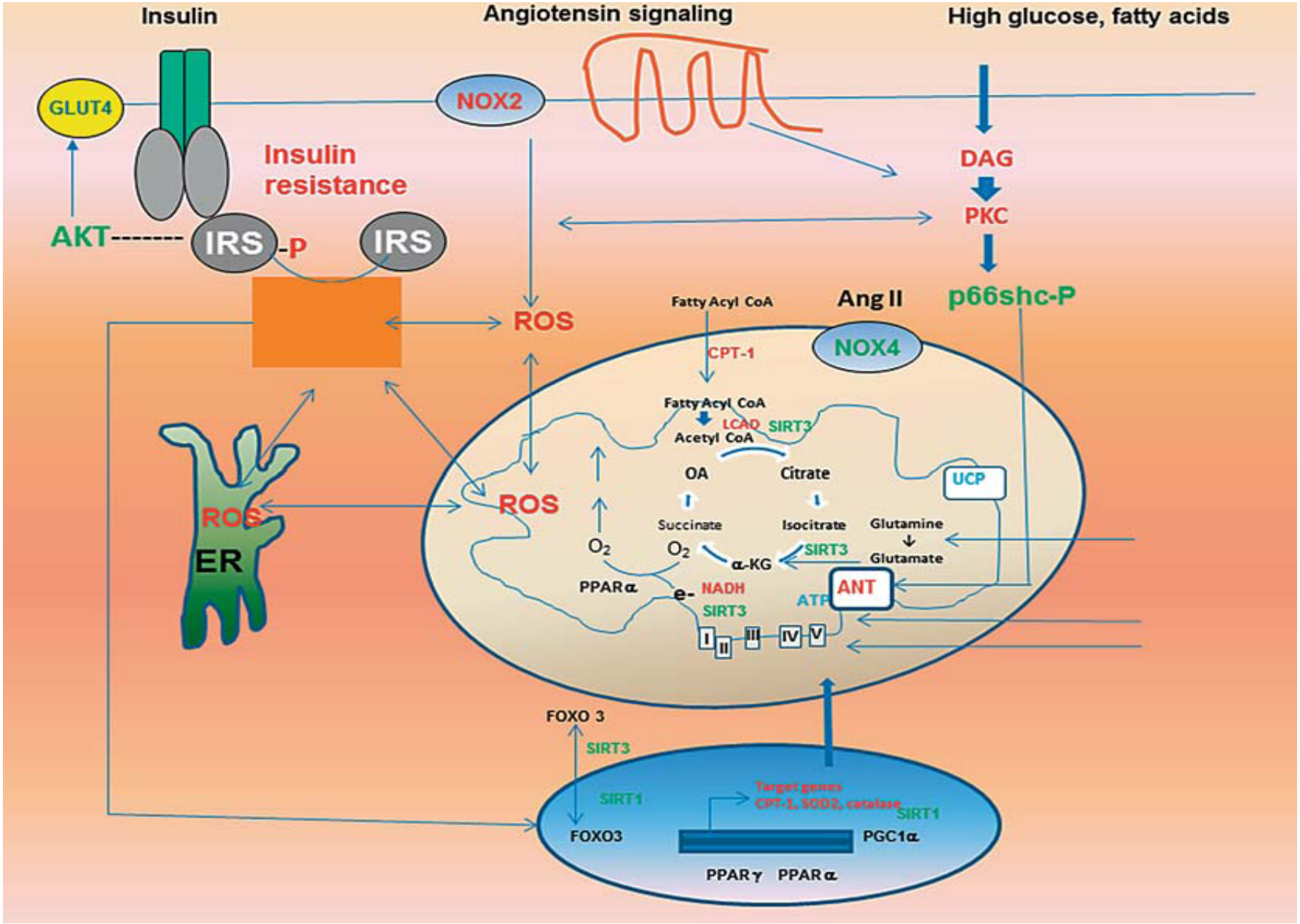
e-mail: nalonso.germanstrias@gencat.cat

Atherosclerosis results from endothelial cell dysfunction and inflammatory processes affecting both macro- and microvasculature which are involved in vascular diabetic complications. Glucagon-like peptide-1 (GLP-1) is an incretin hormone responsible for amplification of insulin secretion when nutrients are given orally as opposed to intravenously and it retains its insulinotropic activity in patients with type 2 diabetes mellitus (T2D). GLP-1 based therapies, such as GLP-1 receptor (GLP-1R) agonists and inhibitors of dipeptidyl peptidase-4, an enzyme that degrades endogenous GLP-1 are routinely used to treat patients with T2D. Recent experimental model studies have established that GLP-1R mRNA is widely expressed in several immune cells. Moreover, its activation contributes to the regulation of both thymocyte and peripheral T cells proliferation and is involved in the maintenance of peripheral regulatory T cells. GLP-1R is also expressed in endothelial and smooth muscle cells. The effect of incretin hormones on atherosclerogenesis have recently been studied in animal models of apolipoprotein E-deficient mice (apoE$^{-/-}$). These studies have demonstrated that treatment with incretin hormones or related compounds suppresses the progression of atherosclerosis and macrophage infiltration in the arterial wall as well as a marked anti-oxidative and anti-inflammatory effect on endothelial cells. This effect may have a major impact on the attenuation of atherosclerosis and may help in the design of new therapies for cardiovascular disease in patients with type 2 diabetes.

Keywords: atherosclerosis, diabetes, GLP-1, incretins, GIP



Direct and indirect effects of GLP-1 on the cardiovascular system.


Insulin
Angiotensin signaling
High glucose, fatty acids
GLUT4
NOX2
Insulin resistance
DAG
PKC
AKT-------
IRS
-P
IRS
ROS
Fatty Acyl CoA
Ang II
p66shc-P
CPT-1
NOX4
Fatty Acyl CoA
LCAD
SIRT3
Acetyl CoA
OA
Citrate
UCP
ROS
ROS
ER
Succinate
Isocitrate
Glutamine
Glutamate
O2
O2
α-KG
SIRT3
PPARα
e-
NADH
SIRT3
ATP
ANT
I
II
III
IV
V
FOXO 3
SIRT3
SIRT1
Target genes
CPT-1, SOD2, catalase
SIRT1
FOXO3
PGC1α
PPARγ
PPARα