Casual Friday Presents

Peptide Primer I (GLP-1)



### Questions:

- How do I feel about the current landscape?
- What is my perspective on peptides?
- What is my perspective on natural vs enhanced programming?
- How do we help patients navigate their current options?



## Peptides

- 2 to 50+ amino acids in the structure
- Receptor site activation (like a hormone)
- Antimicrobial actions
- Immunotherapy

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- Delivery: oral, subcutaneous, and cell penetrating models
- Oncology/Immunology
- Infectious disease/Cardio/GI
- \*Metabolic\*



#### **Medical Dictionary**

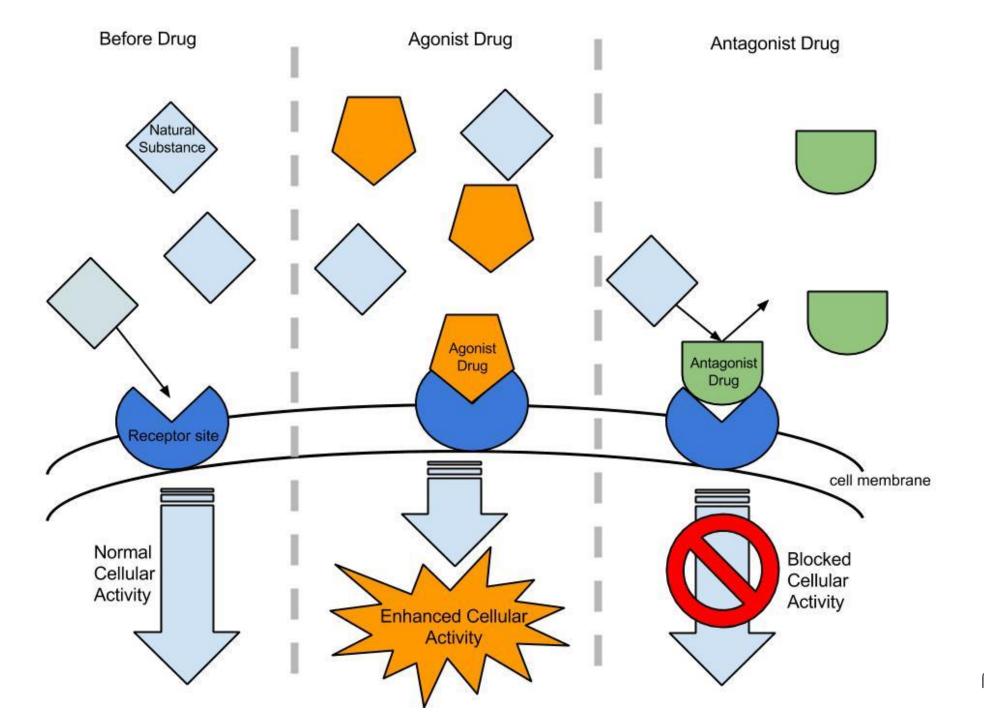
### **DEFINITION OF MIMESIS**

Medical Editor: Jay W. Marks, MD

**Mimesis:** Imitation or mimicry. Mimesis in medicine refers to the hysterical simulation of organic disease and to the imitation of one organic disease by another. Mimesis in aesthetic or artistic theory refers to the attempt to imitate or reproduce reality.

The word "mimesis" comes from the Greek verb "mimeisthai" meaning "to imitate" and from "mimos" meaning "mime." The English word "mime" also comes from "mimos" as do "mimic" and "mimicry."







#### Therapeutic peptides: current applications and future directions

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Therapeutic peptides are a unique class of pharmaceutical agents composed of a series of well-ordered amino acids, usually with molecular weights of 500-5000 Da<sup>1</sup>. Research into therapeutic peptides started with fundamental studies of natural human hormones, including insulin, oxytocin, vasopressin, and gonadotropin-releasing hormone (GnRH), and their specific physiological activities in the human body<sup>2</sup>. Since the synthesis of the first therapeutic peptide, insulin, in 1921, remarkable achievements have been made resulting in the approval of more than 80 peptide drugs worldwide. The development of peptide drugs has thus become one of the hottest topics in pharmaceutical research.

The first half of the 20th century witnessed the discovery of several life-saving bioactive peptides, such as insulin and adrenocorticotrophic hormone, which were initially studied and isolated from natural sources. The discovery and development of insulin, a peptide with 51 amino acids, has been considered as one of the monumental scientific achievements in drug discovery. It was first isolated by Frederick Banting in 1921 and further developed by Frederick and Charles Best<sup>3,4</sup>, and was already available for patients with diabetes mellitus just a year after its first isolation. In 1923, insulin became the first commercial peptide drug and has since benefited thousands of diabetes patients to date. However, the production of human insulin during the 20th century could not keep up with the high market demand, and animal-derived insulins, such as bovine and porcine insulin, dominated the insulin market for almost 90 years until they were replaced by recombinant insulin<sup>5,6</sup>.



#### Therapeutic peptides: current applications and future directions

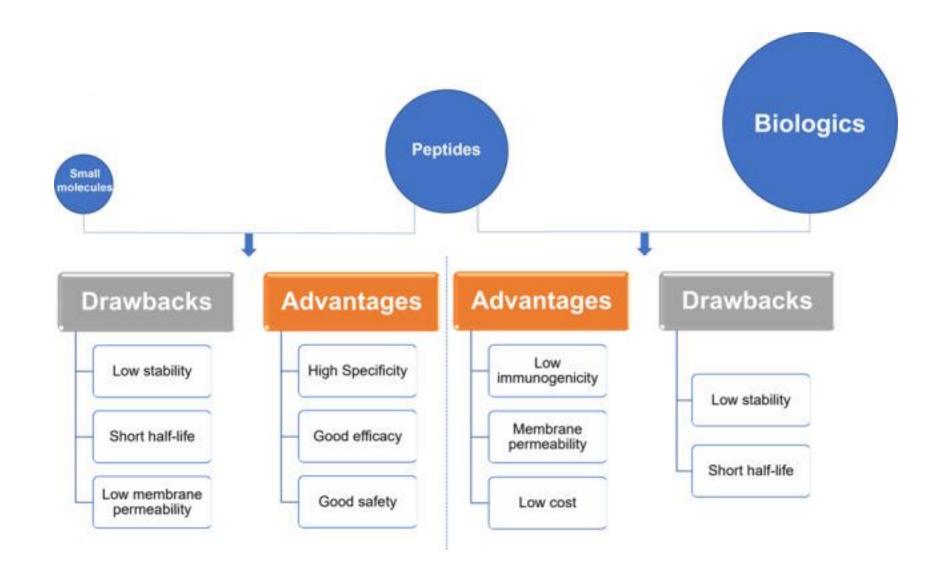
Lei Wang <sup>1,#</sup>, Nanxi Wang <sup>2,#</sup>, Wenping Zhang <sup>1,#</sup>, Xurui Cheng <sup>1,#</sup>, Zhibin Yan <sup>1</sup>, Gang Shao <sup>3</sup>, Xi Wang <sup>3</sup>, Rui Wang <sup>4,5,®</sup>, Caiyun Fu <sup>1,®</sup>

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PMCID: PMC8844085 PMID: 35165272

More peptide hormones and their receptors with therapeutic potential were identified and characterized from the 1950s to the 1990s<sup>Z</sup>. Meanwhile, the technologies used for protein purification and synthesis, structure elucidation, and sequencing made substantial progress, thus accelerating the development of peptide drugs, leading to nearly 40 peptide drugs being approved worldwide. Notably, synthetic peptides such as synthetic oxytocin<sup>8</sup>, synthetic vasopressin<sup>9</sup>, and recombinant human insulin<sup>10,11</sup> began to be developed in addition to natural peptides.







#### Therapeutic peptides: current applications and future directions

<u>Lei Wang <sup>1,#</sup>, Nanxi Wang <sup>2,#</sup>, Wenping Zhang <sup>1,#</sup>, Xurui Cheng <sup>1,#</sup>, Zhibin Yan <sup>1</sup>, Gang Shao <sup>3</sup>, Xi Wang <sup>3</sup>, Rui Wang <sup>4,5,®</sup>, Caiyun Fu <sup>1,®</sup></u>

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#### Peptides mimicking hormones

GLP-1 derived peptide drugs (Fig. 4a): GLP-1 is a 37-amino acid peptide that regulates insulin production and secretion 49, with a very short half-life in vivo. Extensive efforts have been made to modify its sequence to enhance the stability of this hormone, while maintaining its potency and pharmacological effect 50,51, leading to the development of the three top-selling anti-T2DM peptide drugs: Trulicity (dulaglutide), Victoza (liraglutide), and Ozempic (semaglutide).



Glucagon like peptide-1 agonists' mechanism involves regulating appetite and blood sugar. It acts as an incretin.

It signals the brain to increase feelings of fullness, slowing gastric emptying and reducing food intake. It also stimulates the pancreas to release insulin and inhibits glucagon, which lowers blood sugar levels.

#### Action:

#### •Regulates appetite and satiety:

•GLP-1 acts on brain regions that control hunger and fullness, making you feel full longer and eat less.

#### •Slows gastric emptying:

•It slows the rate at which food leaves the stomach, which helps control blood sugar spikes after meals.

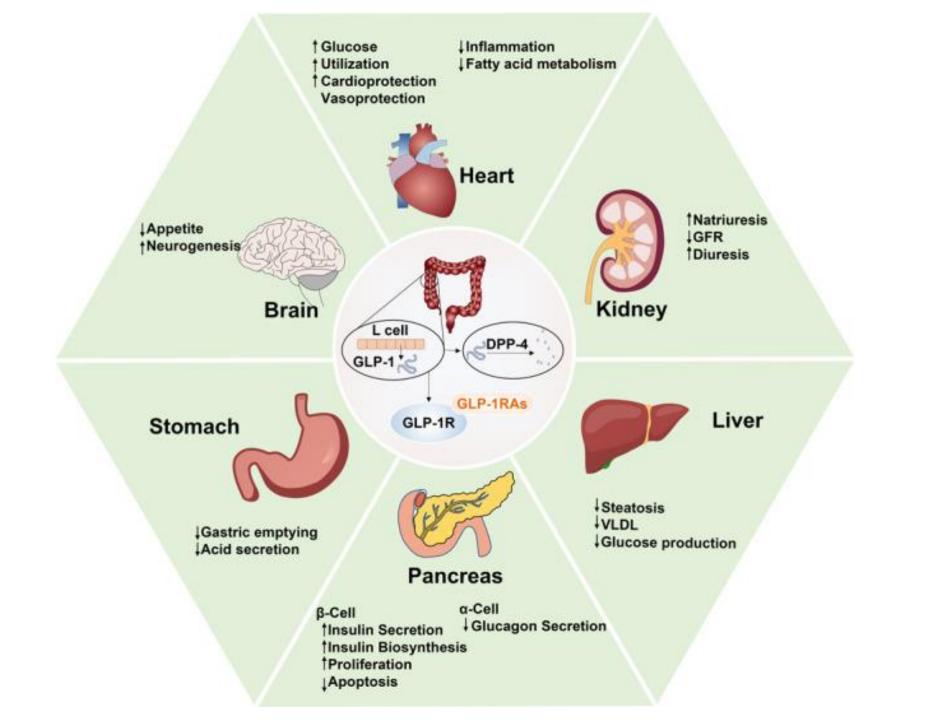
#### •Stimulates insulin secretion:

•It prompts the pancreas to release insulin in response to increased blood sugar levels, helping the body use glucose for energy.

#### •Inhibits glucagon:

•It reduces the amount of glucagon, a hormone that raises blood sugar, preventing the liver from releasing stored energy into the bloodstream.





Biogenetix

### The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed obesity management, offering substantial weight loss and metabolic benefits. This review examines their expanding role, evaluating efficacy compared to alternative treatments, emerging indications, ongoing challenges, and future directions. Beyond obesity and type 2 diabetes, the therapeutic potential of GLP-1 RAs extends to a range of conditions such as cardiovascular disease, liver disease, neurodegenerative disease, and substance abuse disorders. While early concerns regarding pancreatic and thyroid cancer have been largely attenuated by recent evidence, issues such as gallbladder and biliary disorders, psychiatric safety, and perioperative aspiration risk require ongoing investigation. Additionally, observations of weight regain after treatment discontinuation and reductions in lean mass highlight the need for long-term, individualized strategies to sustain clinical benefits. The high cost and limited access to these medications raise critical policy and equity challenges. Future research must address these gaps, focusing on long-term safety, optimizing combination approaches, and evaluating the broader clinical and economic implications of widespread GLP-1 RA use.



### The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions

Areesha Moiz <sup>a</sup>, Kristian B Filion <sup>a,b,c</sup>, Michael A Tsoukas <sup>c,d</sup>, Oriana HY Yu <sup>a,b,c,d</sup>, Tricia M Peters <sup>a,b,c,d</sup>, Mark J Eisenberg <sup>a,b,c,e,\*</sup>

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#### Body composition and muscle preservation

As GLP-1 RAs become more widely used for weight management, attention has turned to their effects on body composition. Evidence from dual-energy X-ray absorptiometry and MRI sub-studies suggests that 25–45% of total weight loss with semaglutide and tirzepatide may come from reductions in lean body mass. 90 Although this proportion is similar to that seen with lifestyle interventions, 11 the decline in lean mass may have implications for mobility, metabolic rate, and physical function, particularly in older adults or those with sarcopenic obesity. These concerns have prompted interest in strategies to mitigate muscle loss. In addition to resistance training and adequate protein intake, investigational therapies such as myostatin inhibitors and selective androgen receptor modulators are being evaluated for their ability to preserve or enhance lean mass in conjuction with GLP-1 RA use. 92,93



## The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions

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#### Weight regain and cardiometabolic effects after treatment discontinuation

Another important concern regarding GLP-1 RA use is potential weight regain upon discontinuation of treatment. In an extension of the STEP-1 trial, participants originally randomized to semaglutide regained 68% of their lost weight after one year of discontinuing treatment. Cardiometabolic improvements achieved with semaglutide also reverted towards baseline for most risk factors after one year. The STEP-4 trial included a 20-week run-in period during which participants achieved a mean weight loss of 10.6% after treatment with weekly semaglutide. From week 20 to week 68, participants who discontinued the drug regained an average of 6.9% of their baseline body weight, while those who continued treatment lost an additional 7.9%. These findings suggest ongoing treatment with GLP-1 RAs is required to maintain improvements in weight and health, highlighting the chronicity of obesity. Recognizing obesity as a chronic disorder underscores the need for long-term pharmacological treatment, similar to the approach used for managing type 2 diabetes or hypertension to achieve optimal control.



Report

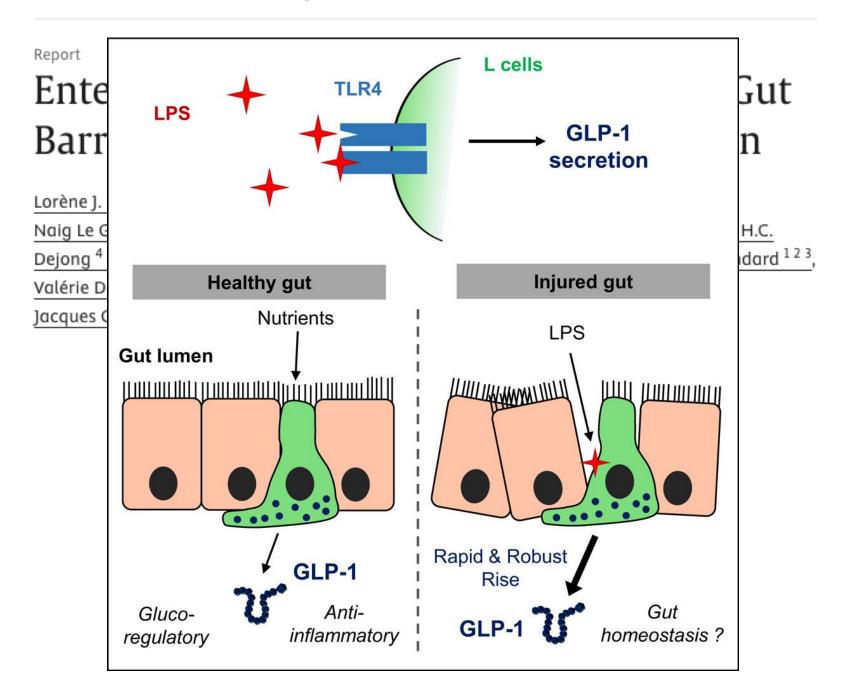
### Enteroendocrine L Cells Sense LPS after Gut Barrier Injury to Enhance GLP-1 Secretion

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Lorène J. Lebrun <sup>1 2 3</sup>, Kaatje Lenaerts <sup>4</sup>, Dorien Kiers <sup>5</sup>, Jean-Paul Pais de Barros <sup>1 2 3</sup>, Naig Le Guern <sup>1 2 3</sup>, Jiri Plesnik <sup>1 2 3</sup>, Charles Thomas <sup>1 2 3</sup>, Thibaut Bourgeois <sup>1 2 3</sup>, Cornelis H.C.

Dejong <sup>4 6</sup>, Matthijs Kox <sup>5</sup>, Inca H.R. Hundscheid <sup>4</sup>, Naim Akhtar Khan <sup>1 2 3</sup>, Stéphane Mandard <sup>1 2 3</sup>,
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- LPS induce GLP-1 secretion from L cells through a TLR4-dependent mechanism
- Gut ischemic injury is coupled to immediate GLP-1 secretion in mice and humans
- L cells are mucosal sensors of LPS after gut injury
- GLP-1 secretion is closely related to gut inflammation



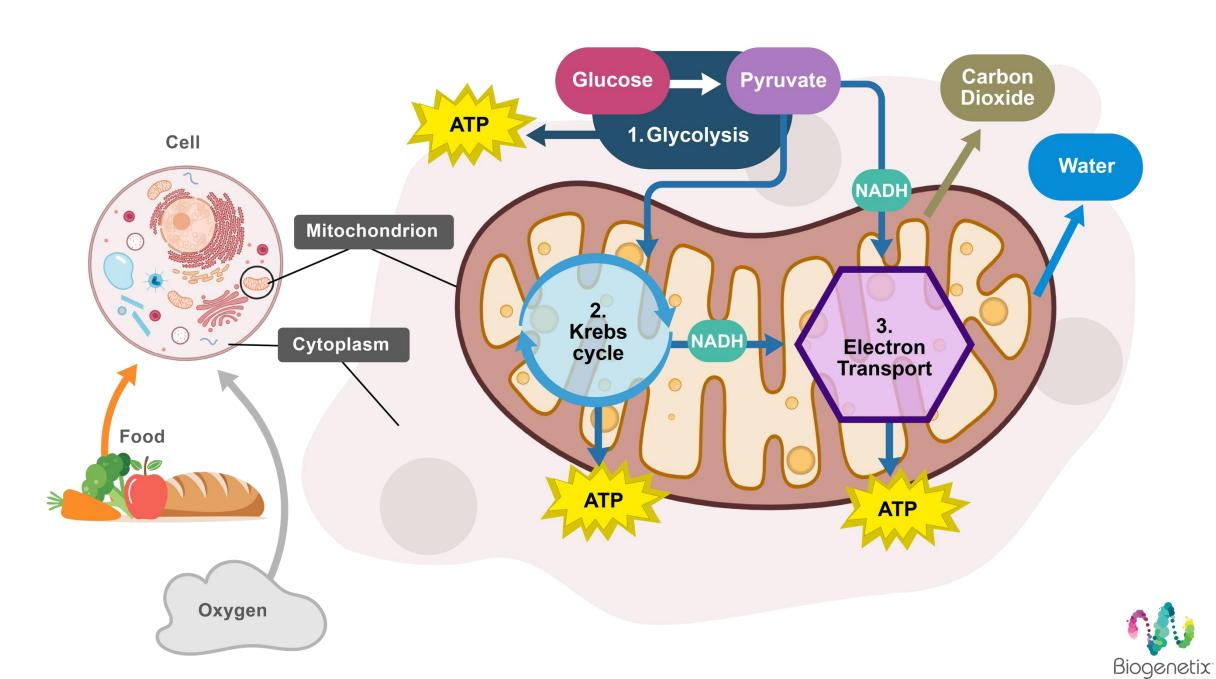




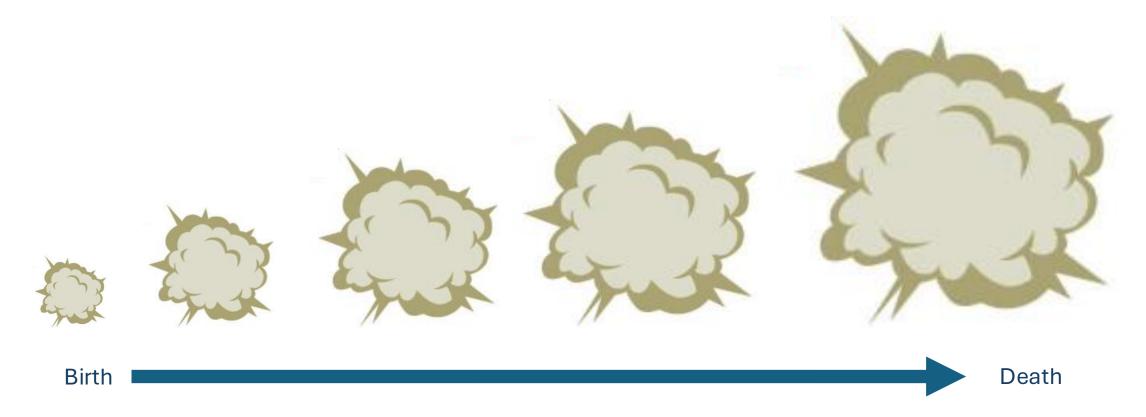
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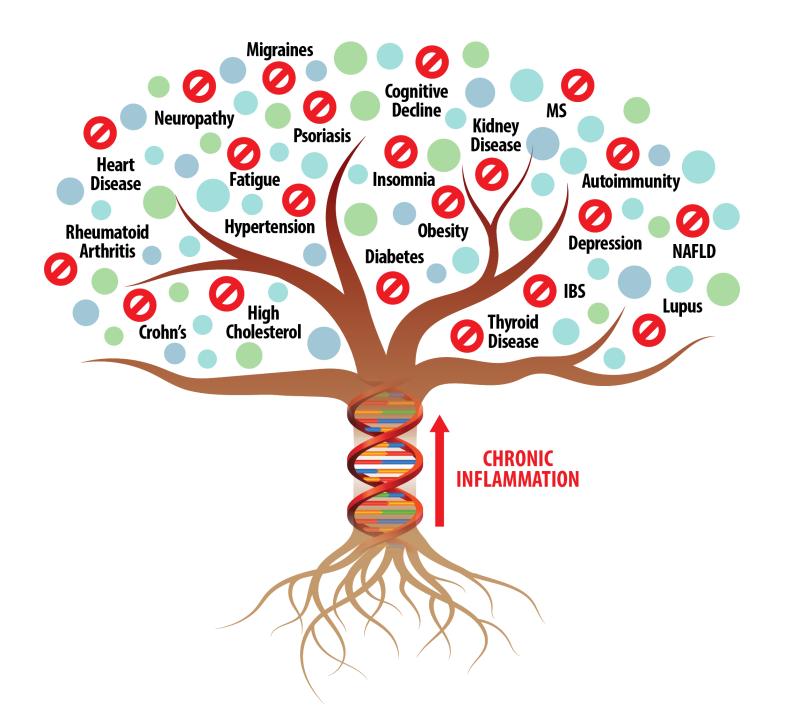




## The Antigenic Cloud









▶ HSS J. 2025 Jul 31:15563316251355551. Online ahead of print. doi: 10.1177/15563316251355551 ☑

## Emerging Use of BPC-157 in Orthopaedic Sports Medicine: A Systematic Review

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Nikhil Vasireddi <sup>1,8</sup>, Henrik Hahamyan <sup>2</sup>, Michael J Salata <sup>1,3</sup>, Michael Karns <sup>1,3</sup>, Jacob G Calcei <sup>1,3</sup>, James E Voos <sup>1,3</sup>, John M Apostolakos <sup>1,3</sup>
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PMCID: PMC12313605 PMID: 40756949



▶ HSS J. 2025 Jul 31:15563316251355551. Online ahead of print. doi: 10.1177/15563316251355551 🗷

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> Eur J Endocrinol. 1998 Nov;139(5):552-61. doi: 10.1530/eje.0.1390552.

# Ipamorelin, the first selective growth hormone secretagogue

K Raun <sup>1</sup>, B S Hansen, N L Johansen, H Thøgersen, K Madsen, M Ankersen, P H Andersen

Affiliations + expand

PMID: 9849822 DOI: 10.1530/eje.0.1390552



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### Ipamorelin, the first selective growth hormone

#### COCTATAGOGIA

▶ Aging Pathobiol Ther. Author manuscript; available in PMC: 2022 Jan 25.

Published in final edited form as: Aging Pathobiol Ther. 2020 Mar 27;2(1):58−61. doi: 10.31491/apt.2020.03.014 ☑

#### The potential of GHK as an anti-aging peptide

Yan Dou a, Amanda Lee a, Lida Zhu a, John Morton a, Warren Ladiges a,\*

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PMCID: PMC8789089 NIHMSID: NIHMS1754259 PMID: 35083444



▶ HSS J. 2025 Jul 31:15563316251355551. Online ahead of print. doi: 10.1177/15563316251355551 ☑

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EDITORIAL ▶ Clin Interv Aging. 2006 Dec;1(4):307–308. doi: 10.2147/ciia.2006.1.4.307 ☑

## Sermorelin: A better approach to management of adult-onset growth hormone insufficiency?

Richard F Walker 1

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PMCID: PMC2699646 PMID: 18046908

