OBESITY WEEK

SETTIMANA PER LA PREVENZIONE DELL'OBESITA' E PER UN CORRETTO STILE DI VITA

I MARTEDÌ DELL'ORDINE

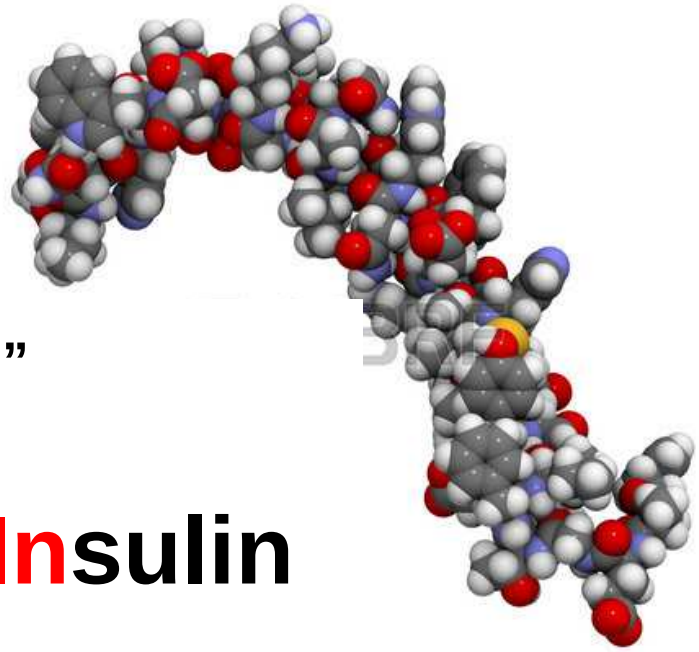
MICROBIOTA INTESTINALE, OBESITÀ E DIABETE

LE INCRETINE

Elisabetta Dall'Aglio
Centro per la Cura del Diabete
Azienda Ospedaliero-Universitaria

7 ottobre 2014

“Gut derived factors that increase Glucose stimulated insulin secretion”



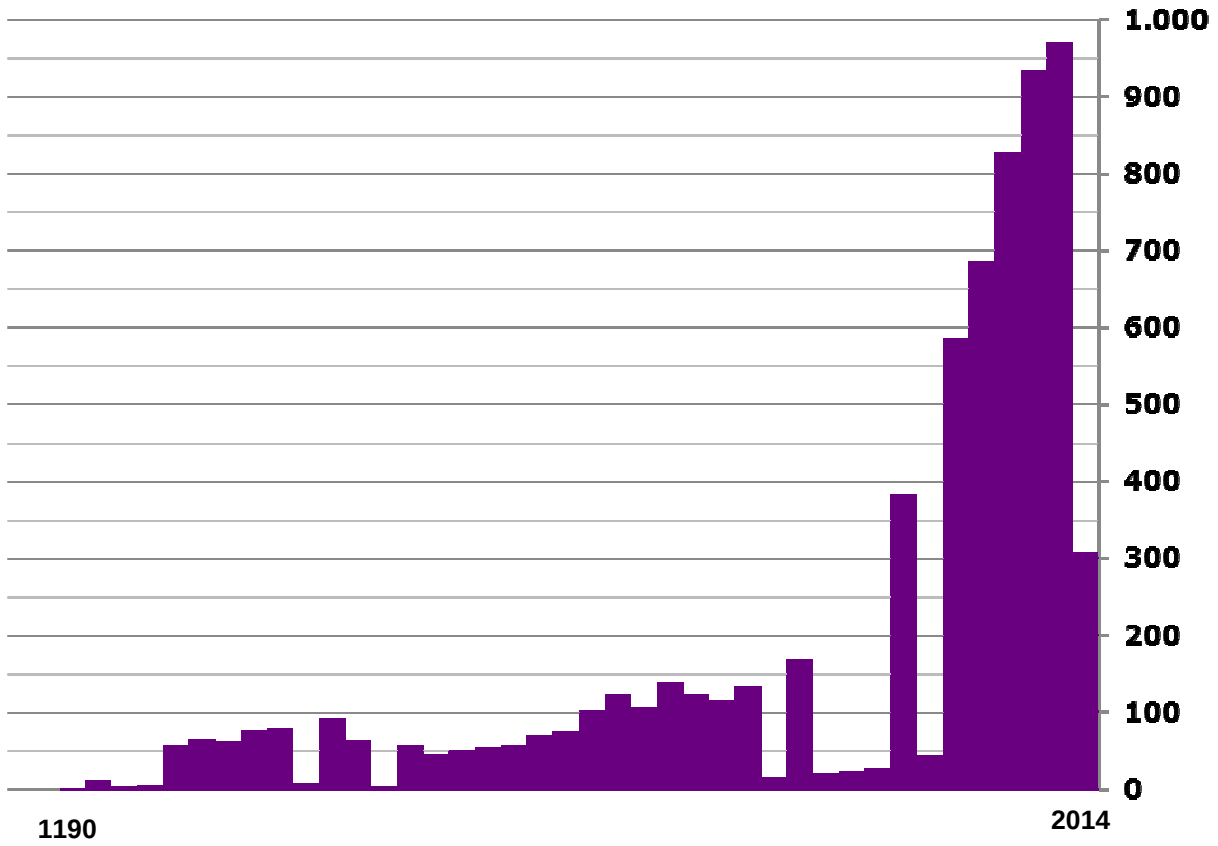
Intestinal Secretion Insulin

In – Cret – In

La Barre. 1930 Am J Physiol. 91: 649

PubMed

Results by year



La Barre J, Still EU.
Studies on the physiology of secretin.
Am J Physiol 91: 649-53, 1930

Elrick H, Stimmler L, Hlad CJ Jr, Arai Y. *Plasma insulin response to oral and intravenous glucose administration.*
J Clin Endocrinol Metab 1964;24:976-1082.

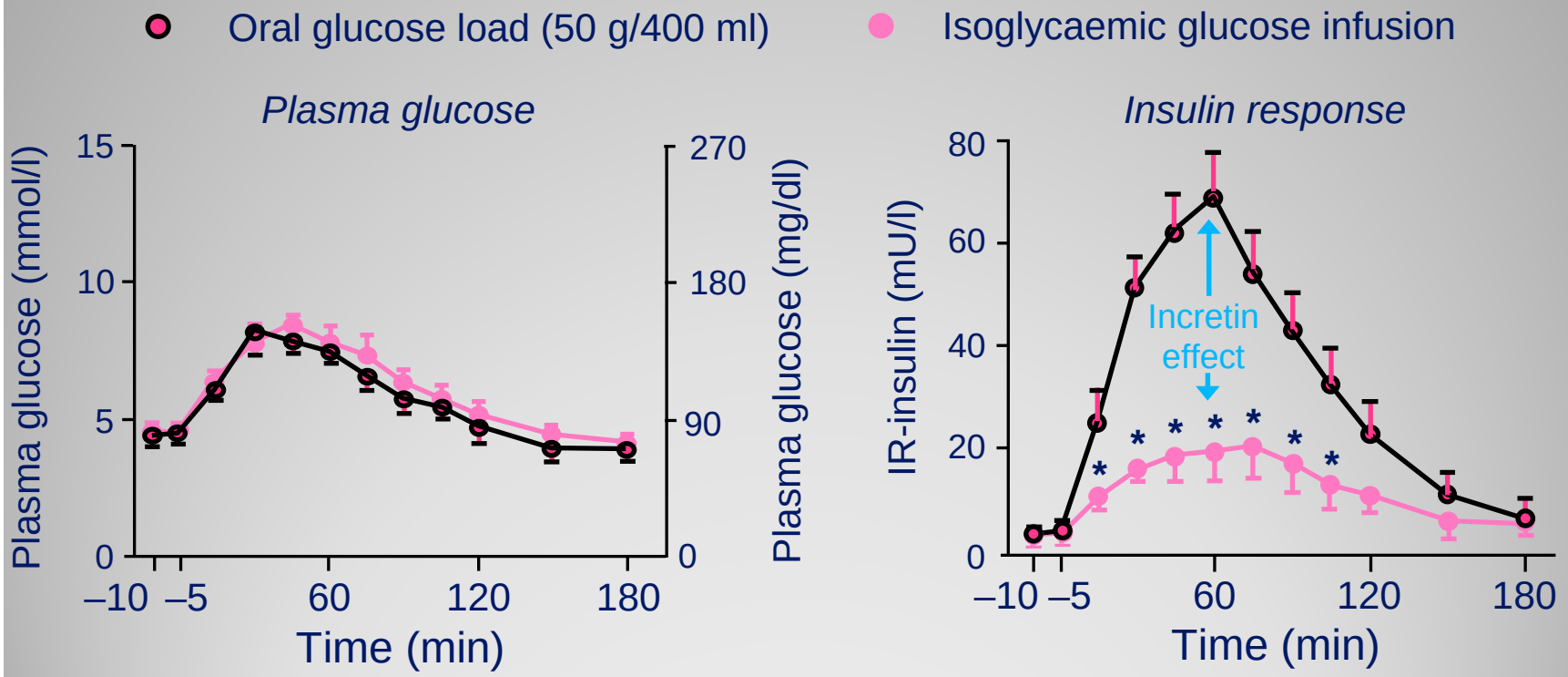
Nauck M, Stockmann F, Ebert R, Creutzfeldt W. *Reduced incretin effect in type 2 (non-insulin-dependent) diabetes.*
Diabetologia 1986;29:46-54.

COMPROMISSIONE PRECOCE DELL'ASSE ENTERO-INSULARE IN CORSO DI DIABETE MELLITO TIPO 2 (NON INSULINO-DIPENDENTE

R. LUGARI, A. DEI CAS, D. UGOLOTTI, C. DELL'ANNA, L. FINARDI, L.A. BARILLI, C. OGNIBENE*, B. MARANI*, M. IOTTI*, A. ORLANDINI*, R. ZANDOMENEGHI*, A. GNUDI
Dipartimento di Medicina Interna e Scienze Biomediche, Università degli Studi di Parma, Parma;
*Dipartimento di Medicina Interna, Università degli Studi di Modena, Modena

GI*DM* 21, 221-227, 2001

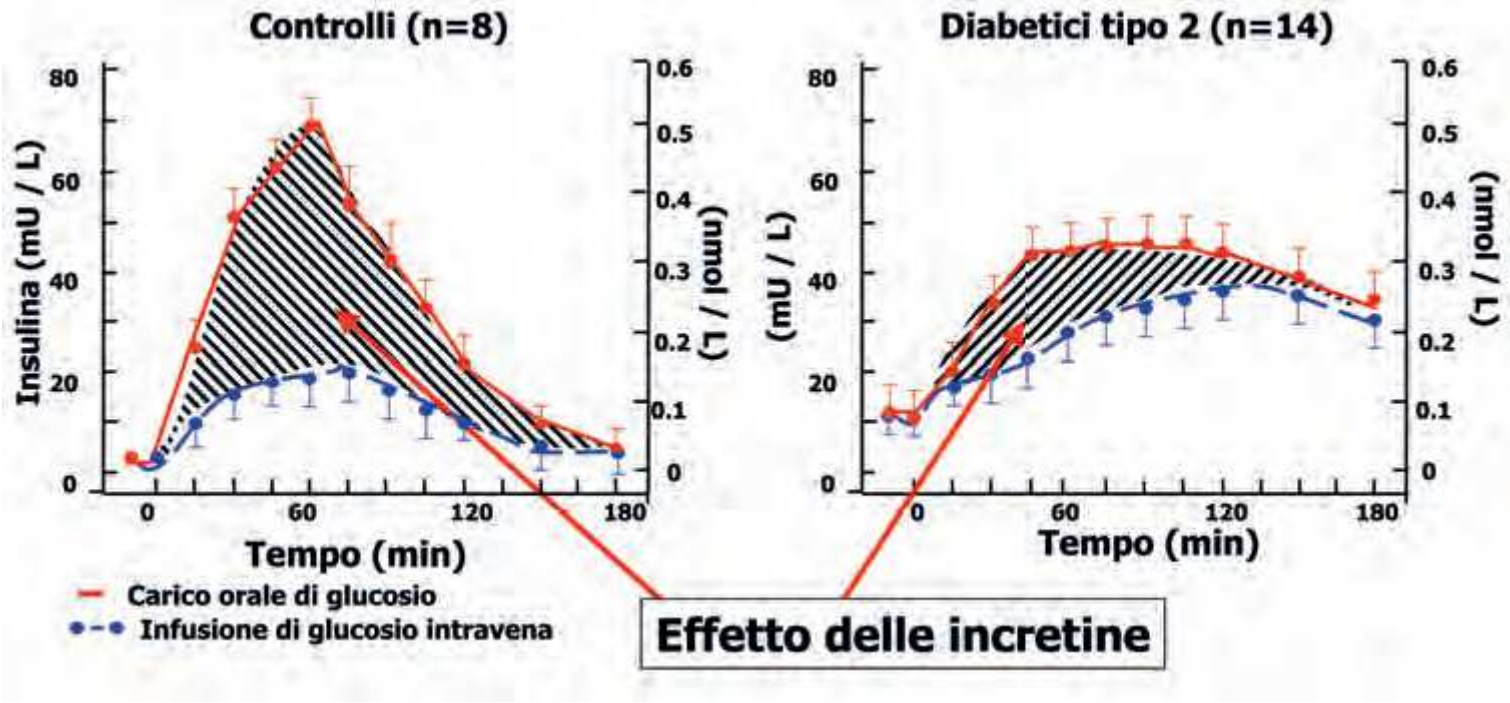
The incretin effect



- Insulin response is greater following oral glucose than i.v glucose, despite similar plasma glucose concentration

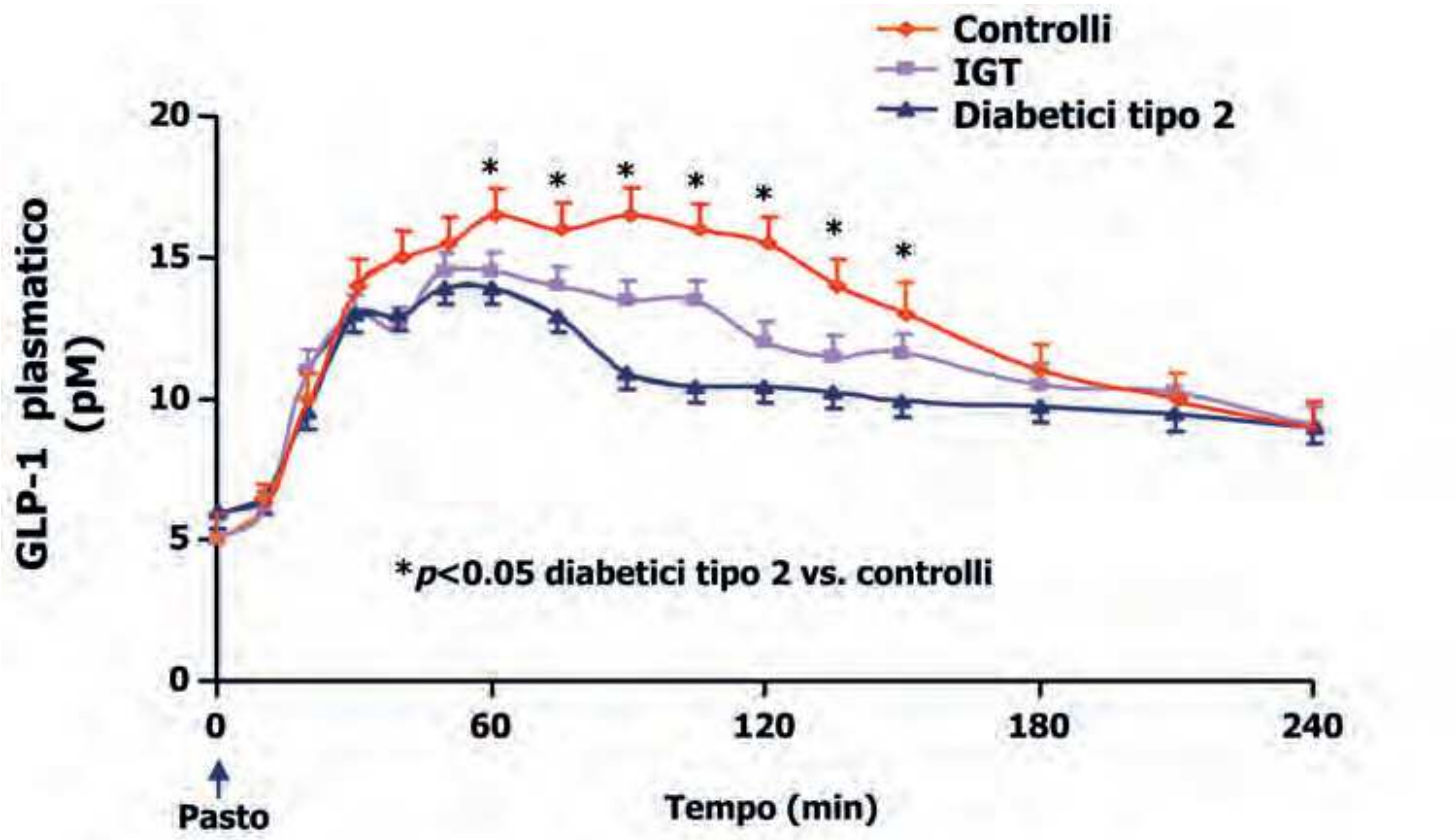
Nauck et al. Diabetologia 1986;29:46–52,

L’effetto incretinico è responsabile per il 60% della secrezione totale d’insulina dopo un pasto



L'effetto delle incretine è ridotto in soggetti con diabete di tipo 2.
Il grafico a sinistra mostra i livelli plasmatici di insulina dopo carico orale (linea rossa) o iniezione endovena (linea blu) di glucosio; analogamente a quanto mostrato in Figura 1, la differenza tra le due curve (area tratteggiata) viene attribuita all'effetto delle incretine.
Nel grafico sulla destra si può osservare come tale area tratteggiata sia significativamente ridotta nei soggetti con diabete di tipo 2 che presentano inoltre una risposta alterata sia al carico orale (linea rossa), sia all'iniezione endovena (linea blu) di glucosio

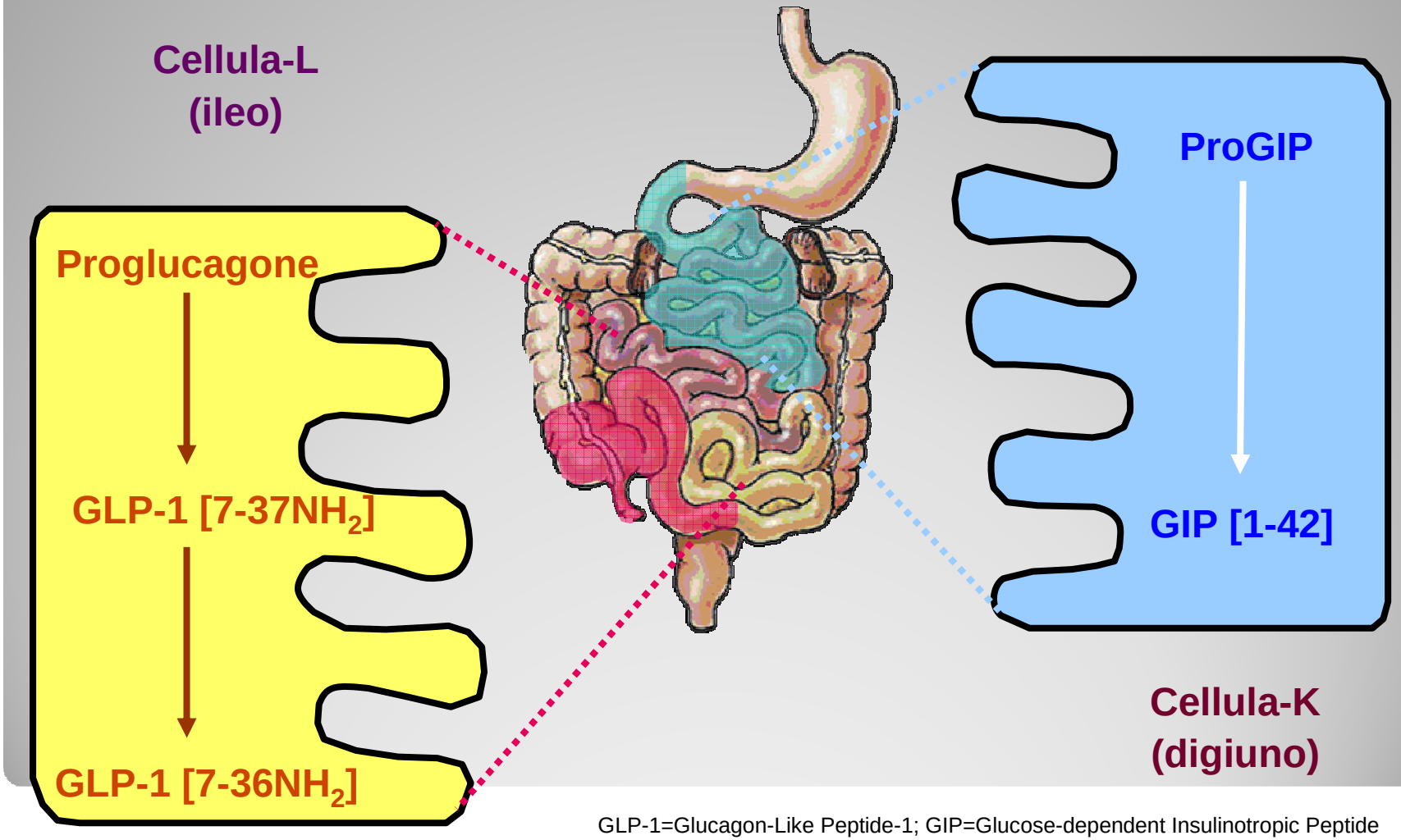
Nauck et al, 1986



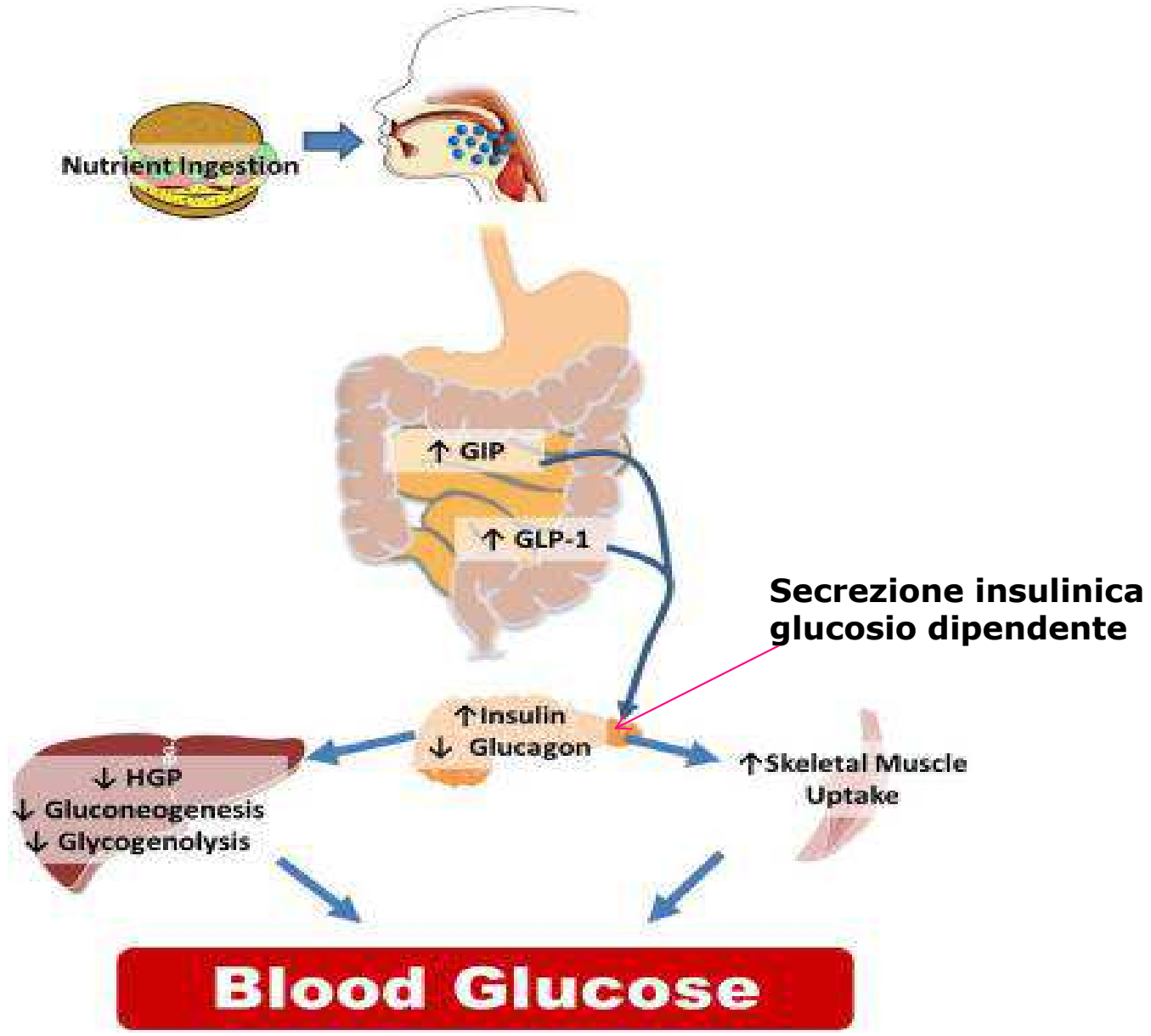
La secrezione di GLP-1 in risposta a un pasto è ridotta in soggetti con diabete di tipo 2. Livelli di GLP-1 plasmatico in soggetti con diabete di tipo 2 (linea blu), soggetti con alterata tolleranza glicidica (IGT, linea viola) e soggetti di controllo (linea rossa) in risposta a un pasto. La secrezione di GLP-1 è significativamente ridotta nei soggetti diabetici rispetto ai controlli (p <0,05 a 60, 72, 84, 96, 120, 132, 144 minuti dopo il pasto), i soggetti con IGT presentano ridotti livelli di GLP-1 ai medesimi punti, ma tale riduzione non raggiunge la significatività

Toft-Nielsen et al., 2001

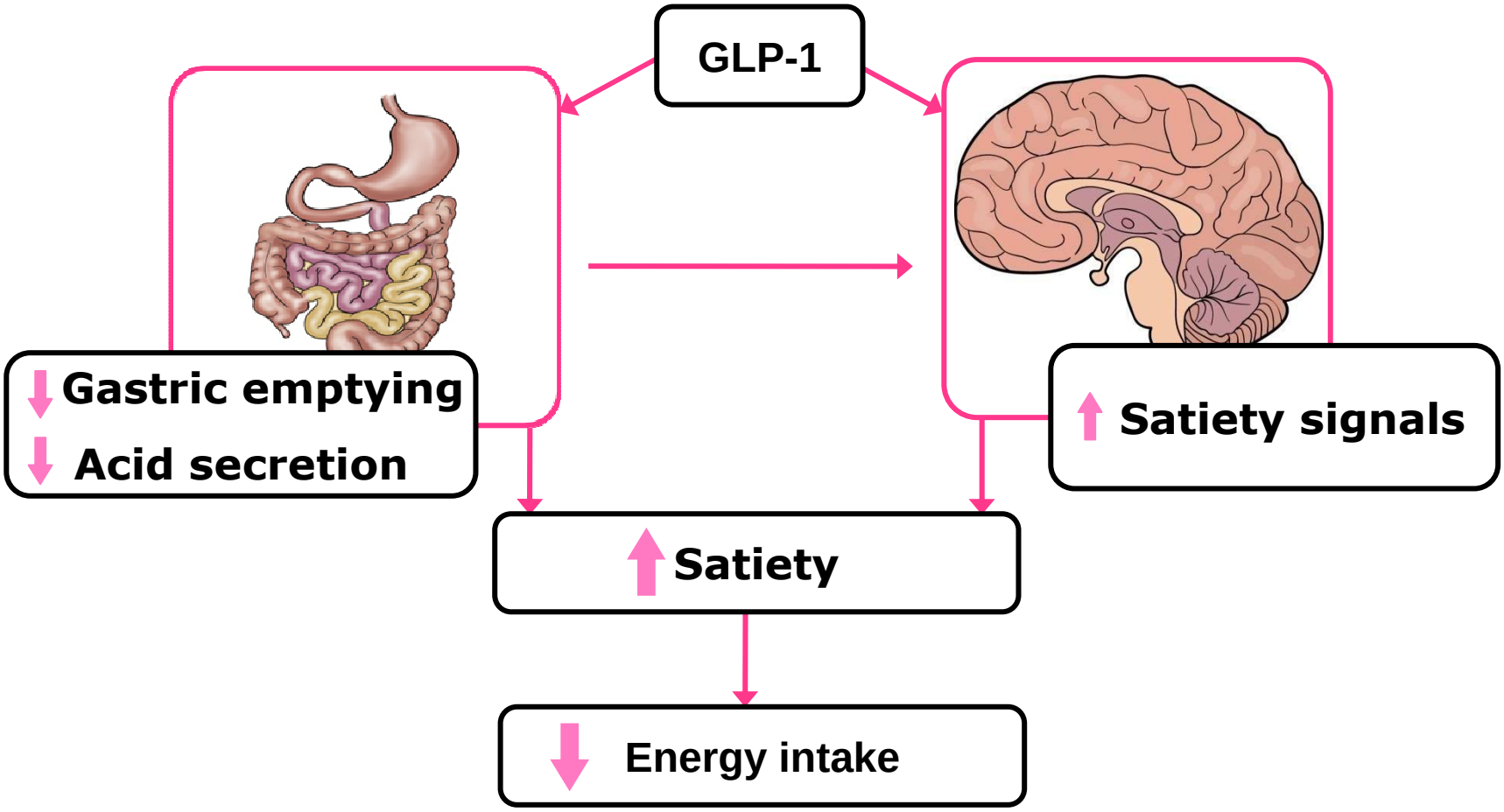
GLP-1 e GIP sono sintetizzati e secreti dall'intestino in risposta all'assunzione di cibo



GLP-1=Glucagon-Like Peptide-1; GIP=Glucose-dependent Insulinotropic Peptide
Adattato da Drucker DJ. *Diabetes Care.* 26:2929-2940.

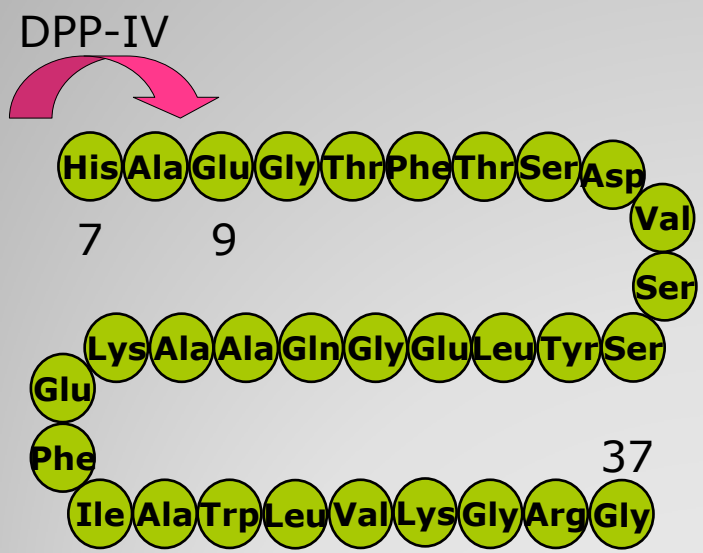

Nutrient Ingestion
↑ GIP
↑ GLP-1
Secrezione insulinica
glucosio dipendente
↑Insulin
↓ Glucagon
↓ HGP
↓ Gluconeogenesis
↓ Glycogenolysis
↑Skeletal Muscle
Uptake
Blood Glucose

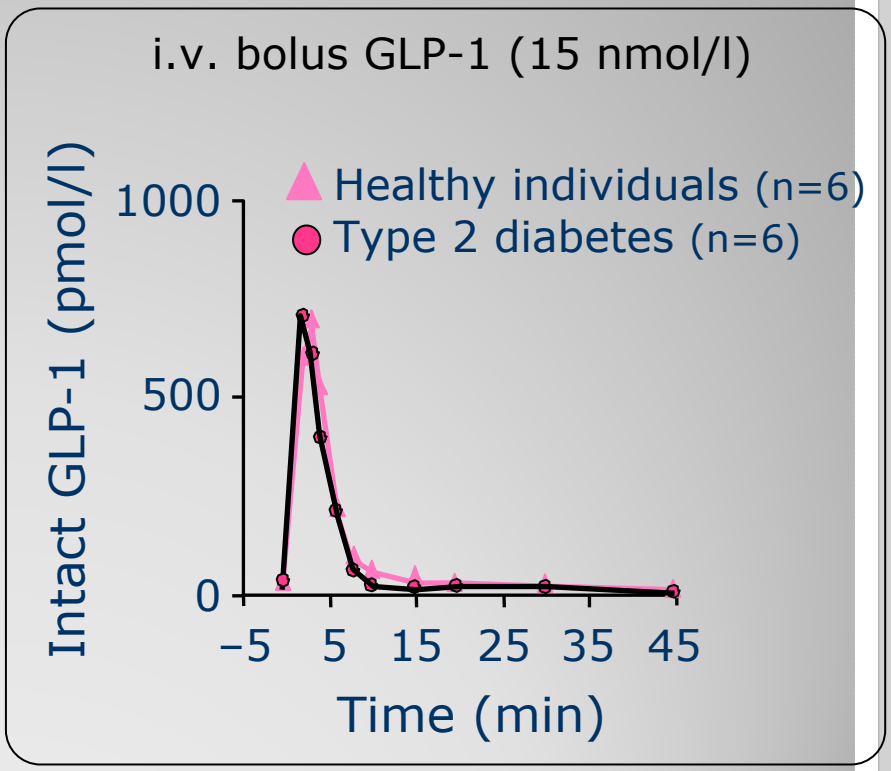
GLP-1 and satiety



Holst. *Physiol Rev*. 2007;87:1409–39.

Native GLP-1 has limited clinical value because of its short half-life





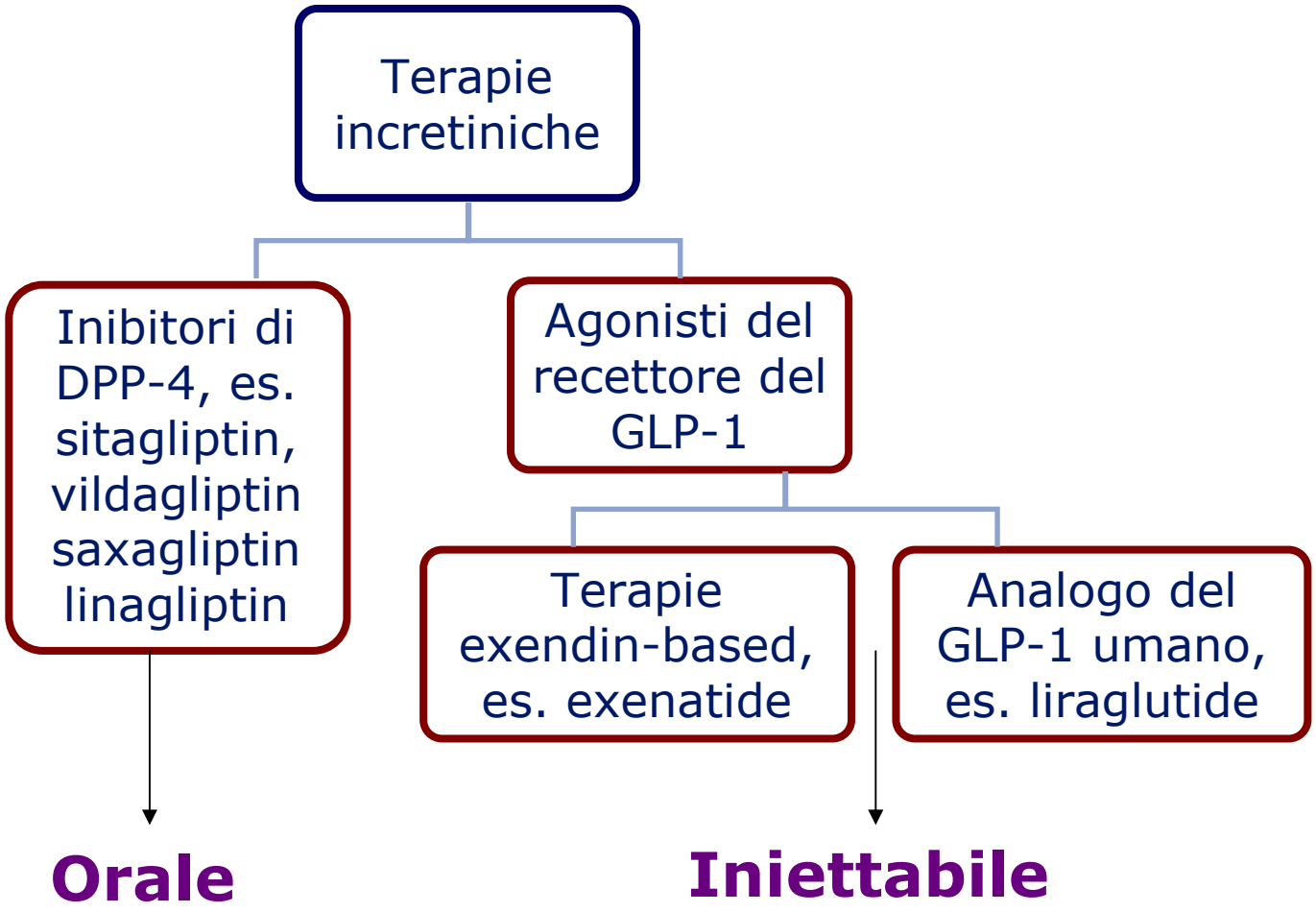
Enzymatic cleavage

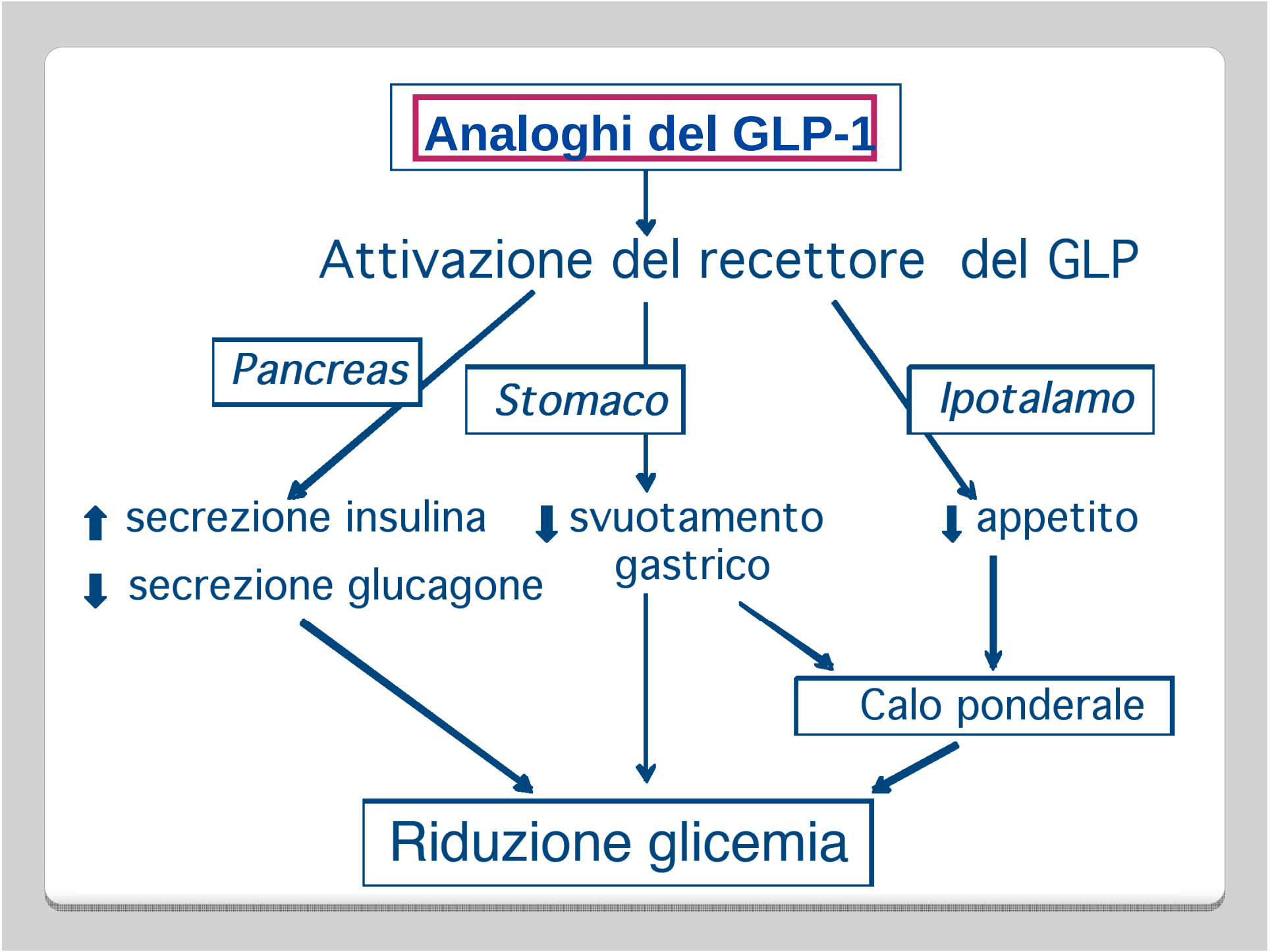
High clearance (4–9 l/min)

→ $t_{½}$ = 1.5–2.1 minutes (i.v. bolus 2.5–25.0 nmol/l)

Adapted from Vilsbøll et al. J Clin Endocrinol Metab 2003;88:220–224.

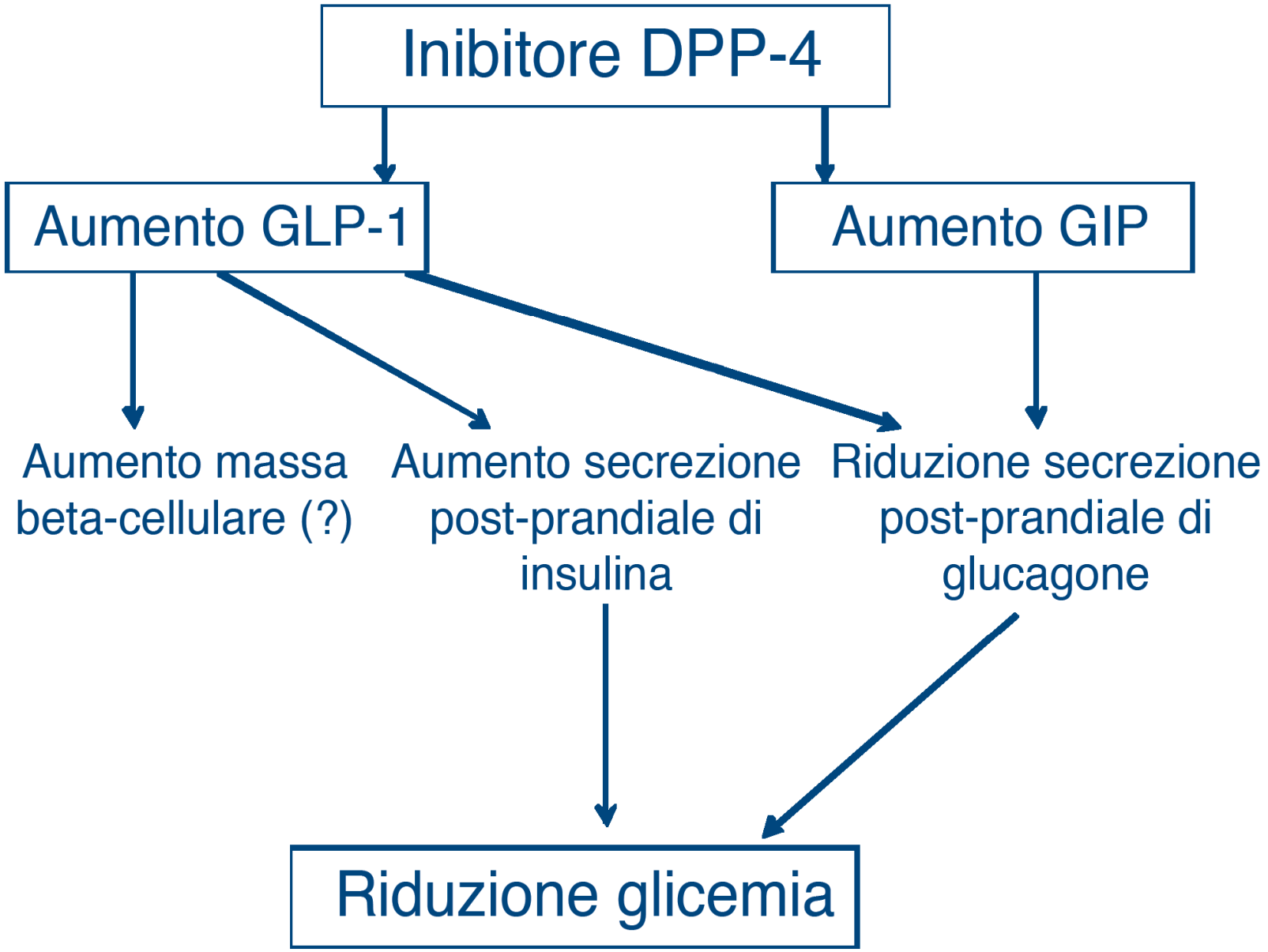
Incretino-MIMETICI




Analoghi del GLP-1
Attivazione del recettore del GLP
Pancreas
Stomaco
Ipotalamo
⬆ secrezione insulina
⬇ secrezione glucagone
⬇ svuotamento gastrico
⬇ appetito
Calo ponderale
Riduzione glicemia

Agonisti GLP-1 RA

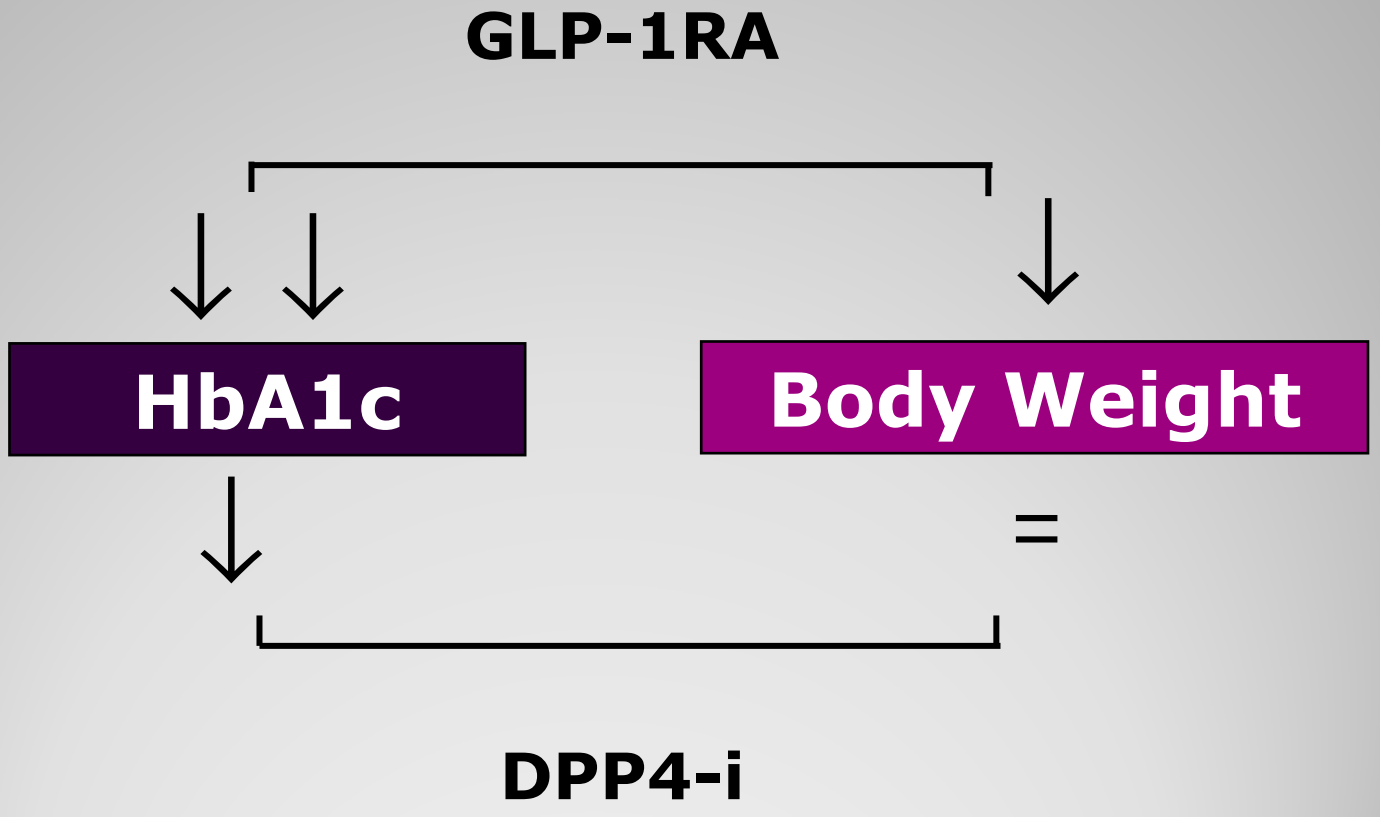
Principio attivo	Nome commerciale	Durata d'azione
Exenatide 2005	Byetta	2-5 ore
Exenatide LAR 2014	Bydurion	7 giorni
Liraglutide 2010	Vyctoza	12 ore
Lixisenatide 2014	Lyxumia	2-5 ore
Albiglutide	Tanzeum	7 giorni


Inibitore DPP-4
Aumento GLP-1
Aumento GIP
Aumento massa beta-cellulare (?)
Aumento secrezione post-prandiale di insulina
Riduzione secrezione post-prandiale di glucagone
Riduzione glicemia

Inibitori DPP-4

Trattamento	Nome commerciale	Posologia
Sitagliptina 2006	Januvia	100 mg
Vildagliptina 2008	Galvus	50 mg x 2
Saxagliptina 2009	Onglyza	5 mg
Linagliptina 2013	Trajenta	5 mg
Alogliptina 2014	Vipidia	25 mg

T2DM



Riduzione glicata

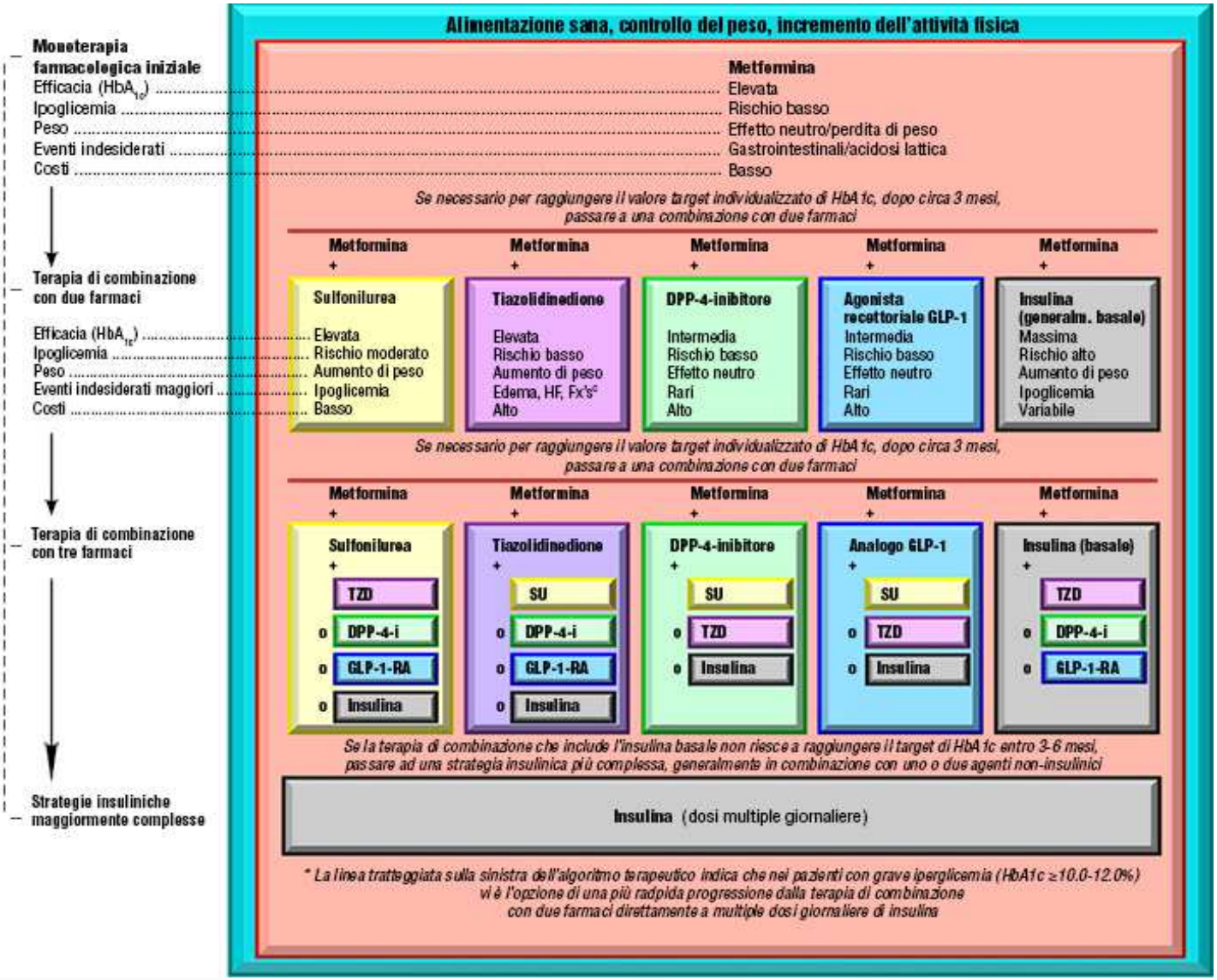
	Riduzione HbA1c %
Metformina	1.5
TZDs	0.5-1.4
Sulfaniluree	1.5
Glinidi	1.0-1.5
Inibitori-α glucosidasi	0.5-0.8
Insulina	1.5-2.5
Analoghi GLP-1	0.8-1.0
Inibitori DPP-IV	0.6-1.0

GLP-1R Agonists vs DPP-4 Inhibitors

	GLP-1R Agonists	DPP-4 Inhibitors
Administration	Injection	Orally Available
GLP-1 concentrations	Pharmacological	Physiological
Mechanisms of action	GLP-1	GLP-1 + GIP
Activation of portal glucose sensor	No	Yes
↑Insulin secretion	+++	+
↓Glucagon secretion	++	++
Gastric emptying	Inhibited	+/-
Weight loss	Yes	No
Expansion of beta-cell mass		
In preclinical studies	Yes	Yes
Nausea and vomiting	Yes	No
Potential immunogenicity	Yes	No

Endocrine Reviews, April 2007, 28(2):187–218

Algoritmo terapeutico



Piano Terapeutico per la prescrizione di Incretine/ Inibitori DPP-4 nel trattamento del diabete tipo 2

Nuove modalità compilazione Piano Terapeutico Incretine (03/09/2014)

Agenzia Italiana del Farmaco

AIFA

Si informano gli utenti dei Registri di Monitoraggio che, in funzione di quanto stabilito dalla determina AIFA n. 878/2014, pubblicata in Gazzetta Ufficiale n. 200 del 29/08/2014 (pag. 25), i Piani Terapeutici per il monitoraggio delle "Incretine", pubblicati in allegato alle Determine delle singole specialità medicinali, sono da intendersi sostituiti integralmente dal **Piano terapeutico unico, disponibile sul sito istituzionale dell'Agenzia**.

Si precisa altresì che detto Piano Terapeutico unico comprende una modifica delle limitazioni precedentemente individuate in relazione alla possibilità, in alcuni casi (inibitori DPP-4), di prescrivere in associazione con l'insulina basale.

Si specifica che il Piano Terapeutico, nelle more della definizione del PT web-based, è da compilarsi ai fini della rimborsabilità a cura dei Centri specializzati, Universitari o delle Aziende Sanitarie, individuati dalle Regioni e dalle Province autonome di Trento e Bolzano, da rinnovarsi semestralmente e consegnare al paziente in formato cartaceo.

Si rammenta ai referenti regionali, che non lo avessero ancora fatto, di procedere alla individuazione dei Centri sanitari autorizzati alla prescrizione di questa classe farmaceutica.

Agenzia Italiana del Farmaco

AIFA

HbA1c ≥7.5% (58 mmol/mol)

HbA1c ≤8.5% (69 mmol/mol)

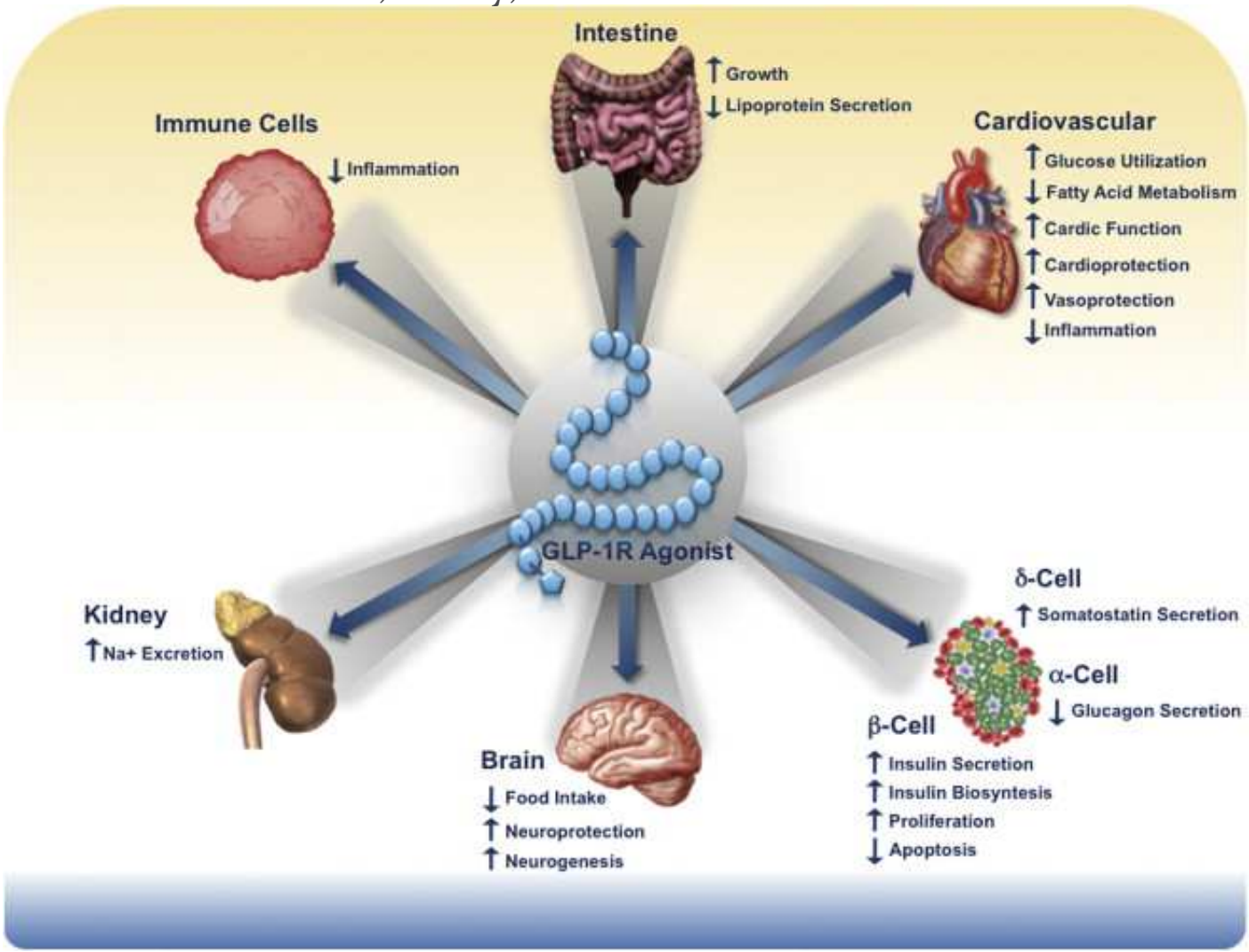
ma puo' estendersi al 9% (75 mmol/mol) in caso di fragilita per eta' >75 anni, insufficienza renale cronica di grado severo (GFR <30 ml/min) e/o complicanze e/o patologie concomitanti che riducano l'attesa di vita.

Vildagliptin/ metformina	- 50/850 mg/die x 2 ☐ - 50/1,000 mg/die x 2 ☐		*In associazione con:* - Sulfonilurea ☐ - Insulina basale ☐

a In pazienti in cui l'aggiunta della metformina sia controindicata o non tollerata;
b Rimborsabile in monoterapia soltanto in pazienti con creatinina clearance secondo Cockcroft-Gault <50 ml/min.

Direct Pharmacological Actions of GLP-1R Agonists

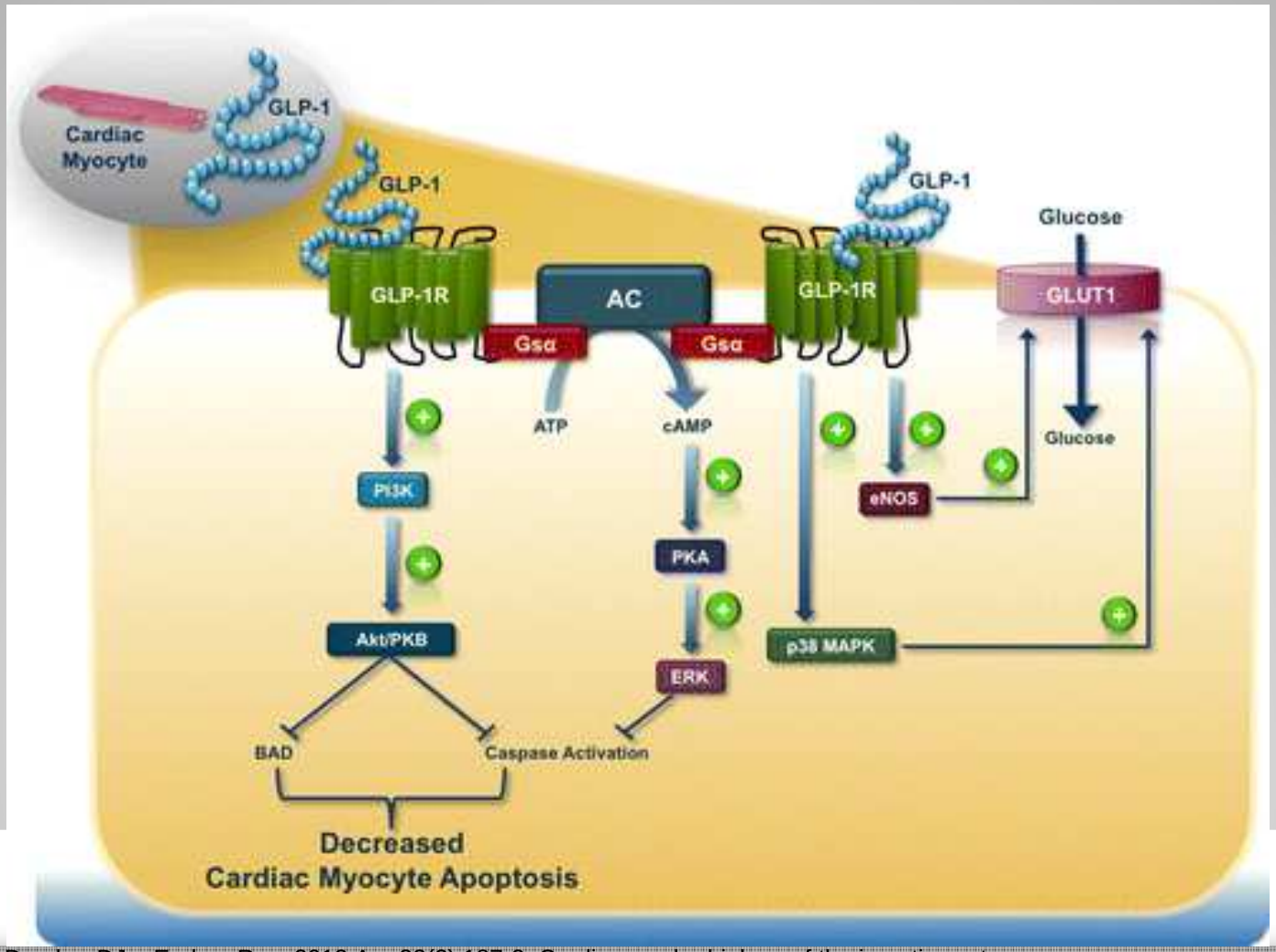
GLP-1R agonists act directly via the GLP-1R on pancreatic islets, heart, intestine, subpopulations of immune cells, kidney, and brain.



Campbell JE1, Drucker DJ Cell Metab. 2013 Jun 4;17(6):819-37.

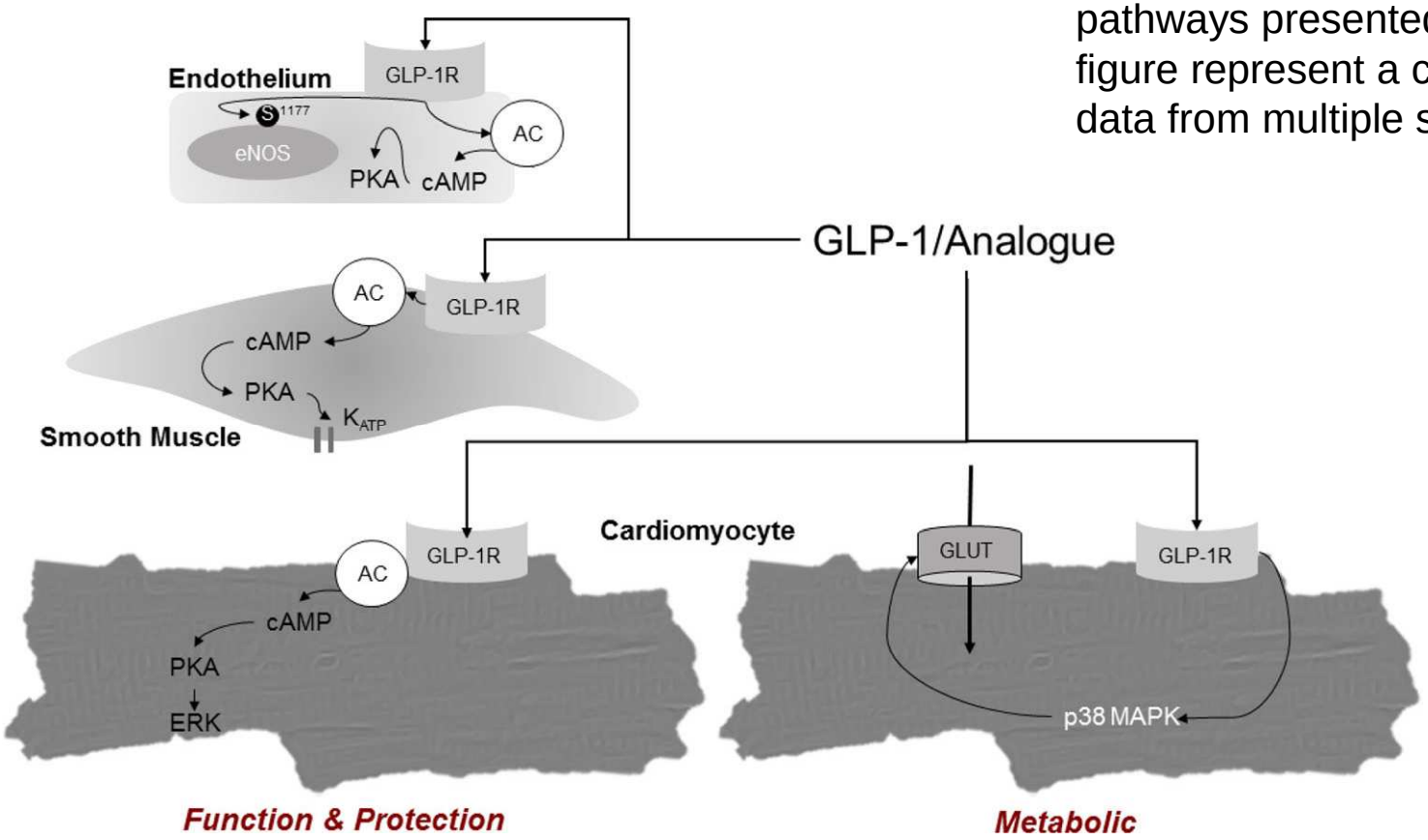
GLP-1R-dependent intracellular signal transduction pathways in the cardiomyocyte.

The signaling pathways engaged downstream of the cardiomyocyte GLP-1R lead to a reduction in apoptosis and increase in glucose uptake independent of the classical insulin-dependent pathway. ROS, Reactive oxygen species. AC, Adenylate cyclase.



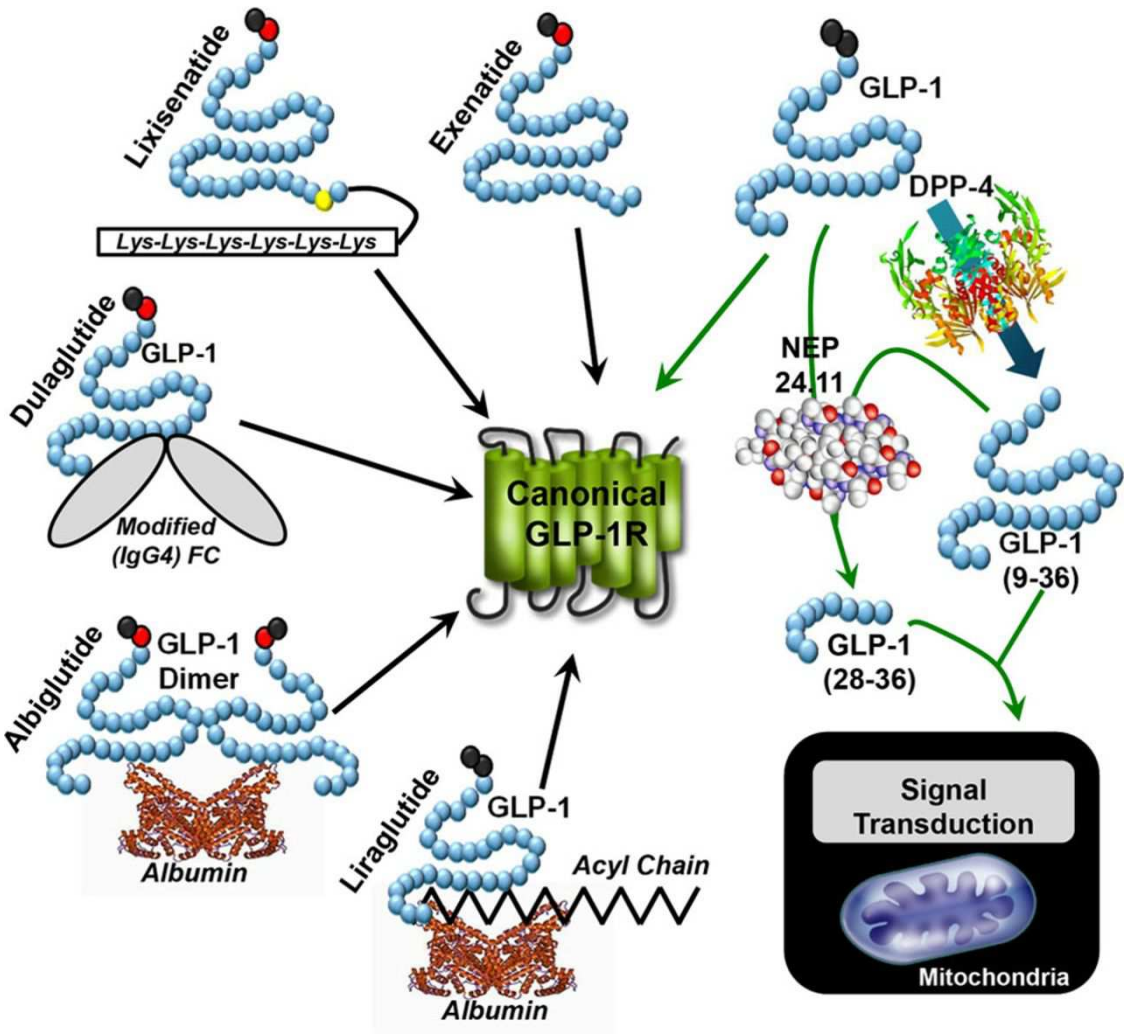
Ussher JR1, Drucker DJ. Endocr Rev. 2012 Apr;33(2):187-2. Cardiovascular biology of the incretin system

A graphical representation of putative pathways downstream from GLP-1 receptor activation in endothelial cells, vascular smooth muscle cells and cardiomyocytes. pathways presented within this figure represent a compilation of data from multiple species



Rev Endocr Metab Disord (2014) 15:209–217

Glucagon-like peptide-1 (GLP-1) enzymatic cleavage, GLP-1 metabolites, and GLP-1 receptor (GLP-1R) agonists.



Ussher J R , and Drucker D J Circulation Research. 2014;114:1788-1803

The gut-renal axis: do incretin-based agents confer renoprotection in diabetes?

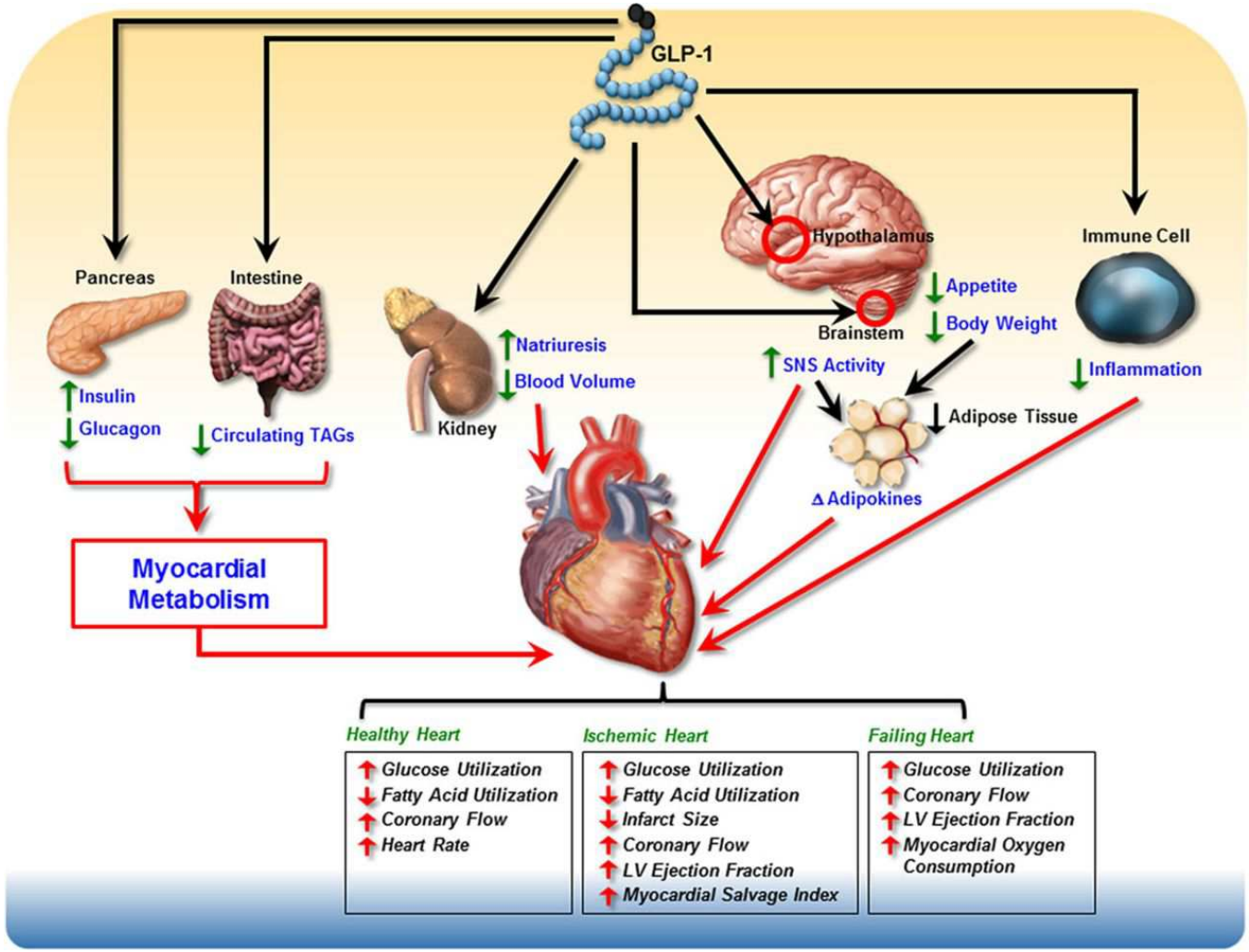
Muskiet MH, Smits MM, Morsink LM, Diamant M

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide, and is associated with a high risk of cardiovascular morbidity and mortality. Intensive control of glucose levels and blood pressure is currently the mainstay of both prevention and treatment of diabetic nephropathy. However, this strategy cannot fully prevent the development and progression of diabetic nephropathy, and an unmet need remains for additional novel therapies. The incretin-based agents--agonists of glucagon-like peptide 1 receptor (GLP-1R) and inhibitors of dipeptidyl peptidase 4 (DPP-4), an enzyme that degrades glucagon-like peptide 1--are novel blood-glucose-lowering drugs used in the treatment of type 2 diabetes mellitus (T2DM). Therapeutic agents from these two drug classes improve pancreatic islet function and induce extrapancreatic effects that ameliorate various phenotypic defects of T2DM that are beyond glucose control**.**

Agonists of GLP-1R and inhibitors of DPP-4 reduce blood pressure, dyslipidaemia and inflammation, although only GLP-1R agonists decrease body weight. Both types of incretin-based agents inhibit renal tubular sodium reabsorption and decrease glomerular pressure as well as albuminuria in rodents and humans. In rodents, incretin-based therapies also prevent onset of the morphological abnormalities of diabetic nephropathy.

Nat Rev Nephrol. 2014

Potential indirect cardiovascular effects of glucagon-like peptide-1 receptor (GLP-1R) agonists.



Ussher J R , and Drucker D J Circulation Research. 2014;114:1788-1803

Studi in corso sui farmaci antidiabetici e sugli esiti CV

	Sitagliptina	Saxagliptina	Linagliptina	Liraglutide	Exenatide QW	Lixisenatide
Nome dello studio	TECOS	SAVOR-TIMI 53	CAROLINA	LEADER	EXSCEL	ELIXA
Bracci con funzione di comparatori di riferimento	Sitagliptina vs. placebo	Saxagliptina vs. placebo	Linagliptina vs. glimepiride	Liraglutide vs. placebo	Exenatide vs. placebo	Lixisenatide vs. placebo
Coorte di pazienti	DMT2 + storia di malattia CV	DMT2 + malattia CV o fattori di rischio multipli	DMT2 + malattia CV o ≥ 2 fattori di rischio	DMT2 + pre-gressa malattia CV o età oltre 60 anni e fattori di rischio	DMT2 in tratta-mento stabile + ≤ 3 OAD per ≥ 3 mesi	DMT2 con sindrome coronarica acuta
Dimensioni dello studio	~14,000	~16,500	~6000	8723	~9500	~9600
Endpoint primario	Morte CV, IM non fatale, attacco ischemico non fatale o ospedalizzazione per angina instabile	Morte CV, IM non fatale o attacco ischemico non fatale	Morte CV, IM non fatale, ictus non fatale o ospedalizzazione per angina instabile	Morte CV, IM non fatale o ictus non fatale	Morte CV, IM non fatale o ictus non fatale	Morte CV, IM non fatale o ictus non fatale
Durata (anni)	≤ 5	~5	~7.5	≤ 5	~5.5	~6.5
Completamen-to previsto per	2014	2013	2018	2016	2017	2014

Gut microbiota, enteroendocrine functions and metabolism.

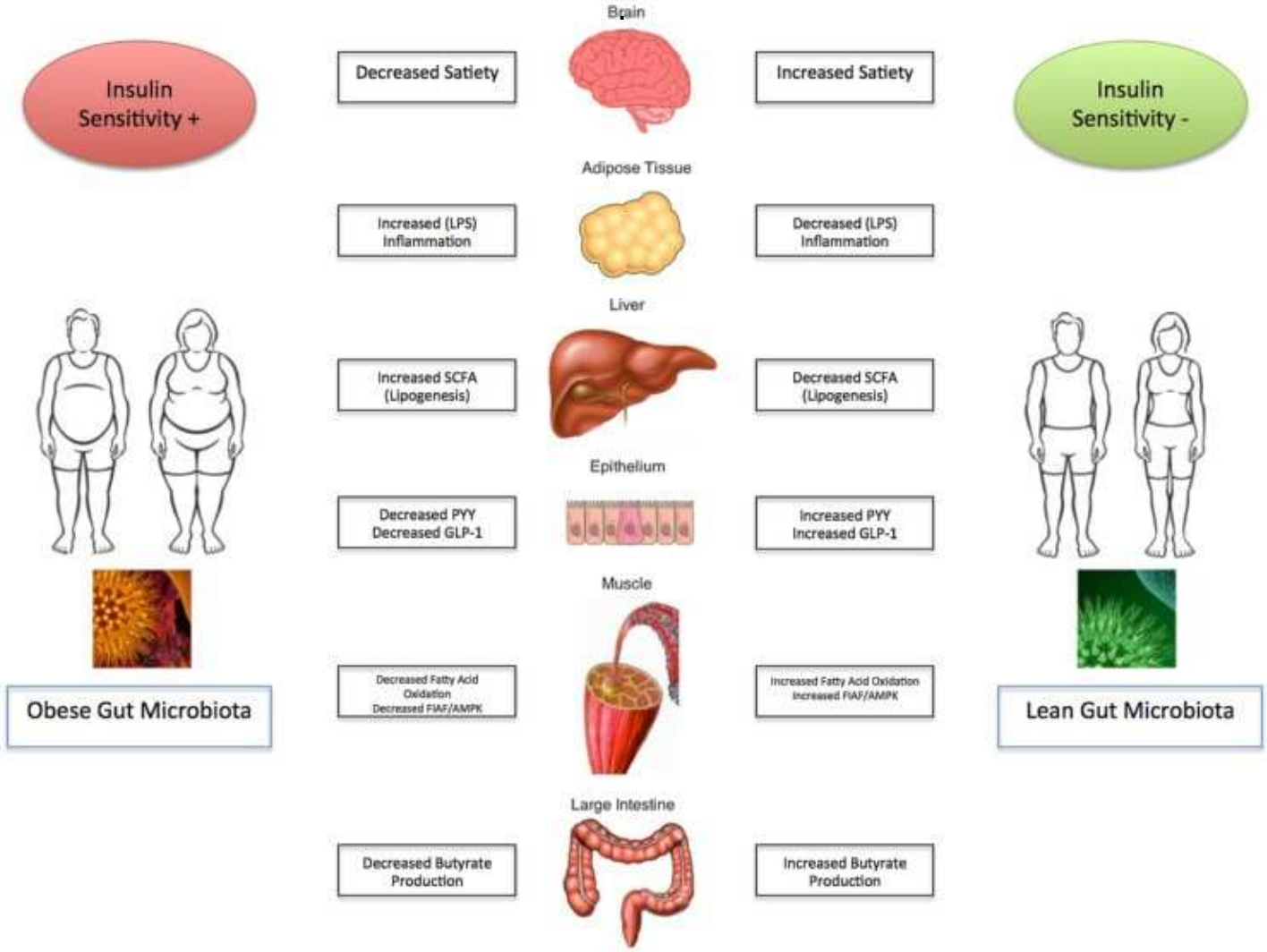
Cani PD[1], Everard A, Duparc T.

The gut microbiota affects host metabolism through a number of physiological processes. **Emerging evidence suggests that gut microbes interact with the host through several pathways involving enteroendocrine cells (e.g. L cells).** The activation of specific G protein coupled receptors expressed on L cells (e.g. GPR41, GPR43, GPR119 and TGR5) triggers the secretion of glucagon-like peptides (GLP-1 and GLP-2) and PYY. These gut peptides are known to control energy homeostasis, glucose metabolism, gut barrier function and metabolic inflammation.

Here, we explore how crosstalk between **the ligands produced by the gut microbiota (short chain fatty acids, or SCFAs), or produced by the host but influenced by gut microbes (endocannabinoids and bile acids), impact host physiology.**

Curr Opin Pharmacol 2013 Dec;13(6):935-40

Gut microbiota and its influence on obesity and the metabolic syndrome



Front Endocrinol. 2014; 5: 47

The action of gut microbiota is needed to digest some polysaccharides

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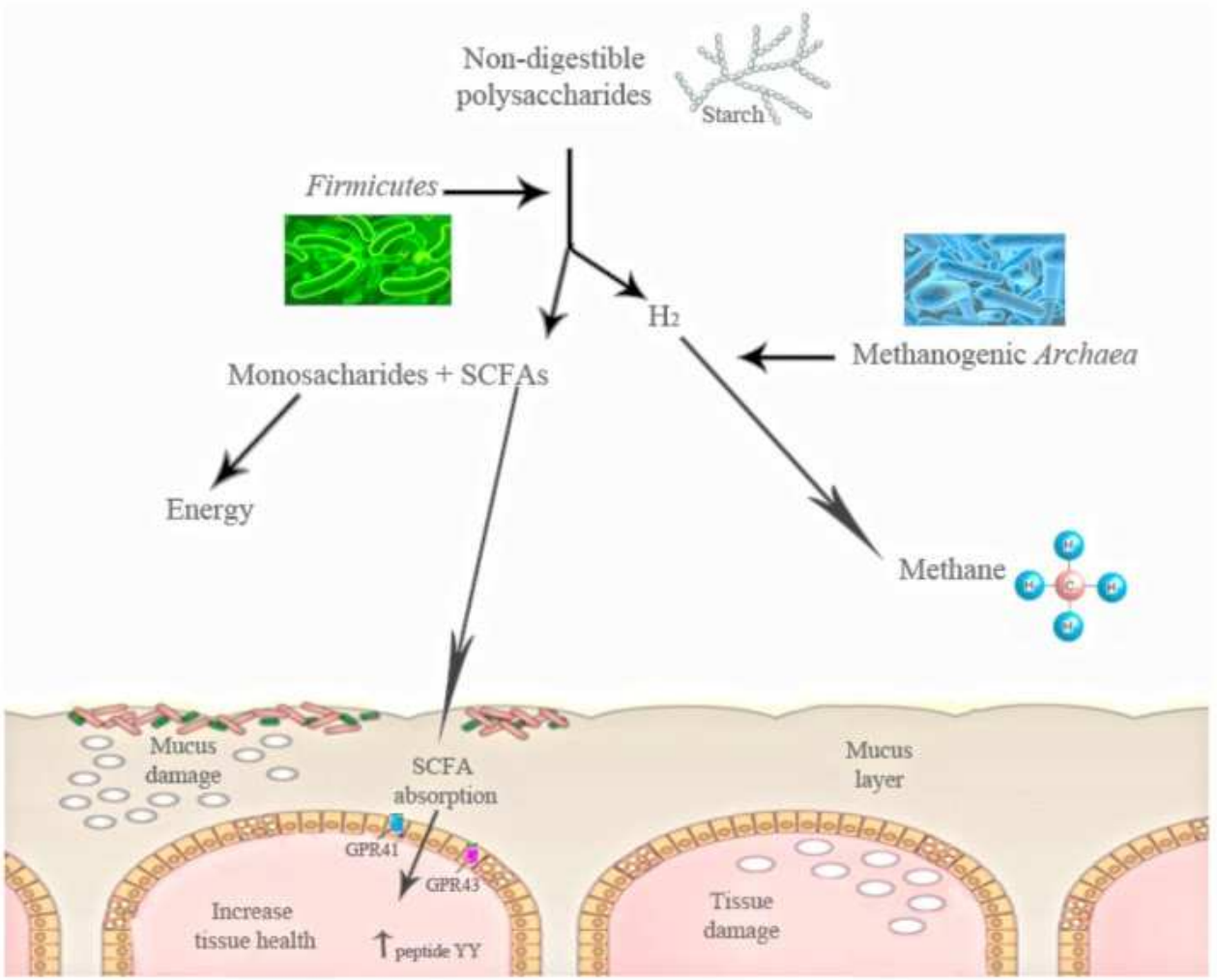
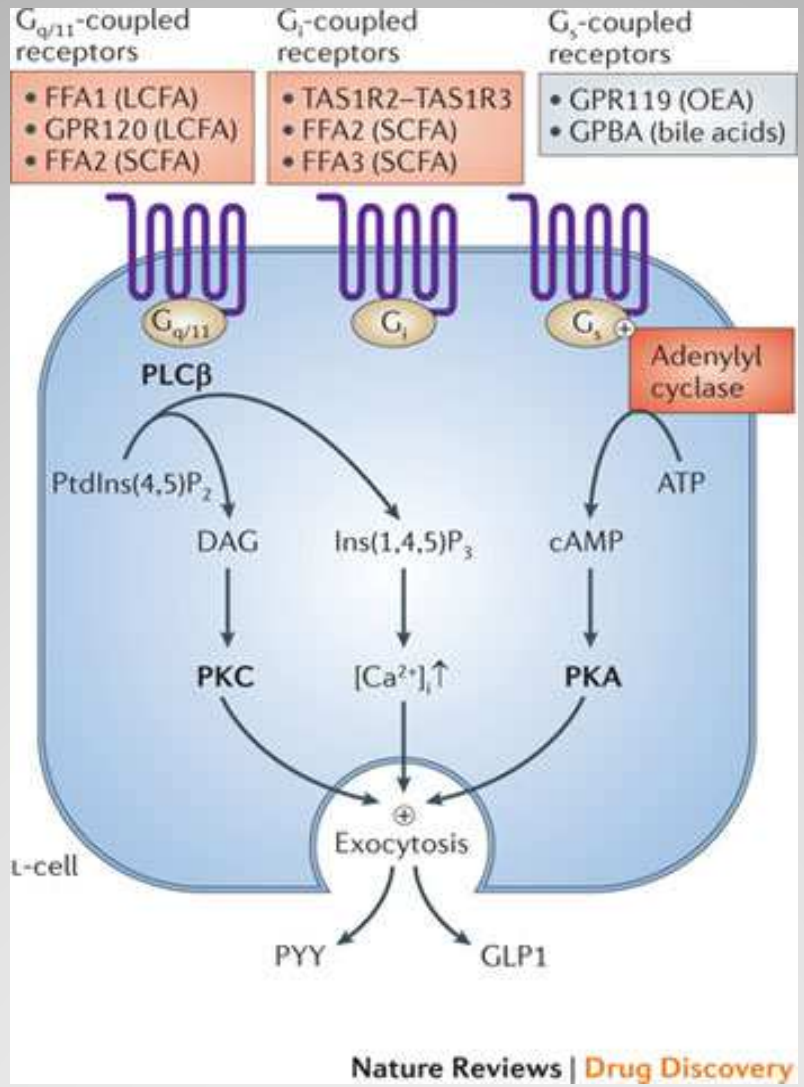


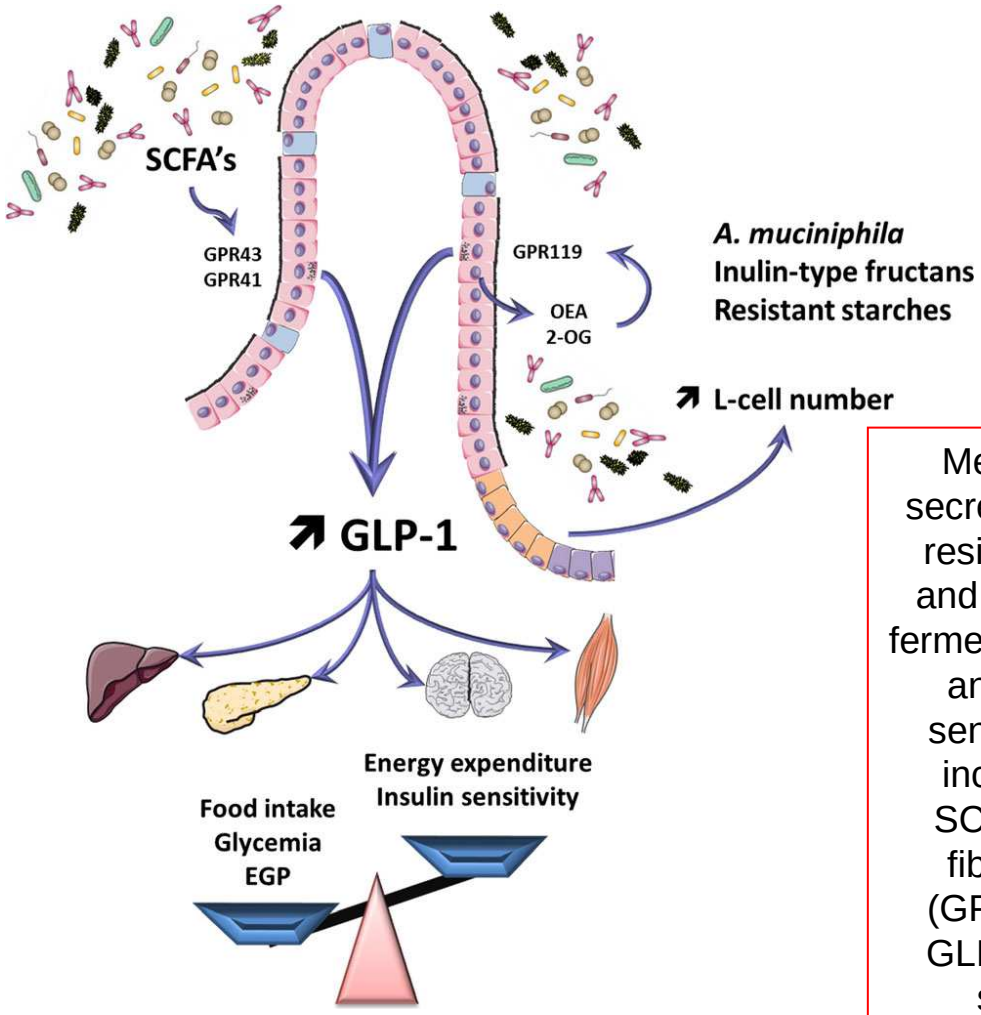
Front Microbiol. 2014; 5: 190



Simplified schematic diagram of the regulation of enteroendocrine cell function through GPCRs.

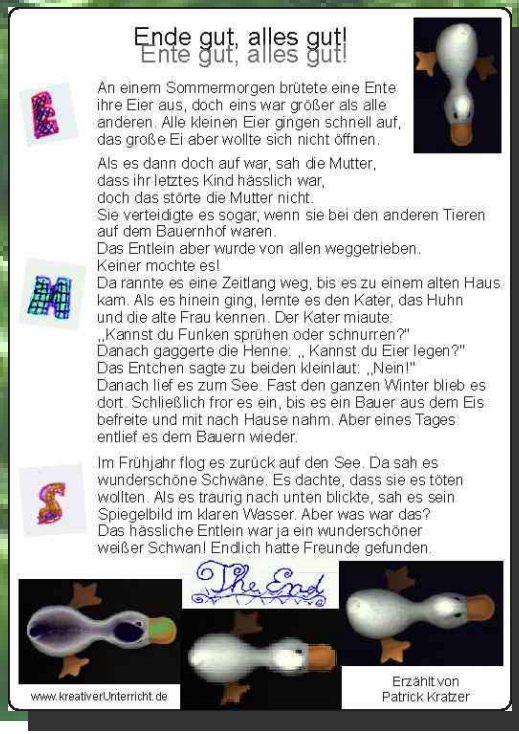
| AUGUST 2012

Rev Endocr Metab Disord (2014) 15:189–196



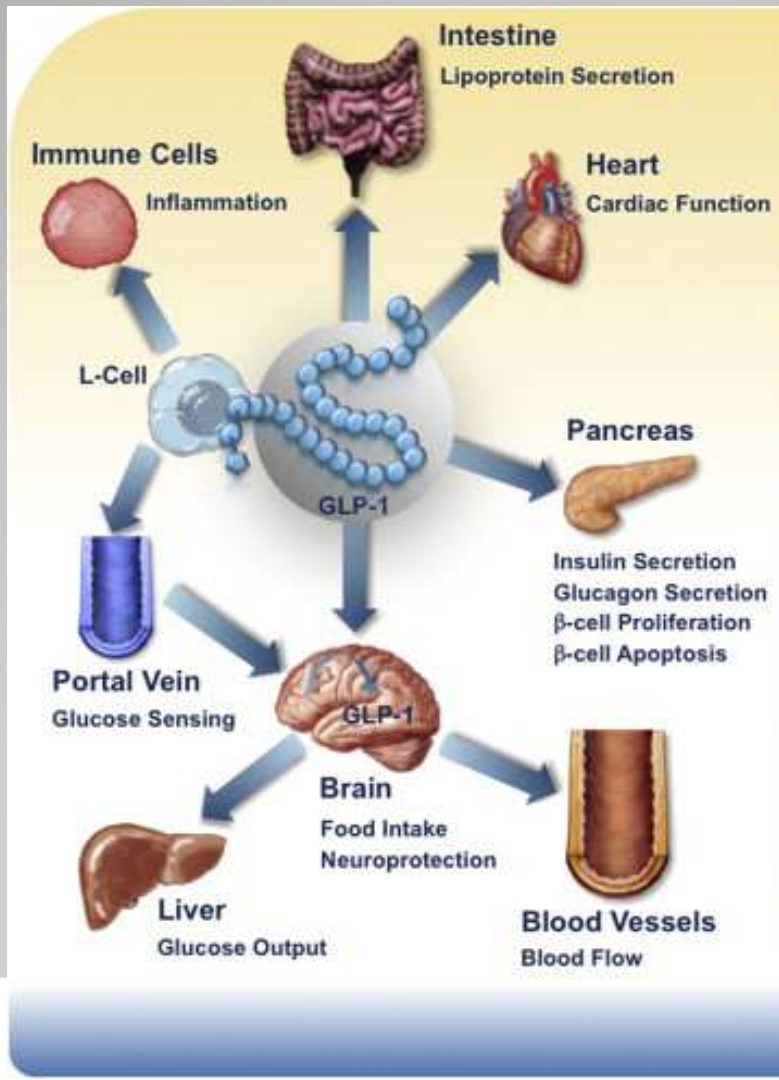
Mechanisms linking gut microbiota and GLP-1 secretion. The ingestion of inulin-type fructans and resistant starches reduce food intake, glycaemia and endogenous glucose (EGP), conversely their fermentation by the gut microbiota is associated with an increase in energy expenditure and insulin sensitivity. These effects are associated with an increased GLP-1 secretion and L-cell number. SCFAs produced by the fermentation of dietary fibres bind to the G-protein-coupled receptors (GPCRs)GPR41 and GPR43, thereby triggering GLP-1 secretion by the L-cells. GPR119 ligands such as oleoylethanolamide (OEA) and 2-oleoylglycerol (2-OG) trigger GLP-1 secretion. Specific microbes such as Akkermansia muciniphila are able to regulate intestine endocannabinoid-like compounds such as 2-OG.

Grazie della pazienza e dell’attenzione



Physiological Roles of Endogenous GLP-1

The biological actions of GLP-1 as revealed by loss-of-function studies utilizing Glp1r−/− mice or antagonists of the GLP-1R are shown and summarized in the accompanying table



Physiological Actions of GLP-1

Physiology	Impairment of GLP-1 action
Fasting Glucose	Increased
Glucose-Dependent Insulin Secretion	Decreased
Glucagon Secretion	Increased
β-cell Signal Transduction	Abnormal
β-cell Apoptosis	Increased
β-cell Proliferation	Decreased
Islet Size	Decreased
Food Intake	Increased
Energy Expenditure	Increased
Locomotion	Increased
Body Weight	Increased
Portal Glucose Sensing	Decreased
Postprandial Lipid Metabolism	Decreased
CNS Control of Blood Flow	Decreased
Cardiovascular Function	Decreased
CNS Stress Response	Increased
Susceptibility to Neural Injury	Increased
Immune System	Decreased
Gastric Emptying	Normal
Susceptibility to Pancreatitis	Normal

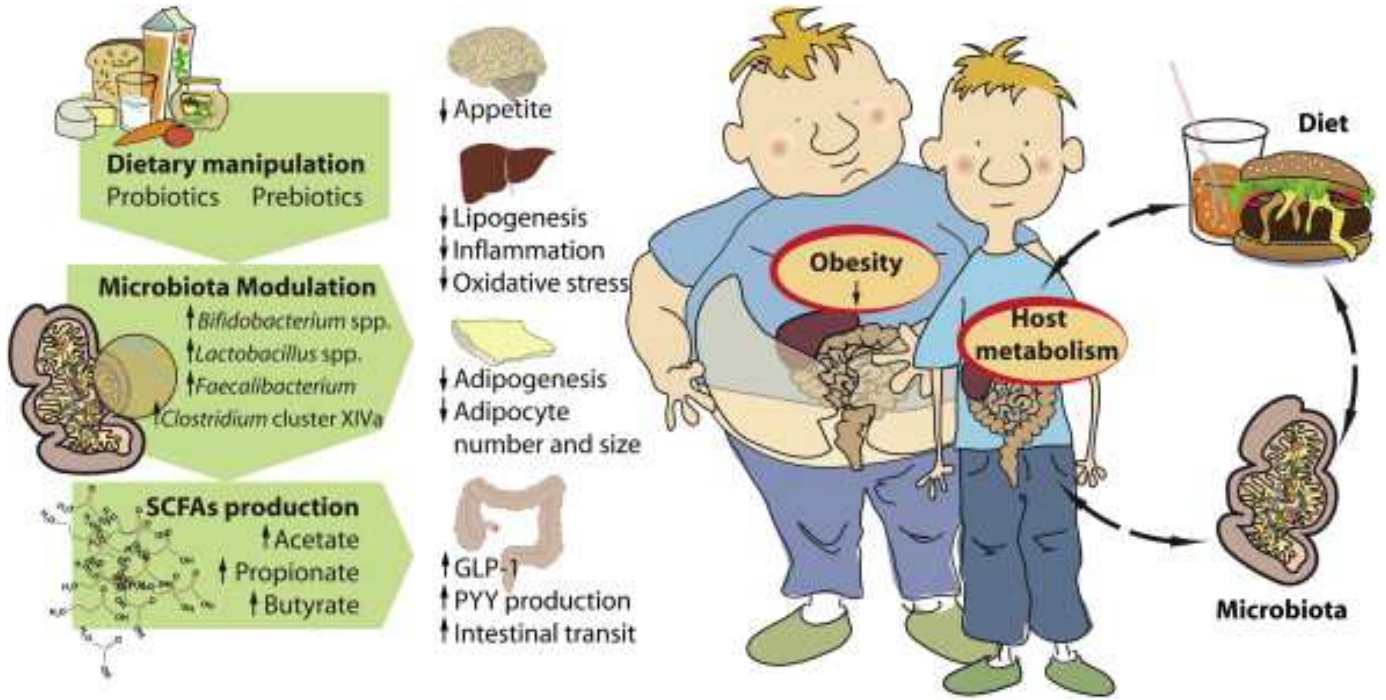
Pharmacokinetics, safety, and efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus and renal or hepatic impairment. A systematic review of the literature

Carlo B. Giorda · Elisa Nada · Barbara Tartaglino

Half of all patients in the global development program exposed to the marketed doses of **vildagliptin as monotherapy** had either **mild or moderate renal impairment** at study baseline, and vildagliptin was **effective and well tolerated in this population**. When given at a **reduced dose of 50 mg once daily**, vildagliptin added to ongoing antidiabetic therapy in patients with **T2DM and moderate or severe renal impairment had a safety profile similar to placebo**, while significantly **improving the glycemic control** in both subgroups.

Giorda et al; Endocrine 2014

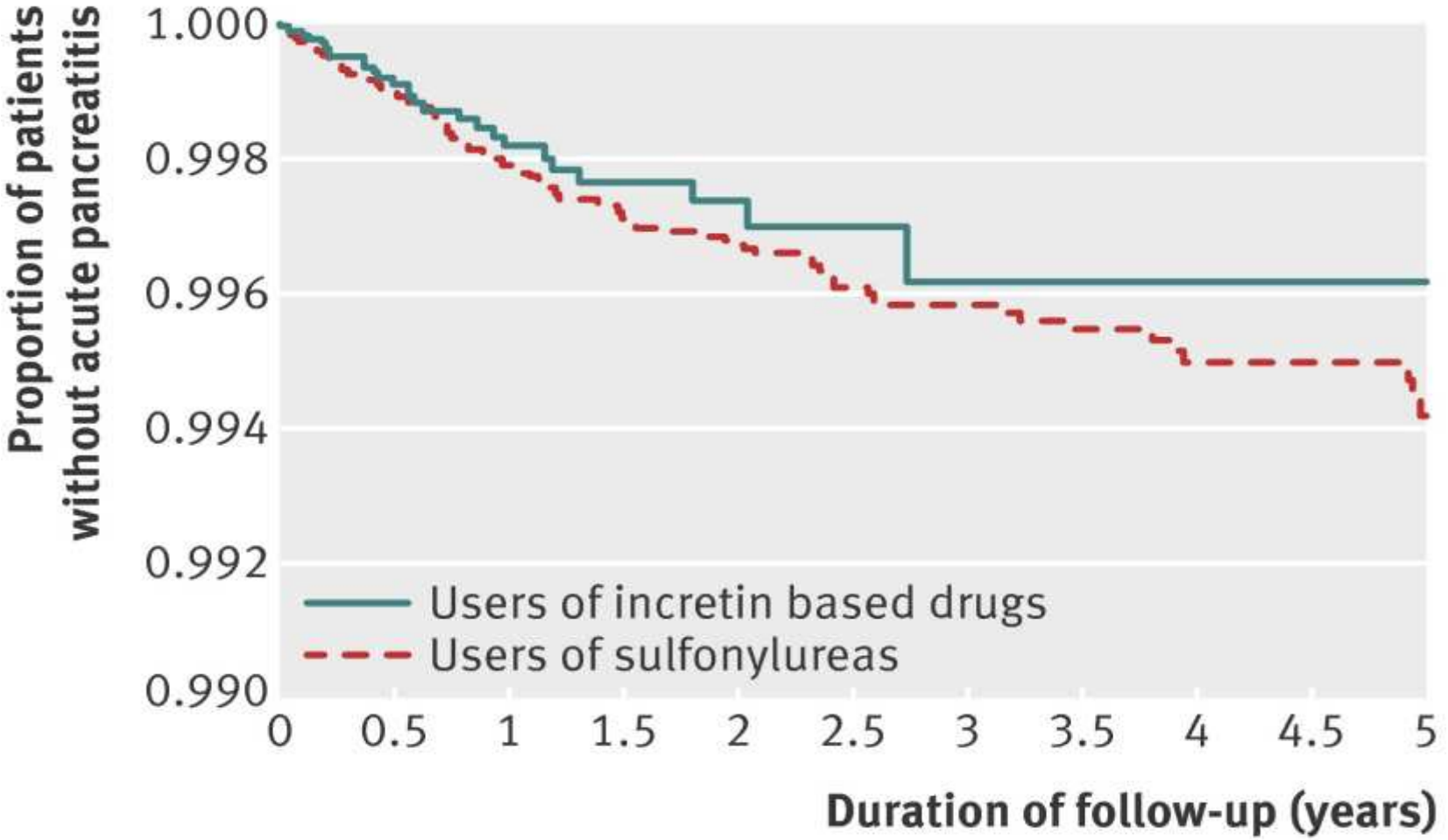
Nutrition, the gut microbiome and the metabolic syndrome



Interaction between diet and gut microbiota affects host metabolism
. Dietary manipulation with probiotics and prebiotics alters the composition and metabolic capacity of gut microbiota
. Dietary manipulation in obesity with prebiotics and probiotics

Best Practice & Research Clinical Gastroenterology, Volume 27, Issue 1, 2013, 59 - 72

Kaplan-Meier curves for acute pancreatitis in users of incretins compared with users of sulfonylurea (log rank P=0.36)



BMJ. 2014; 348: g2780.

Una revisione sistematica condotta dal centro di Evidence-Based Medicine dell'Università cinese di Sichuan esclude che l'impiego di incretine nei pazienti con diabete mellito di tipo 2 aumenti il rischio di pancreatite. A questa conclusione i ricercatori sono giunti dopo aver selezionato dalla letteratura scientifica 60 studi controllati con placebo, modificazione dello stile di vita o altri farmaci ipoglicemizzanti che avevano coinvolto nel complesso 353.639 pazienti.
In particolare, dai 55 studi randomizzati (33.350 pazienti, 37 casi di pancreatite, tasso grezzo 0,11%) emerge un'incidenza di pancreatite simile a quella dei gruppi di controllo (odds ratio 1,11, limiti di confidenza al 95% da 0,57 a 2,17), anche considerando separatamente gli agonisti recettoriali del peptide glucagone-simile 1 (odds ratio 1,05, limiti di confidenza al 95% da 0,37 a 2,94) o gli inibitori della dipeptidil-peptidasi 4 (odds ratio 1,06, limiti di confidenza al 95% da 0,46 a 2,45). Non si osservano differenze significative neppure nelle analisi per sottogruppi in funzione delle modalità di controllo metabolico, durata del trattamento, singolo farmaco.
Tra i 5 studi osservazionali (320.289 pazienti), i 3 studi retrospettivi di coorte (1.466 casi di pancreatite, tasso grezzo 0,47%) non evidenziano un aumento del rischio di pancreatite sia con exenatide (in uno studio odds ratio 0,93, limiti di confidenza al 95% da 0,63 a 1,36; in un altro studio odds ratio 0,9, limiti di confidenza al 95% da 0,6 a 1,5) o con sitagliptin (hazard ratio 1, limiti di confidenza al 95% da 0,7 a 1,3); mentre i 2 studi caso controllo fornidscono risultati discordanti: il primo (1.003 casi con pancreatite *vs* 4.012 casi di controllo) conferma l'assenza di un'associazione (odds ratio 0,98, limiti di confidenza al 95% da 0,69 a 1,38); l'altro (1.269 casi con pancreatite e altrettanti di controllo) individua un aumento del rischio di pancreatite acuta con l'assunzione per almeno 2 anni di exenatide o sitagliptin (odds ratio 2,07, limiti di confidenza al 95% da 1,36 a 3,13).
A parte uno studio osservazionale, i dati disponibili non individuano un'associazione tra uso di incretine e aumento dell'incidenza di pancreatite.
Li L, Shen J, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. BMJ. 2014;348:g2366. doi: 10.1136/bmj.g2366

Aggiornamento dei Piani Terapeutici per le Incretine e simili (09/12/2013)

Farmaci sottoposti a monitoraggio

Agenzia Italiana del Farmaco
AIFA

L'Agenzia Italiana del Farmaco comunica che sono disponibili le nuove Determinazioni AIFA per singolo *principio attivo* e medicinale per la classe delle Incretine e simili (aggiornamento del 9 dicembre 2013).
Si ricorda che il Piano Terapeutico pubblicato in forma di allegato cartaceo alla Determinazione in GU, nelle more della definizione del PT web-based, è da compilarsi ai fini della rimborsabilità a cura dei Centri specializzati, Universitari o delle Aziende Sanitarie, individuati dalle Regioni e dalle Province autonome di Trento e Bolzano, da rinnovarsi semestralmente e consegnare al paziente in formato cartaceo.

PIANO TERAPEUTICO

per prescrizione di incretine/Inibitori DPP-4 nel trattamento del DM 2 da compilarsi, ai fini della rimborsabilità, a cura delle strutture diabetologiche ospedaliere o territoriali del SSN o convenzionate con il SSN (da rinnovarsi semestralmente)

The potential for renoprotection with incretin-based drugs.

Tanaka T, Higashijima Y, Wada T, Nangaku M

Incretin-based drugs, i.e., glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, are widely used for the treatment of type 2 diabetes. In addition to the primary role of incretins in stimulating insulin secretion from pancreatic β-cells, they have extra pancreatic functions beyond glycemic control. Indeed, recent studies highlight the potential beneficial effects of incretin-based therapy in diabetic kidney disease (DKD). Experimental studies using various diabetic models suggest that incretins protect the vascular endothelium from injury by binding to GLP-1 receptors, thereby ameliorating oxidative stress and the local inflammatory response, which reduces albuminuria and inhibits glomerular sclerosis. In addition, there is some evidence that GLP-1 receptor agonists and DPP-4 inhibitors mediate sodium excretion and diuresis to lower blood pressure. The pleiotropic actions of DPP-4 inhibitors are ascribed primarily to their effects on GLP-1 signaling, but other substrates of DPP-4, such as brain natriuretic peptide and stromal-derived factor-1α, may have roles. In this review, we summarize recent studies of the roles of incretin-based therapy in ameliorating DKD and its complications.

Kidney Int. 2014 Jul 9.

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Short-chain fatty acid receptor and its contribution to glucagon-like peptide-1 release.

Kaji I[1], Karaki S, Kuwahara A.

BACKGROUND:
Gut microbiota affects host homeostasis and dysbiosis causes host diseases. Therefore, uncovering the sensing mechanism of bacterial metabolites such as short-chain fatty acid (SCFA) may help us to understand the host-microbiota interaction both in physiological and nonphysiological conditions.
SUMMARY:
The colonic lumen is continually exposed to many kinds of chemicals, including beneficial and harmful compounds that are produced by gut microbiota in addition to ingested nutrients. In the mammalian colon SCFAs such as acetate, propionate and butyrate are produced by bacterial fermentation and reach about 100 mM under physiological conditions. In this decade, SCFA receptor genes and their expression in the intestine have been identified as free fatty acid receptor (FFA)2 and FFA3. The FFAs are located in colonic enteroendocrine L cells producing and releasing an insulinotropic hormone, glucagon-like peptide-1 (GLP-1), and an anorectic hormone, peptide YY. Recent in vivo and in vitro studies suggest that SCFAs stimulate gut hormone secretion. Therefore, the SCFA-FFA signal is likely to be important for gut physiological functions.
KEY MESSAGE:
Colonic epithelial cells express chemical receptors that detect the luminal contents, particularly bacterial metabolites, and may be involved in the host's energy metabolism via GLP-1 release, as well as the mucosal defense system.

Digestion. 2014;89(1):31-6.

The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents.

Psichas A[1], Sleeth ML[1], Murphy KG[2], Brooks L[2], Bewick G[2], Hanyaloglu AC[3], Ghatei MA[2], Bloom SR[2], Frost G[1].

Background and Objectives:The gut hormones PYY and GLP-1 acutely suppress appetite. The short chain fatty acid (SCFA) receptor, free fatty acid receptor 2 (FFA2) is present on colonic enteroendocrine L cells, and a role has been suggested for SCFAs in appetite regulation. Here we characterise the in vitro and in vivo effects of colonic propionate on PYY and GLP-1 release in rodents, and investigate the role of FFA2 in mediating these effects using FFA2 knockout mice.Methods:We used Wistar rats, C57BL6 mice and free fatty acid receptor 2 knockout ($FFA^{-/-}$) mice on a C57BL6 background to explore the impact of the SCFA propionate on PYY and GLP-1 release. Isolated colonic crypt cultures were used to assess the effects of propionate on gut hormone release in vitro. We subsequently developed an in vivo technique to assess gut hormone release into the portal vein following colonic infusion of propionate.Results:Propionate stimulated the secretion of both PYY and GLP-1 from wild type primary murine colonic crypt cultures. This effect was significantly attenuated in cultures from $FFA2^{-/-}$ mice. Intra-colonic infusion of propionate elevated PYY and GLP-1 levels in jugular vein plasma in rats and in portal vein plasma in both rats and mice. However, propionate did not significantly stimulate gut hormone release in $FFA2^{-/-}$ mice.Conclusions:Intra-colonic administration of propionate stimulates the concurrent release of both GLP-1 and PYY in rats and mice. These data demonstrate that FFA2 deficiency impairs SCFA-induced gut hormone secretion both in vitro and in vivo.

Int J Obes (Lond). 2014 Aug 11.

Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal.

Cani PD[1], Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, De Backer F, Neyrinck AM, Delzenne NM.

BACKGROUND:
We have previously shown that gut microbial fermentation of prebiotics promotes satiety and lowers hunger and energy intake in humans. In rodents, these effects are associated with an increase in plasma gut peptide concentrations, which are involved in appetite regulation and glucose homeostasis.
OBJECTIVE:
Our aim was to examine the effects of prebiotic supplementation on satiety and related hormones during a test meal for human volunteers by using a noninvasive micromethod for blood sampling to measure plasma gut peptide concentrations.
DESIGN:
This study was a randomized, double-blind, parallel, placebo-controlled trial. A total of 10 healthy adults (5 men and 5 women) were randomly assigned to groups that received either 16 g prebiotics/d or 16 g dextrin maltose/d for 2 wk. Meal tolerance tests were performed in the morning to measure the following: hydrogen breath test, satiety, glucose homeostasis, and related hormone response.
RESULTS:
We show that the prebiotic treatment increased breath-hydrogen excretion (a marker of gut microbiota fermentation) by approximately 3-fold and lowered hunger rates. Prebiotics increased plasma glucagon-like peptide 1 and peptide YY concentrations, whereas postprandial plasma glucose responses decreased after the standardized meal. The areas under the curve for plasma glucagon-like peptide 1 and breath-hydrogen excretion measured after the meal (0-60 min) were significantly correlated ($r = 0.85$, $P = 0.007$). The glucose response was inversely correlated with the breath-hydrogen excretion areas under the curve (0-180 min; $r = -0.73$, $P = 0.02$).
CONCLUSION:
Prebiotic supplementation was associated with an increase in plasma gut peptide concentrations (glucagon-like peptide 1 and peptide YY), which may contribute in part to changes in appetite sensation and glucose excursion responses after a meal in healthy subjects.

Am J Clin Nutr. 2009 Nov;90(5):1236-43

Gut microbiota, enteroendocrine functions and metabolism.

Cani PD[1], Everard A, Duparc T.

The gut microbiota affects host metabolism through a number of physiological processes. **Emerging evidence suggests that gut microbes interact with the host through several pathways involving enteroendocrine cells (e.g. L cells).** The activation of specific G protein coupled receptors expressed on L cells (e.g. GPR41, GPR43, GPR119 and TGR5) triggers the secretion of glucagon-like peptides (GLP-1 and GLP-2) and PYY. These gut peptides are known to control energy homeostasis, glucose metabolism, gut barrier function and metabolic inflammation.
Here, we explore how crosstalk between **the ligands produced by the gut microbiota (short chain fatty acids, or SCFAs), or produced by the host but influenced by gut microbes (endocannabinoids and bile acids), impact host physiology.**

Curr Opin Pharmacol. 2013 Dec;13(6):935-40

Copenhagen, Copenhagen, Denmark.
[3]NNF Centre for Basic Metabolic Research, Panum Institute, University of Copenhagen, Copenhagen, Denmark; Department of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.
Abstract
Bariatric surgery is the most effective treatment for obesity and also greatly improves glycaemic control, often within days after surgery, independently of weight loss. Laparoscopic adjustable gastric banding (LAGB) was designed as a purely restrictive procedure, whereas vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) induce changes in appetite through regulation of gut hormones, resulting in decreased hunger and increased satiation. Thus, VSG and RYBG more frequently result in remission of type 2 diabetes than does LAGB. With all three of these procedures, remission of diabetes is associated with early increases in insulin sensitivity in the liver and later in peripheral tissues; VSG and RYBG are also associated with improved insulin secretion and an exaggerated postprandial rise in glucagon-like peptide 1. The vagal pathway could have a role in the neurohumoral regulatory pathways that control appetite and glucose metabolism after bariatric surgery. Recent research suggests that changes in bile acid concentrations in the blood and altered intestinal microbiota might contribute to metabolic changes after surgery, but the mechanisms are unclear. In this Series paper, we explore the possible mechanisms underlying the effects on glucose metabolism and bodyweight of LAGB, VSG, and RYGB surgery. Elucidation of these mechanisms is providing knowledge about bodyweight regulation and the pathophysiology of type 2 diabetes, and could help to identify new drug targets and improved surgical techniques.

Obesity and the Gastrointestinal Tract: You Are What You Eat.

Wolfe MM[1], Boylan MO.

Obesity represents a complex multifactorial syndrome that develops from interactions among genetic and environmental factors and is a leading cause of illness and death. The prevalence of obesity in the United States has increased dramatically since 1975. Although often ignored, the gastrointestinal tract, and the gastrointestinal regulatory peptides in particular, constitutes an ideal starting point for defining and investigating obesity as it represents the route by which all nutrients are ingested, processed, and absorbed. Another important factor to consider when evaluating the etiology of obesity is the capacity for all animals to store nutrients. Insulin is the most potent anabolic hormone, and it appears to have evolved from the need to maximize energy efficiency, obviating the requirement to continuously forage for food. Organisms expressing this important peptide possessed a distinct survival advantage and flourished. During the course of evolution, insulin biosynthesis translocated from the intestine to pancreatic islets, which necessitated a messenger from the intestine to complete the "enteroinsular axis." The eventual development of glucose-dependent insulinotropic polypeptide (GIP) and other incretins fulfilled this requirement. GIP appears to offer an additional survival benefit by not only stimulating intestinal glucose transport and maximally releasing insulin to facilitate nutrient storage but also by its insulin-mimetic properties, including enhanced uptake of glucose by adipocytes. This physiological redundancy offered by insulin and GIP ensured the survival of organisms during times when food was scarce. As food is no longer scarce, at least in the West, this survival advantage appears to have contributed to the current obesity epidemic

J Clin Gastroenterol. 2014 May 13.

Studi in corso sui farmaci antidiabetici e sugli esiti CV

	Sitagliptina	Saxagliptina	Linagliptina	Liraglutide	Exenatide QW	Lixisenatide
Nome dello studio	TECOS	SAVOR-TIMI 53	CAROLINA	LEADER	EXSCEL	ELIXA
Bracci con funzione di comparatori di riferimento	Sitagliptina vs. placebo	Saxagliptina vs. placebo	Linagliptina vs. glimepiride	Liraglutide vs. placebo	Exenatide vs. placebo	Lixisenatide vs. placebo
Coorte di pazienti	DMT2 + storia di malattia CV	DMT2 + malattia CV o fattori di rischio multipli	DMT2 + malattia CV o ≥ 2 fattori di rischio	DMT2 + pre-gressa malattia CV o età oltre 60 anni e fattori di rischio	DMT2 in tratta-mento stabile + ≤ 3 OAD per ≥ 3 mesi	DMT2 con sindrome coronarica acuta
Dimensioni dello studio	~14,000	~16,500	~6000	8723	~9500	~9600
Endpoint primario	Morte CV, IM non fatale, attacco ischemico non fatale o ospedalizzazione per angina instabile	Morte CV, IM non fatale o attacco ischemico non fatale	Morte CV, IM non fatale, ictus non fatale o ospedalizzazione per angina instabile	Morte CV, IM non fatale o ictus non fatale	Morte CV, IM non fatale o ictus non fatale	Morte CV, IM non fatale o ictus non fatale
Durata (anni)	≤ 5	~5	~7.5	≤ 5	~5.5	~6.5
Completamen-to previsto per	2014	2013	2018	2016	2017	2014

PRINCIPALI CARATTERISTICHE DEI DPP4

- **BUONA EFFICACIA (HbA1c, FPG,PPG)**

Numerosi trial clinici randomizzati dimostrano che, in aggiunta a metformina, pioglitazone, sulfoniluree, repaglinide, inibitori del DPP-4 (gliptine), agonisti del recettore del GLP-1 e inibitori del SGLT-2 (gliflozine) hanno una simile efficacia nel ridurre l'emoglobina glicata

- **BUONA TOLLERABILITA'**
- **NO AUMENTO DI PESO**
- **NO IPOGLICEMIE**
- **MIGLIORAMENTO DELLA FUNZIONE BETA CELLULARE**

Standard di cura del Diabete SID AMD 2014

Summary

- GLP-1 insulin secretion and glucagon secretion in glucose dependent manner
- GLP-1 appetite and gastric emptying
- GLP-1 Analogs provide long-acting GLP-1 activity
- Reduce blood glucose and promote weight loss
- Reduce SBP and improve lipid profile
- May reduce CV risk profiles and events
- DPP4 Inhibitors prolong activity of native GLP-1
- Reduce blood glucose and are weight neutral
- GLP-1 Analogs and DPP4 Inhibitors are effective alone, in combination with Oral Agents or with Insulin

Nat Rev Nephrol. 2014

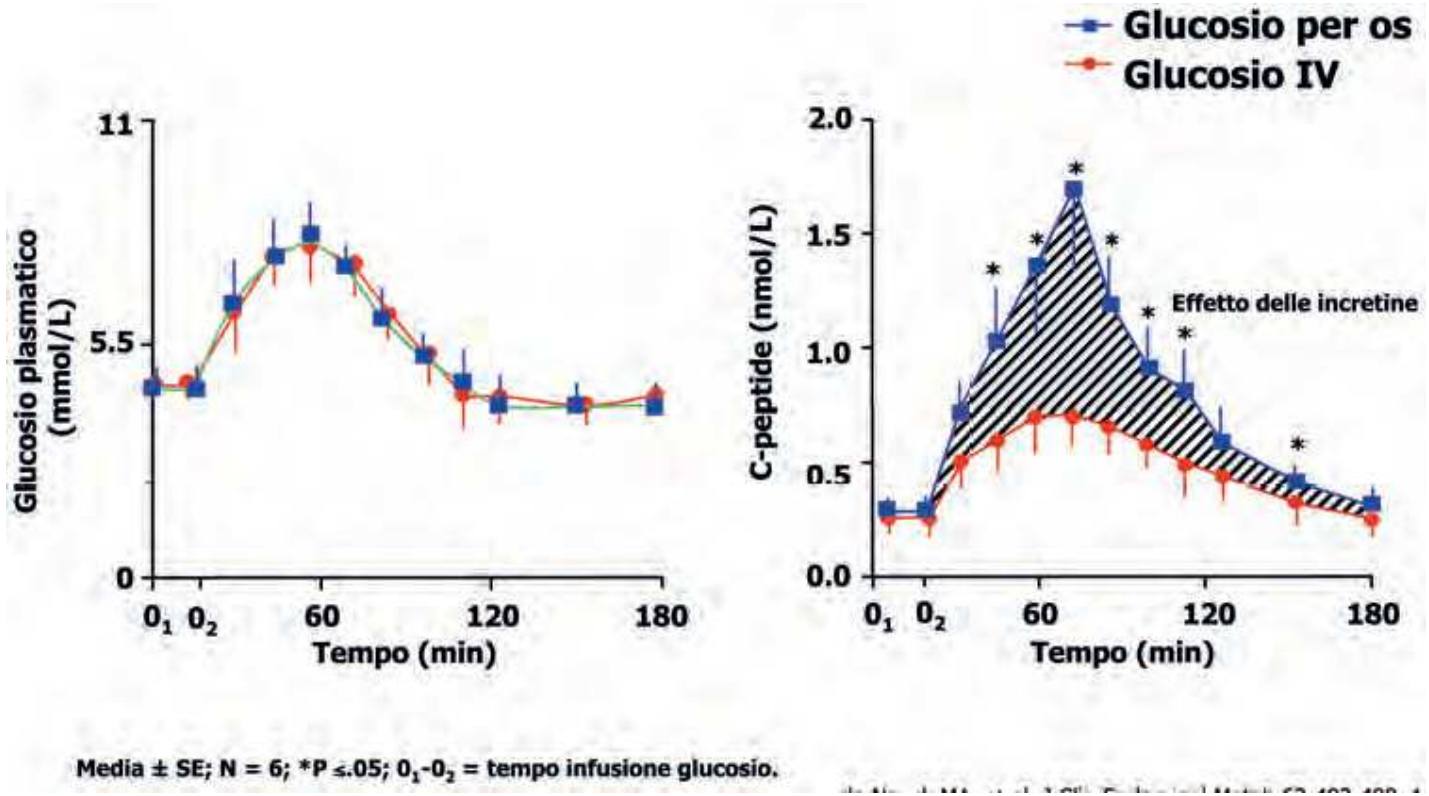
The gut-renal axis: do incretin-based agents confer renoprotection in diabetes?

Muskiet MH, Smits MM, Morsink LM, Diamant M

Diabetic nephropathy is the leading cause of end-stage renal disease worldwide, and is associated with a high risk of cardiovascular morbidity and mortality. Intensive control of glucose levels and blood pressure is currently the mainstay of both prevention and treatment of diabetic nephropathy. However, this strategy cannot fully prevent the development and progression of diabetic nephropathy, and an unmet need remains for additional novel therapies. The incretin-based agents--agonists of glucagon-like peptide 1 receptor (GLP-1R) and inhibitors of dipeptidyl peptidase 4 (DPP-4), an enzyme that degrades glucagon-like peptide 1--are novel blood-glucose-lowering drugs used in the treatment of type 2 diabetes mellitus (T2DM). Therapeutic agents from these two drug classes improve pancreatic islet function and induce extrapancreatic effects that ameliorate various phenotypic defects of T2DM that are beyond glucose control. Agonists of GLP-1R and inhibitors of DPP-4 reduce blood pressure, dyslipidaemia and inflammation, although only GLP-1R agonists decrease body weight. Both types of incretin-based agents inhibit renal tubular sodium reabsorption and decrease glomerular pressure as well as albuminuria in rodents and humans. In rodents, incretin-based therapies also prevent onset of the morphological abnormalities of diabetic nephropathy.

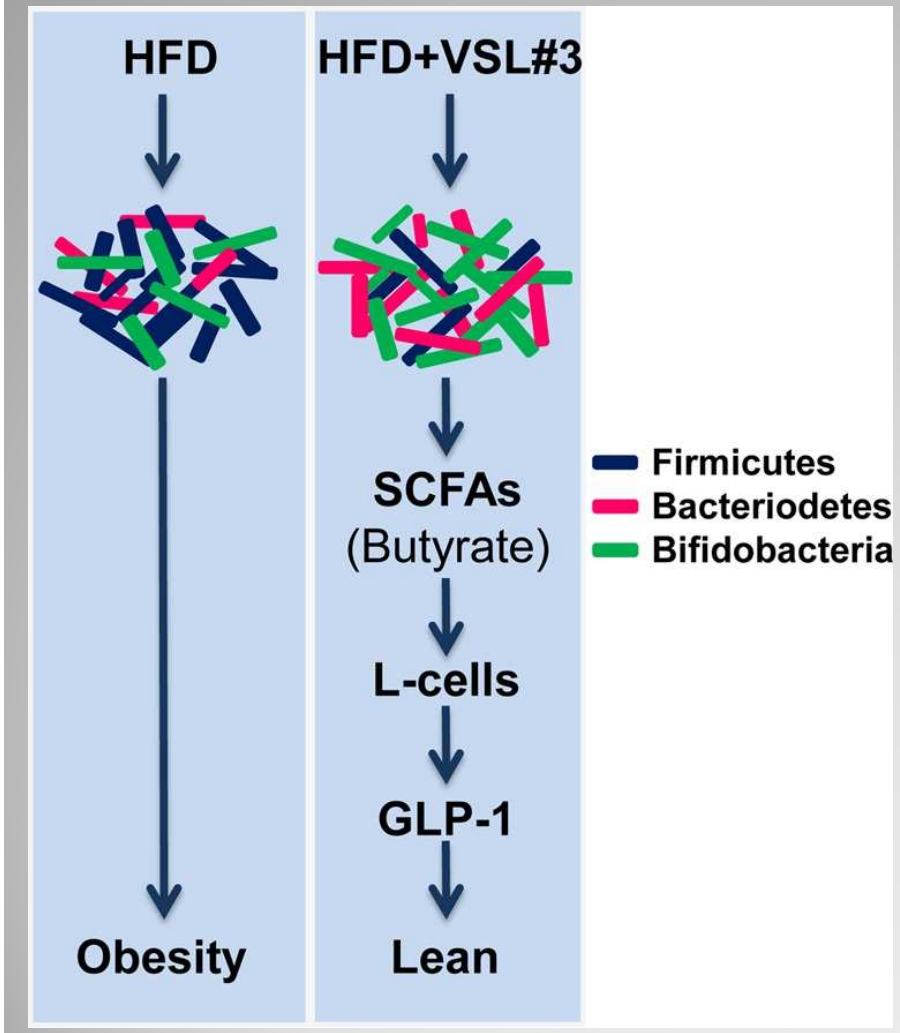
Concetto di incretina

Il concetto di incretina si sviluppa a partire dagli anni trenta del secolo scorso e definisce l'insieme di quelle sostanze, successivamente identificate come ormoni, responsabili del fenomeno per cui la risposta della secrezione di insulina ad una dose standard di glucosio è significativamente superiore se lo stesso glucosio viene somministrato per via orale rispetto alla via endovenosa.



La secrezione insulinica in risposta a carico di glucosio è maggiore quando tale carico è effettuato per via orale rispetto a quando è effettuato per via endovenosa.
Il grafico sulla sinistra mostra come i livelli di glicemia nel plasma in seguito a carico di glucosio effettuato per via orale (linea blu) o per via endovenosa (linea rossa) aumentino in modo assolutamente sovrapponibile; al contrario il grafico sulla destra mostra come le concentrazioni plasmatiche di C-peptide siano significativamente più alte a tutti i tempi esaminati se il carico avviene per via orale (linea blu) rispetto a quando il glucosio viene iniettato endovena (linea rossa).
La differenza tra le due curve, evidenziata dall'area tratteggiata, viene attribuita all'effetto delle incretine

Perley M, et al. J Clin Invest1967; 46:1954-1962



Proposed mechanism of action of VSL#3 against obesity and diabetes

J Biol Chem. 2013 Aug 30;288(35):25088-97.
Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. Yadav H

The potential for renoprotection with incretin-based drugs.

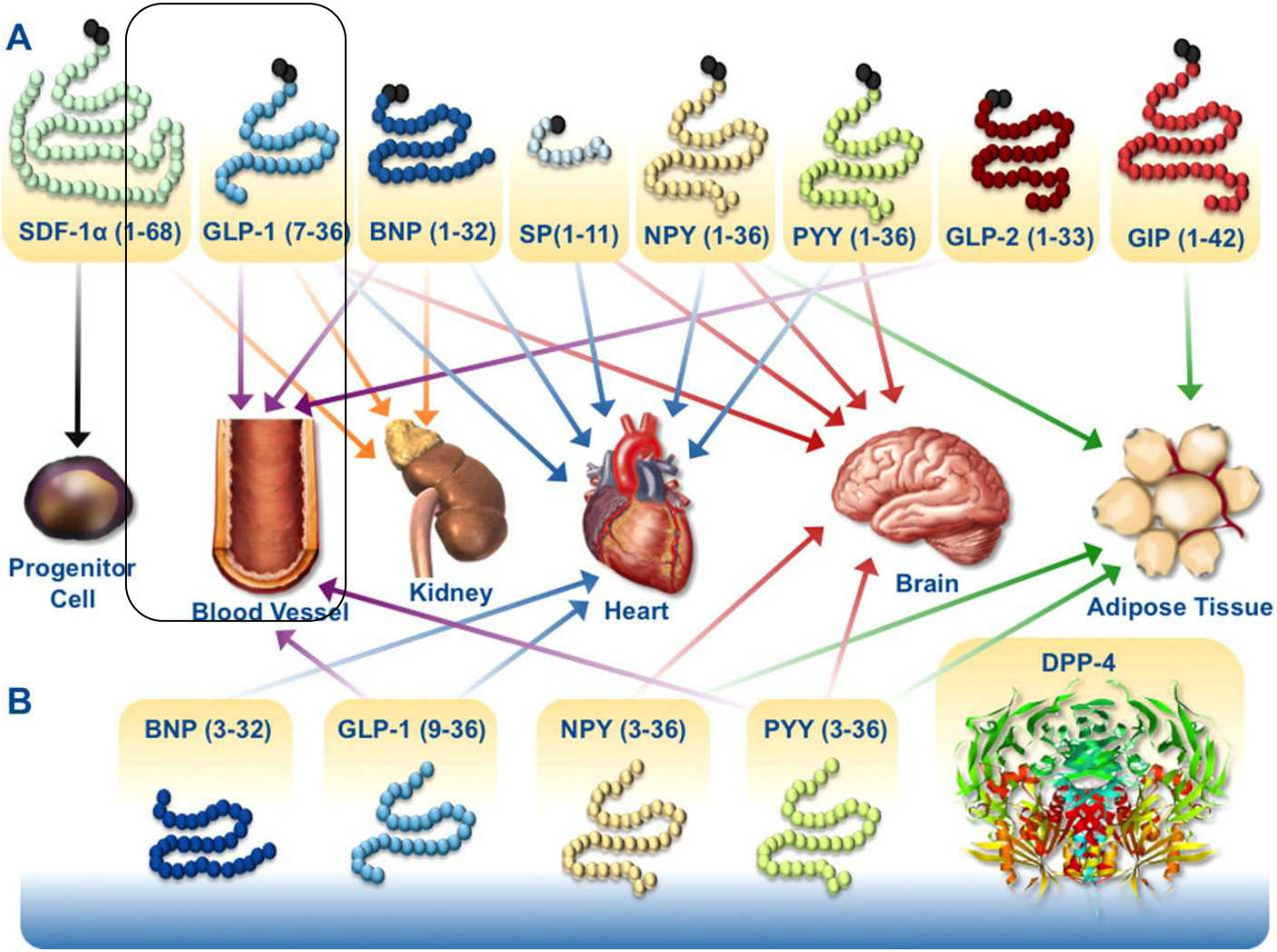
Tanaka T, Higashijima Y, Wada T, Nangaku M

Incretin-based drugs, i.e., glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, are widely used for the treatment of type 2 diabetes. In addition to the primary role of incretins in stimulating insulin secretion from pancreatic β-cells, they have extra pancreatic functions beyond glycemic control. Indeed, recent studies highlight the potential beneficial effects of incretin-based therapy in diabetic kidney disease (DKD). Experimental studies using various diabetic models suggest **that incretins protect the vascular endothelium from injury by binding to GLP-1 receptors, thereby ameliorating oxidative stress and the local inflammatory response, which reduces albuminuria and inhibits glomerular sclerosis.** In addition, there is some evidence that GLP-1 receptor agonists and DPP-4 inhibitors mediate sodium excretion and diuresis to lower blood pressure. The pleiotropic actions of DPP-4 inhibitors are ascribed primarily to their effects on GLP-1 signaling, but other substrates of DPP-4, such as brain natriuretic peptide and stromal-derived factor-1α, may have roles. In this review, we summarize recent studies of the roles of incretin-based therapy in ameliorating DKD and its complications.

Kidney Int. 2014 Jul 9.

DPP-4 substrates that directly or indirectly regulate cardiovascular function.

ENDOCRINE REVIEWS

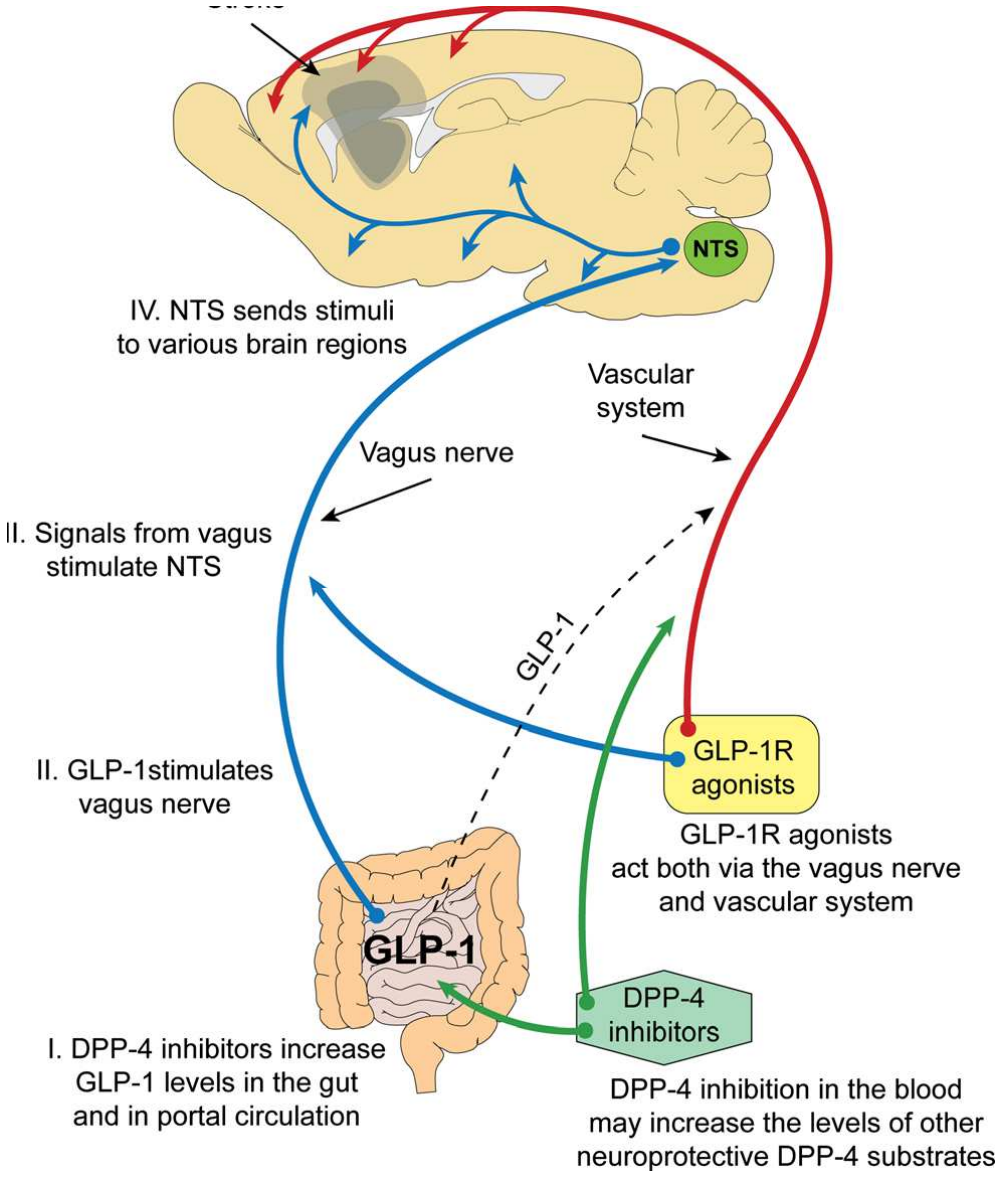


Ussher J R , Drucker D J Endocrine Reviews 2012;33:187-215

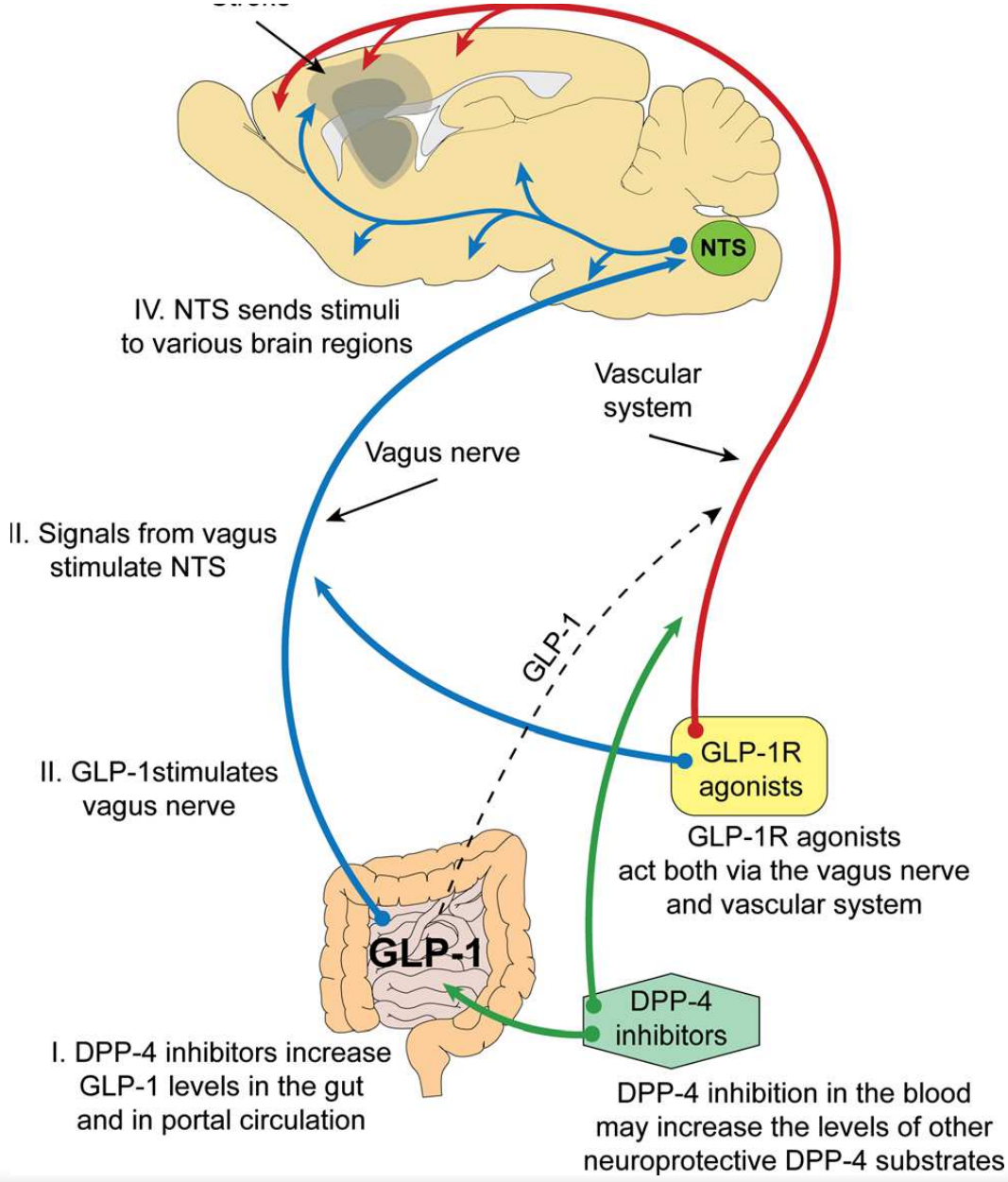
Analoghi del GLP-1 e DPP-4i a confronto

	Analoghi del GLP-1	Inibitori della DPP-4
Somministrazione	SC	OS
Concentrazione del GLP-1	farmacologica	fisiologica
Meccanismo d'azione	GLP-1	GLP-1 e GIP
Incremento della secrezione insulinica	si	si
Riduzione della secrezione di glucagone	si	si
Effetto sul peso	Riduzione	Neutro
Espansione della massa β-cellulare (dati preclinici)	si	si
Potenziale immunogenicità	si	no
Nausea e vomito	si	no

Drucker DJ *J Clin Invest 2007; 117: 24-32*



Potential neuroprotective mechanisms induced by GLP-1R agonists and DPP-4 inhibitors. GLP-1R agonists and DPP-4 inhibitors may have a variety of targets in the brain including neuronal cells, different glia cells and neural stem cells. Evidence is accumulating that pharmacological concentrations of GLP-1R agonists could induce both direct neuroprotection from the systemic circulation (via the bbb; red line) and indirectly by stimulating the vagus nerve that via the nucleus of the tractus solitaries (NTS) projects to the forebrain (blue line).Alternatively, increased GLP-1 levels by DPP-4 inhibitors in the intestine and in the portal vein could stimulate mainly the vagus nerve (blue line) thus inducing neuroprotection indirectly. DPP-4 inhibitors could also modulate systemically the activity of other neuroprotective factors (red line). The mechanisms of action of GLP-1R agonists and DPP-4 inhibitors are discussed in more detail in the text


NTS
IV. NTS sends stimuli
to various brain regions
Vascular
system
Vagus nerve
II. Signals from vagus
stimulate NTS
GLP-1
II. GLP-1stimulates
vagus nerve
GLP-1R
agonists
GLP-1R agonists
act both via the vagus nerve
and vascular system
GLP-1
DPP-4
inhibitors
I. DPP-4 inhibitors increase
GLP-1 levels in the gut
and in portal circulation
DPP-4 inhibition in the blood
may increase the levels of other
neuroprotective DPP-4 substrates

Do incretins improve endothelial function?. Pleiotropic effects of GLP-1.

Jun-ichi Oyama, et al. Cardiovasc Diabetol. 2014;13:21-21.