ECHO IDAHO

Diabetes and Metabolic Conditions

GLP-1 and Dual Agonists in Metabolic Disease

30-May-2026

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EIRMC – Family Medicine Residency

FQHC – Community Family Clinic

University of Idaho
School of Health and Medical Professions

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Disclosures

- I wish

Learning Objectives

- Learn how GLP-1 / GIP agonists work
- Understand best use practices
- Understand treatment complications
- Have fun

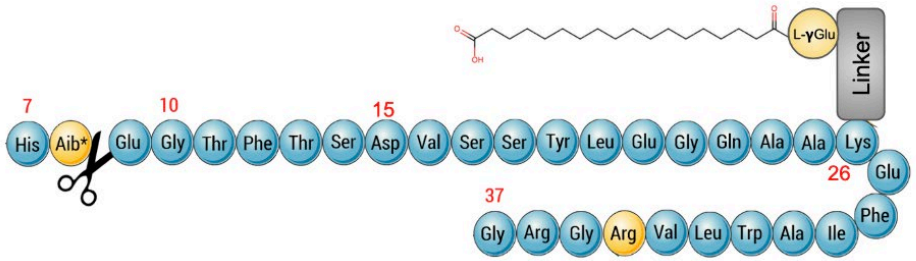
Don't only practice your art, but force your way into its secrets, for it and knowledge can raise men to the divine.”

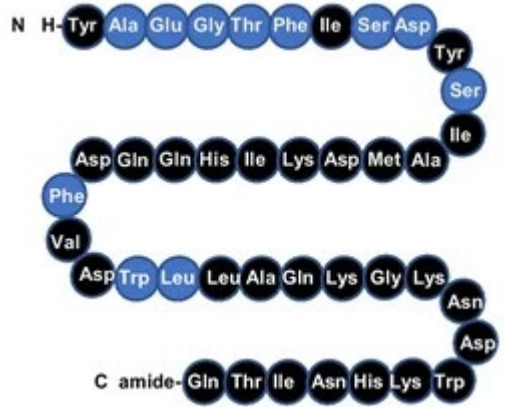
— Ludwig van Beethoven

Definitions & brief history

The Players

- **GLP-1 = Glucagon-like Peptide-1**
  - Really GLP's are "Glucagon-like Peptide-1 Receptor Agonist" (aGOnist)
- **GIP = Gastric Inhibitory Polypeptide**
  - AKA: "Glucose-dependent insulinotropic polypeptide"





Both are "incretin mimetics" that are structurally similar (but modified) to endogenous hormones produced in the body

Development of GLP-1

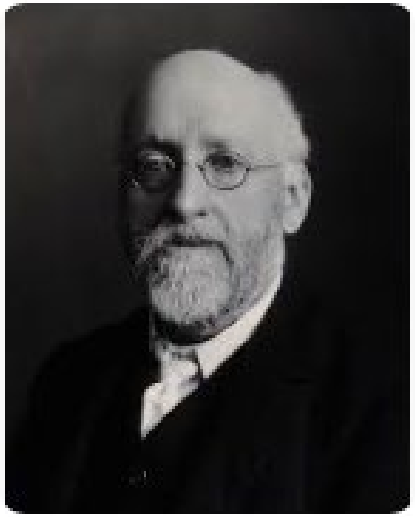
- Understanding mechanism requires a little bit of physiology
- Need time machine

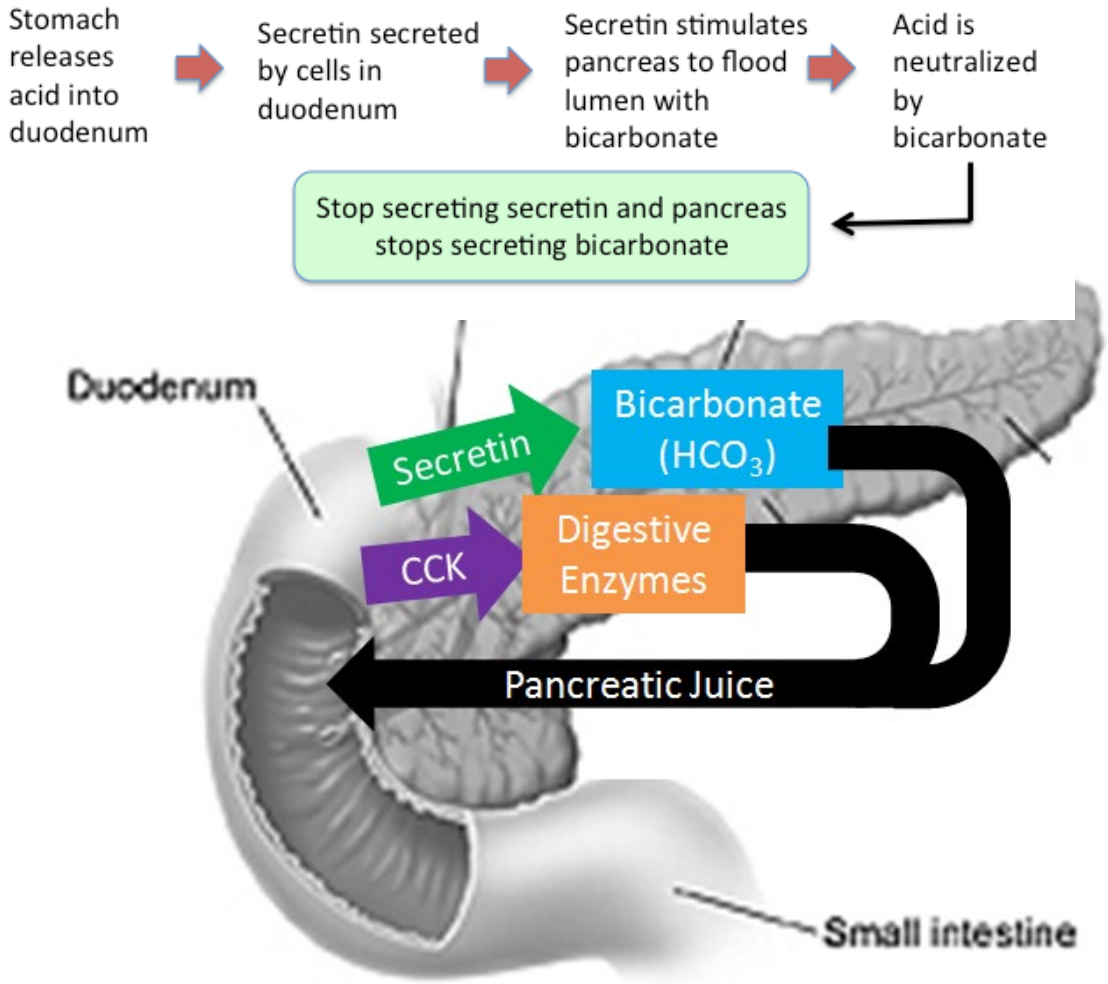
Long history

- 𓄿𓂧𓇋𓄿𓃀𓇋𓏏𓇋𓋴
  - 𓉔𓇋𓇋𓂋𓅱𓎼𓃭𓇋𓉔𓇋𓋴𓉔𓂋𓅱𓎼
  - 𓇋𓄿𓂧𓇋𓄿𓇋 ["glucose"]
  - 𓂀𓋹𓊽𓇳𓆣𓂋𓅱𓎼𓃭𓇋𓉔𓇋𓋴𓉔 𓂋𓅱
- 𓄿𓂧𓇋𓄿𓅓𓂋
- 𓋴𓄿𓃀𓎡𓂀𓋹𓊽𓇳𓆣𓂋𓅱𓎼𓃭𓇋𓈖 (*"prior authorization denial"*) 𓆑𓅱𓏏𓂝𓁹𓇳𓆣𓉐𓋞

(1902) Secretin – The first digestive hormone

- William Bayliss and Ernest Starling.





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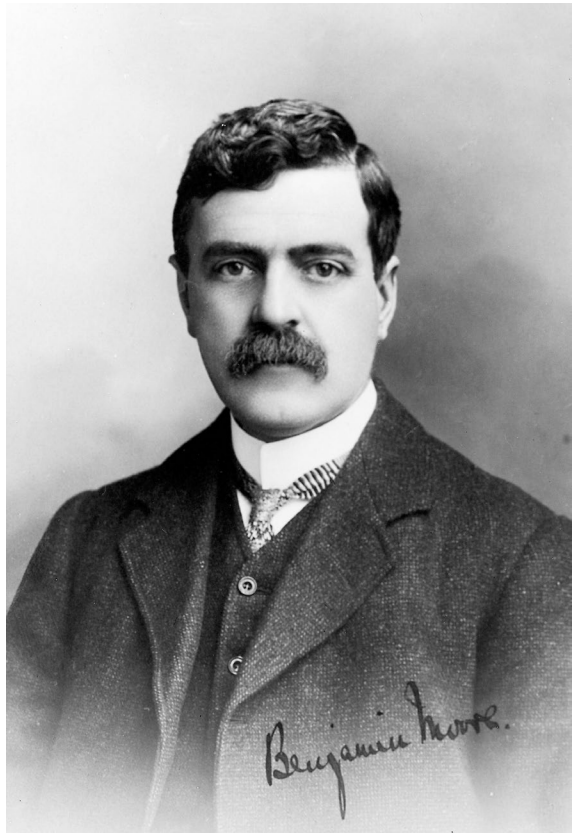
(1906) Dreams of an “Incretin”

- Benjamin Moore (1906)

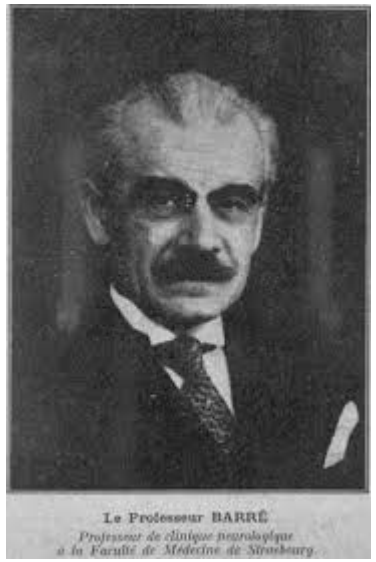


- Not the paint producer
- Dies

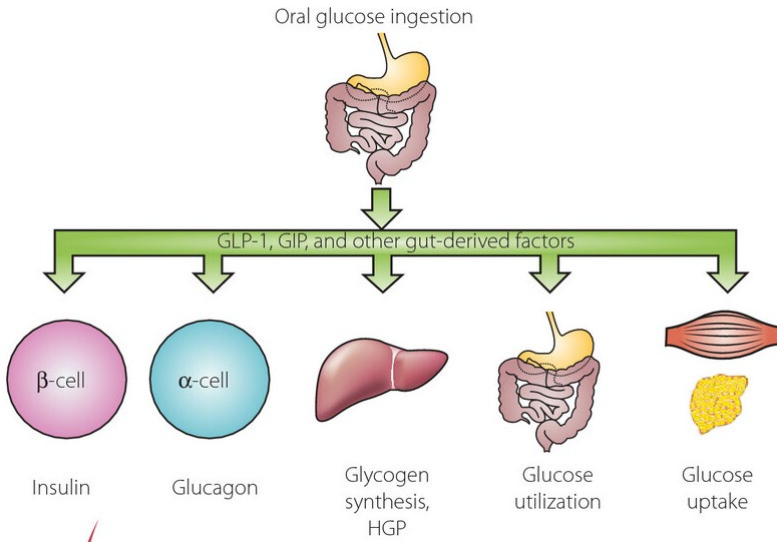
(before insulin is even discovered)

(1932) The Elusive incretin sneaks away

- La Barre & Eugene Still



INtestine seCRETtion InsulIN



STUDIES ON THE PHYSIOLOGY OF SECRETIN

III. Further Studies on the Effects of Secretin on the Blood Sugar

JEAN LA BARRE and EUGENE U. STILL

From the Laboratories of Physiology and Pharmacology of The University of Chicago

Received for publication August 16, 1929

There is not a unanimity of opinions concerning the effects of secretin on the blood sugar. Some authors have described hyperglycemia after the injection of secretin in rabbits, dogs, and man; others have described hyperglycemia followed by hypoglycemia; while another group have observed only hypoglycemia. Mellanby (1928) described a new method of purification of secretin yielding a product which he says possesses great secretagogue activity and no effects on either blood pressure or blood sugar of rabbits or cats. However, Zunz and La Barre (1929; this paper contains a complete bibliography) using a product prepared in Mellanby's laboratory found on injecting large enough doses in dogs to obtain rapid secretion of the pancreas, that there also was a lowering of the blood pressure and sugar. Still and Shipner (1929) reported that highly purified secretin did not possess hypoglycemic properties in normal or diabetic dogs. They used both barbitalized and unanesthetized animals.

One of us (E. U. S., 1929) described a method of preparing a crude secretin which was a powerful secretagogue but possessed no vaso-dilatin. It consisted of precipitating an acid extract of the fresh duodenum with solid NaCl, subsequent solution of the precipitate formed in acid and reprecipitation by trichloracetic acid. This second precipitate was dried by mixing with absolute alcohol and acetone and the addition of ether.

Series I. In this series of experiments we have studied the effects of this crude secretin on the blood sugar. We used chloralosed dogs (80 mgm. in saline per kilo intravenously) having the necessary cannulae in place for the collection of pancreatic juice, samples of blood or injections. A sample of blood was taken, then 1 to 2 mgm. of crude secretin per kilo was injected by vein. Subsequent samples of blood were collected at 15 or 30 minute intervals for 2 hours. Blood sugar determinations were made on Folin and Wu filtrates by the method of Hagedorn and Jensen. Figure 1 shows the results of four experiments of this kind. In these experiments there seemed to be a relationship between the dosage of crude secretin and the change in blood sugar. In experiment I of this group the effects were minimal. The

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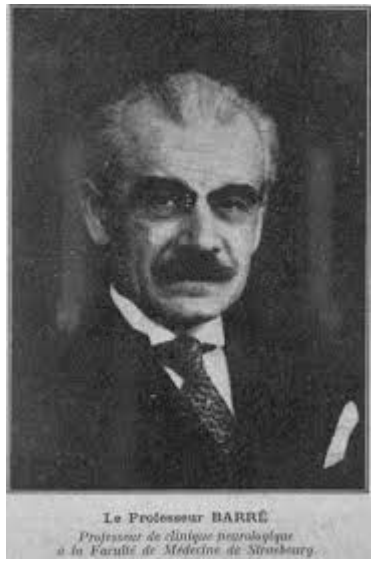
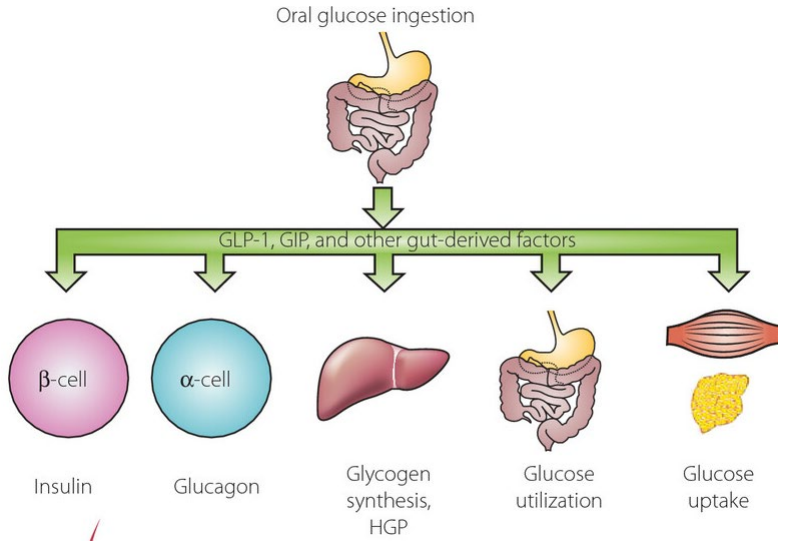
(1932) The Elusive incretin sneaks away

La Barre



<u>IN</u>testine se<u>CRET</u>tion Insul<u>IN</u>



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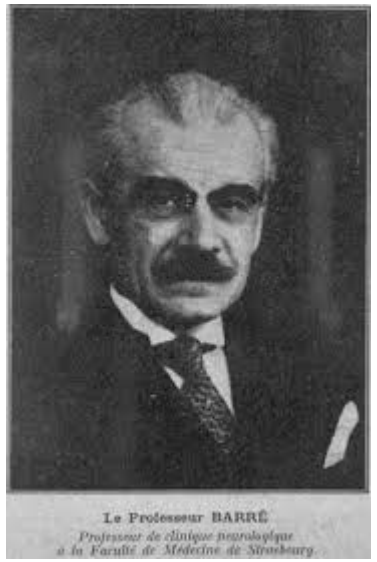
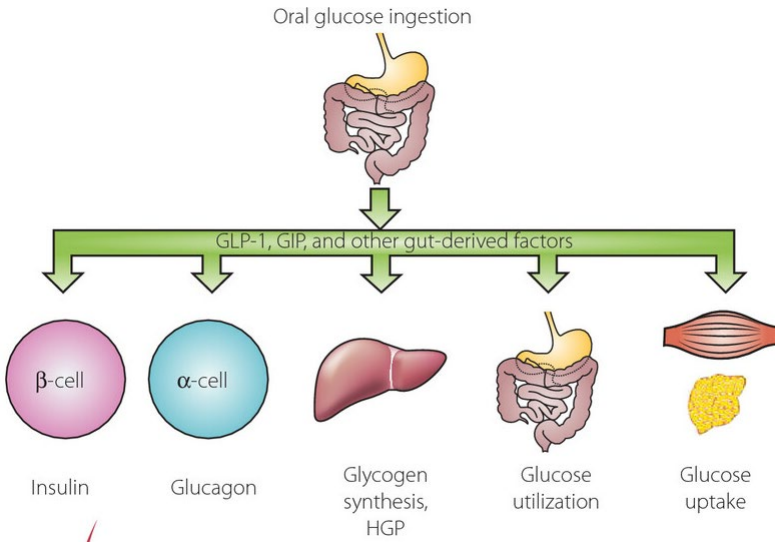


INCRETIN



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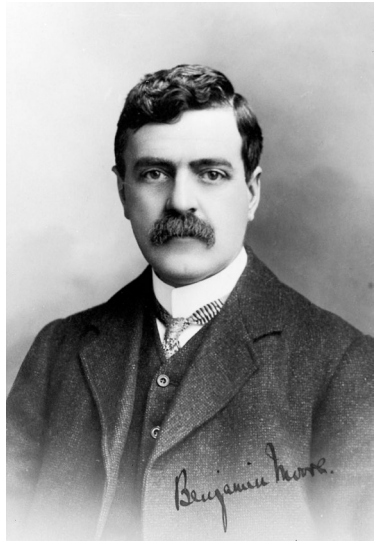
(1959) Radioimmunoassay

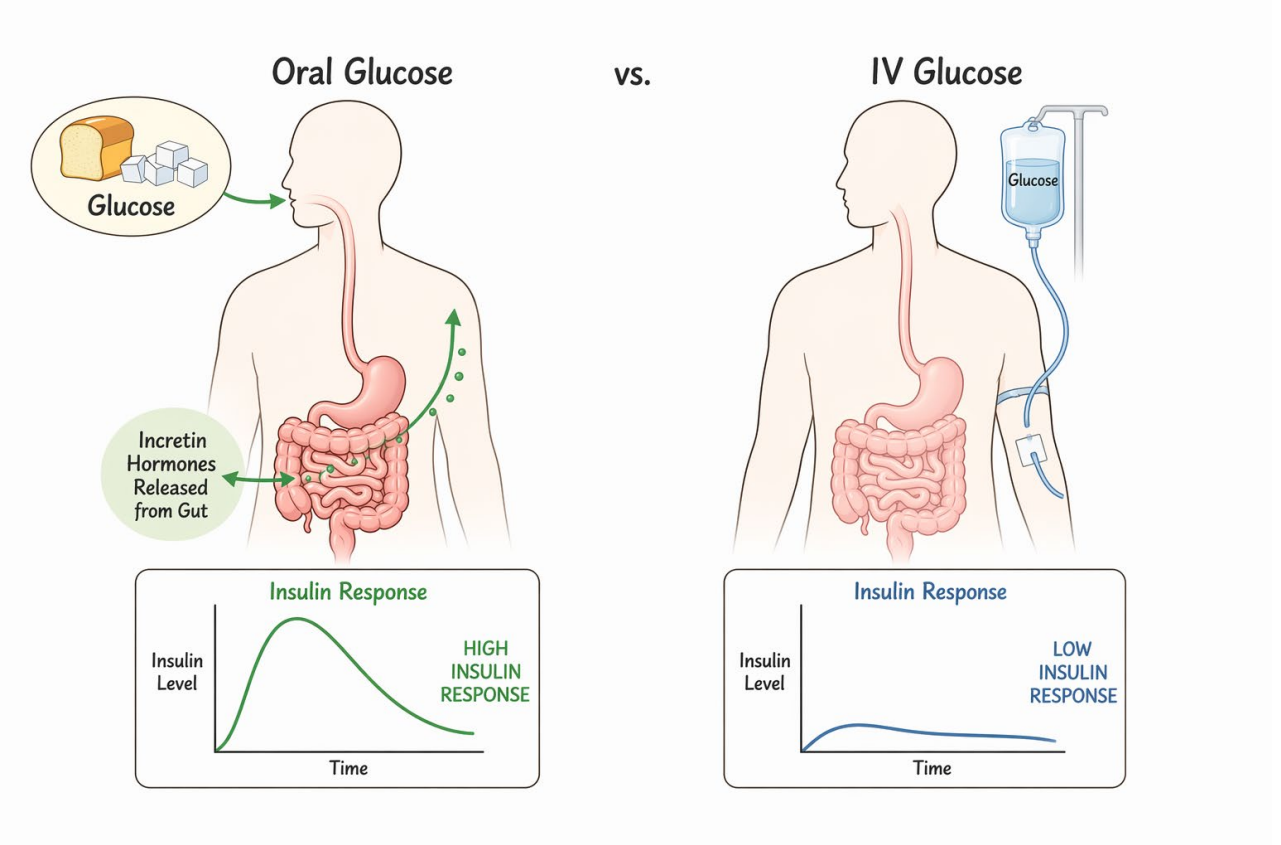
- We can now check insulin!

(Yalow and Berson)

(1964) Incretins found

- Glucose eaten increased insulin MORE than glucose in the blood
- Incretins exist





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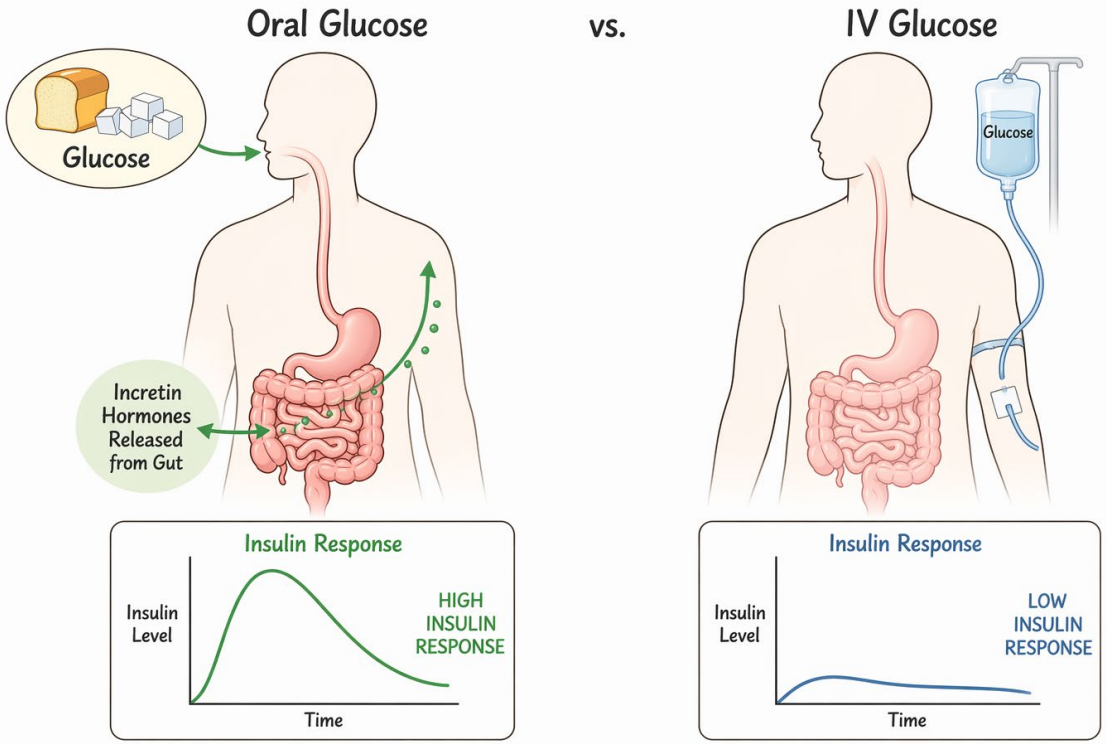

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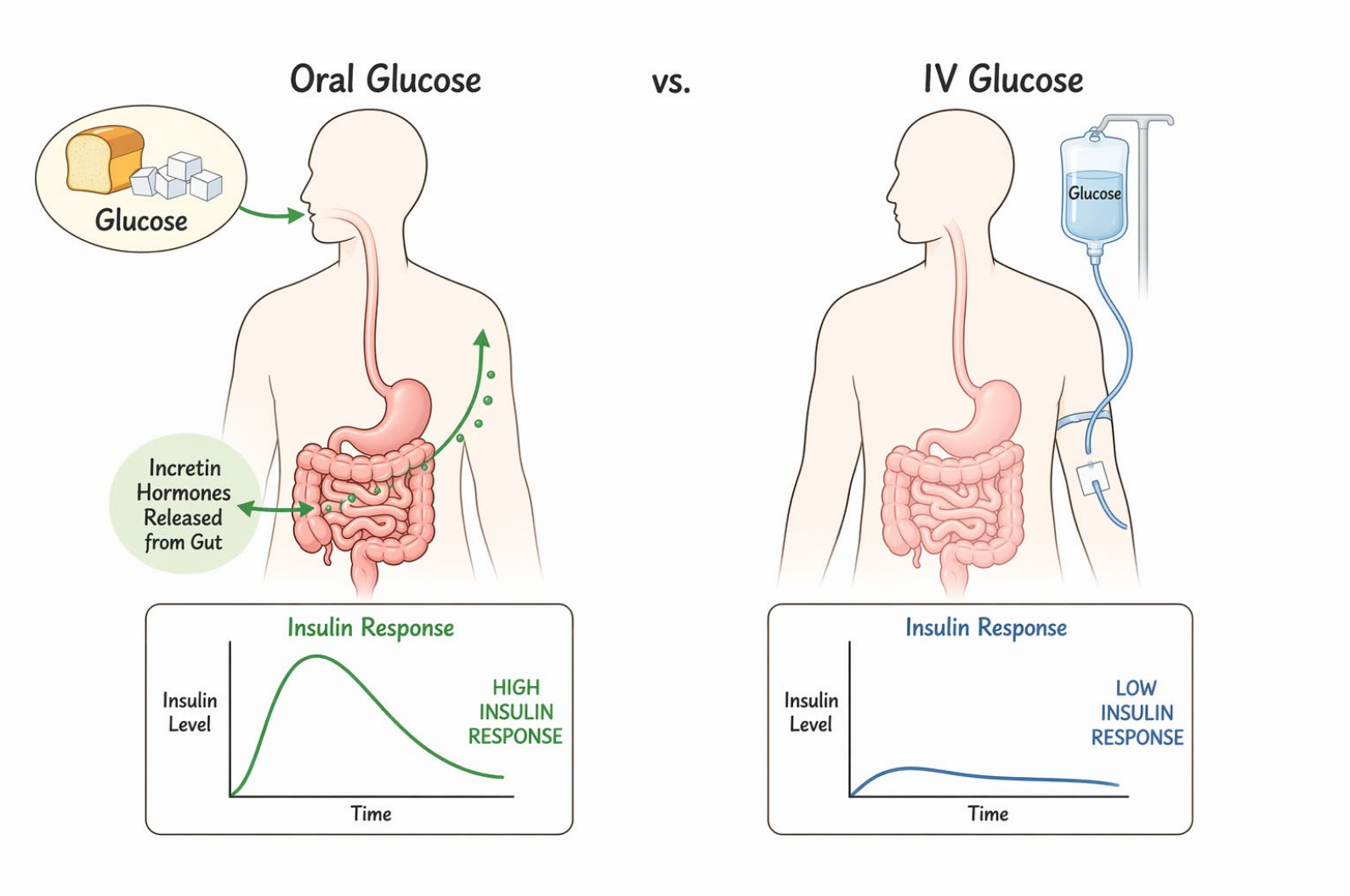
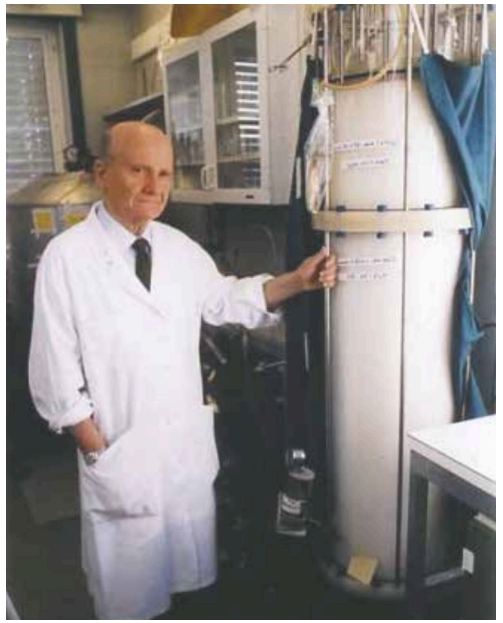


(1969-1975) GIP Discovered

- John Brown and Raymond Pederson at the University of British Columbia



1987 – GLP-1 (and other's) discovered

- GLP discovered by Mojsov

- 100% certified BA ->

1989 GLP-1 discovered

- Discovers GLP-1 in human
- Doesn’t last
- IV = insta vomiting
- T½ life is seconds
  - Bummer

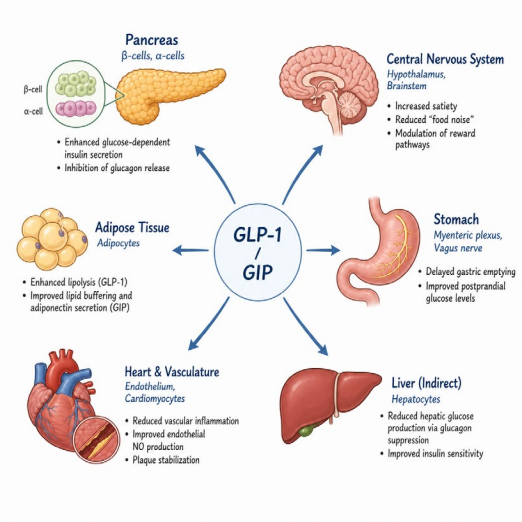
1992 The elusive exendin

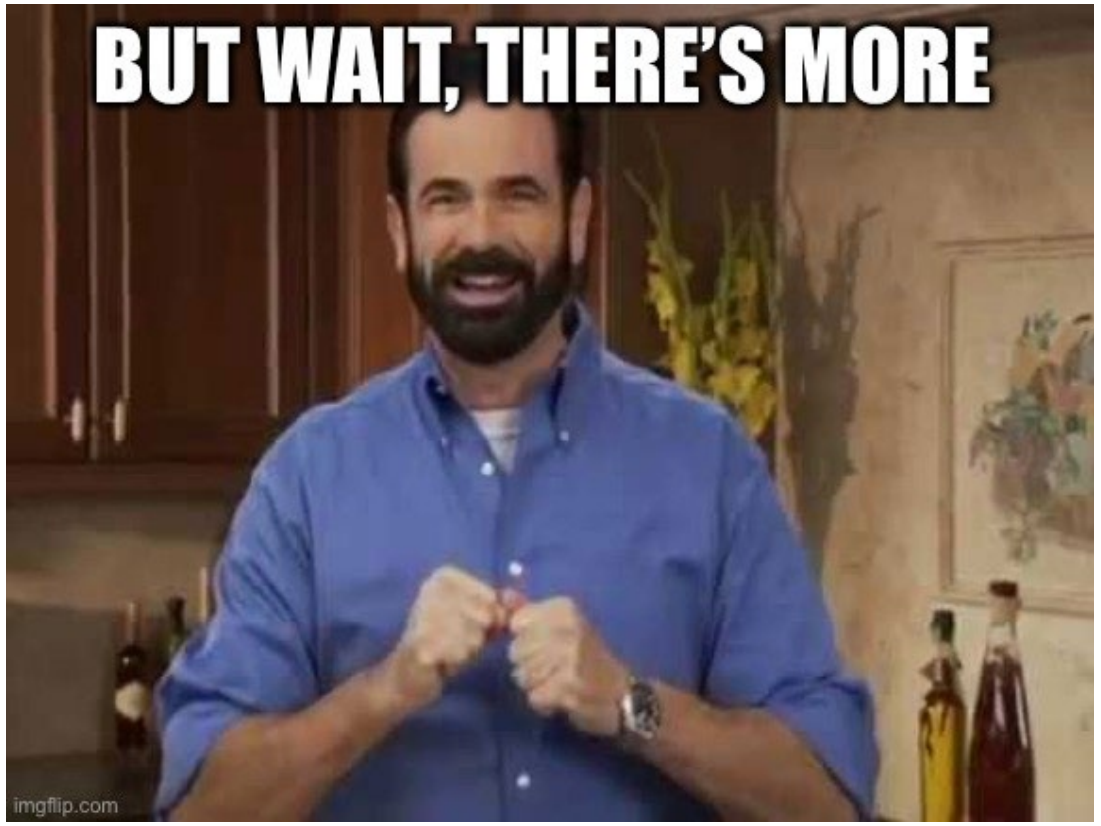
- Exendin-4
- Looks like GLP-1
  - Avoids degradation by DDP-4

2005 – The age of GLP-1RA begin

Mechanism(s) of action

- Mimic hormones
  - not a single target
- Synergistic effect
  - Incretin effect (glucose)
  - CNS effects





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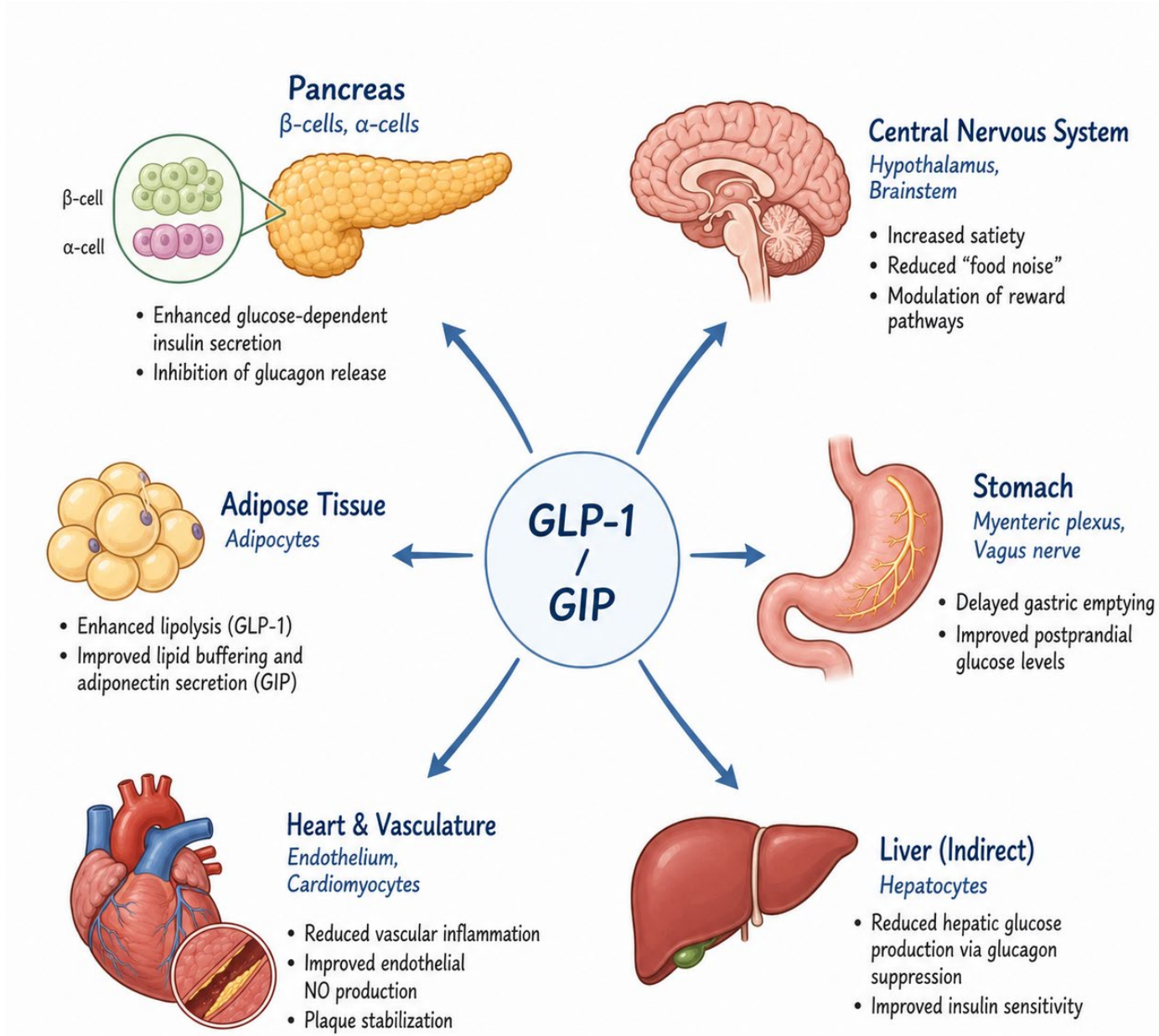
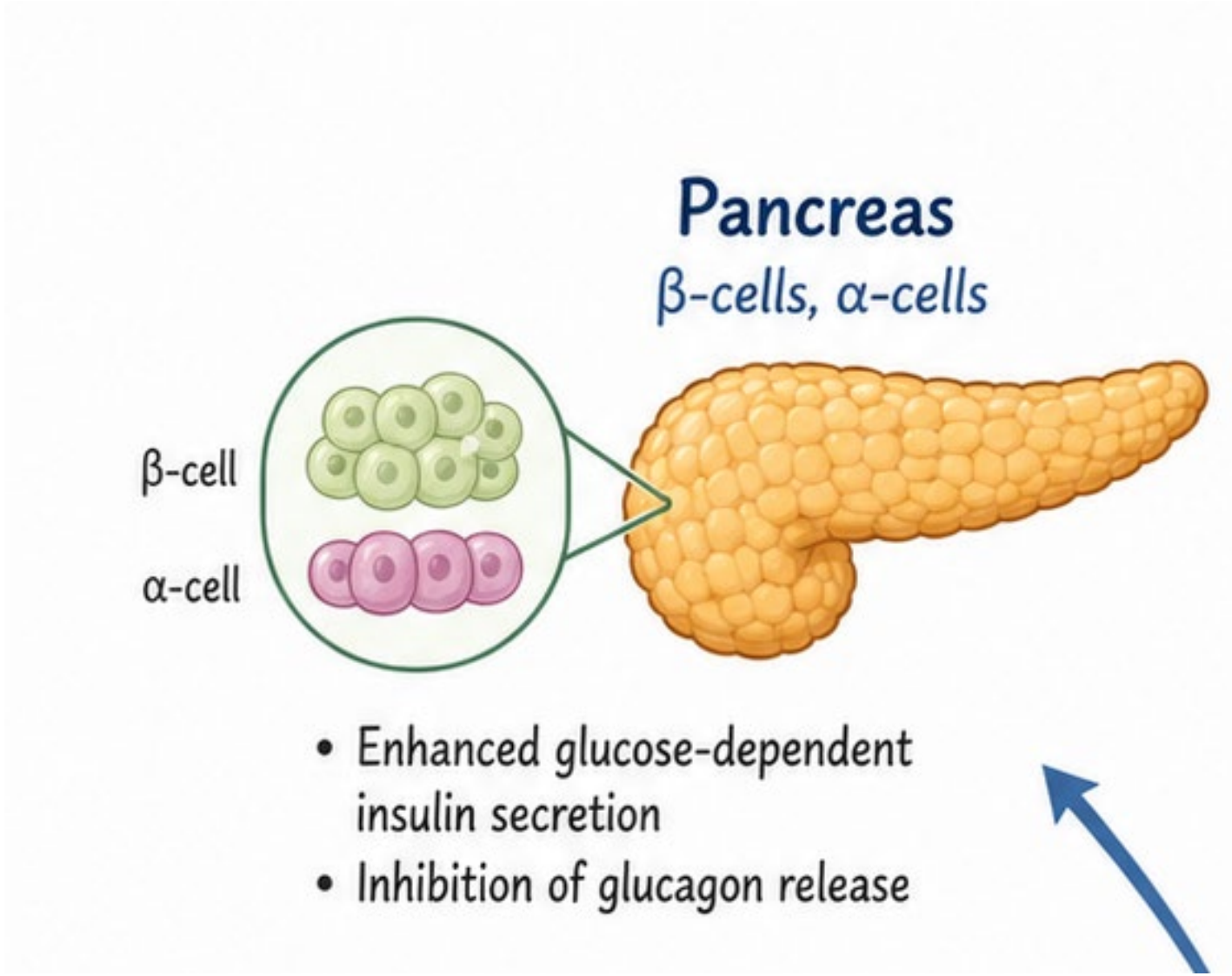
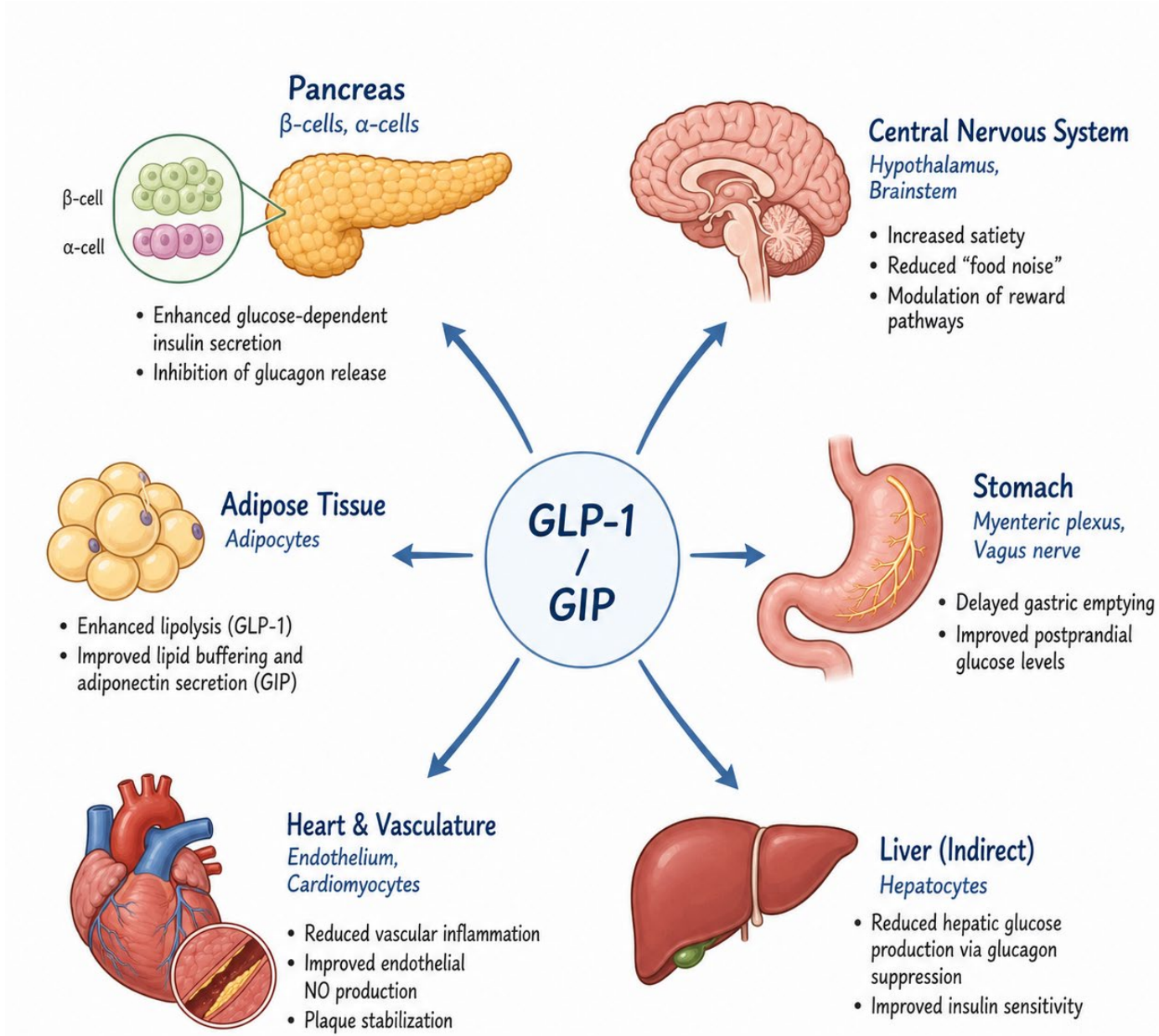

Pancreas
β-cells, α-cells
β-cell
α-cell
• Enhanced glucose-dependent insulin secretion
• Inhibition of glucagon release
Central Nervous System
Hypothalamus, Brainstem
• Increased satiety
• Reduced "food noise"
• Modulation of reward pathways
GLP-1 / GIP
Adipose Tissue
Adipocytes
• Enhanced lipolysis (GLP-1)
• Improved lipid buffering and adiponectin secretion (GIP)
Stomach
Myenteric plexus, Vagus nerve
• Delayed gastric emptying
• Improved postprandial glucose levels
Heart & Vasculature
Endothelium, Cardiomyocytes
• Reduced vascular inflammation
• Improved endothelial NO production
• Plaque stabilization
Liver (Indirect)
Hepatocytes
• Reduced hepatic glucose production via glucagon suppression
• Improved insulin sensitivity



Main “Incretin” effect: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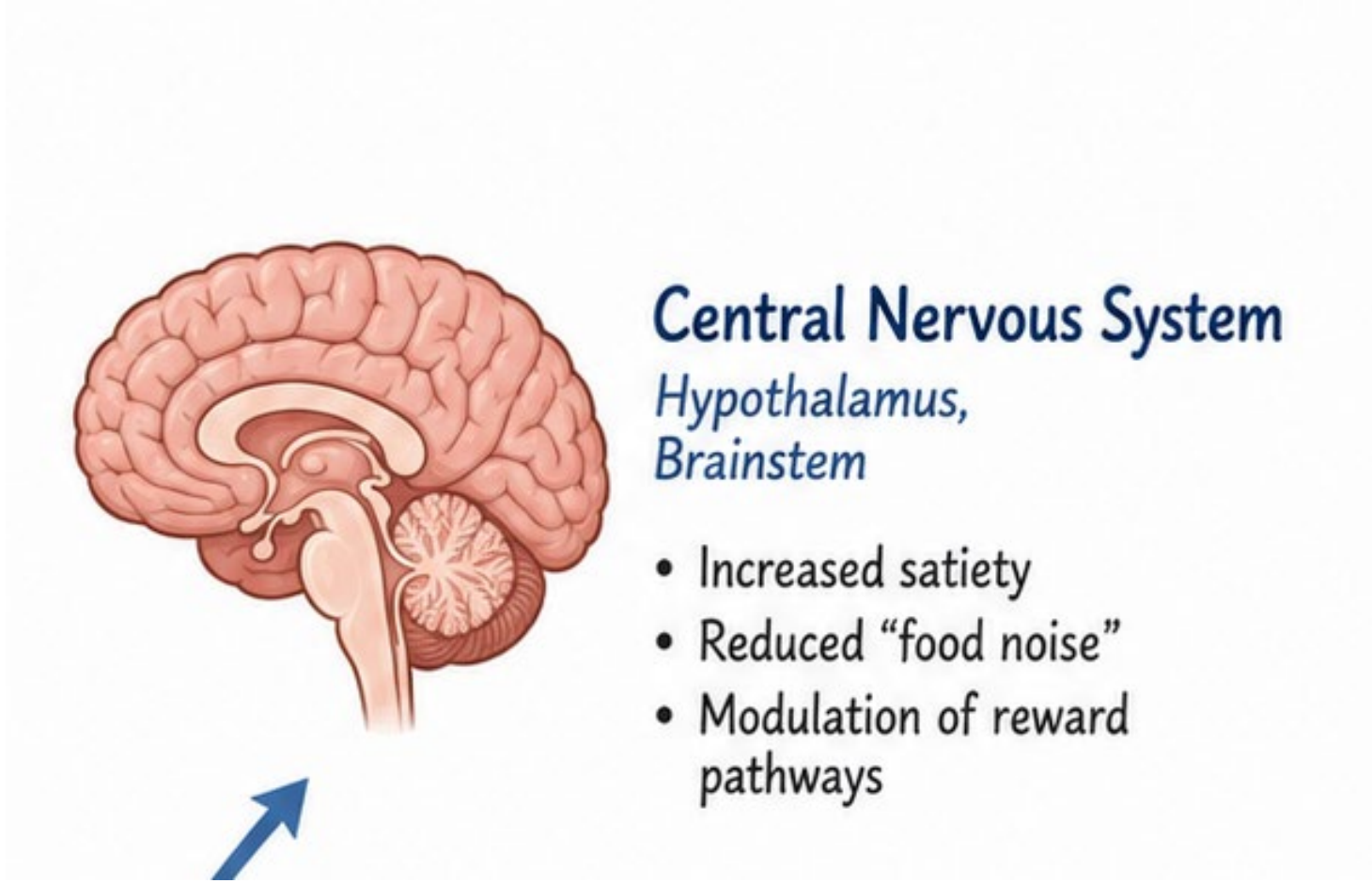

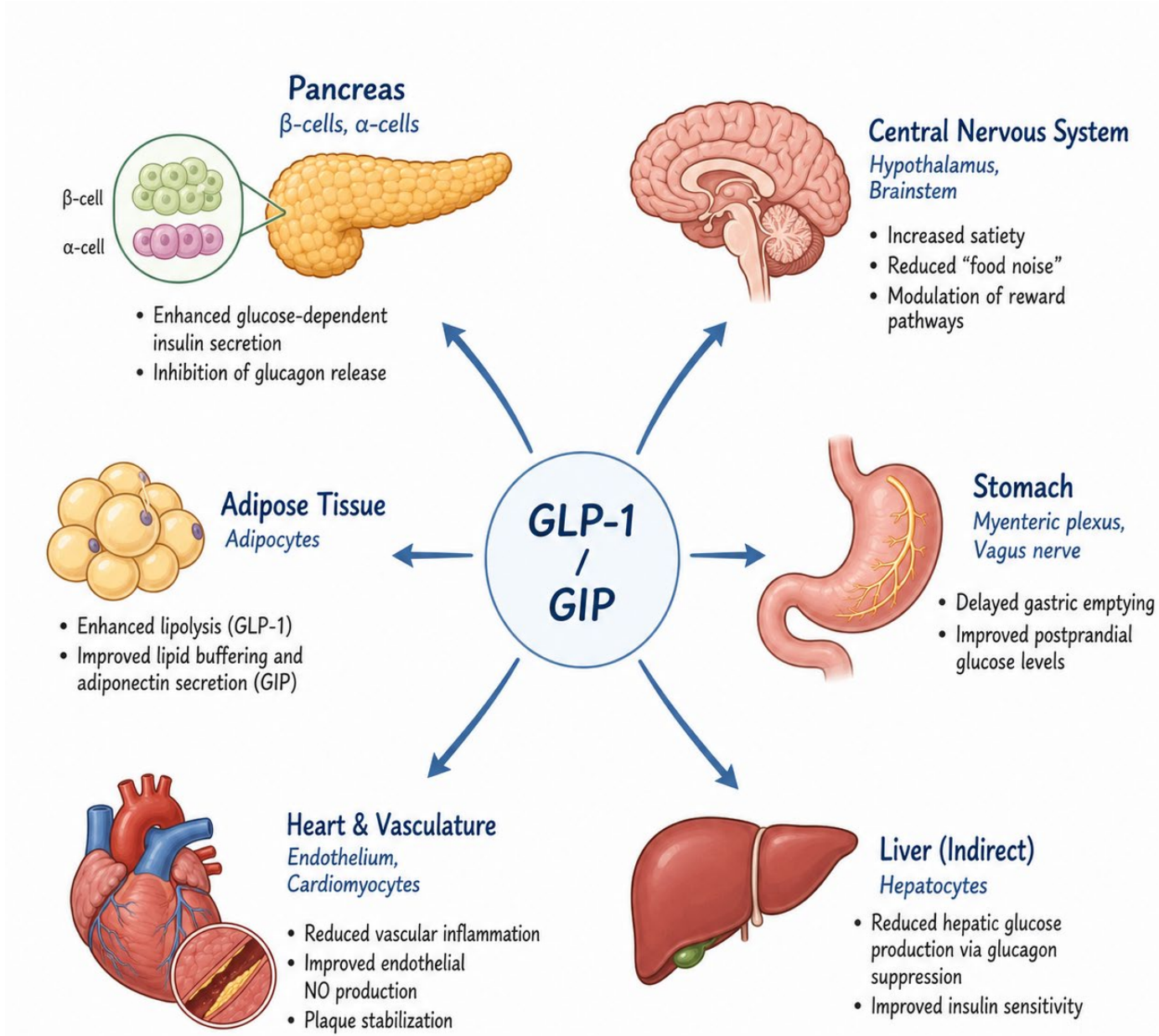
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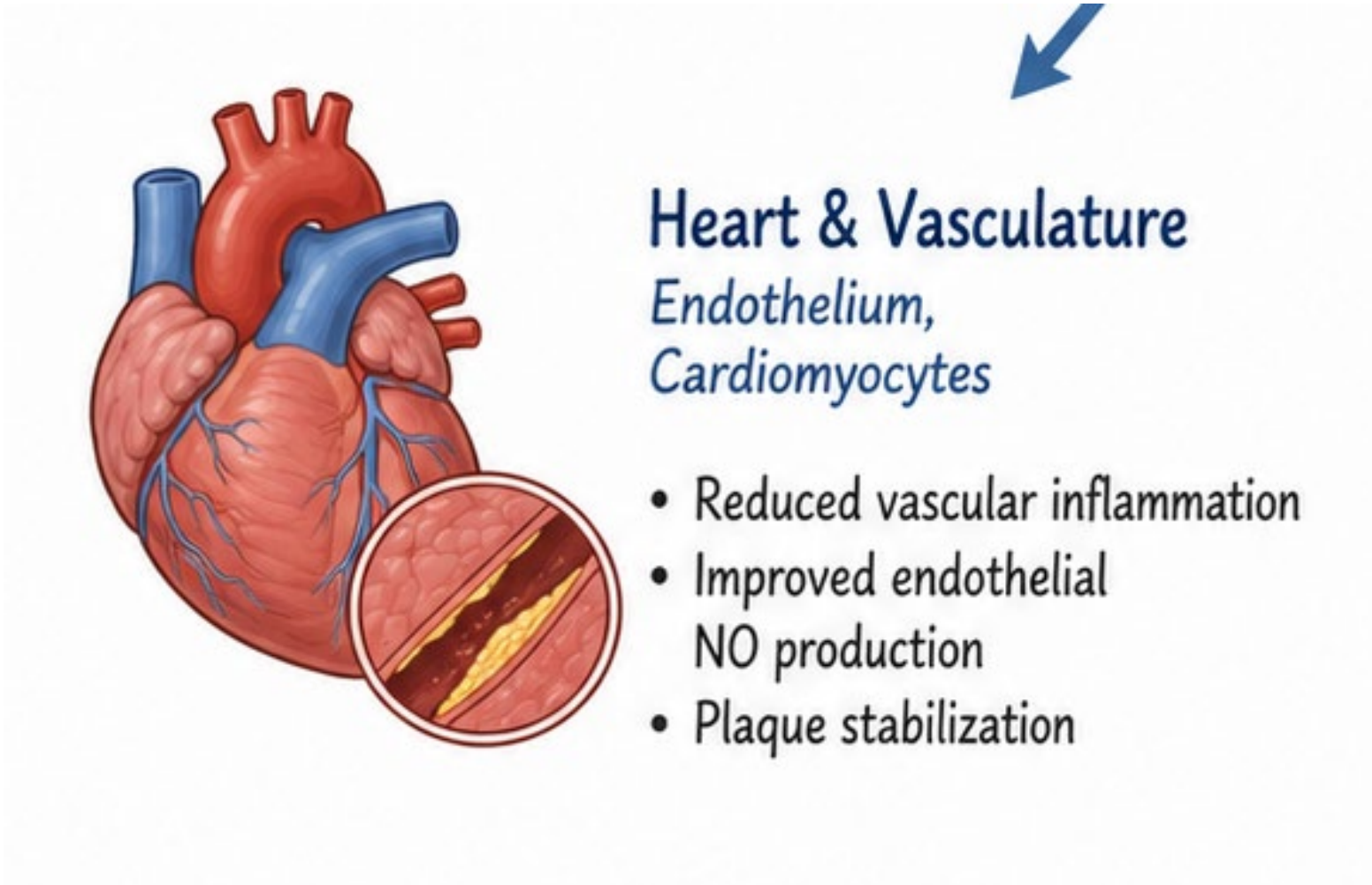

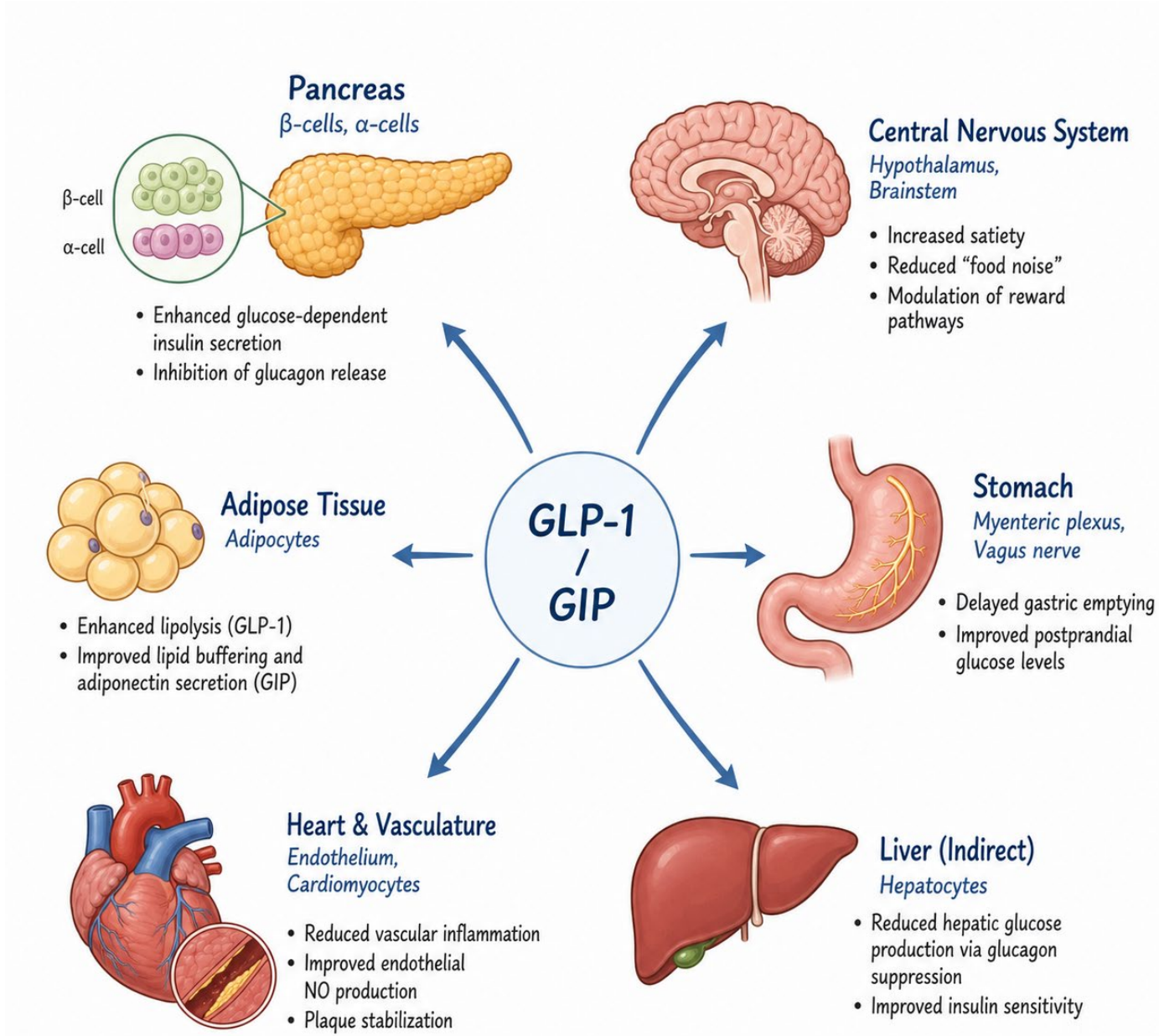
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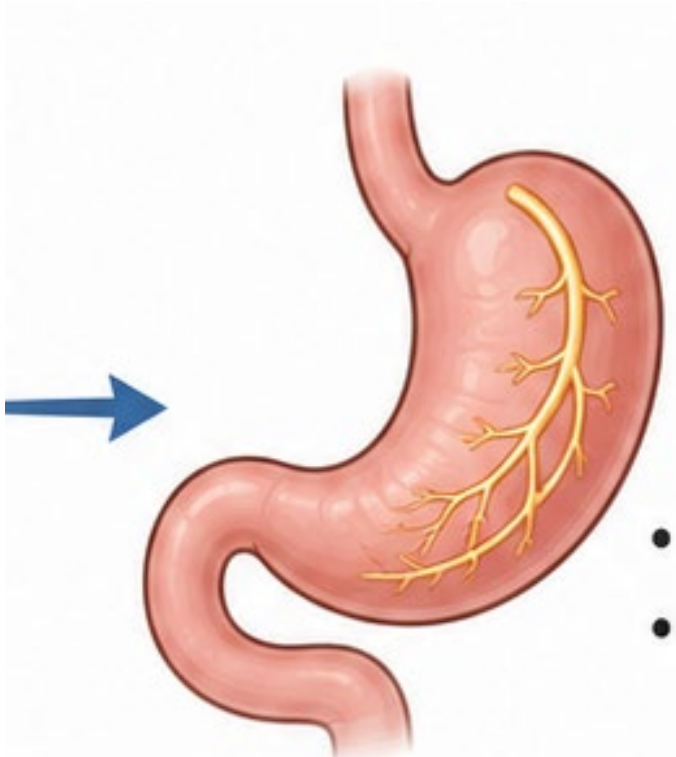

Stomach

Myenteric plexus,
Vagus nerve

- Delayed gastric emptying
- Improved postprandial glucose levels

Risks

Adverse Event	Incidence (GLP-1RAs)	Incidence (Placebo)	Number Needed to Harm (NNH)
Nausea	25–44%	8%	3–5
Vomiting	8–24%	2%	5–10
Diarrhea	19–30%	8%	5–9
Constipation	11–24%	5%	6–11
Discontinuation due to AE	6–14%	2%	10–12

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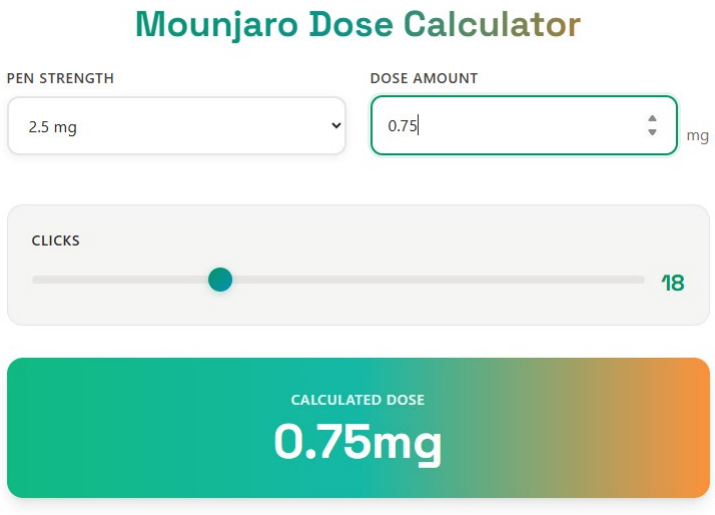
DoseWise



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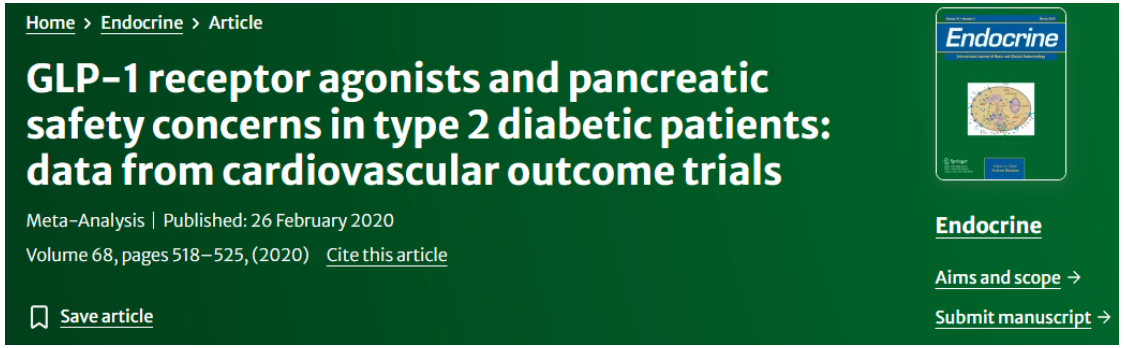
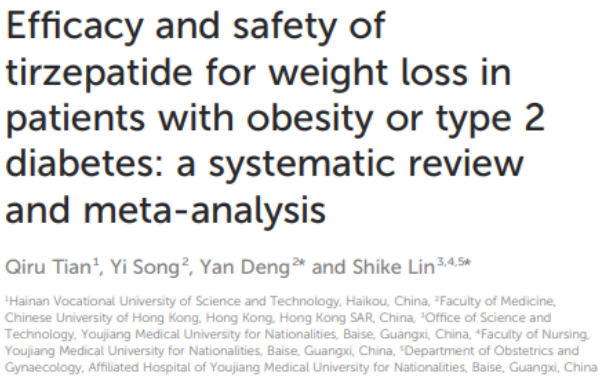
Other Risks

- **Pancreatitis:**




Efficacy and safety of tirzepatide for weight loss in patients with obesity or type 2 diabetes: a systematic review and meta-analysis

Qiru Tian[1], Yi Song[2], Yan Deng[2*] and Shike Lin[3,4,5*]

[1]Hainan Vocational University of Science and Technology, Haikou, China, [2]Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China, [3]Office of Science and Technology, Youjiang Medical University for Nationalities, Baise, Guangxi, China, [4]Faculty of Nursing, Youjiang Medical University for Nationalities, Baise, Guangxi, China, [5]Department of Obstetrics and Gynaecology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, Guangxi, China

- **Cholelithiasis**

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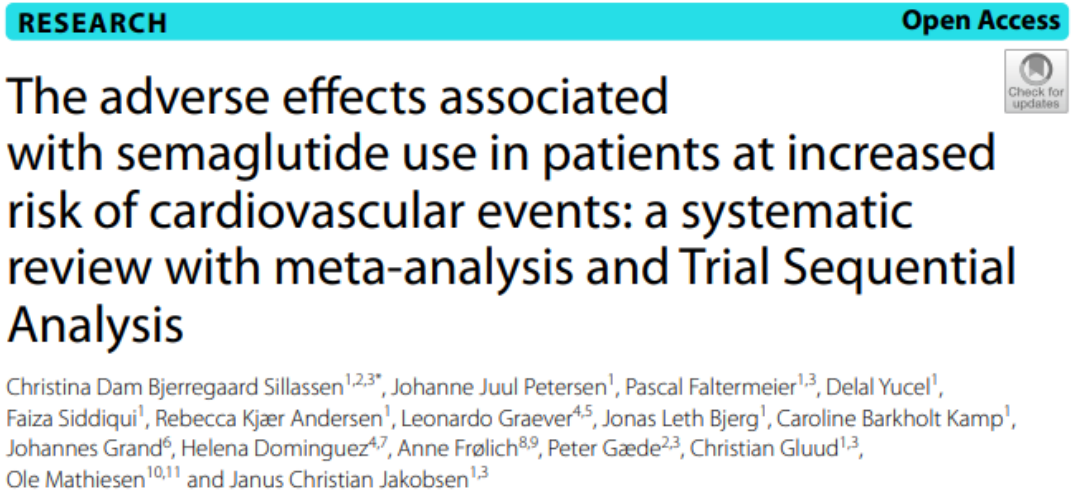
Other Risks

- **Ischemic Optic Neuropathy** -specifically: non-arteritic anterior ischemic optic neuropathy (NAION)

- **Acute Kidney injury**
  - If people get sick enough
  - Hypovolemia



RESEARCH Open Access

The adverse effects associated with semaglutide use in patients at increased risk of cardiovascular events: a systematic review with meta-analysis and Trial Sequential Analysis

Christina Dam Bjerregaard Sillassen[1,2,3*], Johanne Juul Petersen[1], Pascal Faltermeier[1,3], Delal Yucel[1], Faiza Siddiqui[1], Rebecca Kjær Andersen[1], Leonardo Graever[4,5], Jonas Leth Bjerg[1], Caroline Barkholt Kamp[1], Johannes Grand[6], Helena Dominguez[4,7], Anne Frølich[8,9], Peter Gæde[2,3], Christian Gluud[1,3], Ole Mathiesen[10,11] and Janus Christian Jakobsen[1,3]

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Contraindications

- Medullary thyroid cancer
- Multiple Endocrine neoplasia-type 2 (MEN2)

Pitfalls

- Cost
- Duration of treatment
  - Discontinuation
- Drug-Drug interactions
  - **Hypoglycemia with concomitant Use of Insulin Secretagogues or Insulin**
  - Mostly absorption
    - OCPs
    - Warfarin
- Equity
- Kids

Alternatives

- Phentermine/Topiramate 8–10%

FDA Approvals

- Semaglutide
  - Ozempic/Rybelsus (T2DM)
  - Wegovy (KIDS! BMI, CVD, MASH)
- Tirzepatide
  - Mounjaro (KIDS! T2DM)
  - Zepbound (BMI, OSA)
- Orforglipron
  - Foundayo (BMI)
- Liraglutide
  - Victoza (T2DM)
  - Saxenda (BMI)


US011357820B2

(12) **United States Patent**
Corvari et al.

(10) **Patent No.: US 11,357,820 B2**
(45) **Date of Patent: Jun. 14, 2022**

(54) **GIP/GLP1 AGONIST COMPOSITIONS**

(71) Applicant: **Eli Lilly and Company**, Indianapolis, IN (US)

(72) Inventors: **Vincent John Corvari**, Carmel, IN (US); **Christopher Sears Minie**, Zionsville, IN (US); **Dinesh Shyamdeo Mishra**, Carmel, IN (US); **Ken Kangyi Qian**, Carmel, IN (US)

(73) Assignee: **Eli Lilly and Company**, Indianapolis, IN (US)

(56) **References Cited**

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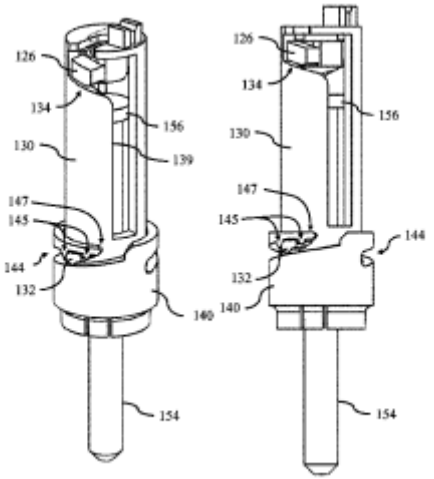
FOREIGN PATENT DOCUMENTS



University of Idaho
School of Health and Medical Professions

Project ECHO

Medication	FDA Approved Conditions	Notes
Tirzepatide (Mounjaro)	• T2DM • Pediatric T2DM 10+	
Tirzepatide (Zepbound)	• Obesity (BMI >30) • Overweight (BMI>27) and 1+ BMI comorbidity • Moderate/severe OSA + Obesity (BMI > 30) • Pediatric Obesity (12+)	• Comorbidities: HTN, HLD, CVD, PAD, OA, MASH • AHI (4%) must be ≥ 15 • Pediatric patients must have BMI >95 percentile
Semaglutide (Ozempic)	• T2DM • T2DM + MACE (CVD, PAD, CAD, NSTEMI) • T2DM + CKD	
Semaglutide (Wegovy)	• Obesity • Obesity + MACE • NAFLD/MASH/NASH *+ Fibrosis* • Pediatric Obesity (12+)	• Cannot be alcoholic cirrhosis, Fibrosis F2/F3 • Pediatric patients must have BMI >95 percentile
Semaglutide (Rybelsus)	• T2DM	
Liraglutide (Saxenda)	• Obesity (BMI >30) • Pediatric obesity (12+)	• Daily injectable • Pediatric patients must have BMI >95 percentile
Liraglutide (Victoza)	• T2DM • T2DM + MACE (CVD, PAD, CAD, NSTEMI) • Pediatric T2DM 10+	• Daily injectable
Dulaglutide (Trulicity)	• T2DM	

Medication	FDA Approved Conditions	Notes
Tirzepatide (Mounjaro)	• T2DM • Pediatric T2DM 10+	
Tirzepatide (Zepbound)	• Obesity (BMI >30) • **Overweight (BMI>27) and 1+ BMI comorbidity** • **Moderate/severe OSA + Obesity (BMI > 30)** • **Pediatric Obesity (12+)**	• Comorbidities: HTN, HLD, CVD, PAD, OA, MASH • AHI (4%) must be ≥ 15 • Pediatric patients must have BMI >95 percentile
Semaglutide (Ozempic)	• T2DM • T2DM + MACE (CVD, PAD, CAD, NSTEMI) • T2DM + CKD	
Semaglutide (Wegovy)	• Obesity • Obesity + MACE • **NAFLD/MASH/NASH *+ Fibrosis*** • Pediatric Obesity (12+)	• **Cannot be alcoholic cirrhosis, Fibrosis F2/F3** • Pediatric patients must have BMI >95 percentile
Semaglutide (Rybelsus)	• T2DM	
Liraglutide (Saxenda)	• **Obesity (BMI >30)** • Pediatric obesity (12+)	• Daily injectable • **Pediatric patients must have BMI >95 percentile**
Liraglutide (Victoza)	• T2DM • T2DM + MACE (CVD, PAD, CAD, NSTEMI) • Pediatric T2DM 10+	• Daily injectable
Dulaglutide (Trulicity)	• T2DM	

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