Swimming with the (pep)tides

Science Circle
April 6th 2024

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Researcher
Company that has nothing to do with this talk
Former University Biology Instructor

Overview

I. Peptides in energy homeostasis

II. So you would like an easy tan? and peptides in light sensitivity therapy

III. How was your tan? What was that you said?

IV. Market

Body's response to food/lack of food

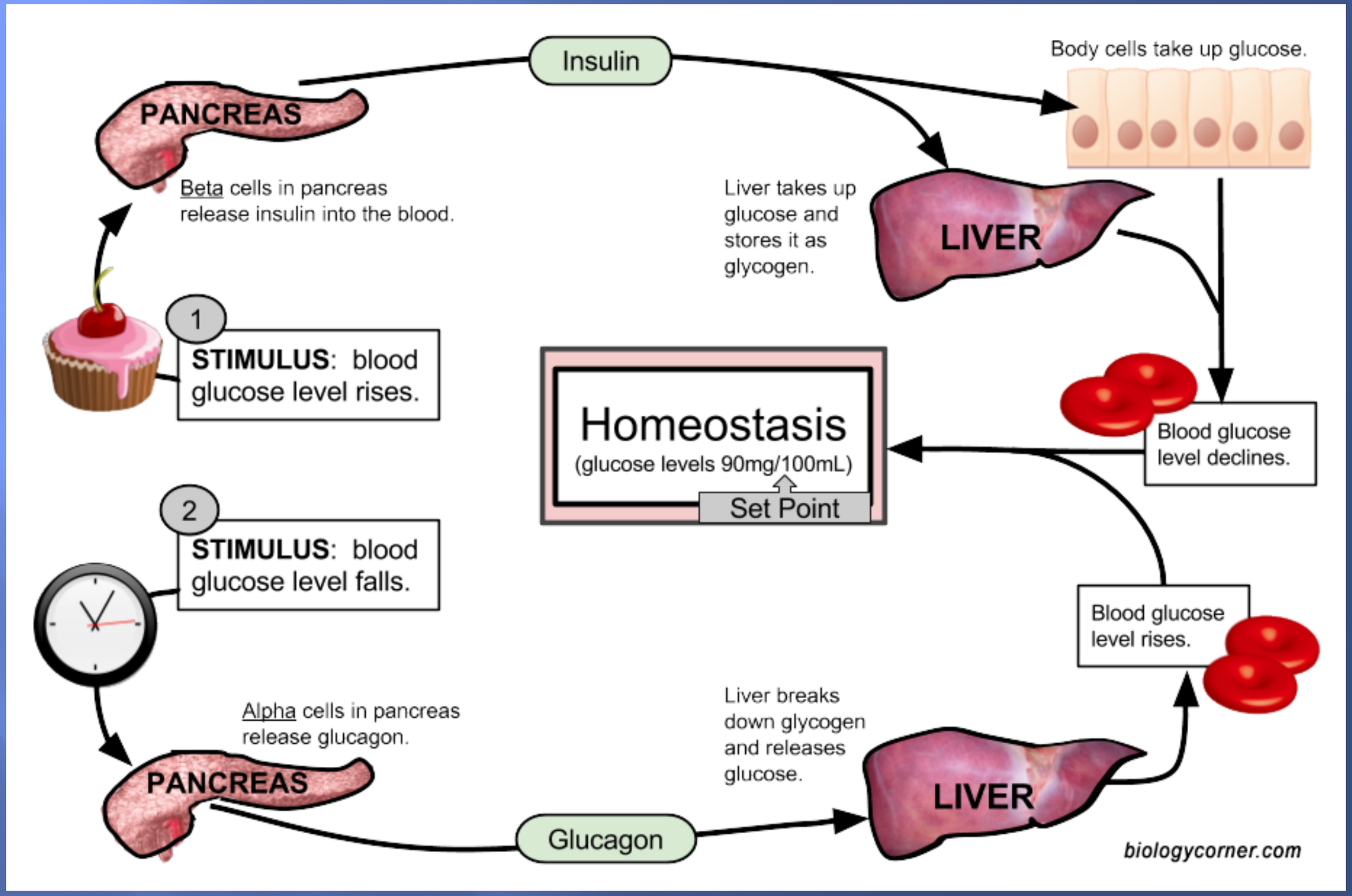
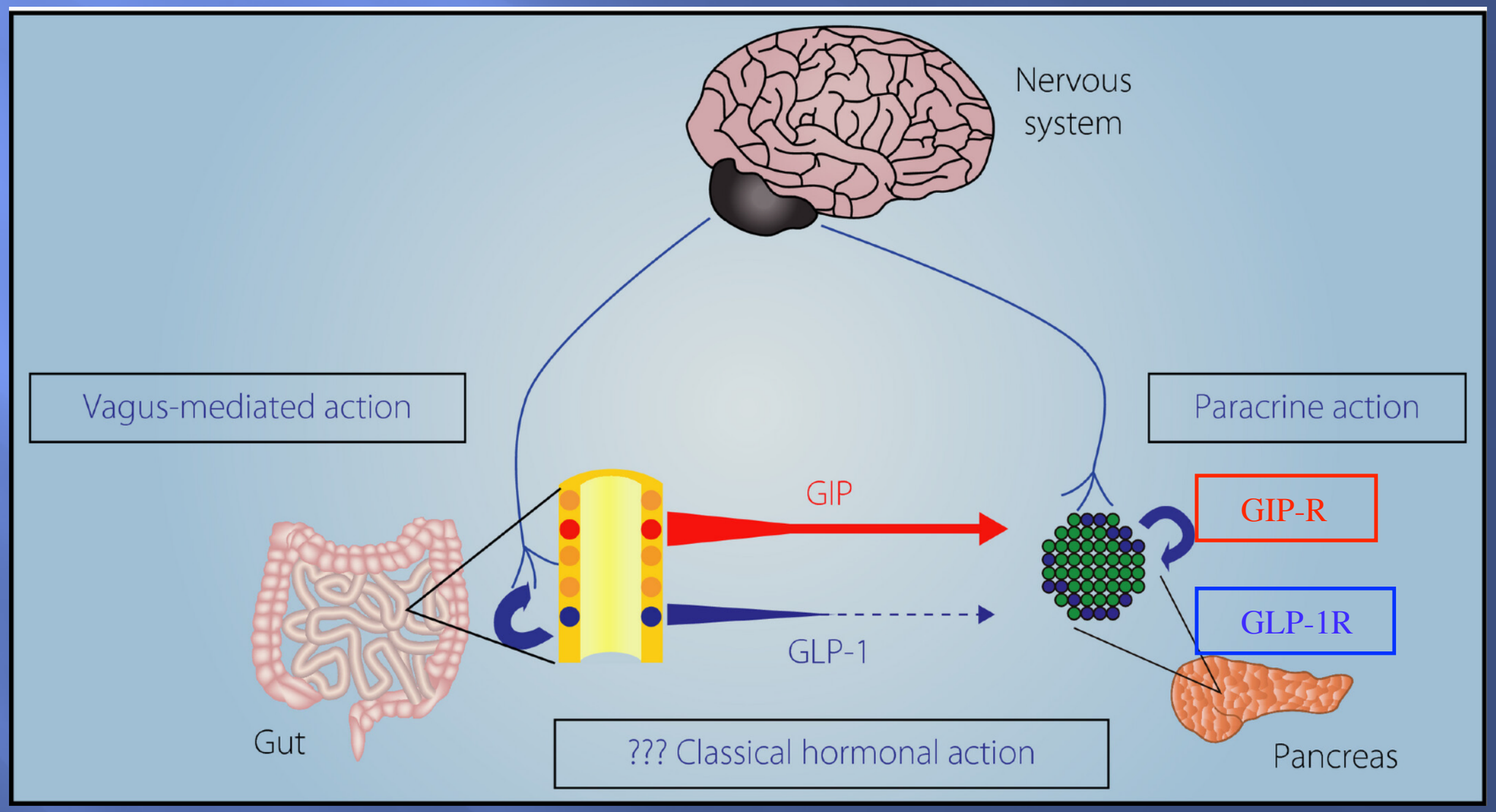


Figure is by: Shannan Muskopf from BiologyCorner.com

Body's response to food

incretin hypothesis: hormone from gut activates insulin from (1906) gut extracts reduce urinary glucose excretion in individuals with diabetes

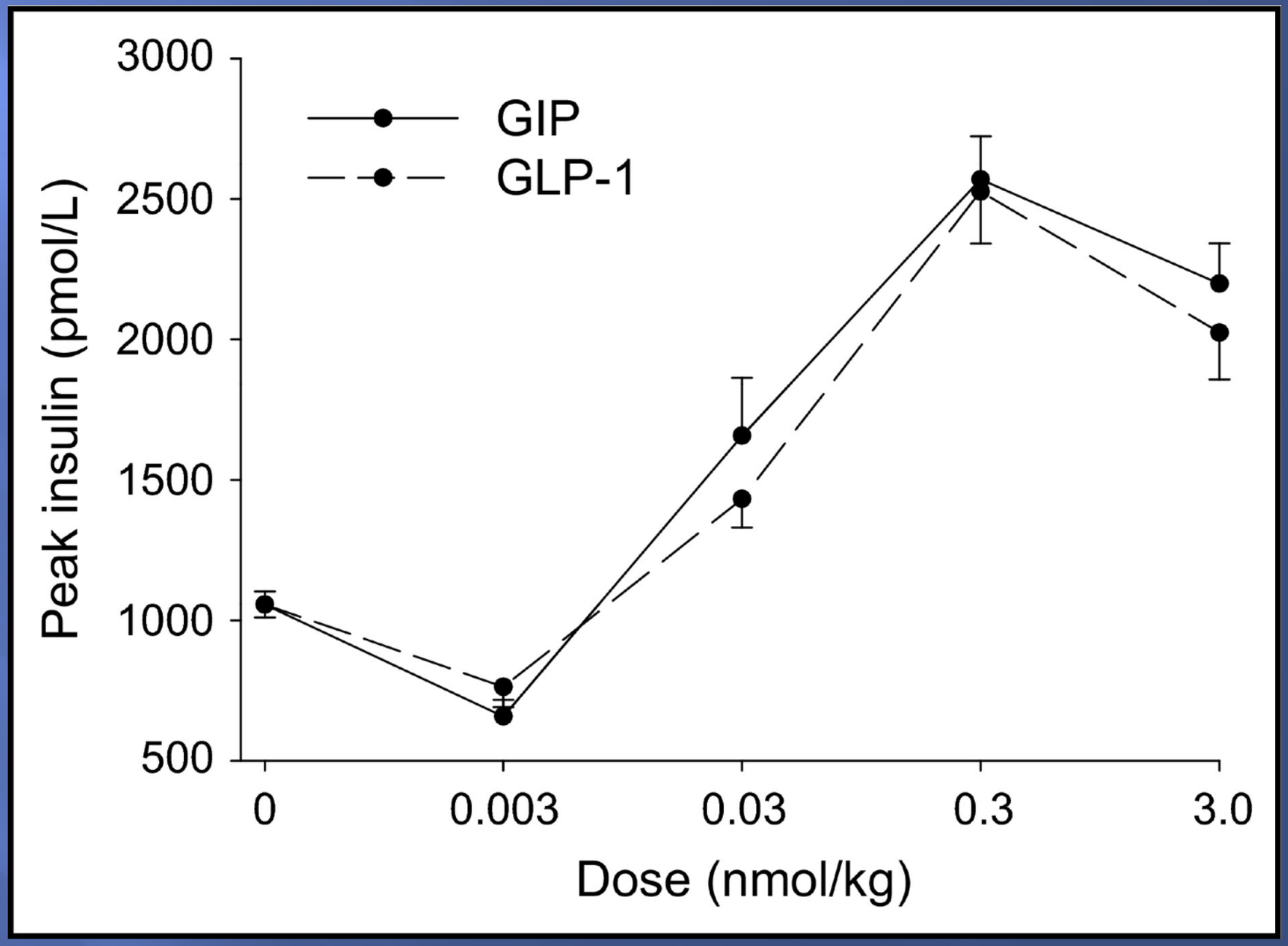


Yabe, D., Seino, Y., & Seino, Y. (2018). Incretin concept revised: The origin of the insulinotropic function of glucagon-like peptide-1–the gut, the islets or both?. *Journal of diabetes investigation*, 9(1), 21-24.

Body's response to food

example of dose response of insulin to peptides

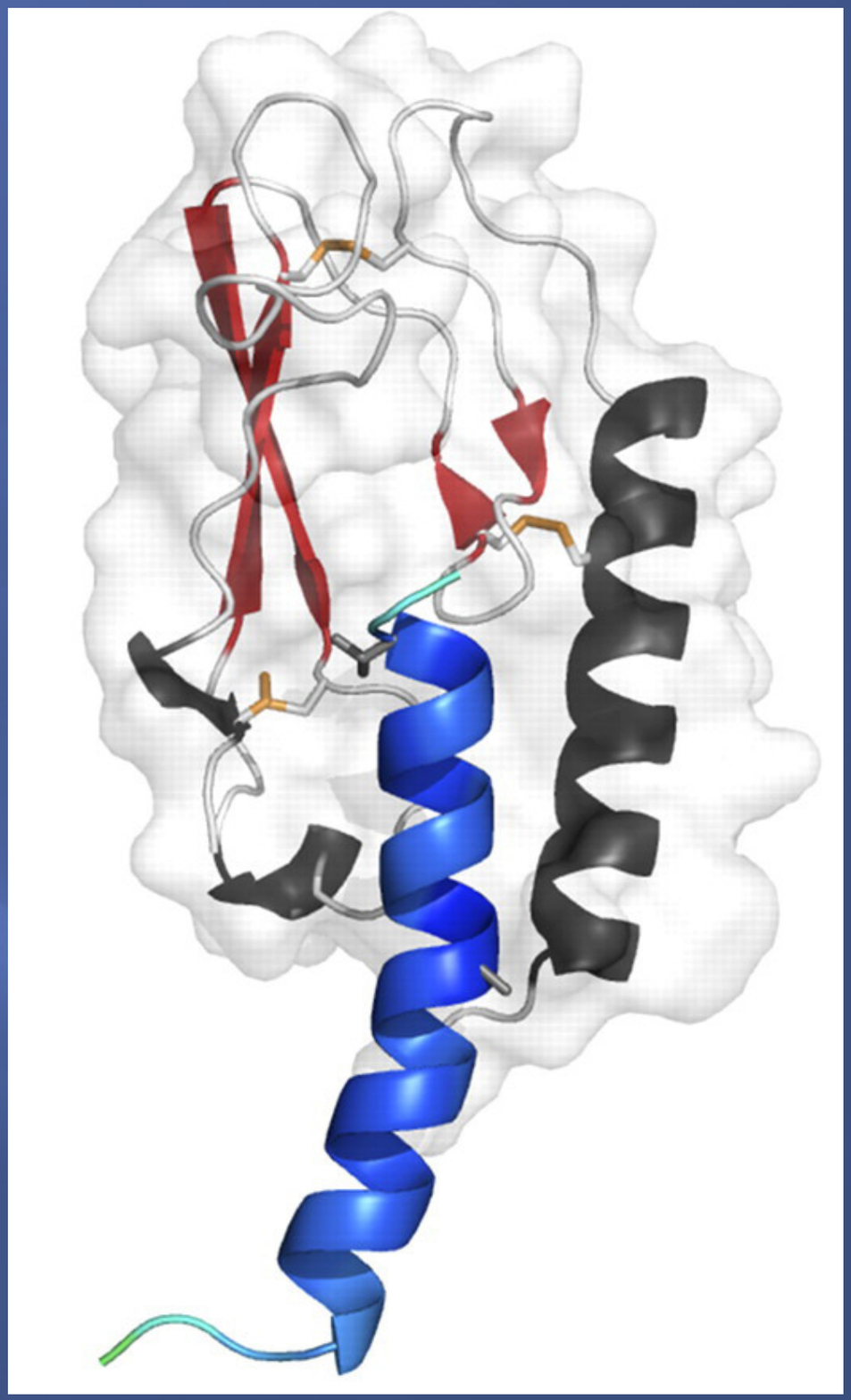
(IV of mice)



Pacini, G., & Ahrén, B. (2017). Glucagon-like peptide-1 and glucose-dependent insulinotropic peptide: effects alone and in combination on insulin secretion and glucose disappearance in mice. *Physiological reports*, 5(11), e13280.

GLP-1R

GLP-1 (blue) bound to the extracellular domain of the GLP-1R (α-helix in black, β-strands in red, and loops in gray).



Underwood, C. R., Garibay, P., Knudsen, L. B., Hastrup, S., Peters, G. H., Rudolph, R., & Reedtz-Runge, S. (2010). Crystal structure of glucagon-like peptide-1 in complex with the extracellular domain of the glucagon-like peptide-1 receptor. *Journal of Biological Chemistry*, 285(1), 723-730.

a promising weight loss mechanism….

"Transplantable glucagonomas derived from pluripotent rat islet tumor tissue cause severe anorexia and adipsia"

https://depositphotos.com/vector/rat-cartoon-8416177.html

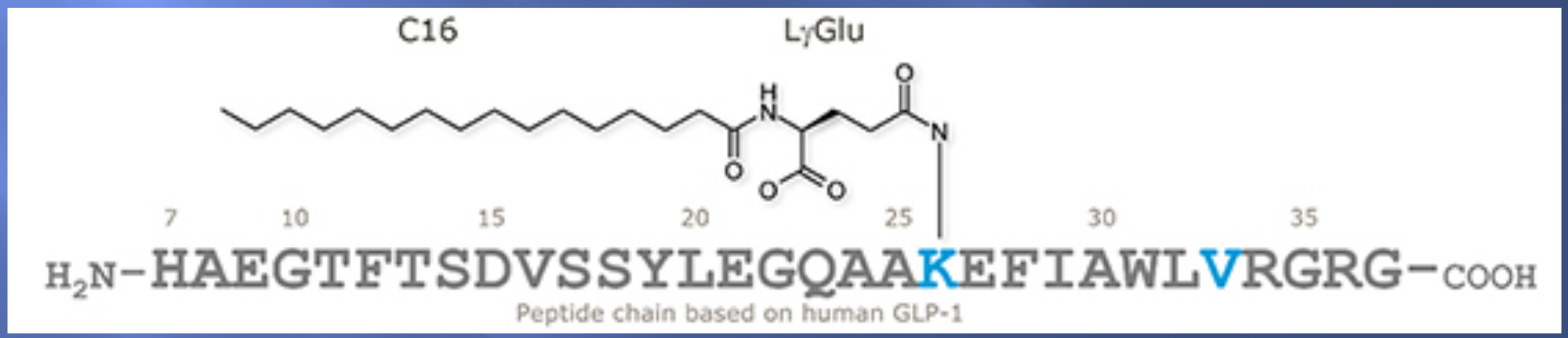
Madsen, O. D., Karlsen, C., Blume, N., Jensen, H. I., Larsson, L. I., & Holst, J. J. (1995). *Scandinavian Journal of Clinical and Laboratory investigation*. Supplementum, 220, 27-35.

like GLP-1 but longer lasting

half-life: 1.5 min half-life (all via IV)

<u>exendin-4 peptide</u> (a naturally occurring peptide obtained from *Heloderma* lizard venom, with 53% homology to human GLP-1): ~30 min

<u>liraglutide</u> (GLP-1 variant with palmitate via a γGlu linker): 13 hours



Knudsen, L. B., & Lau, J. (2019). The discovery and development of liraglutide and semaglutide. *Frontiers in endocrinology*, 10, 440904.

Liraglutide

—Liraglutide as daily injection was approved by the U.S. Food and Drug Administration (FDA) in 2014,

—and by the European Medicines Agency (EMA) in 2015,

—for adults with a body mass index (BMI) of 30 or greater (obesity) or a BMI of 27 or greater (overweight) who have at least one weight-related condition.

—sold under the brand names Victoza and Saxenda among others

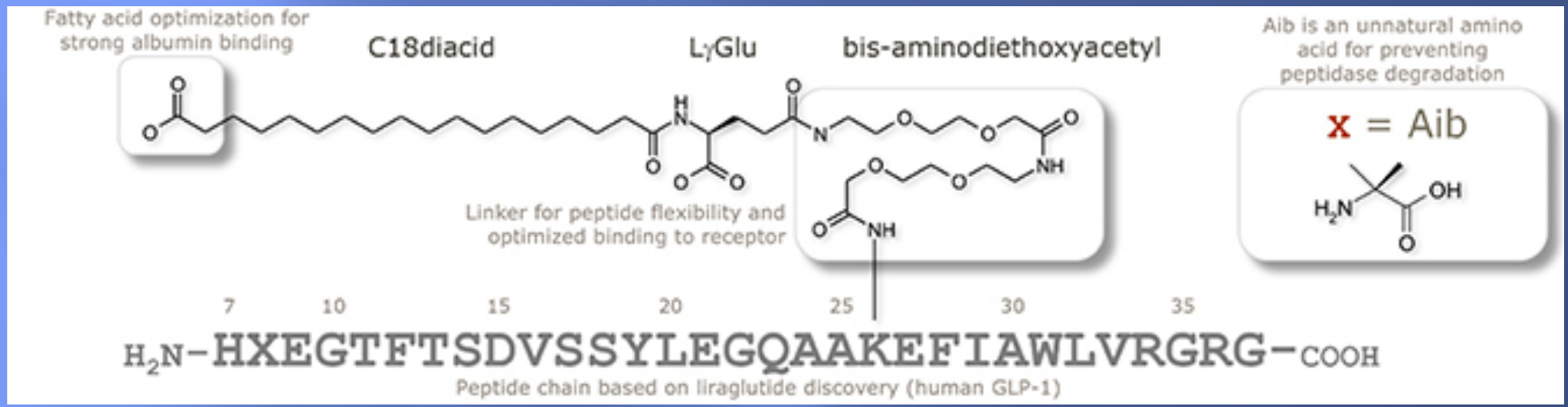
—Common side effects include low blood sugar, nausea, dizziness, abdominal pain, and pain at the site of injection.

—Other serious side effects may include angioedema, pancreatitis, gallbladder disease, and kidney problems.

—**daily** injection

Semaglutide

—half-life 55 hours (72 via subcutaneous)



—0.25 mg once-weekly dose for type II diabetes, up to 2.0 mg (Ozempic)

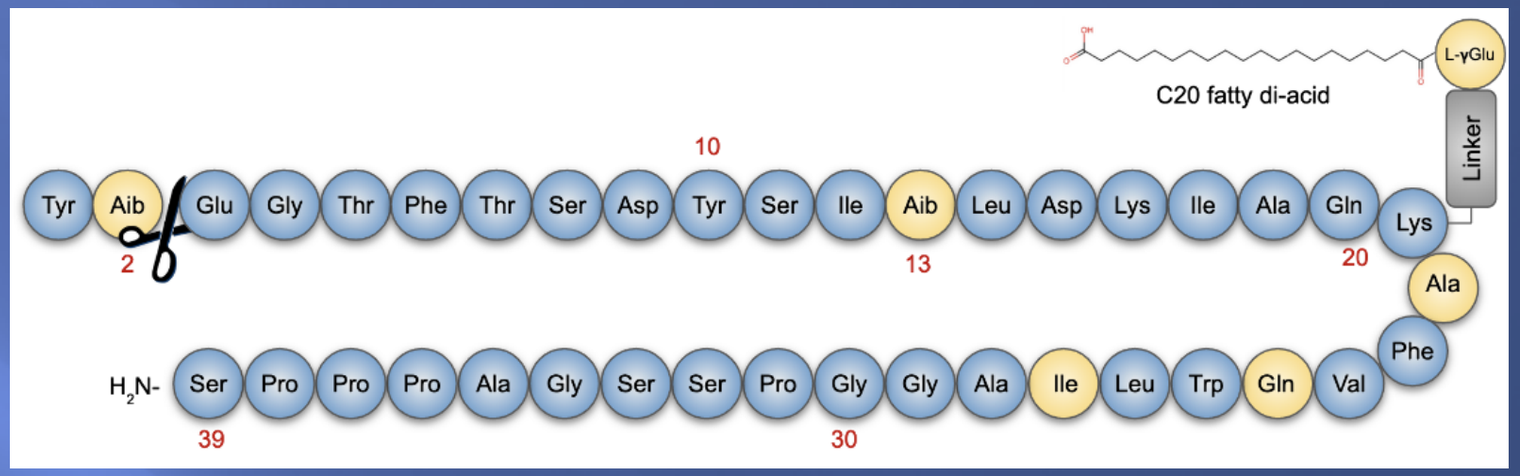
—0.25 mg once-weekly dose for obesity put to 2.4 mg (Wegovy)

—7 mg to 14 mg daily oral tablet (Rybelsus)

— Possible side effects include nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, indigestion/heartburn, dizziness, abdominal distension, belching, hypoglycemia (low blood glucose) in people with type 2 diabetes, flatulence, gastroenteritis, and gastroesophageal reflux disease (GERD). **More severe effect are pancreatitis, gastroparesis, and bowel obstruction**

Tirzepatide

— glucose-dependent insulinotropic polypeptide (GIP) mimic



—brand name Mounjaro

—once weekly subcutaneous injections

https://pdb101.rcsb.org/global-health/diabetes-mellitus/drugs/incretins/drug/tirzepatide/tirzepatide

—most common side effects include nausea, vomiting, diarrhea, decreased appetite, constipation, upper abdominal discomfort, and abdominal pain.

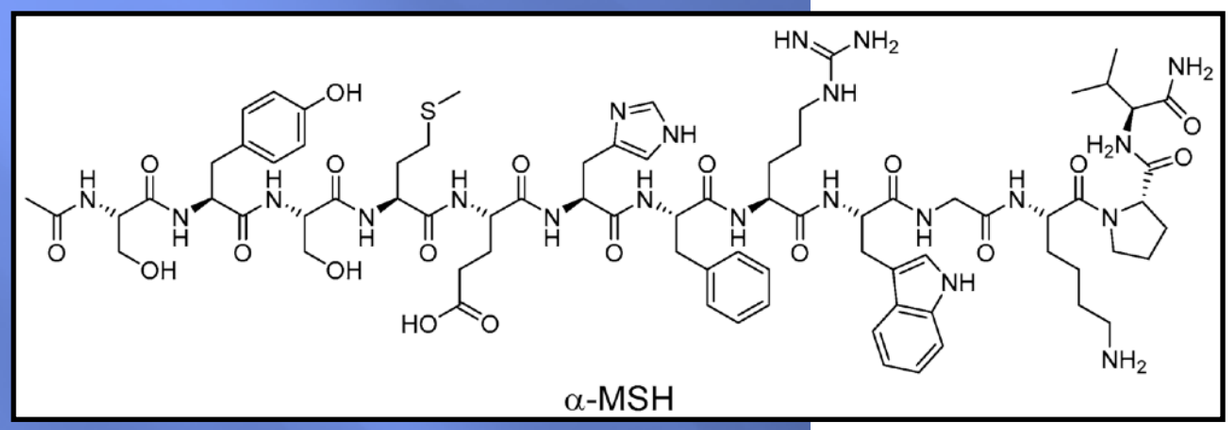
—approved for treatment of diabetes in the United States in May 2022, in the European Union in September 2022, in Canada in November 2022,and in Australia in December 2022.

—It was approved by the FDA for weight loss in November 2023, under the brand name Zepbound.

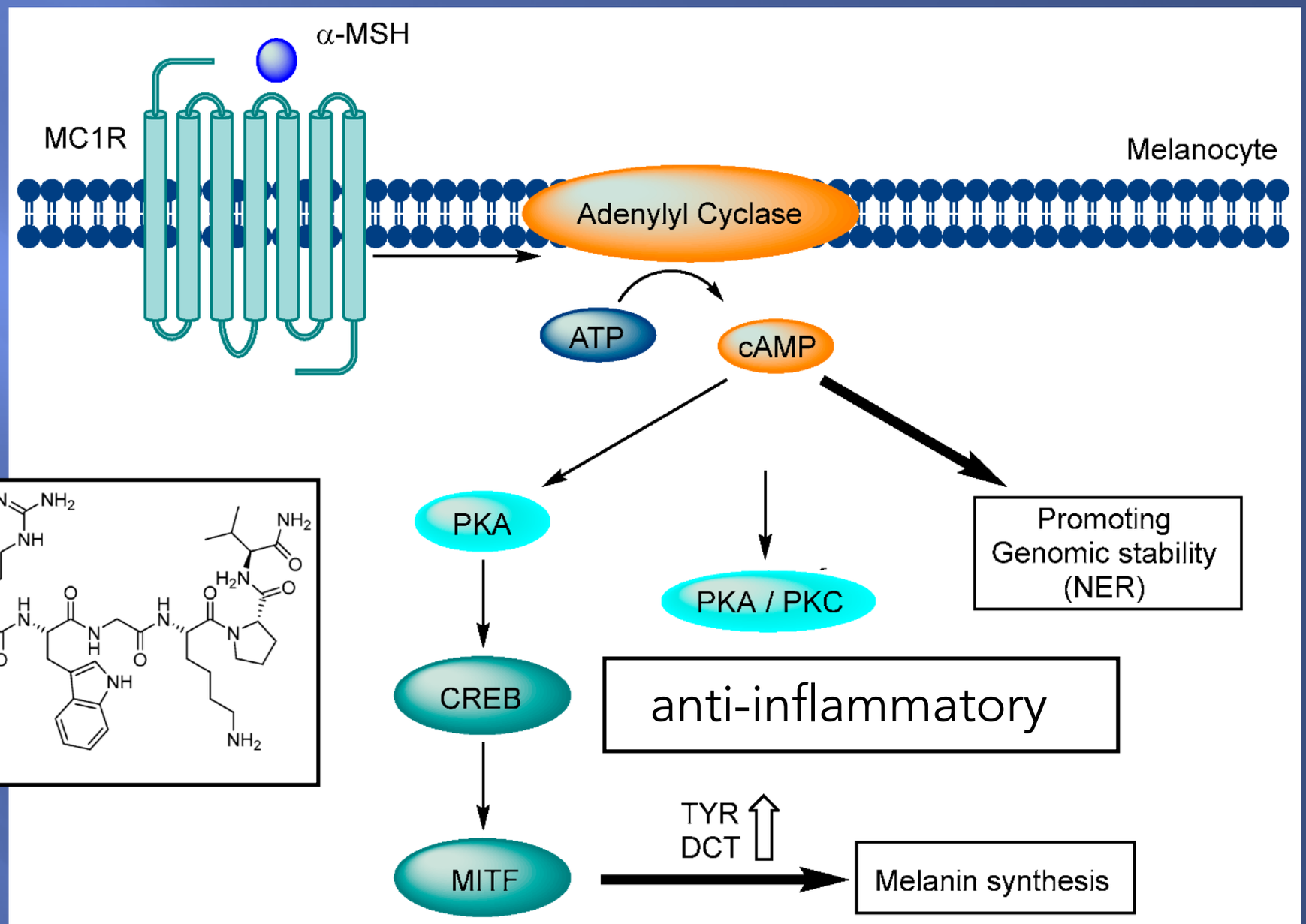
Body's response to light

alpha-melanocyte stimulating hormone

first isolated in the 1950s



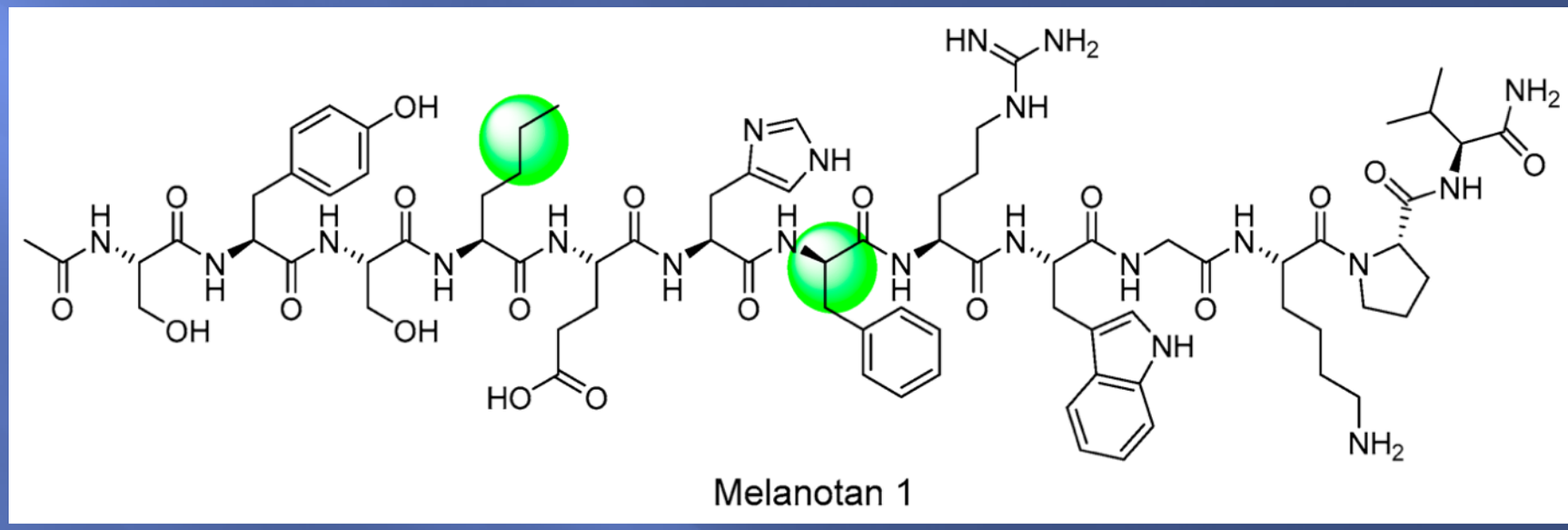
melanocortin 1 receptor



Mun, Y., Kim, W., & Shin, D. (2023). Melanocortin 1 Receptor (MC1R): Pharmacological and Therapeutic Aspects. *International journal of molecular sciences*, 24(15), 12152.

Body's response to light

Melanotan I is an early analog of α-MSH that acts as a non-selective agonist of melanocortin receptors and stimulates melanin production



Melanotan 1

—activates microphthalmia transcription factor (MITF) expression, which induces the expression of enzymes for eumelanin production. This process increases the production of —activates tyrosinase and induces an increase in eumelanin content in melanocytes

Mun, Y., Kim, W., & Shin, D. (2023). Melanocortin 1 Receptor (MC1R): Pharmacological and Therapeutic Aspects. *International journal of molecular sciences*, 24(15), 12152.

Afamelanotide

international nonproprietary name of melanotan I

—approved for use to treat erythropoietic protoporphyria (EPP) since 2019. (brand name Scenesse)

— EPP is a disease that causes abnormal hemoglobin synthesis in red blood cells, which can cause skin damage even with a little sunlight

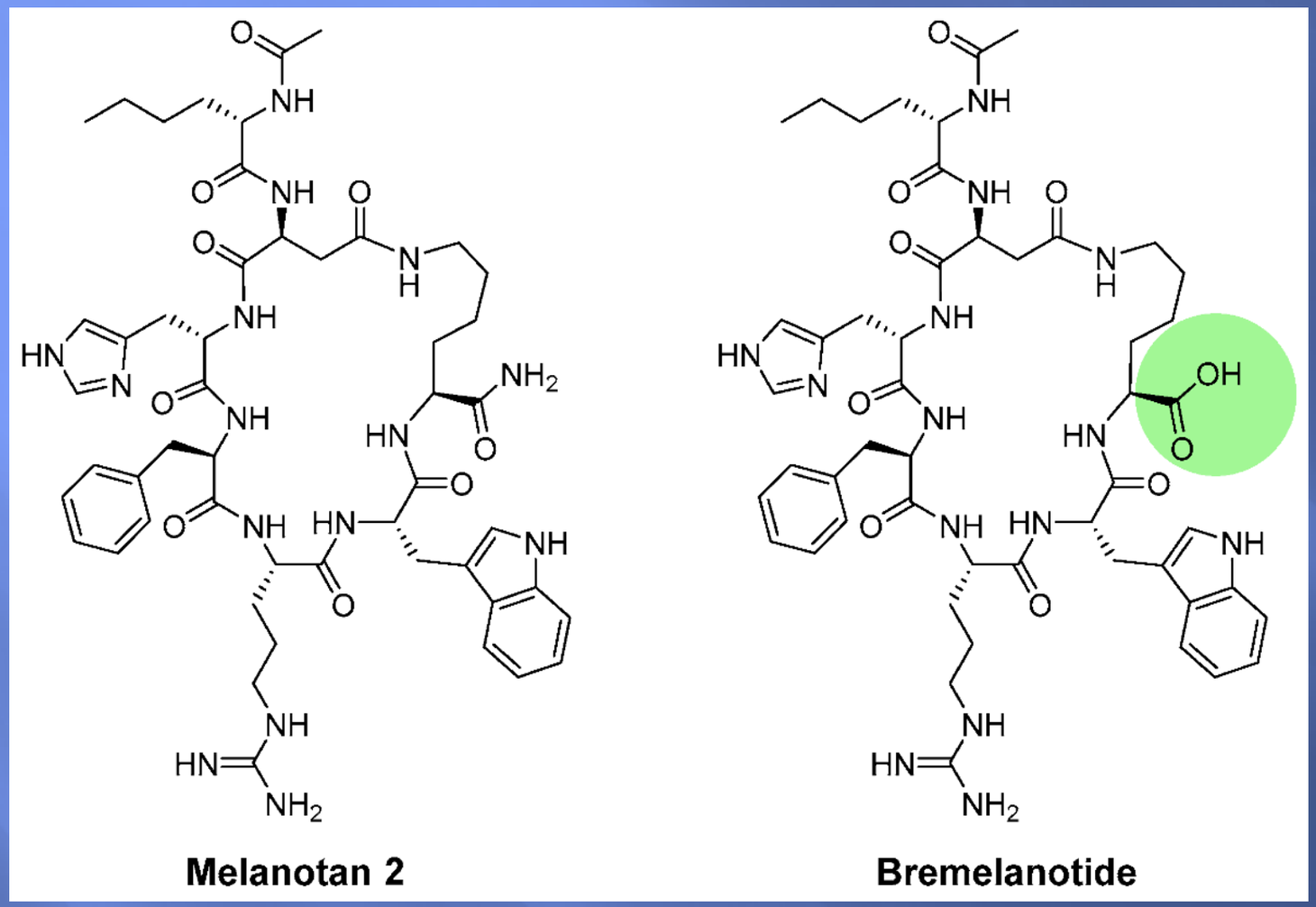
—caused by mutations leading to impaired activity of ferrochelatase, an enzyme involved in heme production. The decrease in ferrochelatase activity leads to an accumulation of protoporphyrin IX (PPIX) in the body. Light reaching the skin can react with PPIX causing intense skin pain and skin changes, such as redness and thickening.

FDA NEWS RELEASE: FDA approves first treatment to increase pain-free light exposure in patients with a rare disorder

Body's response to a-MSH analogs

Melanotan II and Bremelanotide

cyclic heptapeptide lactam analogue



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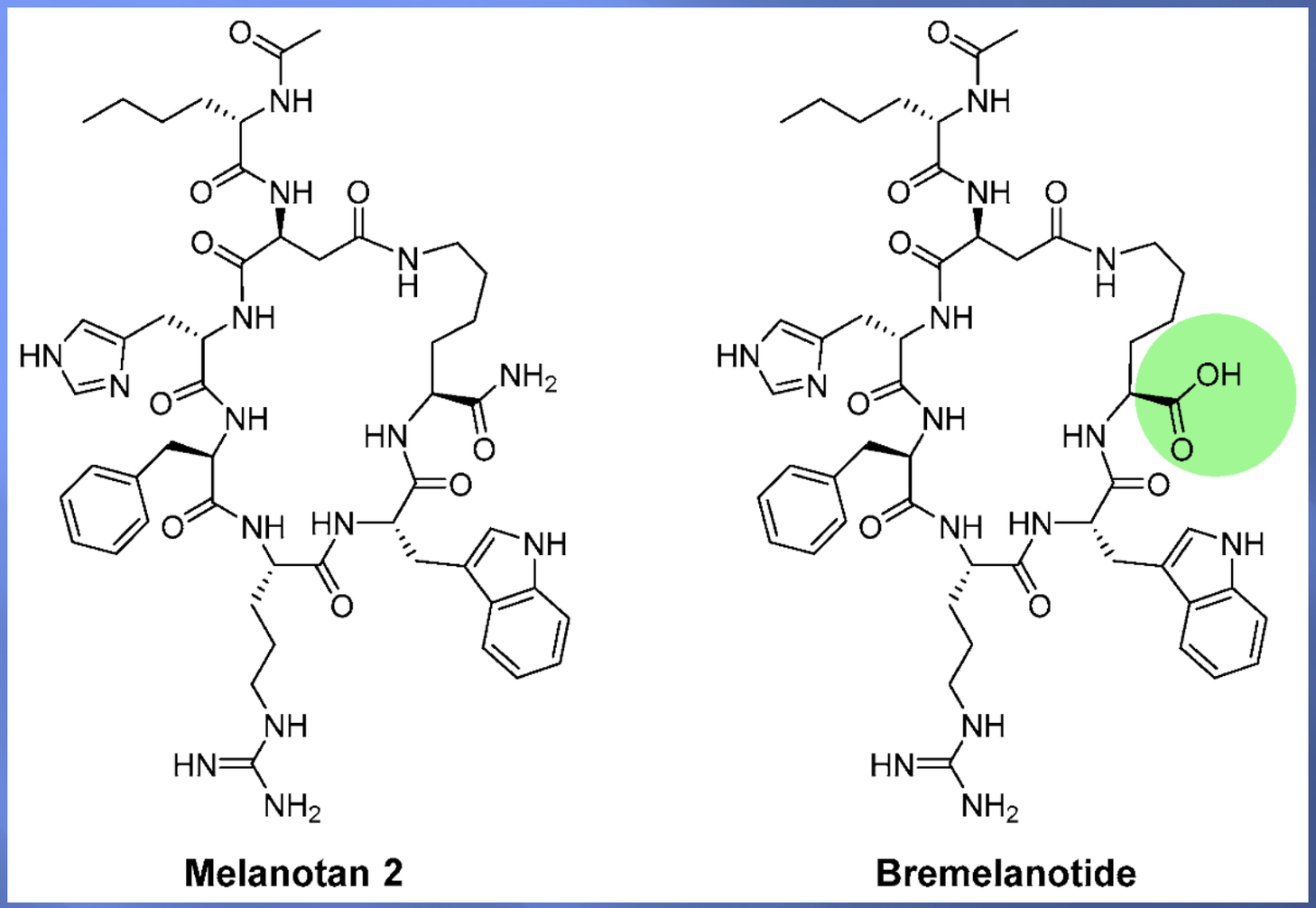
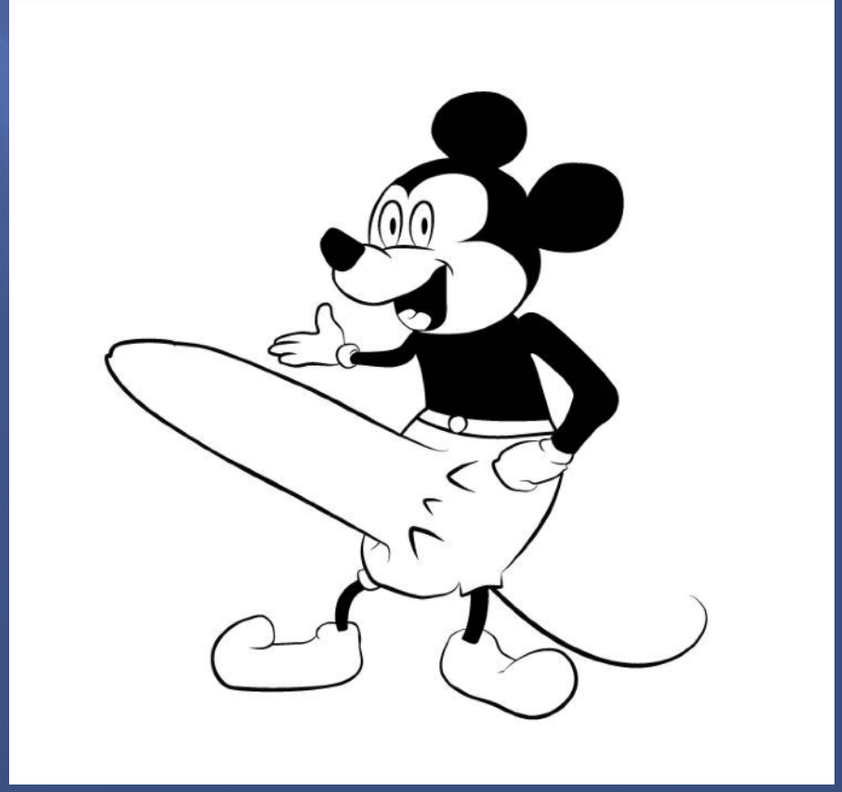


http://newimagesolutions.us/

Mun, Y., Kim, W., & Shin, D. (2023). Melanocortin 1 Receptor (MC1R): Pharmacological and Therapeutic Aspects. *International journal of molecular sciences*, 24(15), 12152.



https://www.deviantart.com/garrett-btm/art/Mickey-Mouse-151051484

Body's response to a-MSH analogs

During initial testing (2005) of a novel synthetic agent intended for artificial tanning, melanotan-II, a self described "human pincushion/ guinea pig" inadvertently self-administered a dose twice the expected concentration. To his surprise, he experienced an 8 hour-long erection, along with some nausea and vomiting. Gastrointestinal effects aside, the potential therapeutic effect of this agent for erectile dysfunction was immediately recognized.

King, S. H., Mayorov, A. V., Balse-Srinivasan, P., Hruby, V. J., Vanderah, T. W., & Wessells, H. (2007). Melanocortin receptors, melanotropic peptides and penile erection. *Current topics in medicinal chemistry*, 7(11), 1111-1119.

Bremelanotide

sold under the brand name Vyleesi (also known as PT-141)

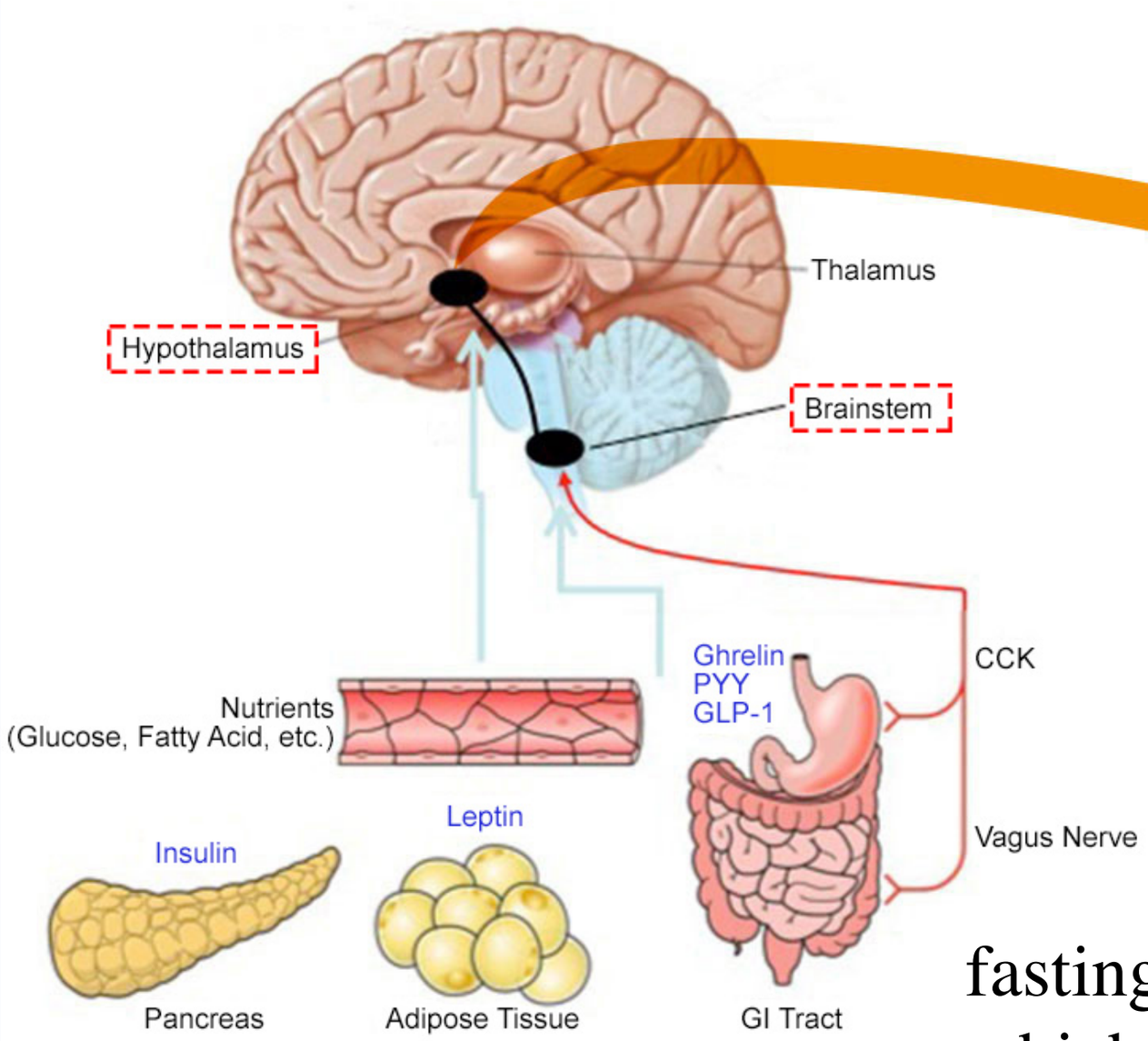
— FDA approved for generalized hypoactive sexual desire disorder (HSDD) in premenopausal **women** (2019). Specifically it is used for low sexual desire which occurs before menopause and is not due to medical problems, psychiatric problems, or problems within the relationship.

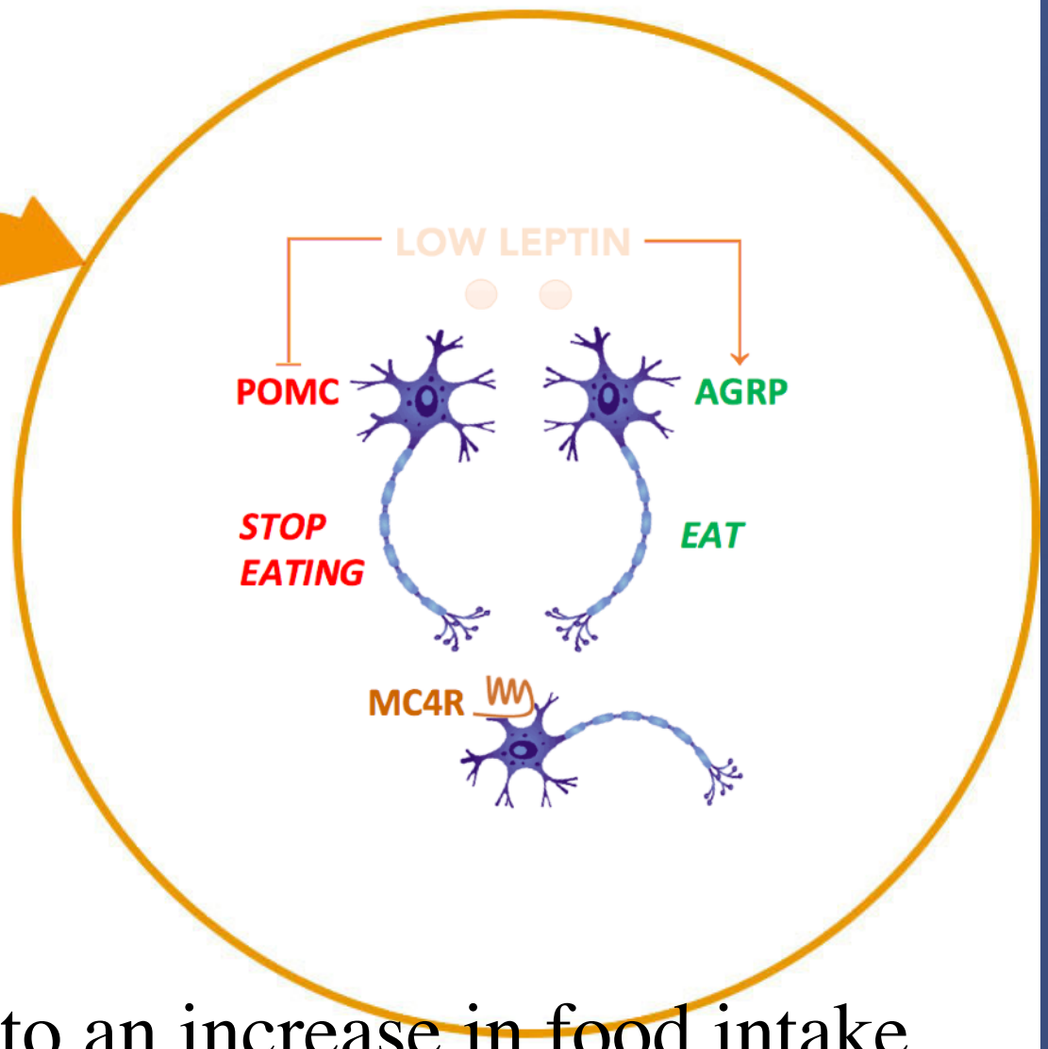
—It is typically given by an injection just under the skin of the thigh or abdomen

—Common side effects include nausea, pain at the site of injection, and headache. It may also cause a temporary increase in blood pressure and decrease in heart rate after each dose, and darkening of the gums, face, and breasts.

—also a nasal inhaler version (Phase II showed adverse events)

MCR4 is multifaceted





fasting leads to an increase in food intake which restores energy balance.

Disruption of MC4R in mice leads to obesity demonstrating that this pathway is critical for the control of appetite and body weight. These findings in animals paved the way for studies in humans and in 1998, we and colleagues in France identified the first mutations in the MC4R gene in people with severe obesity from early childhood.

MCR4 is multifaceted

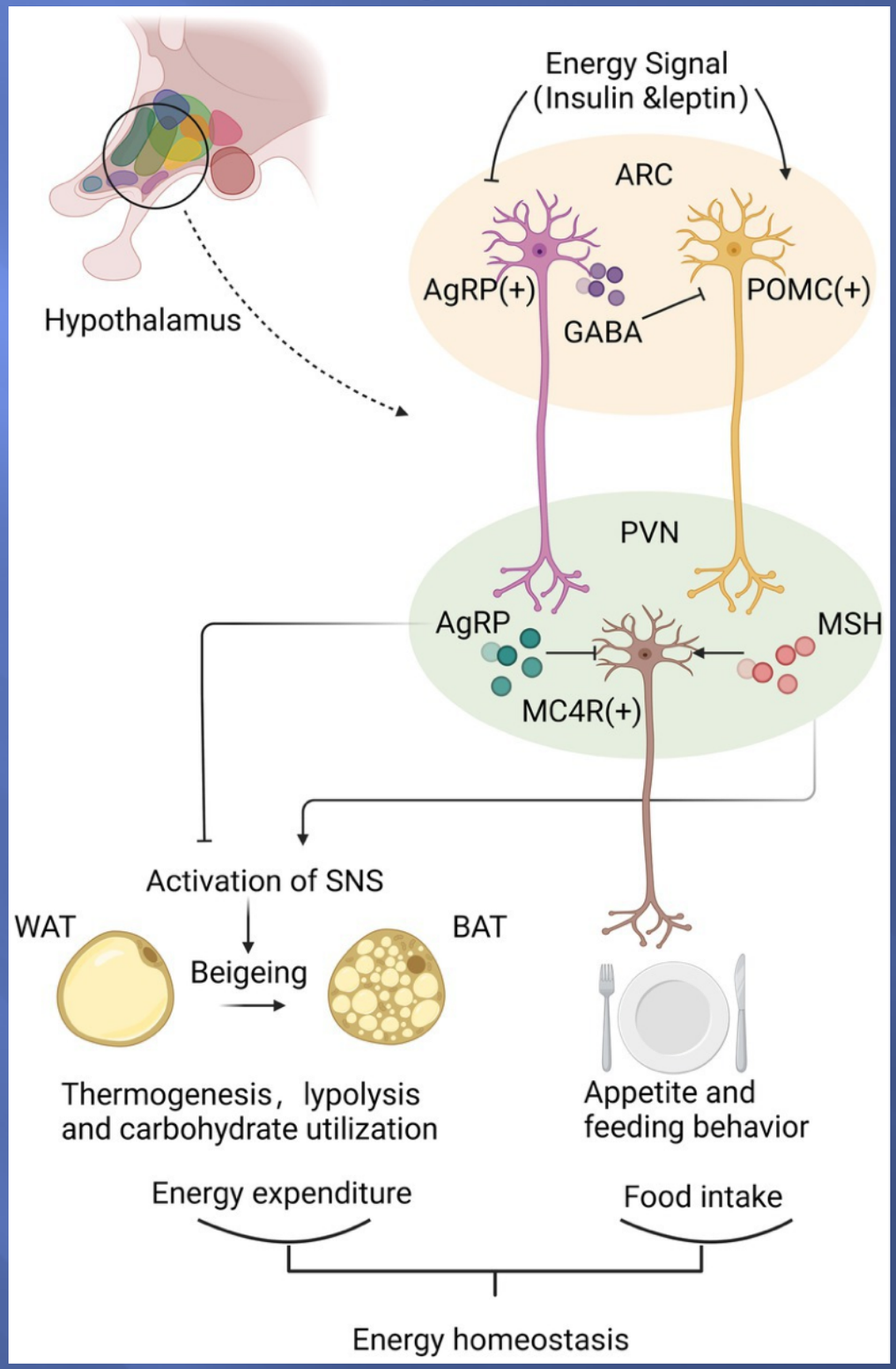
—mutations in the MC4R are the most common monogenic form of obesity, with more than 150 distinct mutations reported thus far

—MC4R antagonists such as HS014 and HS024 provided further supporting evidence that MC4R is important in regulating food intake. For example, ICV infusions of these antagonists stimulate feeding in satiated rats, and long-term infusion leads to increased food intake and body weight

—*Mc4r* knockout mouse model that provided the definitive evidence that the MC4R is critical for regulating energy homeostasis in mice. The homozygous knockout mice have maturity-onset obesity, hyperphagia, increased linear growth, hyperinsulinemia, and hyperglycemia.

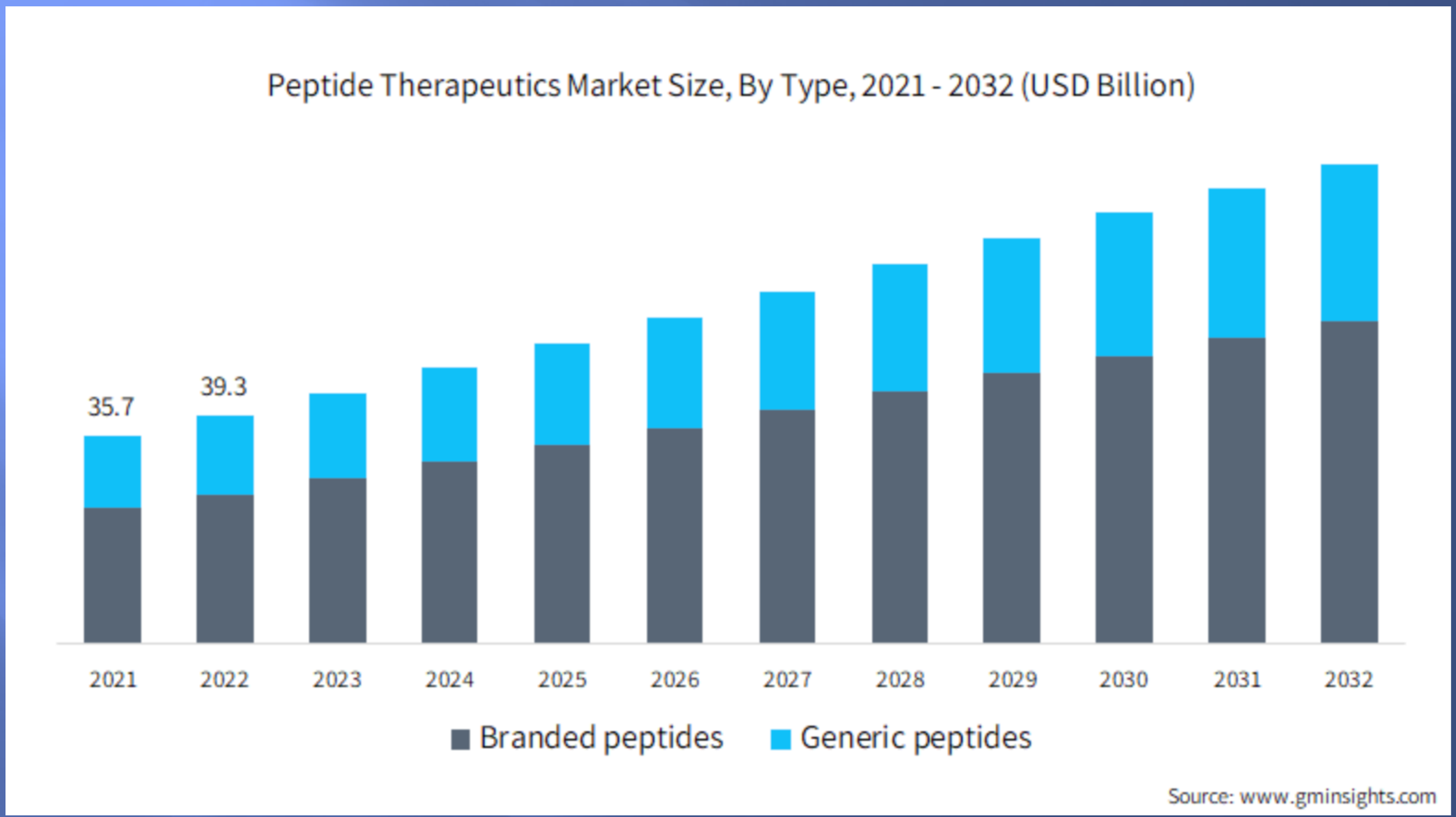
Tao, Y. X. (2010). The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology. *Endocrine reviews*, 31(4), 506-543.

The larger circuit



Zhang, J., Li, S., Luo, X., & Zhang, C. (2023). Emerging role of hypothalamus in the metabolic regulation in the offspring of maternal obesity. *Frontiers in Nutrition*, 10, 1094616.

The Peptides Market



https://www.gminsights.com/industry-analysis/peptide-therapeutics-market

Future Outlook

(from a science perspective and not investor advice)

peptides as analogs of body messengers is very flexible/specific/and robust

factors to enhance stability and delivery are being better and better understood