The Story of Incretin Therapies

Grace B. Athas, Ph.D., MLS
Department of Pathology LSUHSC – NO

CLPC Spring series

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Learning Objectives

- Explain the physiology of incretins and incretin receptor agonists on regulating blood sugar and metabolic homeostasis
- Identify indications and contraindications for treatment with incretins
- Discuss side effects and multifaceted roles for incretin therapies

Lecture outline

- Incretins – definitions & discoveries
- Diabetes & pharmacologic therapies
- Obesity – definitions & treatments
- Incretin drugs –mechanisms of action, affects on other organs, adverse reactions
- Societal repercussions ramifications
- Future outlook

Incretins

- Incretins are gut derived hormones that amplify insulin secretion after meals
- "Incretin Effect" 1964 Oral intake of glucose resulted in greater insulin secretion vs. IV infusion of glucose

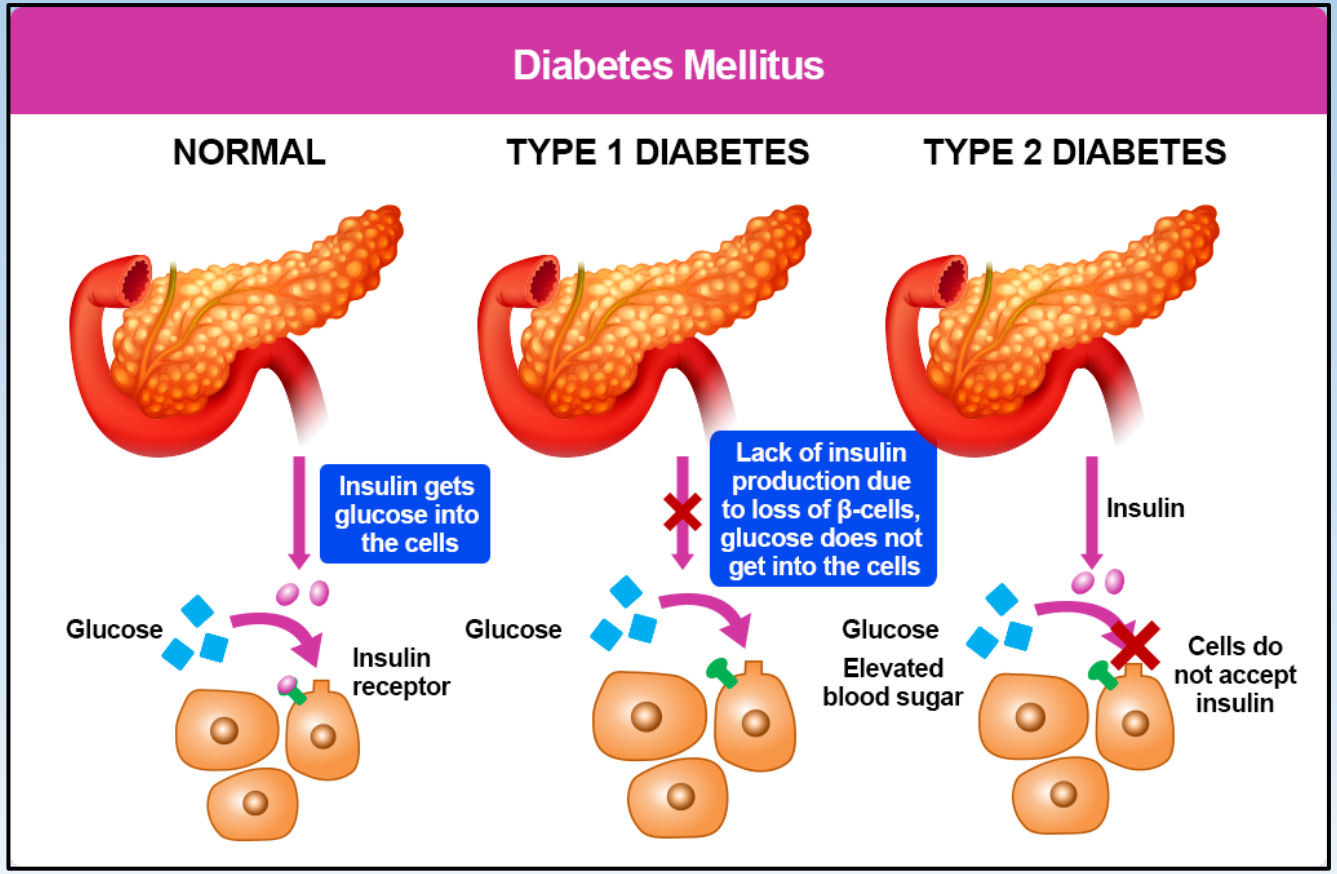
The reason this class of medications, including semaglutide (Ozempic for diabetes and Wegovy for weight loss and tirzepatide ((Mounjaro for Diabetes and Zepbound for weight loss), have captivated society is because of their "unparalleled ability to help patients in their weight loss journey."

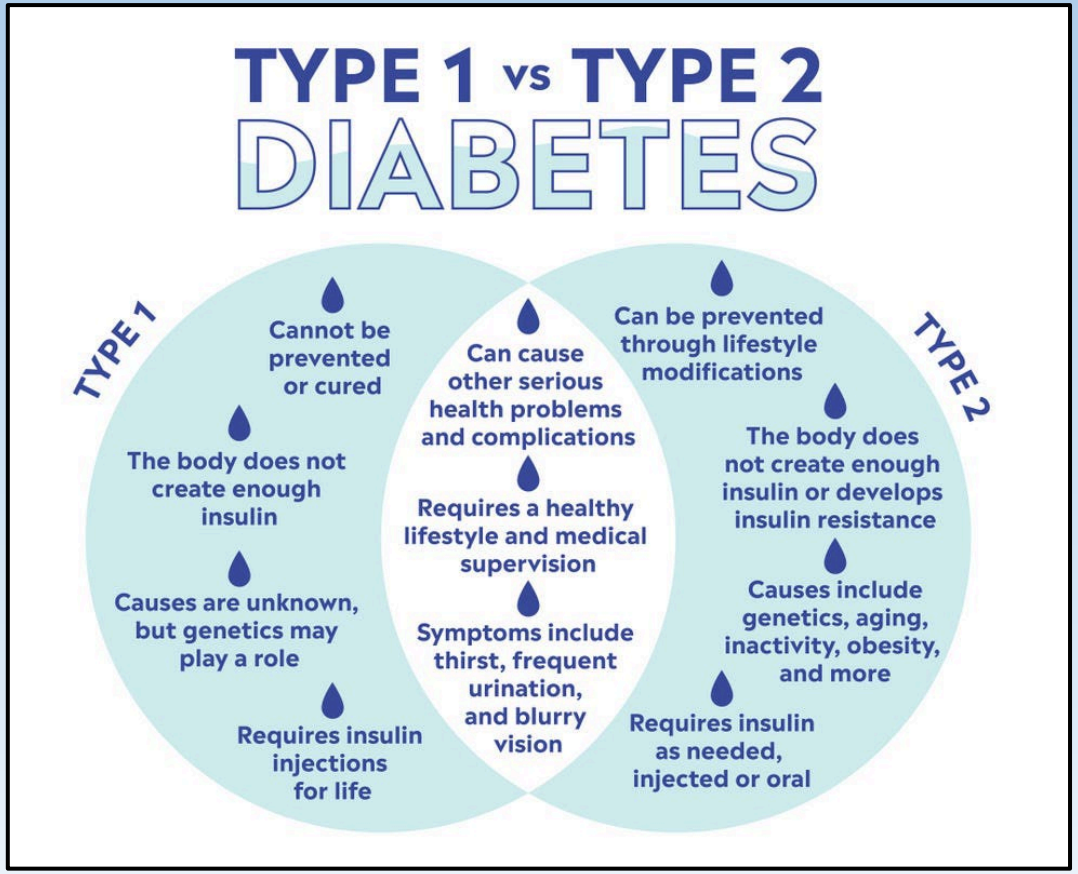
"Discovery" of Incretins follows discovery of Insulin

- In 1889 – research found if removed pancreas from dogs they developed symptoms of diabetes and died soon after "pancreatic substances" were responsible
- Later experiments –narrowed down on the Islets of Langerhans. Hypothesized that one substance was missing from people with diabetes – "Insulin"
- 1921 – removed the "muck" from the pancreas, injected into a dog with surgically induced diabetes & this kept the dog alive (until they ran out of extract.)
- 1922 -Further refined the extraction process in cattle & injected a 14 yr old dying of diabetes –he was saved
- 1923 Nobel prize. Patent sold to U Toronto for $1-believed saving lives should not be profited from
- Eli Lilly started large scale production of insulins from cattle & pigs
- Human insulin cloned in bacteria in 1978

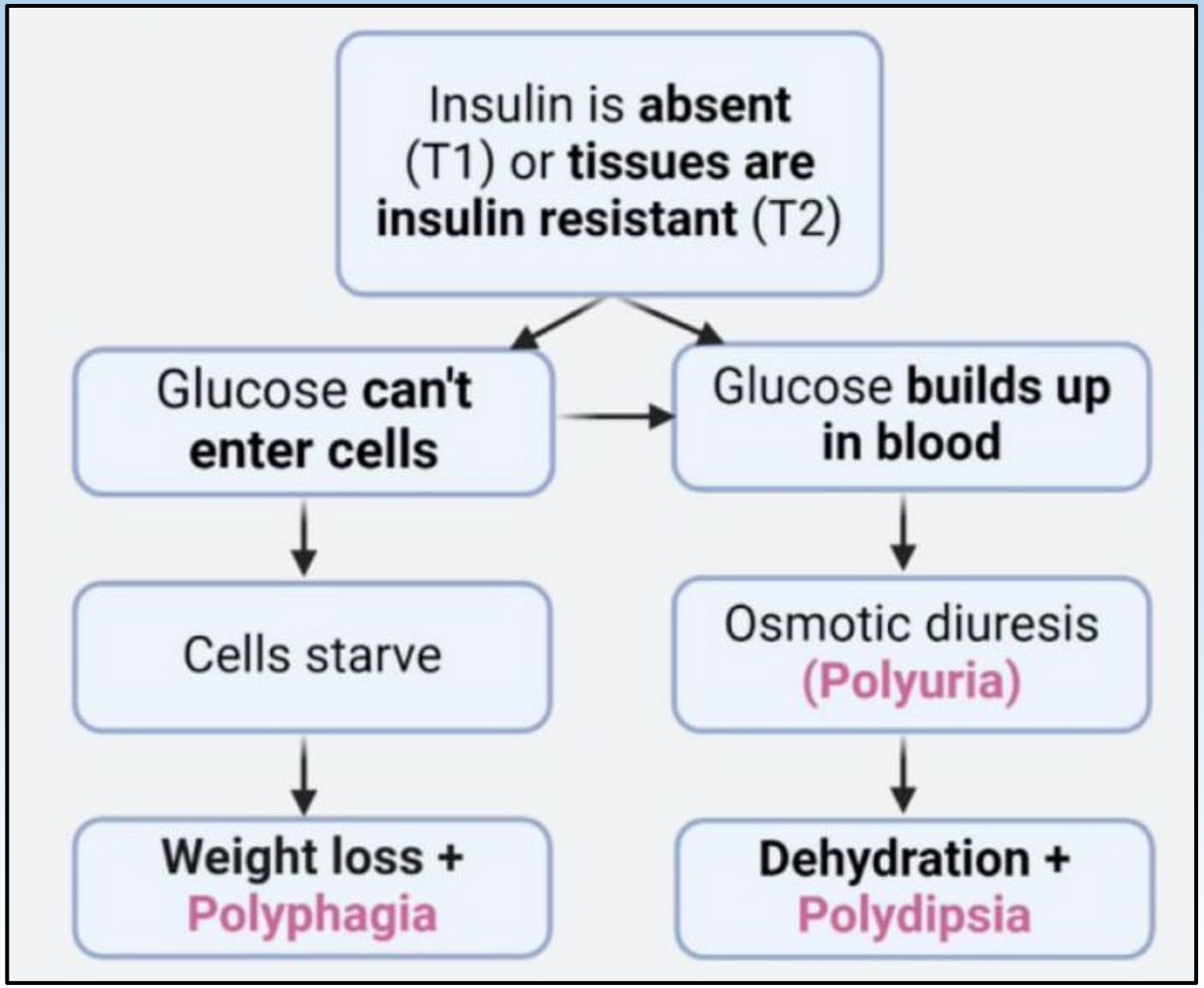
(Before discovery of insulin -Diabetes was a death sentence, usually treated with extreme starvation diets.)

Diabetes

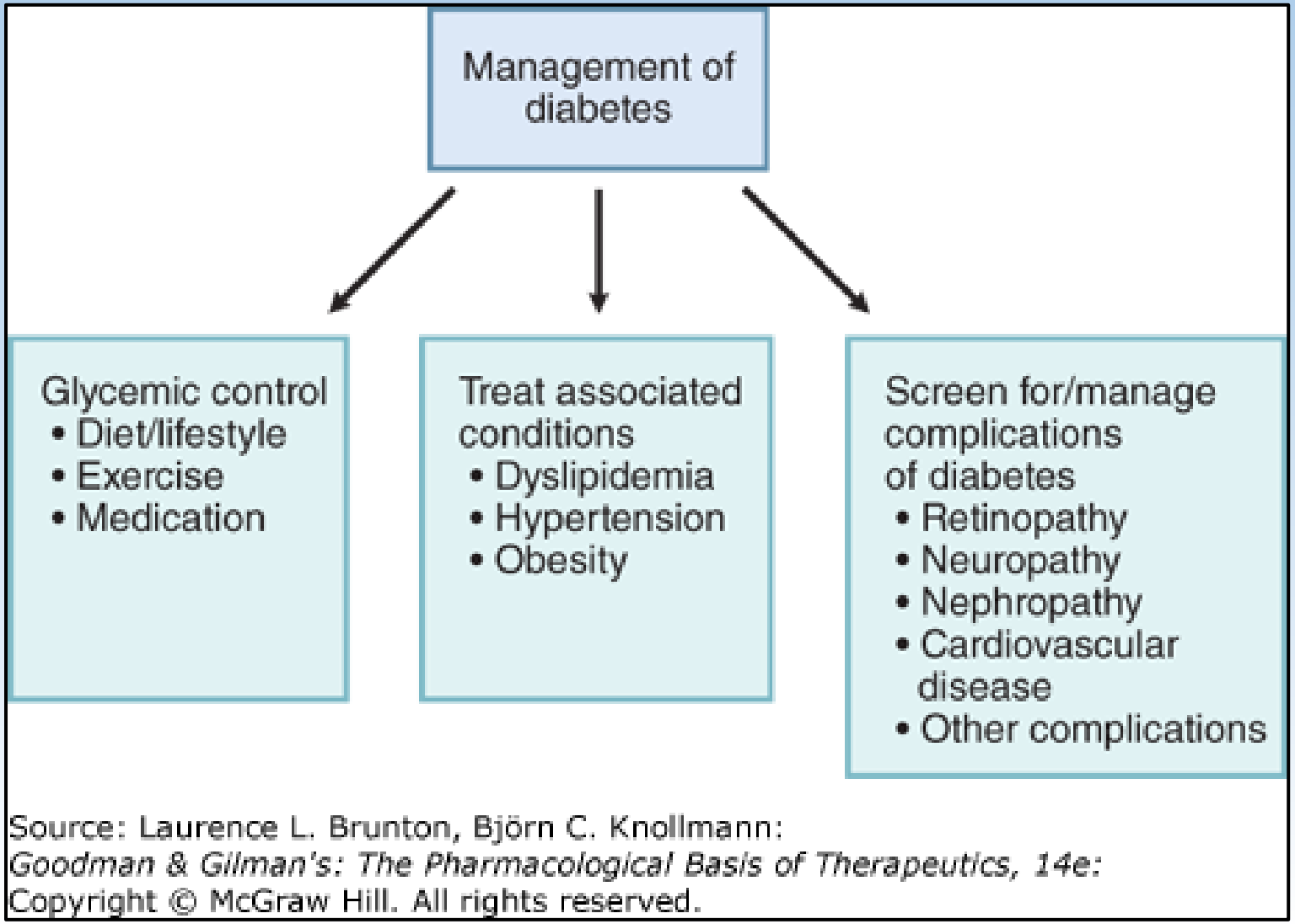

Diabetes Mellitus
NORMAL
TYPE 1 DIABETES
TYPE 2 DIABETES
Insulin gets glucose into the cells
Lack of insulin production due to loss of β-cells, glucose does not get into the cells
Insulin
Glucose
Insulin receptor
Glucose
Glucose
Elevated blood sugar
Cells do not accept insulin


TYPE 1 vs TYPE 2
DIABETES
TYPE 1
Cannot be prevented or cured
The body does not create enough insulin
Causes are unknown, but genetics may play a role
Requires insulin injections for life
Can cause other serious health problems and complications
Requires a healthy lifestyle and medical supervision
Symptoms include thirst, frequent urination, and blurry vision
Can be prevented through lifestyle modifications
TYPE 2
The body does not create enough insulin or develops insulin resistance
Causes include genetics, aging, inactivity, obesity, and more
Requires insulin as needed, injected or oral

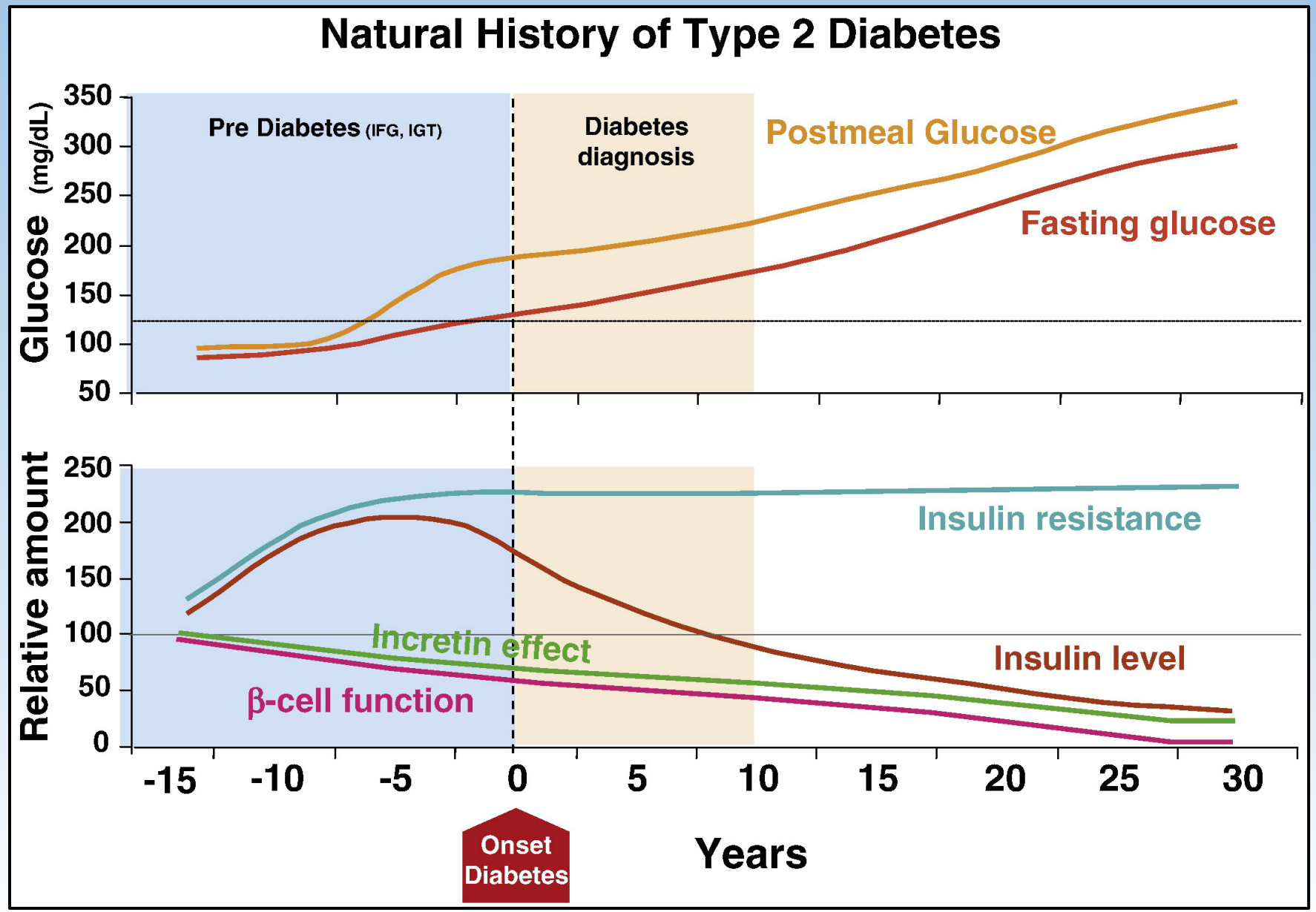
Acute manifestations of Diabetes – the 3 Ps

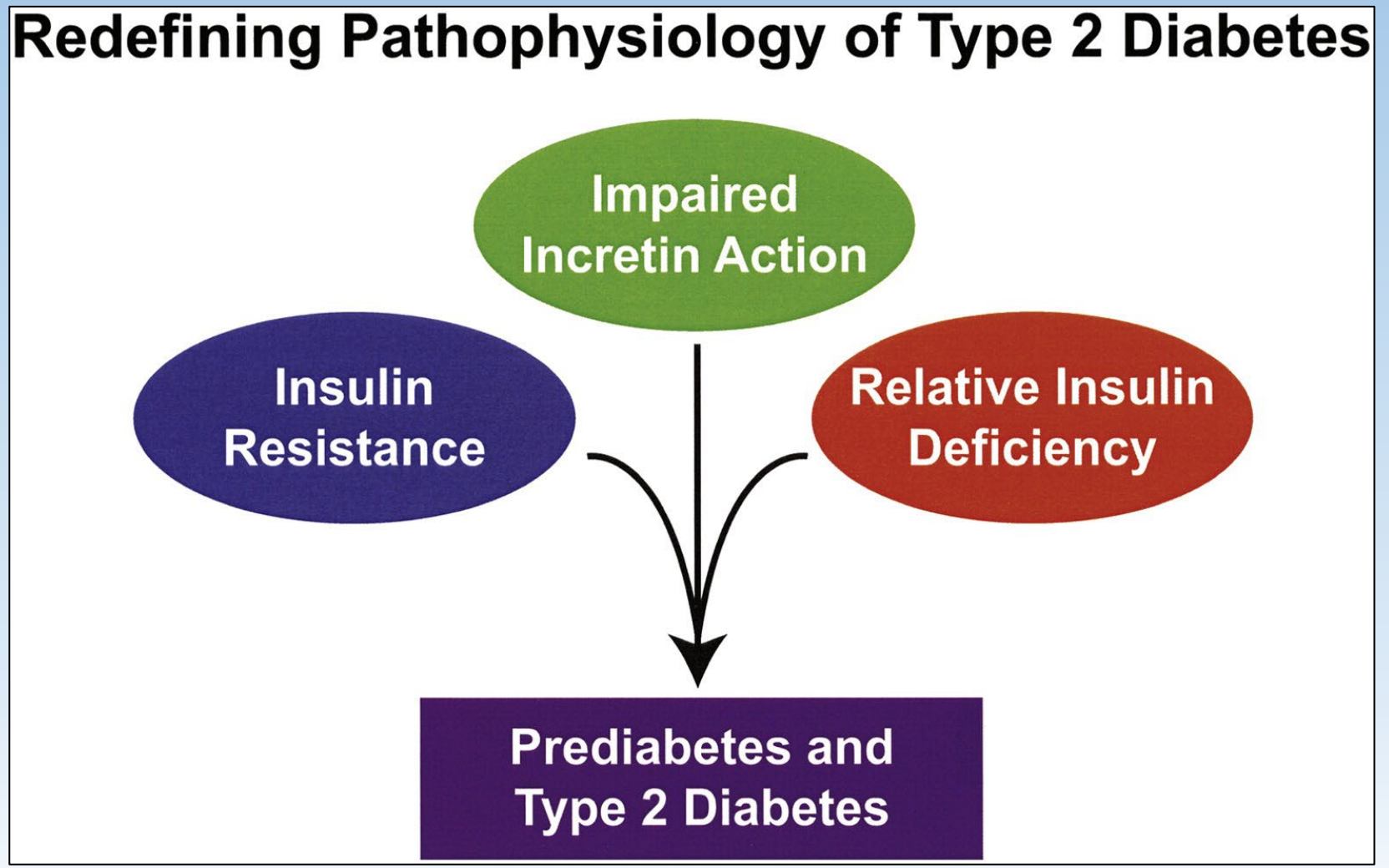


Goals of therapy for Diabetes



Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:


Natural History of Type 2 Diabetes
Glucose (mg/dL)
350
300
250
200
150
100
50
Pre Diabetes (IFG, IGT)
Diabetes diagnosis
Postmeal Glucose
Fasting glucose
Relative amount
250
200
150
100
50
0
Insulin resistance
Incretin effect
β-cell function
Insulin level
-15
-10
-5
0
5
10
15
20
25
30
Onset Diabetes
Years


Redefining Pathophysiology of Type 2 Diabetes
Impaired Incretin Action
Insulin Resistance
Relative Insulin Deficiency
Prediabetes and Type 2 Diabetes

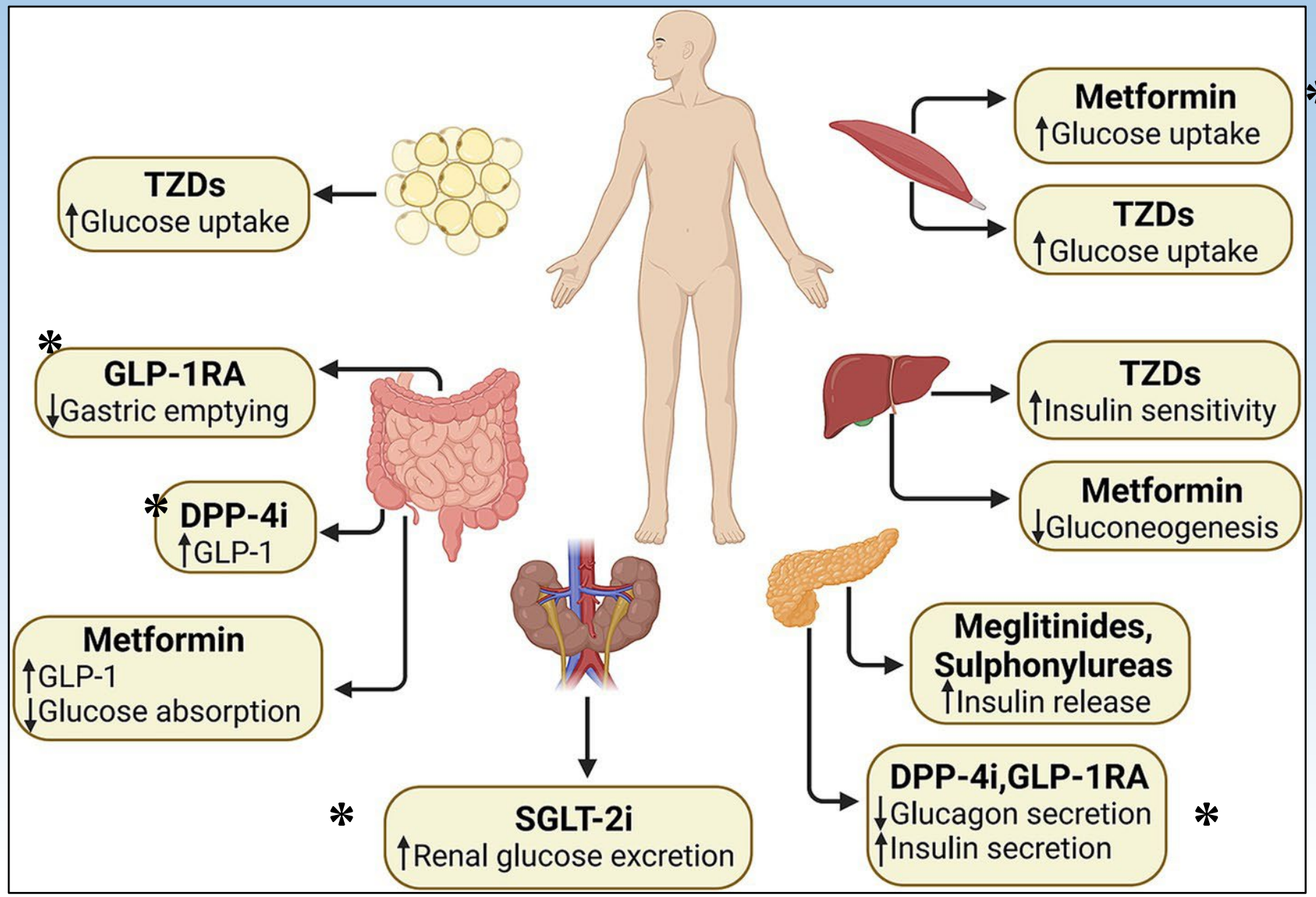
Diabetes Pharmacotherapy

- Type 1 DM: insulin replacement

- Type 2 DM: oral agents (metformin is first line for most; GLP-1 agonist and SGLT2 inhibitors can be first line for certain patient populations), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose

- Gestational DM: insulin replacement if nutrition therapy and exercise alone fail; regular insulin is preferred

Pharmacological treatment of Diabetes



Role of insulin in glucose metabolism

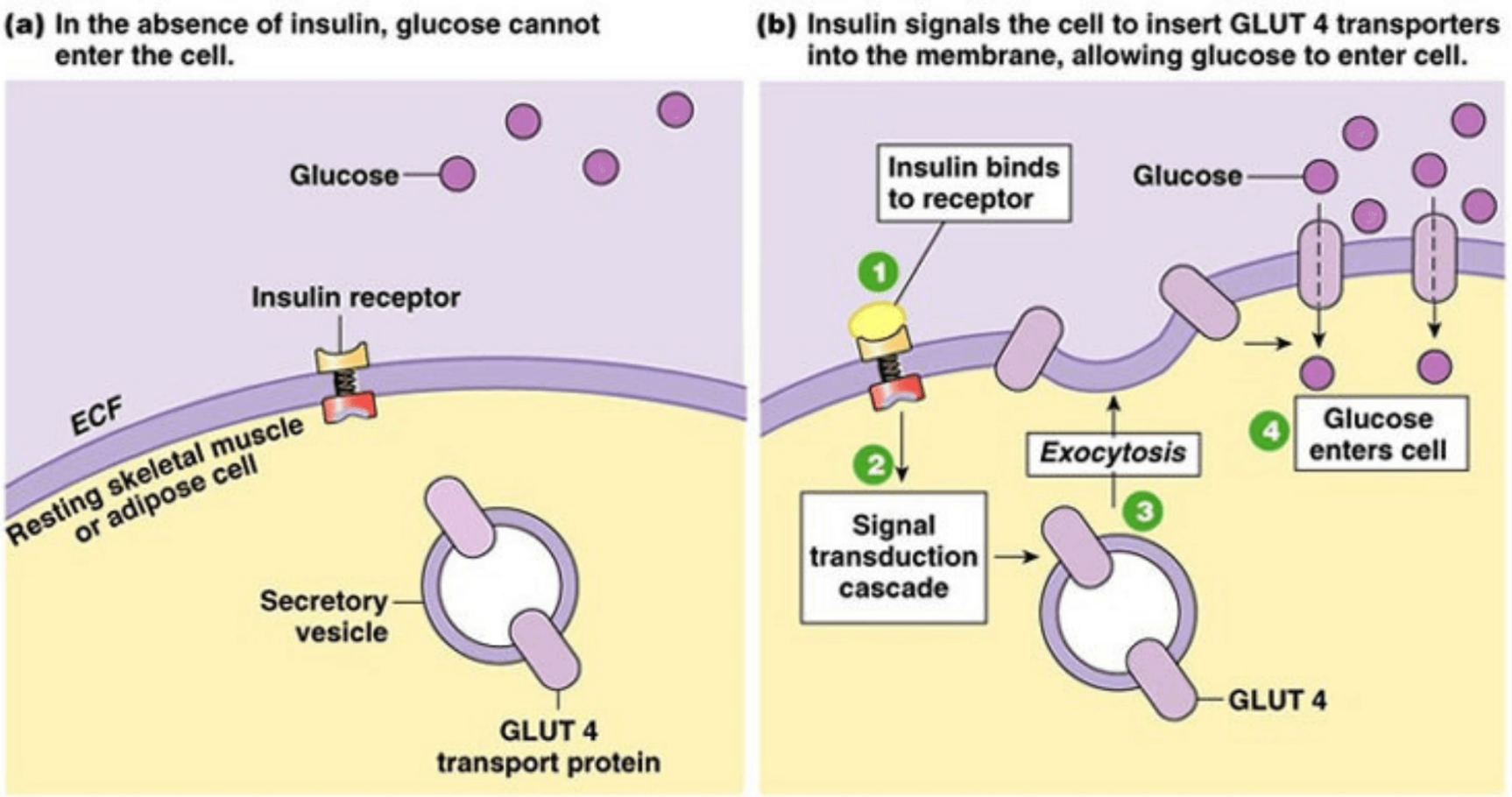


Fig. 22-12

Glucose transporters

GLUT1

- CNS, widely expressed

GLUT2

- Low affinity; glucose transport when [glucose] high
- Pancreas ß-cells, liver, intestine & kidney: "glucose sensor"

GLUT3

- Major neuronal GLUT, lowest Km

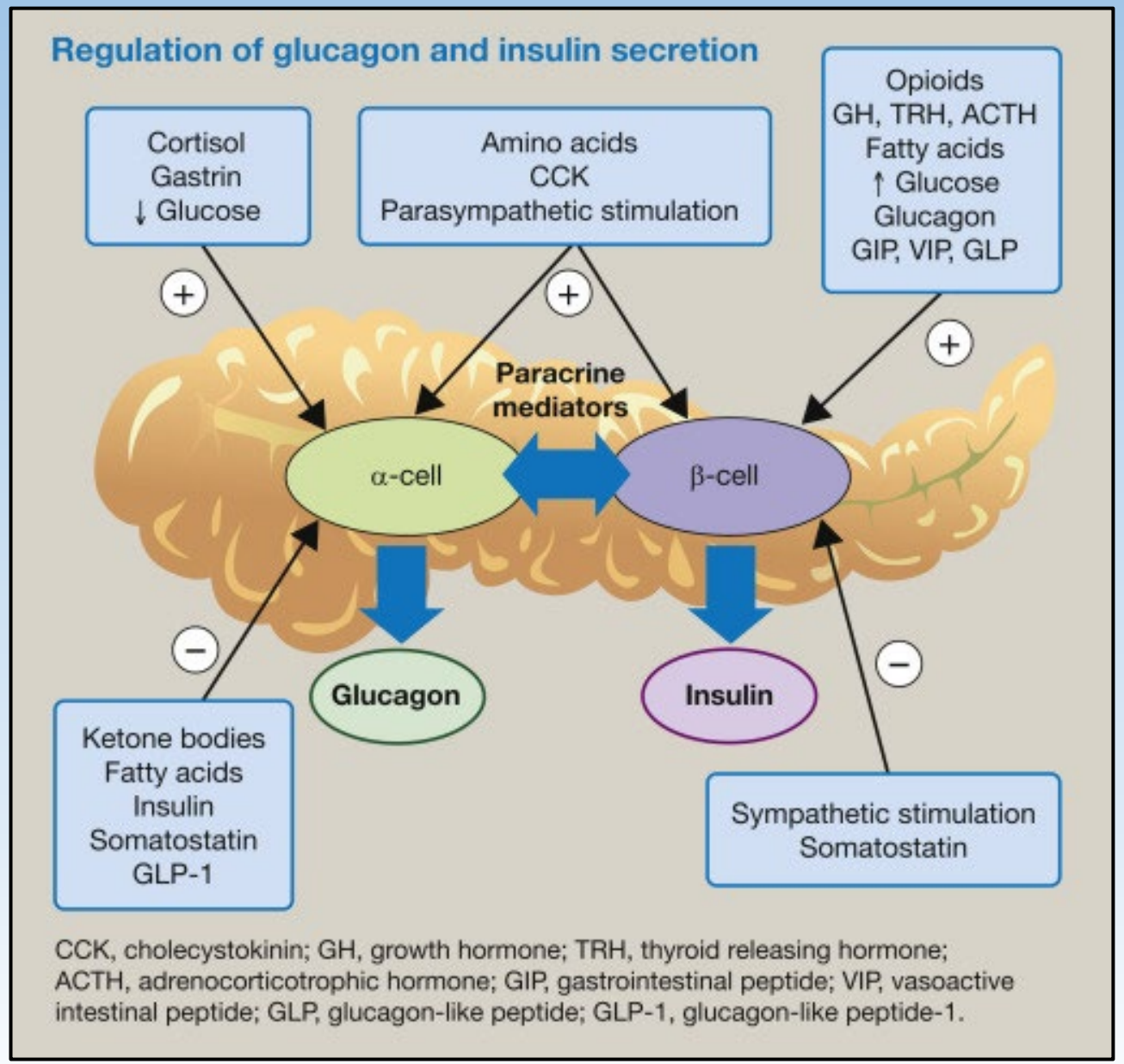
GLUT4

- Major insulin-responsive transporter, striated muscle & adipose

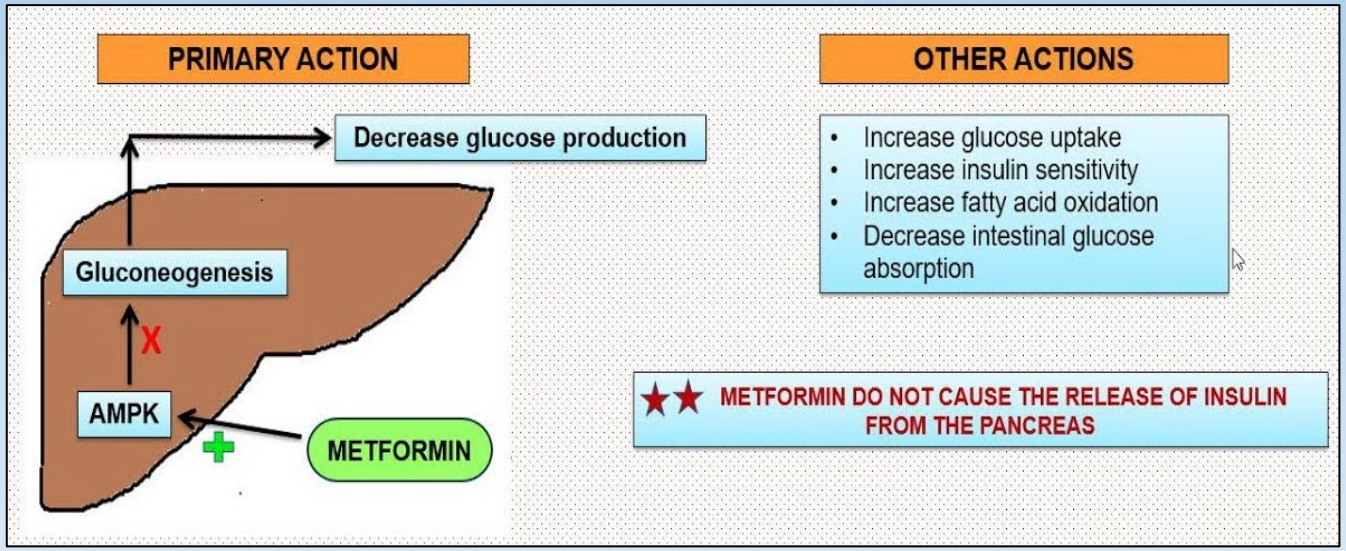
GLUT5

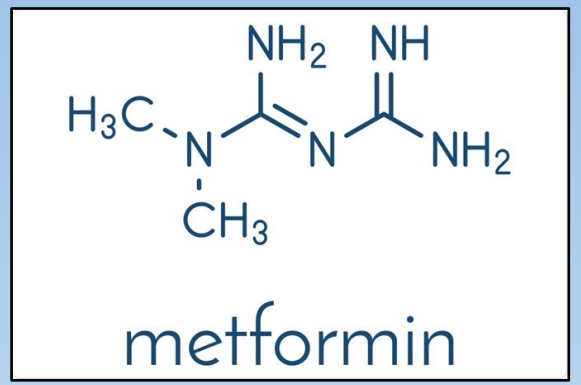
- Fructose transporter in spermatozoa and small intestine.

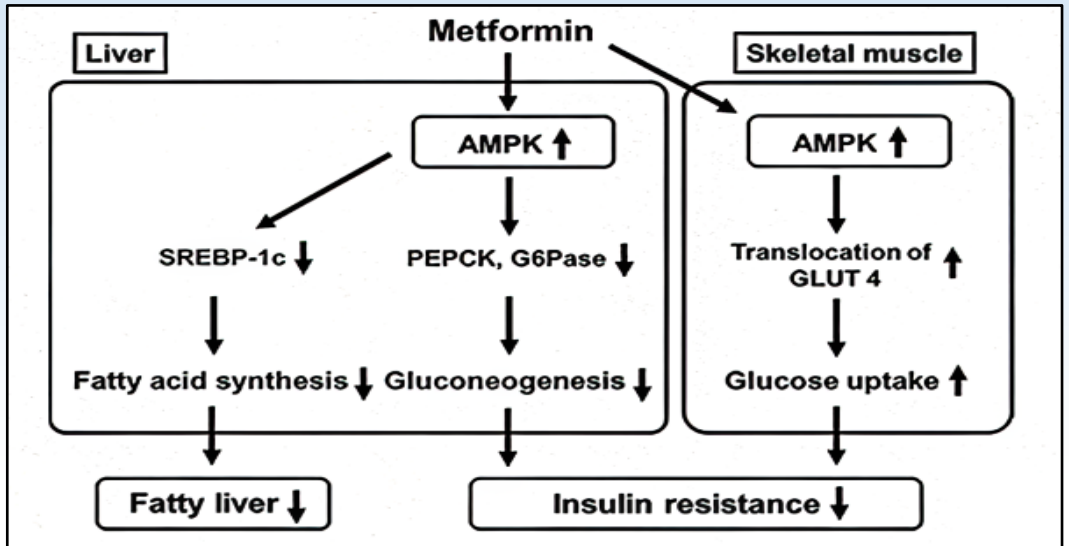
Insulin and Glucagon



Metformin (a biguanide)



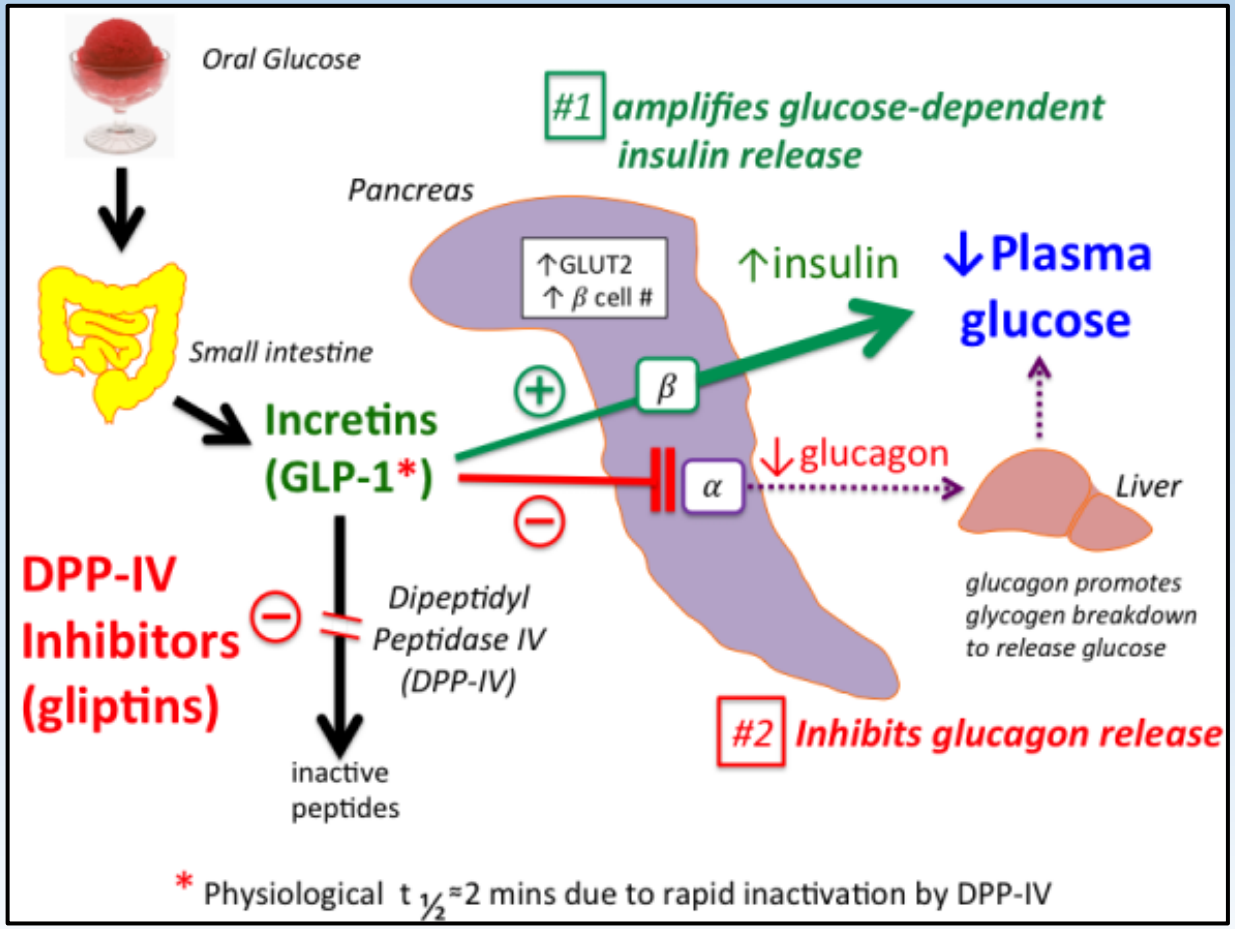




- First line treatment for T2DM. Does NOT present with increased risk of hypoglycemia since it does not increase insulin levels
- Adverse effects: GI upset including nausea, vomiting, diarrhea, lactic acidosis (very rare), impedes absorption of vitamin B12 in small intestine
- Metformin is substantially excreted by the kidney, so the dose must be reduced in patients with renal impairment., contraindicated if eGFR < 30 mL/min
- For most patients, metformin should be stopped at the time of contrast administration. There have been case reports of patients developing lactic acidosis after receiving iodinated contrast material while on metformin

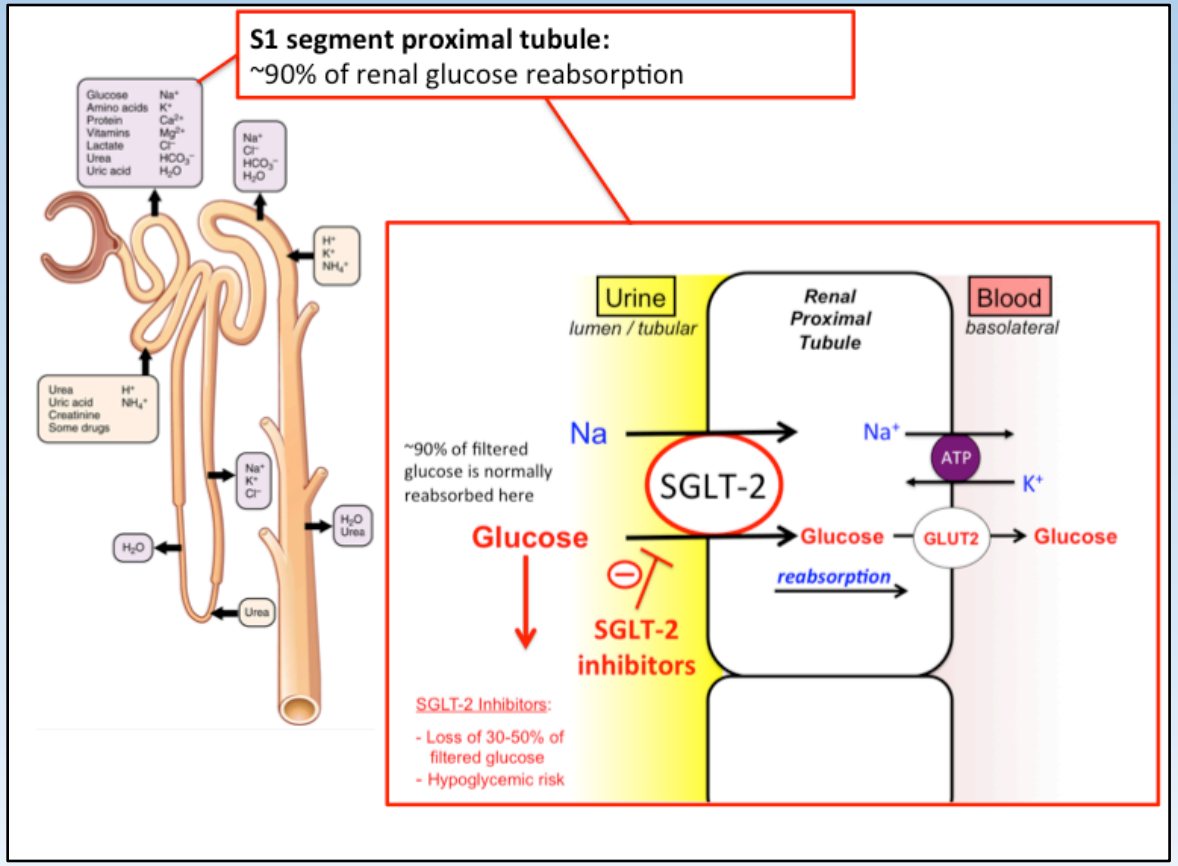
Dipeptidyl Peptidase-4 (DPP4) Inhibitors (Gliptins)

- **GLP-1** stimulates insulin release, inhibits glucagon release, and stimulates β-cell proliferation
- **DPP4** degrades GLP-1
- **DPP4-Inhibitors** - inhibits degradation of GLP-1, leads to subsequent increase in GLP-1 = increased release of insulin + β-cell proliferation and inhibited glucagon release



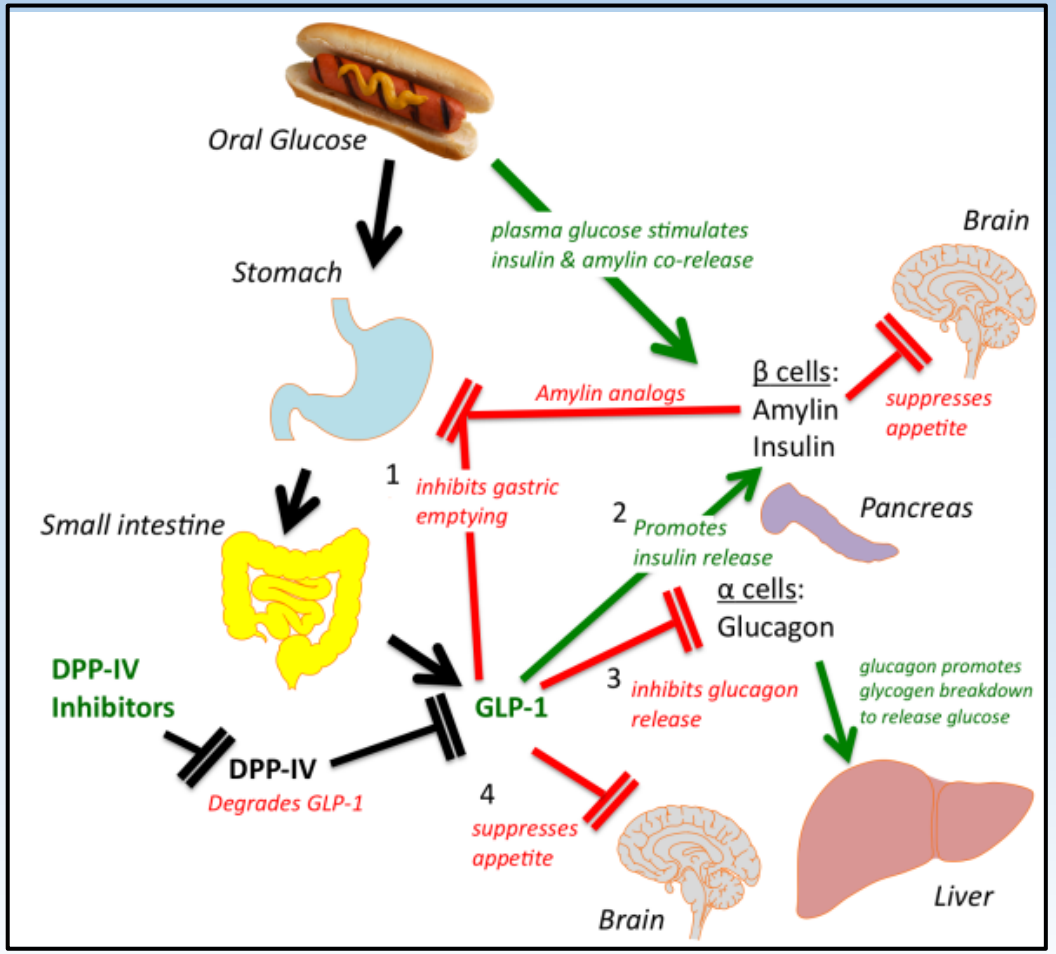
Sodium-Glucose Co-transporter -2 (SGLT inhibitors)
Empagliflozin - Jardiance

- SGLT2 is responsible for reabsorbing ~90% of filtered glucose in the proximal renal tubules
- Reduces absorption of filtered glucose & lowers renal threshold for glucose –increases urinary excretion of glucose which reduces plasma glucose
- Adverse effects: AKI (acute kidney injury), hyperkalemia, hypersensitivity, hypovolemia, hypotension, infections (especially UTI), ketoacidosis



Glucagon-like peptide-1(GLP-1)receptor agonists (GLP-1RA)

- "Glucose-dependent insulinotropic peptide agonists"
- Agonists bind to the GLP-1 receptors - mimicking GLP-1 and promote glucose mediated insulin release
- Several additional mechanisms of action: reduction of gastric emptying, inhibition of glucagon secretion, beneficial changes in the intestinal microbiome, and direct effects on hypothalamic nuclei to enhance satiety



Genetics and Blood Sugar Regulation

Regulating Insulin Release

KCNJ11 gene: Genetic variants in KCNJ11 can decrease the beta cell's insulin response to blood glucose.

CDKAL1 gene: Is part of the signaling pathway that causes insulin release. Genetic variants in this gene can cause decreased insulin release, which then keeps blood glucose levels higher when eating carbs/sugar.

Insulin Resistance Genes

The **IRS1** gene codes for a key protein in the insulin-stimulated signal pathway. Variants in IRS1 have links to an increase in the risk of type-2 diabetes.

The **ENPP1** gene encodes an enzyme that downregulates the signal from insulin by interacting with one of the insulin receptor subunits. Genetic variants in this gene are associated with insulin resistance.

Genetics and GLP-1

GLP1 levels are impacted by genetic variants.

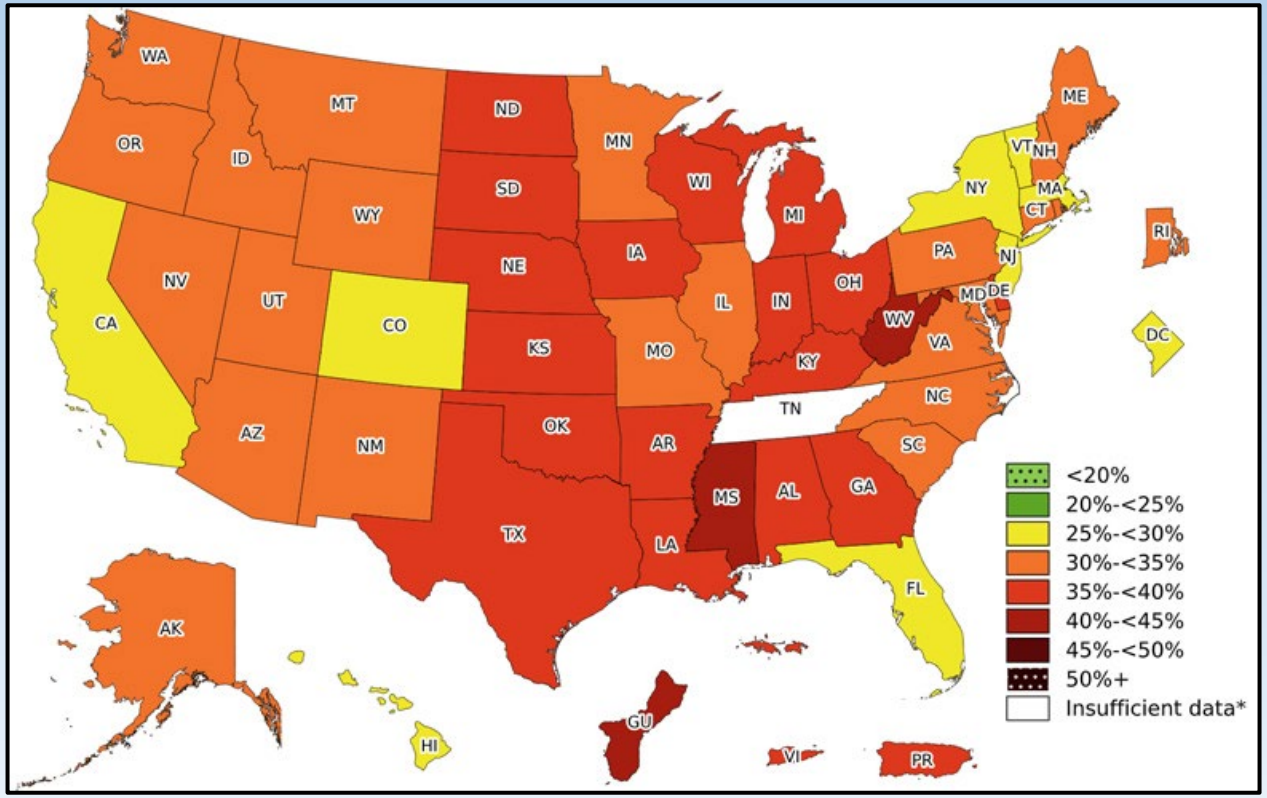
GLP1R (receptor) receives the signal from GLP-1. Variants in GLP1R have associations with altered BMI, weight, and insulin resistance.

Aside from diabetes, there are three ways that higher blood glucose concentrations are bad:

- **Damage due to osmosis**
- **Increased oxidative stress**
- **Advanced glycation end products**

Genetic Lifehacks
Learn. Experiment. Optimize.

Obesity



LA- 39.2%
https://www.cdc.gov/obesity/data-and-statistics/adult-obesity-prevalence-maps.html

USA 2024 obesity prevalence 25% or higher (CDC)

- Eight states and the District of Columbia had an obesity prevalence between 25% and less than 30%.
- 22 states had an obesity prevalence between 30% and less than 35%.
- 17 states, Puerto Rico, and Virgin Islands had an obesity prevalence between 35% and less than 40%.
- Two states (Mississippi and West Virginia), and Guam had an obesity prevalence of 40% or greater.
- Obesity prevalence 25% or higher overall

Root Causes of Obesity

- Several intertwined factors fuel the obesity crisis:

- **Poor Diet Quality:** Highly processed, calorie-dense foods dominate the American diet. Foods high in added sugars, refined grains, and saturated fats are often cheaper and more accessible than healthier options.
- **Physical Inactivity:** Sedentary lifestyles, influenced by desk jobs, screen time, and urban planning that discourages walking or biking, have contributed to declining physical activity.
- **Socioeconomic Disparities:** Lower-income families often live in "food deserts" with little access to fresh produce. In these areas, fast food is more available and affordable than healthier alternatives.
- **Mental Health and Stress:** Chronic stress and mental health issues are linked to emotional eating and metabolic changes that promote fat storage. The COVID-19 pandemic further intensified these stressors.
- **Genetic and Hormonal Factors:** Although lifestyle plays a significant role, some individuals are more genetically predisposed to weight gain. Hormonal imbalances, such as insulin resistance, also play a part.

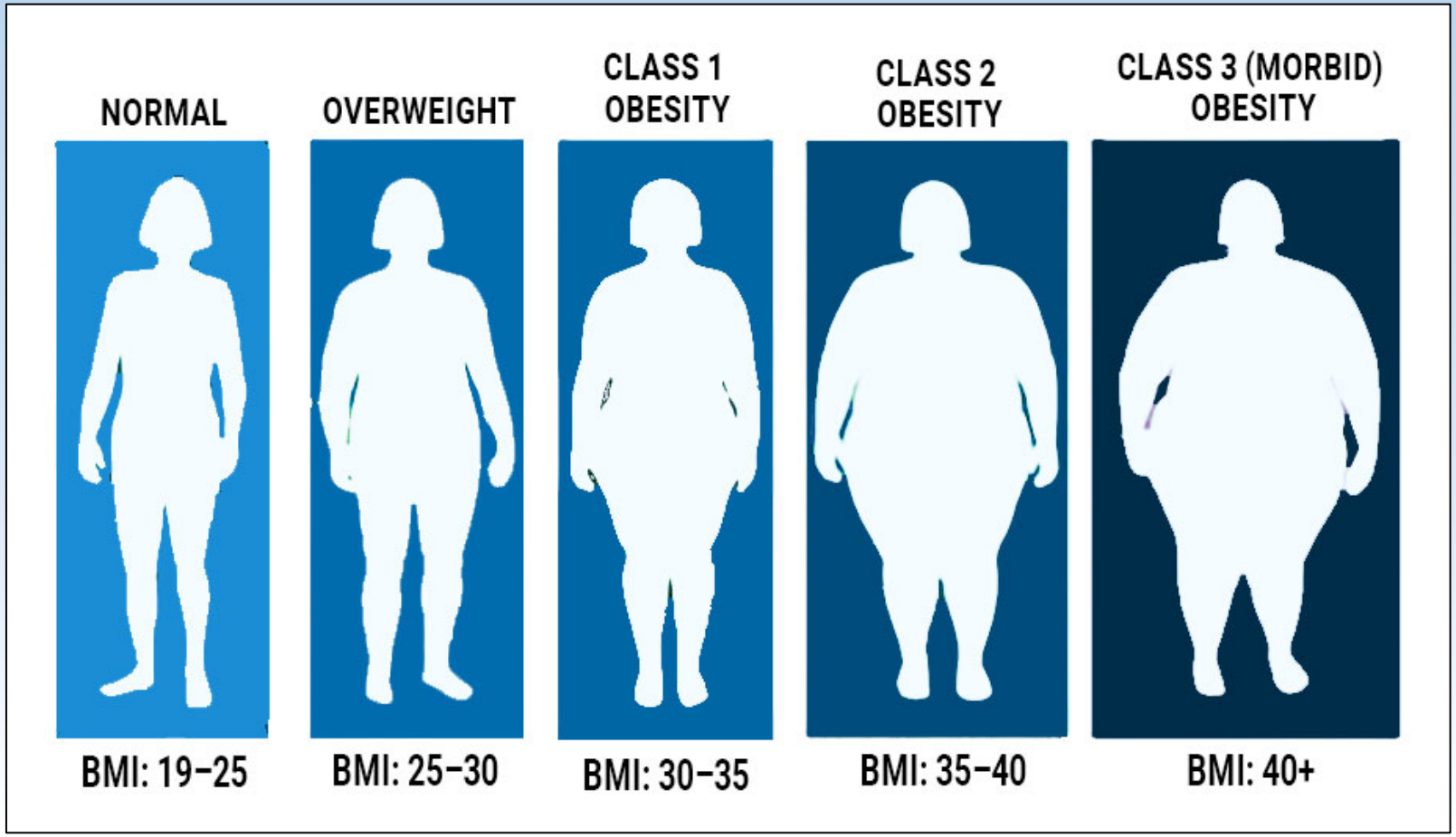
Obesity

- Obesity defined by BMI for past 5 decades (from Metropolitan Life Insurance actuarial tables from the 1950's)
  - BMI > 30 obese
    - Class I (BMI 30-34.9)
    - Class II (BMI 35-39.9)
    - Class III (BMI >40)
- BMI has substantial limitations –cannot distinguish between lean muscle & fat, assess body shape, evaluate metabolic capacity, or info on adiposity-related organ disfunction.
- Currently, obesity is characterized as a distinct illness with measures to create a diagnostic framework: Assessed by direct measurement (DEXA scan- Dual energy X-ray absorptiometry or at least 2 anthropometric measurements: BMI, waist circumference (WC), waist-to-hip ratio (WHR) or waist-to-height ratio
- Further classifications by obesity-related conditions, classifications, and staging

Obesity definitions & staging (Lancet Commission, WHO, Edmonton Obesity Staging System)

Anthropometrics	BMI	32 kg/m^2	27 kg/m^2	33 kg/m^2	35 kg/m^2
	Waist circumference	32 inches	36 inches	38 inches	40 inches
	Waist–hip ratio	0.8	1.0	0.9	1.2
Obesity-related conditions	Conditions	None	Diabetes	Prediabetes	Heart failure
Obesity classifications	WHO	Class I	Overweight	Class I	Class II
	Lancet	No obesity	Clinical	Preclinical	Clinical
Obesity staging	EOSS	Stage 0	Stage 2	Stage 1	Stage 3

BMI calculators https://www.nhlbi.nih.gov/calculate-your-bmi



Treatment of obesity

- Nutrition therapy
- Physical activity
- Behavior modifications
- Personalized care stressed
- Medical interventions
  - Bariatric surgery (metabolic surgery)
  - Anti-obesity medications (AOMs)
    - Injectables
      - Zepbound
      - Wegovy
      - Saxenda
    - Pills
      - Qsymia
      - Contrave
      - Oral semaglutide

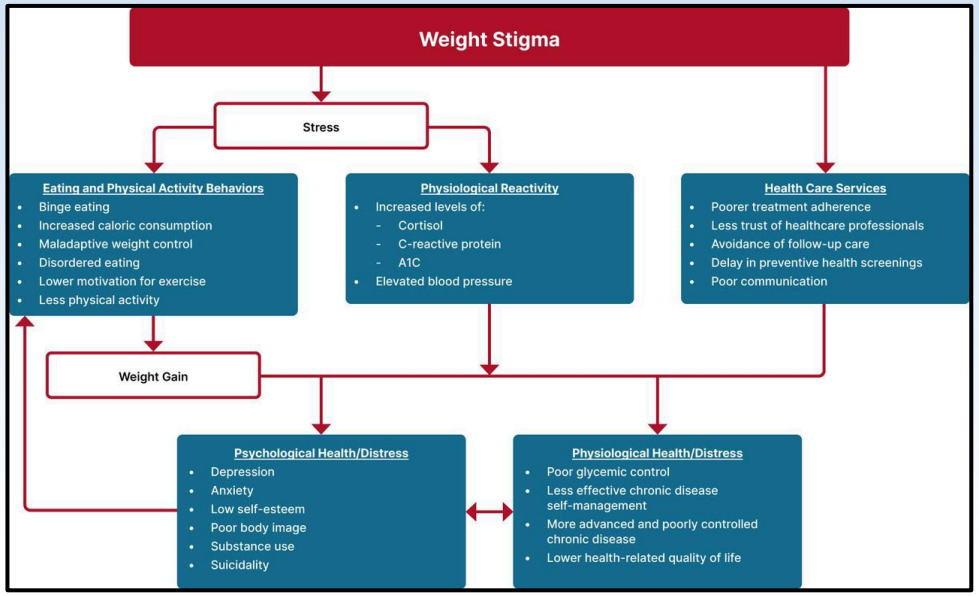
Obesity –some Policies & prevention

- **Healthcare Interventions:** More healthcare providers are integrating obesity screening and management into routine care. FDA-approved drugs like Wegovy (semaglutide) and Zepbound (tirzepatide) have shown promising results in weight management and diabetes control.
- **Public Policy:** Sugar taxes, improved food labeling, and zoning laws to limit fast food outlets in low-income areas are some strategies gaining traction.
- **School Programs:** Nutrition education and physical activity requirements in schools aim to prevent childhood obesity before it starts.
- **Technology and Apps:** Digital health platforms now offer telehealth coaching, calorie tracking, and remote monitoring tools that personalize lifestyle interventions.
- **Community-Based Approaches:** Partnerships between healthcare providers, local governments, and nonprofits can help deliver targeted programs to underserved populations.

Standards of care in overweight and obesity
Jan 13, 2026 American Diabetes Association

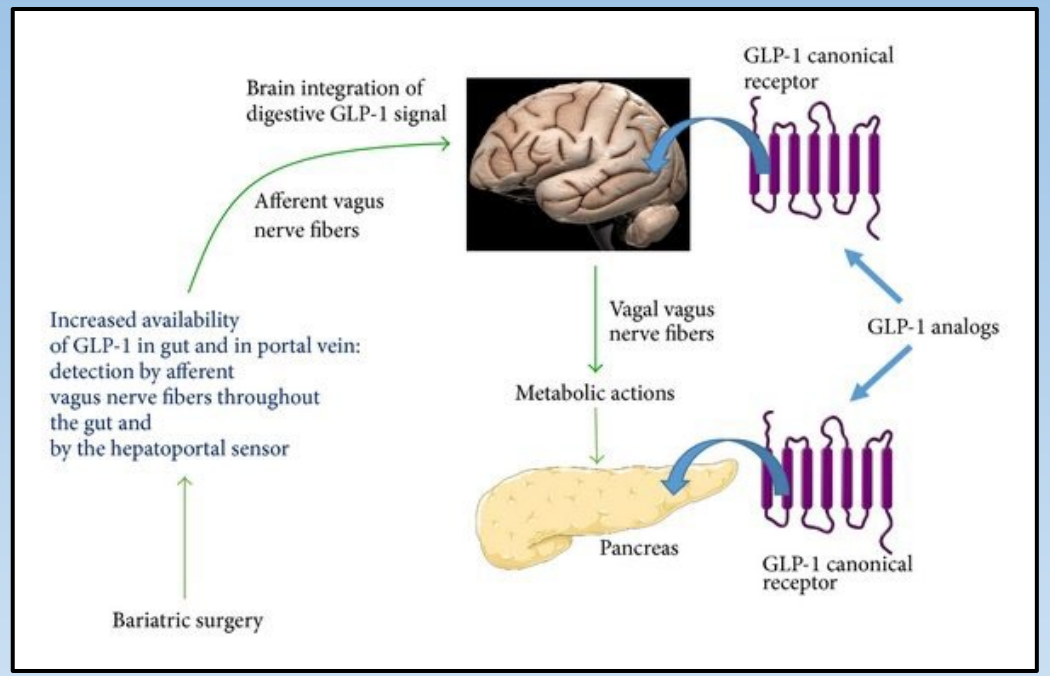
- Uses an evidence based grading system. (A to E)
- Sections include:
  - Weight stigma and bias
  - Clinical practice checklist – minimum accommodations
  - Pharmacologic treatment of obesity in adults

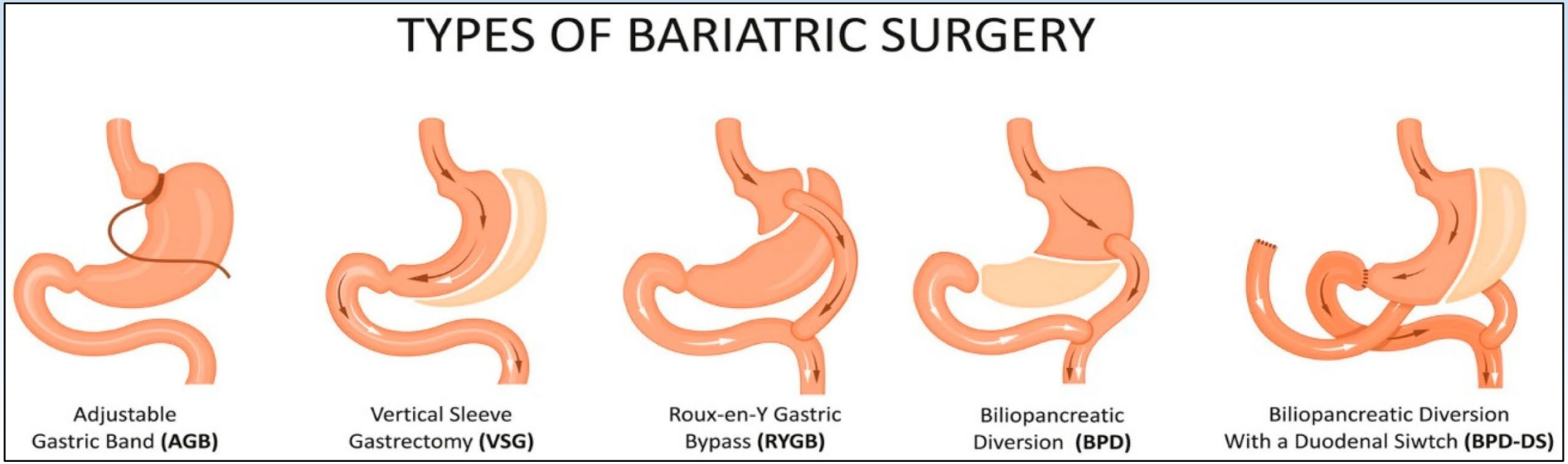
https://diabetesjournals.org/docm-care/article/1/1/5/164233/Pharmacologic-Treatment-of-Obesity-in-Adults



How Bariatric surgery works

Dramatically reduced size of stomach
Increased secretion of GLP-1





BARIATRIC SURGERY VS. GLP-1

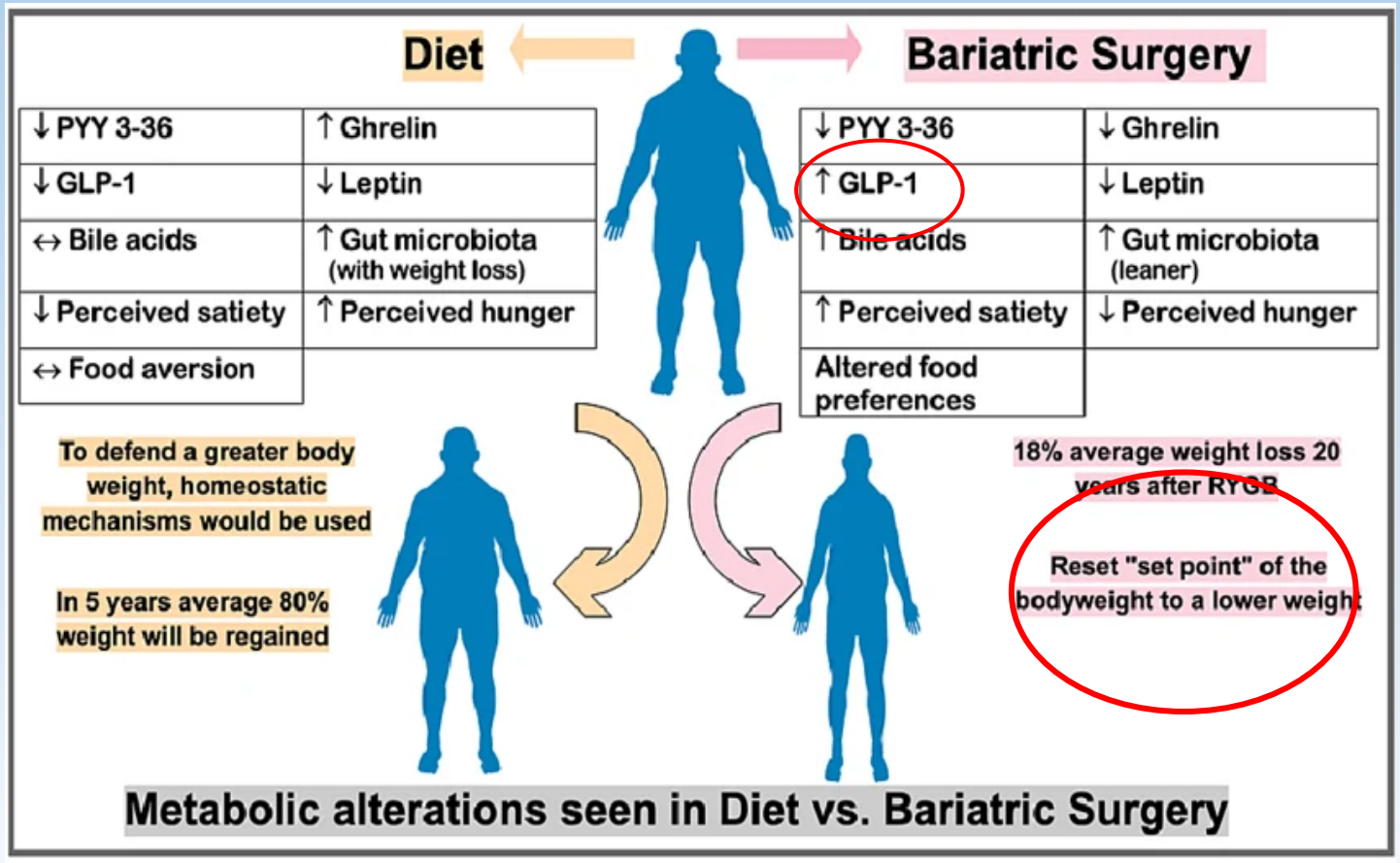
Studies show that bariatric surgery consistently produces greater reductions in total body weight, BMI, and waist circumference*

MEXICO® BARIATRIC CENTER

*Comparative Efficacy of Metabolic/Bariatric Surgery Versus GLP-1 Receptor Agonists: A Network Meta-Analysis of Randomized Controlled Trials 2025

Post bariatric surgeries
VSG Vertical Sleeve Gastrectomy; RYGB Roux en Y Gastric Bypass

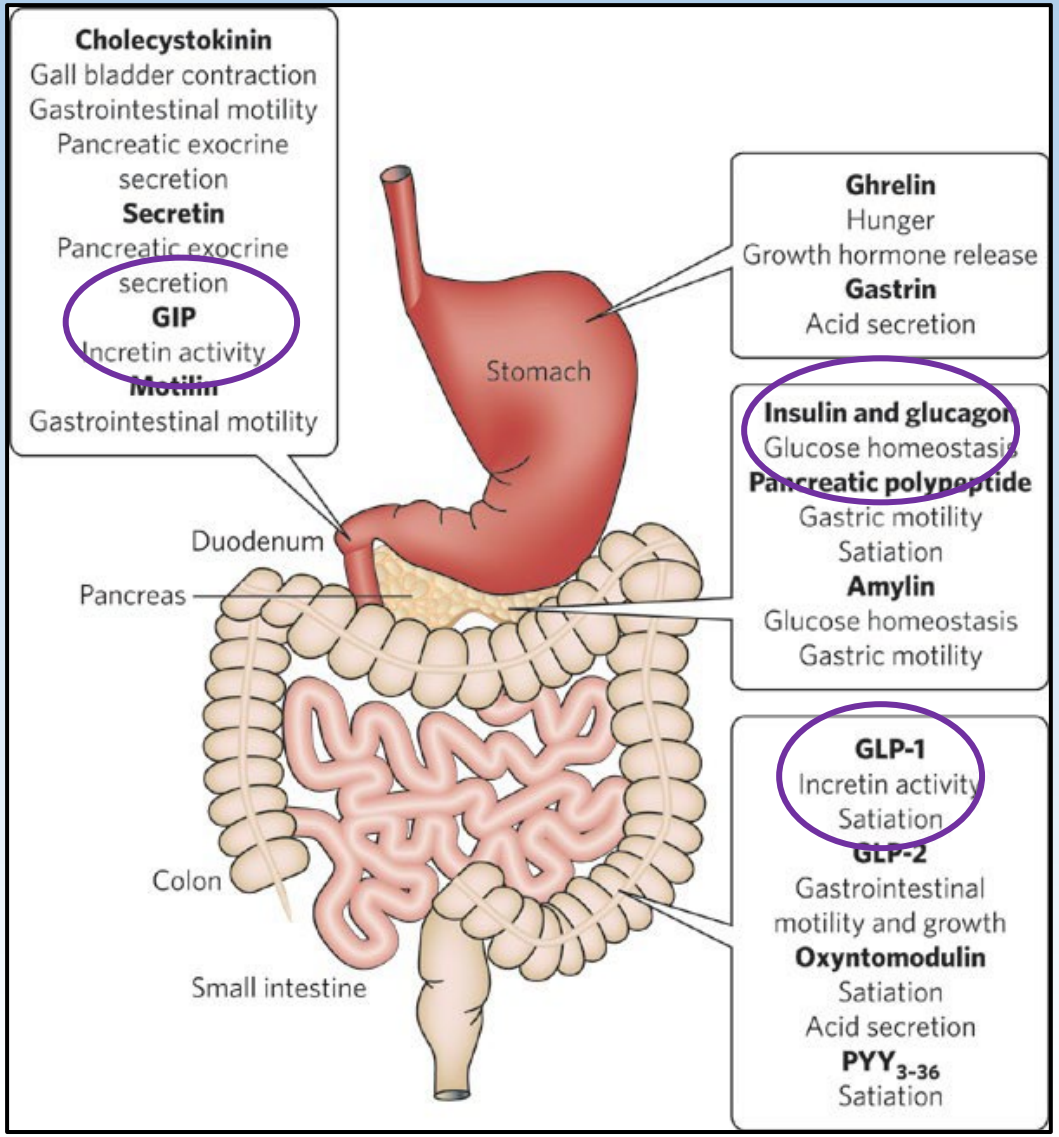
Biomarkers	VSG		RYBG	
GLP-1	↑	↑	↑	↑
GIP	↑	↑	↔	↔
PYY	↑	↑	↑	↑
Ghrelin	↓	↓	↔	↔
CCK	↑	↔	↑	↑
OXY	N/A	N/A	↑	N/A
Bile acids	↑	↑	↑	↑
Insulin	↑	↑	↑	↑



Metabolic "Set points"

- The body's preferred weight range ~ 10-15 lbs
- Regulated primarily by the hypothalamus which it actively defends through adjustments in metabolism and hunger hormones: (Leptin – fullness; Ghrelin –hunger)
- Famine response – when calories drop dramatically, the body interprets this as a threat & lowers your resting metabolic rate to conserve energy
- . When you try to lose weight, your body responds by slowing your metabolism and increasing hunger cues, making weight loss and long-term maintenance challenging.
- Genetics, yo yo dieting, stress can affect hormones and set point

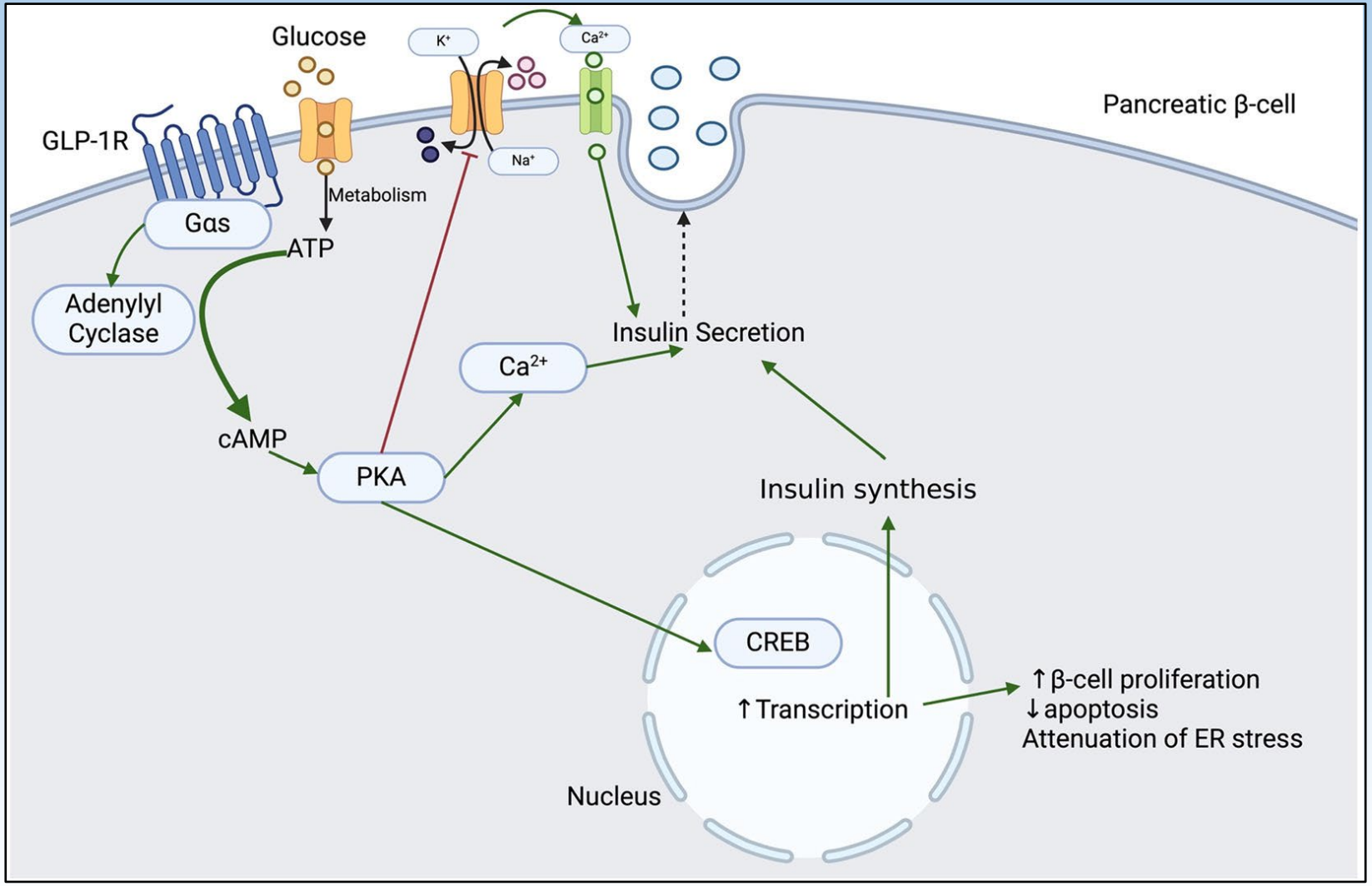
"Gut Hormones" and Homeostasis



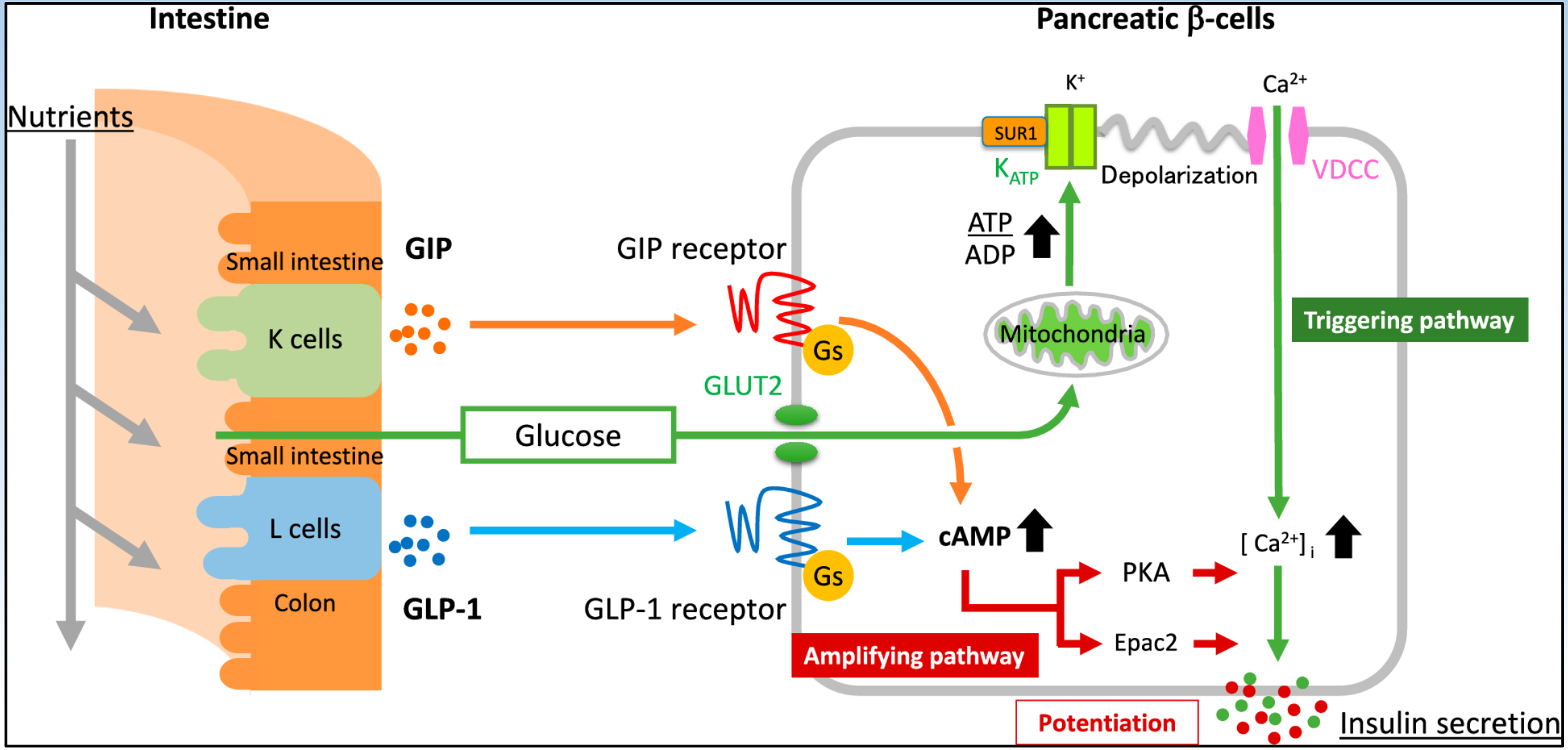
Incretins: GLP-1 RA & others

- Glucagon-like peptide 1, GLP-1
- Glucose dependent insulinotropic peptide, GIP
- Glucagon

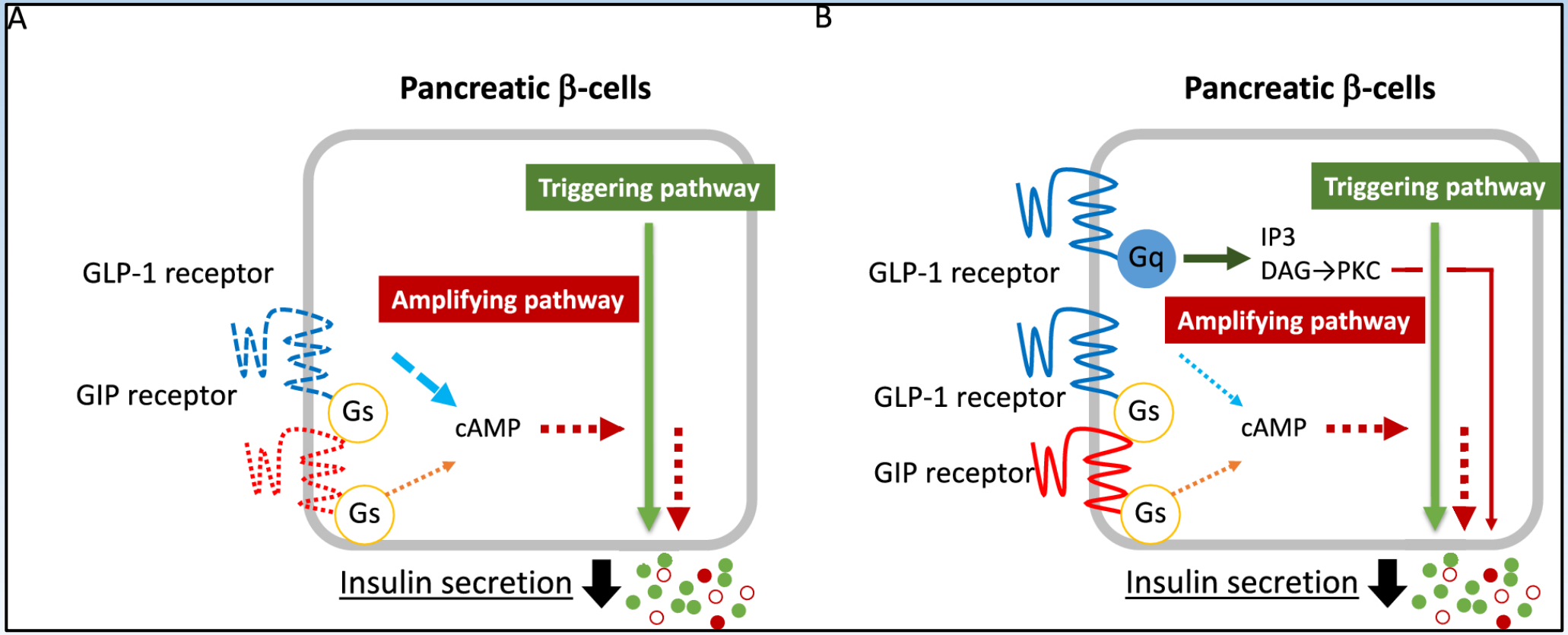
Mechanism of GLP-1 action in pancreas



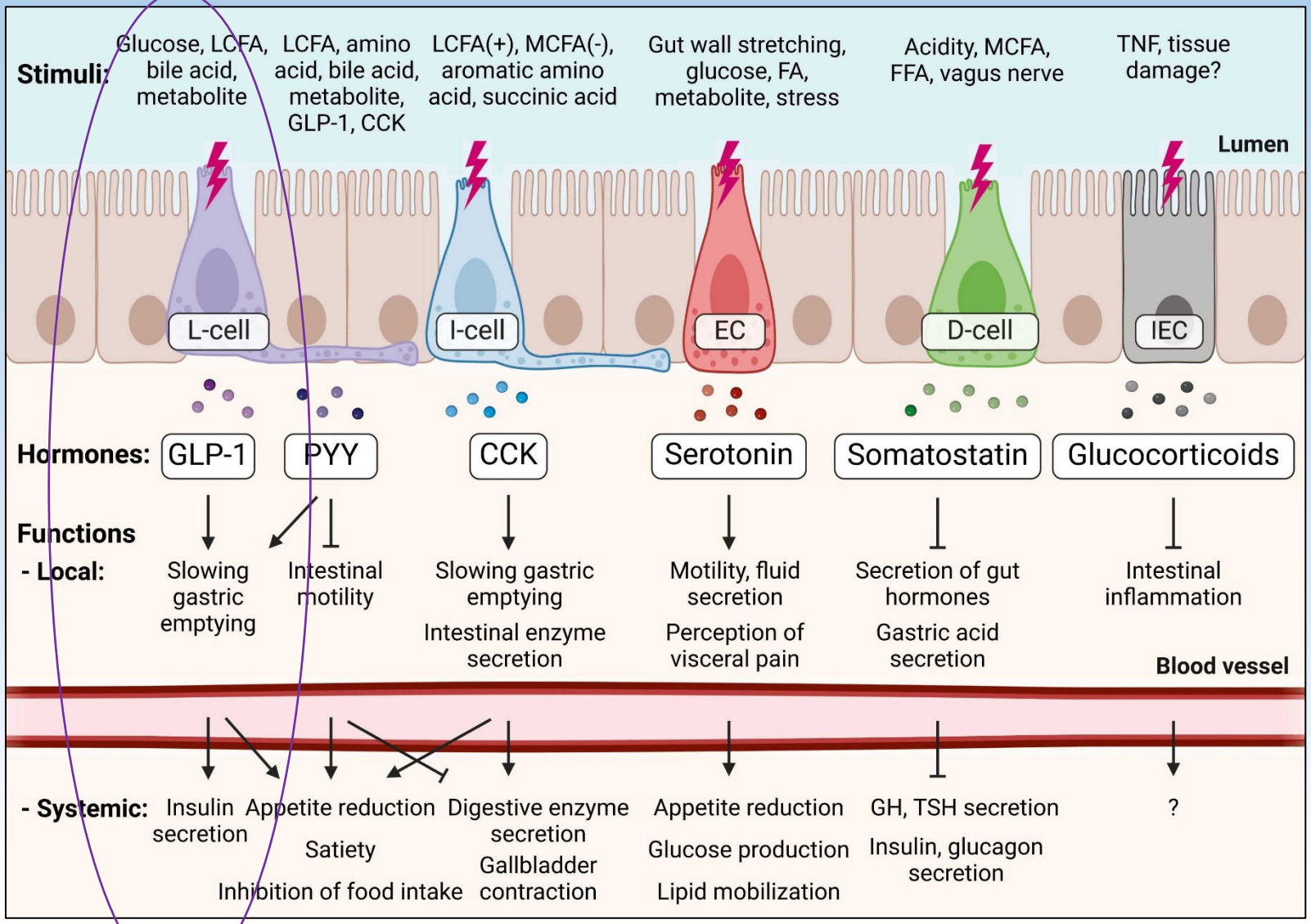
Insulin secretion from pancreatic β-cells & Incretin Potentiation



Causes of reduced incretin effect in pancreatic β-cells under diabetic condition



Many gut hormones

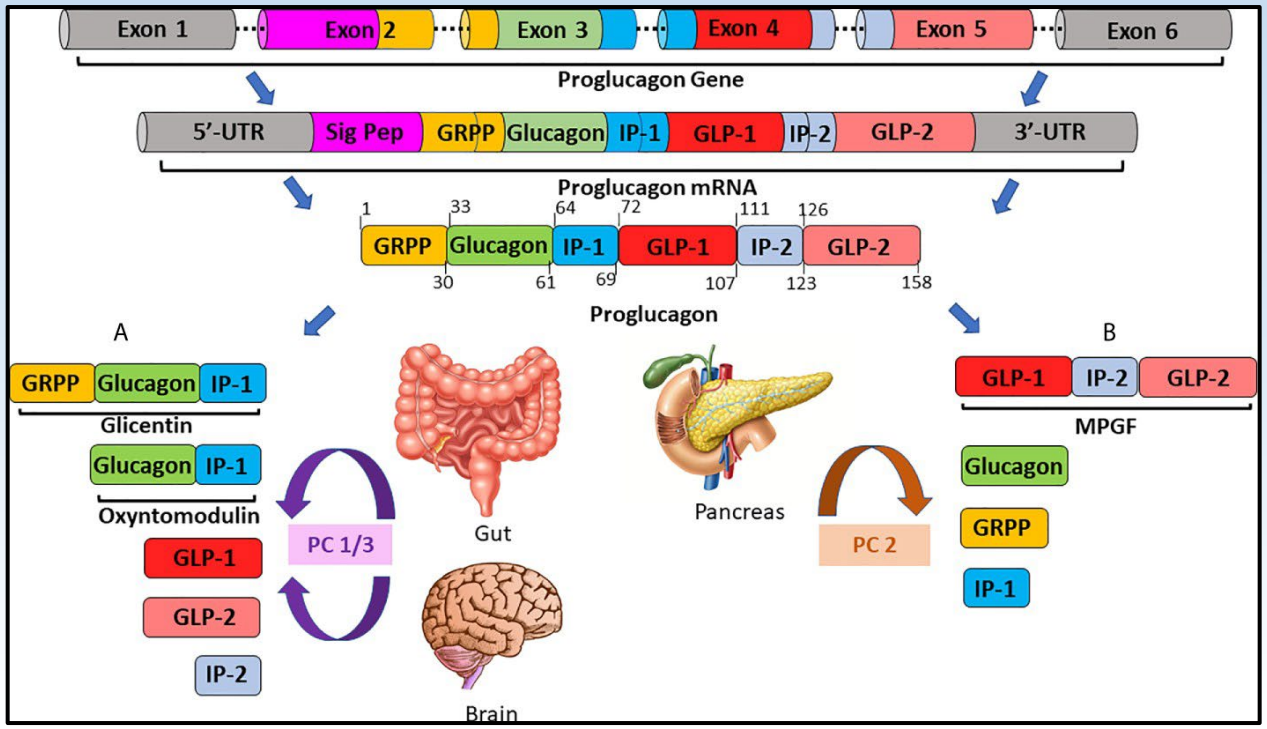


Incretin drug breakthrough

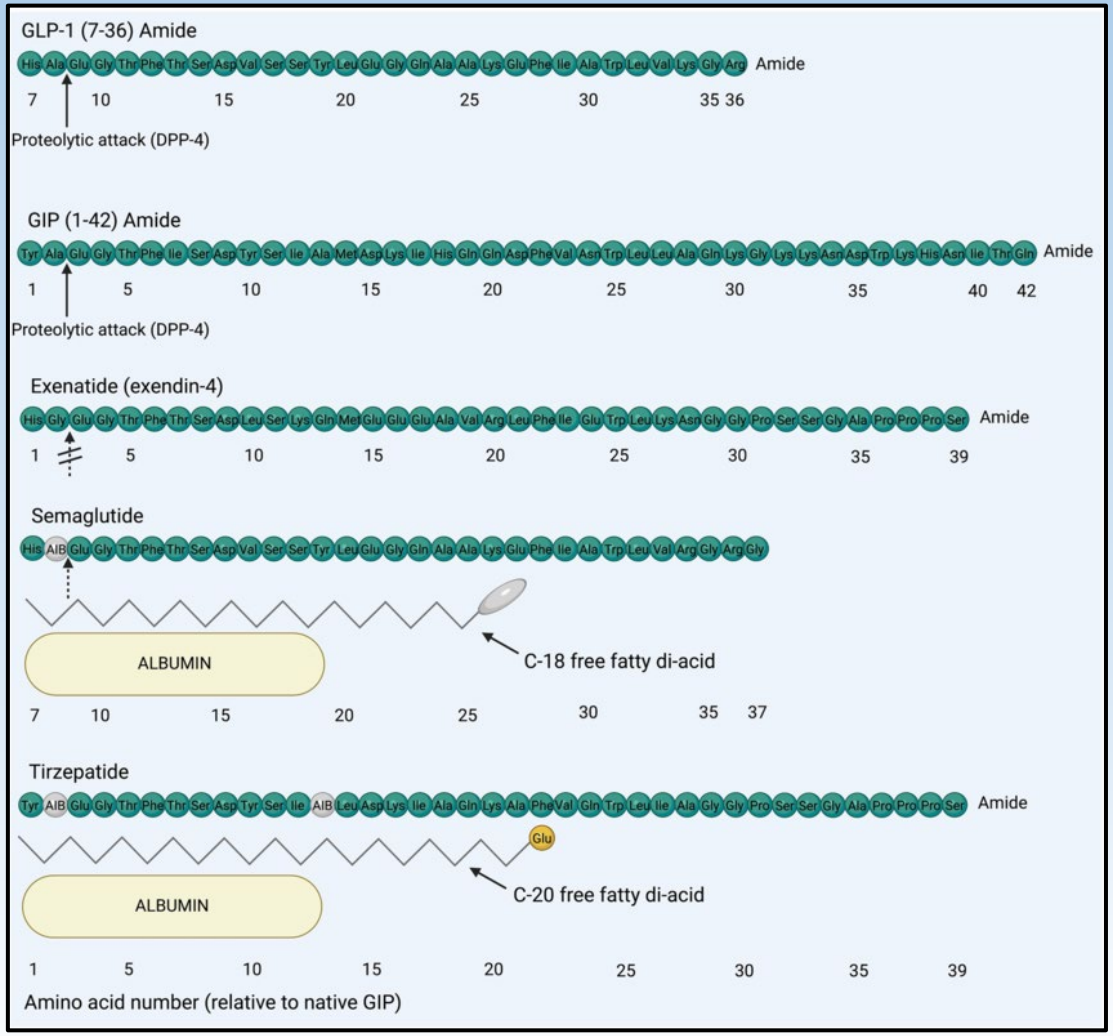
- 1980's GLP-1 discovered as the body's natural incretin (But it degrades within minutes)
- **1992 Extendin -4 found in venom of the Gila monster. It acted like human GLP-1 but resisted enzymatic breakdown.**
- More research; Comparative clinical trials with or without Metformin. Combination reduced A1C to 7% or less
- 2005 "Byetta" –first FDA approved GLP-1 RA for human use in T2DM Exenatide based on Extendin4)
- Half life 2-4 hours requiring 2X day administration)
- 2010 – present. DM patients experienced significant weight loss, so began development as anti-obesity medications

Proglucagon gene (chromosome 2)

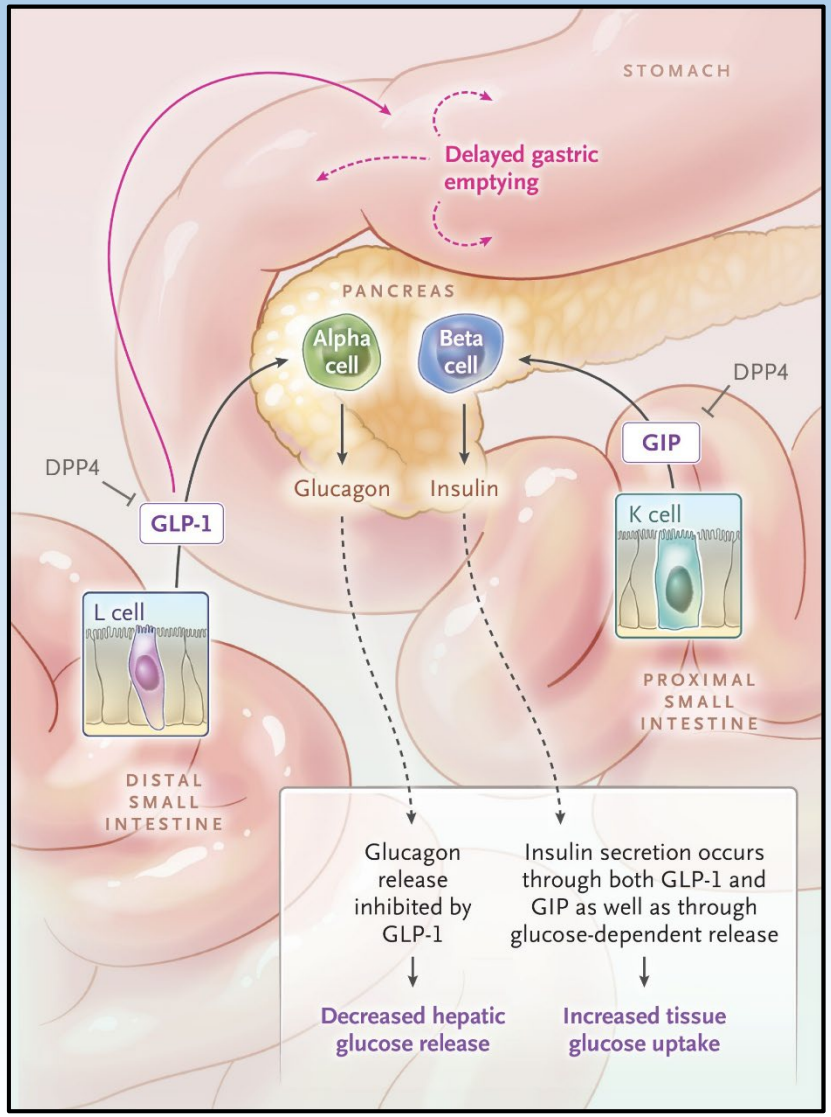
- Encodes a large precursor protein that is processes into several distinct peptide hormone
- Expressed in different tissues with distinct enzymes that cleave it in a tissue specific manner to generate different hormones
  - Alpha cells of pancreas – ***glucagon*** –raises blood glucose production by liver, responding to tissue specific transcription factors and nutrient signal
  - Intestinal L cells and brain – ***GLP-1*** – stimulates insulin secretion

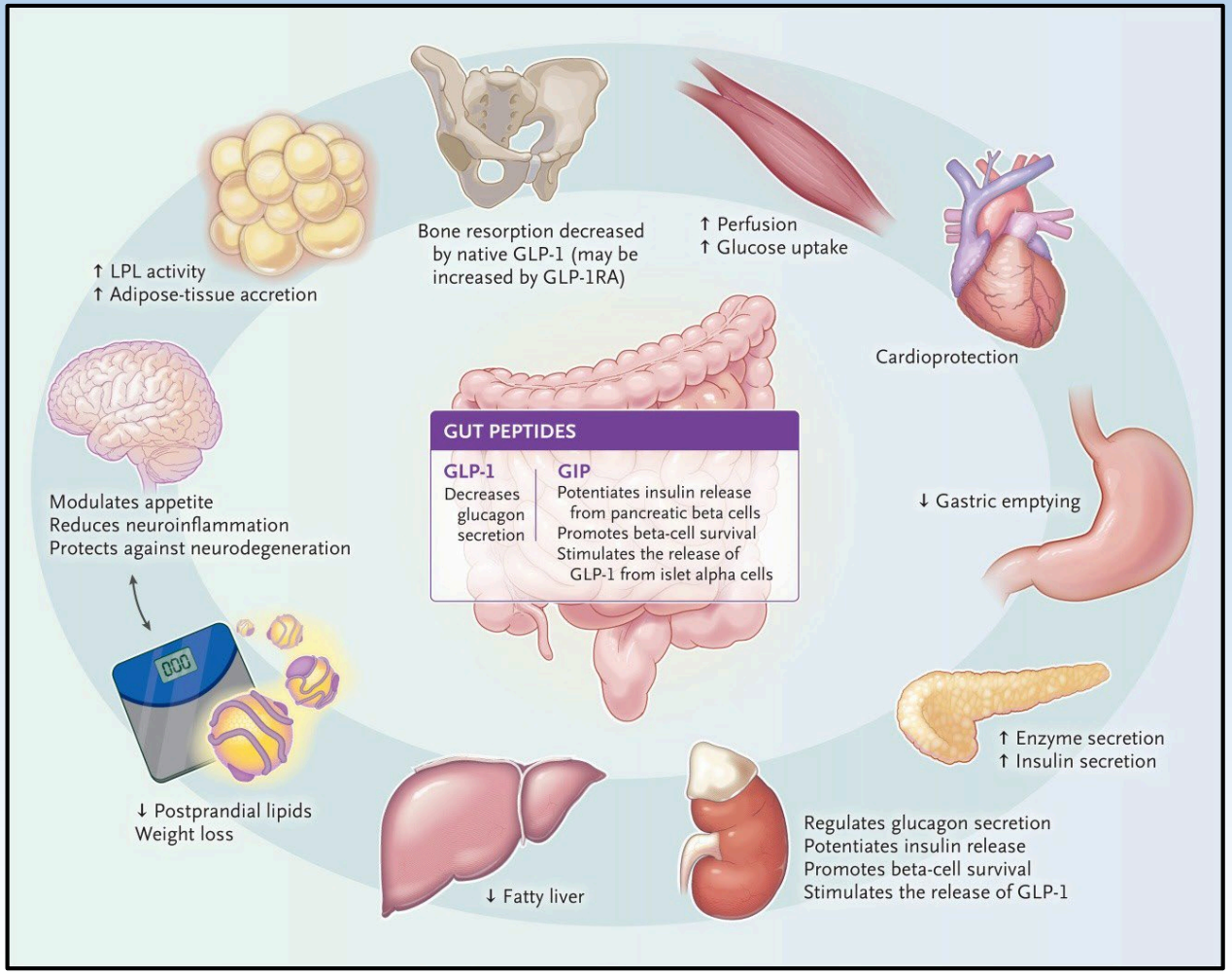


Amino acid Structure of GLP-1 and GLP-1 RAs

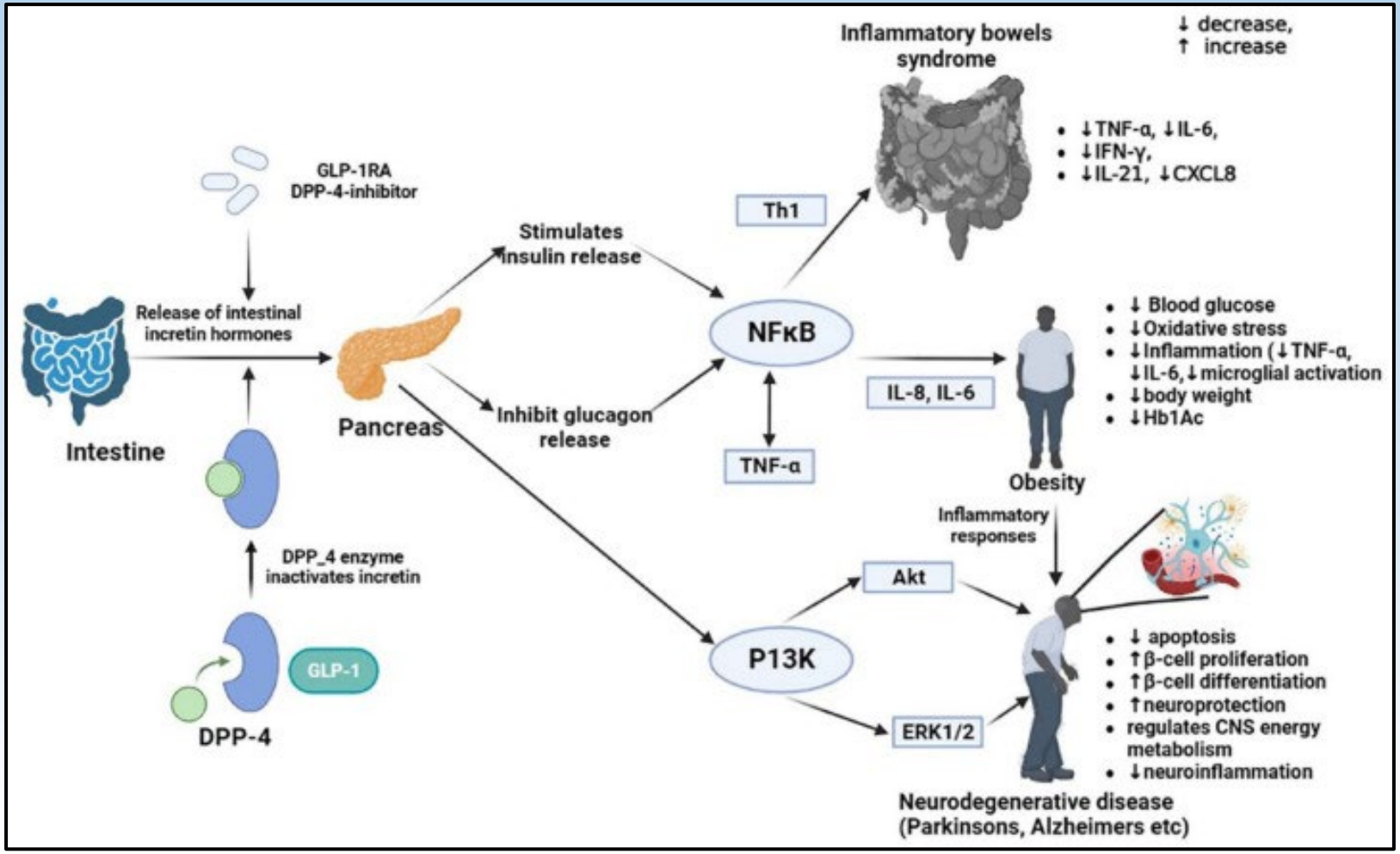


Physiologic effects of the GLP-1 family

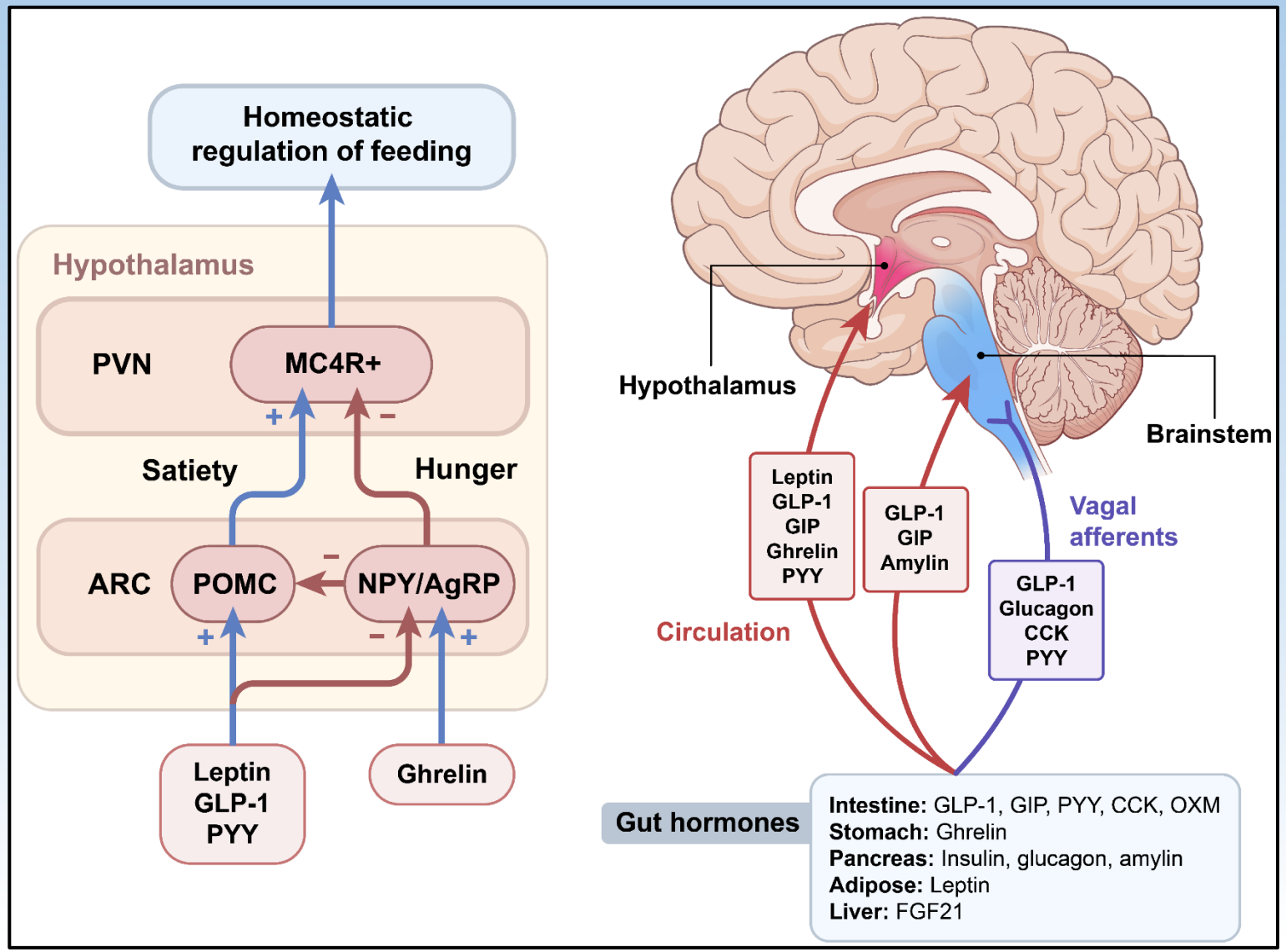




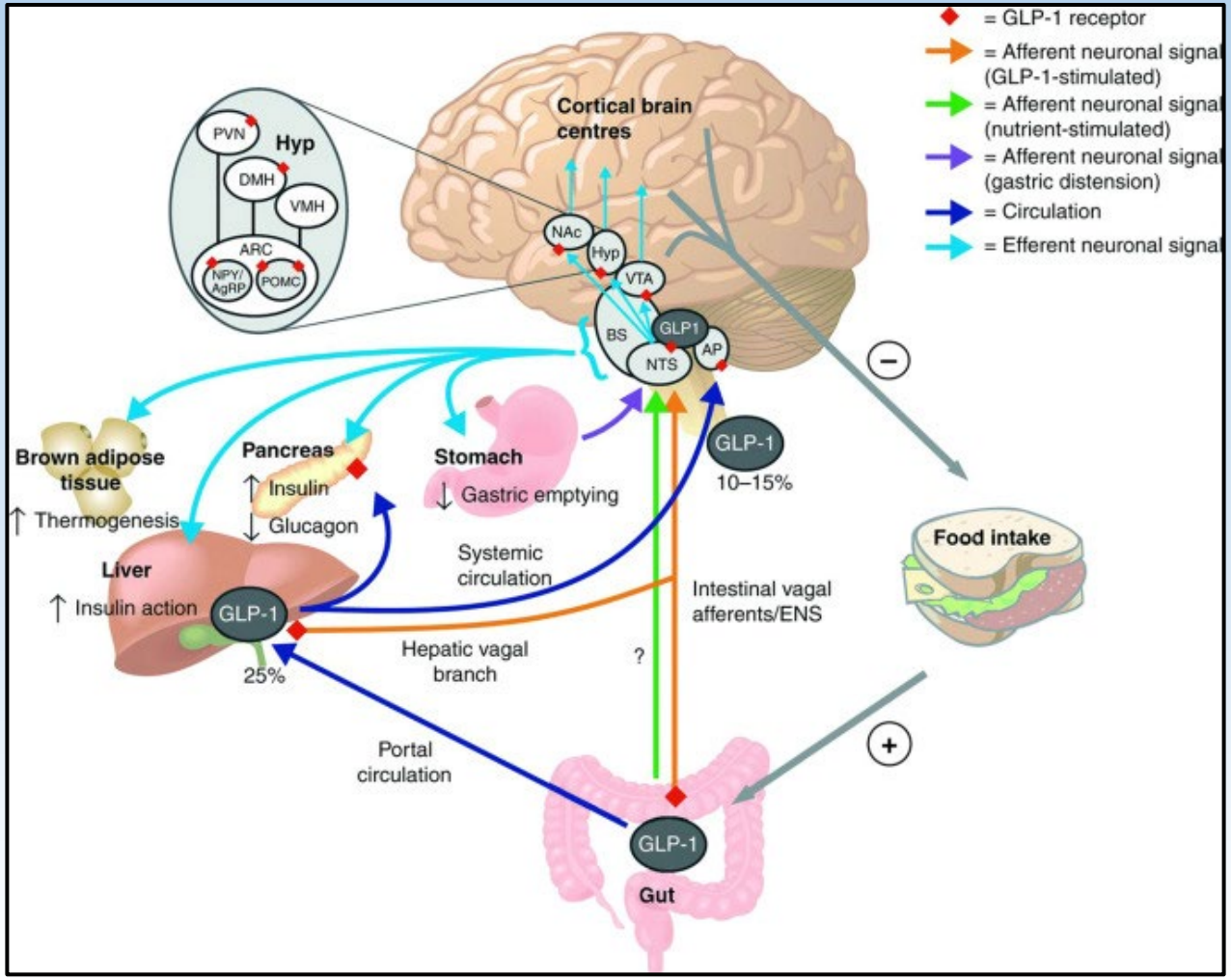
Anti-inflammatory response by GLP-1 RAs



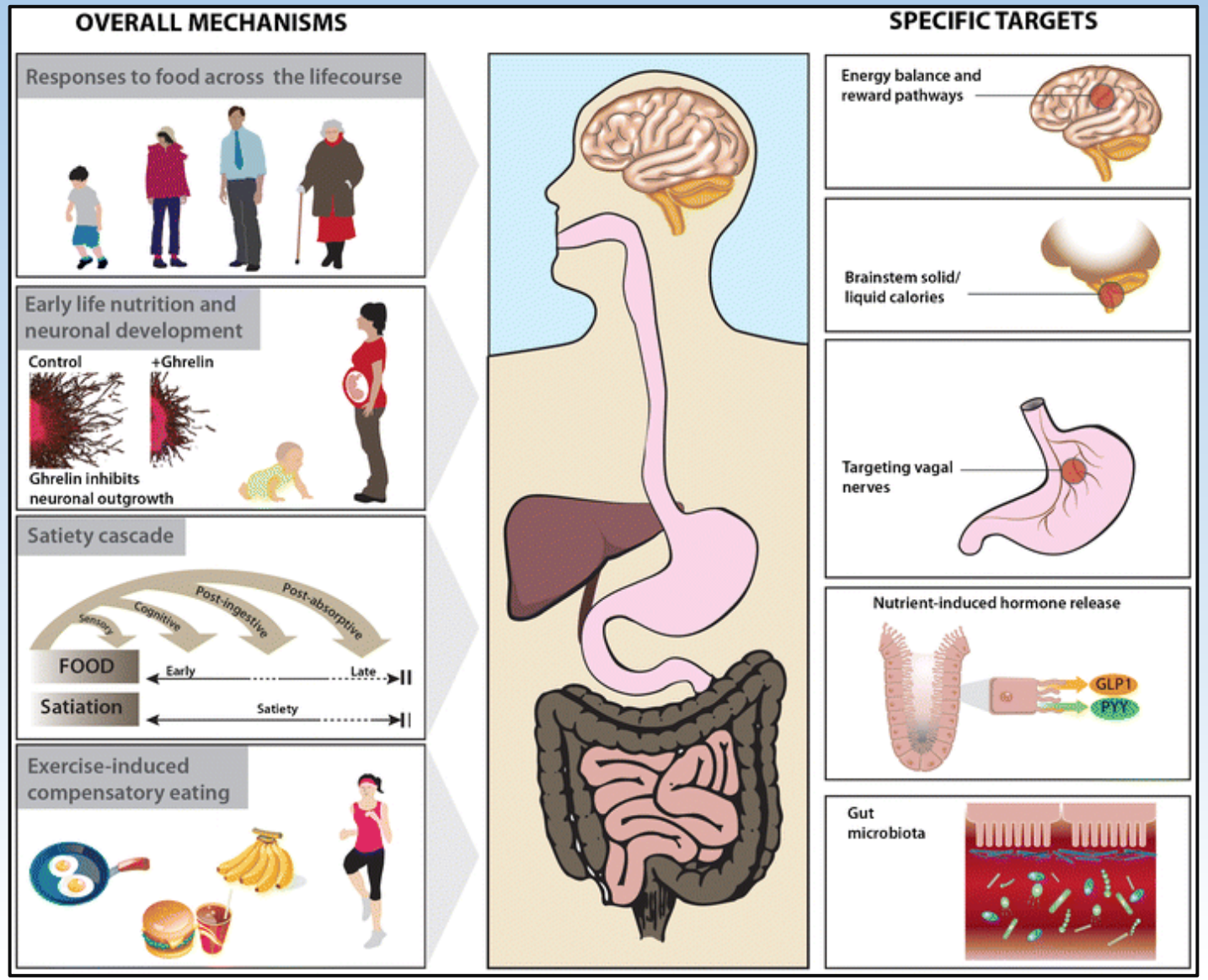
*Gut-**Brain** Regulation of Food Intake*



Proposed routes of action of GLP-1 in the central regulation of feeding and glucose metabolism.



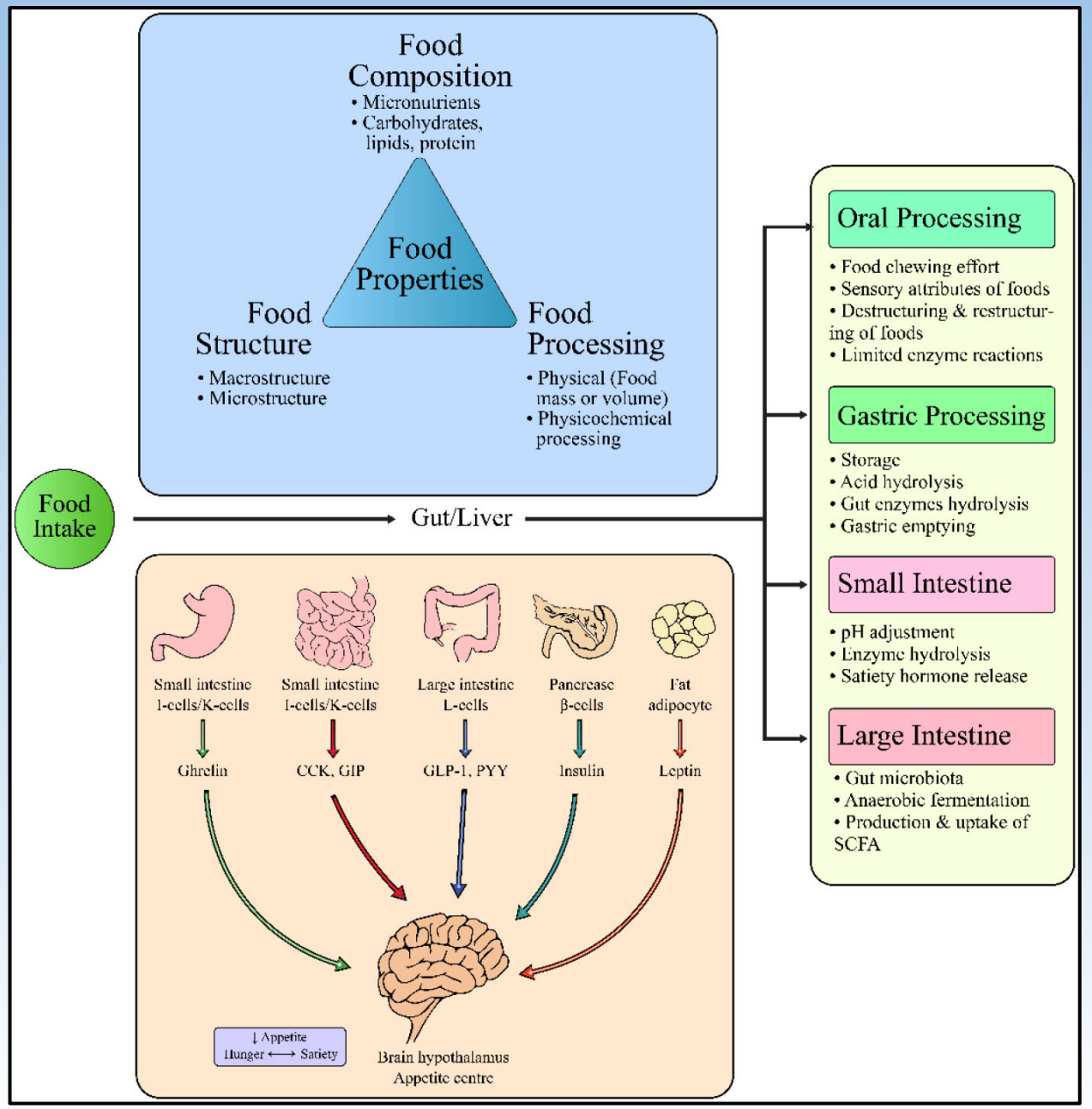
Hunger & Satiety mechanisms



Satiety & Satiation

- The physiological and psychological state of fullness that occurs after eating, which suppresses the desire to consume more food and determines the time interval before hunger returns
- The **hypothalamus** acts as your brain's central appetite control center
- The GI tract sends updates about nutrient status through the vagus nerve and direct hormonal pathways
- As you become satiated, areas like the **orbitofrontal cortex** (which processes the pleasure and reward value of taste and smell) reduce their response to food
- Satiation –when you eat, food stretches your stomach & small intestine. The gut releases Cholecystokinin (CKK) & Peptide YY(PYY) which travel through the vagus nerve to the brain the signal that the meal should end

Interrelation of food properties and internal factors controlling food intake, satiation or satiety



Overall external factors affecting food intake, satiety, & satiation

HIGH-SATIETY FOODS

egg whites (100%)

spinach (100%)

Greek yogurt (low fat) (94%)

asparagus (88%)

oysters (80%)

turkey breast (74%)

shrimp/prawns (72%)

chicken breast (71%)

salmon (70%)

cottage cheese (low fat) (70%)

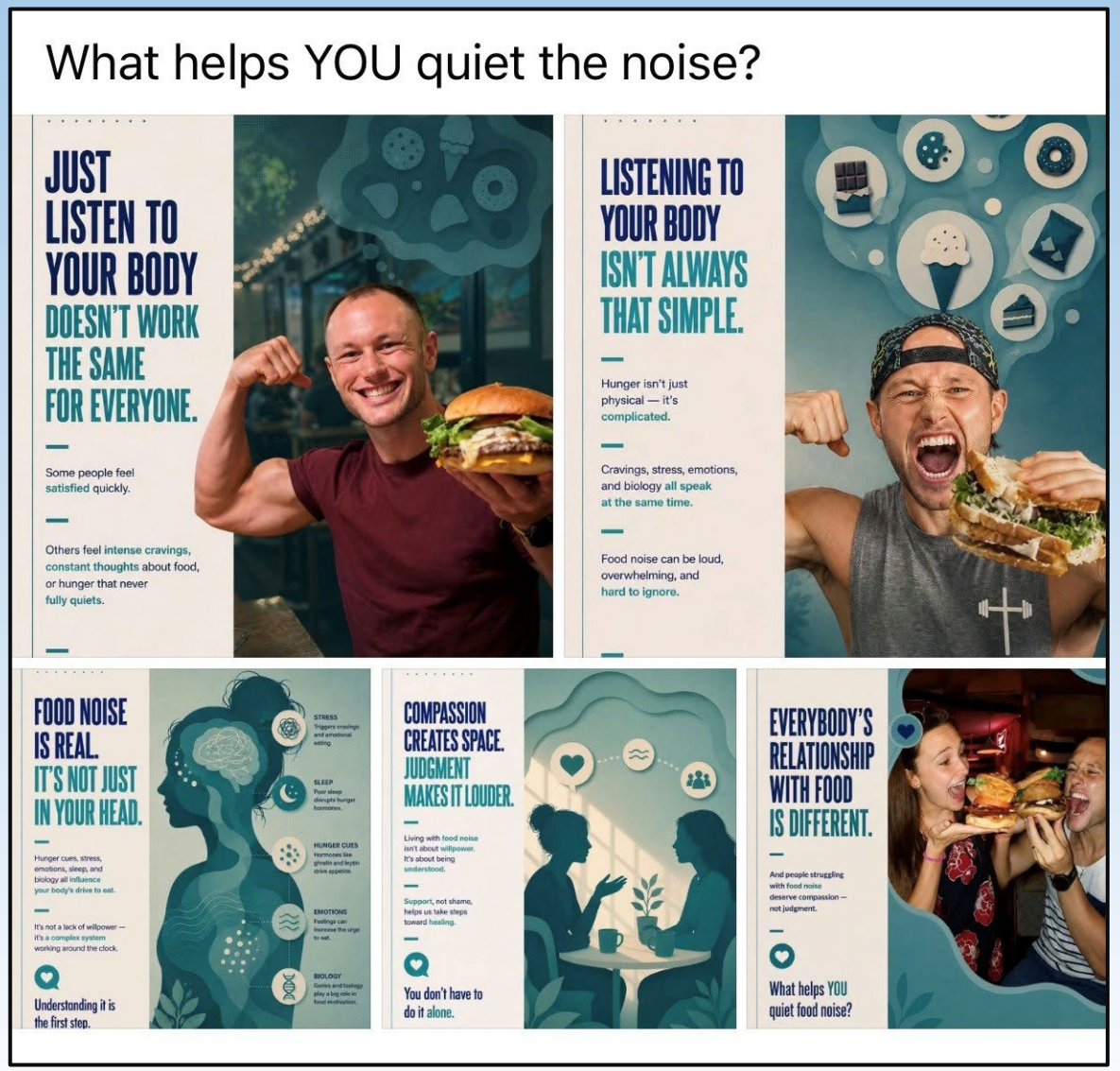
sirloin steak (69%)

broccoli (65%)

OPTIMISING NUTRITION

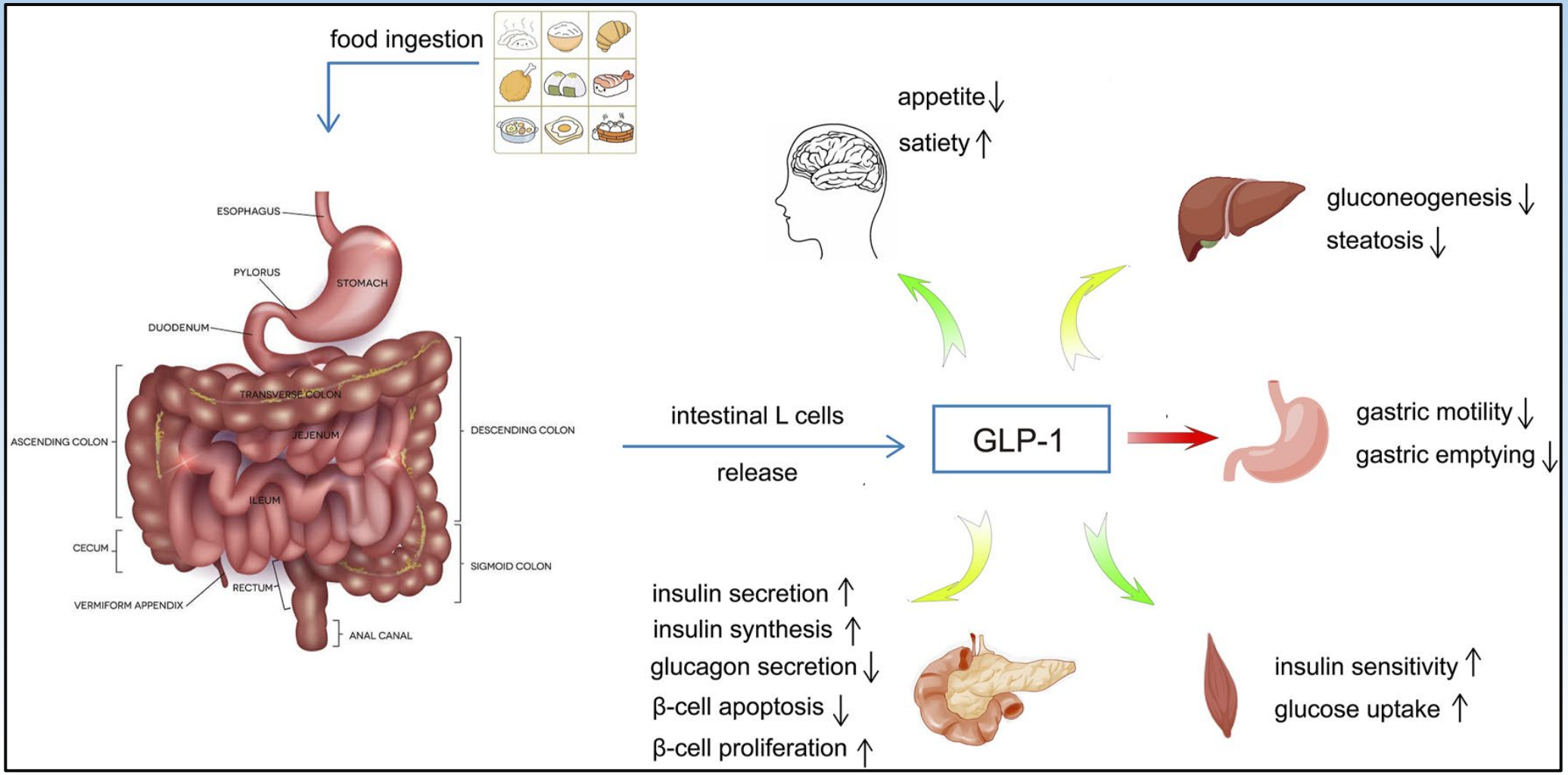
% = satiety score (per calorie)

Food Noise – feeling hungry all the time; preoccupation with food



Dr. Tommy Martin

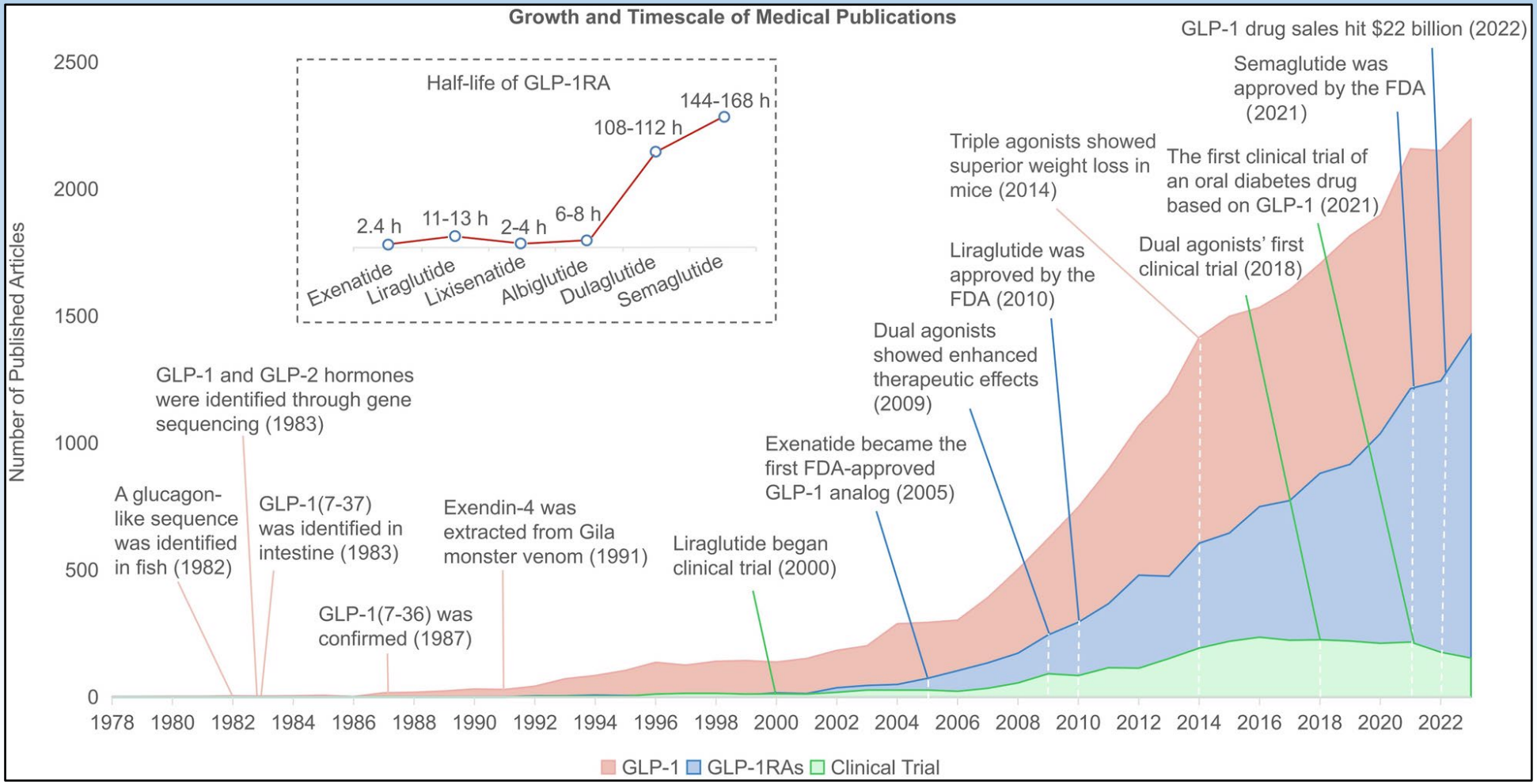
Actions of GLP-1



Milestones of GLP-1 research and drug development

- **1906 Duodenal extracts shown to stimulate internal pancreatic secretions**
- **1964 Incretin effect observed & quantified**
- **1983 GLP-1 encoding sequence identified in proglucagon gene**
- **1987 GLP-1 shown to trigger insulin release in vivo; GLP-1 exhibits incretin effect in humans**
- **1987 DPP-4 degradation of GLP-1 discovered**
- **1992 Extendin-4 identified in Gila monster venom**
- **1992 GLP-1R cloned**
- **1993 GLP-1 inactivation shown to be caused by DPP-4**
- **2005 First injectable GLP-1RA (Byetta) licensed for T2DM**
- **2006 First DPP-4 inhibitor licensed for T2DM**
- **2010 Liraglutide (Victoza) approved for T2DM**
- **2012 First once weekly GLP-1RA approved for T2DM**
- **2014 First GLP-1RA (Liraglutide) approved for obesity**
- **2017 Semaglutide (Ozempic) approved for T2DM**
- **2019 First oral GLP-1RA (Rybelsus) for T2DM**
- **2020 Saxenda (semaglutide) approved for obesity –twice daily injection**
- **2021 Wegovy (semaglutide) approved for obesity –once weekly injection**
- **2022 Tirzepatide, GLP-1/GIP RA, (Mounjaro) approved for T2DM**
- **2023 FDA approval of Tirzepatide (Zepbound) for obesity –once weekly injection**

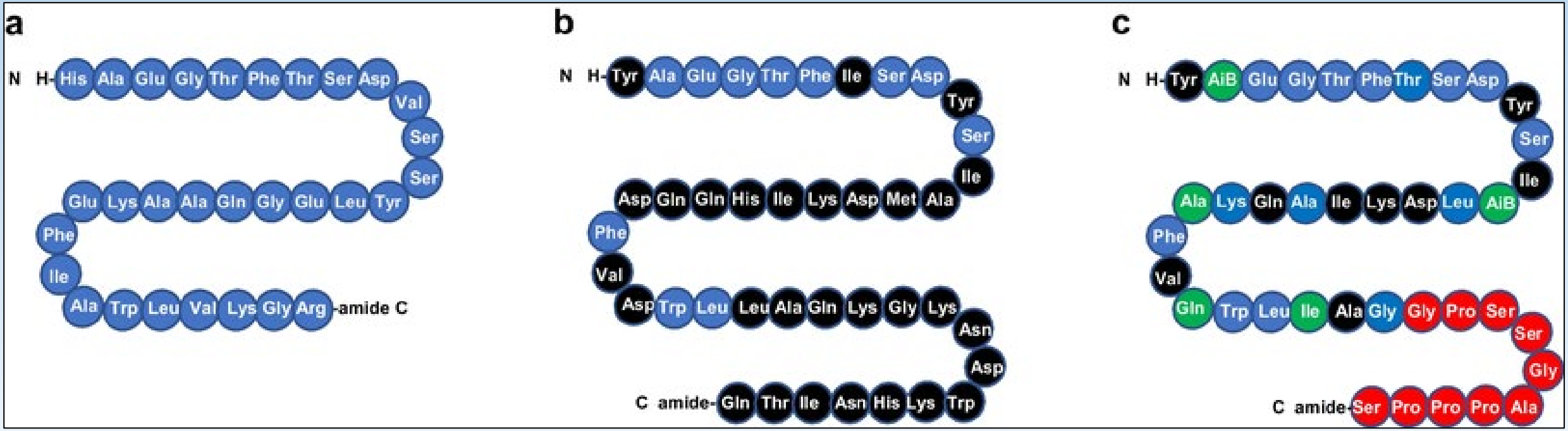
Timeline of medical publications on GLP-1 and GLP-1RAs



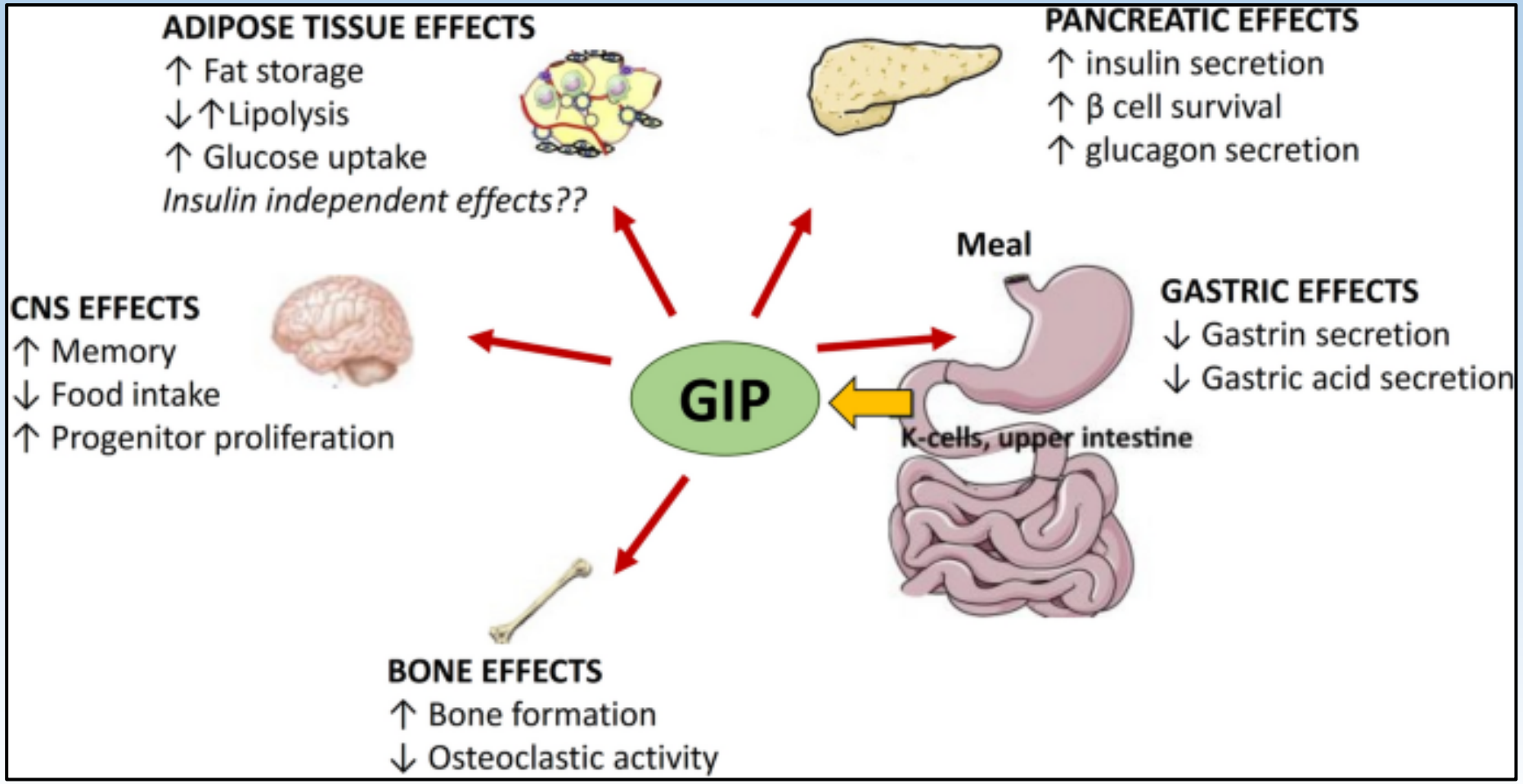
½ life of native GLP-1 in the body

- **Natural GLP-1 (1–2 min):** Rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) and cleared by the kidneys.
- **Short-Acting Agents (e.g., Exenatide):** Have a 2.4-hour half-life, leaving the body within 12–24 hours.
- **Long-Acting Agents (e.g., Semaglutide):** Engineered for ~7-day half-life, allowing for weekly injections.
- **Other Agents:** Liraglutide has a half-life of ~13 hours, while newer ones like tirzepatide have extended durations.
- **Elimination Time:** Medications like Wegovy or Zepbound can take roughly 30 days to fully leave the system after the final dose.
- The very short half-life of natural GLP-1 is a major limitation, necessitating engineered agonists that resist degradation.

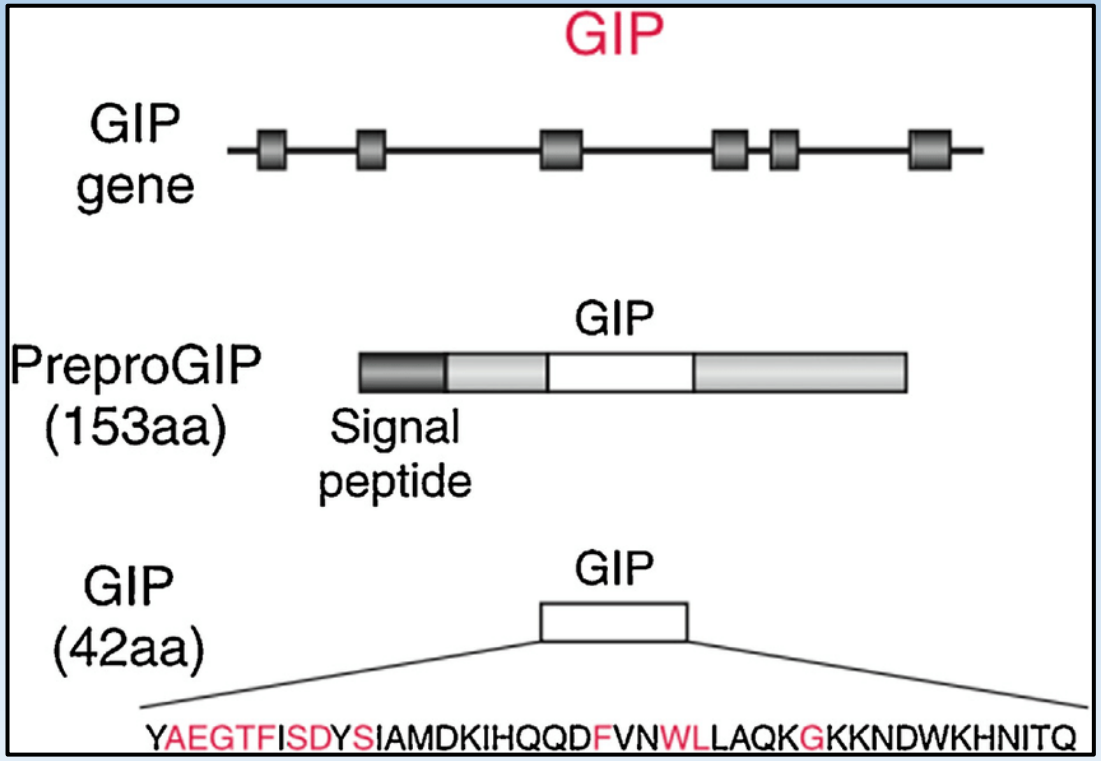
Structures of a. GLP-1; b.GIP; c.Tirzepatide

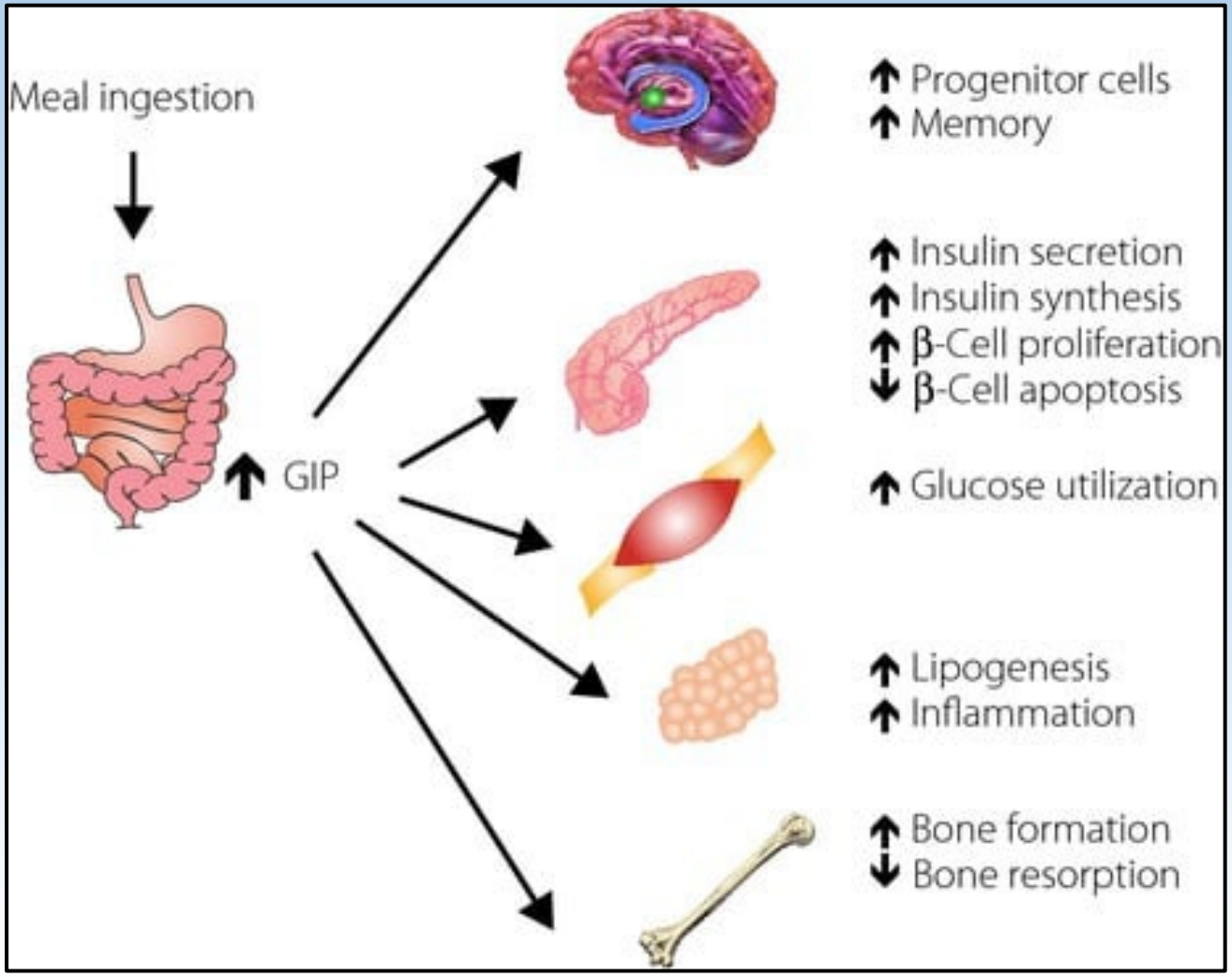


Glucose dependent Insulinotropic Peptide, GIP (formerly Gastric Inhibitory Peptide) Chromosome 17

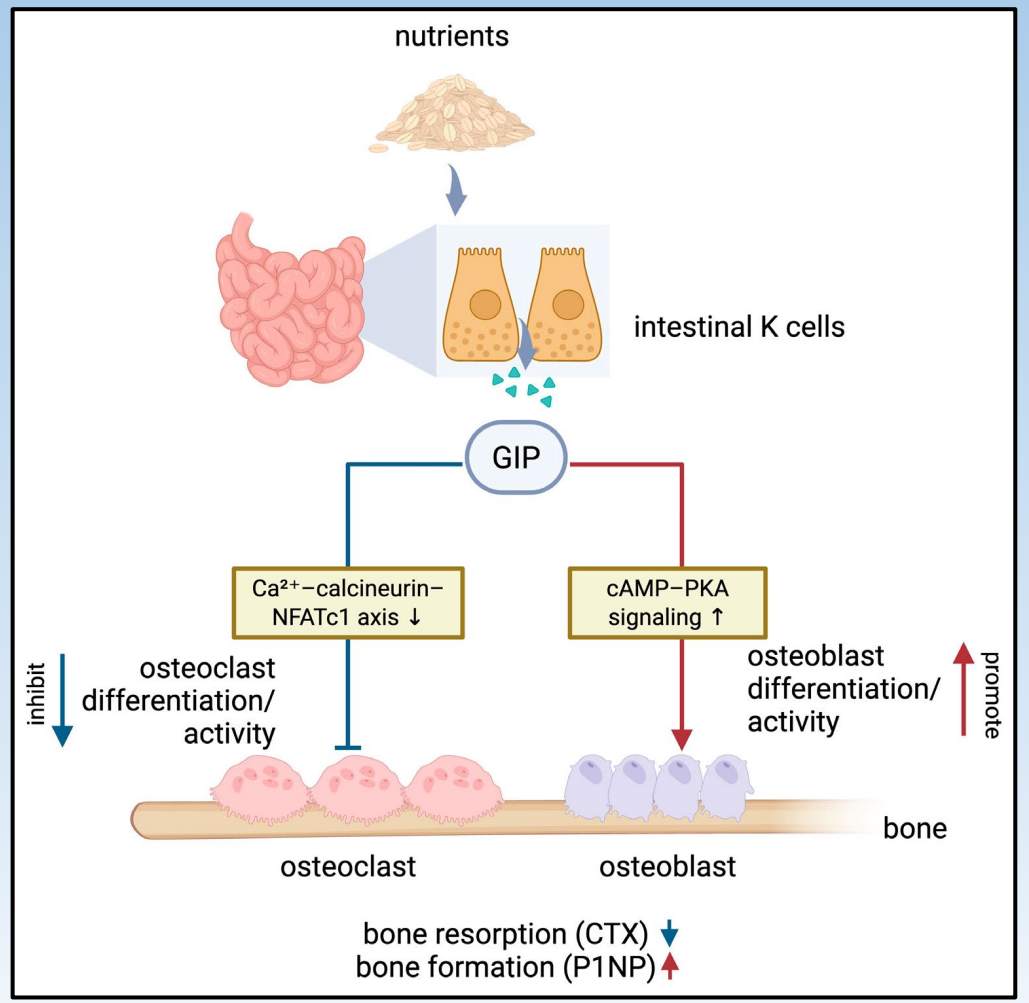


GIP gene expression and actions



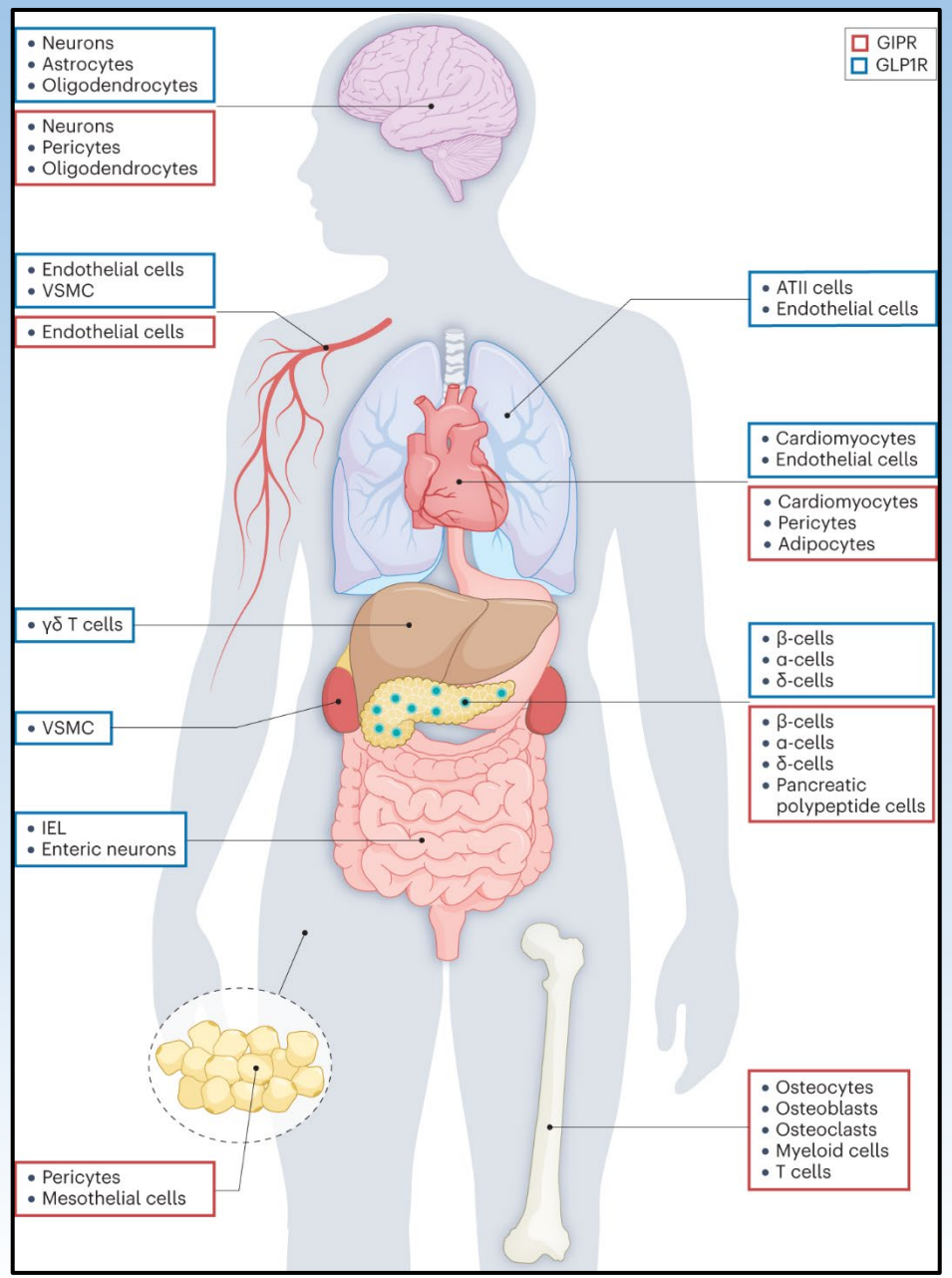


GIP and bone metabolism

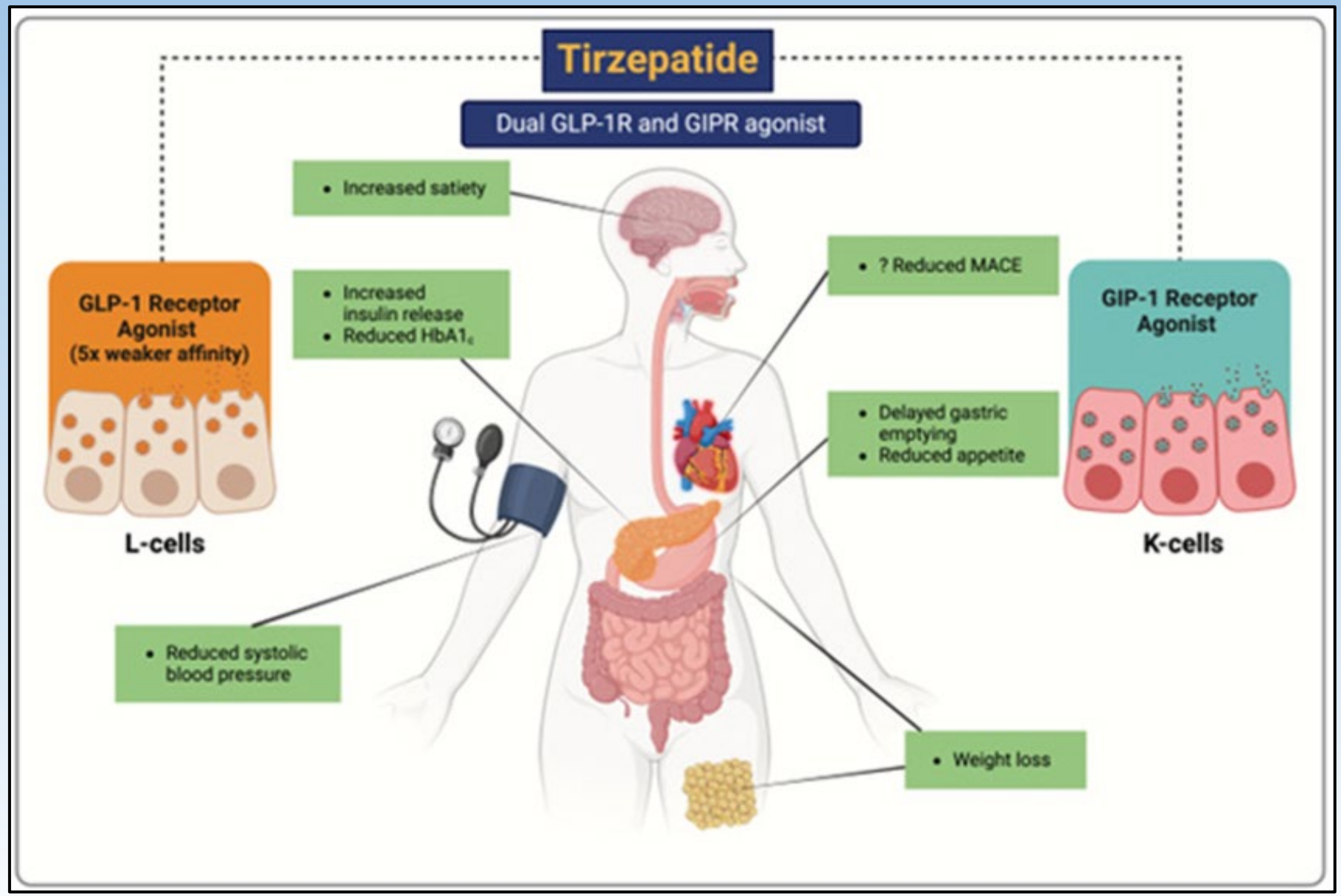


Int. J. Mol. Sci. **2026**, *27*(2), 600; https://doi.org/10.3390/ijms27020600

Tissue-specific expression of GLP-1R and GIPR



Nature Reviews Endocrinology | Volume 19 | April 2023 | 201–216


Tirzepatide
Dual GLP-1R and GIPR agonist
Increased satiety
Increased insulin release
Reduced HbA1c
Reduced systolic blood pressure
? Reduced MACE
Delayed gastric emptying
Reduced appetite
Weight loss
GLP-1 Receptor Agonist (5x weaker affinity)
L-cells
GIP-1 Receptor Agonist
K-cells

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide vs. Semaglutide for the Treatment of Obesity

A Research Summary based on Aronne LJ et al. | 10.1056/NEJMoa2416394 | Published on May 11, 2025

WHY WAS THE TRIAL DONE?

Tirzepatide and semaglutide are part of a new generation of highly effective medications for the management of obesity. Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, and semaglutide is a long-acting GLP-1 receptor agonist. How the two drugs compare with each other in adults with obesity but without type 2 diabetes is unknown.

HOW WAS THE TRIAL CONDUCTED?

Adults without diabetes who had a body-mass index (BMI) of 30 or higher, or a BMI of 27 or higher and at least one prespecified obesity-related complication, and who reported at least one unsuccessful dietary effort for weight reduction were assigned to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. The primary end point was the percent change in body weight from baseline to week 72.

TRIAL DESIGN

- Phase 3b
- Open-label
- Randomized
- Controlled
- Location: 32 sites in the United States and Puerto Rico

RESULTS

At week 72, participants in the tirzepatide group had lost significantly more weight than those in the semaglutide group. In both groups, the most common adverse events were gastrointestinal; these events were usually mild to moderate in severity and occurred most often during dose escalation.

LIMITATIONS AND REMAINING QUESTIONS

- The trial was not blinded.
- Although the effect of semaglutide on cardiovascular outcomes has been reported, the effect of tirzepatide on such outcomes is unknown. An ongoing trial may provide data on the use of tirzepatide for both primary and secondary prevention of cardiovascular disease.

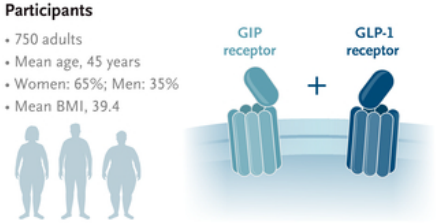
CONCLUSIONS

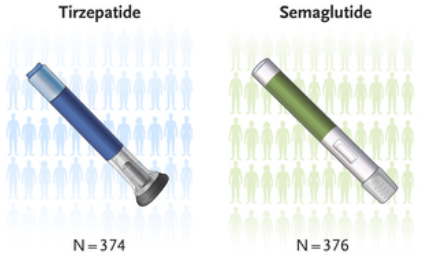
In adults with obesity but without diabetes, weekly treatment with tirzepatide led to significantly greater weight loss than weekly treatment with semaglutide over 72 weeks.

NEJM QUICK TAKE | EDITORIAL

Participants

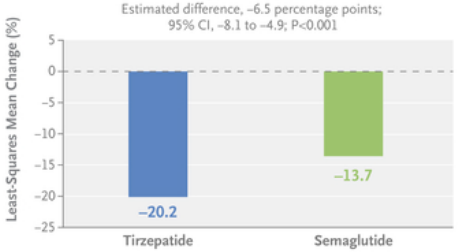
- 750 adults
- Mean age, 45 years
- Women: 65%; Men: 35%
- Mean BMI, 39.4





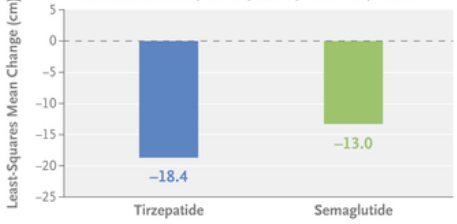
Change in Body Weight

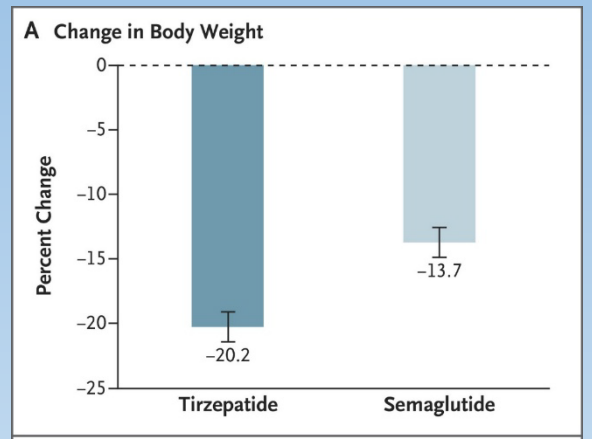
Estimated difference, −6.5 percentage points; 95% CI, −8.1 to −4.9; P<0.001

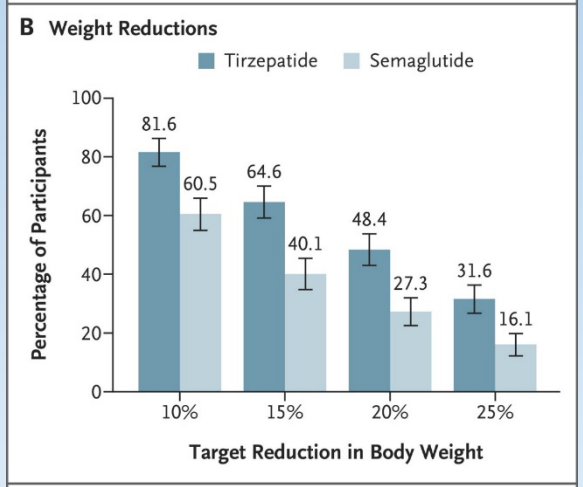


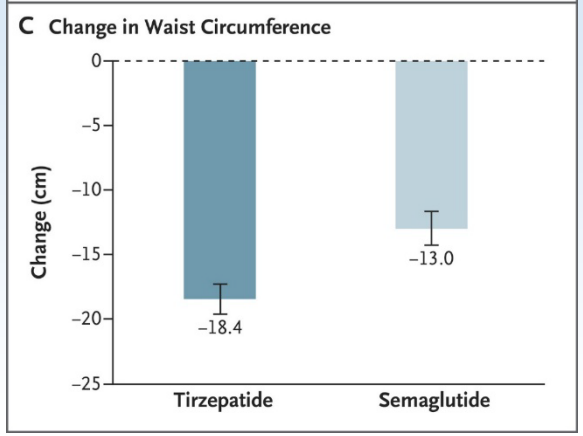
Change in Waist Circumference

Estimated difference, −5.4 cm; 95% CI, −7.1 to −3.6; P<0.001

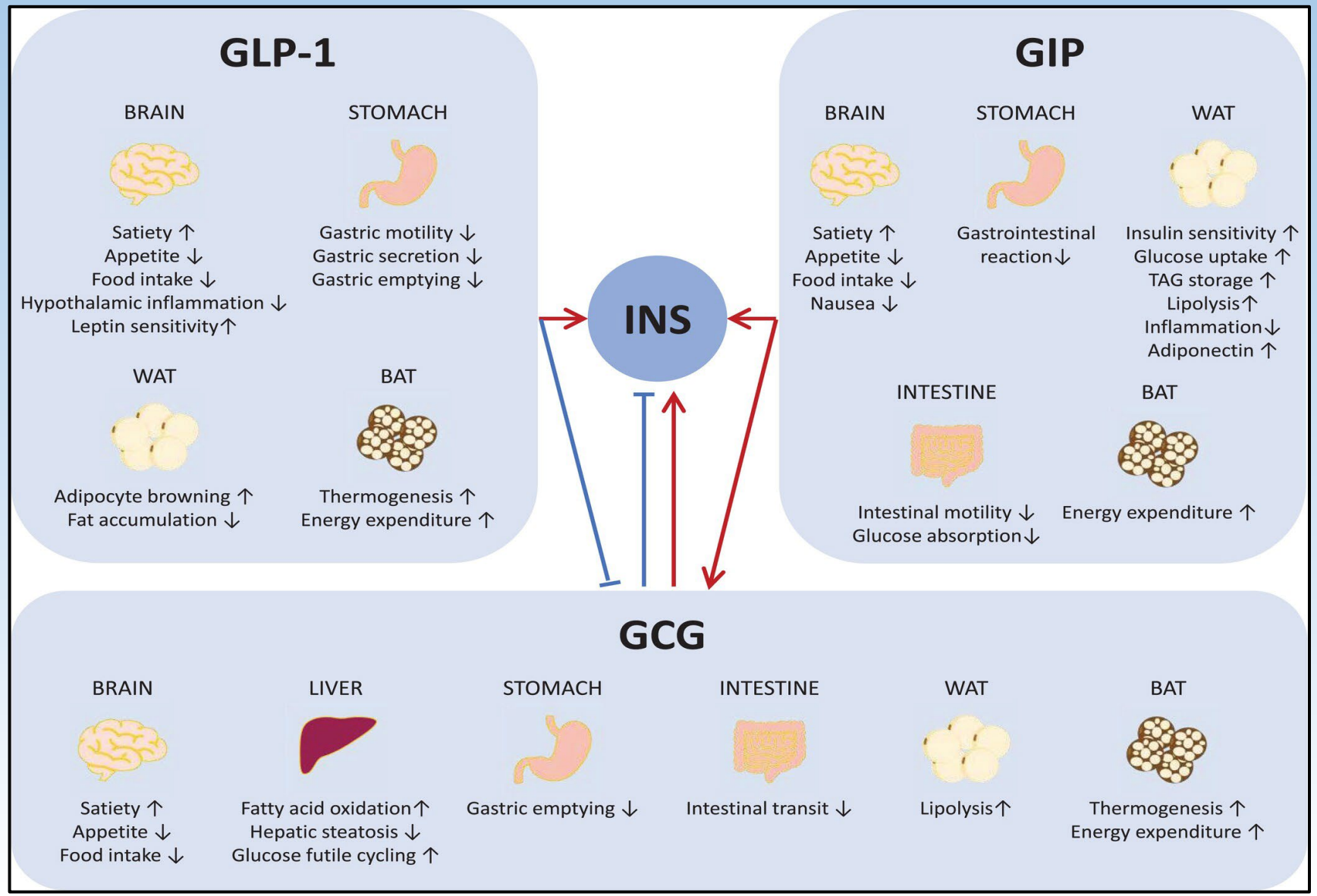








Why does GLP-1 agonist combined with GIP and/or GCG agonist have greater weight loss effect than GLP-1 agonist alone in obese adults without type 2 diabetes?



Diabetes Obesity Metabolism, Volume: 27, Issue: 3, Pages: 1079-1095, First published: 26 November 2024, DOI: (10.1111/dom.16106)

SURMOUNT TRIALS – landmark phase 3 clinical trials for evaluating efficacy & safety of Tirzepatide for weight management (Randomized, Double Blind control trials)

- SURMOUNT 1 Evaluated obese adults without diabetes over 72 weeks (Tirzepatide vs Placebo) – once weekly injections led to body weight reductions up to 22.5%
- SURMOUNT 2 Evaluated obese adults with diabetes –showed significant weight reduction & improvements in cardiometabolic health measures
- SURMOUNT 3 – Evaluated Tirzepatide in obese patients without diabetes who had already lost weight (6.9% loss) by intense lifestyle modifications for 12 weeks; followed by 72 weeks of Tirzepatide or placebo. Participants lost and additional 18.4 % body weight on medication & 2.5 % on placebo with better BP
- SURMOUNT 4 Continued treatment with Tirzepatide sustains weight loss
- SURMOUNT 5 Compared Tirzepatide & Semaglutide. Tirzepatide led to greater weight reductions & waist circumference

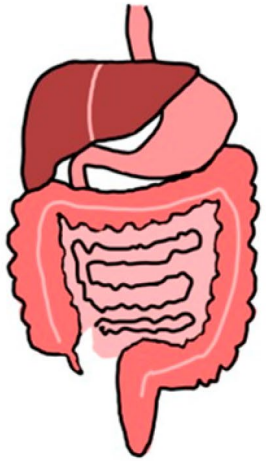
GI side effects of GLP-1 RAs are COMMON

- Approximately 40 -70%, of persons, dose dependent, transient, however ~ 15% will discontinue use
- Nausea
- Vomiting
- Diarrhea
- Stomach pain
- Decreases gastric emptying - obstruction or perioperative aspiration are major concerns
- Gall bladder – biliary disease

Recognized Adverse Effects of GLP -1 Class Drugs

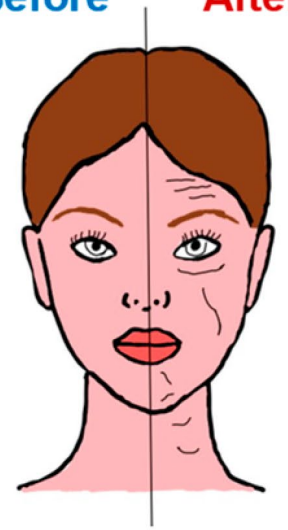
Gastrointestinal:

- diarrhea
- vomiting
- nausea
- constipation
- pancreatitis

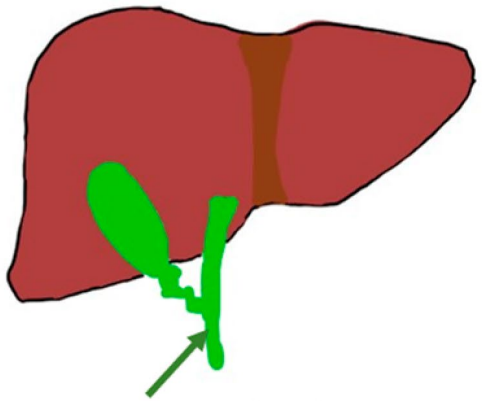


"Ozempic" face

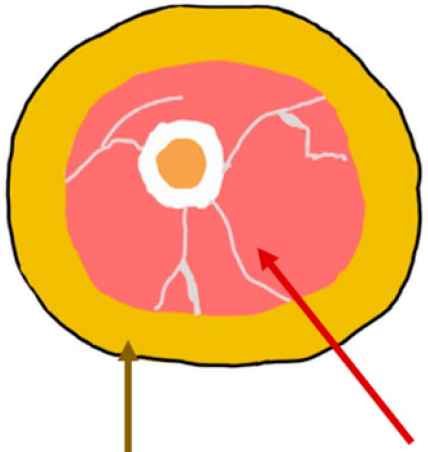
Before After



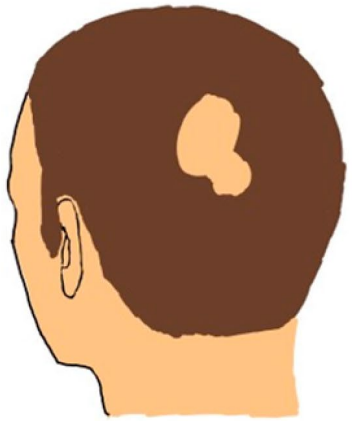
Biliary Disease



Sarcopenia

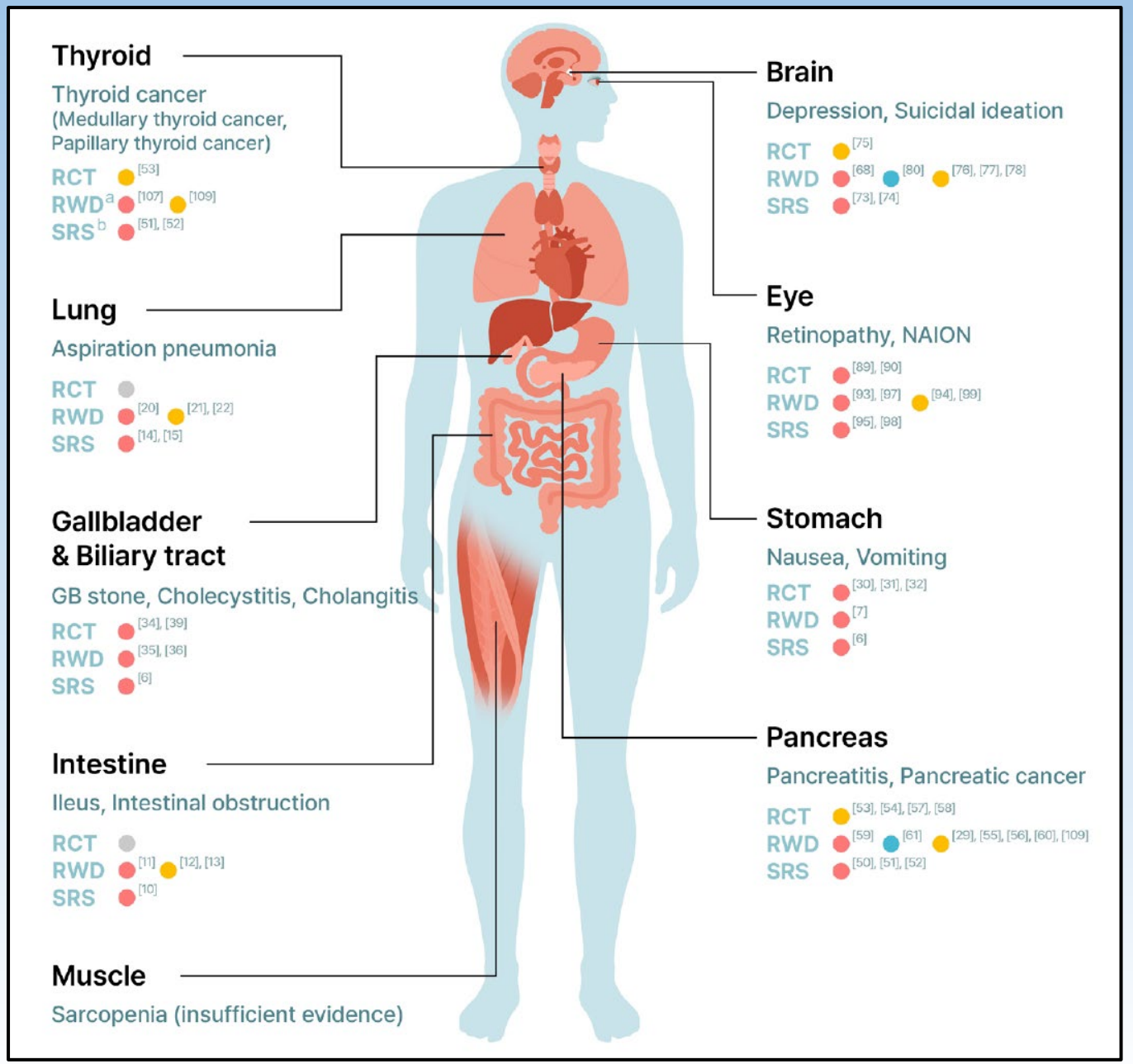


Alopecia



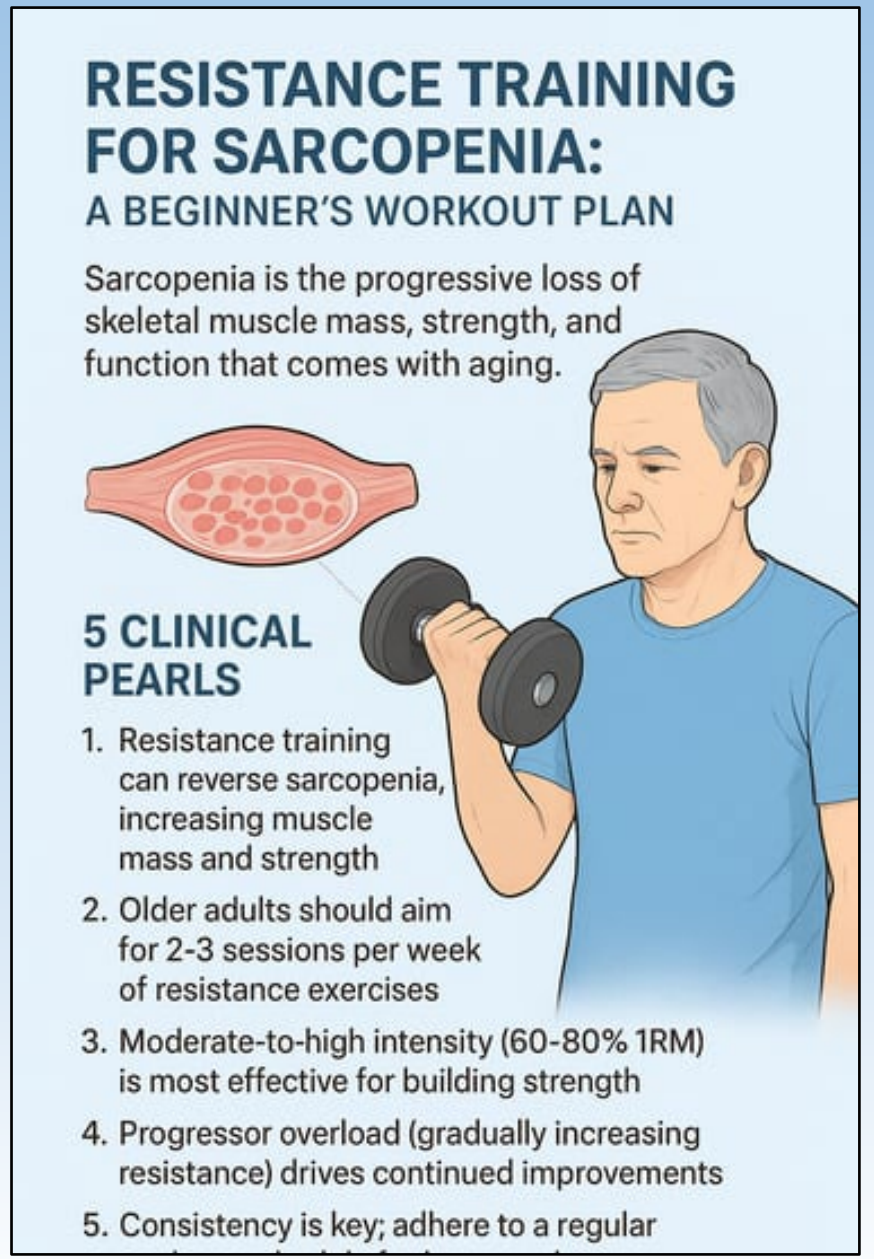
Literature on Adverse Effects

Pink –research indicates increases of adverse effects
Blue–research evidence indicates decreased incidence of side effects
Orange –research show not significantly associated
Grey – absence of research



Side effect – Sarcopenia

- Progressive loss of muscle mass, strength & functioning, typically associated with aging affecting 10-20% of older adults
- Associated with any dramatic weight loss
- GLP-1RAs can cause a significant reduction in muscle mass (15-20% of total weight loss)
- Over age 65, those with pre-existing low muscle mass, frailty, chronic illnesses most at risk
- Increase protein intake to support muscle maintenance

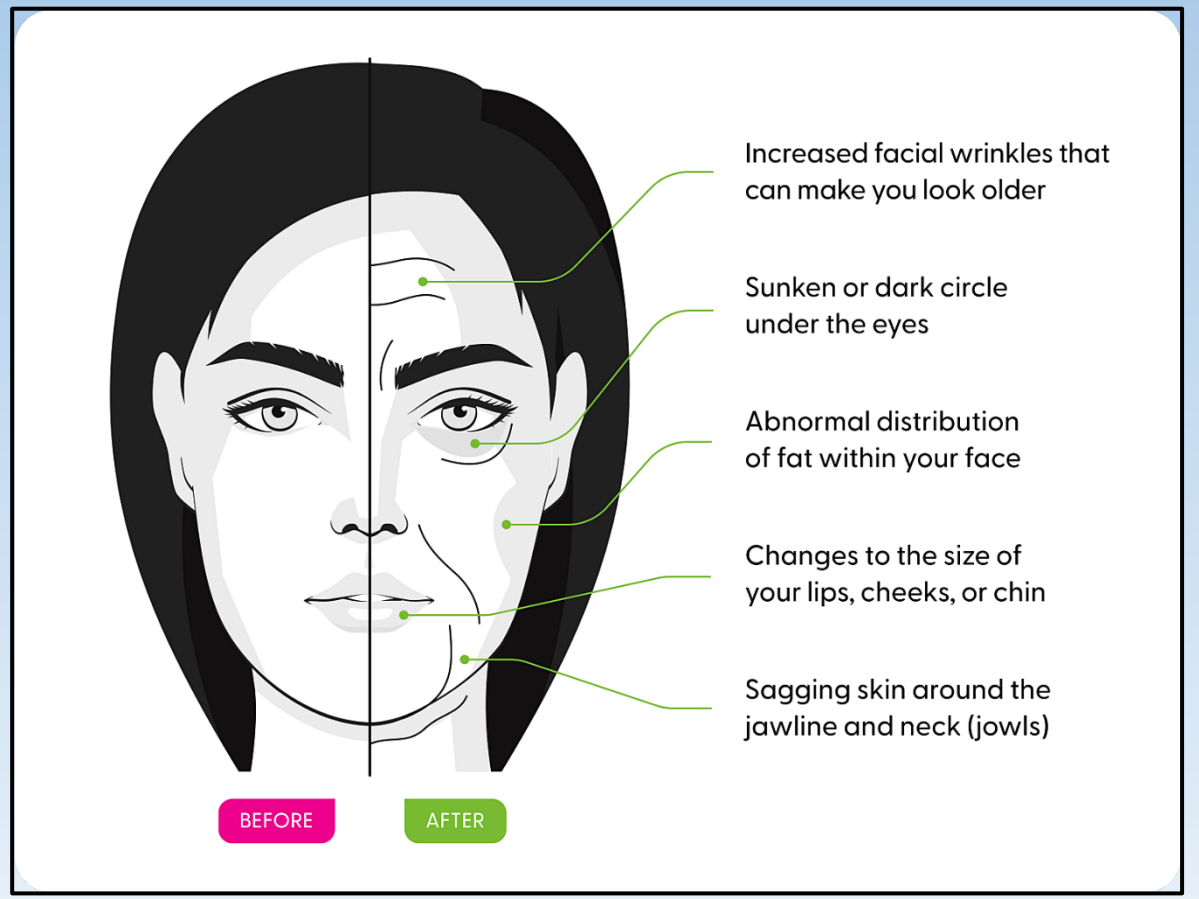


Alopecia –balding

- GLP-1 RAs reduce appetite, & patients often eat less, leading to inadequate intake of key hair-building nutrients like protein, iron, zinc, and Vitamin B12
- Linked to rapid weight loss rather than the drug itself
  - Rapid weight loss is metabolic stress & a shock to the system
  - Hair follicles enter a premature resting phase
- Telogen Effluvium – Premature resting phase causes heavy diffuse shedding ~ 2-4 months after med is started, possibly stress related
- Adrogenetic pattern baldness –GLP-1RAs may accelerate hereditary pattern hair loss
- Alopecia Areata – autoimmune hair loss –emerging & contradictory findings:
  - Some studies show increased risk
  - Some who already have it show hair regrowth (anti-inflammatory action)

"Ozempic Face"

- Accelerated facial aging—sunken eyes, hollow cheeks, and sagging skin—caused by rapid fat loss, not a direct drug side effect.
- Common in those losing weight quickly on GLP-1 agonists, it creates a gaunt, older appearance due to lost facial volume.
- Symptoms, including increased wrinkles and sagging
- May require cosmetic procedures like fillers or lifestyle adjustments to treat



Other less common side effects

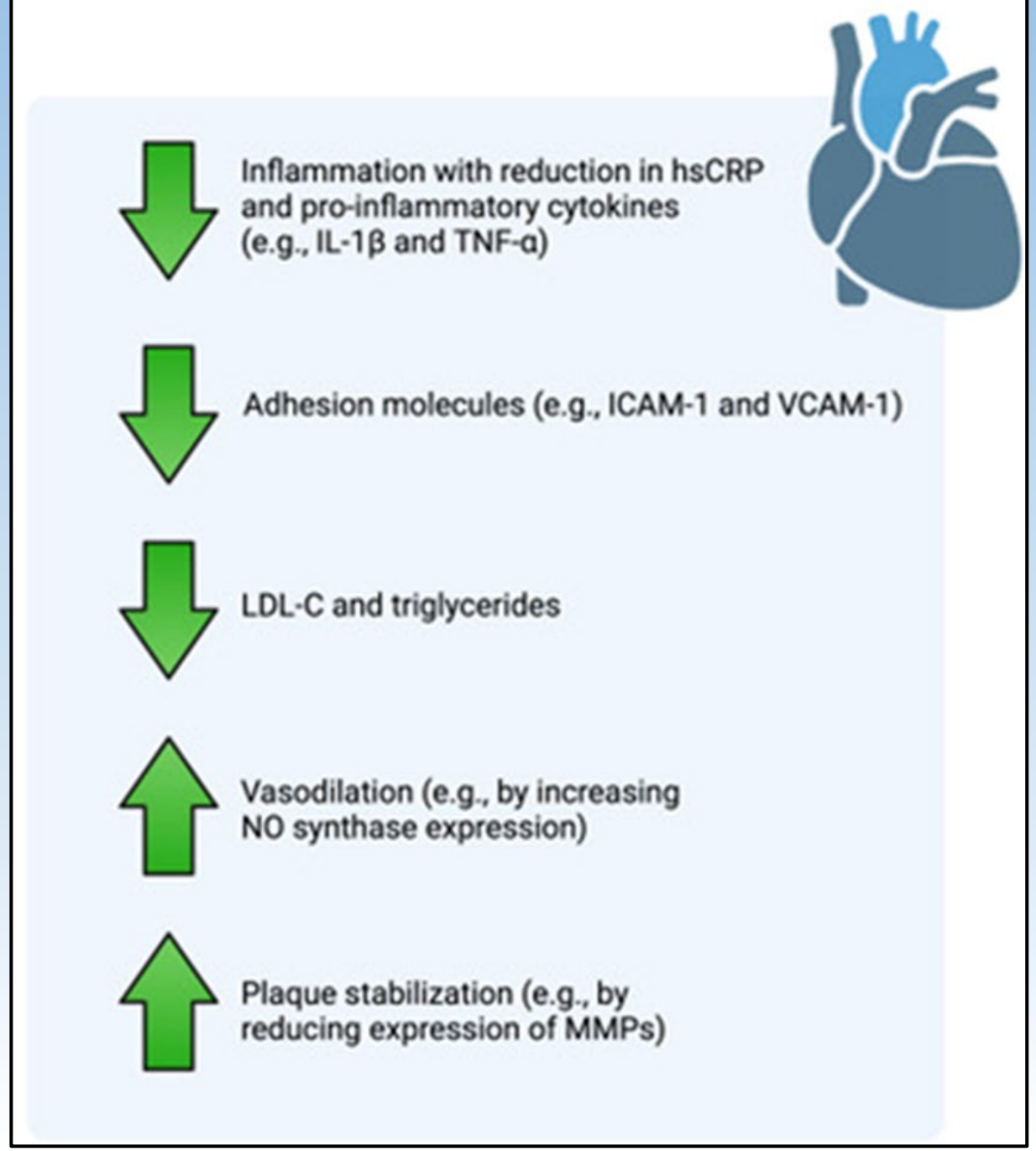
- Retinopathy (damage to the retina)
- NAION (Non-arteritic anterior ischemic optic neuropathy) –loss of vision in one eye due to restricted blood flow to the optic nerve
- Medullary thyroid cancer (animal studies)

Positive effects on other body organs

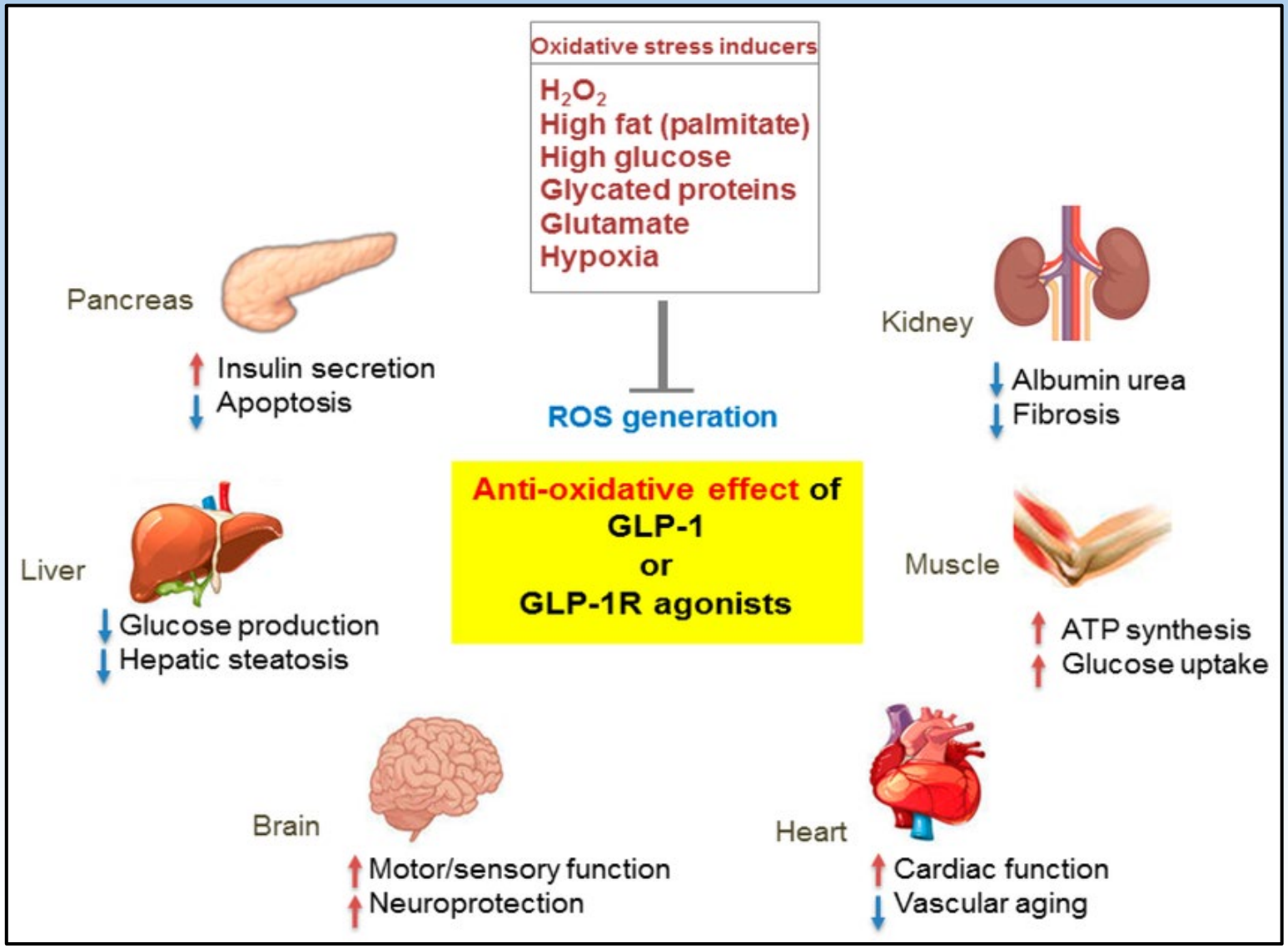
Cardiovascular Benefits

- First shown in Semaglutides (Ozempic/Wegovy) –reduces major cardiovascular events (MACE) -MI, stroke in up to 20% compared to placebo. FDA approved

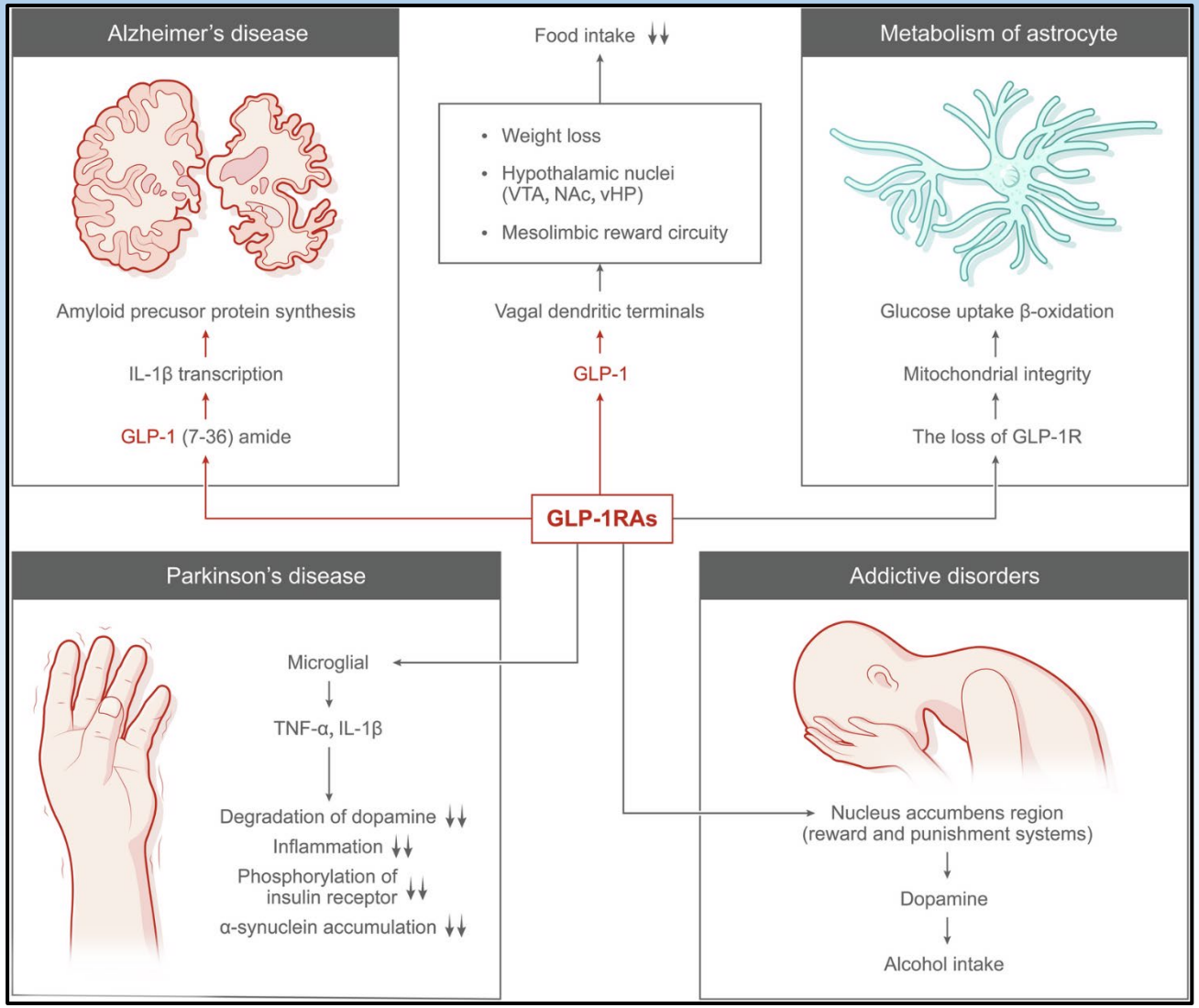
- GLP-1 medications are powerful tools, but they work best when combined with healthy habits

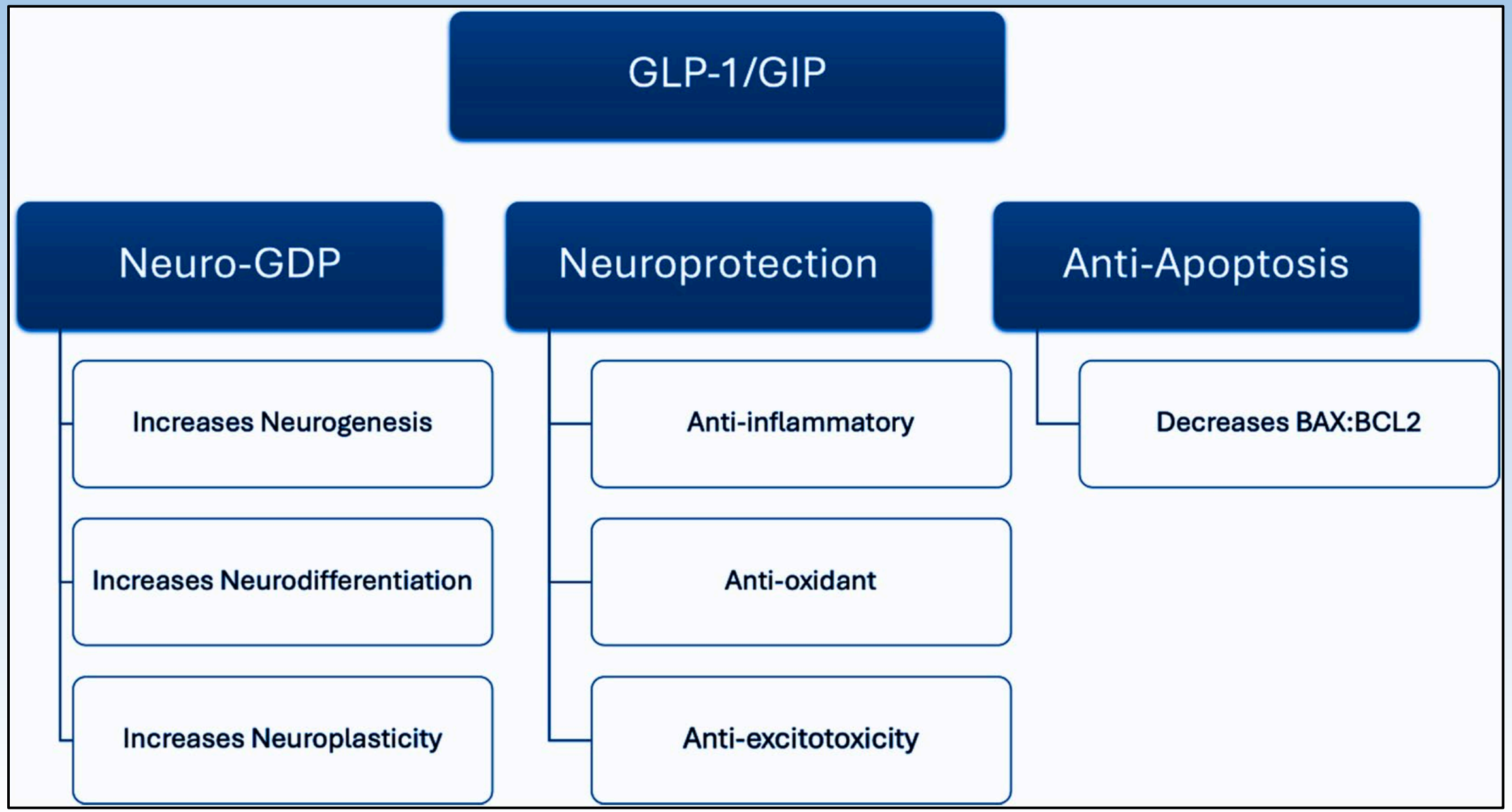


Anti-oxidant effects



The effects of GLP-1RAs on nervous system




GLP-1/GIP
Neuro-GDP
Neuroprotection
Anti-Apoptosis
Increases Neurogenesis
Increases Neurodifferentiation
Increases Neuroplasticity
Anti-inflammatory
Anti-oxidant
Anti-excitotoxicity
Decreases BAX:BCL2

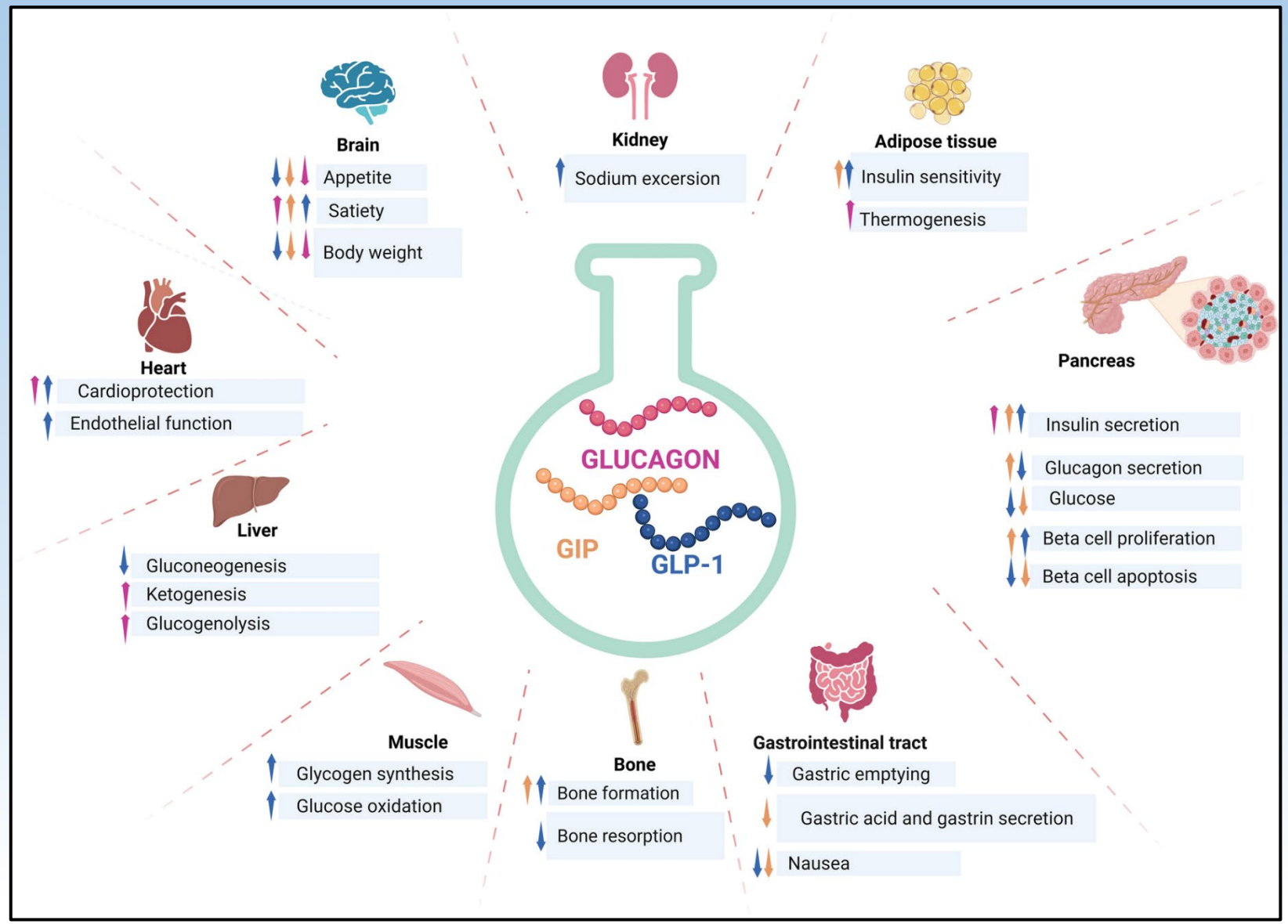
GLP-1RAs in pain management

- **Mechanism of Action**: GLP-1RAs exert analgesic effects through **regulation of inflammation** pathway such as PI3K/AKT mediated NFKB activation, macrophage sub-type repolarization, reducing oxidative stress, microglial regulation, inhibition of Na^+/K^+ -ATPase in choroid plexus. GLP-1 agonists also modulate dopaminergic pathways potentiating its use in substance use disorders.
- **Osteoarthritis Pain**: GLP-1RAs reduce osteoarthritis-related pain via anti-inflammatory mechanisms, cartilage preservation, and potential direct analgesic effects beyond weight loss.
- **Diabetic Neuropathy Pain**: These agents enhance nerve function, reduce oxidative stress, and improve pain perception.
- **Headaches and Intracranial Hypertension**: GLP-1RAs show promise in lowering intracranial pressure and reducing neurogenic inflammation, suggesting therapeutic applications in migraines and idiopathic intracranial hypertension.
- **Substance Use Disorder**: Preclinical and early clinical studies indicate that GLP-1RAs may modulate reward pathways, reducing alcohol cravings, though further research in reward pathways for other substances like cocaine and nicotine is needed.
- **Clinical Implications**: Future studies should explore GLP-1RA efficacy in non-obese, non-diabetic pain populations and evaluate their role as a primary or adjunctive pain management therapy and medications to control substance use disorder.
- **Future Directions**: Development of GLP-1RAs regulatory approval for pain indications, and integration into multimodal pain management strategies are anticipated over the next decade.

New studies on GLP-1RAs and cancer

- American Society of Clinical Oncology continuing to evaluate the role of GLP-1s in oncology
- 2026 ASCO Annual Meeting (Abstract 3143) 5/30/26
- Cleveland Clinic
  - GLP-1 users have significantly lower incidence of obesity related cancers compared to non-users (thought to be due to anti-inflammatory mechanism)
  - Pts with higher GLP-1 receptors in tumors (breast cancer) have lower mortality risks)
  - Reduced risk of metastatic progression
- Anti-inflammatory (?)

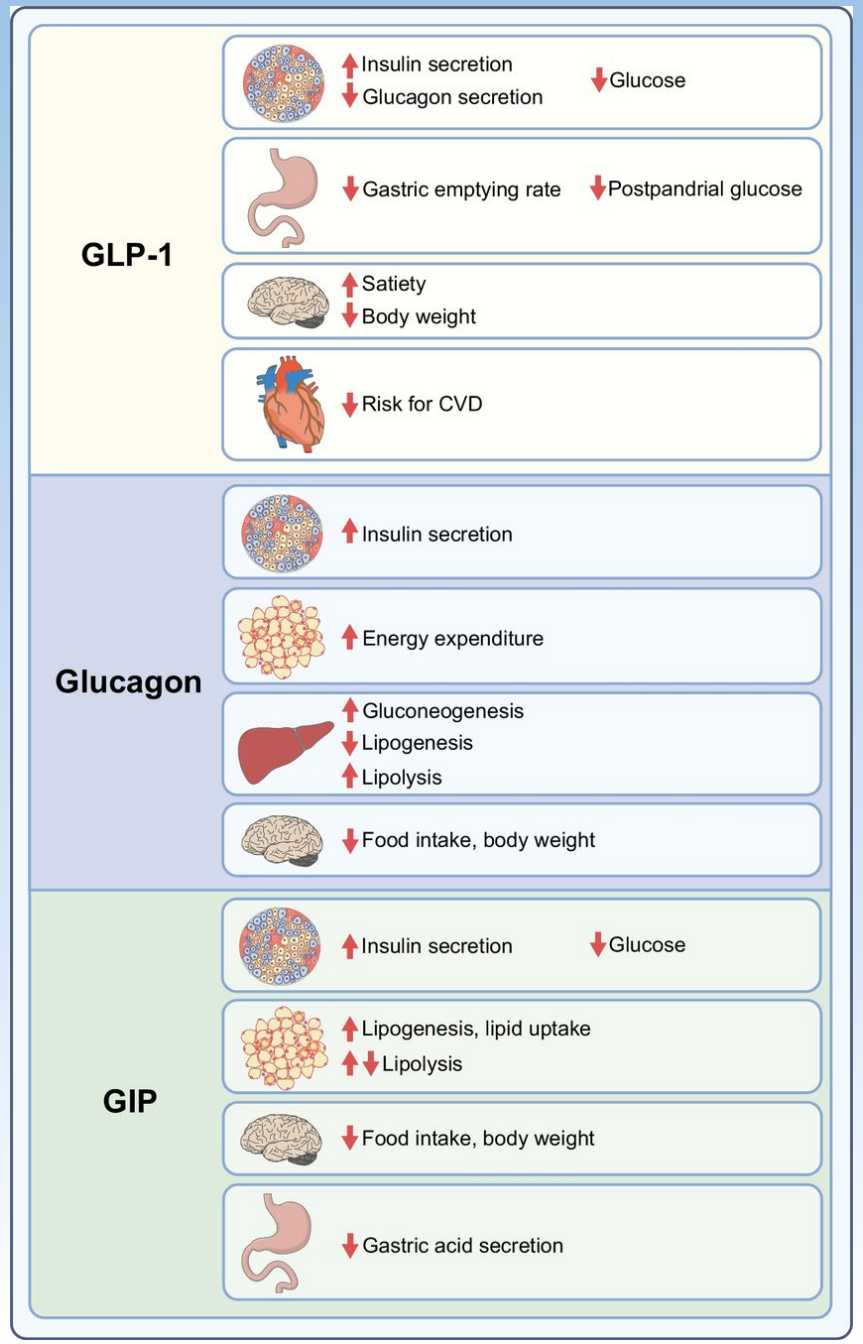
Role of GLP-1, GIP, & glucagon on body organs



Mechanisms of GLP-1, Glucagon & GIP

Provides basis for use of GLP-1 RA

Dual & Triple receptor agonists in treatment of T2DM



GLP-1 MEDICATIONS FOR WEIGHT LOSS

Semagultide

~15%

Average Weight Loss

GLP-1 agonist

Pros

- FDA-approved for weight loss
- Proven effectiveness
- Improves blood sugar control

Cons

- Less potent than newer drugs
- Gastrointestiitinal

Tirzepatide

~20%

Mechanism

GLP-1 + GIP agonist

Pros

- FDA-approved for weight loss
- More effective than semaglutide

Cons

- Side effects can be more pronounced
- Newer, less long-term data

Retatrutide

~25%

Average Weight Loss

GLP 1 + GIP + glucagon agonist

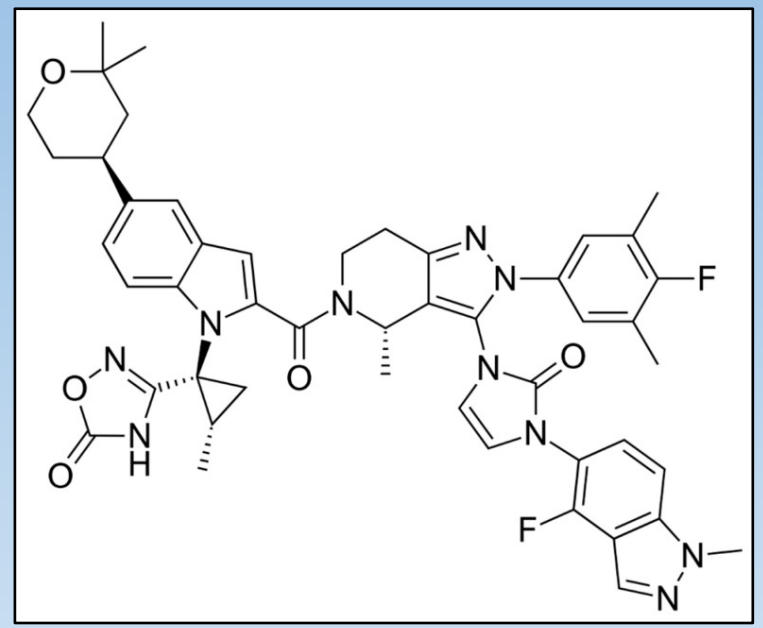
Pros

- Most effective of the three
- Currently in clinical trials

Cons

- Not yet FDA-approved
- Long-term safety unknown

Oforglipron (Foundayo)



- Daily oral pill; **non-peptide** GLP-1RA – chemically stable in acid environment of stomach and is not cleaved by DPP-4 enzyme
- FDA approved April 2026 for T2DM
- Decreases A1C & weight
- ½ life of 29-49 hours
- Significantly cheaper than injectables ($149-299 through GoodRx)

Concerns about weight gain after stopping GLP-1 RAs

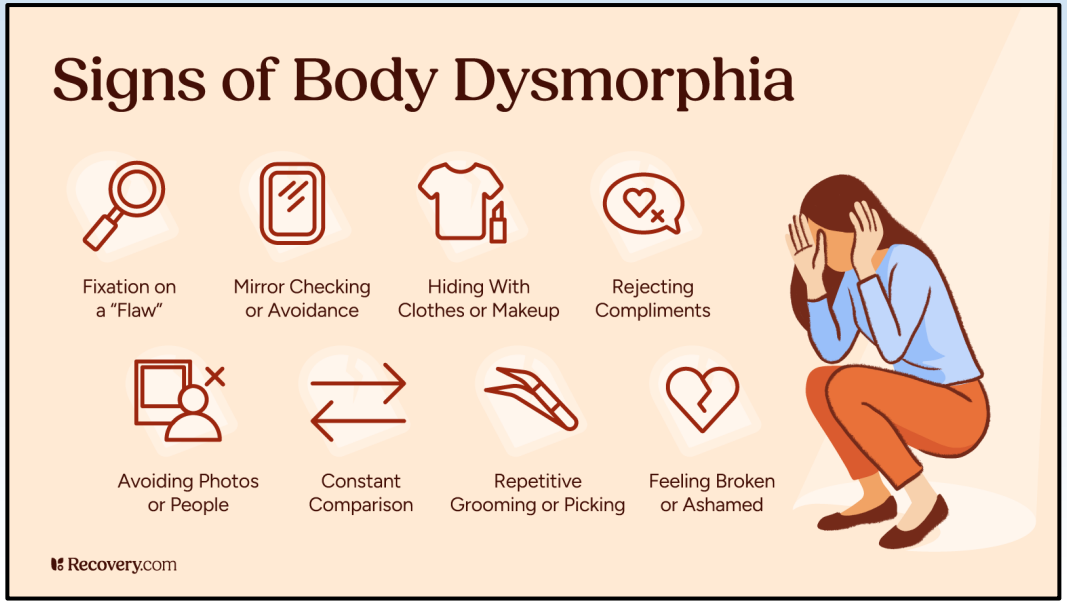
- GLP-1s are typically intended for long-term or lifelong use to effectively manage the chronic nature of obesity
- Most patients regain a significant portion of weight that they lost within 1-2 years of stopping.
- GLP-1RAs target underlying signals that regulate hunger & fullness
- Once medication is removed, the signals & cravings return
- Strategies to prevent weight regain: resistance training, prioritizing protein & fiber, gradual tapering, behavioral support

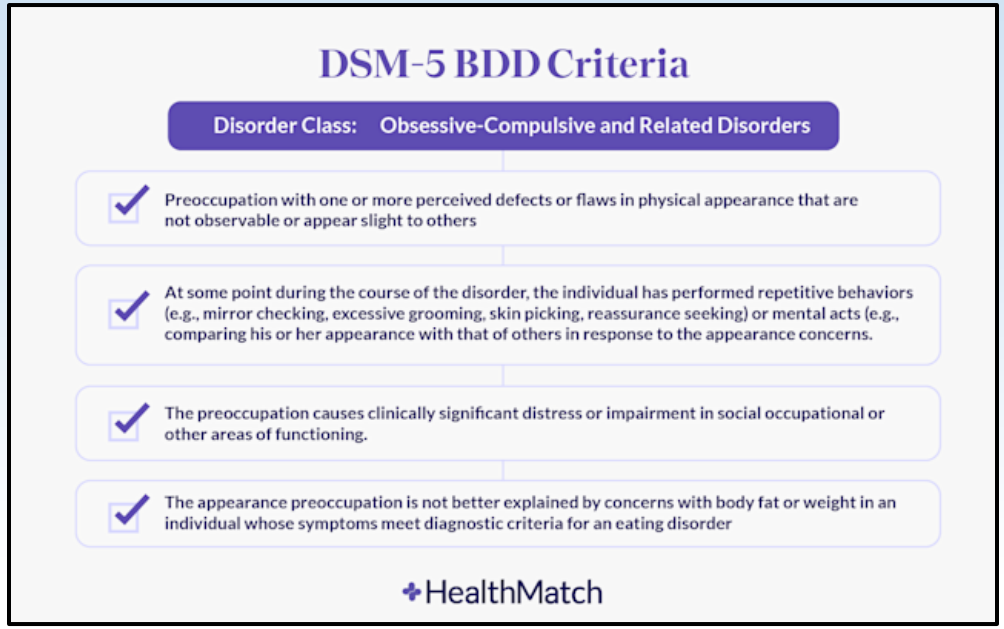
SURMOUNT – MAINTAIN TRIAL –Tirzepatide 9/2023 – 1/2026

- US –based, multicenter, double-blind, randomized, placebo-controlled trial conducted @ 20 sites. 91% completion rate
- Two phases –
    1. 60 weeks of tirzepatide (441) -starting @ 2.5 mg & escalating every 4 weeks to 10 or 15 mg. After this phase, if participants tolerated 10 mg & lost 5% of body weight were eligible for randomization
    2. At week 60, 378 participants were randomized in a 3:3:2 ratio – continuing tirzepatide: 140 maintain max dose; 144 decrease to 5 mg, 91 switch to placebo for a further 52 weeks. Primary endpoint % change in body weight from baseline to week 112.
    3. Starting at week 84, if participants had regained 50% of weight they lost in phase 1, they could receive rescue tirzepatide.
- Full dose was best, but low dose helped maintenance: 77.5% retaining 80% of initial weight loss on maximum dose, 42.4% on 5 mg, and 10.4% on placebo
- Cardiometabolic improvements mirrored weight findings – BP, lipids
- "Dose reduction" may be considered a novel patient-centered approach

Social media, standards of beauty & weight

- Fuels unrealistic weight and beauty standards
  - Bombards users with heavily edited, idealized images
  - Triggers cyclers of social comparison
  - Users frequently experience severe psychological harm including low self-esteem, depression, body dysmorphia, and increased risk of eating disorders
- Weight shaming - Taking medicine is not the "easy way out" – there is lots of hate about people with health conditions taking them in addition to Hollywood stars





Social media & weight loss methods

- Amphetamines
- Bariatric surgery
- GLP-1 RAs
- Social media backlash - Hollywood use of GLP-1 RAs created shortages in the market
- Expensive ($1000/month)
- Compounded drugs – to determine if legitimate – must have a doctor's prescription. Pharmacy should have a Certificate of Analysis, professional pharmacy labeling, must come from an FDA-registered outsourcing facility or a state-licensed compounding pharmacy
  - Red flags –no prescription required, labeled as "for research purposes only" or "not fit for human use", label shows brand names (counterfeit), abnormally low price, suspicious appearance

Demi Moore's "toned arms" @ Cannes May, 2026

1997 GI Jane

1985

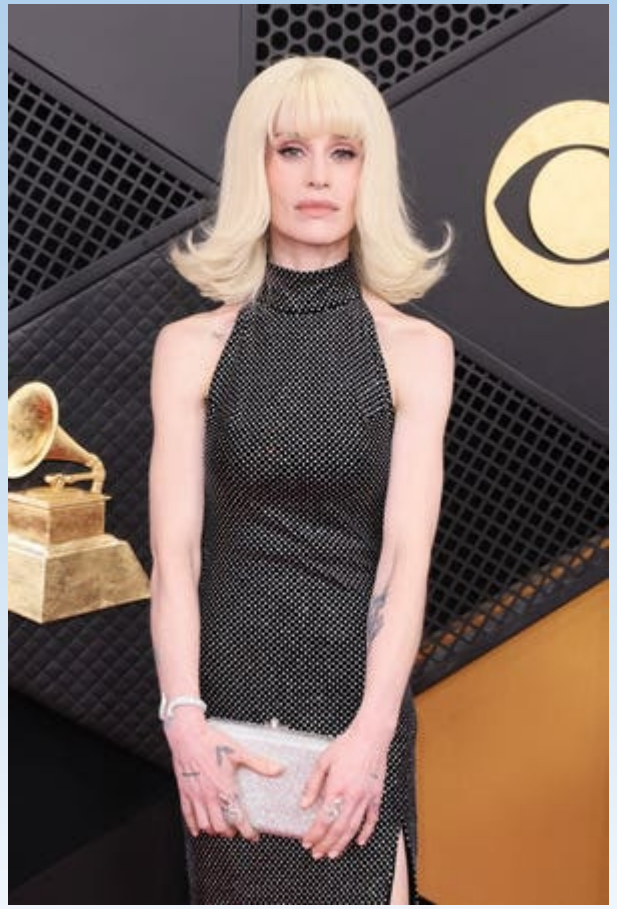
2006

2016

Celebrities and weight loss get called out on social media

2018 Gastric sleeve surgery –lost 85 lbs

12/2025

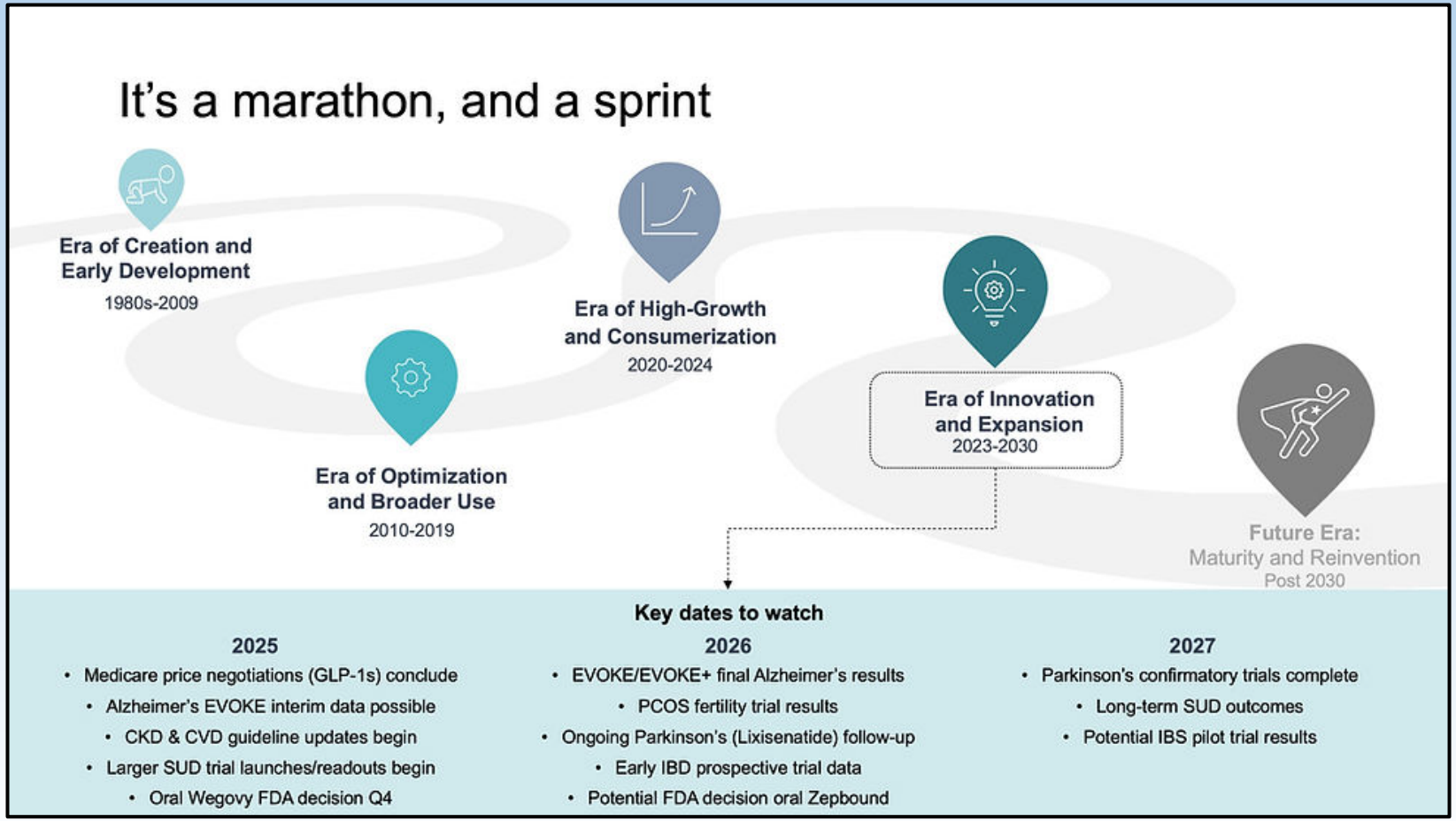


2026

Other social media trends

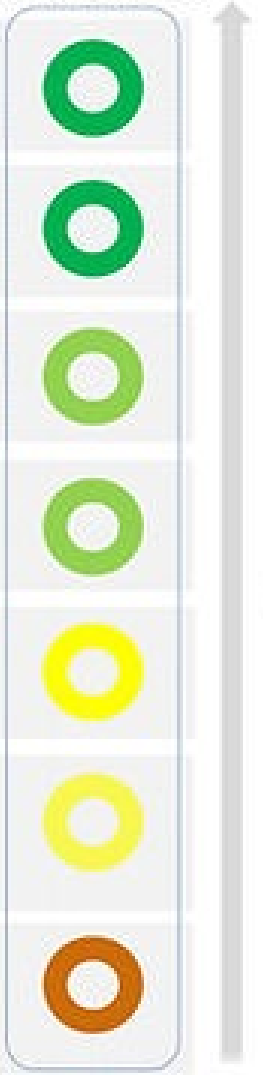
- Compounded GLP-1 RA drugs – need a reputable pharmacy; not just some pop up wellness spa
- Baking soda, ginger, turmeric, NAD
- Apple cider vinegar, cinnamon
- Bariatric gelatin

GLP-1 Drug development



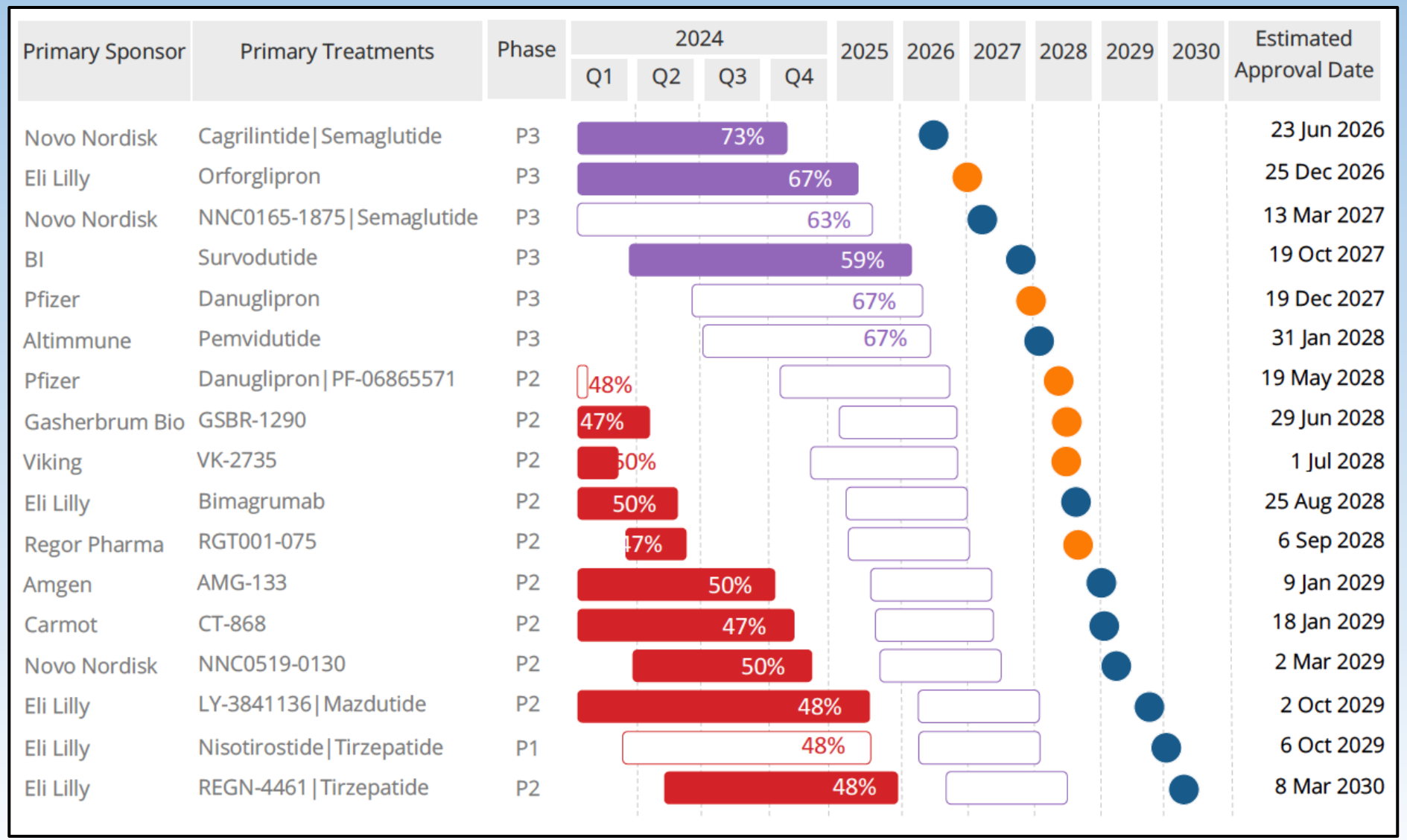
New indications could further grow the potential user base

	Obesity and Diabetes Overweight/obesity and Type 2 diabetes	281M	T2D glycemic control + risk reduction, legacy agents discontinued but launch of generics, obesity + OSA approved, oral GLP-1s on the horizon
	Cardiovascular disease Secondary prevention in overweight/obesity without diabetes	128M	FDA approved (Wegovy) risk reduction CV death, MI, stroke in adults with CVD + obesity; ongoing uptake in cardiology
	Mental health and sleep Depression, anxiety, sleep apnea (OSA)	80M	Meta-analysis for mental health showed no increased psychiatric AEs, NIH-funded OUD trial underway; FDA approval for OSA (Zepbound)
	Gut and Kidney disease Chronic kidney disease (T2D + CKD), IBD (Crohn's/UC) and IBS	75M	No approval for IBD/IBS, emerging RWE and cohort data; CKD risk-reduction added by FDA (Ozempic)
	Neurodegenerative disease Early Alzheimer's Disease, Parkinson's Disease, Huntington's Disease	8M	No approvals, investigational; no efficacy readout yet in AD; mixed findings in PD; HD animal models suggest disease-modifying potential, but no symptomatic relief
	Obesity-linked cancers Lower-risk of obesity-linked cancers (e.g., esophageal, colorectal, endometrial, gallbladder, kidney, liver, ovarian)	7M	GLP-1s lower drivers of obesity-linked cancers (insulin resistance, inflammation); Trials ongoing exploring prevention and survivorship
	Reproductive health Polycystic Ovary Syndrome (PCOS), infertility	7M	Preclinical models of reversed polycystic ovarian morphology; Anecdotal evidence increased fertility, but current guidance is **discontinuing GLP-1s before conceiving** to avoid unknown fetal risks



Market maturity/Readiness

Future GLP-1RA drugs - approval estimates



Primary Sponsor	Primary Treatments	Phase	Estimated Approval Date
Novo Nordisk	Cagrilintide|Semaglutide	P3	23 Jun 2026
Eli Lilly	Orforglipron	P3	25 Dec 2026
Novo Nordisk	NNC0165-1875|Semaglutide	P3	13 Mar 2027
BI	Survodutide	P3	19 Oct 2027
Pfizer	Danuglipron	P3	19 Dec 2027
Altimmune	Pemvidutide	P3	31 Jan 2028
Pfizer	Danuglipron|PF-06865571	P2	19 May 2028
Gasherbrum Bio	GSBR-1290	P2	29 Jun 2028
Viking	VK-2735	P2	1 Jul 2028
Eli Lilly	Bimagrumab	P2	25 Aug 2028
Regor Pharma	RGT001-075	P2	6 Sep 2028
Amgen	AMG-133	P2	9 Jan 2029
Carmot	CT-868	P2	18 Jan 2029
Novo Nordisk	NNC0519-0130	P2	2 Mar 2029
Eli Lilly	LY-3841136|Mazdutide	P2	2 Oct 2029
Eli Lilly	Nisotirostide|Tirzepatide	P1	6 Oct 2029
Eli Lilly	REGN-4461|Tirzepatide	P2	8 Mar 2030

Orange –oral
Blue -injectables

Market Overview: GLP-1 Agonists and the Obesity Market
https://www.ozmosi.com/market-overview-glp-1-agonists-and-the-obesity-market/

On the horizon…….. Research on Pythons

- Can eat a large amount (up to their body weight)
- Dramatic physiological response to feeding – metabolism revs up, within hours, heart has expanded by > 50%, pancreatic beta cells explode
- More than 200 metabolites increase, one pTOS increases >1000 fold
- pTOS, - breakdown product of tyrosine
- pTOS injected into obese laboratory mice causes them to shun their food pellets and lose weight; no changes in organ size or metabolism
- Appears to act on the hypothalmus not the gut (so no GI issues)

Questions?

- Thank you!

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