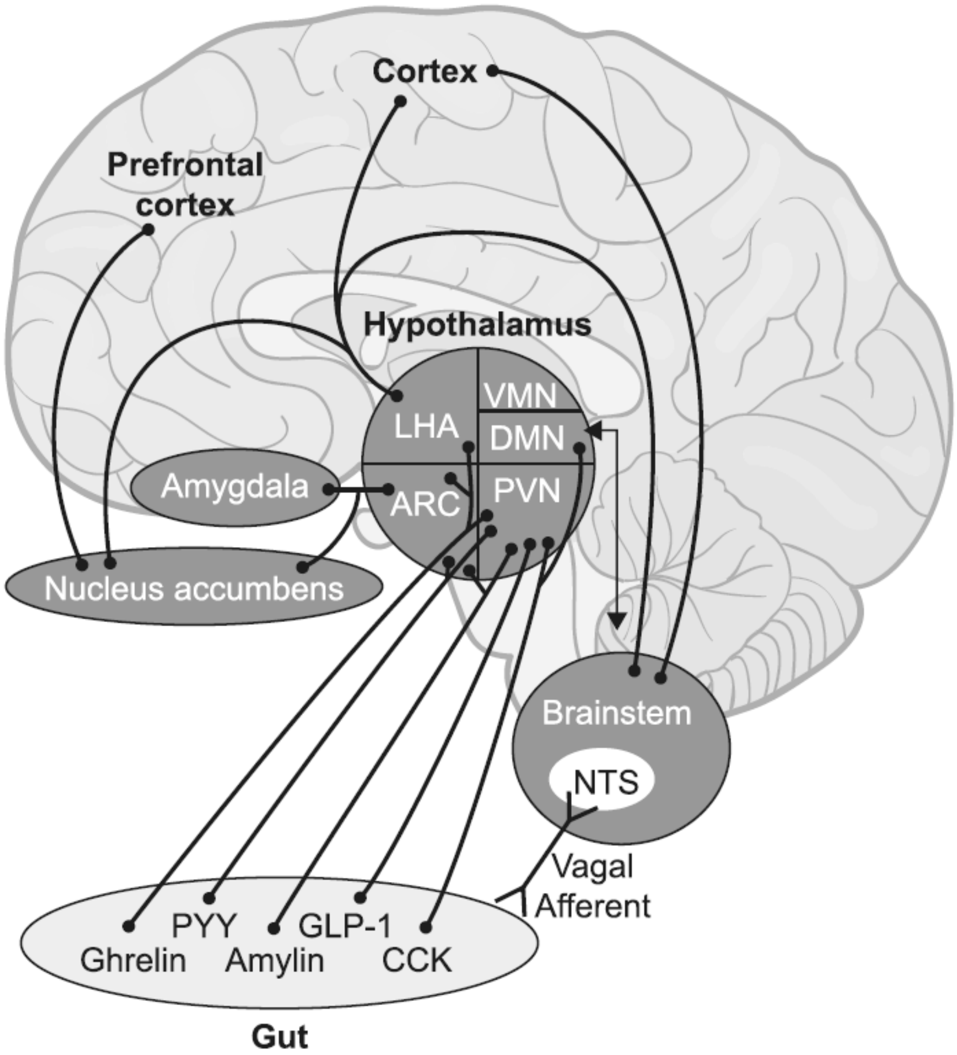
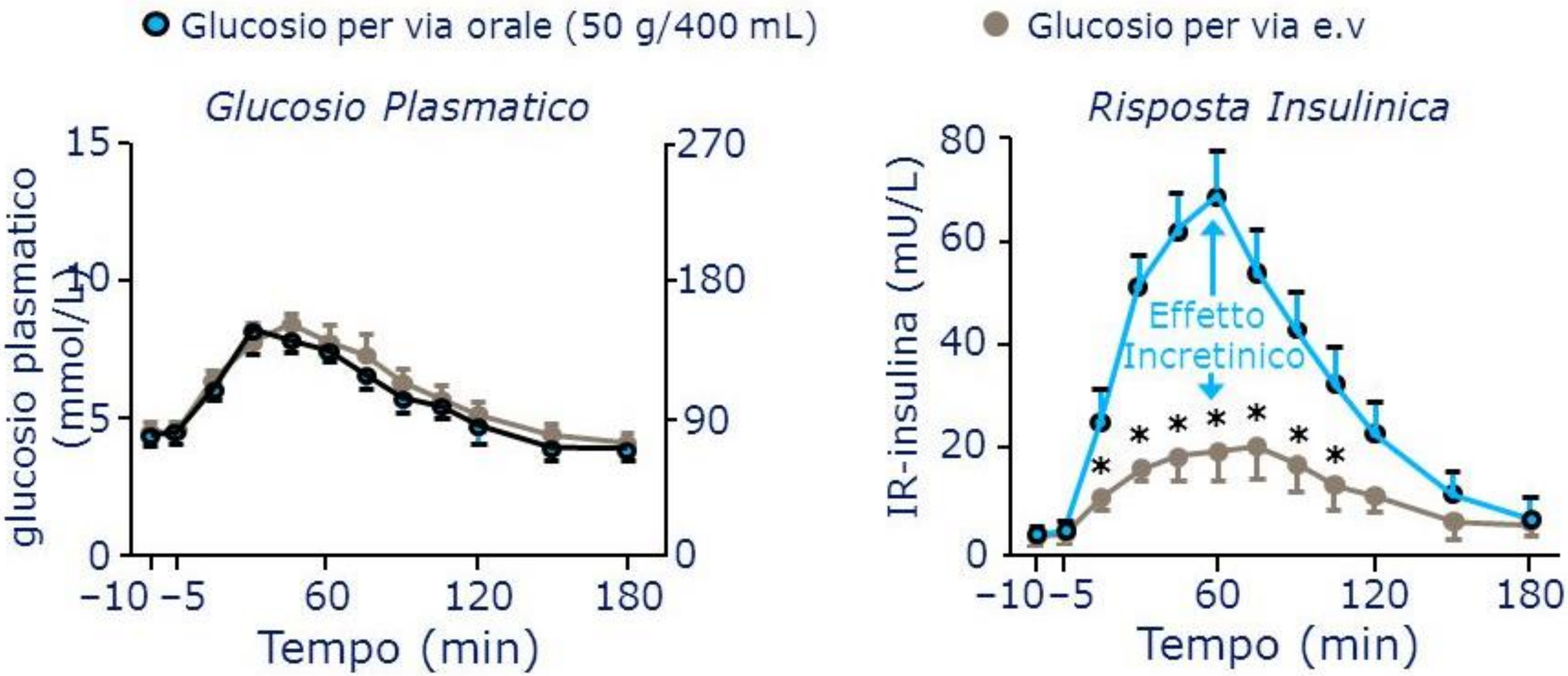
LIRAGLUTIDE: UN AGONISTA DEL RECETTORE DI GLP-1 PER IL TRATTAMENTO FARMACOLOGICO DI SOVRAPPESO E OBESITA’

ASSE INTESTINO-CERVELLO


Cortex
Prefrontal cortex
Hypothalamus
VMN
LHA
DMN
Amygdala
ARC
PVN
Nucleus accumbens
Brainstem
NTS
Vagal Afferent
PYY
GLP-1
Ghrelin
Amylin
CCK
Gut

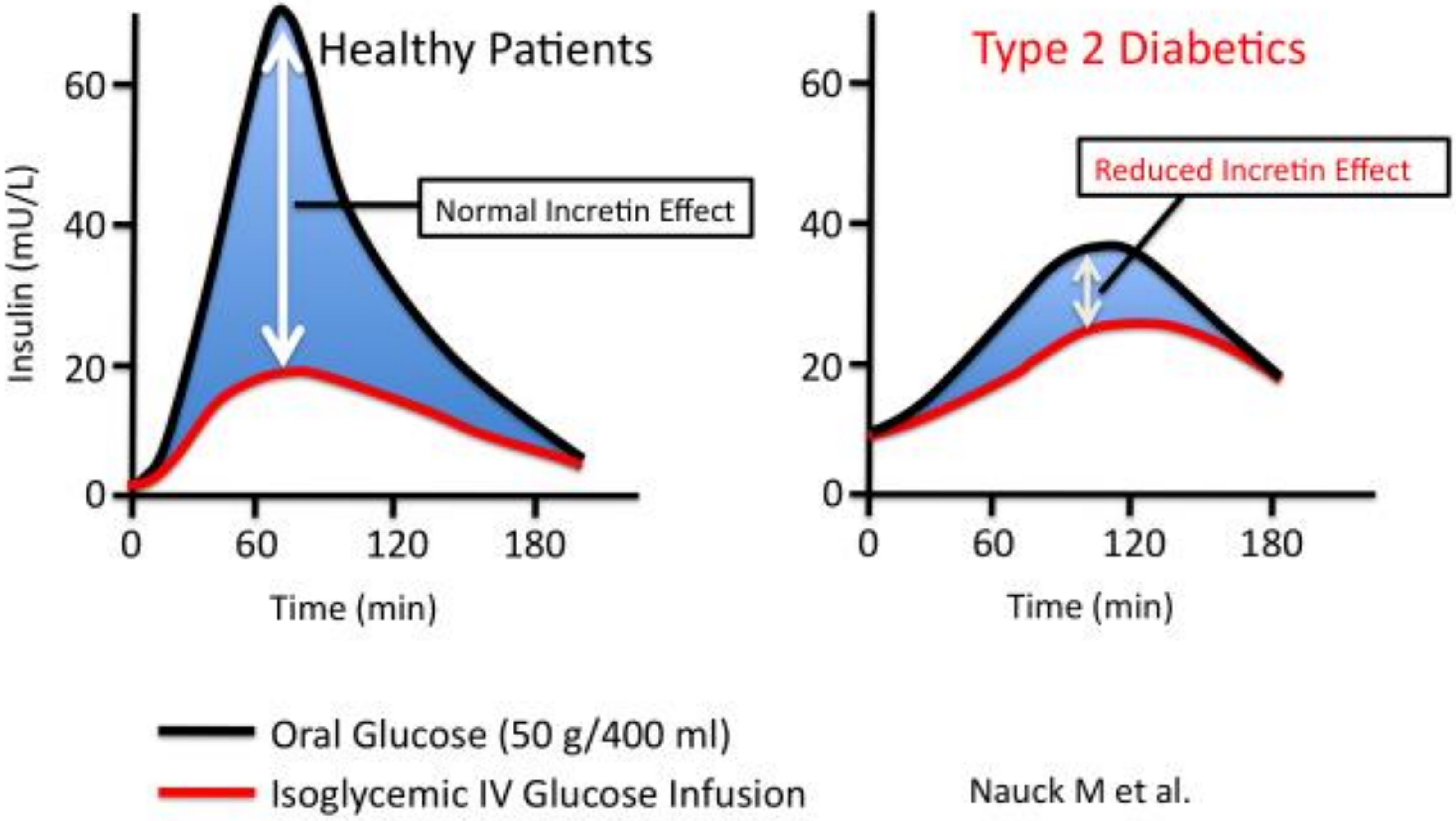
EFFETTO INCRETINICO



- La risposta insulinica è maggiore in seguito a carico orale di glucosio rispetto ad una somministrazione di glucosio e.v, nonostante concentrazioni identiche di glucosio plasmatico

Nauck et al. Diabetologia 1986;29:46–52. *p≤0.05. n=8 healthy volunteers

EFFETTO INCRETINICO – PAZIENTI DIABETICI



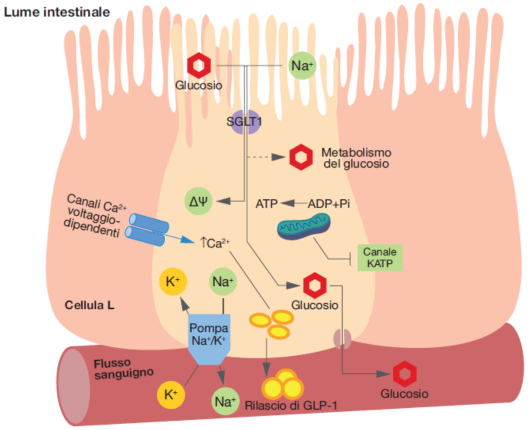
Nauck M et al.
Diabetologia (1986) 29:46-52

INCRETINE

Sono peptidi di origine intestinale secreti in risposta all’ingestione di un pasto che, a concentrazioni fisiologiche, stimolano la liberazione di insulina

- Glucagon-like peptide1 (GLP-1)
- Glucose-dependent insulinotropic peptide (GIP)

GLP-1

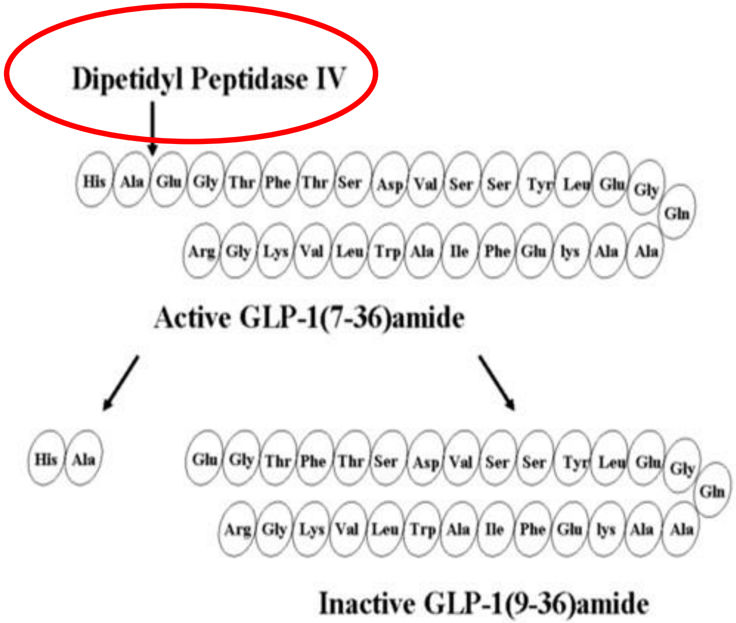

Lume intestinale
Glucosio
Na+
SGLT1
Metabolismo del glucosio
Canali Ca2+ voltaggio-dipendenti
ΔΨ
ATP
ADP+Pi
↑Ca2+
Canale KATP
K+
Na+
Cellula L
Glucosio
Pompa Na+/K+
Flusso sanguigno
K+
Na+
Rilascio di GLP-1
Glucosio

GLP-1 (glucagon-like peptide) è un peptide secreto dalle cellule L dell'intestino in seguito all'assunzione di cibo (glucosio, acidi grassi e alcuni amminoacidi)

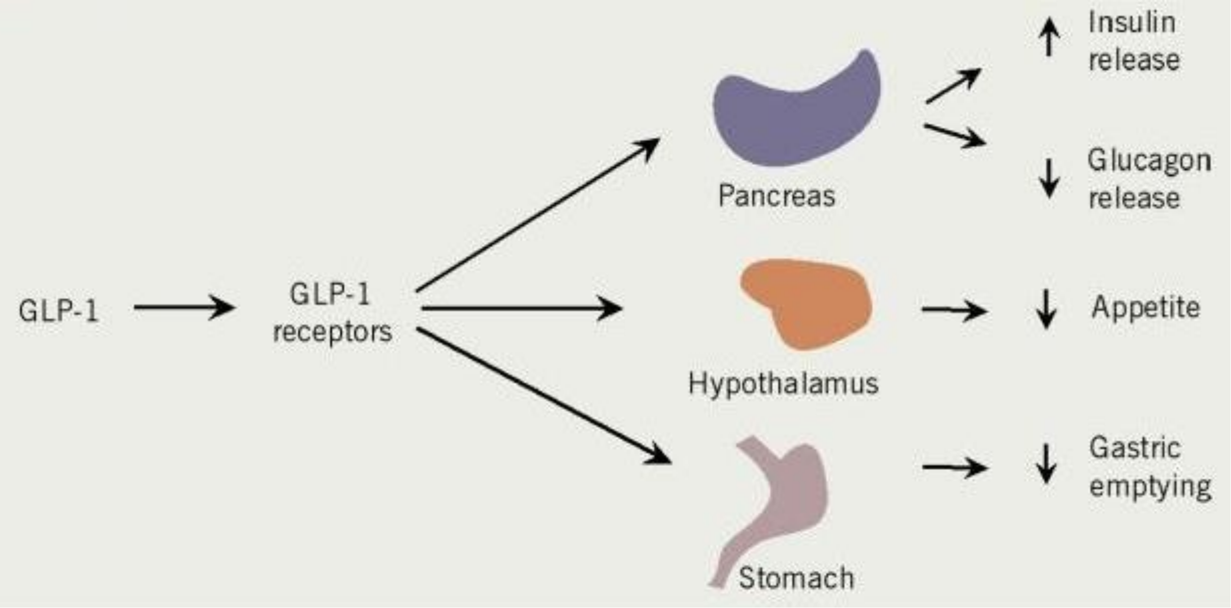
Picco della concentrazione di GLP-1 nel sangue circa 90 min dopo l'assunzione di cibo

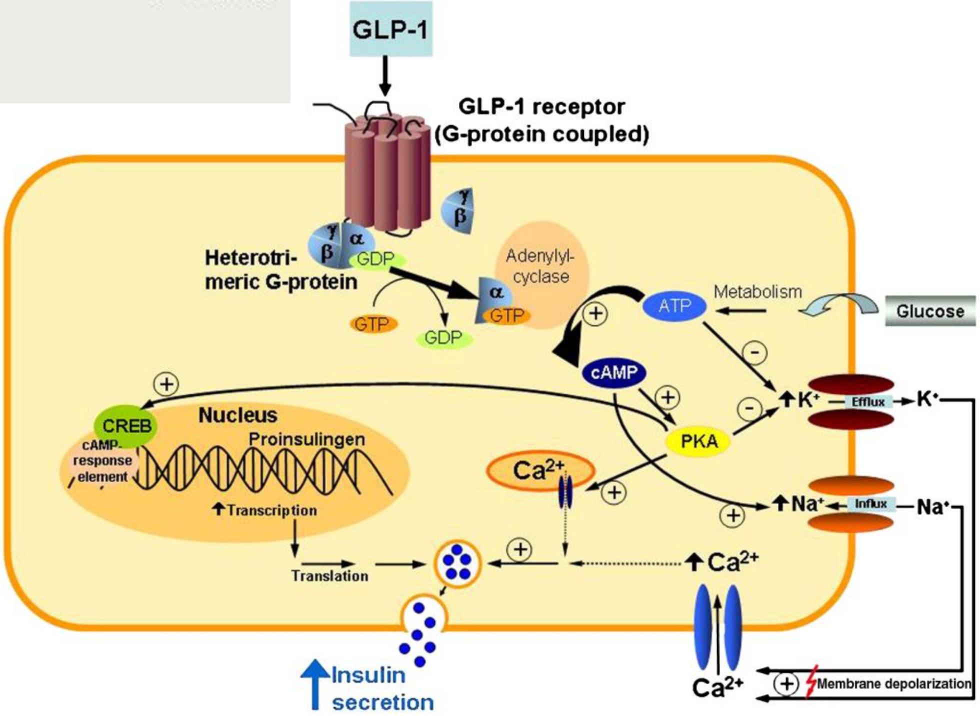
GLP-1 viene sintetizzato a partire dal precursore preproglucagone (179 aa)

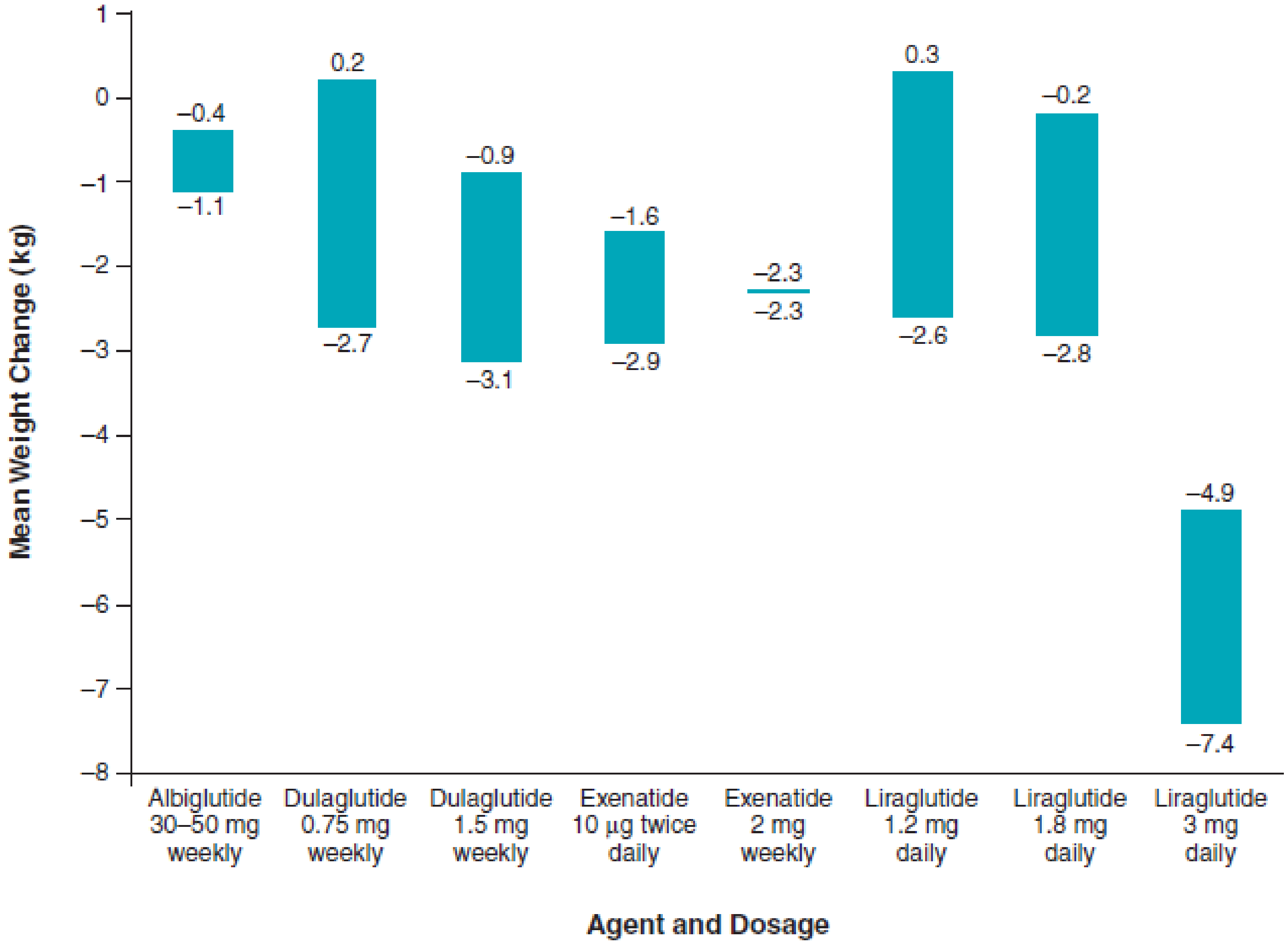
Una volta secreto GLP-1 viene velocemente metabolizzato dagli enzimi DPP-4 – emivita di circa 2 minuti


Dipetidyl Peptidase IV
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
Arg Gly Lys Val Leu Trp Ala Ile Phe Glu lys Ala Ala
Active GLP-1(7-36)amide
His Ala
Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
Arg Gly Lys Val Leu Trp Ala Ile Phe Glu lys Ala Ala
Inactive GLP-1(9-36)amide

RECETTORE GLP-1

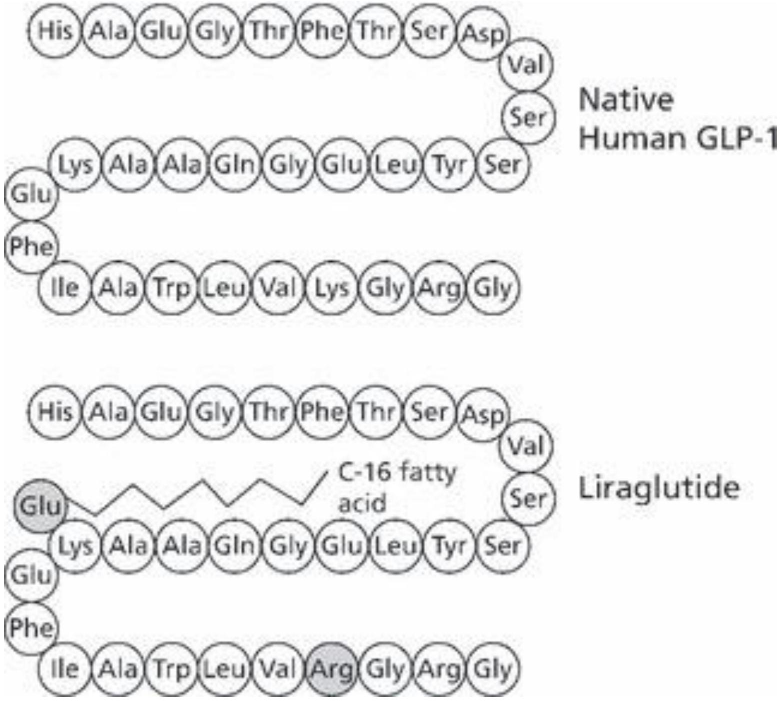

GLP-1
GLP-1 receptors
Pancreas
↑ Insulin release
↓ Glucagon release
Hypothalamus
↓ Appetite
Stomach
↓ Gastric emptying


GLP-1
GLP-1 receptor (G-protein coupled)
γ
β
α
Heterotrimeric G-protein
GDP
GTP
GDP
Adenylyl-cyclase
α
GTP
+
Metabolism
ATP
Glucose
cAMP
-
+
-
↑K+
Efflux
K+
PKA
+
CREB
cAMP-response element
Nucleus
Proinsulingen
↑Transcription
Ca2+
+
+
↑Na+
Influx
Na+
Translation
+
↑Ca2+
↑Insulin secretion
Ca2+
+
Membrane depolarization



Mean Weight Change (kg)
1
0
–1
–2
–3
–4
–5
–6
–7
–8
–0.4
–1.1
0.2
–2.7
–0.9
–3.1
–1.6
–2.9
–2.3
–2.3
0.3
–2.6
–0.2
–2.8
–4.9
–7.4
Albiglutide 30–50 mg weekly
Dulaglutide 0.75 mg weekly
Dulaglutide 1.5 mg weekly
Exenatide 10 µg twice daily
Exenatide 2 mg weekly
Liraglutide 1.2 mg daily
Liraglutide 1.8 mg daily
Liraglutide 3 mg daily
Agent and Dosage

LIRAGLUTIDE


His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly
Native Human GLP-1
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly
Glu
C-16 fatty acid
Liraglutide

Liraglutide si differenzia da GLP-1 soltanto in due amminoacidi e per la presenza di una catena di acido grasso di 16 atomi di carbonio (acido palmitico)

Questa modifica chimica rende liraglutide resistente alla degradazione enzimatica e in grado di legare le proteine plasmatiche. Lirglutide ha un’emivita di circa 13 ore in seguito a somministrazione s.c.

Liraglutide viene somministrata s.c., una volta al giorno, dose 3 mg

NEW
Saxenda®
liraglutide (rDNA origin) injection

STUDI PRECLINICI

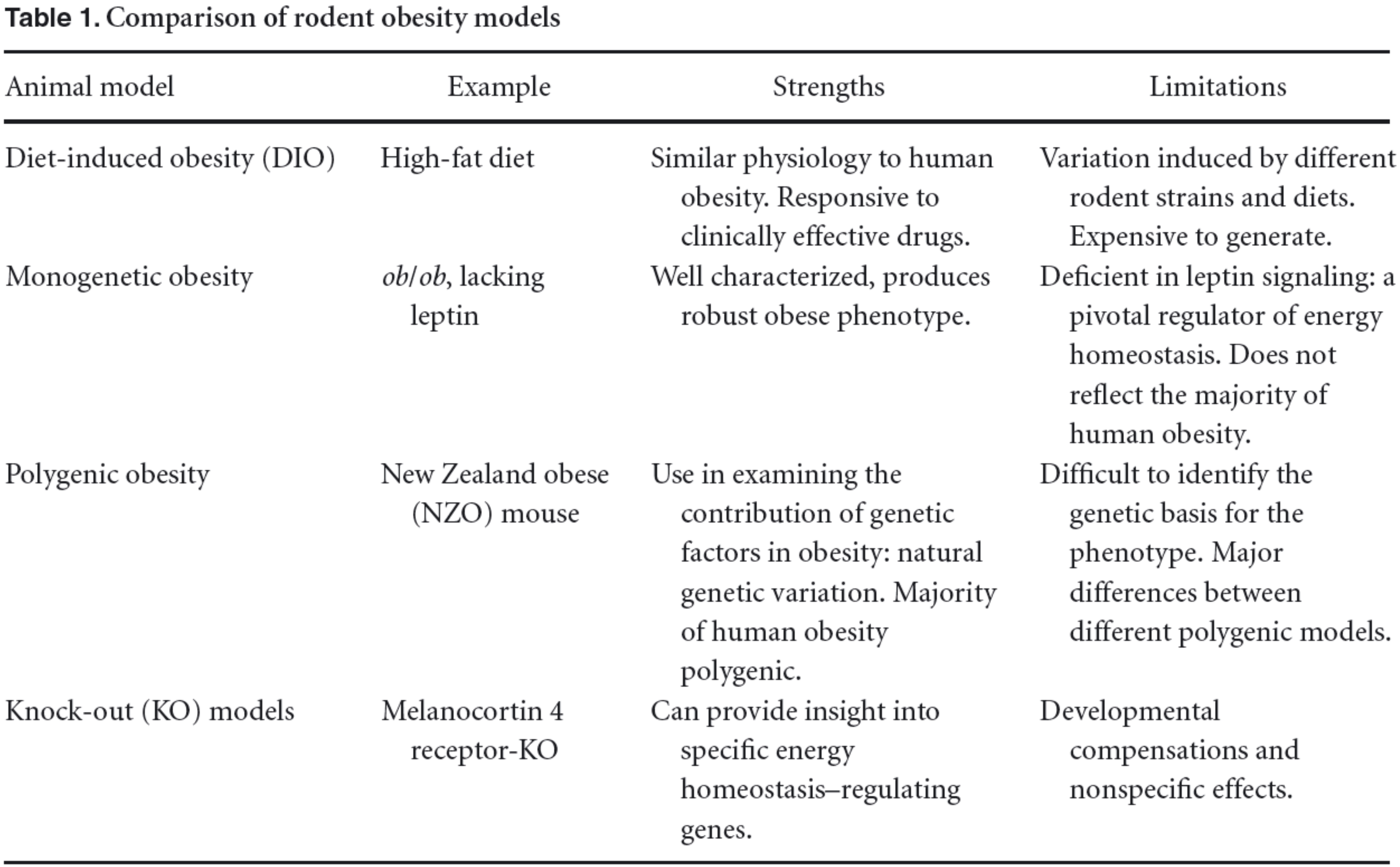
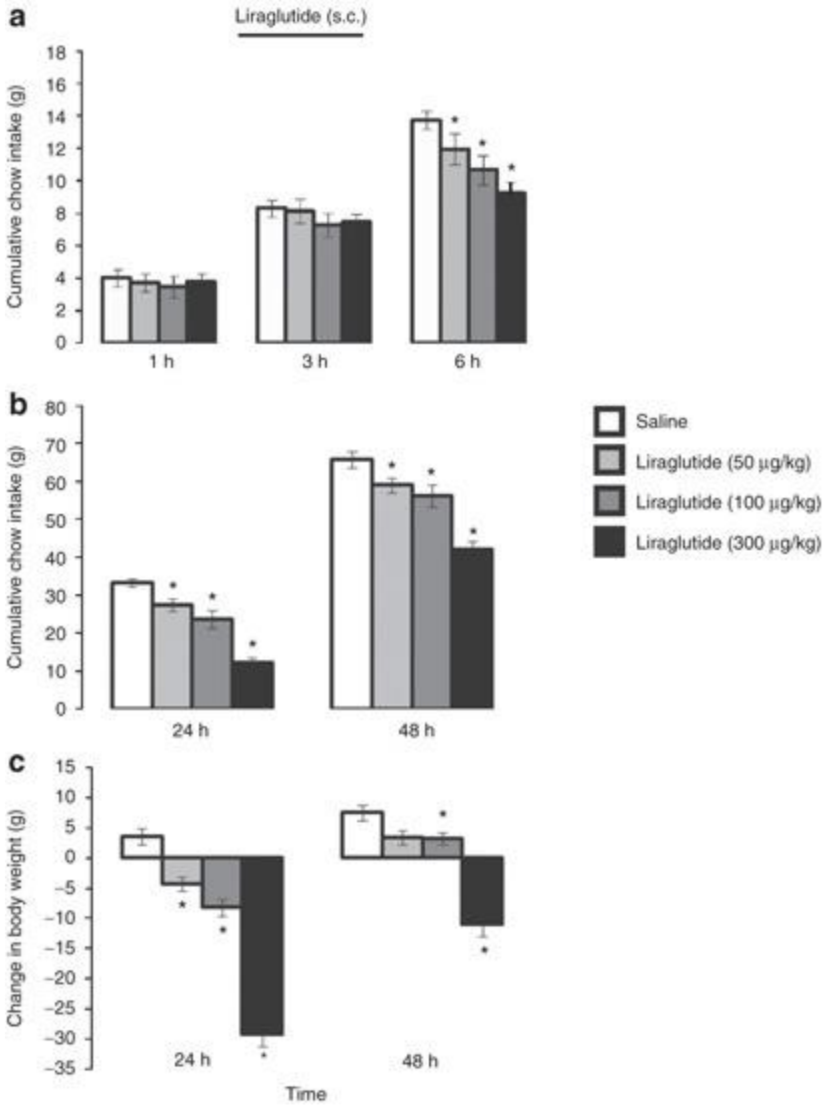


Table 1. Comparison of rodent obesity models

Animal model	Example	Strengths	Limitations
Diet-induced obesity (DIO)	High-fat diet	Similar physiology to human obesity. Responsive to clinically effective drugs.	Variation induced by different rodent strains and diets. Expensive to generate.
Monogenetic obesity	*ob*/*ob*, lacking leptin	Well characterized, produces robust obese phenotype.	Deficient in leptin signaling: a pivotal regulator of energy homeostasis. Does not reflect the majority of human obesity.
Polygenic obesity	New Zealand obese (NZO) mouse	Use in examining the contribution of genetic factors in obesity: natural genetic variation. Majority of human obesity polygenic.	Difficult to identify the genetic basis for the phenotype. Major differences between different polygenic models.
Knock-out (KO) models	Melanocortin 4 receptor-KO	Can provide insight into specific energy homeostasis–regulating genes.	Developmental compensations and nonspecific effects.

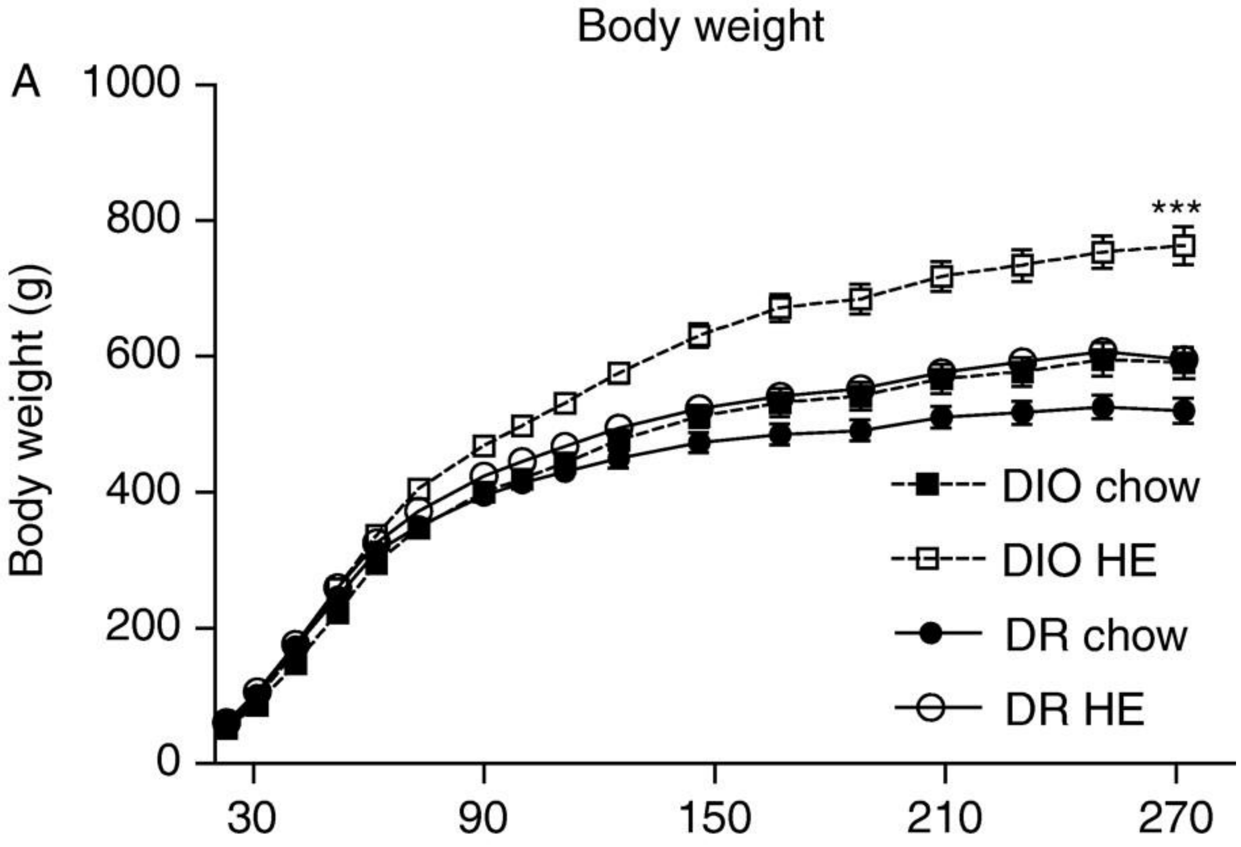
LIRAGLUTIDE – STUDI PRECLINICI

RATTI NORMALI – DIETA NORMALE – SOMMINISTRAZIONE ACUTA



Hayes et al. 2011

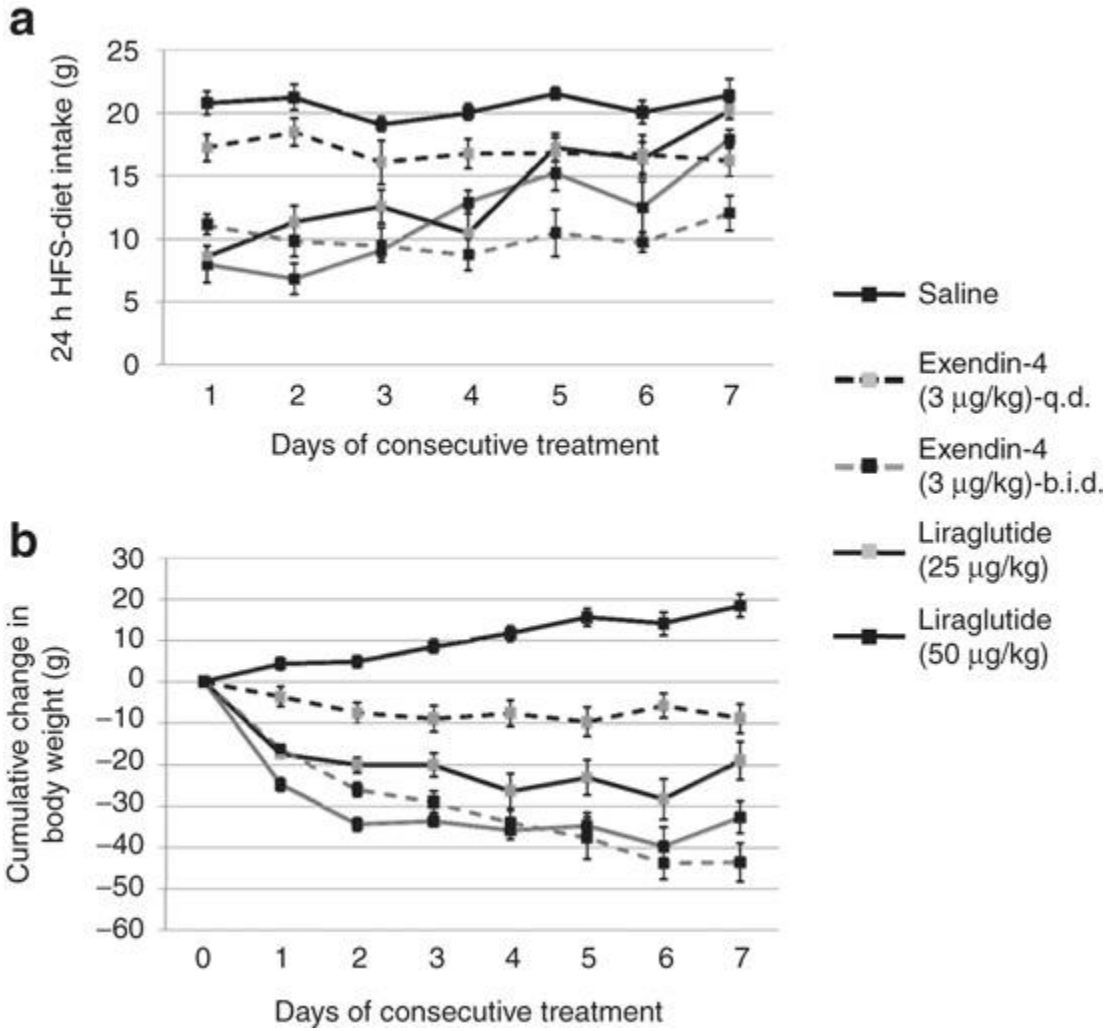
RATTI DIO



Andreas Nygaard Madsen et al. J Endocrinol 2010;206:287-296

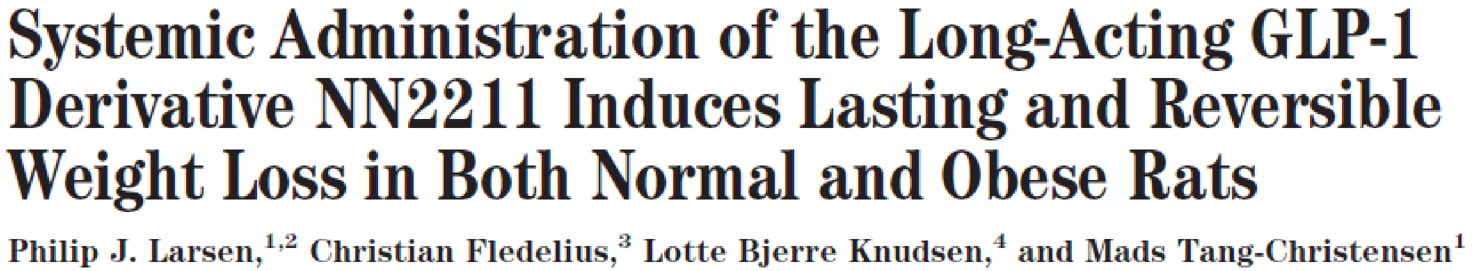
LIRAGLUTIDE – STUDI PRECLINICI

RATTI RESI OBESI CON LA DIETA (DIO) – DIETA RICCA IN ZUCCHERI E GRASSI – SOMMINISTRAZIONE CRONICA



Hayes et al. 2011

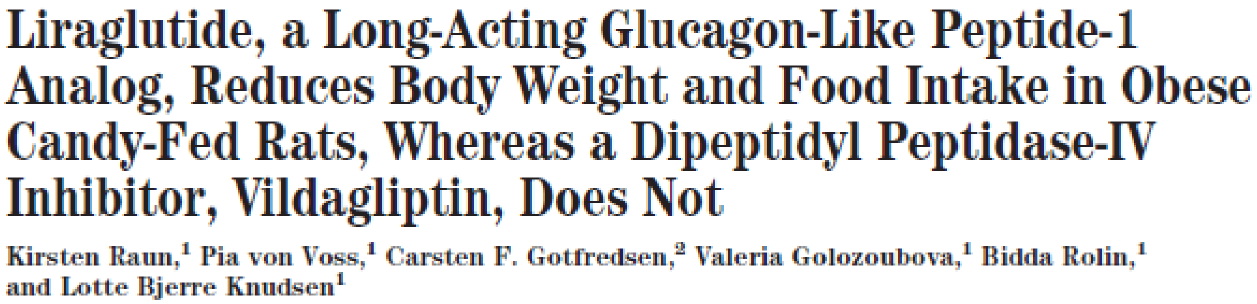
LIRAGLUTIDE – STUDI PRECLINICI



Systemic Administration of the Long-Acting GLP-1 Derivative NN2211 Induces Lasting and Reversible Weight Loss in Both Normal and Obese Rats

Philip J. Larsen,[1,2] Christian Fledelius,[3] Lotte Bjerre Knudsen,[4] and Mads Tang-Christensen[1]

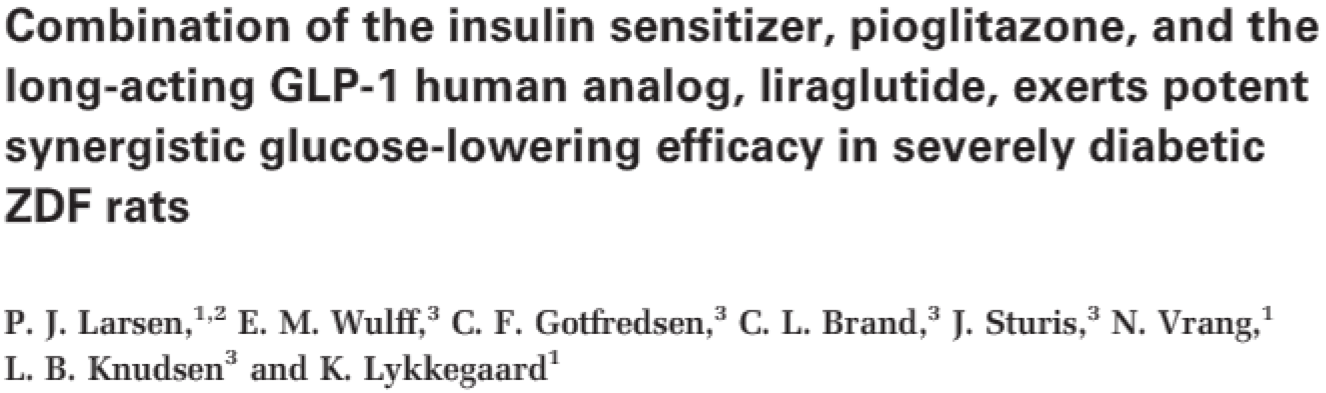
RATTI OBESI MSG (iniezioni di glutammato i primi giorni dopo la nascita)



Liraglutide, a Long-Acting Glucagon-Like Peptide-1 Analog, Reduces Body Weight and Food Intake in Obese Candy-Fed Rats, Whereas a Dipeptidyl Peptidase-IV Inhibitor, Vildagliptin, Does Not

Kirsten Raun,[1] Pia von Voss,[1] Carsten F. Gotfredsen,[2] Valeria Golozoubova,[1] Bidda Rolin,[1] and Lotte Bjerre Knudsen[1]

RATTI SOTTOPOSTI A «DIETA DA BAR»



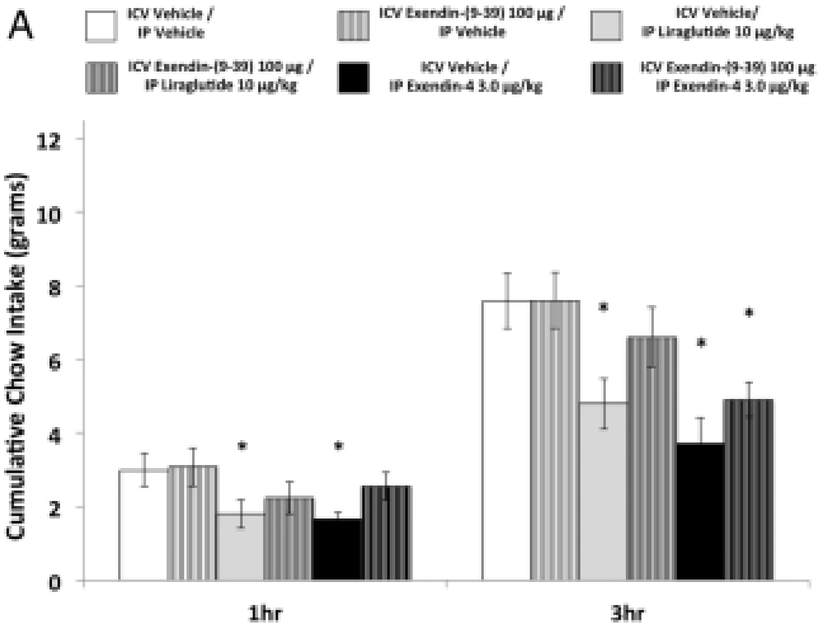
Combination of the insulin sensitizer, pioglitazone, and the long-acting GLP-1 human analog, liraglutide, exerts potent synergistic glucose-lowering efficacy in severely diabetic ZDF rats

P. J. Larsen,[1,2] E. M. Wulff,[3] C. F. Gotfredsen,[3] C. L. Brand,[3] J. Sturis,[3] N. Vrang,[1] L. B. Knudsen[3] and K. Lykkegaard[1]

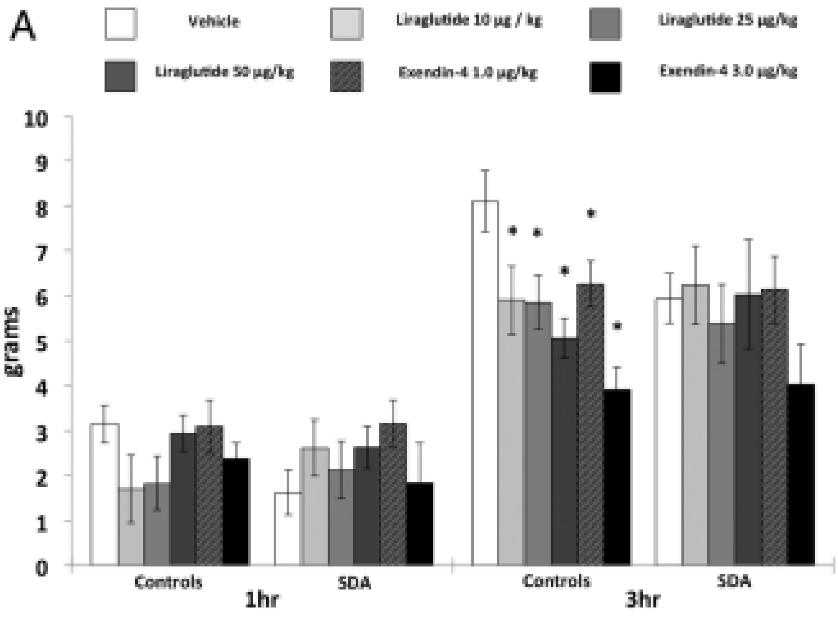
ZUCKER DIABETIC FATTY RATS – linea di ratti obesi che in tarda età sviluppano il diabete

LIRAGLUTIDE – STUDI PRECLINICI

L’antagonista GLP-1R exendin(9-36) dato nel cervello blocca l’effetto di liraglutide ip sull’assunzione di cibo



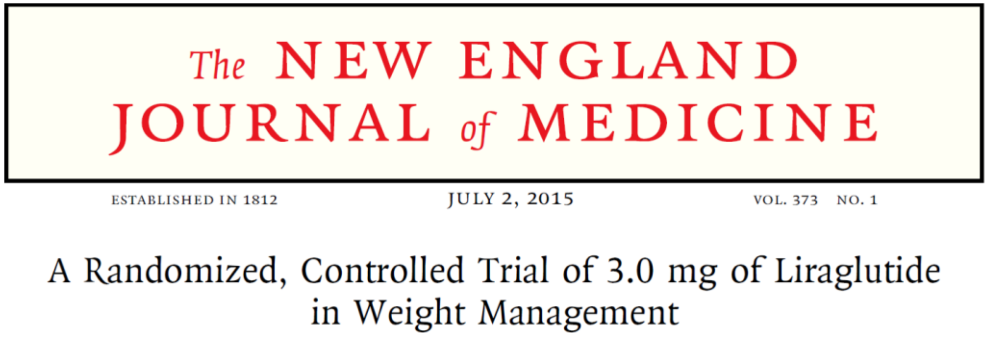
L’effetto di liraglutide sull’assunzione di cibo è ridotto in ratti con lesione subdiaframmatica del nervo vago



Gli studi preclinici dimostrano che liraglutide, in seguito a somministrazione periferica, passa la barriera emato-encefalica e raggiunge i recettori di GLP-1 nel cervello
Sia i recettori presenti nel sistema nervoso centrale che i recettori periferici sul nervo vago sono importanti per l’azione anoresizzante di liraglutide

Kanoski et al. 2011

LIRAGLUTIDE – STUDI CLINICI



The NEW ENGLAND JOURNAL of MEDICINE

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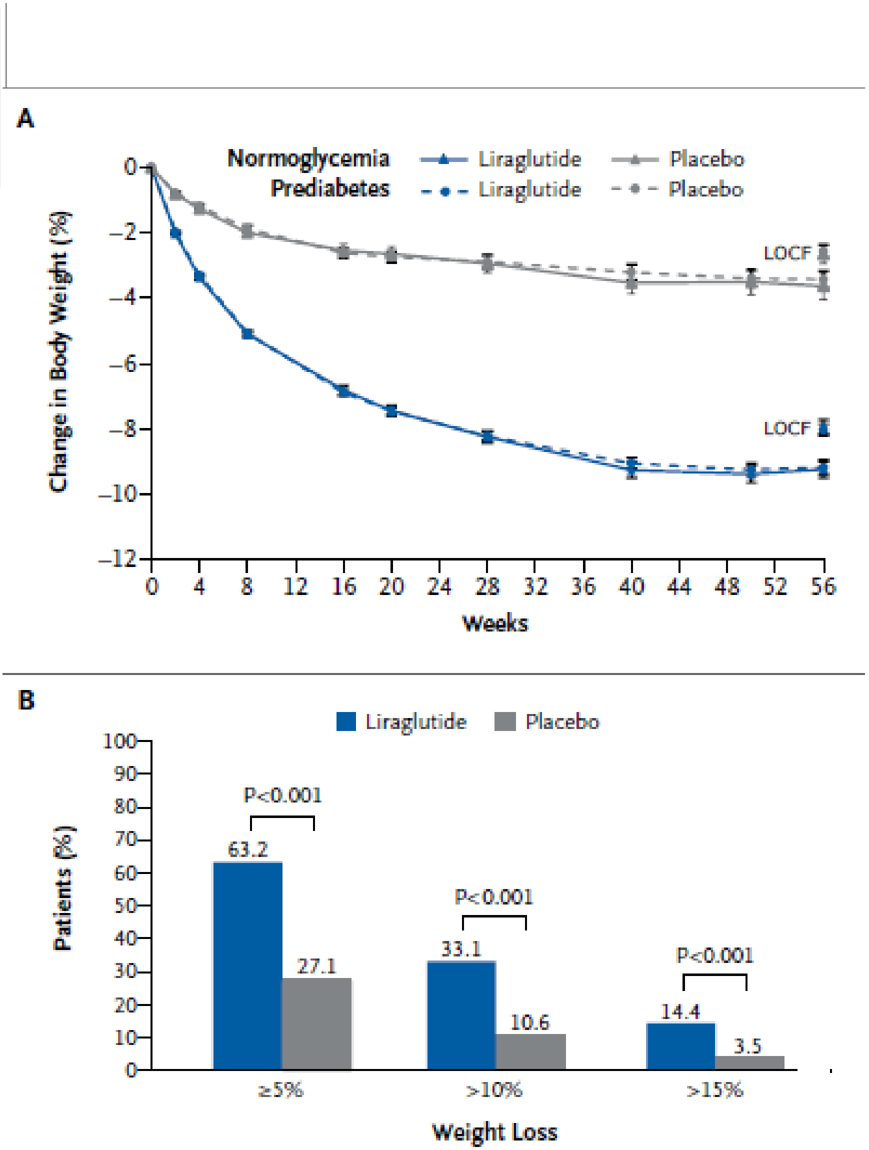
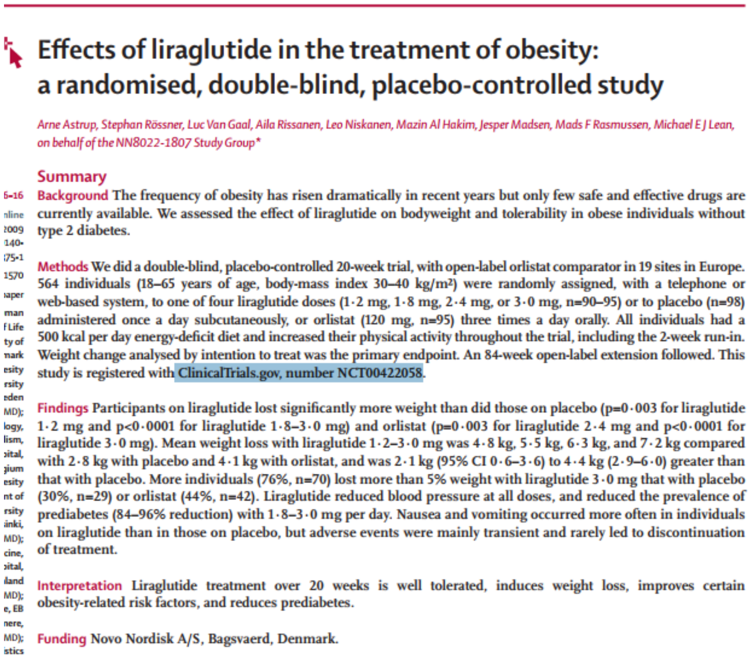
A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management



Pi-Sunyer et al. 2015

LIRAGLUTIDE – STUDI CLINICI



Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study

*Arne Astrup, Stephan Rössner, Luc Van Gaal, Aila Rissanen, Leo Niskanen, Mazin Al Hakim, Jesper Madsen, Mads F Rasmussen, Michael E J Lean, on behalf of the NN8022-1807 Study Group**

Summary

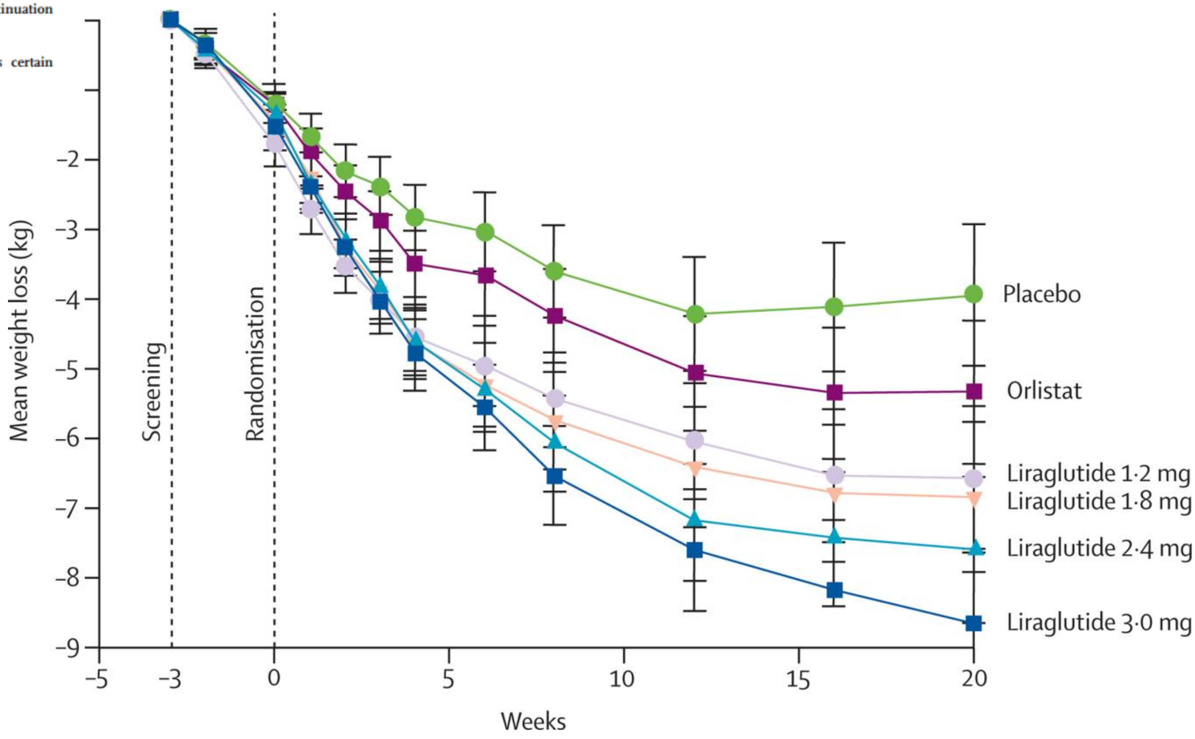
Background The frequency of obesity has risen dramatically in recent years but only few safe and effective drugs are currently available. We assessed the effect of liraglutide on bodyweight and tolerability in obese individuals without type 2 diabetes.

Methods We did a double-blind, placebo-controlled 20-week trial, with open-label orlistat comparator in 19 sites in Europe. 564 individuals (18–65 years of age, body-mass index 30–40 kg/m^2) were randomly assigned, with a telephone or web-based system, to one of four liraglutide doses (1·2 mg, 1·8 mg, 2·4 mg, or 3·0 mg, n=90–95) or to placebo (n=98) administered once a day subcutaneously, or orlistat (120 mg, n=95) three times a day orally. All individuals had a 500 kcal per day energy-deficit diet and increased their physical activity throughout the trial, including the 2-week run-in. Weight change analysed by intention to treat was the primary endpoint. An 84-week open-label extension followed. This study is registered with ClinicalTrials.gov, number NCT00422058.

Findings Participants on liraglutide lost significantly more weight than did those on placebo ($p=0·003$ for liraglutide 1·2 mg and $p<0·0001$ for liraglutide 1·8–3·0 mg) and orlistat ($p=0·003$ for liraglutide 2·4 mg and $p<0·0001$ for liraglutide 3·0 mg). Mean weight loss with liraglutide 1·2–3·0 mg was 4·8 kg, 5·5 kg, 6·3 kg, and 7·2 kg compared with 2·8 kg with placebo and 4·1 kg with orlistat, and was 2·1 kg (95% CI 0·6–3·6) to 4·4 kg (2·9–6·0) greater than that with placebo. More individuals (76%, n=70) lost more than 5% weight with liraglutide 3·0 mg that with placebo (30%, n=29) or orlistat (44%, n=42). Liraglutide reduced blood pressure at all doses, and reduced the prevalence of prediabetes (84–96% reduction) with 1·8–3·0 mg per day. Nausea and vomiting occurred more often in individuals on liraglutide than in those on placebo, but adverse events were mainly transient and rarely led to discontinuation of treatment.

Interpretation Liraglutide treatment over 20 weeks is well tolerated, induces weight loss, improves certain obesity-related risk factors, and reduces prediabetes.

Funding Novo Nordisk A/S, Bagsvaerd, Denmark.



LIRAGLUTIDE – STUDI CLINICI

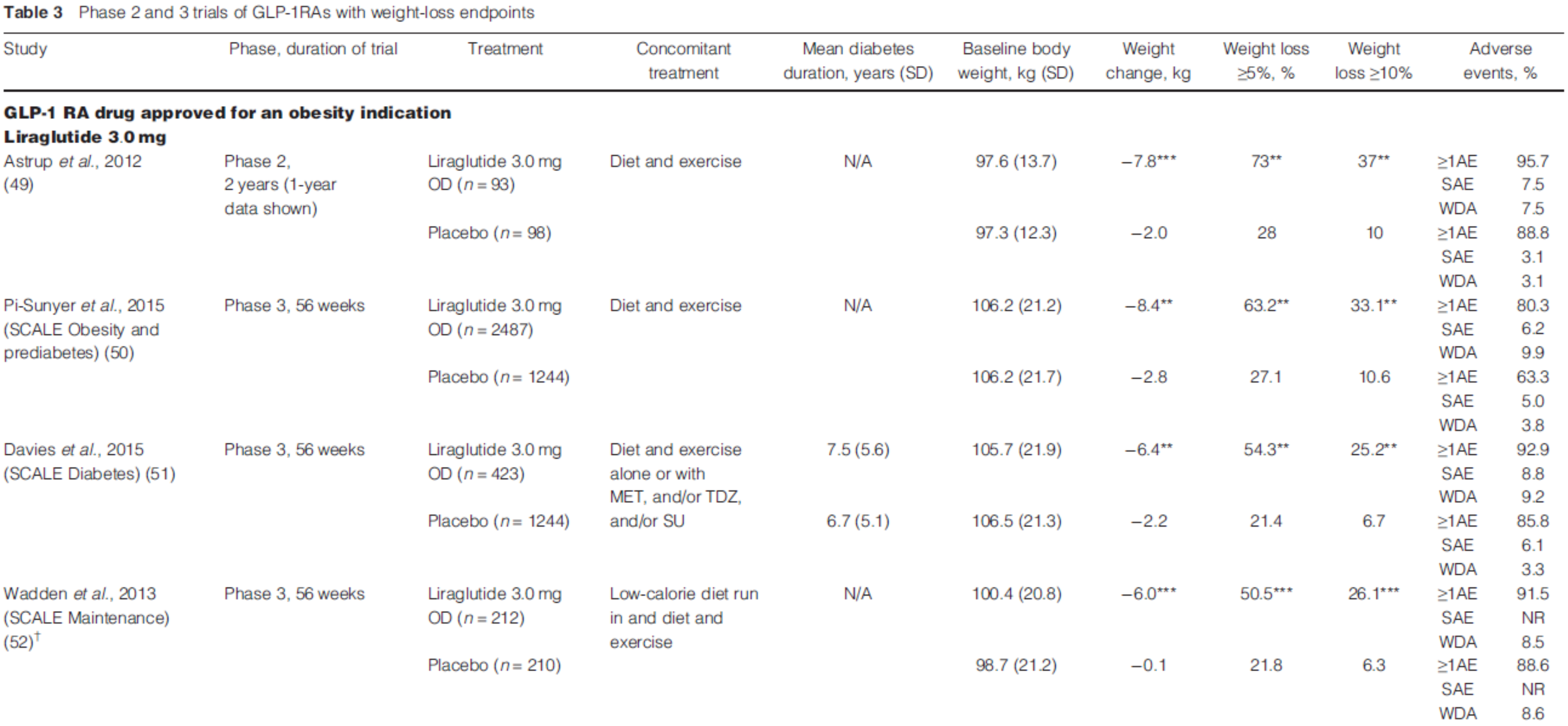


Table 3 Phase 2 and 3 trials of GLP-1RAs with weight-loss endpoints

Study	Phase, duration of trial	Treatment	Concomitant treatment	Mean diabetes duration, years (SD)	Baseline body weight, kg (SD)	Weight change, kg	Weight loss ≥5%, %	Weight loss ≥10%	Adverse events, %	
GLP-1 RA drug approved for an obesity indication										
Liraglutide 3.0 mg										
Astrup *et al.*, 2012 (49)	Phase 2, 2 years (1-year data shown)	Liraglutide 3.0 mg OD (*n* = 93)	Diet and exercise	N/A	97.6 (13.7)	−7.8***	73**	37**	≥1AE SAE WDA	95.7 7.5 7.5
		Placebo (*n* = 98)			97.3 (12.3)	−2.0	28	10	≥1AE SAE WDA	88.8 3.1 3.1
Pi-Sunyer *et al.*, 2015 (SCALE Obesity and prediabetes) (50)	Phase 3, 56 weeks	Liraglutide 3.0 mg OD (*n* = 2487)	Diet and exercise	N/A	106.2 (21.2)	−8.4**	63.2**	33.1**	≥1AE SAE WDA	80.3 6.2 9.9
		Placebo (*n* = 1244)			106.2 (21.7)	−2.8	27.1	10.6	≥1AE SAE WDA	63.3 5.0 3.8
Davies *et al.*, 2015 (SCALE Diabetes) (51)	Phase 3, 56 weeks	Liraglutide 3.0 mg OD (*n* = 423)	Diet and exercise alone or with MET, and/or TDZ, and/or SU	7.5 (5.6)	105.7 (21.9)	−6.4**	54.3**	25.2**	≥1AE SAE WDA	92.9 8.8 9.2
		Placebo (*n* = 1244)		6.7 (5.1)	106.5 (21.3)	−2.2	21.4	6.7	≥1AE SAE WDA	85.8 6.1 3.3
Wadden *et al.*, 2013 (SCALE Maintenance) (52)†	Phase 3, 56 weeks	Liraglutide 3.0 mg OD (*n* = 212)	Low-calorie diet run in and diet and exercise	N/A	100.4 (20.8)	−6.0***	50.5***	26.1***	≥1AE SAE WDA	91.5 NR 8.5
		Placebo (*n* = 210)			98.7 (21.2)	−0.1	21.8	6.3	≥1AE SAE WDA	88.6 NR 8.6

LIRAGLUTIDE – STUDI CLINICI – EVENTI AVVERSI

Frequenti:
Nausea, vomito e diarrea nella fase iniziale del trattamento
Leggera tachicardia

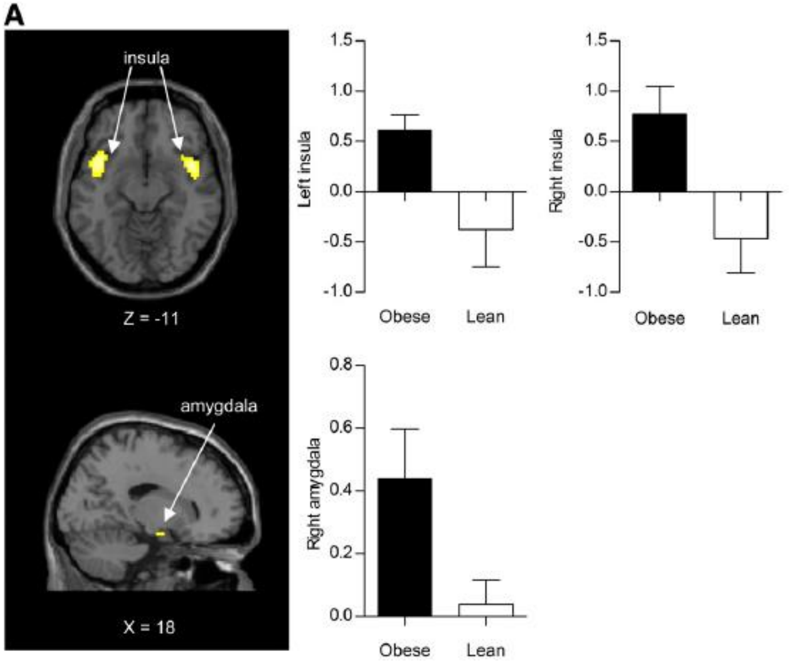
Rari:
Pancratite (< 0.001%)

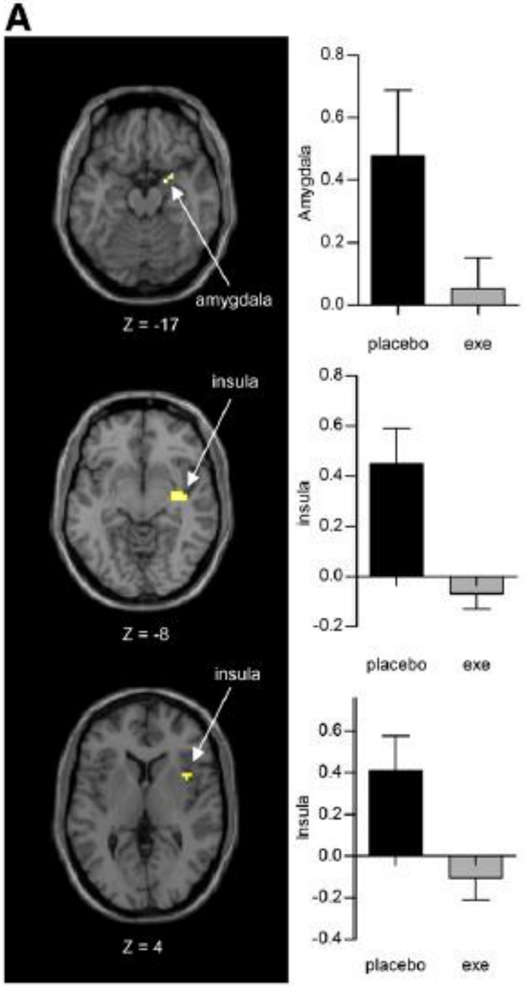
Farmaco complessivamente ben tollerato

Liselotte van Bloemendaal,[1] Richard G. IJzerman,[1] Jennifer S. ten Kulve,[1] Frederik Barkhof,[2]
Robert J. Konrad,[3] Madeleine L. Drent,[4] Dick J. Veltman,[5] and Michaela Diamant[1†]

GLP-1 Receptor Activation Modulates Appetite- and Reward-Related Brain Areas in Humans

Diabetes 2014;63:4186–4196 | DOI: 10.2337/db14-0849


A
insula
Z = -11
amygdala
X = 18
Left insula
1.5
1.0
0.5
0.0
-0.5
-1.0
Obese
Lean
Right insula
1.5
1.0
0.5
0.0
-0.5
-1.0
Obese
Lean
Right amygdala
0.8
0.6
0.4
0.2
0.0
Obese
Lean


A
amygdala
Z = -17
Amygdala
0.8
0.6
0.4
0.2
0.0
placebo
exe
insula
Z = -8
Insula
0.8
0.6
0.4
0.2
0.0
-0.2
placebo
exe
insula
Z = 4
Insula
0.6
0.4
0.2
0.0
-0.2
-0.4
placebo
exe

L'insula e l'amigdala sono aree del cervello importanti per la gratificazione indotta dal cibo e per il desiderio di cibo buono. Uno studio fatto con la **risonanza magnetica funzionale** ha dimostrato che queste aree si attivano quando si guardano immagini di cibi appetibili e questa attivazione è maggiore nei soggetti obesi. L'assunzione di un agonista GLP-1 prima di guardare le immagini riduce l'attivazione di queste aree. L'azione degli agonisti GLP-1 sui meccanismi di gratificazione da cibo potrebbe essere uno dei meccanismi attraverso cui questa classe di farmaci induce diminuzione dell'assunzione di cibo

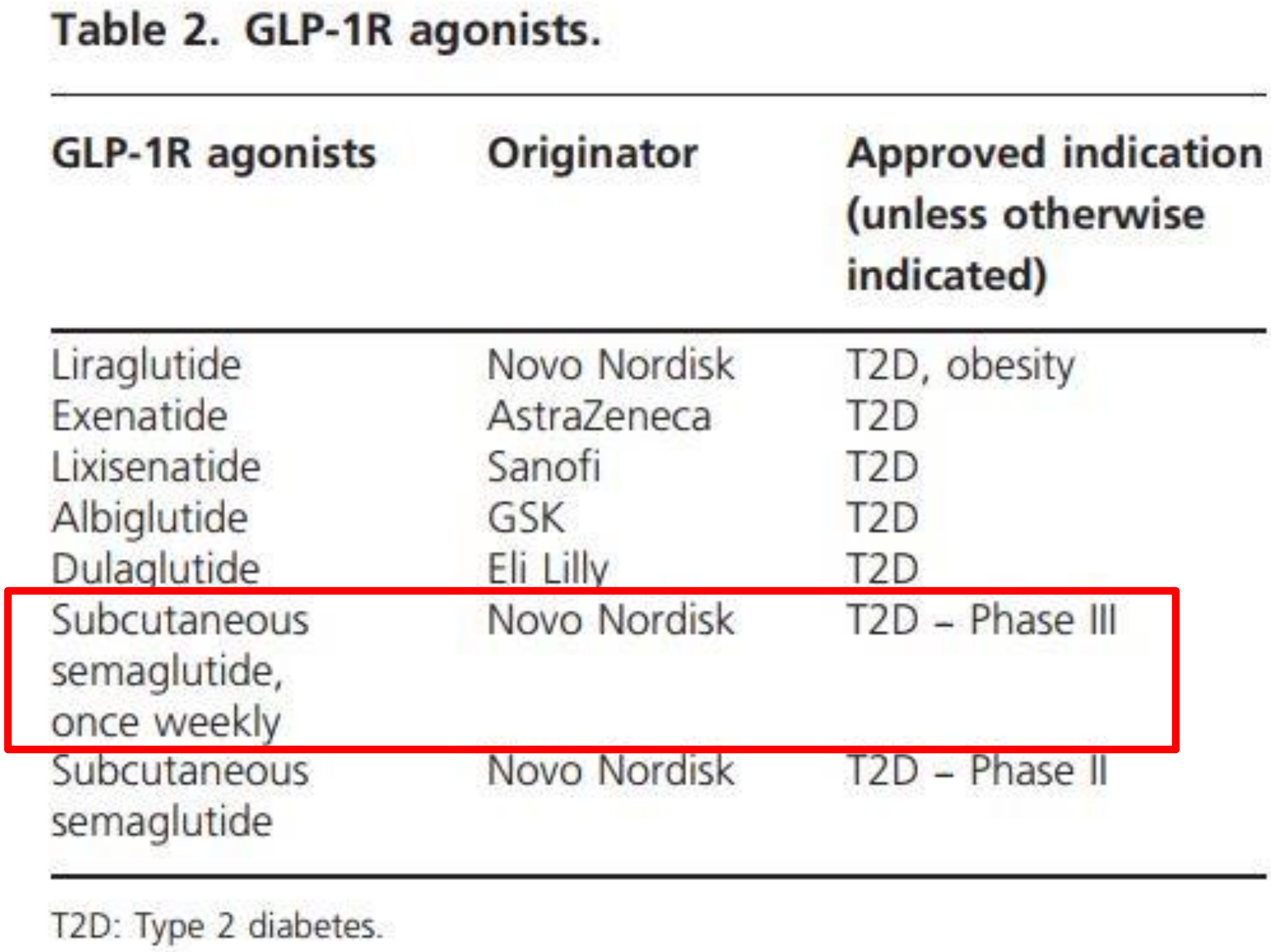


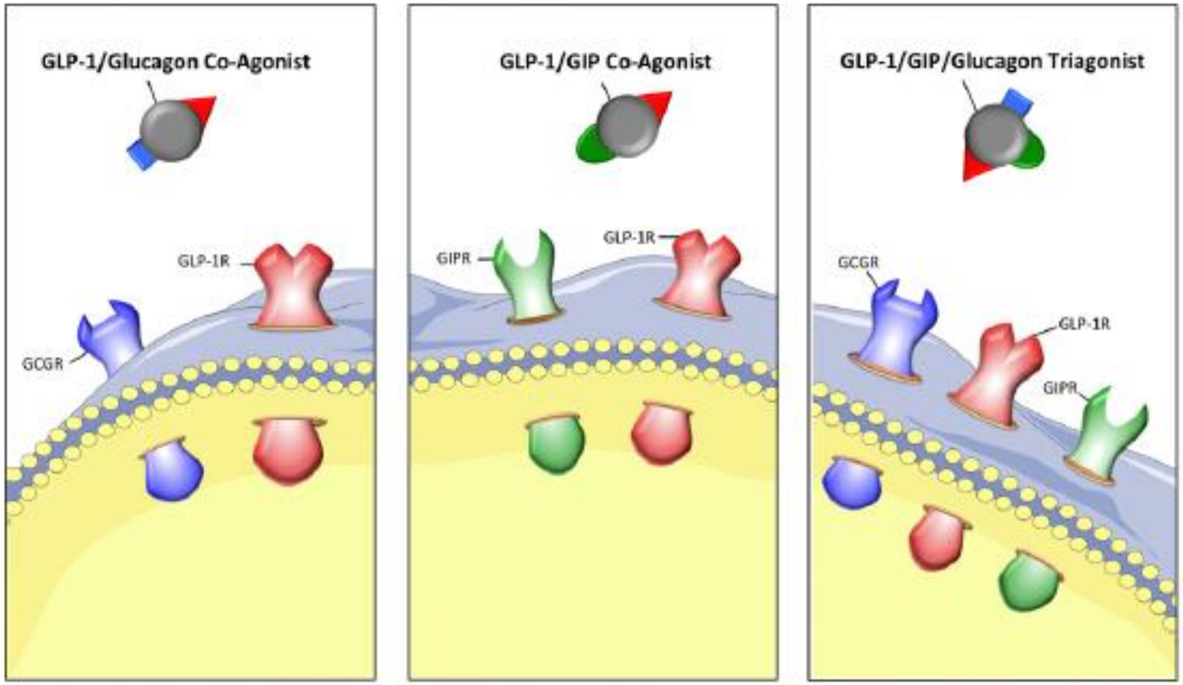
Table 2. GLP-1R agonists.

GLP-1R agonists	Originator	Approved indication (unless otherwise indicated)
Liraglutide	Novo Nordisk	T2D, obesity
Exenatide	AstraZeneca	T2D
Lixisenatide	Sanofi	T2D
Albiglutide	GSK	T2D
Dulaglutide	Eli Lilly	T2D
Subcutaneous semaglutide, once weekly	Novo Nordisk	T2D – Phase III
Subcutaneous semaglutide	Novo Nordisk	T2D – Phase II

T2D: Type 2 diabetes.

Un agonista non peptidico (somministrazione orale) è entrato in sperimentazione clinica (OWL833, Eli Lilly)

PROSPETTIVE FUTURE- agonisti multi-target


GLP-1/Glucagon Co-Agonist
GLP-1R
GCGR
GLP-1/GIP Co-Agonist
GIPR
GLP-1R
GLP-1/GIP/Glucagon Triagonist
GCGR
GLP-1R
GIPR

Improves

Body weight
Energy Expenditure
Glycemic control
Cholesterol

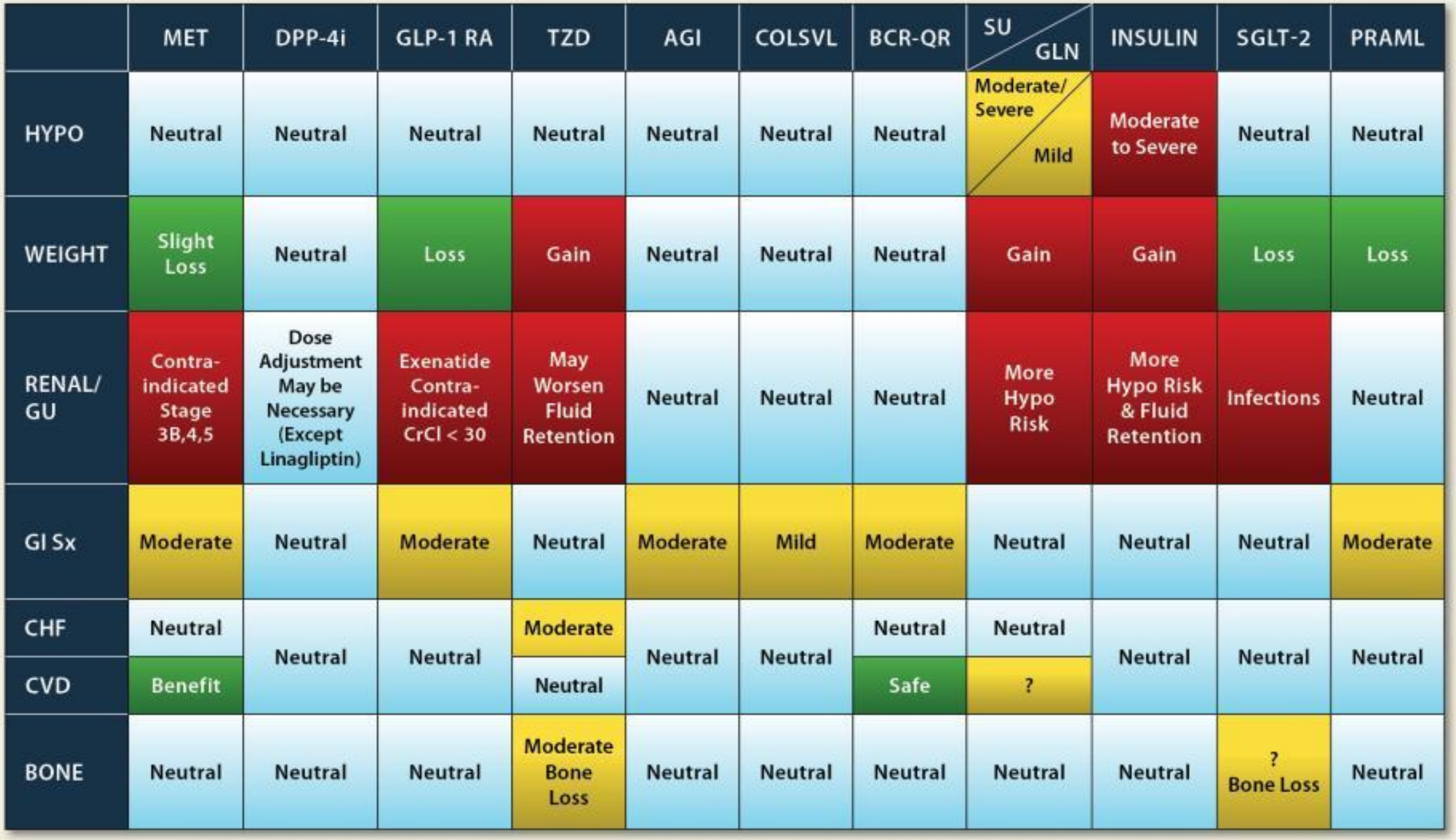
Improves

Glycemic control
Body weight
Lipolysis
Cholesterol

Improves

Body weight
Glycemic control
Hepatosteatosis
Cholesterol
Energy Expenditure
Lipolysis

PROFILES OF ANTIDIABETIC MEDICATIONS



	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU/GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

🟩 Few adverse events or possible benefits 🟨 Use with caution 🟥 Likelihood of adverse effects

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