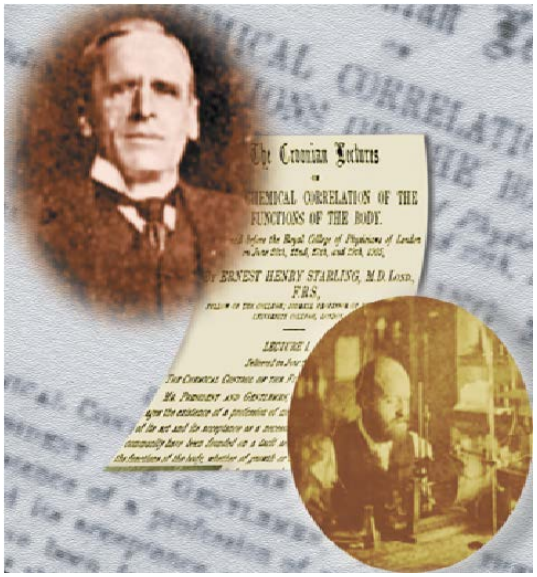
FISIOPATOLOGIA DELL'ASSE INCRETINICO: COSA C'È DI NUOVO?

Relatore

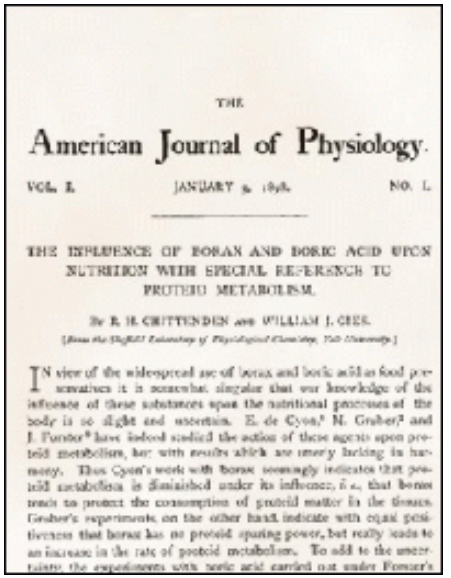
Dott.ssa Alessia D'Introno
UOC Medicina Interna
P.O. Ostuni

LE INCRETINE
Asse pancreas-intestino

Bayliss e Starling 1906



La Barre e Still 1930


THE

American Journal of Physiology.

VOL. I. JANUARY 2, 1898. NO. I.

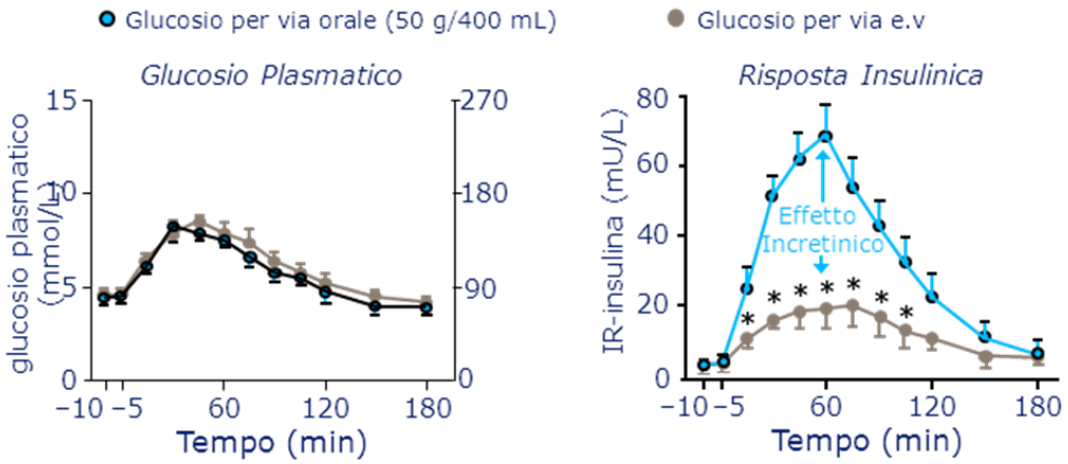
THE INFLUENCE OF BORAX AND BORIC ACID UPON NUTRITION WITH SPECIAL REFERENCE TO PROTEID METABOLISM.

By R. H. CHITTENDEN and WILLIAM J. GIES.

[From the Sheffield Laboratory of Physiological Chemistry, Yale University.]

IN view of the widespread use of borax and boric acid as food preservatives it is somewhat singular that our knowledge of the influence of these substances upon the nutritional processes of the body is so slight and uncertain. E. de Cyon,[1] N. Gruber[2] and J. Forster[3] have indeed studied the action of these agents upon proteid metabolism, but with results which are utterly lacking in harmony. Thus Cyon's work with borax seemingly indicates that proteid metabolism is diminished under its influence; i. e., that borax tends to protect the consumption of proteid matter in the tissues. Gruber's experiments, on the other hand, indicate with equal positiveness that borax has no proteid sparing power, but really leads to an increase in the rate of proteid metabolism. To add to the uncertainty, the experiments with boric acid carried out under Forster's

Elrick e McIntyre 1964



LE INCRETINE

Can J Biochem. 1971 Aug;49(8):867-72. A gastric inhibitory polypeptide. II. The complete amino acid sequence

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
PORCINE:	Tyr	- Ala	- Glu	- Gly	- Thr	- Phe	- Ile	- Ser	- Asp	- Tyr	- Ser	- Ile	- Ala	- Met
HUMAN:	.	.	.	.	.	.	.	.	.	.	.	.	.	.
BOVINE:	.	.	.	.	.	.	.	.	.	.	.	.	.	.
RODENT:	.	.	.	.	.	.	.	.	.	.	.	.	.	.

	15	16	17	18	19	20	21	22	23	24	25	26	27	28
PORCINE:	Asp	- Lys	- Ile	- Arg	- Gln	- Gln	- Asp	- Phe	- Val	- Asn	- Trp	- Leu	Leu	- Ala
HUMAN:	.	.	.	His	.	.	.	.	.	.	.	.	.	.
BOVINE:	.	.	.	.	.	.	.	.	.	.	.	.	.	.
RODENT:	.	.	.	.	.	.	.	.	.	.	.	.	.	.

	29	30	31	32	33	34	35	36	37	38	39	40	41	42
PORCINE:	Gln	- Lys	- Gly	- Lys	- Lys	- Ser	- Asp	- Trp	- Lys	- His	- Asn	- Ile	- Thr	- Gln
HUMAN:	.	.	.	.	.	Asn	.	.	.	.	.	.	.	.
BOVINE:	.	.	.	.	.	.	.	.	Ile	.	.	.	.	.
RODENT:	.	.	.	.	.	Asn	.	.	.	.	.	Leu	.	.

Glucose-dependent insulinotropic polypeptide

- **Gastric Inhibitory Peptide (GIP)**

Diabetologia (1985) 28: 704–707

Diabetologia

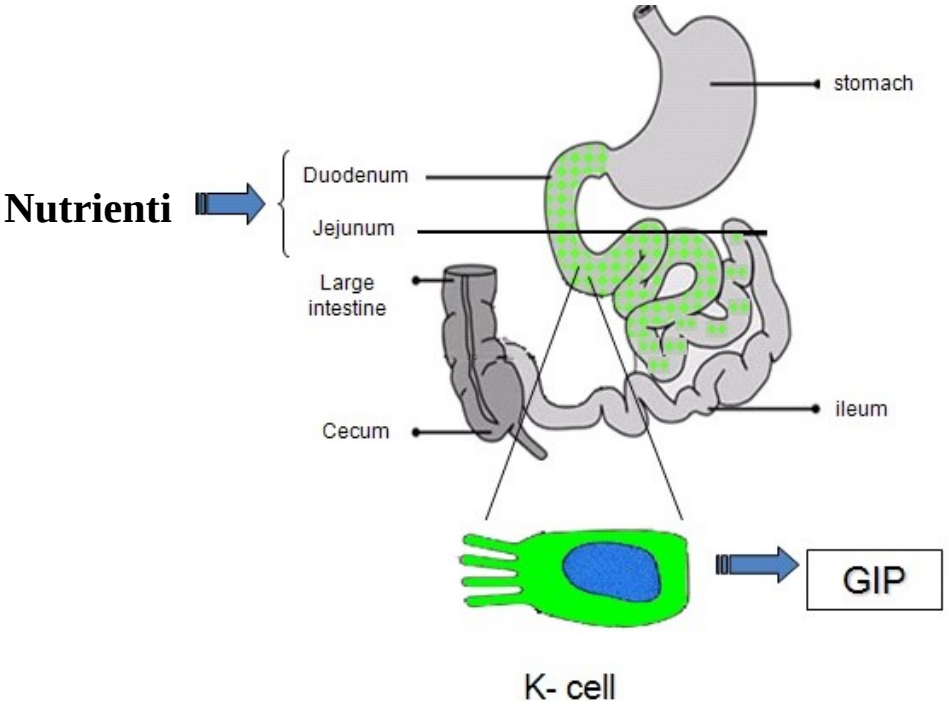
Glucagon-like peptide-1 but not glucagon-like peptide-2 stimulates insulin release from isolated rat pancreatic islets

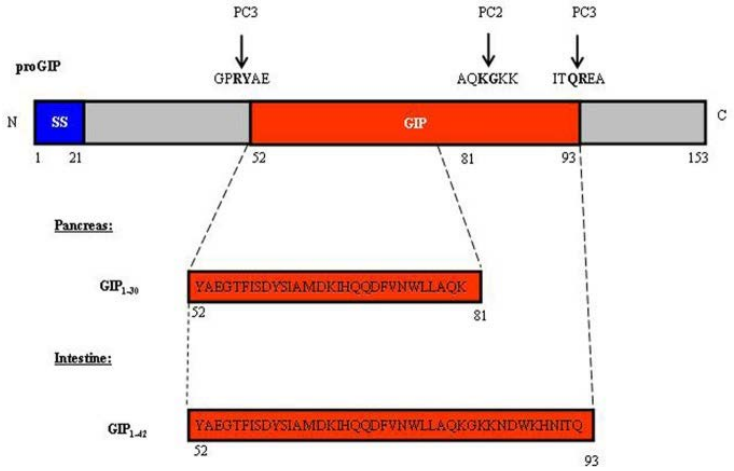
W. E. Schmidt, E. G. Siegel and W. Creutzfeldt

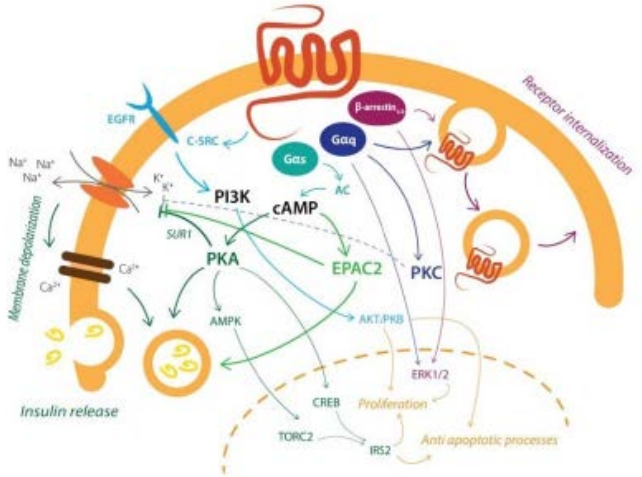
Division of Gastroenterology and Metabolism, Department of Medicine, University of Göttingen, Göttingen, FRG

Summary. Glucagon-like peptide-1 and glucagon-like peptide-2 are encoded by the m-RNA of pancreatic preproglucagon. They show high conservation in different species and substantial sequence homology to glucagon. Because no definite biological activity of these peptides has been reported, we investigated the effect of synthetic C-terminally amidated glucagon-like peptide-1 [1–36] and synthetic human glucagon-like peptide-2 [1–34] with a free C-terminus on insulin release from isolated precultured rat pancreatic islets in the presence 250 nmol/l, with approximately 100% increase over basal at both glucose concentrations. The peptide reaches 63% of the maximal stimulatory effect of glucagon. No stimulation occurs in the presence of 2.8 mmol/l glucose. Glucagon-like peptide-2 has no effect on insulin secretion at any glucose concentration tested. It is concluded that glucagon-like peptide-1, in contrast to glucagon-like peptide-2, exhibits a glucose-dependent insulinotropic action on isolated rat pancreatic islets similar to that of glucagon and gastric inhibitory

Glucose-dependent insulinotropic polypeptide (GIP)

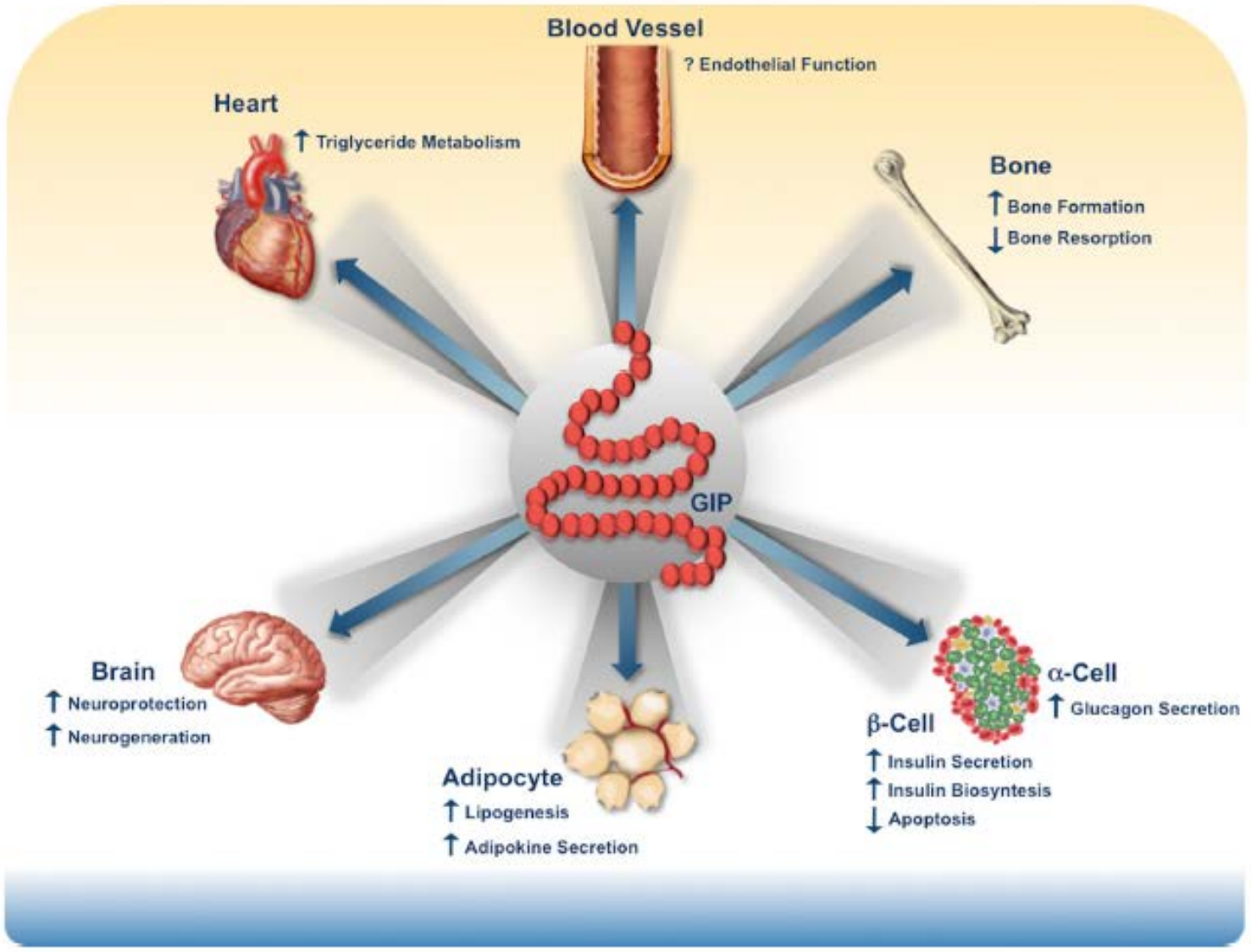






Emivita plasmatica: 4 min
Degradazione mediante clivaggio da parte della DPP-4

Effetti fisiologici del Glucose-dependent insulinotropic polypeptide (GIP)



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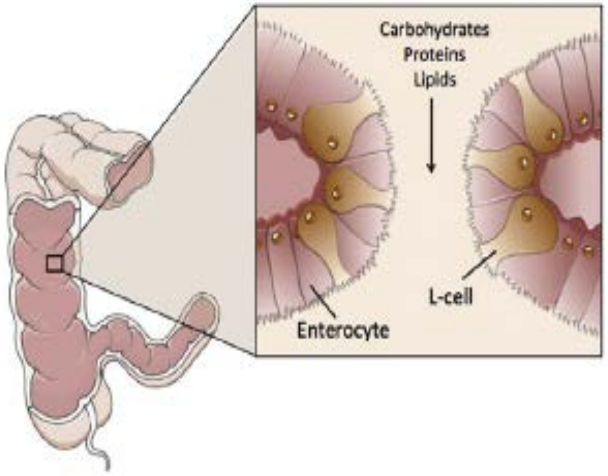
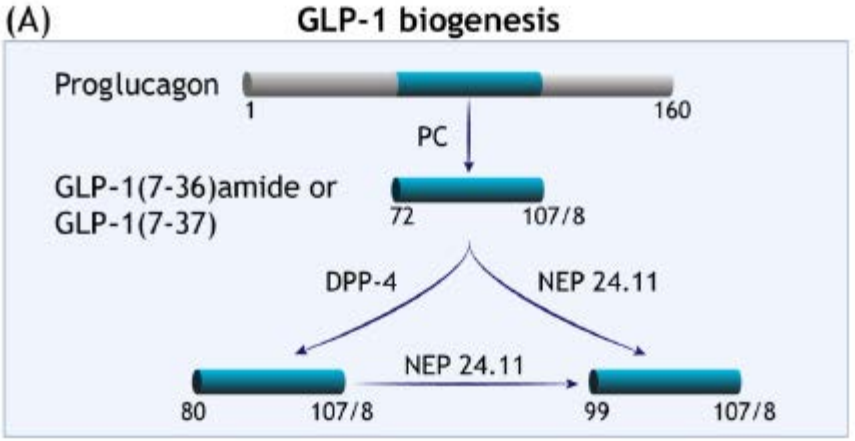
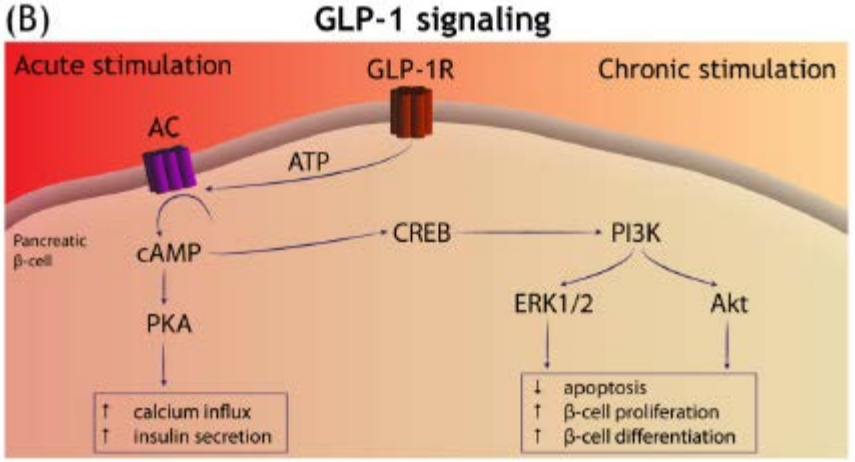
Glucagone-like peptide 1 (GLP-1)

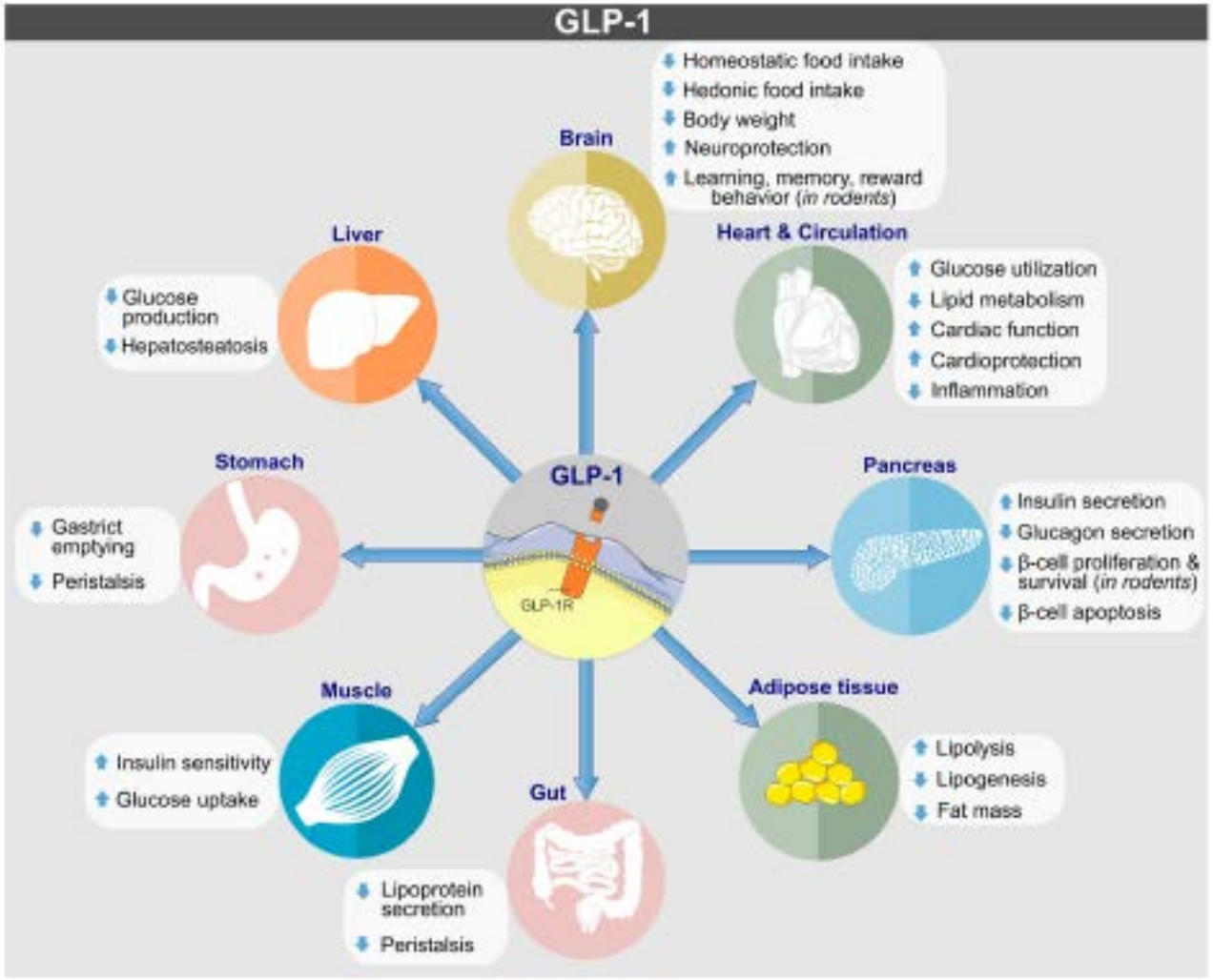






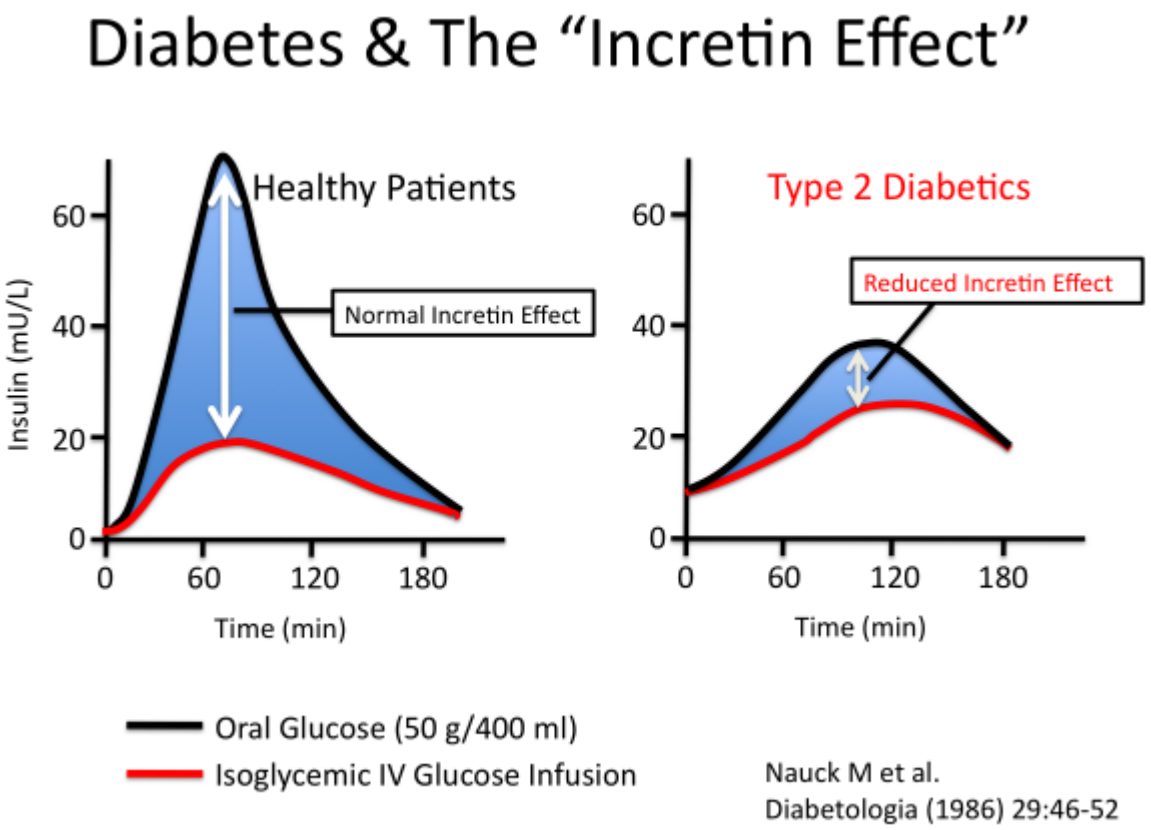
Monti et al. Cells 2022, 11, 2023

Effetti fisiologici del Glucagone-like peptide 1 (GLP-1)



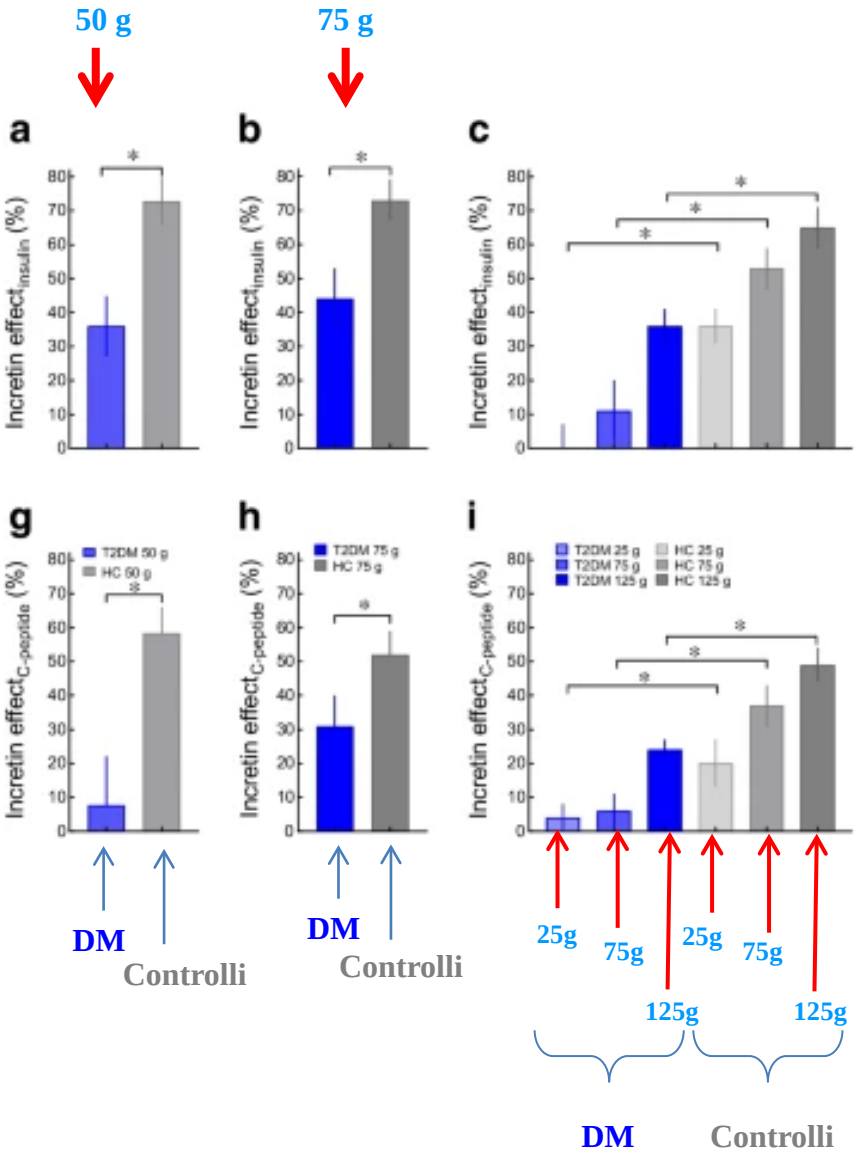
Frontiers in Endocrinol,2022:13

Effetto incretinico e diabete



Effetto incretinico e diabete

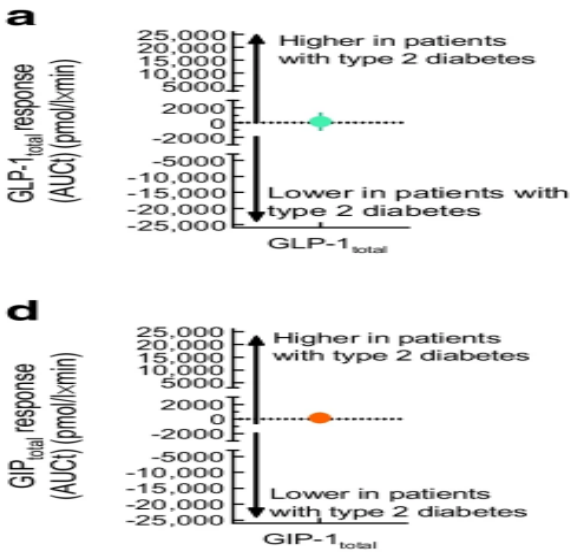
Quantificazione dell'effetto incretinico in soggetti con DM di tipo 2 e soggetti sani di controllo ottenuta mediante misurazione della secrezione di insulina (a–c) e C-peptide (g–i)



Diabetologia 2023, 66:1780-195

Potenziali spiegazioni della differente riduzione dell'attività insulinotropica di GIP e GLP-1 nel diabete di tipo 2

1. Ridotta secrezione



*Diabetologia , 2023; **66**, 1780–1795*

2. Ridotta espressione dei recettori GIP (e in minor misura di GLP-1R) sulle cellule pancreatiche in presenza di iperglicemia

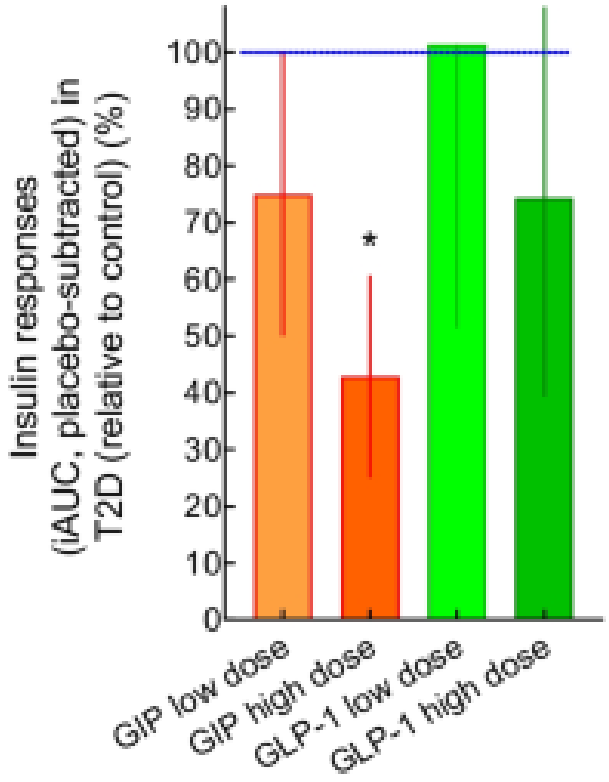
Diabetes 2007; 56:1551–1558.

3. Attivazione di differenti pattern proteici intracellulari da parte di GLP-1 e GIP

J Clin Invest,2020; 130:6639–6655.

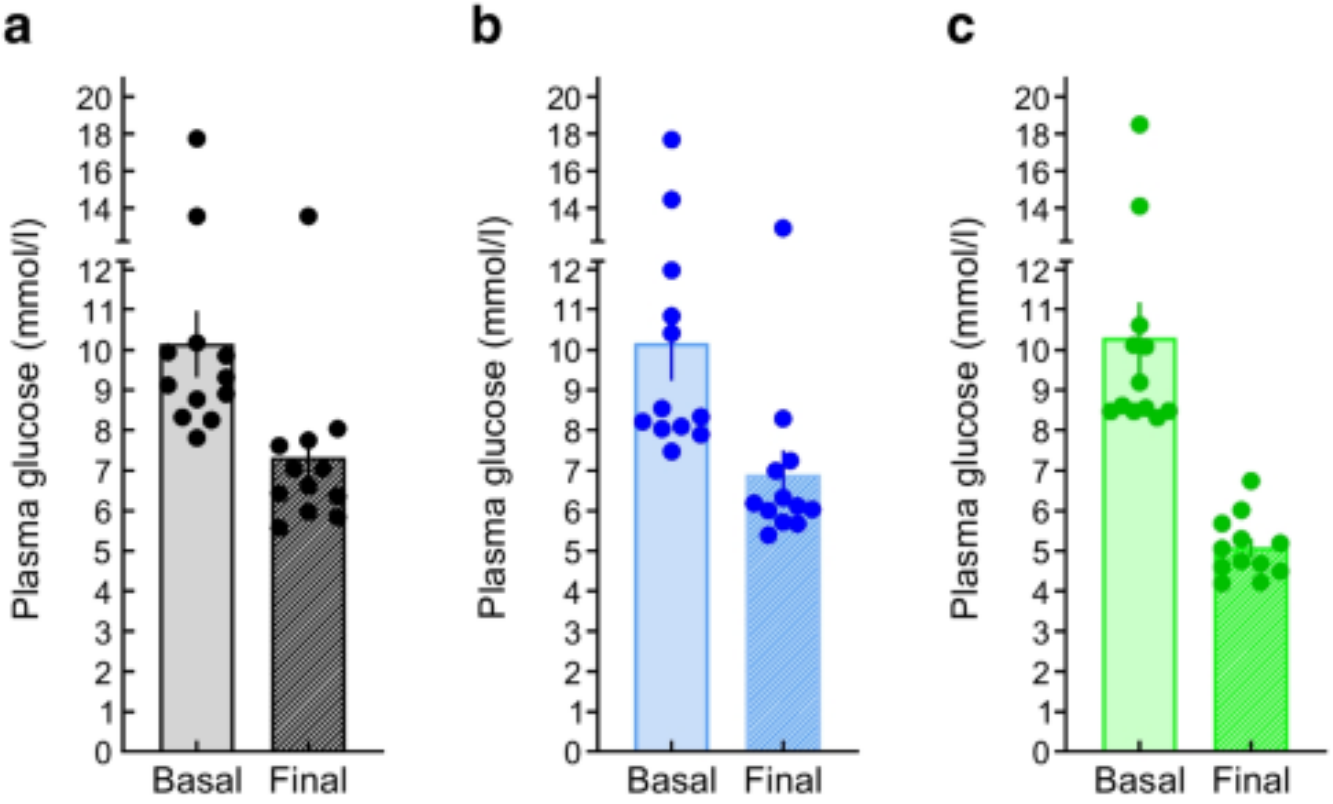
Incretine e diabete

Confronto effetto insulinotropico di GIP e GLP-1 in soggetti con DM di tipo 2 e soggetti sani di controllo il cui valore medio è stato impostato come 100%



*Diabetologia , 2023; **66**, 1780–1795*

Incretine e diabete

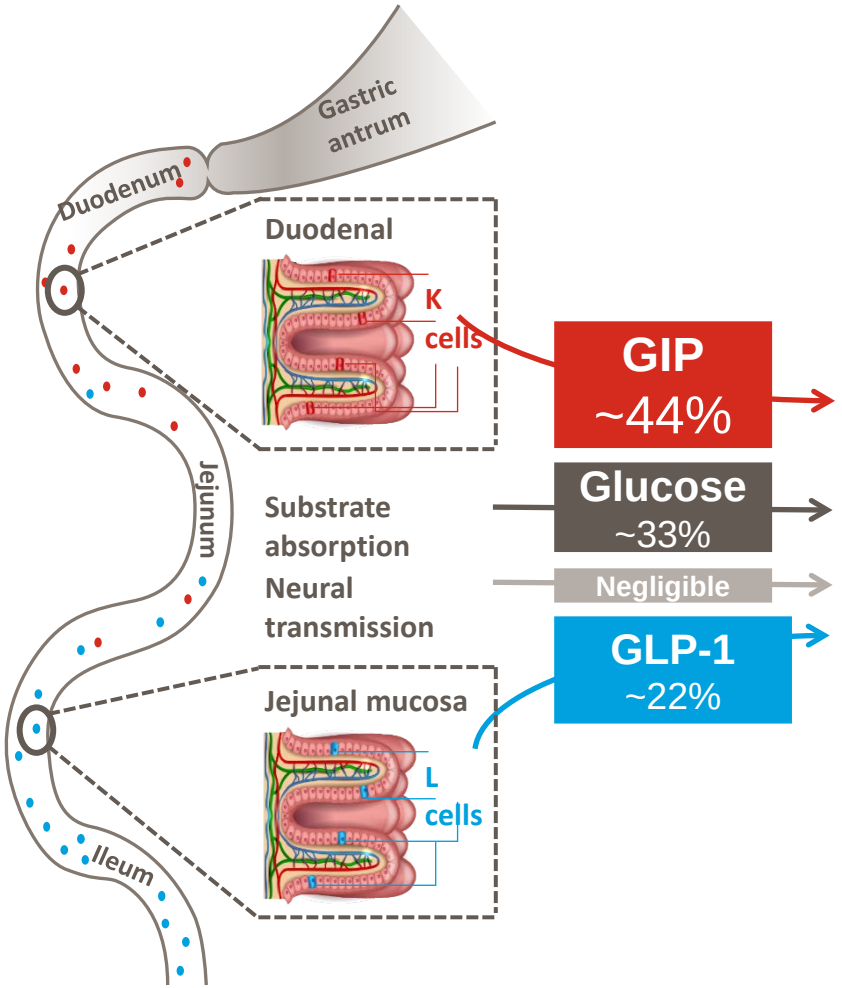


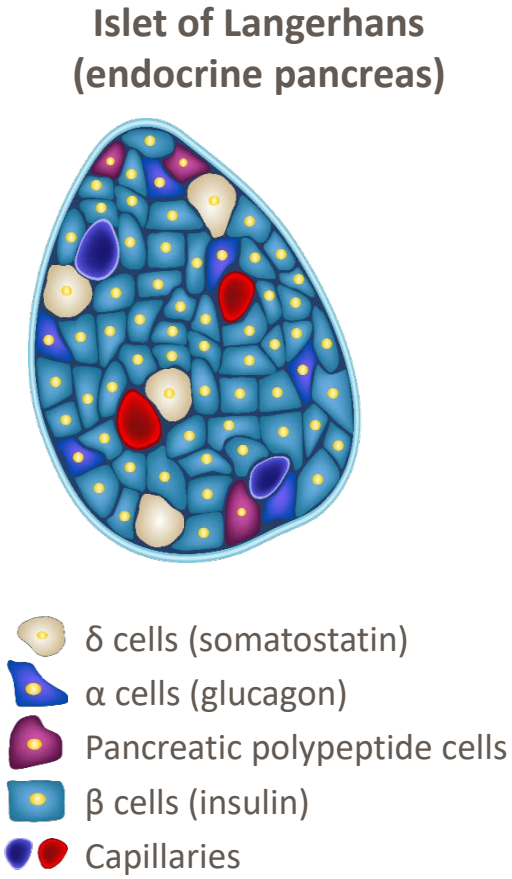
PLACEBO **GIP** **GLP-1**

*Diabetologia , 2023; **66**, 1780–1795*

L’enigma di GIP

- Nei soggetti sani GIP è responsabile del 44% della secrezione insulinica

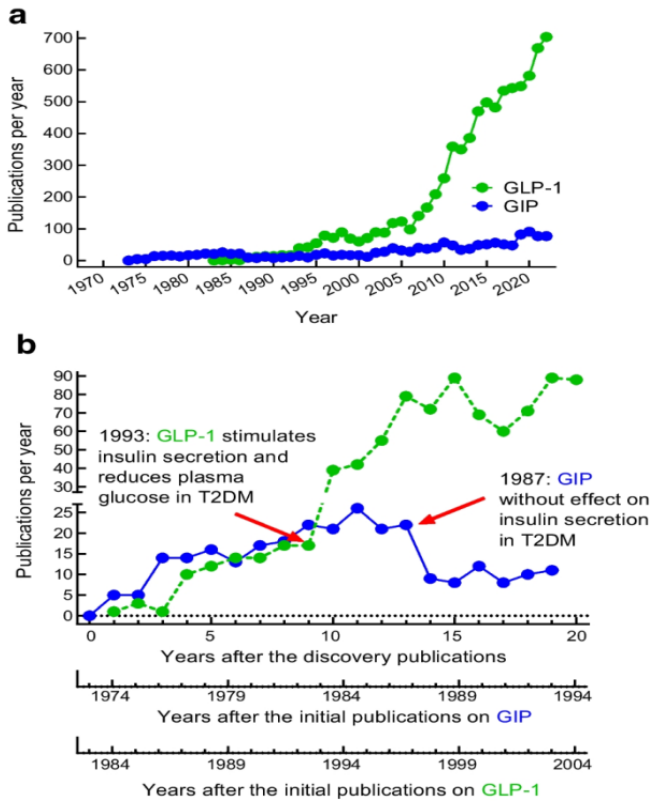




Diabetes. 2019;68(5):897-900.

L’enigma di GIP

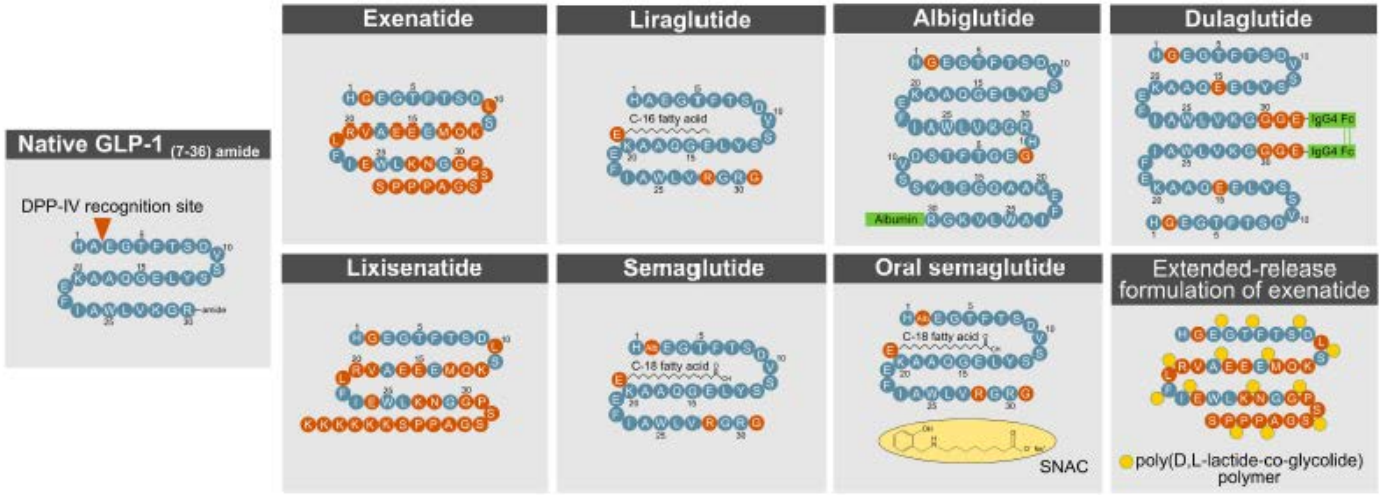
- In condizioni diabetiche è presente resistenza al GIP
- Gli effetti lipogenici di GIP promuoverebbero l’aumento del peso corporeo
- GIP stimola la secrezione di glucagone in condizioni di iperglicemia in DM tipo 2

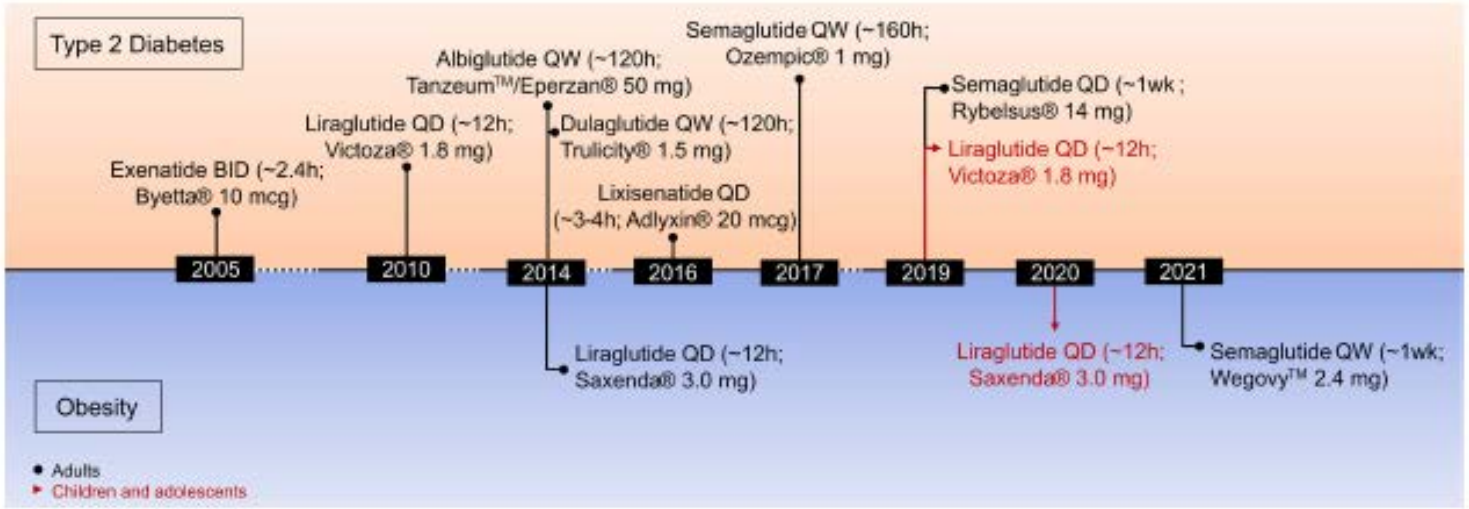


*Diabetologia , 2023; **66**, 1780–1795*

Agonisti del Recettore GLP-1

“ il vecchio”





Frontiers in Endocrinol, 2022, 13

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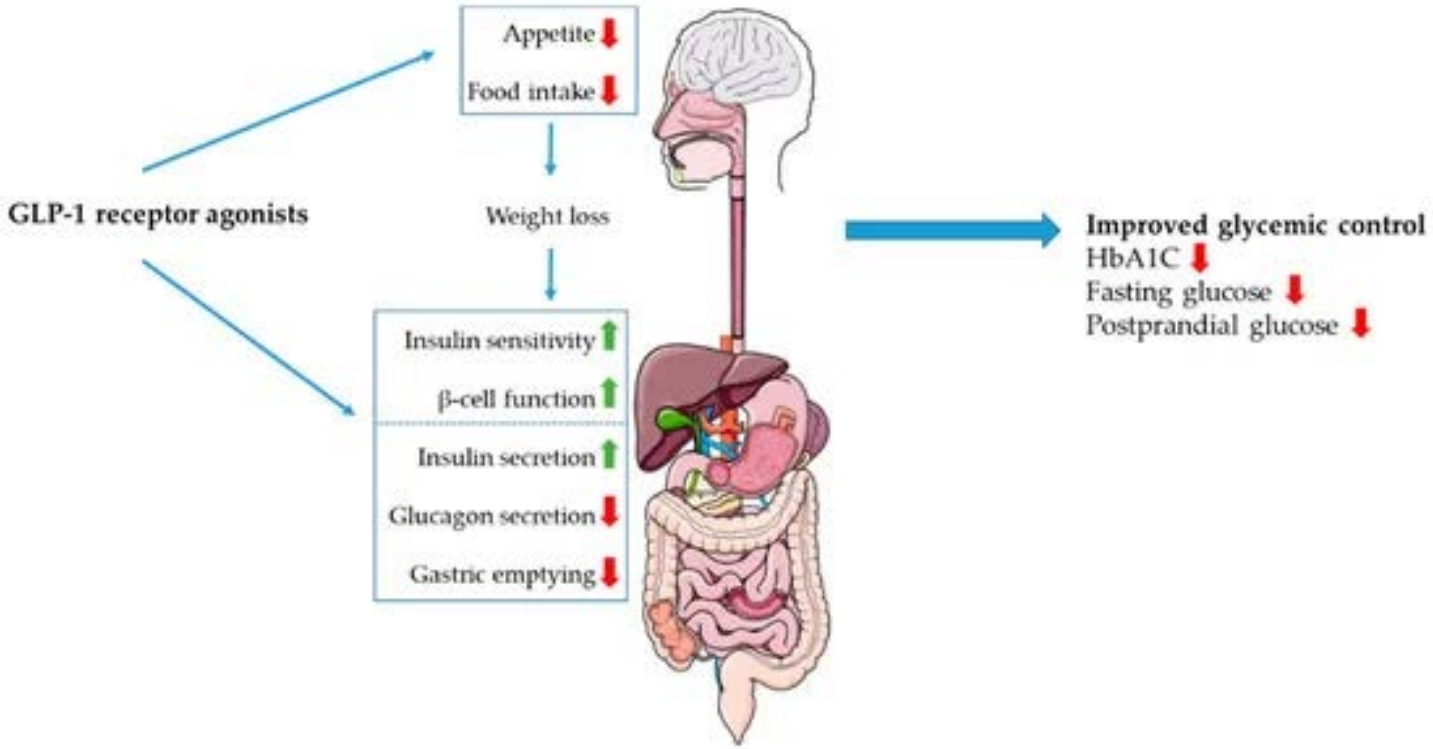

Biology 2020, 9(12), 473

Agonisti del Recettore GLP-1

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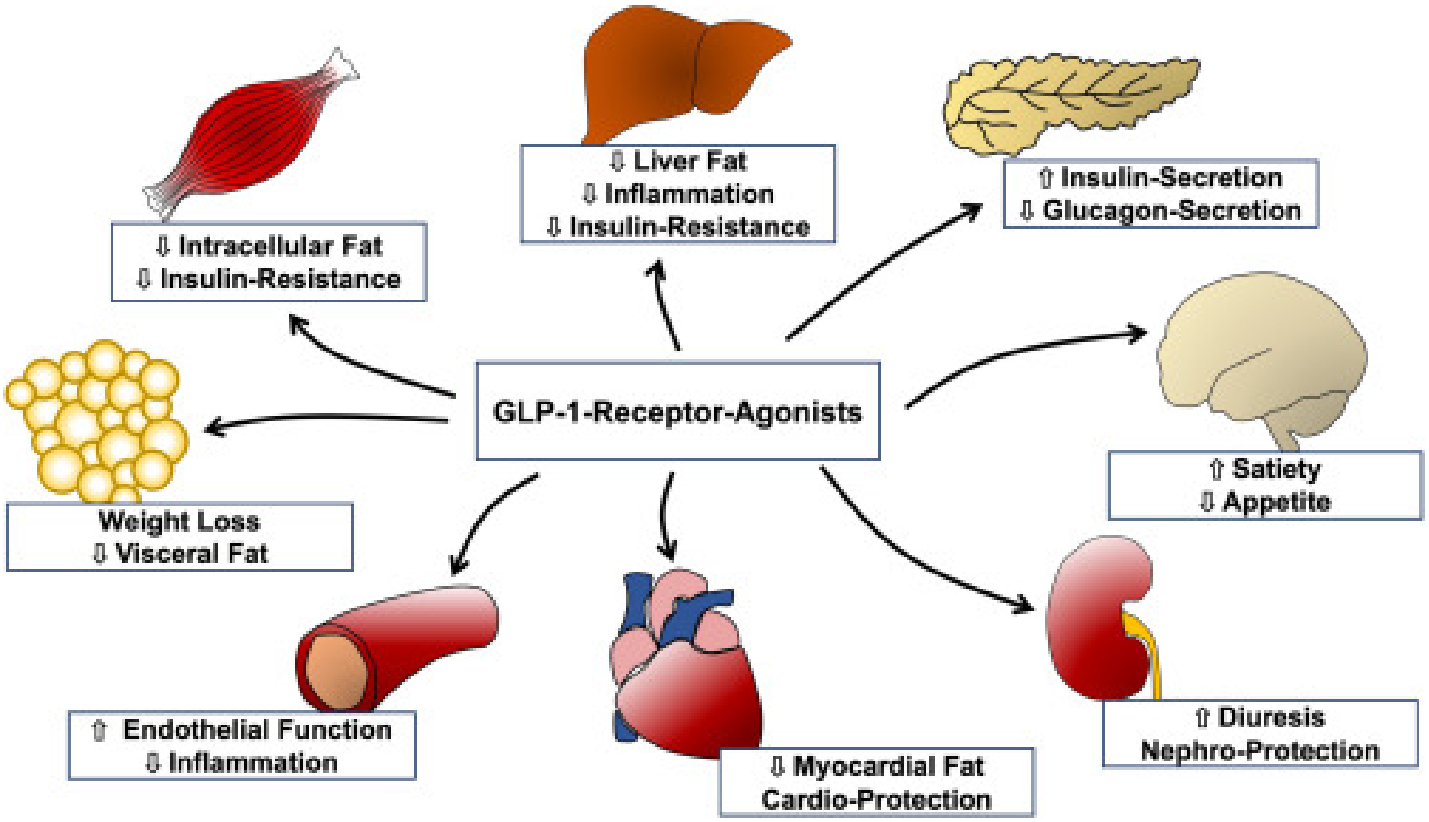
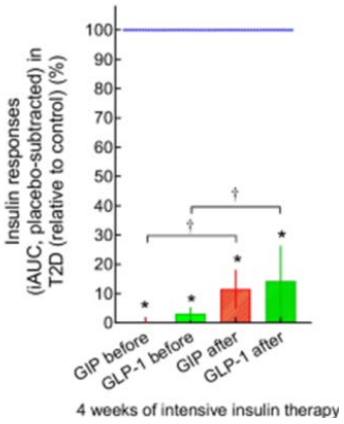


Visceral and Ectopic Fat, 2023

La rinascita di GIP

- L’effetto insulinotropico di GIP migliora dopo terapia con insulina



Diabetologia 2023, 66: 1780-1795

- GIP riduce i livelli post-pandriali di glucosio più di GLP-1

Gasbjerg, L.S. et al. (2019) Diabetes 68, 906–917

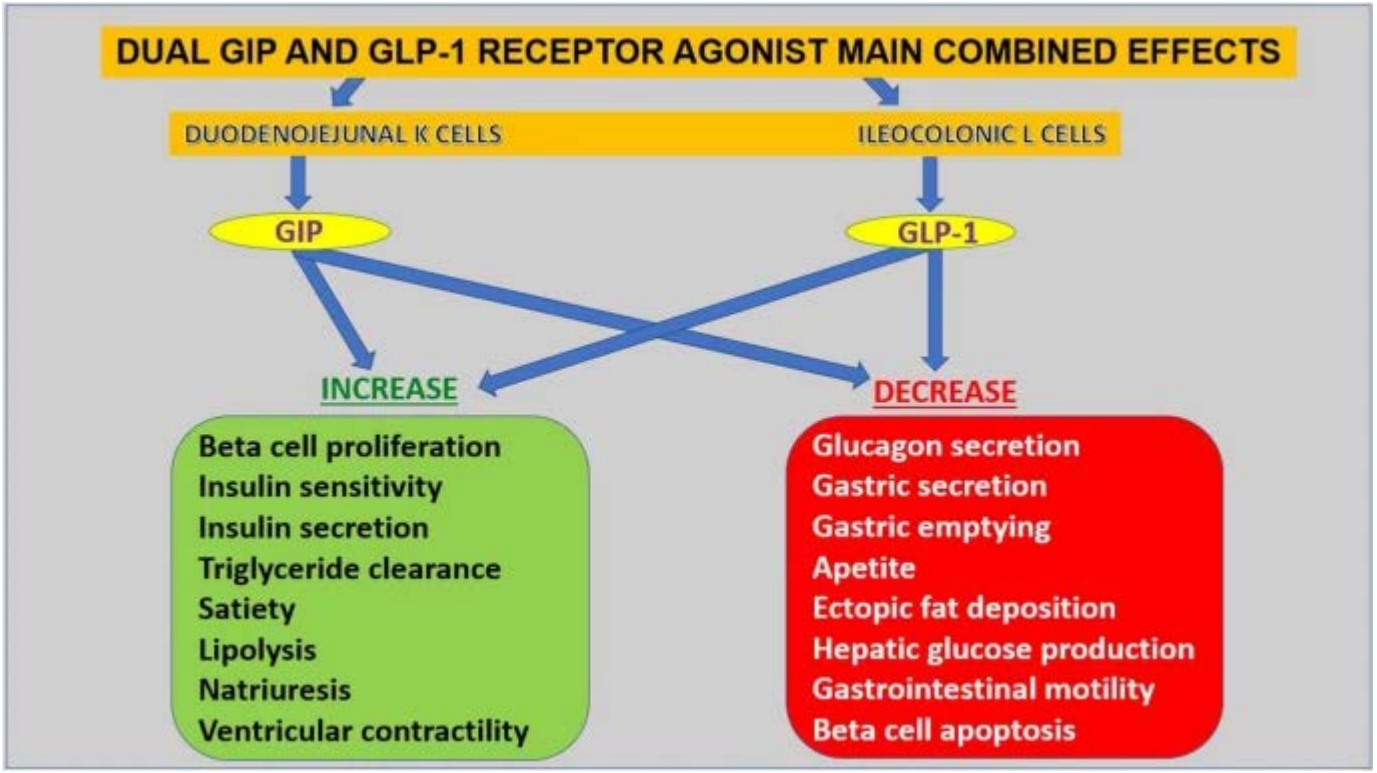
- GIP condiziona la secrezione ormonale e la produzione locale di GLP-1 -→ancor prima che il GLP-1 giunga dall’intestino, il GIP potrebbe preparare l’isola alla sua azione

Gastroenterology 151: 165-179, 2016.

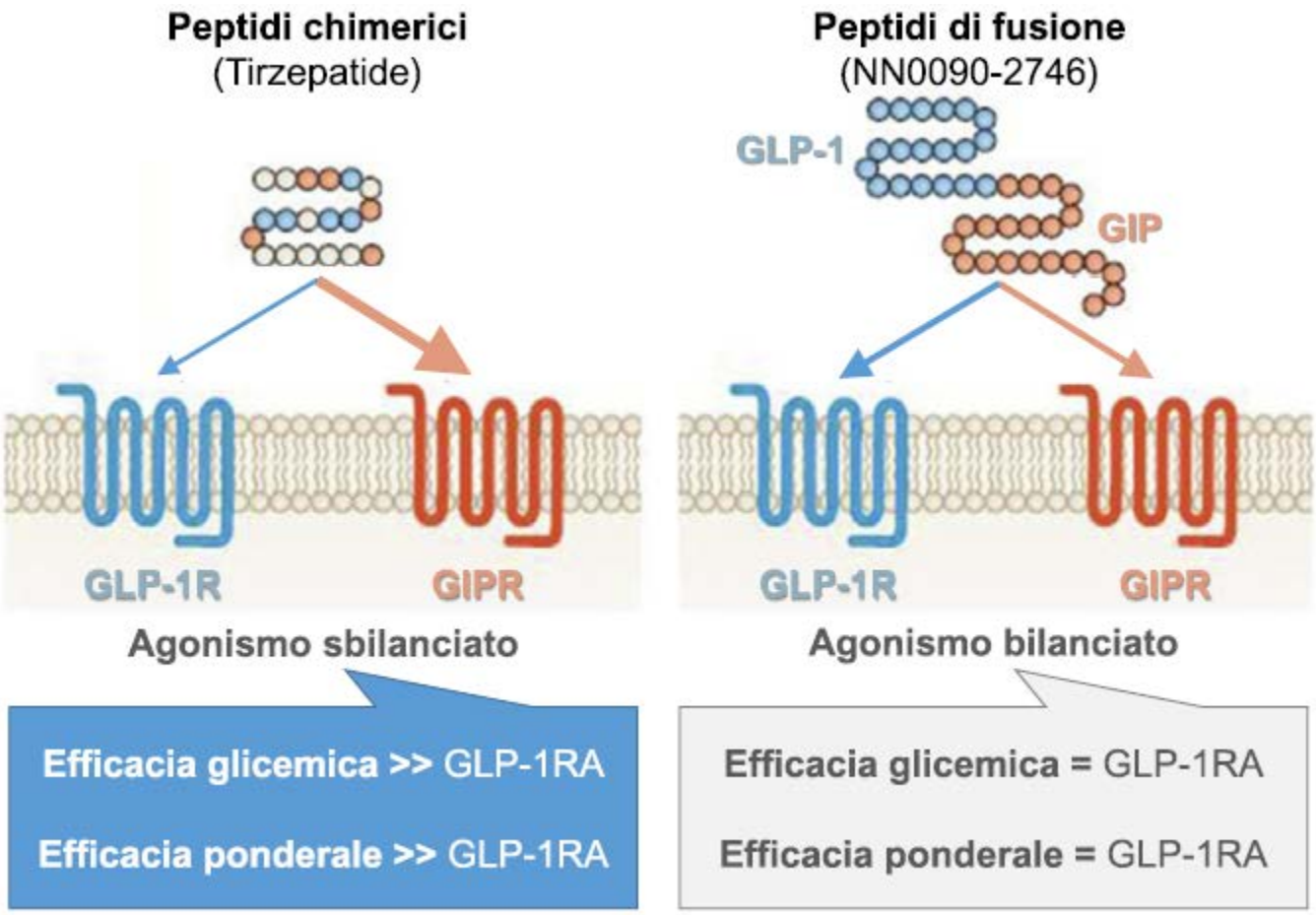
- Gli effetti del GIP sulla secrezione del glucagone e sul tessuto adiposo possono essere contrastati dall’inibizione della secrezione del glucagone e dal ridotto intake di cibo da parte del GLP-1

- La cosomministrazione di agonisti del GIPR e GLP-1R in topi con obesità indotta da dieta determina una maggiore perdita di peso rispetto al solo trattamento con il GLP-1R agonista

Doppio agonismo del recettore di GIP e GLP-1 “il nuovo: due è meglio di uno?”



Doppio agonismo dei recettori GIP /GLP-1
"il nuovo: due è meglio di uno?"



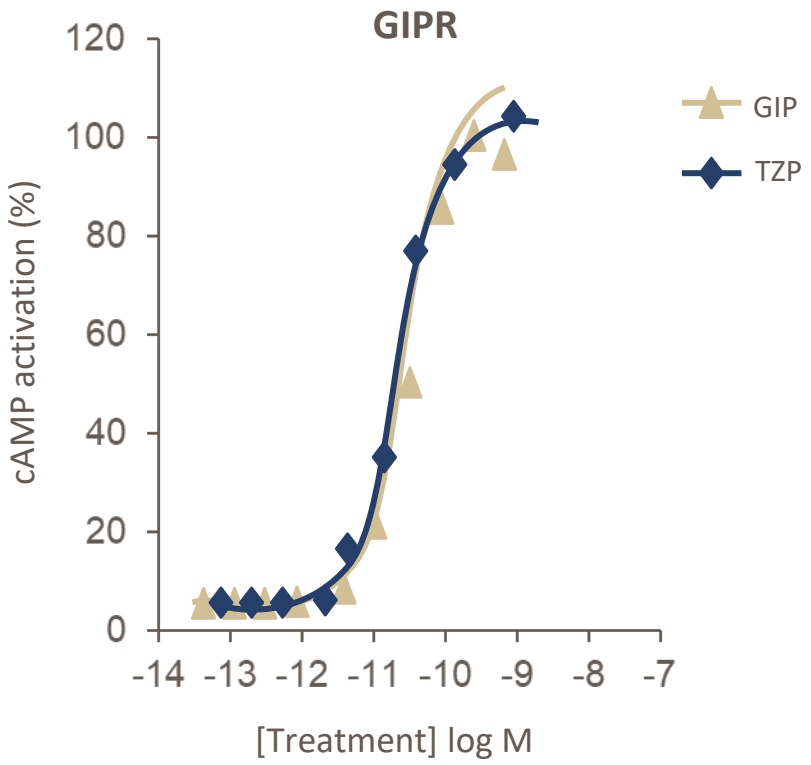
Tirzepatide non è la somma di GIP e GLP-1. E' una singola molecola

L'Endocrinologo 2023; 24: 224-231

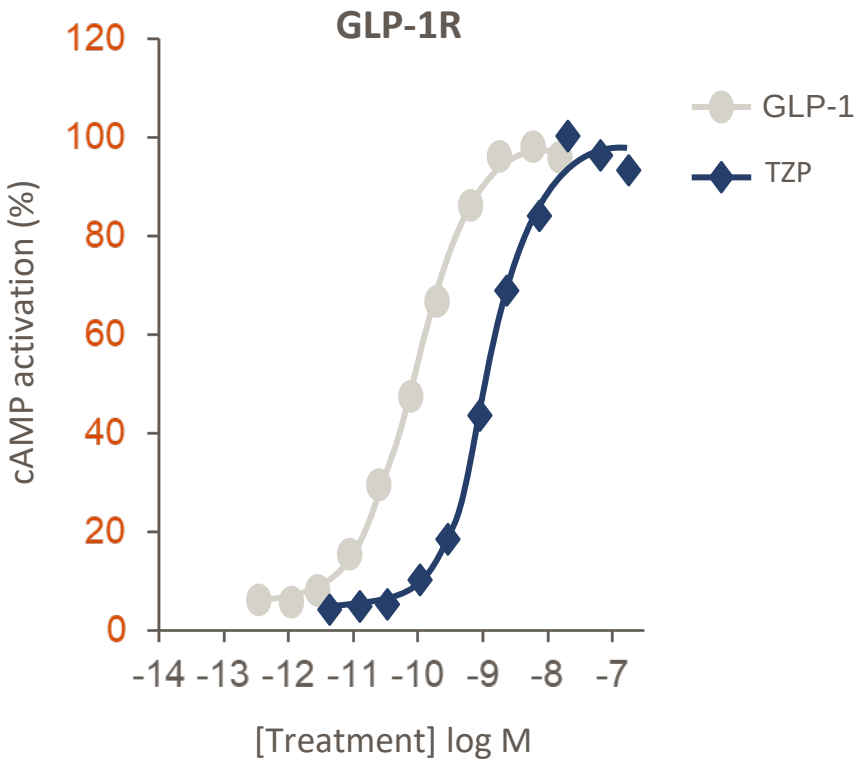
Tirzepatide

Studi in vitro

Potenza per il recettore di GIP simile al GIP nativo.*



Potenza per GLP-1R più debole del GLP-1 nativo.*



cAMP = cyclic adenosine monophosphate; TZP = tirzepatide.

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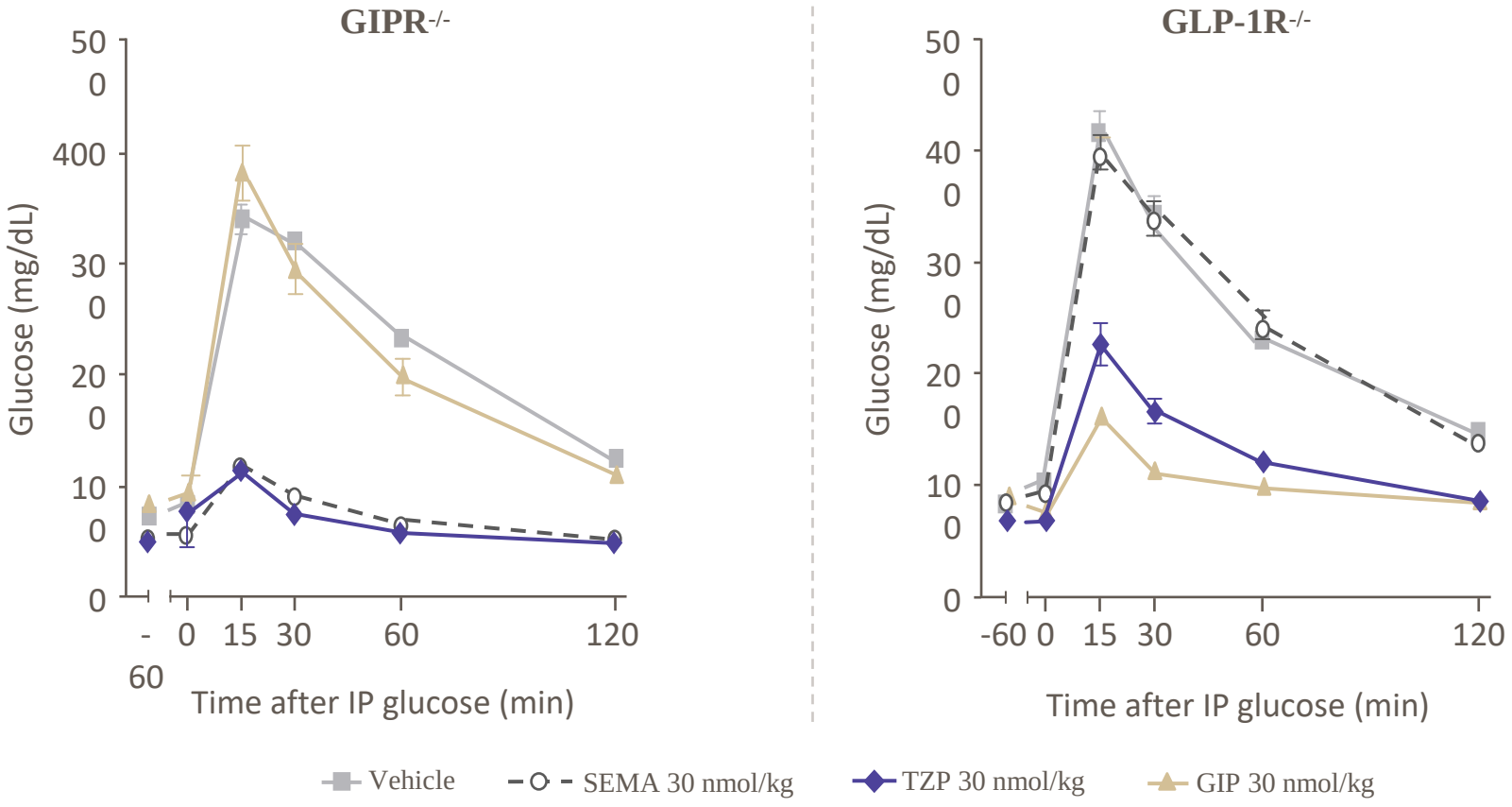
Coskun T, et al. Mol Metab. 2018;18:3-14.

Tirzepatide

Esercita attività ipoglicemizzante agendo su entrambi i recettori

Controllo glicemico dipendente da GLP-1R dimostrato in topi GIPR$^{-/-}$

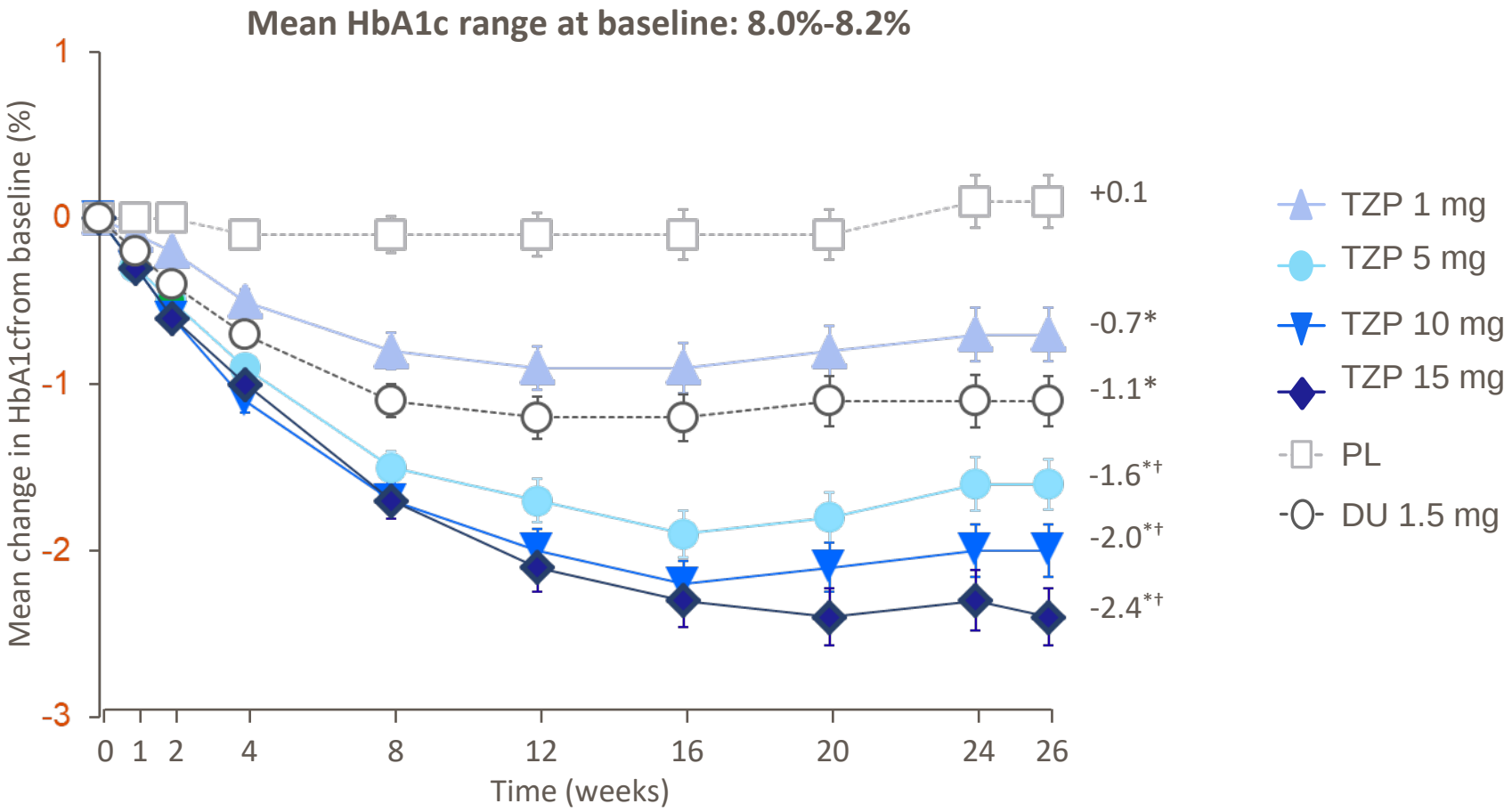
Controllo glicemico dipendente da GIPR dimostrato in topi GIPR$^{-/-}$



SEMA = semaglutide; TZP = tirzepatide.
Coskun T, et al. *Mol Metab*. 2018;18:3-14.

Coskun T, et al. Mol Metab. 2018;18:3-14.

Tirzepatide vs GLP-1RA selettivo

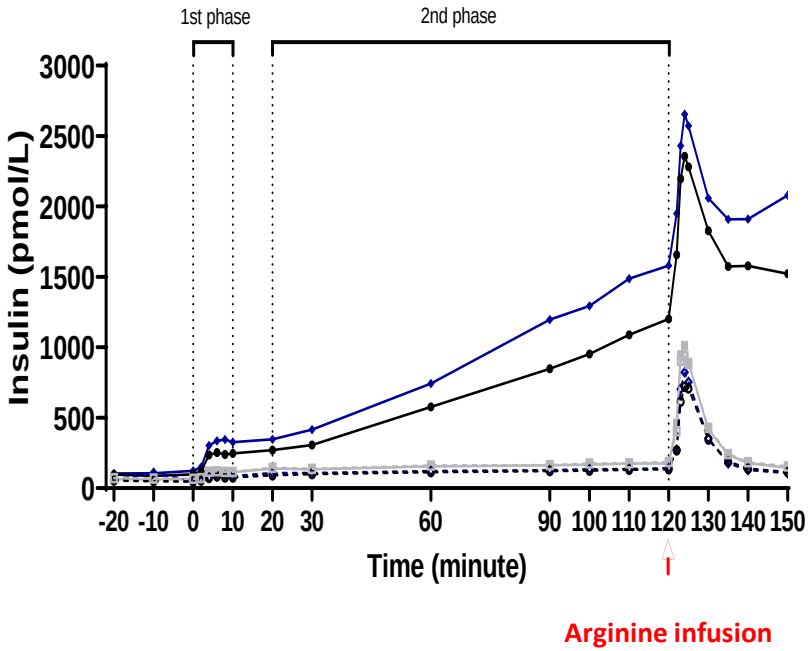


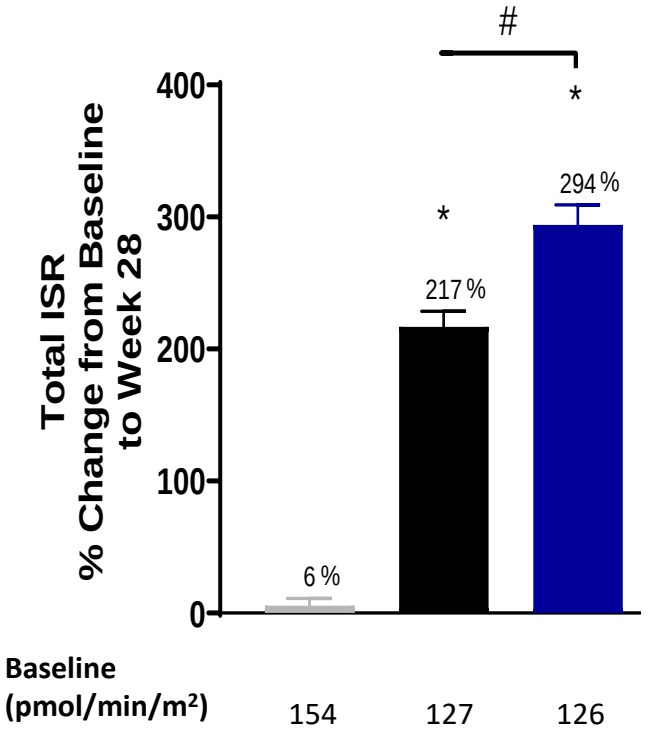
*P<.05 vs PL; †P<.05 vs DU 1.5 mg.
DU = dulaglutide; HbA1c = glycated hemoglobin;; PL = placebo; TZP = tirzepatide.

Frias JP, et al. *Lancet.* 2018;392(10160):2180-2193.

Tirzepatide: controllo glicemico

1. Azione sulla secrezione di insulina



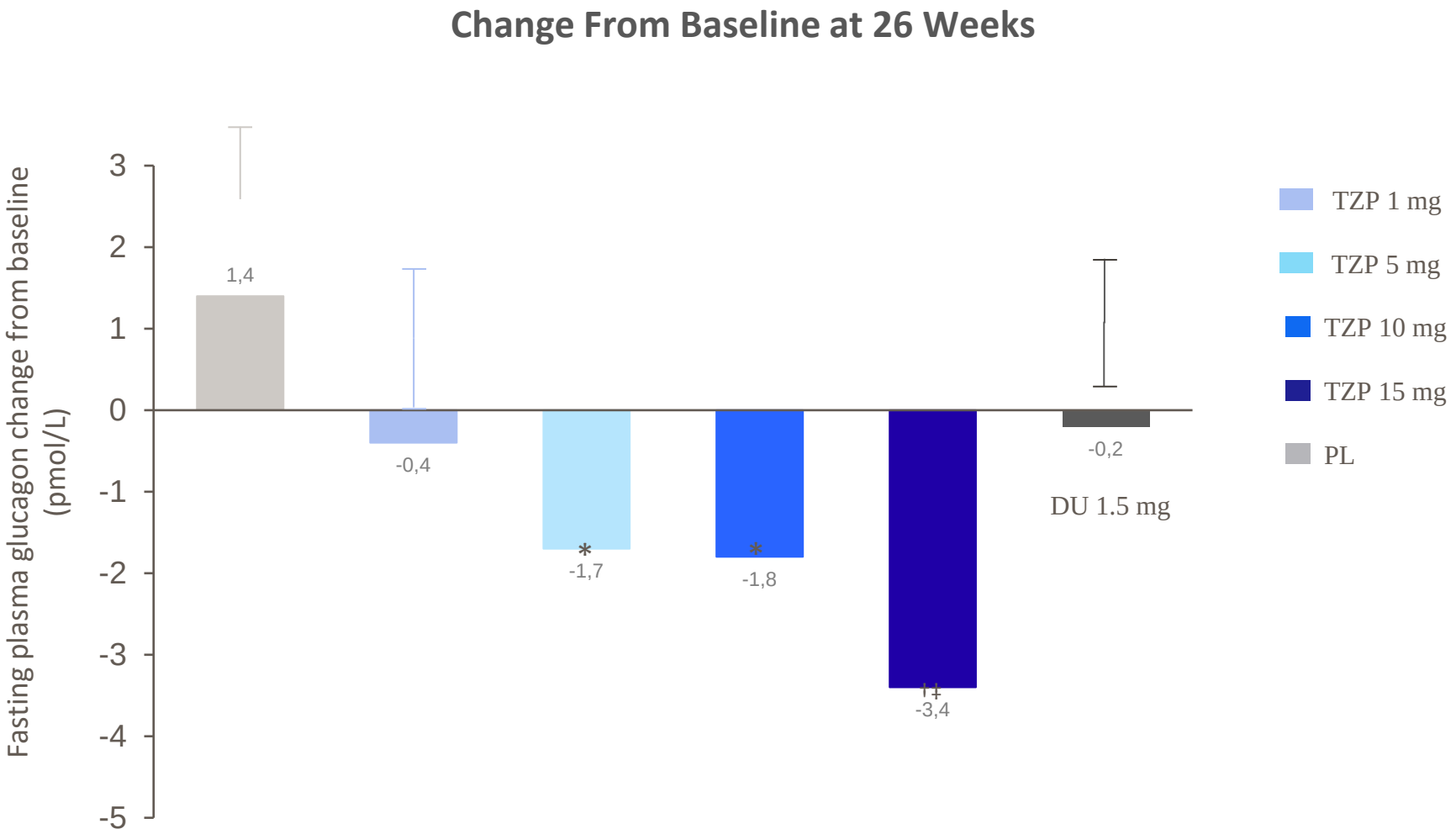


Left: Data are group averages.. Arrow indicates a 5-gram intravenous arginine bolus was administered at 120 minutes.
Right: Data are estimates (with standard errors). *p<0.001 vs placebo, #p=0.003 tirzepatide vs semaglutide

Lancet Diabetes Endocrine Org, 2022; 10:418/29

Tirzepatide: controllo glicemico

2. Azione sulla secrezione di glucagone



*P<.05 vs placebo; †P<.001 vs placebo; ‡P<.05 vs 1.5 mg dulaglutide.
DU = dulaglutide; PL = placebo; TZP = tirzepatide.

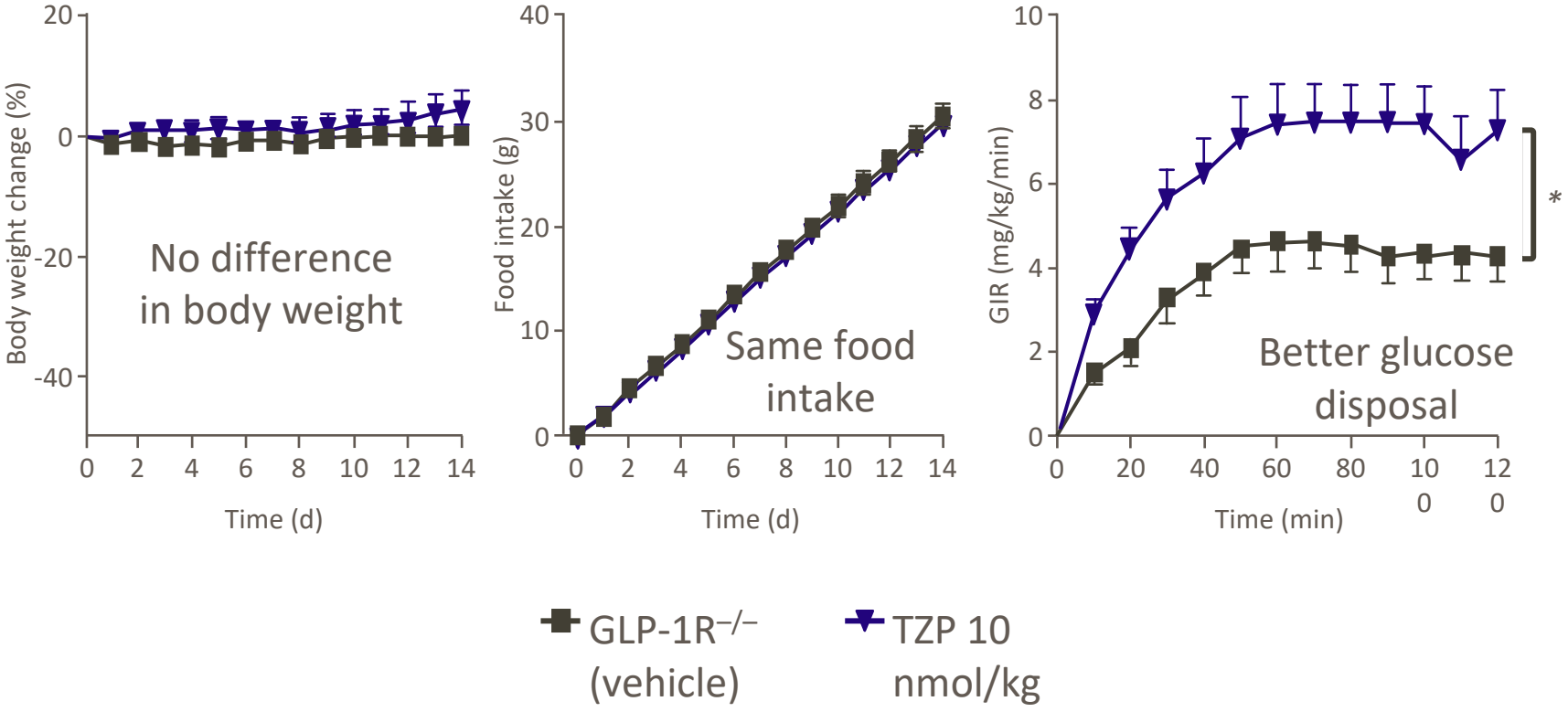
Frias JP, et al. Lancet. 2018;392(10160):2180-2193.

Tirzepatide: controllo glicemico

3. Effetti sulla sensibiltà all'insulina

Migliora la sensibilità insulinica attraverso il recettore GIP indipendentemente dal peso corporeo

Topi GLP-1R ko trattati con TZP *vs* veicolo



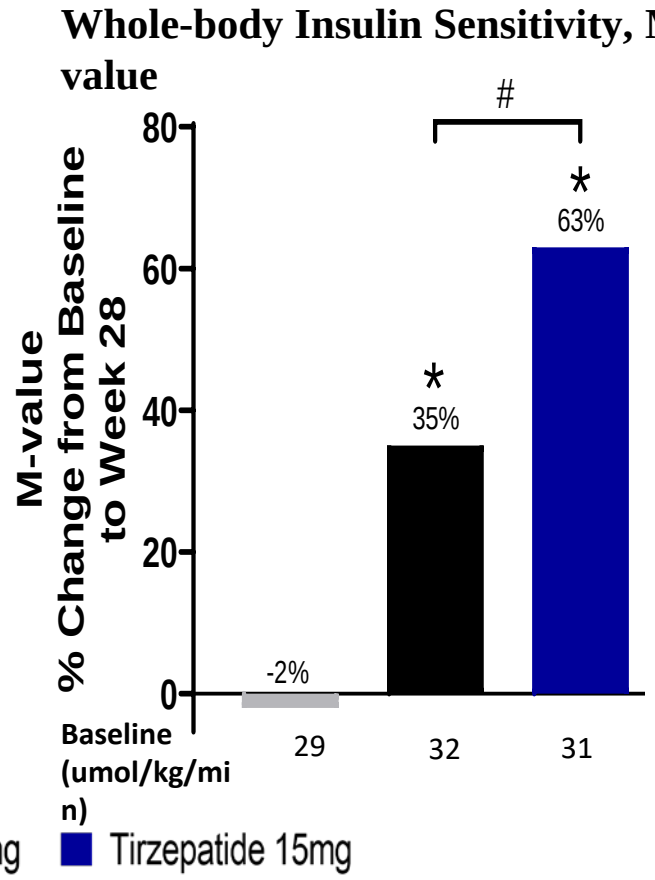
*P<.05. TZP = tirzepatide..

Data on File. Eli Lilly and Company; 2021

Tirzepatide: controllo glicemico

3. Effetti sulla sensibiltà all'insulina

Insulino-sensibilità: migliora in soggetti con DM tipo 2 trattato con TZP *vs* un GLP-1 agonista selettivo (semaglutide)

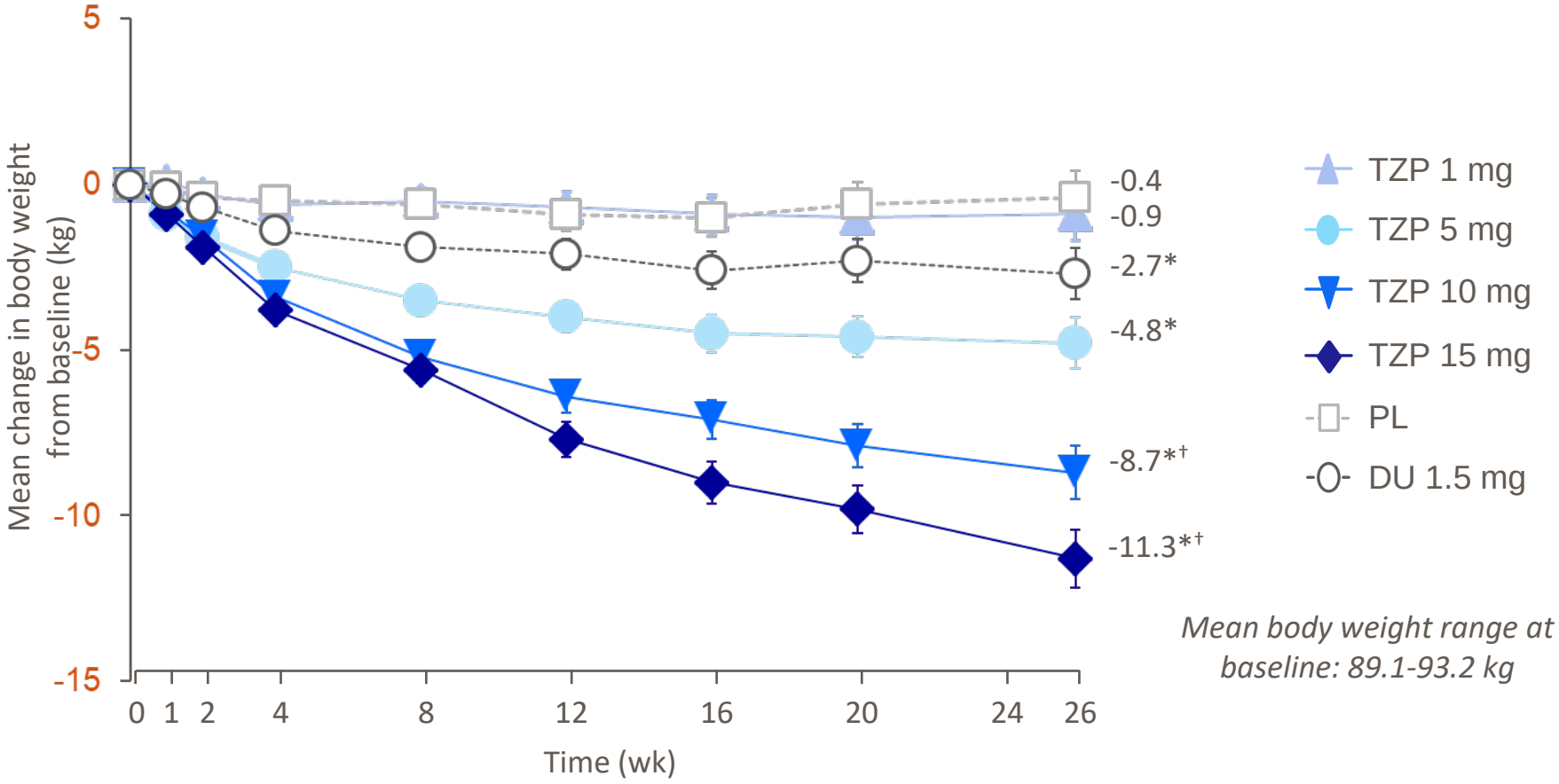


Dashed: baseline Solid: Week 28

Left: Data are group averages. Dashed lines represent baseline values; solid lines represent Week 28 values. Right: estimates.
*p<0.001 vs placebo, #p=0.003 tirzepatide vs semaglutide

Heise T et al Lancet Diabetes Endocrine Org, 2022; 10:418/29

Tirzepatide: riduzione peso corporeo



Mean body weight range at baseline: 89.1-93.2 kg

*P<.05 vs PL; †P<.05 vs DU 1.5 mg.
DU = dulaglutide; HbA1c = glycated hemoglobin;; PL = placebo; TZP = tirzepatide.

Frias JP, et al. Lancet. 2018;392(10160):2180-2193.

Tirzepatide: riduzione peso corporeo

In adulti obesi non diabetici a 72 settiane TZP alla dose di 5 g, 10 mg, o 15 mg riduce in maniera sostanziale il peso corporeo.
(SURMOUNT-1 Clinical Trials, NCT04184622)

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Tirzepatide Once Weekly for the Treatment of Obesity

Jastreboff AM et al. DOI: 10.1056/NEJMoa2206038

CLINICAL PROBLEM

Several clinical guidelines recommend pharmacotherapy for obesity. Tirzepatide — a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist recently approved in the United States to treat type 2 diabetes — induced clinically relevant weight reduction in phase 2 studies of people with diabetes. However, its efficacy for weight reduction in those without diabetes is unknown.

CLINICAL TRIAL

Design: An international, phase 3, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes.

Intervention: 2539 adults with a body-mass index of 30 or higher, or 27 or higher with at least one weight-related complication, were assigned to once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo, in addition to lifestyle intervention. Treatment included a dose-escalation phase and lasted for 72 weeks. The coprimary end points were the percentage change in weight from baseline to week 72 and weight reduction of at least 5% by week 72.

RESULTS

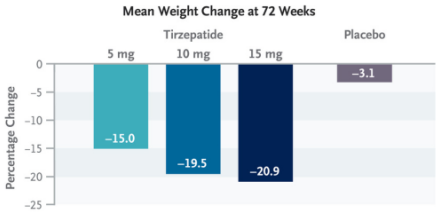
Efficacy: Both the percentage change in weight and the percentage of participants with at least 5% weight reduction were significantly greater with all three doses of tirzepatide than with placebo.

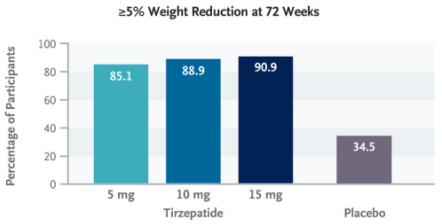
Safety: Gastrointestinal events, including nausea, diarrhea, and constipation, were the most common adverse events seen with tirzepatide; the majority of events were transient and mild to moderate in severity.

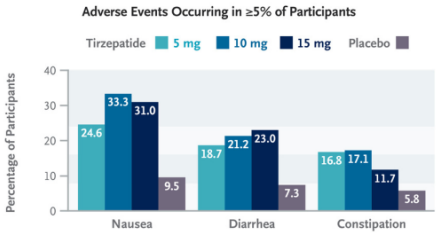
LIMITATIONS AND REMAINING QUESTIONS

- Enrolled participants may have been more committed to weight management than many people with obesity.
- Cardiometabolic variables (e.g., blood pressure and lipid levels) were relatively normal at baseline, so the ability to show a potential improvement within the time frame of this study was limited.
- The number of participants with overweight plus at least one weight-related complication was small (140 of the 2539 participants; 5.5%), which prevented definitive conclusions in this subgroup.

Links: Full Article | NEJM Quick Take | Editorial



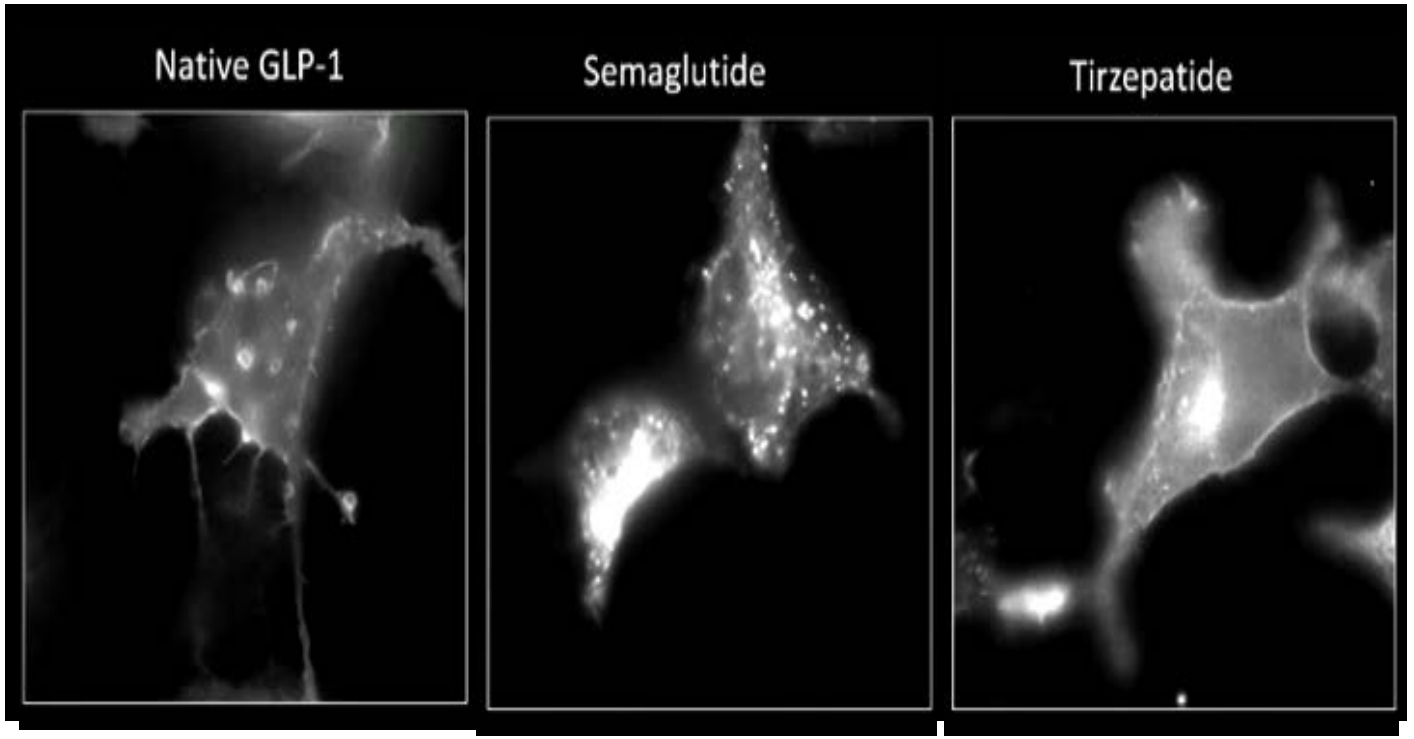




CONCLUSIONS

All three doses of once-weekly subcutaneous tirzepatide led to clinically meaningful and sustained weight reduction in obese adults who did not have diabetes.

Tirzepatide: riduzione peso corporeo
Potenziali meccanismi



GLP-1 e semaglutide causano internalizzazione del recettore del GLP-1 → limitano l'effetto

Tirzepatide determina un più rapido recycling del GLP-1R internalizzato

↓

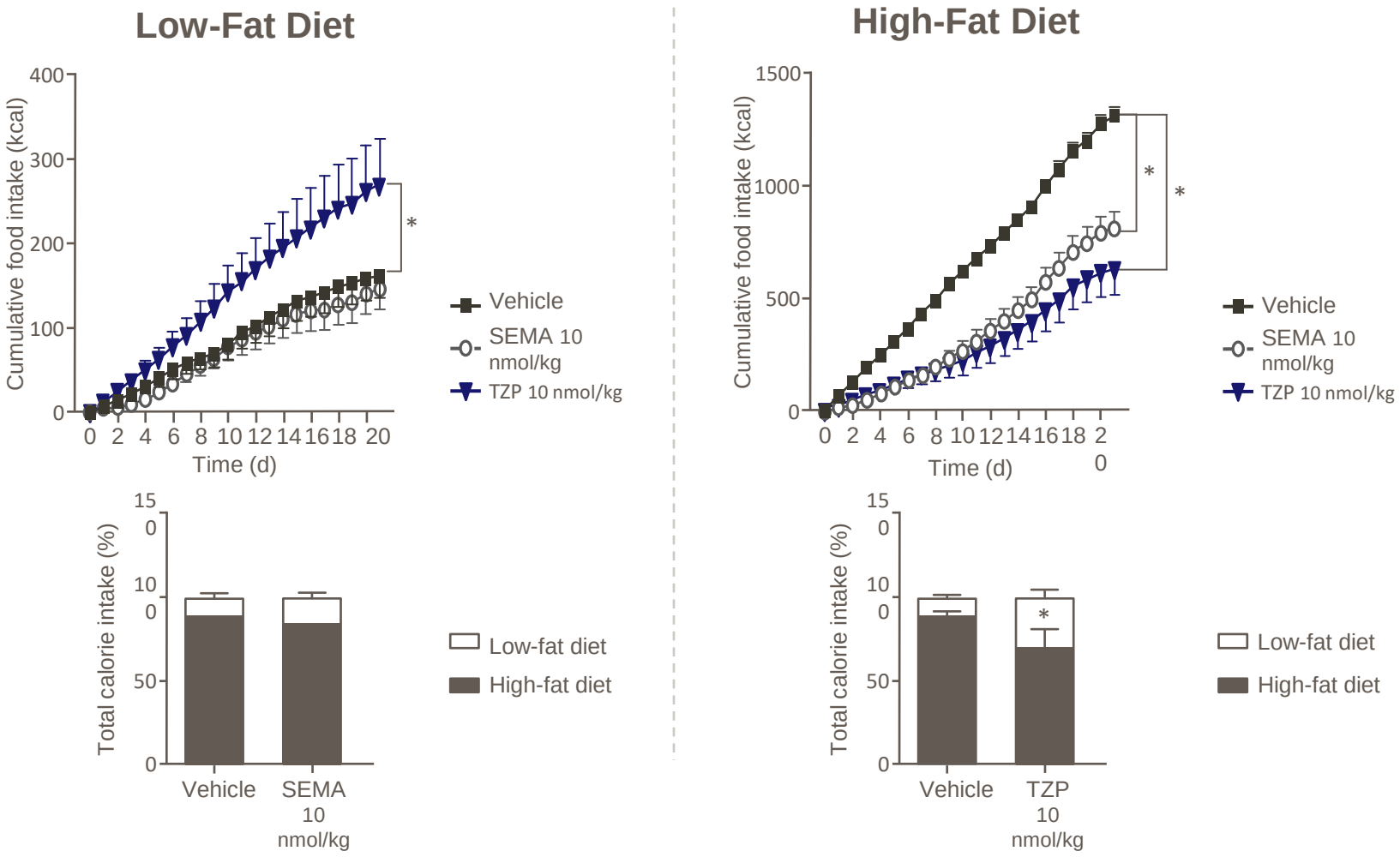
TZP aumenta l'esposizione del GLP-1R sulle membrane→ potenzia l'effetto

Mol Metab. 2021 Jul;49:101181

Tirzepatide: riduzione peso corporeo Potenziali meccanismi

Induce preferenza di cibo a basso contenuto di grassi

Studi in topi obesi

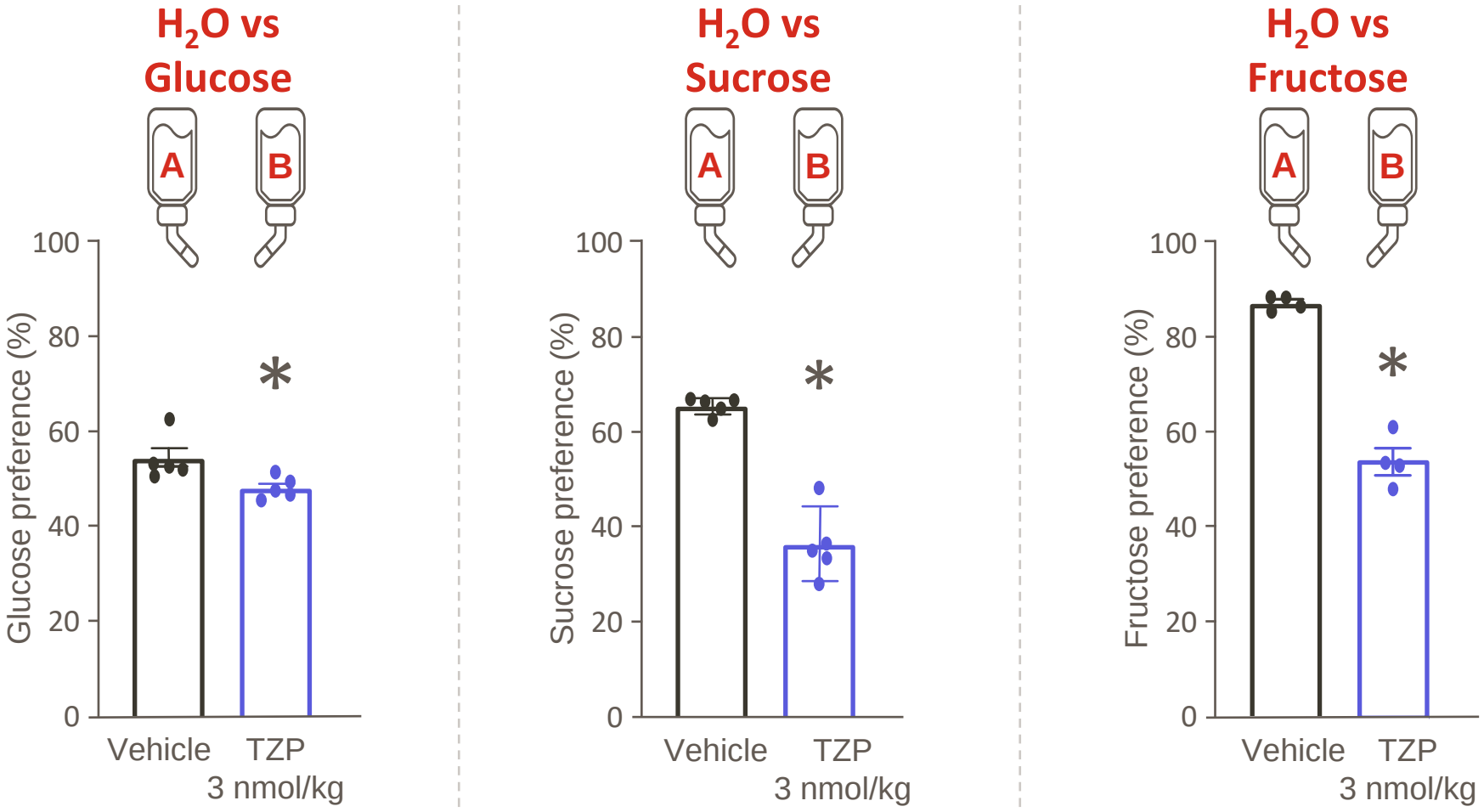


SEMA = semaglutide; TZP = tirzepatide.

Samms RJ, et al. Presented at: Obesity Week 2020; November 2-6, 2020; Atlanta, Georgia. Poster 450.

Tirzepatide: riduzione peso corporeo
Potenziali meccanismi

Riduce la preferenza di assunzione di zuccheri semplici nei topi



Mice were dosed daily for 5 days.
*P<.05.

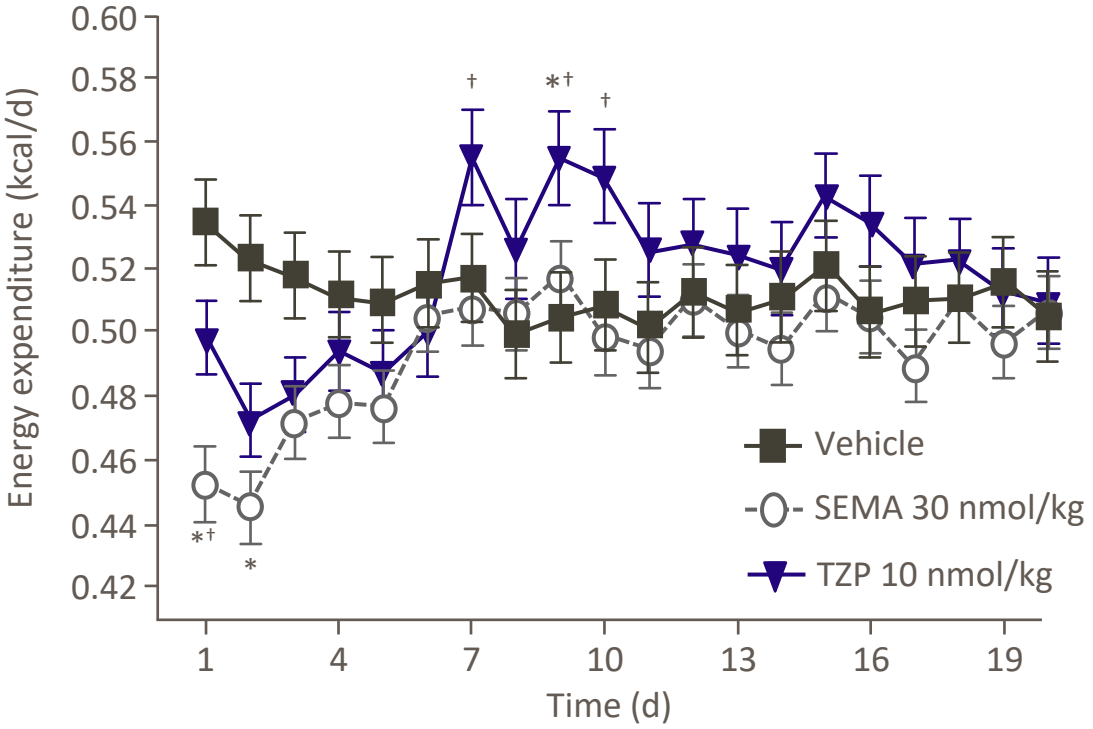
Cosgrove R, et al. Diabetes. 2020;69(suppl 1):-.

Tirzepatide: riduzione peso corporeo
Potenziali meccanismi

Tirzepatide induces a thermogenic-like amino acid signature in brown adipose tissue

MOLECULAR METABOLISM

Tirzepatide demonstrated increased energy expenditure in obese mice beginning after day 7 of treatment

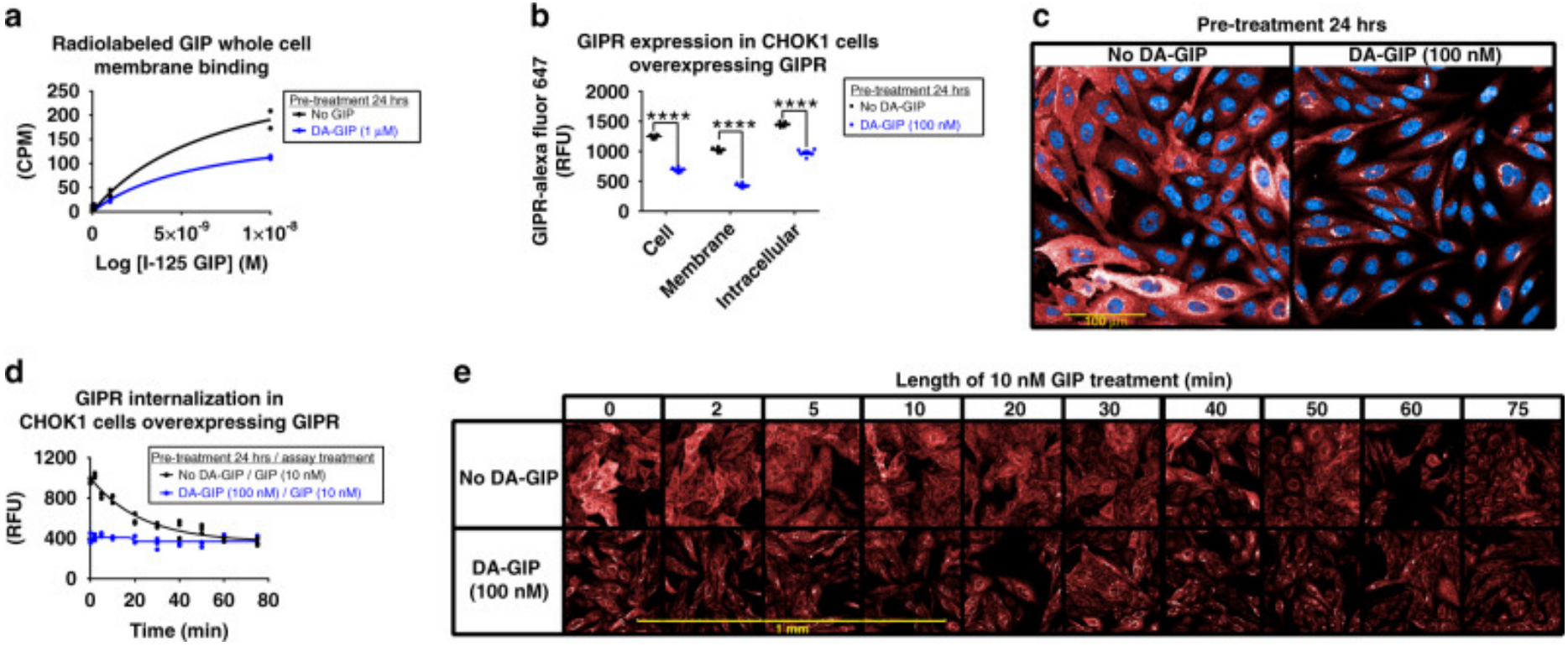


*P<.05 vs vehicle; †P<.05 vs semaglutide.

Coskun T, et al. Mol Metab. 2018;18:3-14.
Samms et al. Mol Metab. 2022 Oct;64:101550

Tirzepatide: riduzione peso corporeo
Potenziali meccanismi

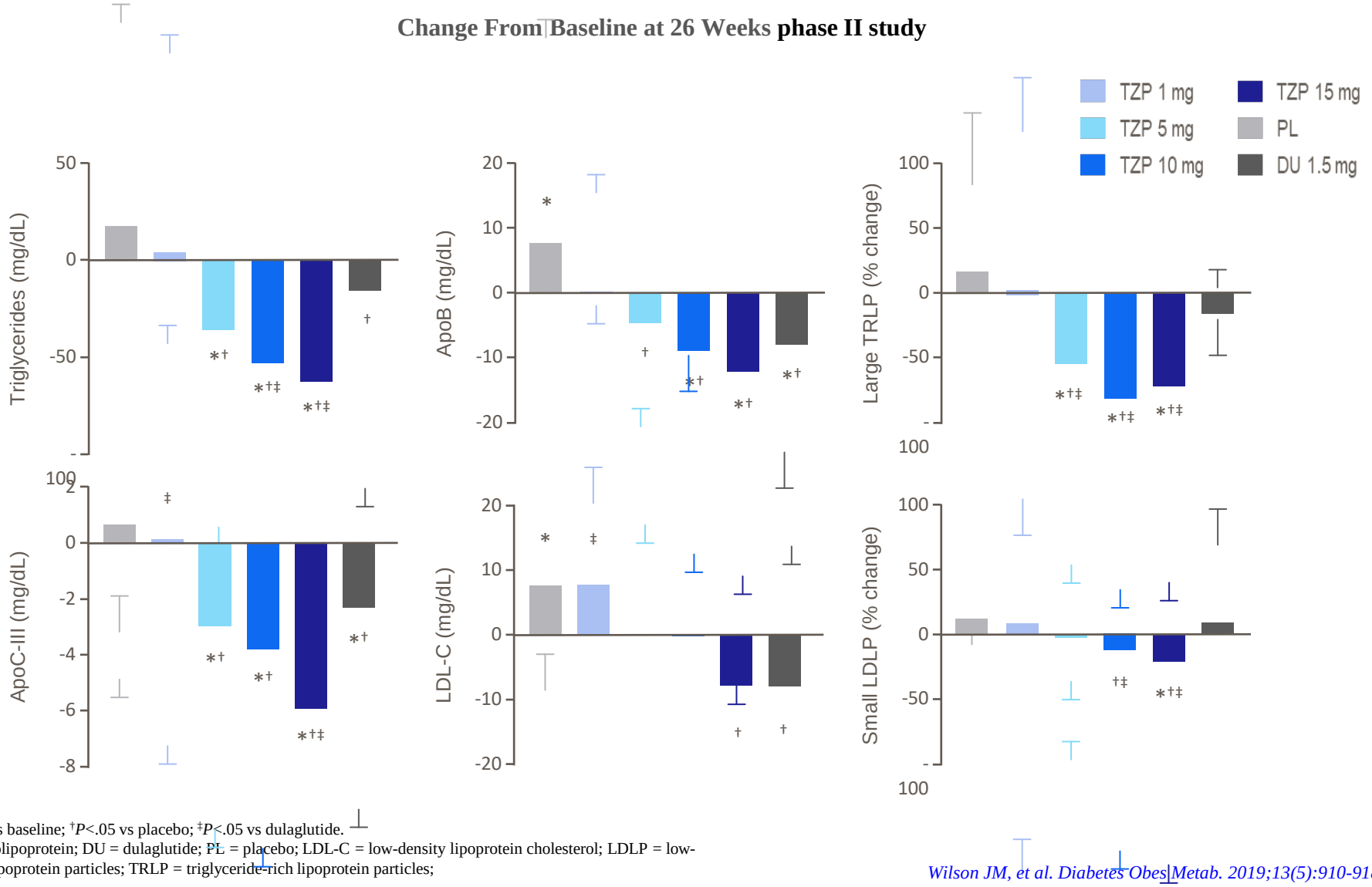
L'agonismo cronico di GIPR determina desensibilizzazione recettoriale con aumento dell'internalizzazione di GIPR



Trends in Endocrinol Metab, 2020; 31 (6): 410-421

Tirzepatide migliora il profilo lipidico

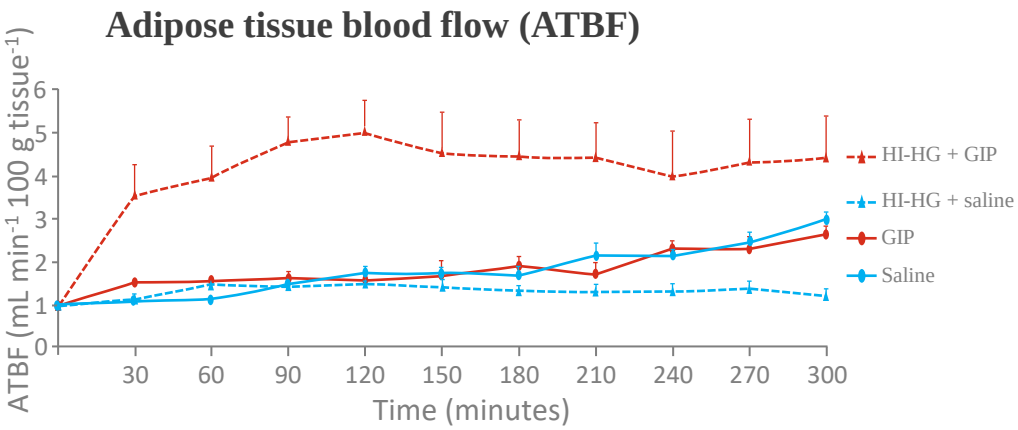
Change From Baseline at 26 Weeks phase II study



*P<.05 vs baseline; †P<.05 vs placebo; ‡P<.05 vs dulaglutide.
apo = apolipoprotein; DU = dulaglutide; PL = placebo; LDL-C = low-density lipoprotein cholesterol; LDLP = low-density lipoprotein particles; TRLP = triglyceride-rich lipoprotein particles;

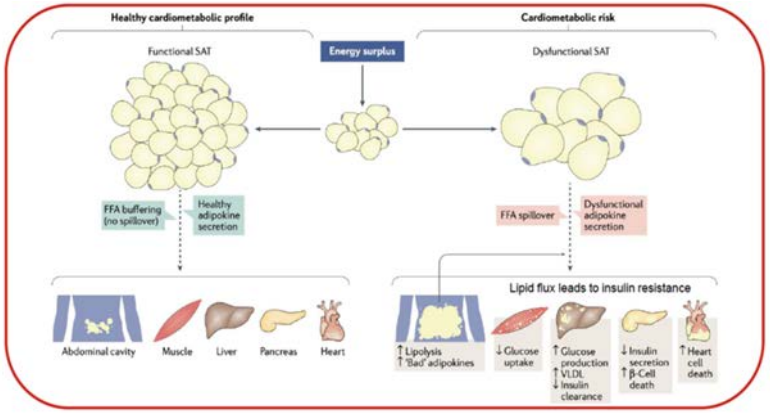
Wilson JM, et al. Diabetes Obes Metab. 2019;13(5):910-918.

Tirzepatide e profilo lipidico



30–300 minutes after commencement of infusions

GIP in presenza di ipeinsulinemia e moderata iperglicemia aumenta la perfusione del tessuto adiposo con conseguente aumento dell'uptake e riesterificaztione di FFA

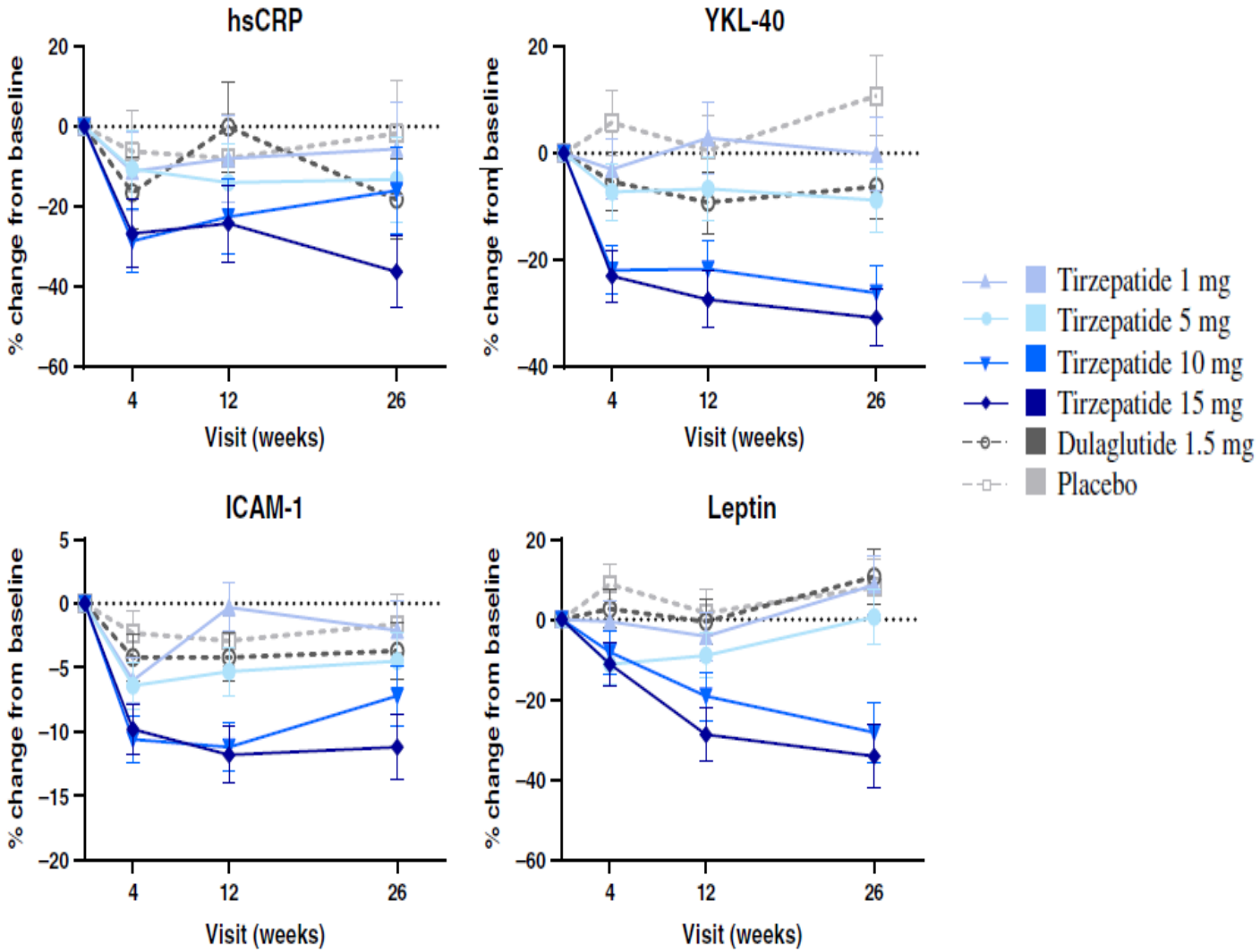


GIP aumenta il reclutamento della lipoprotein lipasi massimizzando l'idrolisi dei TAG e il rilascio di FFA, stimolando di conseguenza l'uptake dei lipidi, facilita l'espansione del WAT

Asmar M et al. Diabetes 2010;59(9): 2160–2163
Ross R et al. Nat Rev Endocrinol 2020, 16: 177-89

Tirzepatide migliora il profilo infiammatorio

Phase II study



Wilson et al. Diabetes Obes Metab. 2021;1–6.

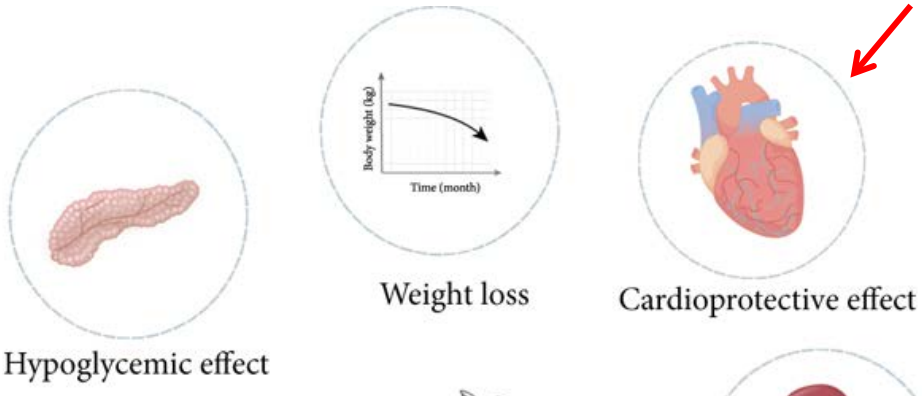
Effetti della Tirzepatide

- Ridotto intake di cibo
- Aumento spesa energetica

- Controllo lipidi plasmatci
- Benefici sull'infiammazione
- Benefici sull'endotelio (*La somministrazione di GIP riduce l'area aterosclerotica - La delezione di GIPR aumenta l'area aterosclerotica*)
- Riduzione PA

Surpass-CVOT trial: in corso

- Aumento secrezione insulina
- Ridotta secrezione glucagone
- Aumento Insulino-sensibilità

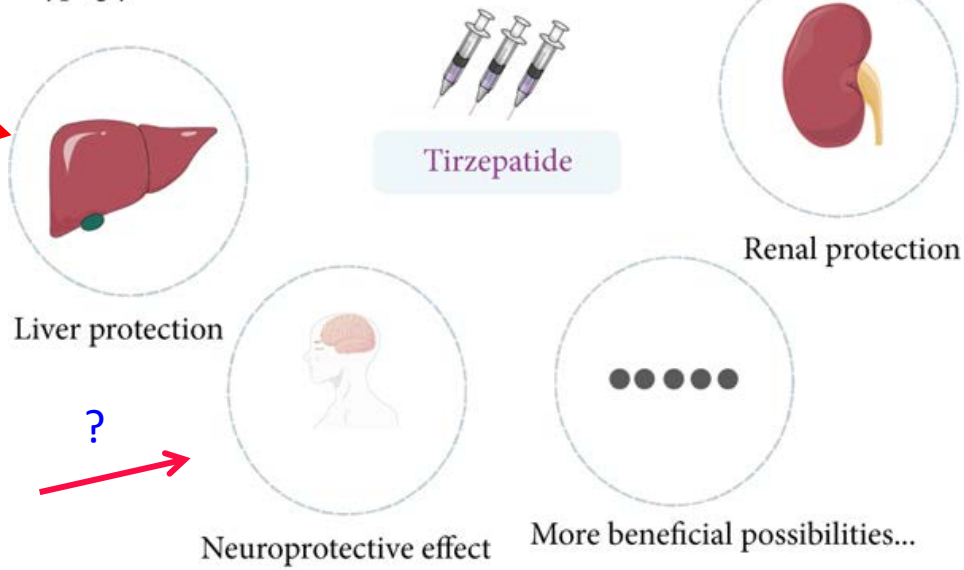


- Riduzione pattern pro.infiammatorio

?

- Effetto protettivo indiretto sulla epatosteatosi

?



Synergy-NASH trial: in corso

- Benefici sulla neuroinfimmazione
- Stimolazione neurogenesi
- Riduziozne deposizione beta-amiloide e proteine tau (*studi su topi*)

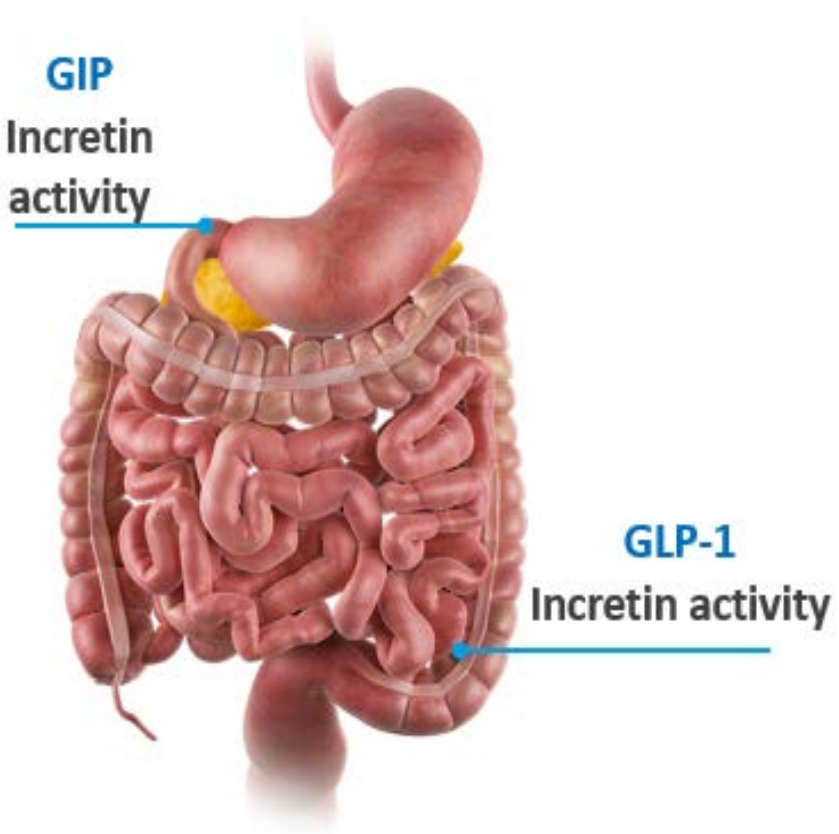
?

Zijun Ma et al. Journal of Diabetes Research. 2023

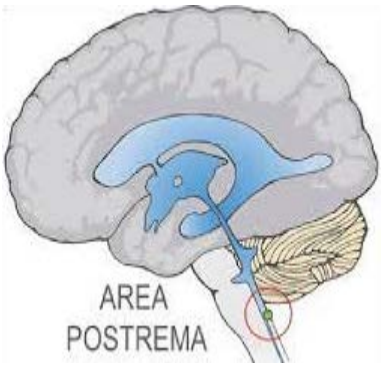
Tollerabilità

- Nella maggioranza dei casi gli effetti avversi gastrointestinali erano di intensità lieve/moderata e transitoria
- Gli eventi avversi gastrointestnali con tirzepatide 15 mg erano sovrapponibili a quelli osservati con dulaglutide 1.5mg

Il diverso sito di produzione può impattare differentemente sullo svuotamento gastrico

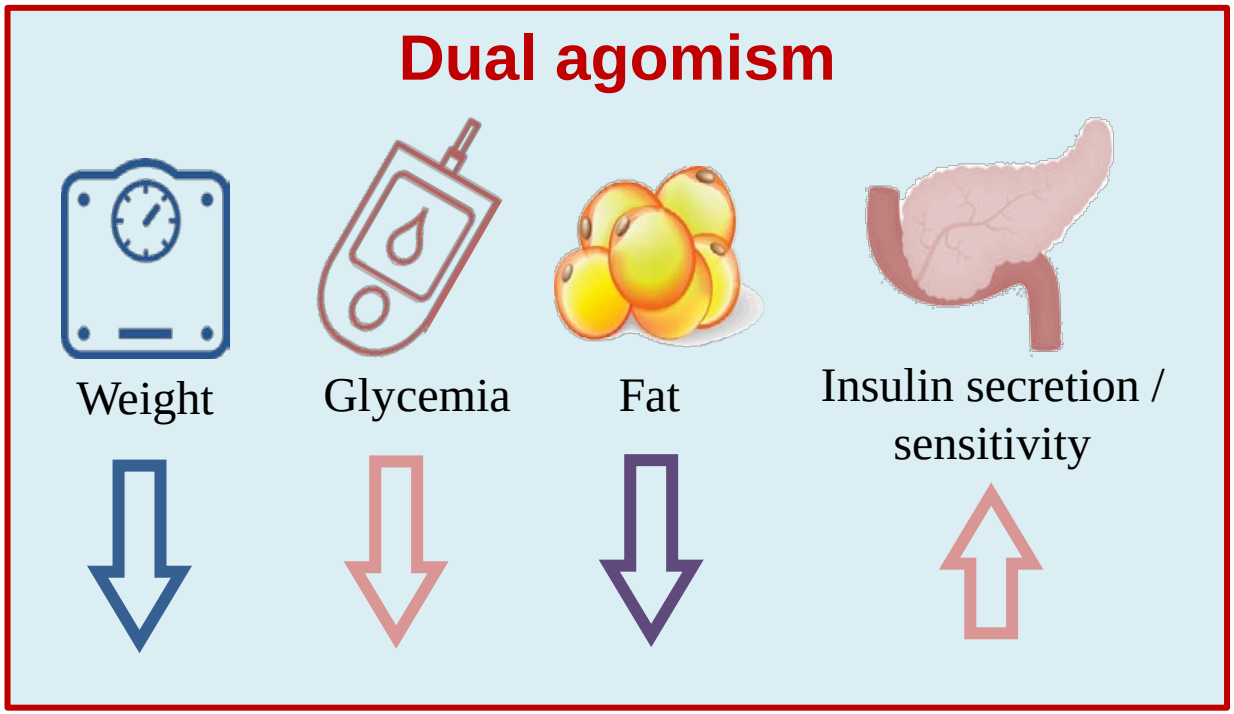


L'effetto agonistico su GIPR attenua la nausea e il vomito indotti da GLP-1



The area postrema and nucleus tractus solitaries

E quindi due è meglio di uno?



- ✓ Il doppio agonismo GIPR/GLP-1R
  → **migliora il recupero delle risposte fisiologiche**

- ✓ Riducendo la tossicità lipidica e glucidica
  → **riduce il peso coporeo e il rischio cardiovascolare**

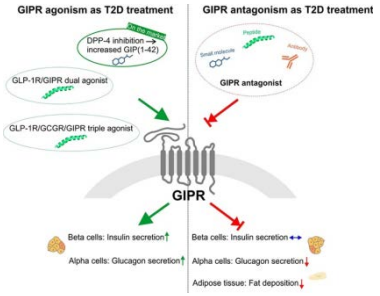
Domande in sospeso

- Può il doppio agonista unimolecolare esercitare effetti benefici attraverso meccanismi ancora sconosciuti?
- Il farmaco bersaglia i recettori GLP-1 e GIP sulla stessa cellula, o su differenti cellule in differenti tessuti, o entrambi?
- L'azione dell'agonismo GIPR sulla cellula beta sembra risentire del meccanismo della tachifilassi riflettendo una desensibilizzazione del recettore: questo meccanismo può essere superato dal co-agonista unimoleocolare GLP-1/GIP?
- L'efficacia e i benefici saranno mantenuti con l'uso sostenuto?
- Quali effetti sulla NASH e sulla protezione cardiovascolare rispetto ai benefici noti dei GLP-1R agonisti?
- Quale protezione sulla nefropatia diabetica e sulle malattie neurodegenerative?
- GIP può inibire il riassorbimento osseo; può il co-agonismo GLP-1/GIP avere un effetto benefico nei soggetti anziani a rischio di osteoporosi?

Prospettive future

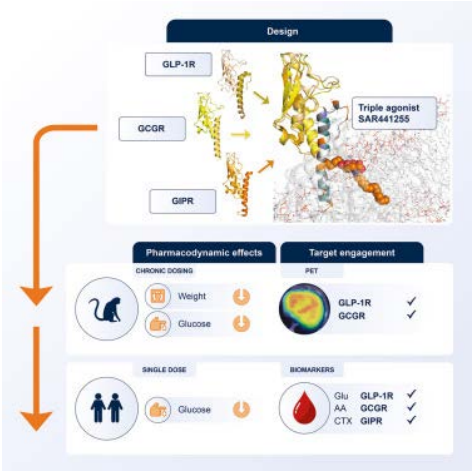
- **GIPR antagonismo + GLP1-R agonismo: possibile ruolo?**

Evidenze suggeriscono un ruolo nel trattamento dell'obesità



LS Gasbjerg et al Peptide, 2018; 100: 173-18

- **Triplo o multiplo agonismo: meglio del doppio agonismo?**



Triplo agonista unimolecolare dei recettori GLP-1/GIP/glucagone: riduzione peso corporeo in scimmie obese e miglioramento controllo glicemico in scimmie con diabete

Bossart et al., 2022, Cell Metabolism 34, 59–74

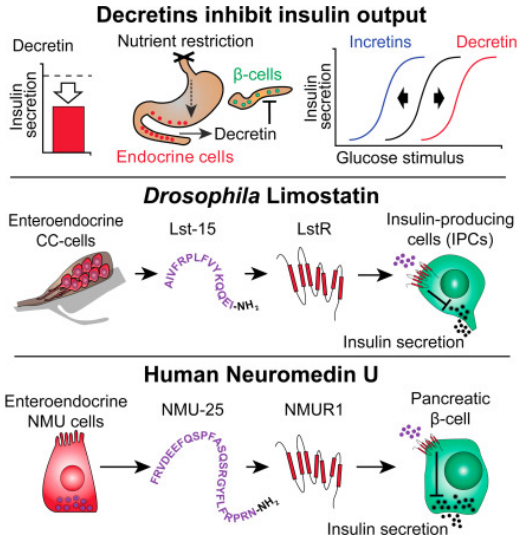
In soggetti con DM di tipo 2, Retatrutide, un agonista del recettore GIP/GLP-1/glucagone, ha dimostrato un miglioramento clinicamente significatvo del controllo glicemico e una consistente riduzione del peso corporeo, con un profilo di sicurezza in linea con quello dei GLP-1R agonisti e del doppio agonista GIPR/GLP-1R

Studio di fase 2 condotto in USA

Lancet 2023 Aug 12;402(10401):529-544

Prospettive future

- **Non solo Incretine ma anche «Decretine»**



Cell Metabolism, 2015; 21, Issue 2: 323-334

GRAZIE PER L'ATTENZIONE

" No matter how counter-intuitive it may seem, basic research has proven over and over to be the lifeline of practical advances in medicine."

Arthur Kornberg