From Hunger to Harmony

Neuroendocrine Pathways and Therapeutic Strategies in Metabolic Disorders Associated with Hyperphagia

By Henry DiPaolo, PharmD, MBA

Mentors: Jenny Lacina, PharmD & Frances Youschak, PharmD

Disclosure

- Neither I, nor the planning committee/peer reviewer, have any relevant financial relationships with ineligible companies to disclose in relation to this activity

Objectives

- Recognize the journey and stigmatization faced by an individual with hyperphagia and obesity
- Describe the neuroendocrine mechanisms and potential disruptions in hunger, satiety, and energy homeostasis
- Evaluate current and emerging therapies targeting neuroendocrine pathways regulating hunger and satiety
- Highlight strategies for specialty pharmacists to manage complications of metabolic disorders associated with hyperphagia

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Patient Journey

- Patient Journey found at... Patients - Rhythm Pharmaceuticals

Rhythm Pharmaceuticals. Patients. Rhythm Pharmaceuticals website. https://rhythmtx.com/patients/. Accessed January 16, 2026

What is Hyperphagia?

Hyperphagia is defined as insatiable hunger

- Shortened duration or failure of satiety following food intake
- Marked preoccupation with food and abnormal food-seeking

Key neuroendocrine pathways centrally regulate energy balance and food intake through the hypothalamus

- Genetic disorders or acquired hypothalamic damage can disrupt signaling

Hyperphagia is a hallmark symptom of rare forms of obesity

- Around a dozen genetically defined forms of rare obesity (ex. Bardet Biedl Syndrome, POMC/LEPR deficiency, Prader Willi Syndrome, Alström Syndrome)

Heymsfield, S.B., Clément, K., Dubern, B. et al. Defining Hyperphagia for Improved Diagnosis and Management of MC4R Pathway–Associated Disease: A Roundtable Summary. Curr Obes Rep 14, 13 (2025). https://doi.org/10.1007/s13679-024-00601-z

General vs. Rare Forms of Obesity

General	Monogenic	Syndromic	Acquired
• Influenced by multiple factors • Age, lifestyle, environment • Onset at any age • Hyperphagia not present	• Single gene mutation • Onset at birth • Hyperphagia present	• Inherited phenotypic trait that is controlled by 2 or more genes • Onset at birth • Hyperphagia present	• Damage/tumor leading to neuroendocrine pathway disruption • Onset at time of trauma/injury • Hyperphagia present

Harrison's Principles of Internal Medicine, 22nd Edition, Chapter 413: Pathobiology of Obesity, Stephen O'Rahilly; I. Sadaf Farooqi

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Normal Homeostatic Regulation of Energy

Energy homeostasis is a key biological process that requires balancing energy intake (food) and energy expenditure (metabolism, activity)

Accomplished through neuroendocrine signaling pathways that either promote hunger or satiety

Coordination of these signals occurs within the hypothalamus

Goel M, Mittal A, Jain VR, et al. Integrative Functions of the Hypothalamus: Linking Cognition, Emotion and Physiology for Well-being and Adaptability. Ann Neurosci. 2025;32(2):128-142. doi:10.1177/09727531241255492

The Hypothalamus

A pea-sized neuroanatomical structure located deep within the brain

- Serves as a vital intermediary in connecting the nervous and endocrine systems

Acts like a “central hub” reading, interpreting, and directing bodily functions

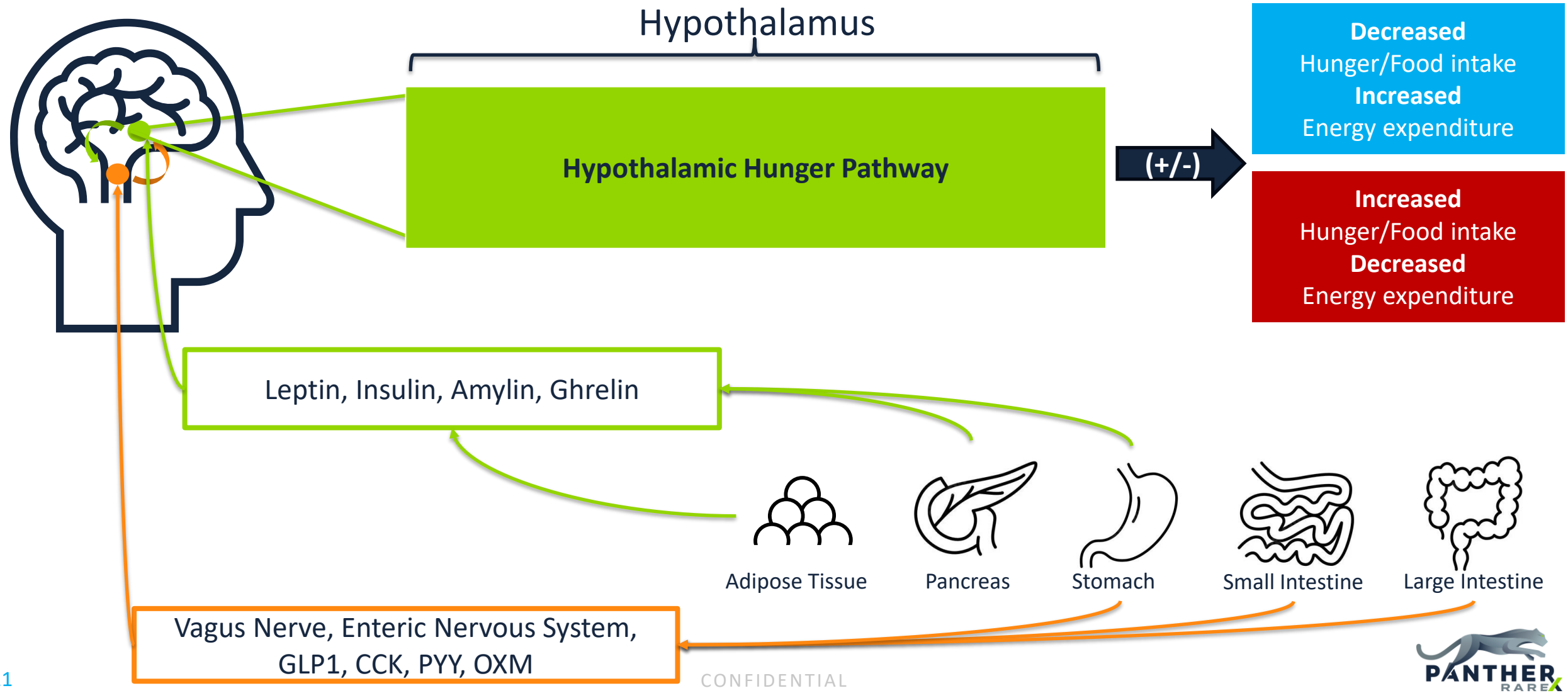
- Coordinates a large variety of physiological processes through the integration of signals from both internal body systems and the external environment

Shapes our instincts, decision-making, and overall behavior, including those relevant to the discussion of hunger, satiety, and metabolic energy expenditure

Goel M, Mittal A, Jain VR, et al. Integrative Functions of the Hypothalamus: Linking Cognition, Emotion and Physiology for Well-being and Adaptability. Ann Neurosci. 2025;32(2):128-142. doi:10.1177/09727531241255492

Hypothalamic Hunger Pathway

Diagram Legend:
- Hypothalamus
- Brainstem



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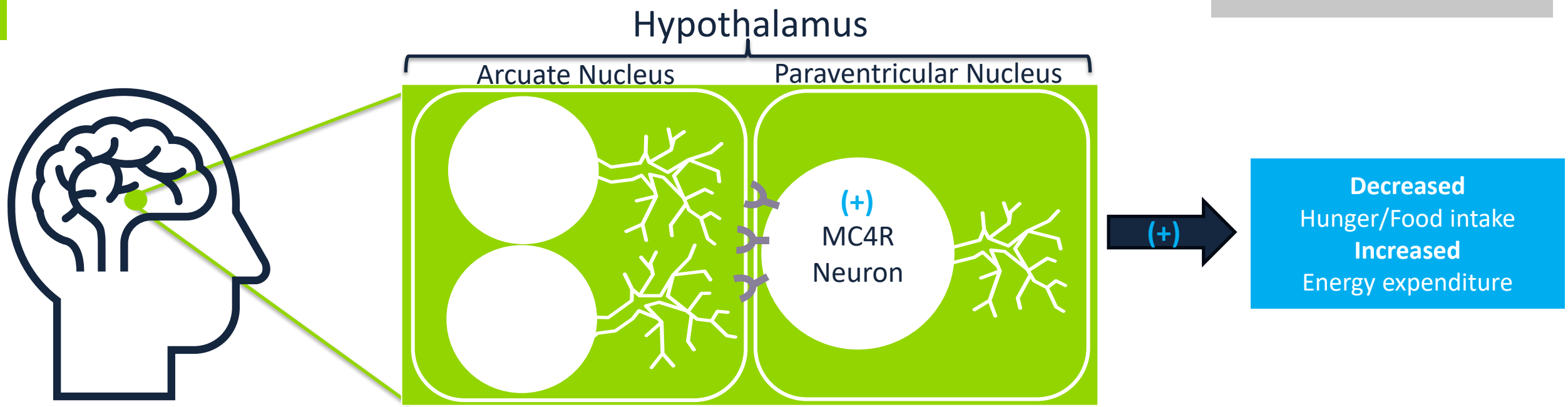
Hypothalamic Hunger Pathway



ARC & PVN Role: The arcuate nucleus (ARC) is the primary center for hunger and satiety with two opposing neurons, and the paraventricular nucleus (PVN) integrates input from ARC regulating energy balance.

MC4R Role: PVN neurons express melanocortin-4 receptors (MC4R) and activation leads to appetite suppression, increased satiety, and higher energy expenditure.

Overall Function: This signaling network maintains energy homeostasis by balancing hunger cues with energy needs.

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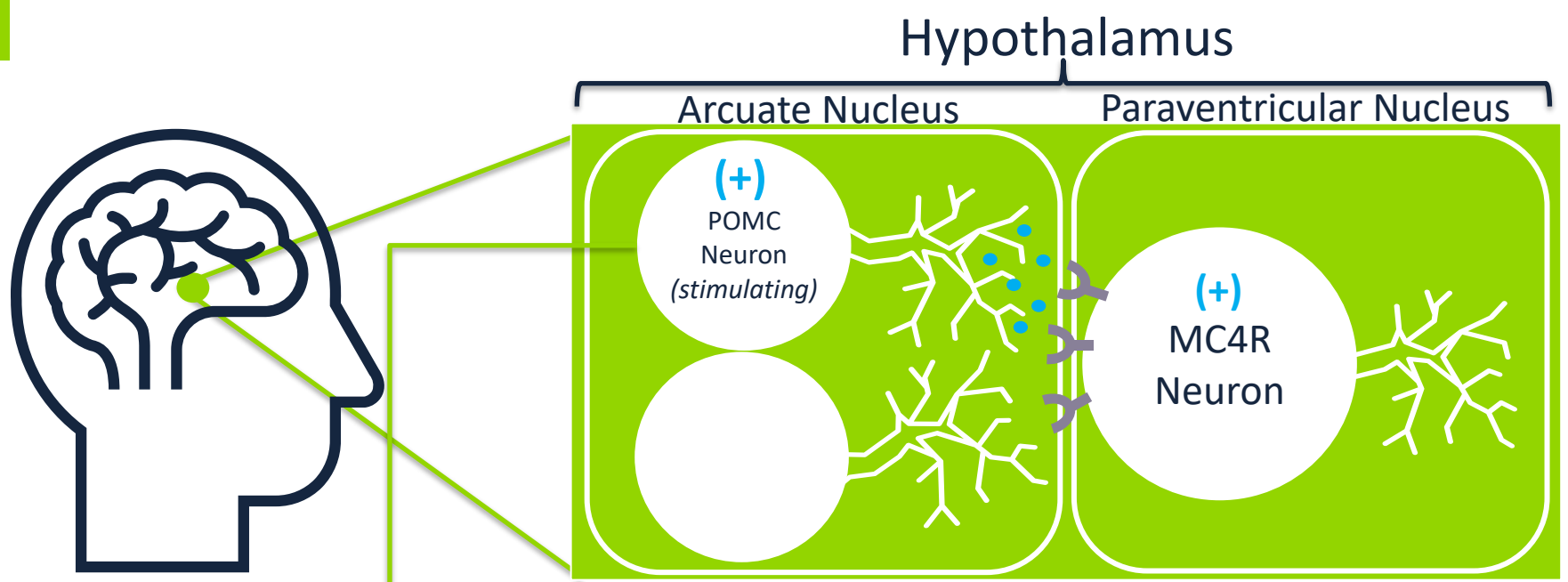
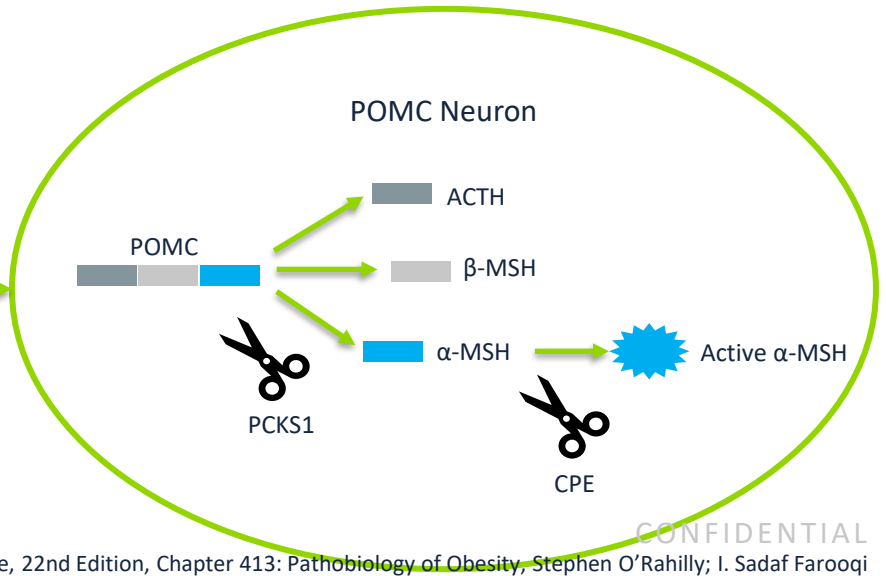
Hypothalamic Hunger Pathway Disruption

Diagram Legend:
Melanocortin 4 Receptor
α-MSH



Decreased
Hunger/Food intake
Increased
Energy expenditure



Satiety signaling in ARC is driven by proopiomelanocortin (POMC)

<u>Key role of α-MSH:</u>

- Primary agonist for MC4R neurons in PVN
- Activation → satiety, appetite suppression, ↑ energy expenditure

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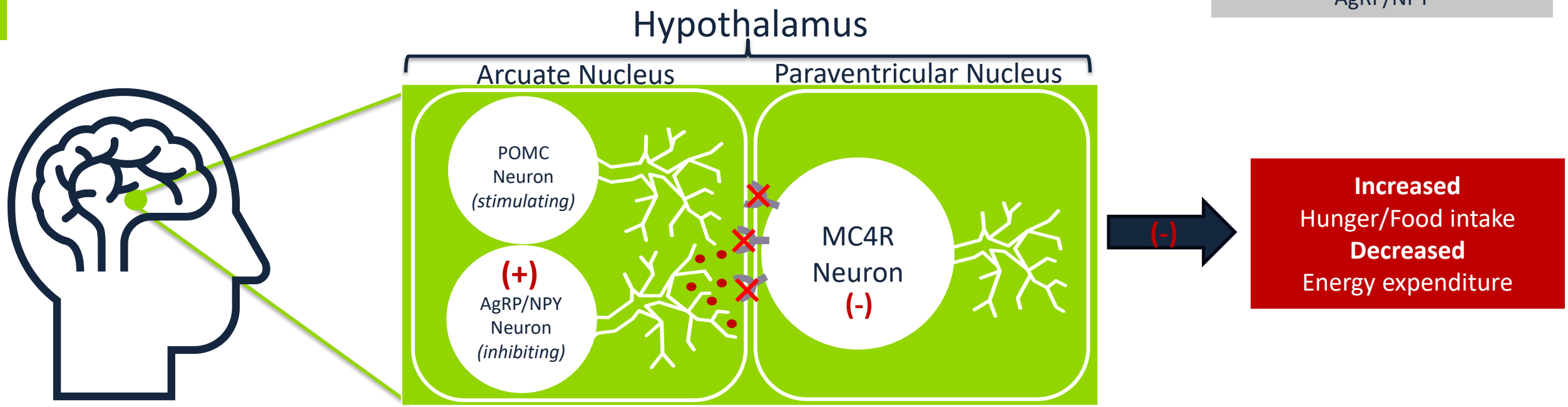
Hypothalamic Hunger Pathway



Satiety inhibition: Mediated by Agouti-related peptide (AgRP) and Neuropeptide Y (NPY)

Role: Promotes feeding behavior during energy deficit

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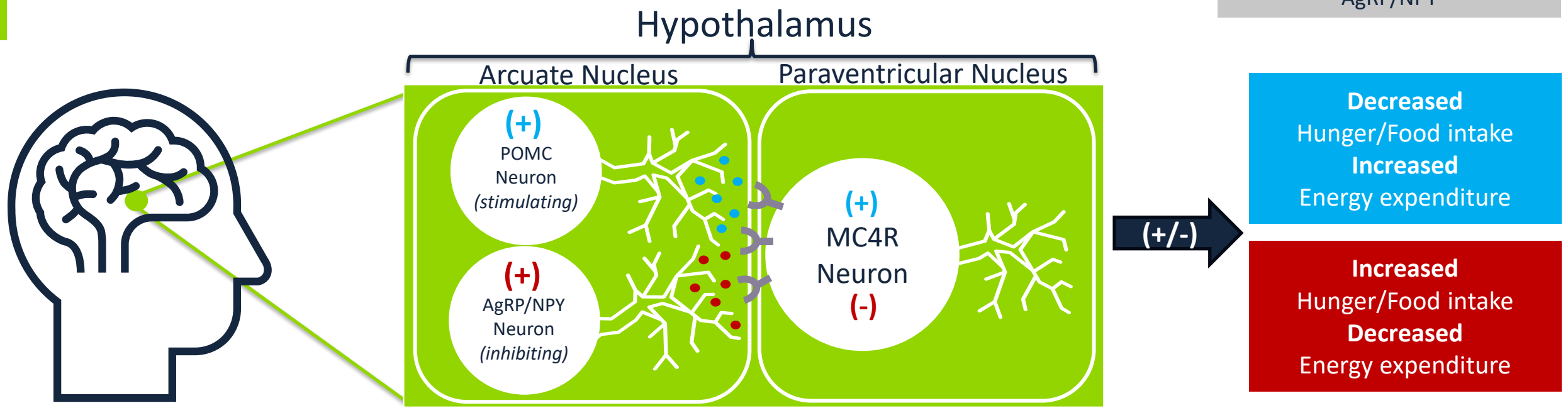
Hypothalamic Hunger Pathway



Balance of signals:

- Satiety via α-MSH activation vs hunger via AgRP/NPY inhibition
- Functions like a seesaw, shifting with energy needs, nutrients, hormones
- Disruptions in signaling cascade can result in an imbalance towards increased hunger and food intake
  - Key source behind metabolic disorders associated with hyperphagia

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Question #1

Which of the following is the key agonist released from POMC neurons in the arcuate nucleus stimulating MC4R neurons leading to satiety?

A. *AgRP*

B. *NPY*

C. *α-MSH*

D. *ACTH*

Question #1

Which of the following is the key agonist released from POMC neurons in the arcuate nucleus stimulating MC4R neurons leading to satiety?

~~*A. AgRP*~~

~~*B. NPY*~~

C. α-MSH

~~*D. ACTH*~~

α-MSH is the principal driver of satiety singling within the hypothalamic hunger pathway. It is derived from the cleavage of POMC by PCSK1, activated by CPE, and will stimulate MC4R neuron, leading to satiety.

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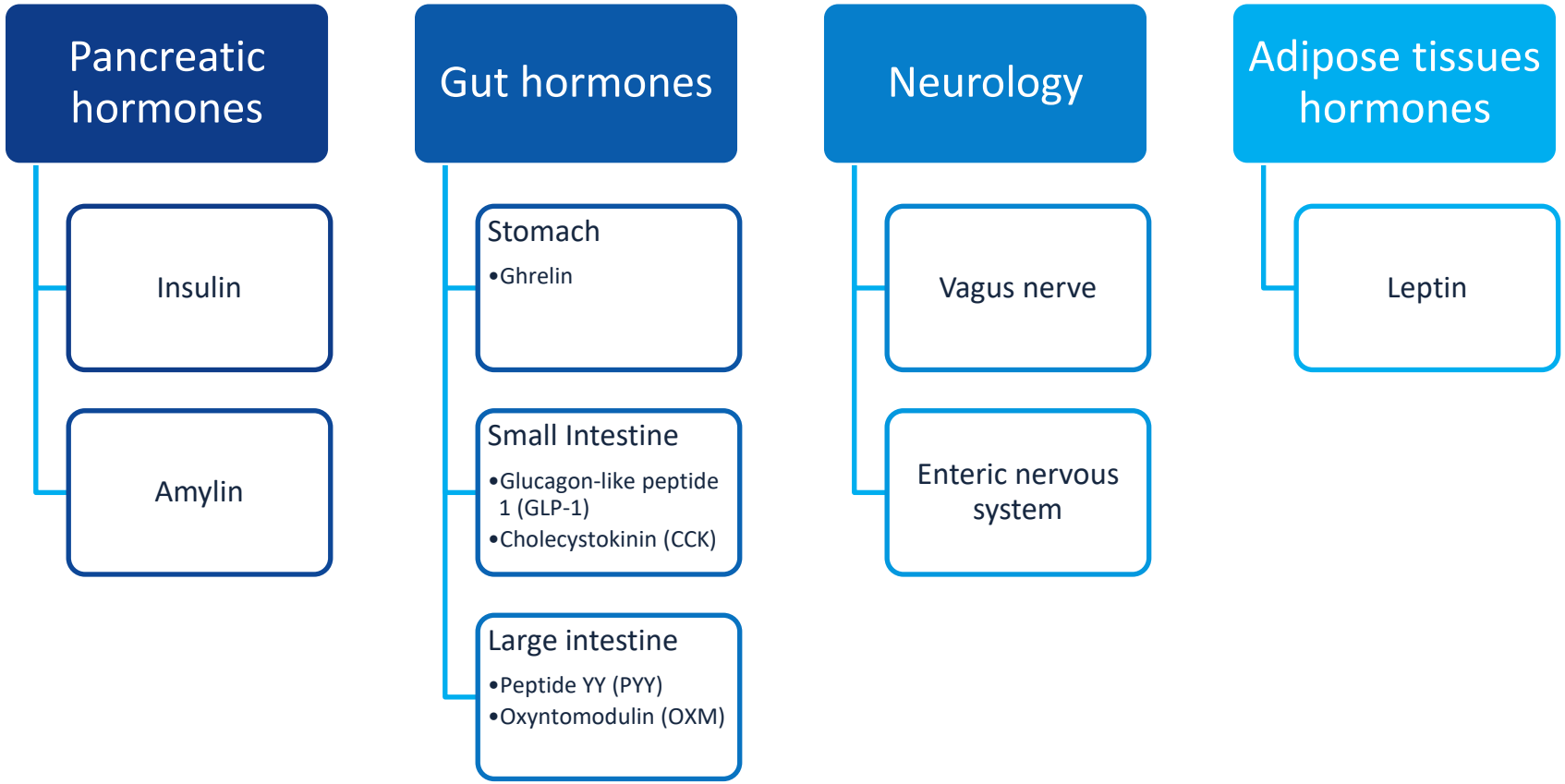
Signals Influencing the Melanocortin Pathway

The hypothalamus, via the melanocortin pathway, will coordinate hunger and energy expenditure through the integration of signals from internal body systems



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Short-Term Energy Homeostatic Regulation

Hormones and neural signals released from the pancreas, stomach, small intestine, and large intestine play a central role in short-term control of hunger and satiety

These signals reflect both the amount and type of food consumed and act on the hypothalamic hunger pathways

Together, they help fine-tune appetite, ensuring a steady supply of energy to the brain and other tissues throughout the day and between meals

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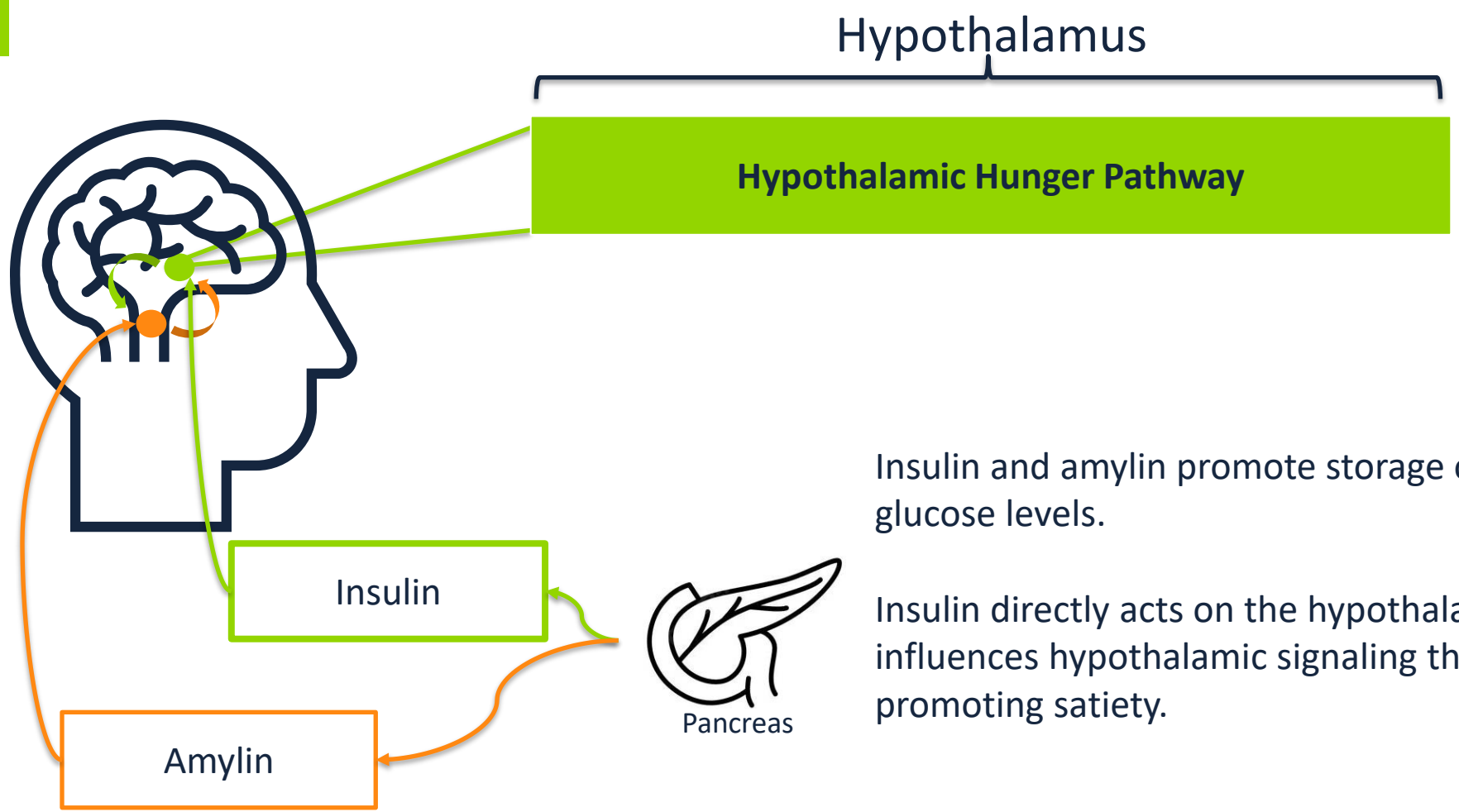
Pancreatic Hormones – Insulin and Amylin

Diagram Legend:
- Hypothalamus
- Brainstem



Insulin and amylin promote storage of energy and balancing blood glucose levels.

Insulin directly acts on the hypothalamus and amylin indirectly influences hypothalamic signaling through the brainstem, both promoting satiety.

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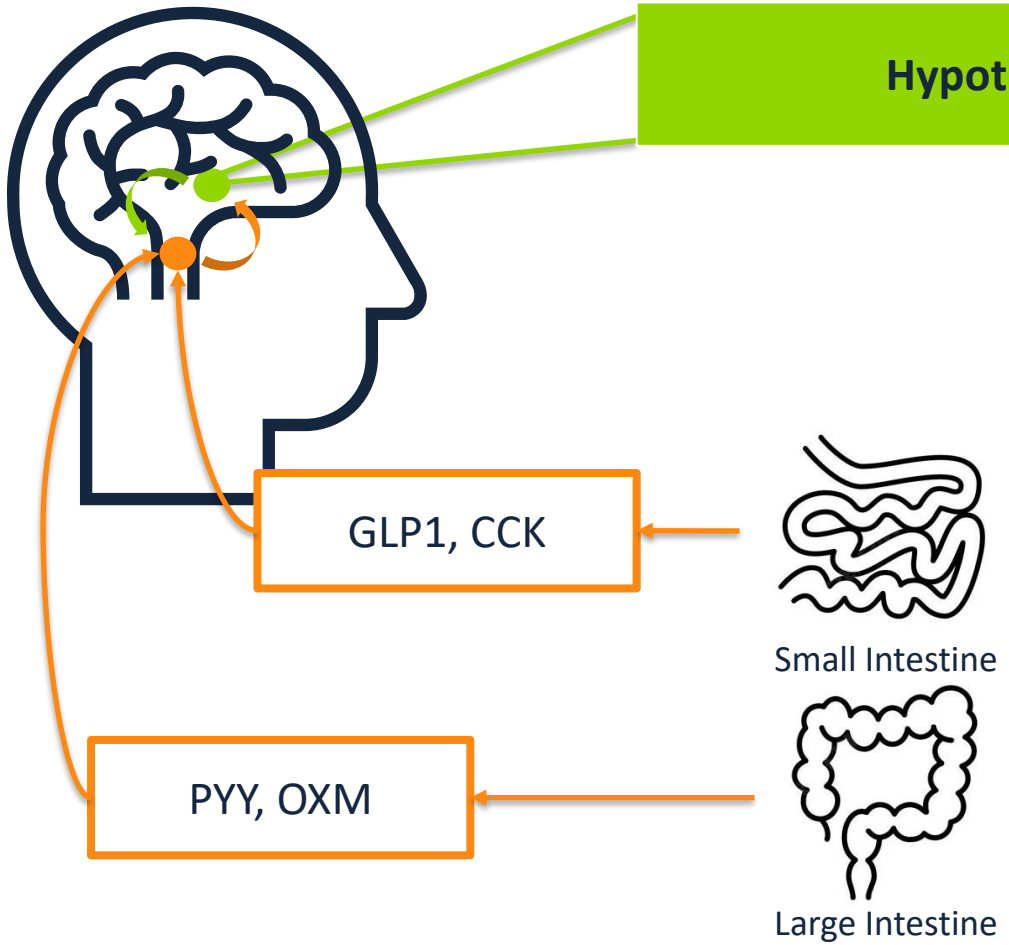
Gut Hormones – GLP1, CCK, PPY, OXM

Diagram Legend:
- Hypothalamus
- Brainstem

Hypothalamus



GLP1 and CCK are both hormones secreted by the small intestine, and PYY and OXM are both hormones secreted by the large intestine in response to meals.

GLP1, CCK, PYY, and OXM all have unique functions, but similarly they all act on the hypothalamus via projections from the brainstem, contributing to satiety.

Cholecystokinin (CCK)
Glucagon-like peptide 1 (GLP-1)
Peptide YY (PYY)
Oxyntomodulin (OXM)

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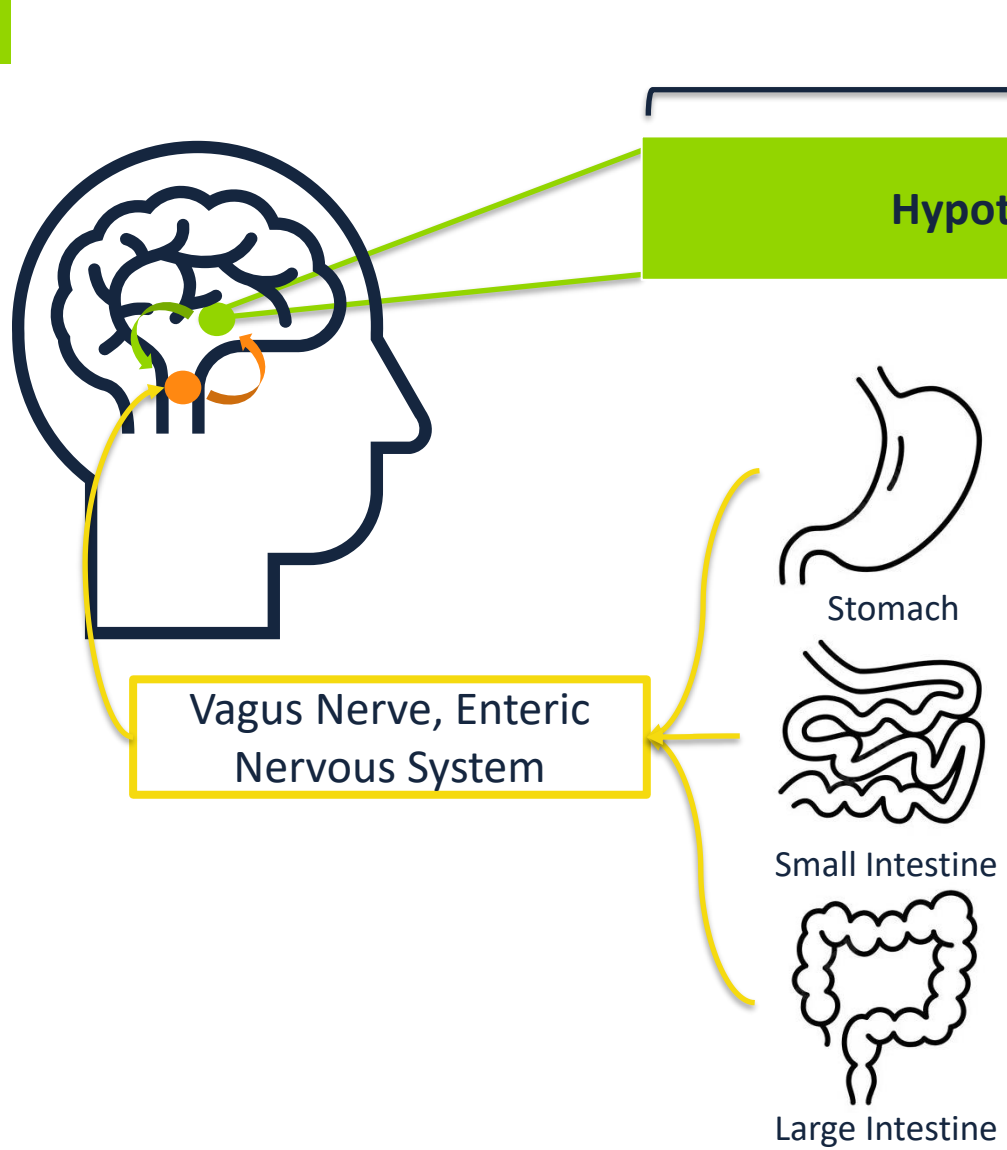
Vagus Nerve and Enteric Nervous System

Diagram Legend:
- Hypothalamus
- Brainstem



The vagus nerve and enteric nervous system detect nutrients, gut-hormone release (GLP-1, CCK, PYY, OXM), and mechanical stretch in the stomach and intestines, and relay this information to the hypothalamus via brainstem pathways, contributing to satiety.

Cholecystokinin (CCK)
Glucagon-like peptide 1 (GLP-1)
Peptide YY (PYY)
Oxyntomodulin (OXM)

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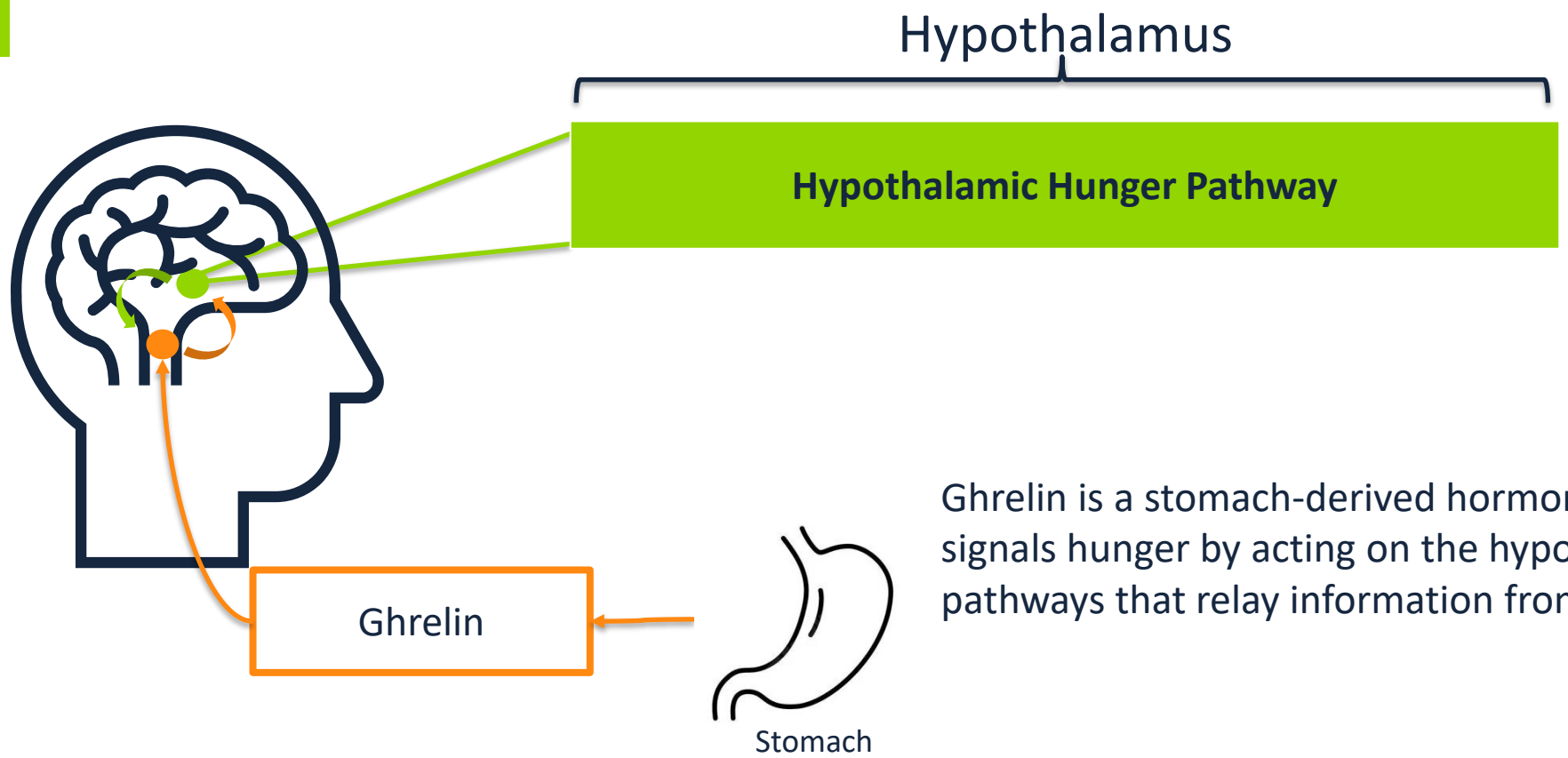
Gut Hormones - Ghrelin

Diagram Legend:
- Hypothalamus
- Brainstem



Ghrelin is a stomach-derived hormone that rises during fasting and signals hunger by acting on the hypothalamus through neural pathways that relay information from the brainstem.

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Long-Term Energy Homeostatic Regulation

Adipocytes, or fat cells, serve as the body's primary long-term energy reservoir, efficiently storing excess calories in the form of triglycerides

- Body relies on adipose tissue when glycogen stores are limited
- Specialized unilocular fat droplets enable flexible storage and release of energy, acting as the true "professionals" of fat storage
- Adipocytes also act as endocrine cells secreting leptin, signaling long-term energy status to the hypothalamus, which helps regulate appetite and energy expenditure

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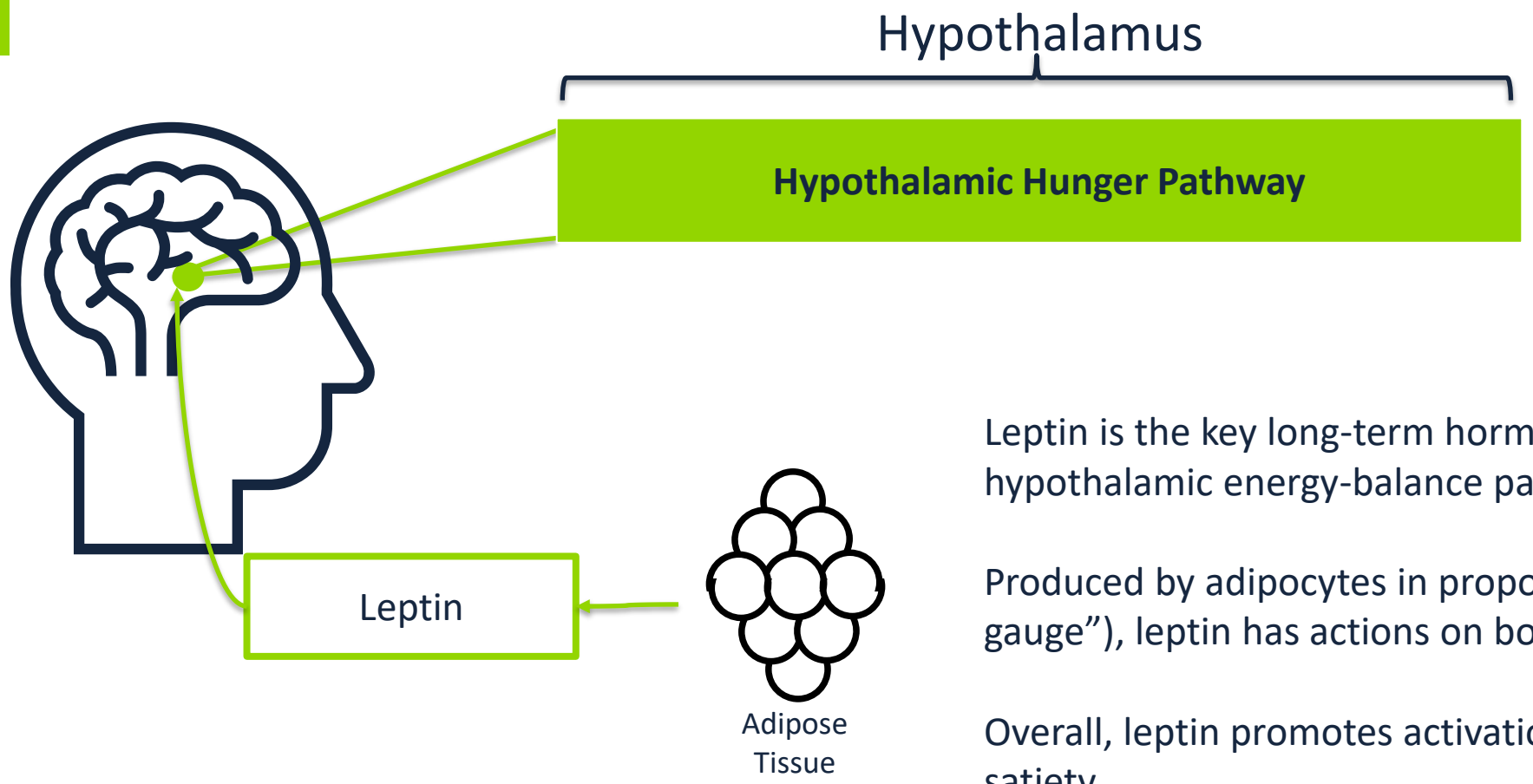
Adipose Tissue Hormone – Leptin

Diagram Legend
Hypothalamus



Leptin is the key long-term hormonal signal regulating the hypothalamic energy-balance pathway

Produced by adipocytes in proportion to total fat mass (“fuel gauge”), leptin has actions on both POMC and AgRP neurons

Overall, leptin promotes activation of MC4R-neurons, promoting satiety.

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Disruptions in the Hypothalamic Hunger Pathway

The following are rare forms of obesity that disrupt of the hypothalamic hunger pathway

Acquired	Monogenic	Syndromic
• Hypothalamic damage/tumor	• MC4R Deficiency • POMC Deficiency • PCSK1 Deficiency • CPE Deficiency • Leptin/LEPR Deficiency	• Bardet Biedl Syndrome • Alström Syndrome • Prader Willi Syndrome

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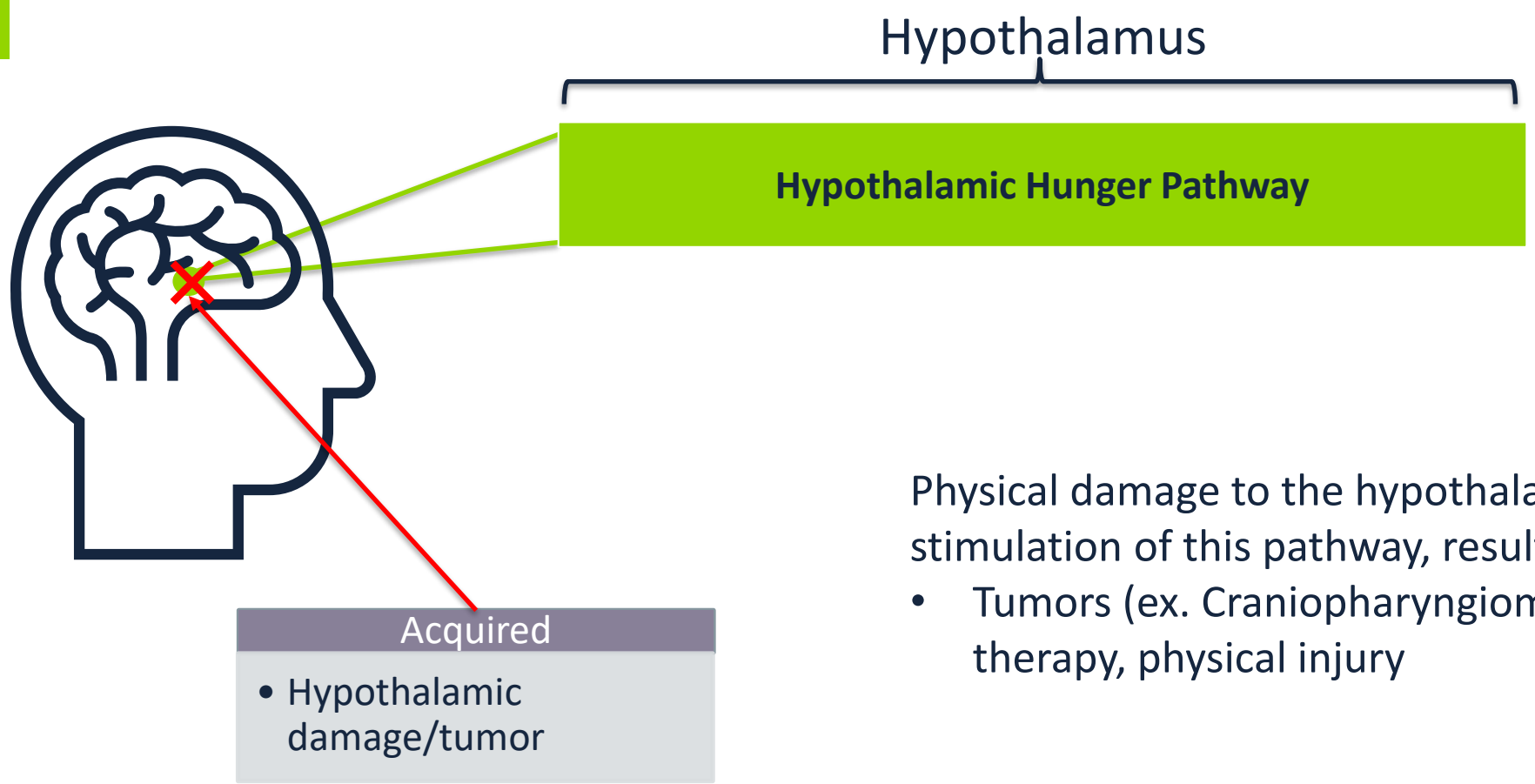
Acquired Hypothalamic Damage

Diagram Legend:
Melanocortin 4 Receptor



Physical damage to the hypothalamus can prevent the stimulation of this pathway, resulting in **hyperphagia**

- Tumors (ex. Craniopharyngioma), brain surgery, radiation therapy, physical injury

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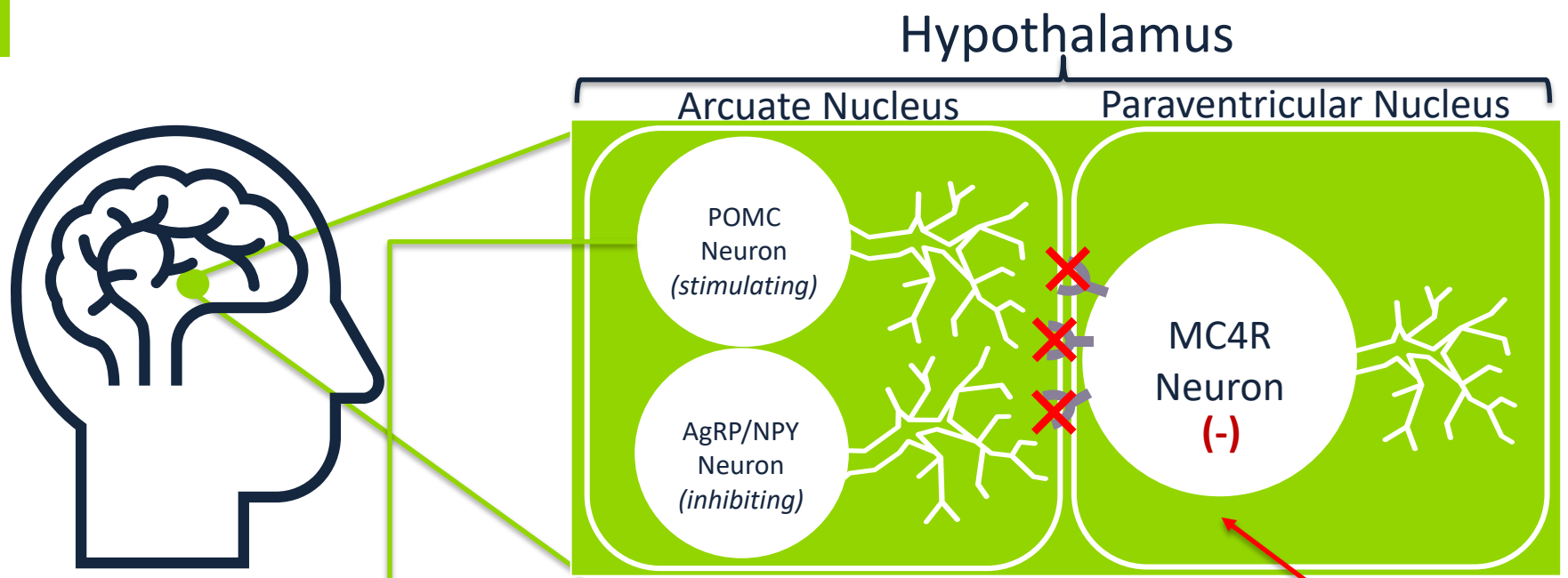
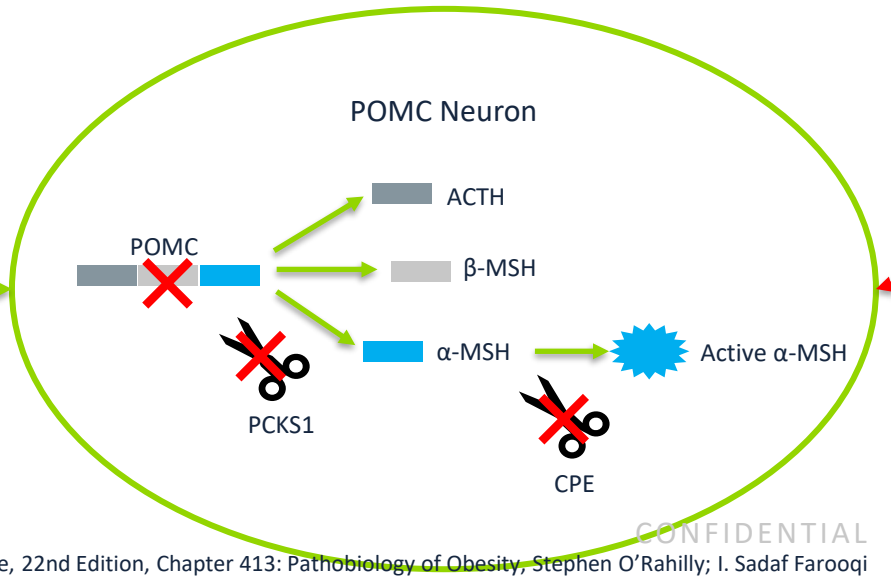
Select Monogenic Deficiencies

Diagram Legend:
Melanocortin 4 Receptor





Monogenic

- MC4R Deficiency
- POMC Deficiency
- PCSK1 Deficiency
- CPE Deficiency

Each of these monogenic deficiencies will lead to disruption of the hypothalamic pathway resulting in **hyperphagia**

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Syndromic Obesity and Melanocortin Disruption

Syndrome	Primary Genetic Defect	Mechanism Affecting Hypothalamic Pathway
Bardet Biedl Syndrome (BBS)	Mutation in BBS genes (ciliopathy)	Disrupts cilia on hypothalamic neurons required for LEPR trafficking and localization
Alström Syndrome	ALMS1 mutation (ciliopathy)	Disrupts cilia on hypothalamic neurons required for LEPR trafficking and localization
Prader-Willi Syndrome (PWS)	Loss of the paternal 15q11q13 chromosome region	Impairs LEPR trafficking and stability, blunting leptin signaling

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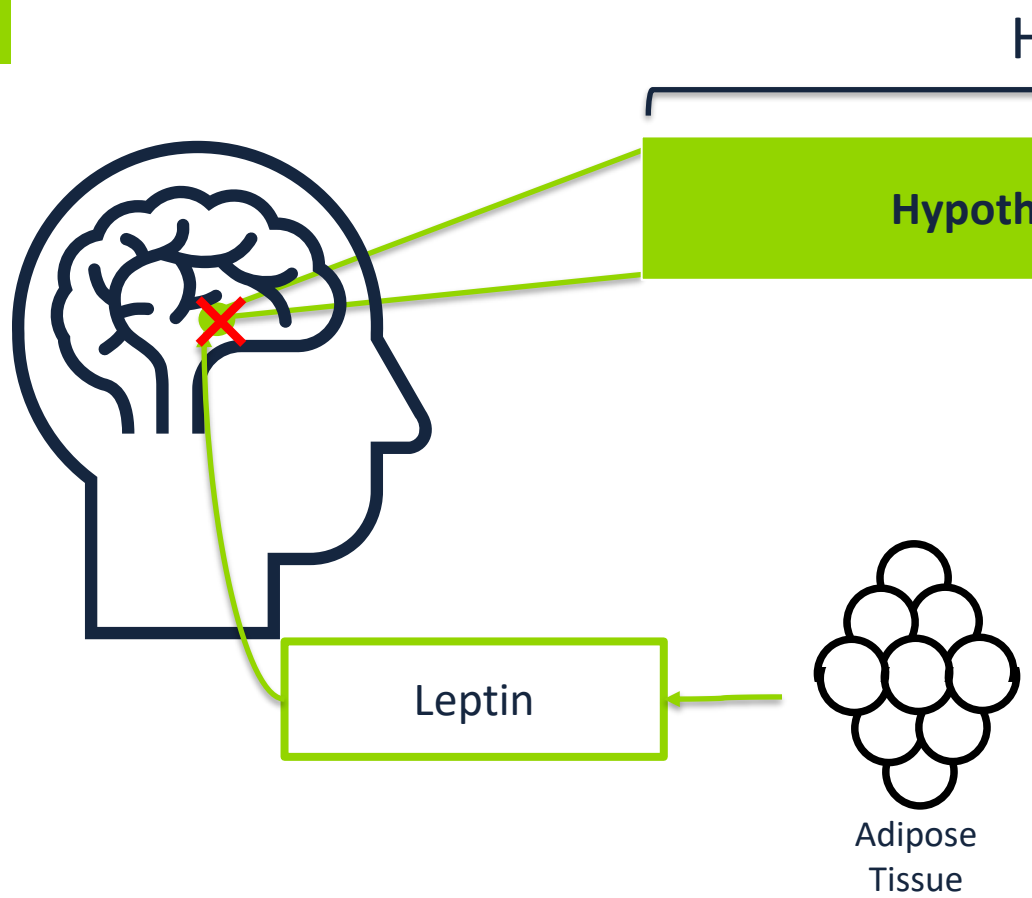
Adipose Tissue Hormone – Leptin

Diagram Legend
- Hypothalamus



Syndromic

- Bardet Biedl Syndrome
- Alström Syndrome
- Prader Willi Syndrome

Each of these syndromic deficiencies result in the disruption of LEPR signaling, and will lead to disruption of the hypothalamic pathway resulting in **hyperphagia**

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Question #2

Which statement best describes the primary role of leptin in energy homeostasis?

A. *It stimulates hunger by activating AgRP/NPY neurons*
B. *It signals long-term energy stores and promotes satiety*
C. *It increases gastric emptying to enhance food intake*
D. *It is released from the stomach during fasting to trigger hunger*

Question #2

Which statement best describes the primary role of leptin in energy homeostasis?

~~A. It stimulates hunger by activating AgRP/NPY neurons~~

B. It signals long-term energy stores and promotes satiety

~~C. It increases gastric emptying to enhance food intake~~

~~D. It is released from the stomach during fasting to trigger hunger~~

Leptin is a hormone produced by adipocytes in proportion to total fat mass. Its primary role is to communicate long-term energy availability to the hypothalamus. When leptin levels are adequate, it activates POMC neurons and suppresses AgRP/NPY neurons, shifting the hypothalamic hunger pathway toward satiety and reduced food intake.

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General Obesity Medications

GLP-1 Receptor Agonists

- Semaglutide – Indicated for chronic weight management in adults and adolescents ≥12 years with obesity or overweight with ≥1 weight-related comorbidities
- Liraglutide – Indicated for chronic weight management in adults and adolescents ≥12 years with obesity or overweight with ≥1 weight-related comorbidities

Dual GLP-1/GIP Receptor Agonist

- Tirzepatide – Chronic weight management in adults with obesity or overweight with ≥1 comorbidity

Triple GLP-1/GIP/Glucagon Receptor Agonist

- Retatrutide – Multiple Phase 3 trials to be completed in 2026

IPD Analytics. Clinical Pipeline. Accessed January 7, 2026. https://clinical-pipeline.ipdanalytics.com/

Summary of Current Rare Obesity Therapies

Setmelanotide and Diazoxide Choline Extended Release (DCCR)

Setmelanotide and Diazoxide Choline Extended Release (DCCR) are the only FDA-approved therapies specifically targeting rare forms of obesity

Both agents represent novel approaches addressing underlying biological mechanisms

Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. Pediatrics. 2023;151(2):e2022060640. doi:10.1542/peds.2022-060640

Setmelanotide

Mechanism of Action

- Melanocortin-4 Receptor (MC4R) agonist

Indication

- To reduce excess body weight and maintain weight reduction long term in adults and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to: Bardet-Biedl syndrome (BBS), Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency

Administration

- Once daily subcutaneous injection

Dose

- Based on age, tolerability, and renal impairment

Common adverse reactions

- Injection site reaction, skin hyperpigmentation, nausea, diarrhea, depression

Rhythm Pharmaceuticals, Inc. IMCIVREE (setmelanotide) injection, for subcutaneous use: Prescribing Information. Boston, MA: Rhythm Pharmaceuticals, Inc.; Revised 2024.

Diazoxide Choline Extended-Release

Mechanism of Action

- ATP-sensitive potassium (KATP) channel activator exact mechanism in treating hyperphagia is unknown

Indication

- Treatment of hyperphagia in adults and pediatric patients 4 years and older with Prader-Willi syndrome

Administration

- Oral extended-release tablet

Dose

- Based on weight and clinical response; typically, once or twice daily

Common adverse reactions

- Hypertrichosis, edema, hyperglycemia

Soleno Therapeutics, Inc. Diazoxide Choline Extended Release (DCCR): Prescribing Information. Redwood City, CA: Soleno Therapeutics, Inc.; Revised 2025.

Acquired Hypothalamic Obesity Emerging Therapies

Acquired Hypothalamic Obesity

- Novel Agents
  - Bivamelagon - MC4R agonist, oral once daily, Phase 3 start 2026, PDUFA 2028+
  - RM-718 - MC4R agonist, subcutaneous weekly, Phase 3 start 2027+, PDUFA 2029+
- Expanded Indication
  - Setmelanotide has PDUFA 3/20/26

IPD Analytics. Clinical Pipeline. Accessed January 7, 2026. https://clinical-pipeline.ipdanalytics.com/

Monogenic Obesity Emerging Therapies

Monogenic Obesity

- Expanded Indication
  - Setmelanotide has further Phase 3 multi-gene data expected in Q1 of 2026 in other monogenic genes such as heterozygous POMC, PCSK1, LEPR, SH2B1, etc.

IPD Analytics. Clinical Pipeline. Accessed January 7, 2026. https://clinical-pipeline.ipdanalytics.com/

Syndromic Obesity Emerging Therapies

Bardet Biedl Syndrome

None

Alström Syndrome

- None

Prader-Willi Syndrome - Hyperphagia Indication

- ARD-101 - TAS2R agonist, Phase 3 data expected Q3 2026, PDUFA 2027
- TNX-2900 - intranasal oxytocin, Phase 2
- PBF-999 - PDE10/A2a inhibitor, Phase 3 start 2026, PDUFA 2029+

Prader-Willi Syndrome - Weight Loss Indication

- Setmelanotide – Phase 3 to start in 2026, PDUFA 2029+

Prader Willi Syndrome - Hyperphagia, Weight Loss, and Neuropsychiatric Symptoms

- BMB-101 - 5-HT2c agonist, oral twice daily, Phase 2

IPD Analytics. Clinical Pipeline. Accessed January 7, 2026. https://clinical-pipeline.ipdanalytics.com/

Summary of Rare Obesity Therapies

FDA Approved Therapies	Emerging Therapies
Setmelanotide	Bivamelagon
Diazoxide Choline Extended-Release	RM-718
	ARD-101
	TNX-2900
	PBF-999
	BMB-101

IPD Analytics. Clinical Pipeline. Accessed January 7, 2026. https://clinical-pipeline.ipdanalytics.com/

Question #3

Which of the following is the correct mechanism of action of setmelanotide?

A. *Melanocortin-4 Receptor (MC4R) agonist*
B. *Leptin Receptor agonist*
C. *AgRP/NPY inhibitor*
D. *ATP-sensitive potassium (KATP) channel activator*

Question #3

Which of the following is the correct mechanism of action of setmelanotide?

A. *Melanocortin-4 Receptor (MC4R) agonist*

~~B. *Leptin Receptor agonist*~~

~~C. *AgRP/NPY inhibitor*~~

~~D. *ATP-sensitive potassium (KATP) channel activator*~~

Setmelanotide is an MC4R agonist, promoting satiety and increased energy expenditure in the hypothalamic hunger pathway

Harrison's Principles of Internal Medicine, 22nd Edition, Chapter 413: Pathobiology of Obesity, Stephen O'Rahilly; I. Sadaf Farooqi

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Impact of Obesity and Hyperphagia

Physical Impact

- Physical limitations, multiple comorbidities

Psychological Effects

- Emotional distress, mental health risks

Weight Stigma

- Healthcare bias, social discrimination, internalized stigma, and social limitations

Nadolsky K, Addison B, Agarwal M, et al. American Association of Clinical Endocrinology Consensus Statement: Addressing Stigma and Bias in the Diagnosis and Management of Patients with Obesity/Adiposity-Based Chronic Disease and Assessing Bias and Stigmatization as Determinants of Disease Severity. Endocr Pract. 2023;29(6):417-427. doi:10.1016/j.eprac.2023.03.272

The Caregiver Burden

Forsythe E, Mallya UG, Yang M, et al. Caregiver burden in Bardet-Biedl syndrome: findings from the CARE-BBS study. *Orphanet J Rare Dis*. 2023;18(1):181. Published 2023 Jul 7. doi:10.1186/s13023-023-02692-8

Goals of Hyperphagia Management

Reduce hyperphagia symptoms through approved therapies and lifestyle management

Manage disease specific comorbidities

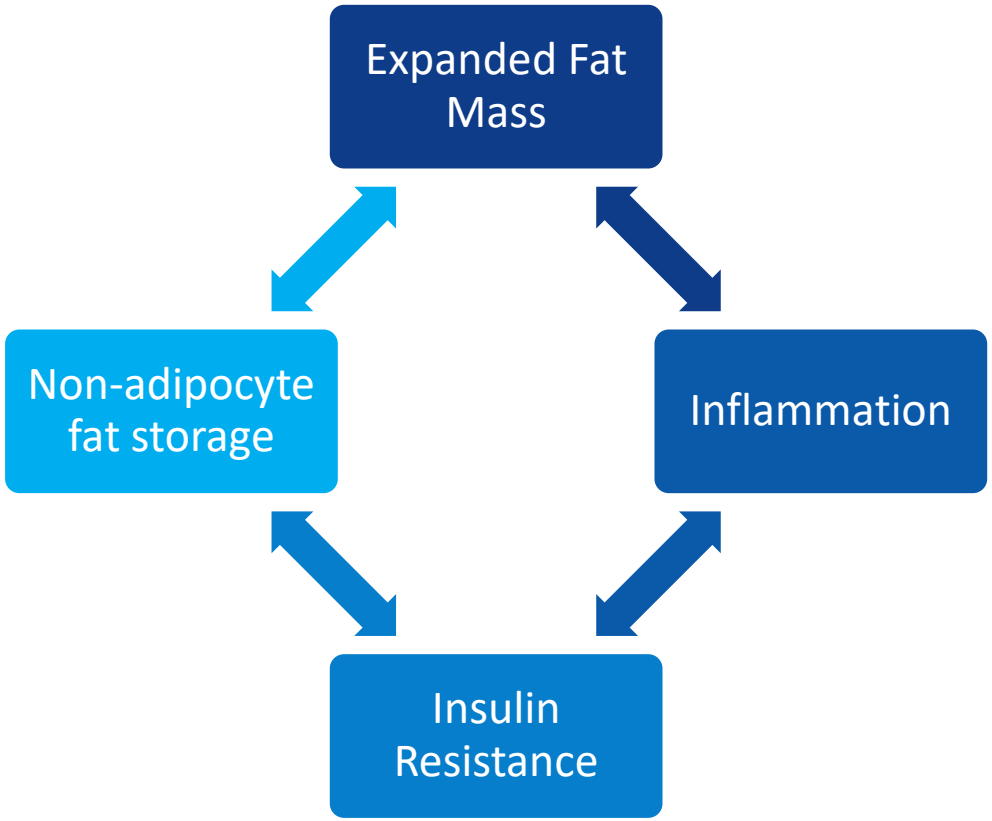
Maintain normal weight and BMI

Improve quality of life for individuals with hyperphagia and their caregivers

Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. Pediatrics. 2023;151(2):e2022060640. doi:10.1542/peds.2022-060640

General Overnutrition Complications

The principal mechanism behind complications of obesity are closely related to the chronic state of overnutrition



Complications

- Endocrine
- Dermatologic
- Cardiovascular
- Respiratory
- Gastrointestinal
- Central Nervous System
- Immune System
- Cancer

Harrison's Principles of Internal Medicine, 22nd Edition, Chapter 413: Pathobiology of Obesity, Stephen O'Rahilly; I. Sadaf Farooqi

Disease Specific Comorbidities Beyond Hyperphagia

Type of Rare From of Obesity	Key Comorbidities Beyond Hyperphagia
Acquired hypothalamic damage	Endocrine deficiencies, sleep disruption, temperature dysregulation, behavioral changes
MC4R Deficiency	Increased growth/bone density/lean mass, hyperinsulinemia
POMC Deficiency	Adrenal insufficiency, pale skin/red hair
PCSK1 Deficiency	Multiple pituitary hormone deficits, malabsorption/diarrhea, hypoglycemia
CPE Deficiency	Intellectual disability, infertility, glucose intolerance
Leptin/LEPR Deficiency	Immune dysfunction, delayed puberty, hypogonadism
Bardet-Biedl Syndrome	Vision loss, renal disease, polydactyly, developmental delay
Alström Syndrome	Vision/hearing loss, cardiomyopathy, insulin resistance, kidney/liver disease
Prader-Willi Syndrome	Hypotonia, short stature, hypogonadism, behavioral issues

These comorbidities highlight the complex management and need for a multidisciplinary approach

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Management Overview

Combination of nutritional, physical, and psychological intervention is recommended for every patient suffering from rare forms of obesity

Multi-Disciplinary Team	Physicians
	Pharmacists
	Dieticians
	Psychologists
	Adapted Physical Activity Teachers
Caregiver Support	Essential in creating and maintaining an environment of control
	Limit development of obesity and eating behavior disorders
	Maintain behaviors throughout life

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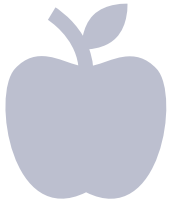
Routine Lifestyle Interventions

Presentations of hyperphagia varies between disease state and individuals



Nutrition

- Promote balanced and nutrient dense meals
- Establish structured eating routines
- Avoid overly sweet foods/drinks

Physical

- Aim for ≥60 minutes of moderate-to-vigorous activity daily (adapted for ability level)

Psychological

- Address psychological challenges such as depression, sleep disorders, emotional dysregulation, and cognitive dysfunction appropriately

Environment

- Provide support during life transition periods and social situations involving food
  - Ex. School, Holidays, Parties

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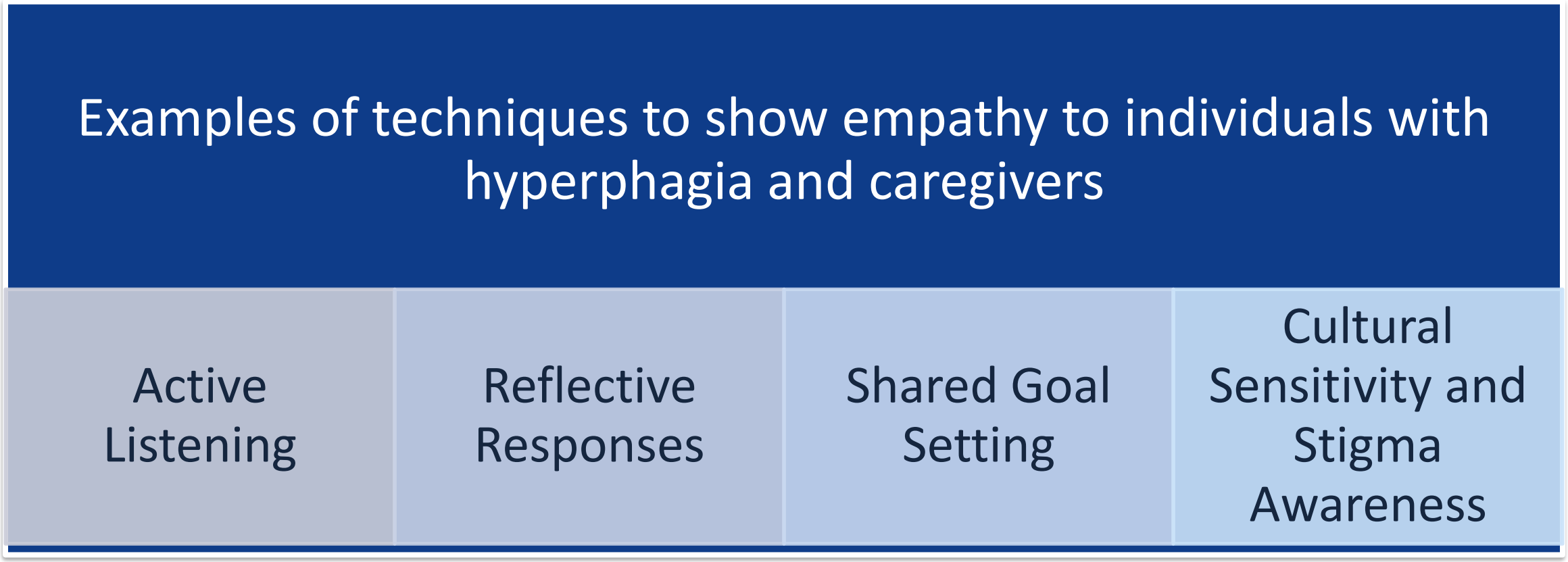
Pharmacist Soft Skills and Empathy

Soft skills are vitally important for showing empathy and providing high quality care for individuals with hyperphagia and their caregivers



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Resources to Learn More

Learn About Rare Genetic Obesity | Different Obesity

- Patient-specific, hyperphagia and hypothalamic pathway information

Different Obesity | HCP Site

- Clinician-specific, disease pathophysiology, tips for supporting patients with hyperphagia

Prader-Willi Syndrome Association USA - Supporting Families

- Patients, caregiver, and clinician information on hyperphagia and behavioral challenges in PWS

Question #4

Which of the following best reflects the role of the specialty pharmacist in managing individuals with rare forms of obesity and hyperphagia?

A. *Focusing primarily on calorie-restricted diet plans*
B. *Promoting access to targeted therapies, routine lifestyle interventions, and showing empathy to patients and caregivers*
C. *Managing only the physical aspects of hyperphagia*
D. *Recommending traditional obesity medications as first-line therapy for all patient*

Question #4

Which of the following best reflects the role of the specialty pharmacist in managing individuals with rare forms of obesity and hyperphagia?

~~*A. Focusing primarily on calorie-restricted diet plans*~~

B. Promoting access to targeted therapies and routine lifestyle interventions, while showing empathy to patients and caregivers

~~*C. Managing only the physical aspects of hyperphagia*~~

~~*D. Recommending traditional obesity medications as first-line therapy for all patient*~~

Conclusion

- Hyperphagia is complex a biologically driven condition, rooted in disruptions of the hypothalamic hunger pathway
- Comprehensive management is essential, combining pharmacotherapy, lifestyle support, and multidisciplinary care to address medical, psychological, and caregiver burdens
- Specialty pharmacists play a critical role in optimizing therapy, monitoring safety, and advocating for patients with rare obesity disorders

QUESTIONS

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