Gut Hormones and Metabolism

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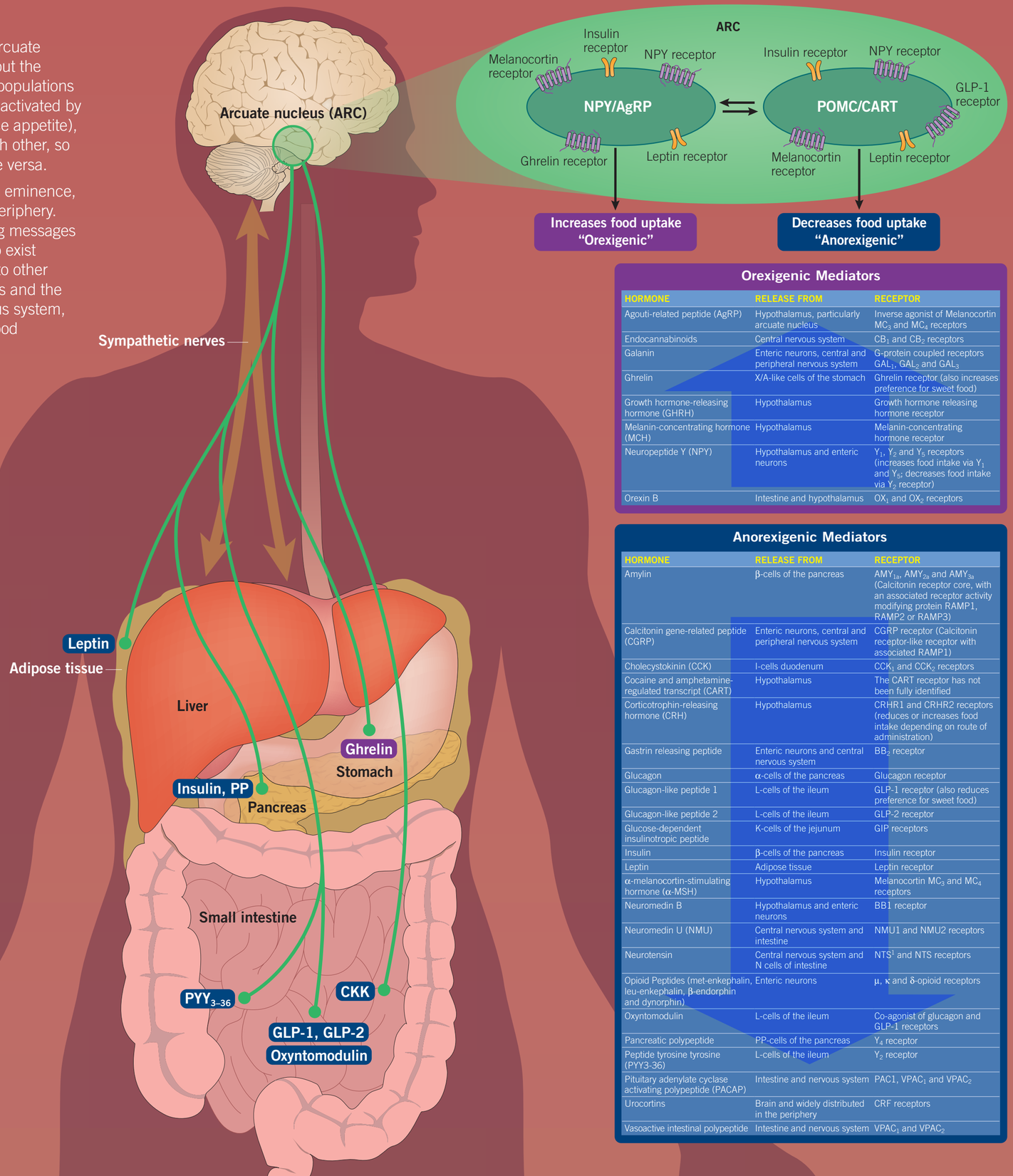
The gut is the largest endocrine organ in the body. More than 30 hormones are produced by the gastrointestinal tract, pancreas and fat, with many other related peptides produced in the brain. Many gut hormones are released by the direct action of ingested nutrients on enteroendocrine cells found within the intestine. These hormones act to control food intake and energy expenditure.

Gut-Brain Axis

The hypothalamus is the co-ordination center for energy homeostasis, and the arcuate nucleus (ARC) in the hypothalamus is the epicenter for integration of signals about the energy status and requirements of an individual. The ARC contains two distinct populations of neurons. NPY and AgRP neurons are orexigenic (stimulate appetite), and are activated by signals such as ghrelin, while CART and POMC neurons are anorexigenic (reduce appetite), and are stimulated by GLP-1 and PYY. These neurons reciprocally innervate each other, so activation of the CART/POMC neurons turns off the NPY/AGRP neurons and vice versa.

The ARC receives inputs from many different sources. It lies close to the median eminence, which lacks a blood brain barrier, allowing direct access to hormones from the periphery. The vagus nerve connects the gastrointestinal tract to the hypothalamus, relaying messages about gut hormones and gastrointestinal distension. Reciprocal connections also exist between the brain stem and the hypothalamus. The ARC then relays messages to other hypothalamic nuclei, such as the ventromedial nucleus, the dorsomedial nucleus and the lateral hypothalamic area. There is subsequent output to the sympathetic nervous system, the thyroid axis, the limbic system, and back to the vagus, which then control food intake and energy expenditure.



Gut Hormones and Obesity

In normal circumstances, co-ordination of the gut-brain axis ensures that an individual maintains their weight within a narrow range. However, persistent excessive food consumption can overcome the normal homeostatic mechanisms and lead to the development of obesity. Furthermore, once a person has become obese, their physiology changes to make weight loss even harder. In obese patients, there is a relative reduction in levels and efficacy of the satiety hormones PYY, PP, GLP-1 and CCK. There is also a resistance to the effects of leptin, and an increased sensitivity to ghrelin. These changes stop people feeling full and increase food consumption.

Hormone	Obesity	Weight loss
PYY	↓ post-prandial rise	↓
PP	↓/↑	↓/↑
GLP-1	↓ post-prandial rise	↓
CCK	↓/↑	↓
Leptin	Increased baseline levels but increased resistance to action	↓
Ghrelin	Reduced baseline levels and failure to suppress post-prandially	↑
Amylin	↑	↓

Unfortunately, when people diet, the body tries to defend against weight loss. The satiety hormones (such as PYY, CCK, leptin and amylin) fall, while the orexigenic NPY and ghrelin increase. Metabolic rate also slows. This makes it progressively harder to lose weight and maintain weight loss.

Gut Hormones Drug Therapies and Bariatric Surgery

Gut hormones can be used as a pharmacological therapy for obesity. Naturally-occurring gut hormones have very short half-lives in the body, which limit their use. However, long-lasting versions are being developed. Exendin-4 is a GLP-1 analog first discovered in the saliva of the Gila monster. It is resistant to the enzyme dipeptidyl peptidase IV, which breaks down GLP-1, and therefore has a prolonged half-life. The synthetic version, exenatide, is a common treatment for diabetes. Another long-acting GLP-1 analog, liraglutide, is available as a treatment for both diabetes and obesity. Stabilized analogs of both PYY and PP have been developed and have entered clinical trials as treatments for obesity. There is increasing evidence for targeting obesity with combinations of gut hormones. Chronic injections of oxyntomodulin, which activates both GLP-1 and glucagon receptors, reduce body weight in obese patients, and a number of oxyntomodulin analogs are in development as a treatment for obesity. Additionally, several drugs targeting both the GLP-1 and GIP pathways, and triple-agonists at the GLP-1, GIP and glucagon receptors, are being developed.

Bariatric surgery is now recognized as the most effective, lasting treatment for obesity. Surgery has two effects. Firstly, the size of the GI tract, particularly the stomach, is made smaller, so patients eat less. Secondly, the levels of gut hormones change, promoting a more anorexic environment. Roux-en-Y bypass is the most common form of bariatric surgery, and after this the post-prandial response is altered so that GLP-1, PPY, oxyntomodulin, glucagon and CCK all increase, while ghrelin and GIP levels fall. Gastrin levels also fall but are elevated by PPI treatment. There is no significant change in PP levels. The changes in gut hormones, particularly GLP-1, may be responsible for the improvement in diabetes seen after bariatric surgery independent of weight loss.

Orexigenic Mediators

HORMONE	RELEASE FROM	RECEPTOR
Agouti-related peptide (AgRP)	Hypothalamus, particularly arcuate nucleus	Inverse agonist of Melanocortin MC_3 and MC_4 receptors
Endocannabinoids	Central nervous system	CB_1 and CB_2 receptors
Galanin	Enteric neurons, central and peripheral nervous system	G-protein coupled receptors GAL_1, GAL_2 and GAL_3
Ghrelin	X/A-like cells of the stomach	Ghrelin receptor (also increases preference for sweet food)
Growth hormone-releasing hormone (GHRH)	Hypothalamus	Growth hormone releasing hormone receptor
Melanin-concentrating hormone (MCH)	Hypothalamus	Melanin-concentrating hormone receptor
Neuropeptide Y (NPY)	Hypothalamus and enteric neurons	Y_1, Y_2 and Y_5 receptors (increases food intake via Y_1 and Y_5; decreases food intake via Y_2 receptor)
Orexin B	Intestine and hypothalamus	OX_1 and OX_2 receptors

Anorexigenic Mediators

HORMONE	RELEASE FROM	RECEPTOR
Amylin	β-cells of the pancreas	AMY_{1a}, AMY_{2a} and AMY_{3a} (Calcitonin receptor core, with an associated receptor activity modifying protein RAMP1, RAMP2 or RAMP3)
Calcitonin gene-related peptide (CGRP)	Enteric neurons, central and peripheral nervous system	CGRP receptor (Calcitonin receptor-like receptor with associated RAMP1)
Cholecystokinin (CCK)	I-cells duodenum	CCK_1 and CCK_2 receptors
Cocaine and amphetamine-regulated transcript (CART)	Hypothalamus	The CART receptor has not been fully identified
Corticotrophin-releasing hormone (CRH)	Hypothalamus	CRHR1 and CRHR2 receptors (reduces or increases food intake depending on route of administration)
Gastrin releasing peptide	Enteric neurons and central nervous system	BB_2 receptor
Glucagon	α-cells of the pancreas	Glucagon receptor
Glucagon-like peptide 1	L-cells of the ileum	GLP-1 receptor (also reduces preference for sweet food)
Glucagon-like peptide 2	L-cells of the ileum	GLP-2 receptor
Glucose-dependent insulinotropic peptide	K-cells of the jejunum	GIP receptors
Insulin	β-cells of the pancreas	Insulin receptor
Leptin	Adipose tissue	Leptin receptor
α-melanocortin-stimulating hormone (α-MSH)	Hypothalamus	Melanocortin MC_3 and MC_4 receptors
Neuromedin B	Hypothalamus and enteric neurons	BB1 receptor
Neuromedin U (NMU)	Central nervous system and intestine	NMU1 and NMU2 receptors
Neurotensin	Central nervous system and N cells of intestine	NTS[1] and NTS receptors
Opioid Peptides (met-enkephalin, leu-enkephalin, β-endorphin and dynorphin)	Enteric neurons	μ, κ and δ-opioid receptors
Oxyntomodulin	L-cells of the ileum	Co-agonist of glucagon and GLP-1 receptors
Pancreatic polypeptide	PP-cells of the pancreas	Y_4 receptor
Peptide tyrosine tyrosine (PYY3-36)	L-cells of the ileum	Y_2 receptor
Pituitary adenylate cyclase activating polypeptide (PACAP)	Intestine and nervous system	PAC1, $VPAC_1$ and $VPAC_2$
Urocortins	Brain and widely distributed in the periphery	CRF receptors
Vasoactive intestinal polypeptide	Intestine and nervous system	$VPAC_1$ and $VPAC_2$

Products available from Tocris

AMPK
A 769662, AICAR, Dorsomorphin, Metformin, PF 06409577, SAMS Peptide

Bombesin Receptors
Bombesin, GRP (human), GRP (porcine), Neuromedin B (porcine), PD 176252

Calcitonin and Related Receptors
BIBN 4096, CGRP 8-37 (human), CGRP 8-37 (rat), α-CGRP (human)

Cannabinoid Receptor
AM 251, AM 281, AM 630, HU 308, JWH 133, SR 141716A

Cholecystokinin1 Receptor
A-71623, CCK Octapeptide, sulfated, CI 988, Devazepide, Gastrin I (human), YM 022

Galanin Receptors
Galanin (1-29) (rat, mouse), Galanin (1-30) (human), M 1145, M40, M617, M871

Ghrelin Receptors
[D-Lys[3]]-GHRP-6, Ghrelin (human), Ghrelin (rat), Tabimorelin, YIL 781

Glucagon Receptor
des-His[1]-[Glu9]-Glucagon (1-29) amide, L-168,049, Oxyntomodulin

Glucagon-Like Peptide Receptors
Exendin-3 (9-39) amide, Exendin-4, Glucagon-like peptide 1 (1-37) (human, rat), Glucagon-like peptide 1 (7-36) amide (human, rat)

Insulin and Insulin-like Receptors
6bK, BMS 536924, Insulin (human) recombinant, Mitoglitazone, NBI 31772, Picropodophyllotoxin

Leptin Receptors
LEP (116-130) (mouse)

Melanocortin Receptors
ACTH (1-39), Melanotan II, ML 00253764, SHU 9119

Motilin Receptors
ANQ 11125, Motilin (human, porcine)

mTOR
AZD 3147, eCF 309, PP 242, Rapamycin, Torin 1, Torin 2

Neuromedin U Receptors
Neuromedin S (rat), Neuromedin U (rat)

NPY Receptors
[Leu[31],Pro[34]]-Neuropeptide Y (human, rat), BIBO 3304, BIIE 0246, GW 438014A, Neuropeptide Y (human, rat), Peptide YY (3-36)

Opioid Receptors
(±)-U-50488, DAMGO, Naltrindole, *nor*-Binaltorphimine, SNC 80, β-Funaltrexamine

Orexin Receptor
[Ala[11],D-Leu[15]]-Orexin B, EMPA, Orexin A (human, rat, mouse), Orexin B (human), SB 334867, TCS OX2 29

Secretin Receptors
Secretin (human), Secretin (rat)

Somatostatin Receptors
Cyclosomatostatin, CYN 154806, L-803,087, Octreotide, Seglitide, Somatostatin

VIP Receptors
[D-p-Cl-Phe[6],Leu[17]]-VIP, Bay 55-9837, VIP (human, rat, mouse, rabbit, canine, porcine)

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