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Feature Review

Old Paradoxes and New Opportunities for Appetite Control in Obesity

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Human obesity is accompanied by alterations in the blood concentrations of multiple circulating appetite regulators. Paradoxically, most of the appetite-inhibitory hormones are elevated in nonsyndromic obesity, while most of the appetite stimulatory hormones are reduced, perhaps reflecting vain attempts of regulation by inefficient feedback circuitries. In this context, it is important to understand which appetite regulators exhibit a convergent rather than paradoxical behavior and hence are likely to contribute to the maintenance of the obese state. Pharmacological interventions in obesity should preferentially consist of the supplementation of deficient appetite inhibitors or the neutralization of excessive appetite stimulators. Here, we critically analyze the current literature on appetite-regulatory peptide hormones. We propose a short-list of appetite modulators that may constitute the best candidates for therapeutic interventions.

Introduction

Obesity is the most prevalent pathological condition of the 21st century. In itself a disease, obesity predisposes to other pathologies, including metabolic syndrome, diabetes, hypertension, arteriosclerosis, and cancer [1]. Thus, obesity can be viewed as the most important risk factor for accelerating the manifestation of age-related diseases, causing a drastic reduction in healthspan and lifespan [2–4].

Given its socioeconomic impact and its individual consequences, the pathophysiology of obesity has come under close scrutiny. Multiple theories have been advanced to explain the mechanisms of obesity. Such theories may invoke psychosocial and behavioral parameters, alterations in central nervous reward centers, shifted endocrine and neuroendocrine circuitries, as well as changes in the composition of the intestinal microbiota affecting the meta-organism [5]. Interestingly, once an individual has transited from normal weight through overweight to obesity, the person appears to be 'locked' in the state of pronounced adiposity, meaning that even drastic dieting and exercising usually only leads to a transient correction of the body mass [6,7]. Thus, although the USA is home to more than 100 million obese adults, the National Weight Control Registry (http://www.nwcr.ws) monitors a rather small number (just above 10 000 cases) of durable weight losers.

The primary cause of lack of durable weight reduction is the excessive caloric intake observed in overweight or obese patients, a tendency that can be explained in part by the weakening of satiation after food intake [8]. Control of food intake by the central nervous system (CNS) involves many regions that respond to sensory (smell, hearing, sight), endocrine (gastrointestinal hormones, leptin, insulin, etc.), and nervous (vagal afferences) signals [9]. Specific centers such as the hypothalamus and the brainstem participate in homeostatic control (i.e., in response to calorie deficit or plethora). Other structures (ventral tegmental area, nucleus accumbens, striatum, etc.) are more involved in the nonhomeostatic control of food intake, responding to motivational or reward stimuli [10]. Figure 1 summarizes the most important actors involved in

Highlights

Multiple protein and peptide hormones produced outside of the central nervous system control food intake. In this feature review, we postulate that peripheral appetite inhibitors that are actually downregulated in human obesity, or, conversely, appetite stimulators that are upregulated in this condition, should be particularly important for the pathogenesis of obesity.

Paradoxically, most appetite inhibitors (exemplified by leptin) are upregulated in obesity while most appetite stimulators (exemplified by ghrelin) are downregulated, perhaps reflecting homeostatic adaptation.

Only three endogenous appetite inhibitors follow a 'coherent' pattern and are downregulated in obesity. This applies to pancreatic polypeptide (PP), peptide tyrosine-tyrosine (PYY), and vasoactive intestinal peptide (VIP).

Among the numerous appetite-stimulatory hormones, only three behave in a 'coherent' fashion and are upregulated in obesity: acyl-coenzyme A binding protein (ACBP), asprosin, and nicotinamide phosphoribosyltranferase (NAMPT).

Remarkably, these factors, ACBP, asprosin, and NAMPT, are phylogenetically ancient (from worms to mammals) and are ubiquitously expressed.

We speculate that ACBP, asprosin, and NAMPT may constitute the backbone of a phylogenetically ancient appetite-stimulatory system that is causally involved in human obesity.

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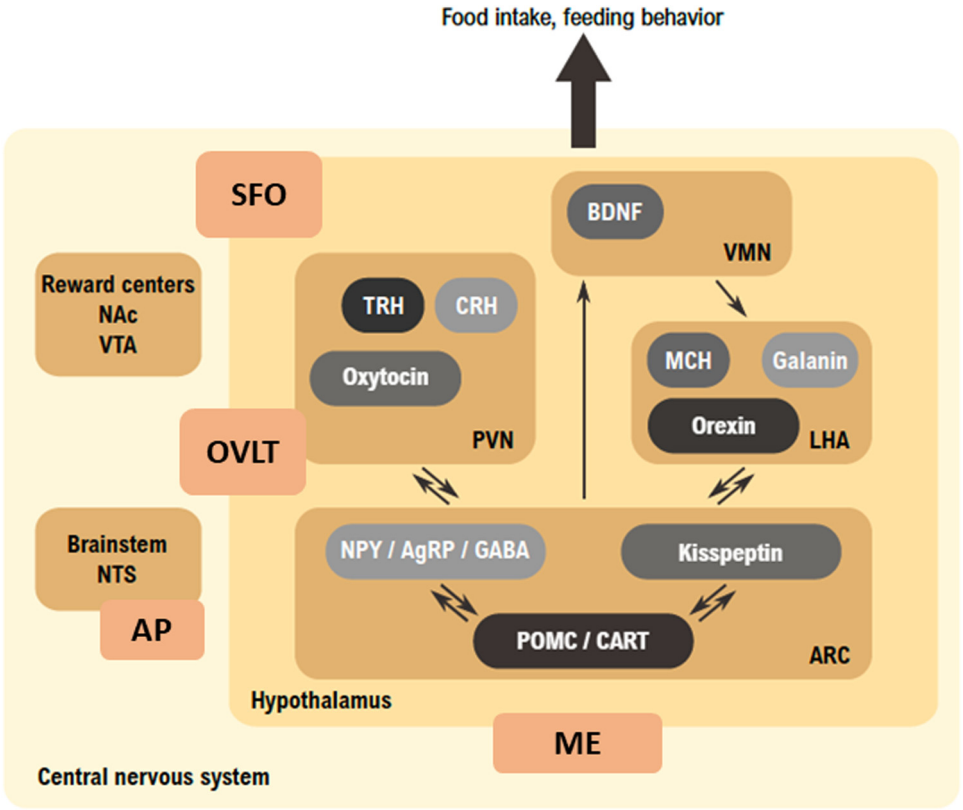

Figure 1. Central Control of Food Intake. The central nervous system integrates mechanical, nervous, hormonal, and metabolic signals from the periphery via the nucleus of the solitary tract (NTS), which receives afferent signals from the vagal nerve and via direct binding of messenger peptides on their receptors located in different neuronal population within the arcuate (ARC) nucleus of hypothalamus. In turn, neuronal projections to other populations located in lateral hypothalamic area (LHA), paraventricular nucleus (PVN), or ventromedian nucleus (VMN), together with other brain areas involved in nutrient sensing and reward, will lead to finely controlled food intake and feeding behavior. Neurons from circumventricular organs such as area postrema (AP), median eminence (ME), subfornical organ (SFO), and the organum vasculosum of the lamina terminalis (OVLT) are also able to sense blood-borne signals. Abbreviations: AgRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; CART, cocaine/amphetamine-related transcript; CRH, corticotrophin releasing hormone; GABA, γ aminobutyric acid; MCH, melanin concentrating hormone; NAc, nucleus accumbens; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; POMC, proopiomelanocortin; TRH, thyroid releasing hormone; VTA, ventral tegmental area.

this homeostatic control of food intake, mainly detailing the hypothalamus towards which many endocrine signals converge. In brief, two major hypothalamic populations of neurons were firstly identified to control appetite in the hypothalamic arcuate nucleus (ARC): an orexigenic population that secretes agouti-related peptide (AgRP), neuropeptide Y (NPY), and γ-aminobutyric acid (GABA), and an anorexigenic population that secretes melanocortin [processed from the polypeptide precursor POMC (proopiomelanocortin)] and cocaine- and amphetamine-regulated transcript (CART). These hypothalamic neurons assimilate a wide range of signals such as chemical inputs from circulating peptides or neuropeptides, neuronal input from various brain areas [11], and peripheral physiological information that is carried by the vagus nerve via the nucleus of the solitary tract (NTS). Several other populations of neurons were identified in hypothalamic areas such as the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA). Moreover, additional factors such as the neuropeptide kisspeptin, melanin concentrating hormone (MCH), brain derived neurotrophic factor (BDNF), and oxytocin play major signaling

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functions (Figure 1). Beyond this homeostatic control of food intake by the hypothalamus, other regions (such as the reward circuits, the cerebral cortex, the limbic system, etc.) trigger behavioral and metabolic responses [12]. In addition, neurons close to circumventricular organs (CVOs, such as area postrema, subfornical organ, organum vasculosum of lamina terminalis or median eminence) are also able to sense blood-borne signals such as hormones due to the particular anatomy of the blood–brain barrier in these CVOs and its highly fenestrated capillaries [13]. Finally, non-neuronal cells such as astrocytes, microglia, and tanycytes of the median eminence act in close interaction with neurons to contribute to the fine control of energy balance [14]. Modulated by all these mechanisms, the activation of anorexigenic neurons promotes meal termination and activates catabolic pathways, whereas orexigenic neuron circuits will stimulate food intake and decrease metabolic energy expenditure [15].

The central appetite system receives inputs from the periphery at short- and long-term. Thus, the nutrient composition, duration, and volume of a meal as well as the levels of circulating nutrients (glucose, fatty acids) and body fat mass are among the many factors that modulate food intake [16]. The information from these distant organs is transmitted electrically, by the vagal afferent nerves, and chemically, by circulating hormonal factors. Leptin is one of the first hormones that was found to modulate food intake and that was explored at the genetic level: sequenced in 1994 by Friedman *et al*., the protein is secreted by adipocytes in quantities proportional to the fat mass and acts as a potent appetite inhibitor in mice or patients with defects in the leptin/leptin receptor (LepR) system [17]. Initially, this discovery raised hope for obesity therapy, but it was soon discovered that leptin regulation is dysfunctional in obese subjects [18,19]. Since then, many other factors capable of inflecting or inducing hunger have been discovered. While several of them are under clinical investigation, the hunt for a magical appetite controller is still under way.

This feature review aims at identifying the known stimulators and inhibitors of appetite and their regulation in the pathological context of obesity. Given the entanglement of the central circuitries of hunger and satiety, we will limit the scope of study to the proteins and peptides that are produced by peripheral cells, outside from the CNS (Figure 2A) and demonstrate effects when administered peripherally while acting on central or peripheral receptors (Figure 2B). Rather than giving a detailed description of the mechanism of action for each factor, we seek to understand if their regulatory functions are altered in the context of obesity, in order to identify the most reliable candidates as a leverage for weight loss in obese subjects. Driven by elementary logics and Occam's razor (Box 1), we postulate that peripheral appetite inhibitors that are actually downregulated in human obesity, or conversely, appetite stimulators that are upregulated in this condition, should be particularly important for the pathogenesis of obesity and hence constitute good targets for therapeutic intervention.

Peripheral Appetite Inhibitors

Assuming that obesity is linked to the failure of homeostatic circuitries that limit caloric intake, it appears logical to identify appetite inhibitors and to supply them to obese patients, hoping to inhibit appetite. Indeed, a number of endogenous appetite inhibitors have been identified (Table 1 and Figure 3). However, the only agent that has undergone successful Phase III evaluation and has recently (November 2020) been FDA approved is liraglutide, an injectable glucagon-like peptide-1 (GLP-1) receptor agonist that likely acts on the CNS to reduce appetite [20].

The Leptin Axis

Leptin, the historical satiety factor, and its receptor were cloned by exploring the genomes of spontaneously obese and diabetic mice: the *ob*/*ob* strain, which lacks leptin, and the *db*/*db* strain, which lacks LepR. These strains exhibit severe hyperphagia and a tendency to develop

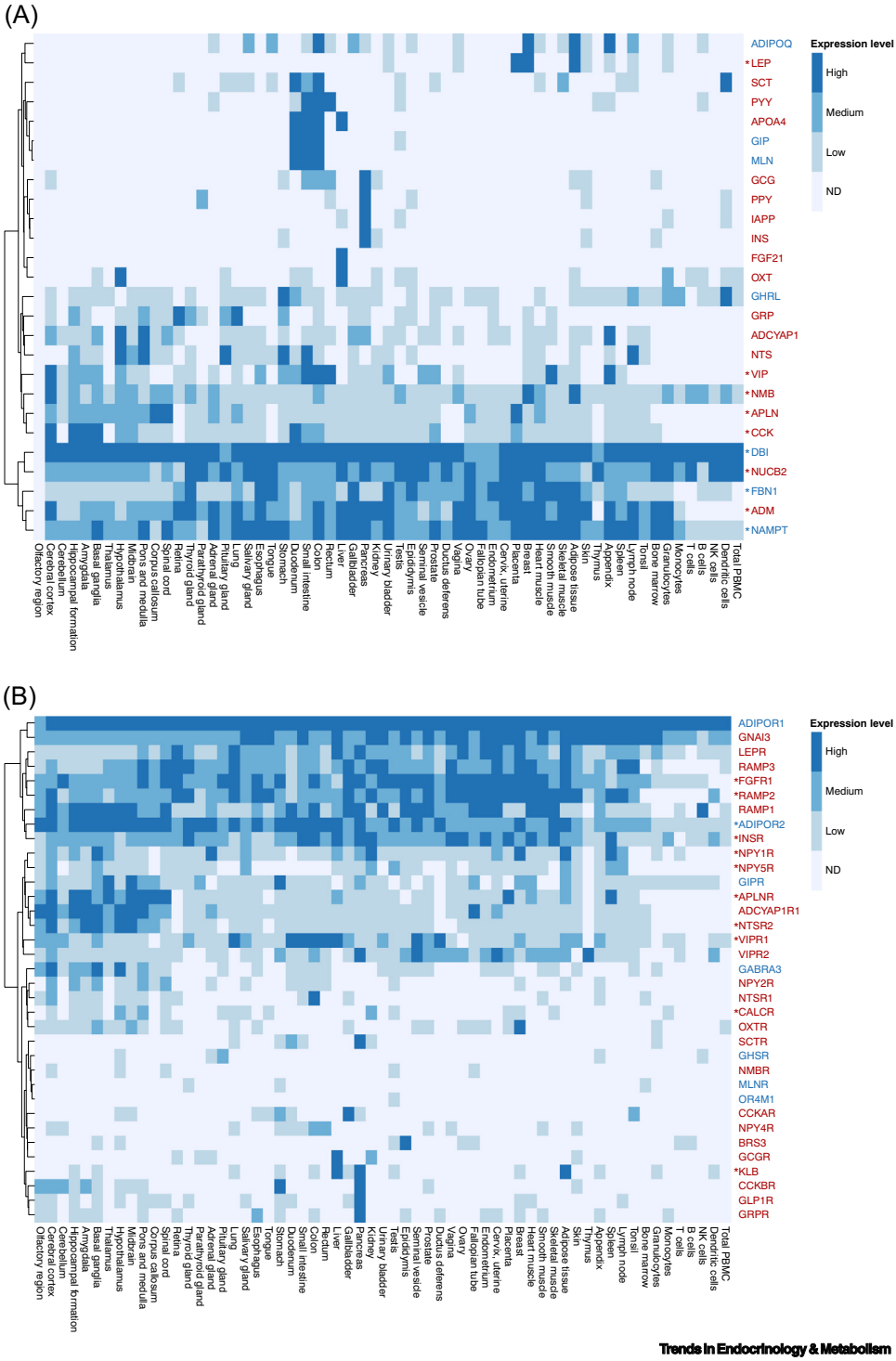

Figure 2. Expression Patterns of Peripheral Appetite Modulators and Their Receptors. Results on protein expression levels (www.proteinatlas.org) were listed for appetite inhibitory (red protein symbols) or stimulatory (blue protein symbols) peptides (A) and their receptors (B) in different human tissues, as determined by immunohistochemistry.

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Box 1. Coherent versus Paradoxical Patterns of Peripheral Appetite Regulators in Obesity

We propose to distinguish two patterns in the variation of appetite controlling regulators as they occur in human obesity.

We refer to a 'paradoxical' pattern when obesity is associated with the increase of measurable concentrations of appetite-inhibitory factors or a decrease in the levels of appetite-stimulatory factors. Indeed, such factors are either misclassified (for instance, as a result of differences between humans and rodents, considering that most studies on appetite control are performed in mice or rats) or their variations cannot be the cause of obesity. At best, their fluctuation constitutes a futile attempt of the organism to return from the pathological (obese) state to the physiological (lean) condition. Of note, most known appetite regulators follow this pattern, as prominently exemplified by leptin (an appetite inhibitor that increases in nonsyndromic obesity) or ghrelin (an appetite stimulator that usually is reduced in obese subjects). It can be attempted to shift the problem to aberrant responses to such mediators ('leptin resistance' or 'ghrelin sensitivity'). Moreover, it can be postulated that without the 'paradoxical' behavior of such mediators, obesity actually would be worse.

We consider that appetite stimulatory molecules that increase in obesity, or appetite inhibitors that decrease, follow a 'coherent' pattern, because such variations may indeed explain the development of obesity and the maintenance of the obese state. Hence, they are potentially involved in the causation of obesity. For this reason, we suggest that appetite regulators that respect a 'coherent' pattern should be considered as prime targets for therapeutic interventions on obesity.

type 2 diabetes due to the lack of stimulation of the 'leptin axis'. Indeed, LepR is involved in all major steps of appetite regulation: binding of leptin on LepR-expressing neurons in the NTS amplifies the signal from the vagus nerve in the NTS, while it has activating effects on the POMC/CART neurons and inactivating effects on the AgRP/NPY neurons in the hypothalamus, inhibits adrenal corticosteroid secretion, and increases energy expenditure [21].

In humans, genetic defects in the leptin gene or its receptor also cause extreme early onset obesity [22]. The severity of leptin deficiency can be partially reduced by leptin supplementation [23]. Although extensively studied, these cases of obesity are extremely rare and only a few dozen cases have been reported. Instead, cohort studies reveal a clear positive correlation between plasma leptin levels and body mass index (BMI) or subcutaneous fat mass, meaning that obesity is usually accompanied by hyperleptinemia [17]. Leptin levels drop drastically when adipose tissue mass is decreased, increasing hunger sensations for as long as 1 year after bariatric surgery or diet-induced weight loss according to one report [24]. Indeed, the individuals with the highest initial leptin levels have the highest chances of regaining weight after diet interventions [25]. The elevated basal leptin levels found in obese patients are thought to cause leptin resistance, rendering leptin treatment inefficient in most obese subjects [19]. However, at largely supraphysiological levels, recombinant leptin therapies allow mild reduction in appetite, which can help with weight maintenance [26]. Co-administration of both leptin and amylin might be also a promising approach [27].

The increase of an appetite-inhibitory factor in the context of obesity appears paradoxical, especially if it assumed that this appetite-inhibitory factor plays a major role in appetite control. However, in view of the current knowledge, that appetite is regulated by dozens of different factors, the paradox may be resolved by invoking a failing homeostatic control. Since obesity causes a deviation in body composition that is sensed by the system, homeostatic mechanisms intended to reduce appetite are activated, yet fail either because of resistance mechanisms or because

Asterisks mark those proteins that rhythmically change their expression level in at least two distinct tissues from mice, according to the CircaDB database (http://circadb.hogeneschlab.org/mouse). Abbreviations: ACBP, acyl-coenzyme A binding protein; ADCYAP1, adenylate cyclase activating polypeptide 1; ADIPOQ, adiponectin; APLN, apelin; ADM, adrenomedullin; APOA4, apolipoprotein A-IV; CCK, cholecystokinin; FGF21, fibroblast growth factor 21; GCG, glucagon; GHRL, ghrelin; GIP, glucose-dependent insulinotropic polypeptide; GRP, gastrin-releasing peptide; IAPP, islet amyloid peptide; LEP, leptin; OXT, oxytocin; PBMC, peripheral blood mononuclear cell; PYY, peptide tyrosine-tyrosine; MLN, motilin; NAMPT, nicotinamide phosphoribosyltransferase; NK, natural killer; NMB, neuromedin beta; SCT, secretin; VIP, vasoactive intestinal peptide.

Table 1. Appetite Inhibitory Hormones with Peripheral Metabolic Effects

Hormone	*In vivo*	Genetic perturbations in human	General trend in obesity	Human studies	Refs
Adrenomedullin (ADM)	Central injections reduce food intake in rodents Deficient ADM signaling in *fa/fa* rats	rs574603859 polymorphism in ADM receptor is associated with a smaller BMI	Increased in women	ADM antibody, which increases long-term plasma ADM, is in Phase II trial for the treatment of sepsis with a good safety profile	[150–152,241]
Amylin	Daily subcutaneous injection of apelin analog decreases food intake and body weight in rodents Antagonists increase food intake	Greater occurrence of a missense mutation in subjects with type 2 diabetes	Increased	Amylin agonists decrease food intake in obese patients, alone or in combination	[132,147,242,243]
Apelin (APLN)	APLN analogs have glucose-lowering and appetite-suppressive effects in mice	SNPs are associated with obesity in women cohorts	Increased	APLN analog under clinical trial for type 2 diabetic patients (NCT02724566)	[165,244–247]
Apolipoprotein A-IV (Apo-A4)	Peripheral injections reduce meal sizes in rats	*Apo-A4* polymorphisms linked to obesity in adult and elderly populations	Increased/decreased	–	[95–99,248]
Cholecystokinin (CCK)	CCK-1R deficiency causes hyperphagy and obesity in rats but not in mice Acute peripheral reduction of food intake in rodents with long-term tolerance to CCK	CCK alleles associated with increased meal size in obese carriers Homozygous polymorphism in the promoter of CCK type A receptor is associated with body fat mass	Unchanged Postprandial secretion is increased after bariatric surgery	CCK terminal octapeptide reduces meal size and duration in lean men	[67,68,70,71,73,74,76,249,250]
Fibroblast growth factor 21 (FGF21)	Peripheral injections decrease food intake and reverse obesity in mice	Variants in FGF21 gene associated with carbohydrate and global intake	Increased	FGF21 analog induces weight loss in type 2 diabetes patients	[167,168,170–173]
Glucose-dependent insulinotropic polypeptide (GIP)	Augmenting GIPR signaling, especially in combination with GLP-1R signaling, reduces food intake in mice However, GIPR-deficient mice strains are resistant to obesity. Inhibition of GIPR by means of a systemically injected antibody reduces high-fat diet-induced weight gain. GIP neutralization decreases weight gain in animal models [251]	Polymorphisms in the GIP receptor gene are linked to obesity, increased BMI, and visceral fat accumulation	Increased postprandial responses, likely as a result of exaggerated meal size	Systemic infusion increases hunger and subcutaneous fat metabolism in lean but not obese subjects Tirzepatide, a dual agonist of GIPR and GLP-1R biased towards GIPR, induces weight loss in type 2 diabetes obese subjects (Phase III clinical trial NCT03954834)	[31,39,53,54,56–60,251–254]
Glucagon-like peptide 1 (GLP-1)	Peripheral injections of GLP-1 or agonist reduces feeding in rodents However, inhibition of GLP-1R by means of a systemically injected antibody reduces high-fat diet-induced weight gain	GLP-1 circuits are more frequently mutated in binge-eating population *GLP1R* mutations associated with obesity	Increased/decreased/unchanged	GLP-1R agonists induce weight loss by diminution of food intake in numerous human studies	[29–31,34–39,255–257]

Table 1. (continued)

Hormone	*In vivo*	Genetic perturbations in human	General trend in obesity	Human studies	Refs
Gastrin-releasing peptide (GRP)	Peripheral injections acutely decrease food intake in primates and mice GRP-R-deficient mice have increased meal size and gain more weight than their wild type counterpart	Rare single variants or copy number variants in *Grp-R* are found in inheritable forms of obesity	–	Intravenous injection decreases food intake in healthy men	[110,258–261]
Insulin (INS)	Intracerebroventricular or intracarotid infusion decreases food intake in non-human rodents	Mutations of insulin are rare causes of diabetes diagnosed in childhood or adulthood but may explain cases of neonatal diabetes	Increased	Common T1DM treatment	[128,262–264]
Leptin (LEP)	Leptin injections decrease food intake and increase energy expenditure in rodents Mice strains deficient for LEP (*ob/ob*) or its receptor (*db/db*) are morbidly obese	Rare genetic defects in leptin or its receptor cause early onset obesity	Increased	Leptin replacement therapy is effective to compensate genetic leptin deficiency Resistance occurs in other cases of obesity	[17–19,21–23, 26,265]
Nesfatin	Peripheral injections decrease food intake in rodents Whole-body overexpression in mice has no effect on food intake and increases the obesogenic effect of a HFD Whole-body knockout mice have increased food intake and body weight	*Nucb2* polymorphisms are associated with protection against obesity	Increased/decreased	–	[177–181,183, 266,267]
Neuromedin beta (NMB)	Peripheral injections reduce food intake in rats, although less potently than GRP NBR-deficient mice are partially resistant to diet-induced obesity NBR antagonism decreases adipocyte differentiation	*Nmb* polymorphisms occur more frequently in obese patients	–	–	[105,107,108,268]
Neurotensin (NT)	Peripheral injections of NT or long-term analog acutely reduce food intake in rodents. NT-deficient mice are protected from HFD-induced abdominal fat accumulation and obesity	The NT/GLP-1 pathway is more frequently mutated in binge-eating population Polymorphisms in NT receptor 1 are associated with addictive behaviors	Increased	Ongoing clinical trials on the appetite-regulating effect of NT alone or in combination with GLP-1 (NCT03522792, NCT04186026)	[34,269–272]
Oxyntomodulin (OXM)	Peripheral injections inhibit food intake and reduce weight in rats	Cf. GLP-1, *GLP1R* polymorphisms are associated with obesity	Unchanged	Administration to lean and obese humans decreases food intake and appetite ratings Many analogs are tested alone or in combination with GLP-1	[62,273–275]

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Table 1. (continued)

Hormone	*In vivo*	Genetic perturbations in human	General trend in obesity	Human studies	Refs
Oxytocin (OXT)	Peripheral injections reduce food intake and body weight in animal models of obesity	Variants in the OXT receptor gene are associated with increased risk of early onset obesity	Increased in most studies/decreased	Obese patients significantly lose weight upon intranasal oxytocin treatment	[187,188,193,276]
Pituitary adenylate cyclase-activating peptide (PACAP)	Peripheral injections reduce food intake in mice and fish *Adcyap1*$^{-/-}$ mice strains have reduced sweet and carbohydrates intake	Mutations in PACAP receptor *ADCYAP1R1* are associated with addictive behaviors	–	Clinical studies with PACAP as a migraine inducer (NCT03881644, etc.)	[121,122,127,277]
Pancreatic polypeptide (PP)	Genetic overexpression lowers food intake and protects mice from obesity *ob/ob* mice lack PP-producing cells and their weight gain can be limited by peripheral PP injections	PWS syndromic obesity is associated with decreased PP secretion and food intake can moderately be diminished by PP injections. Higher copy number of PP receptor *Npy4R* is associated with increased BMI	Decreased	PP infusion decreases short-term food intake in lean and obese subjects	[133–135,137,138, 142,143,278]
Peptide YY (PYY)	Peripheral injections decrease food intake in rodents and macaques Central administration is orexigenic	Q62P mutant is found in familial forms of obesity and has impaired *in vivo* satiative effect Other variants in *Pyy*, its regulatory regions, and in its receptor *Npy2R* are associated with obesity	Decreased	Intravenous infusion decreases the caloric intake from a buffet One clinical study yielded inconclusive results Ongoing clinical trials alone or in combination with GLP-1 (NCT03707990 and NCT03574584)	[81–85,88,279–281]
Secretin (SCT)	Peripheral injections decrease food intake and increase lipolysis in mice but not in other animal models SCT-receptor knockout mice are resistant to HFD-induced obesity	–	–	Intravenous secretin infusion in humans induces activation of brown fat	[115–119]
Vasoactive intestinal peptide (VIP)	Central administration decreases food intake in vertebrates *Vip*$^{-/-}$ mouse strain has reduced food intake and weight gain, as well as abnormal levels of GLP-1, leptin, PYY, adiponectin, and insulin	The VIP pathway is associated with obesity in a genome-wide analysis study	Decreased	Clinical studies of VIP in the context of migraine (most recent NCT03989817, NCT04260035, etc.)	[123,124,126,282]

they are superseded in importance by the true, yet to be defined, dominant drivers of obesity. Despite the great expectation it caused at the end of the 20th century, leptin proved disappointing as a hormonal therapy for obesity. However, the study of its hypothalamic targets helped build the foundations of the current knowledge of appetite regulation. Many other hormonal regulators were subsequently found to regulate food intake through leptin-related or independent pathways.

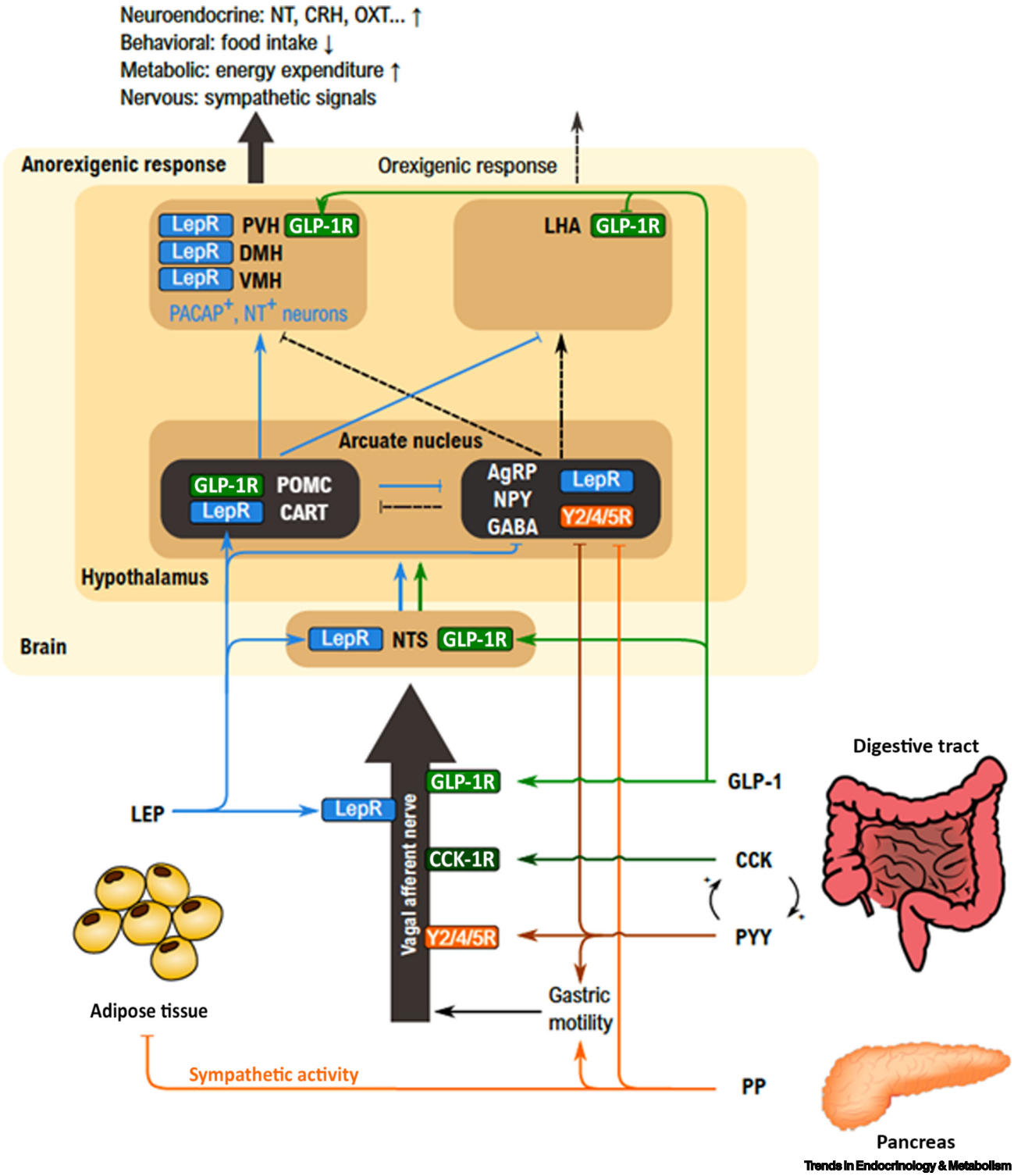

Figure 3. Central Targets of Major Anorexigenic Factors. Leptin (LEP) is secreted by the white adipose tissue and acts through its receptor LepR both peripherally, on the vagal afferences, and centrally. It potentiates the input from the vagal nerve in the nucleus of the solitary tract (NTS), activates anorexigenic neurons in the hypothalamus, and inhibits the orexigenic response. The pancreatic polypeptide (PP) and the intestinal peptide tyrosine-tyrosine

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Intestinal Appetite Regulators

The intestine and the brain are the first organs to sense food intake, making the gut hormones a natural starting point to discover appetite-regulatory factors.

GLP-1

GLP-1 and oxyntomodulin (OXM) are two of the many peptides derived from alternative cleavage of glucagon, which can both affect blood glucose levels. The most studied one, GLP-1, is known to increase after a meal proportionally to its caloric content, slow down gastric emptying, and potentiate the glucose-dependent effects of insulin [28]. Through its receptor, GLP-1R, it exerts strong anorectic effects at the peripheral level, likely by an action on afferent nerves, but may also reach the CNS when its levels are high. These effects have been extensively studied in animals and proved to be able to induce durable weight loss [29,30]. However, neutralization of GLP-1R by systemic (intraperitoneal or subcutaneous) injection of blocking antibodies inhibits high-fat diet (HFD)-induced obesity in mice [31], suggesting that the GLP-1/GLP-1R system may have different roles in the periphery and in the CNS (which is not attained by antibodies). In humans, polymorphisms in the GLP-1R gene have been linked to obesity-related pathologies, such as type 2 diabetes and cardiovascular diseases [32,33], while the GLP-1 axis appears to be more frequently mutated in binge-eating disorders [34]. However, the study of circulating GLP-1 levels in the context of obesity leads to inconsistent results: some studies establish a positive correlation between BMI and GLP-1 levels [35,36], others report attenuated GLP-1 responses to meals in obese compared with lean subjects [37,38], and a third set of studies simply finds no significant link between GLP-1 response and obesity [39]. Thus, the causative implication of GLP-1 in obesity has not been established. Nonetheless, there are multiple GLP-1R agonists in the pharmacopeia currently under trial, either alone or in combination, for the treatment of obesity and type 2 diabetes [40,41]. Some of them, like liraglutide or exenatide, are prescribed to diabetic patients, yielding promising weight-loss results beyond their insulinotropic effects [42] and liraglutide has recently been FDA approved for the treatment of obesity [20]. Dual agonists acting on the receptors for glucagon and GLP-1 are being developed for the treatment of obesity and MEDI0382 as well as SAR425899 caused weight reduction in obese patients with type 2 diabetes [43,44].

There is now more and more convincing evidence that intestinal peptides like GLP-1 not only regulate the quantity of calories ingested but also their quality. In fact, the signaling pathways of these peptides [GLP-1 but also glucose-dependent insulinotropic polypeptide (GIP)] are not only activated in the homeostatic regions of the CNS (hypothalamus or brainstem), but also in nonhomeostatic regions [45,46] such as certain areas of the limbic system (striatum, ventral tegmental area), the hippocampus, or the olfactory bulb, which strongly expresses GLP-1 receptors [47]. Thus, these peptides control the quantity of food ingested but also participate in our food choices and preferences [48,49]. It is therefore conceivable that future classes of compounds that target receptors of these peptides (alone, in combination, or in the form of di- or triagonists) may impact our feeding behavior, thus inducing a preference for, or an aversion to, certain types of food with equal caloric intake acting in addition to their effects on homeostatic regulation [50]

(PYY) share the family of Y-receptors and exert their anorexigenic effects through vagal and hypothalamic regulation. Cholecystokinin, in a positive control loop with PYY, exerts most of its function by vagal nerve activation though its receptor CCK-1R. Finally, glucagon-like peptide-1 (GLP-1) activates the vagal nerve, increases the integration of its signals by the NTS, and exerts direct anorexigenic actions on hypothalamic nuclei though a leptin-independent pathway, which relies on the GLP-1R receptor. Abbreviations: AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; DMH, dorsomedial hypothalamic; GABA, γ-aminobutyric acid; LHA, lateral hypothalamic area; NPY, neuropeptide Y; NT, neuropeptide T; OXT, oxytocin; PACAP, pituitary adenylate cyclase-activating polypeptide; POMC, proopiomelanocortin; PVH, paraventricular hypothalamic; VMH, ventromedial hypothalamic nuclei.

GIP

Gastric inhibitory polypeptide (also called GIP) was initially considered as the orexigenic member of the incretin family, given that chemical inhibition of the GIP receptor (GIPR) or its genetic deletion in mice protected them from diet and genetically induced obesity by reducing food intake and stimulating catabolism. However, its metabolic actions are twofold: after a meal, it stimulates insulin release, but in the fasted state, it enhances glucagon release [51]. Moreover, in mice activation of GIPR-positive neurons in the hypothalamus reduced food intake, suggesting that the role of GIP in central appetite control is complex, in line with the fact that GLP-1 positive neurons can coexpress GIPR [52].

Pharmacological GIPR agonists, especially if combined with GLP-1R agonists, reduce food intake in mice [53,54]. Indeed, dual agonists that activate both GIPR and GLP-1R such as LY3298176 (also called tirzepatide) have been shown to reduce body weight in type 2 diabetes patients [53,55], suggesting that GIP actually may serve as an anorexigen when acting in the presence of GLP-1. A Phase III study that evaluates LY3298176 for the treatment of obesity is underway.

Increased levels of circulating GIP are measured in obese patients, especially after a meal [51,56]. Genetic perturbations in GIP signaling favor the development of obesity: polymorphisms near the GIPR locus are associated with an increased risk of obesity and perturbations in glucose metabolism [57,58], while variants in the GIP gene have been linked with increased adiposity [59,60].

OXM

OXM more recently emerged as an alternative to GLP-1 because of their overlapping activity: OXM activates GLP-1R and the glucagon receptor (GCGR), causing both satiation and an increase in energy expenditure [61]. Like other anorexigenic gut hormones, OXM strongly increases after bariatric surgery. However, its basal level does not seem to be disturbed in obese compared with lean patients, suggesting that OXM cannot be involved in the etiology of obesity [62]. Notwithstanding this limitation, OXM administration to obese subjects successfully dampened appetite and improved energy expenditure, leading to a significant loss in body weight [63]. Such a 'dual agonism' is a tempting approach to compensate the decrease in energy expenditure usually caused by a decreased food intake, but still requires a better understanding of the balance between its metabolic and anorexigenic effects.

Cholecystokinin

Cholecystokinin (CCK), a hormone secreted by the intestine after ingestion of lipids and proteins, slows gastric emptying and triggers satiety in a wide variety of species [64]. Its effects are additive or even synergic to leptin, perhaps because of the colocalization of LepR and CCK receptors on vagal afferent fibers and in the NTS [65], but are also likely to involve descending projections from the hypothalamus to the hindbrain that are activated by leptin acting in the hypothalamus [66]. Rats bearing a genetic deletion of the CCK receptor are hyperphagic and obese [67]. However, such a clear effect has not been reproduced in mice [68]. Despite a dose-dependent acute diminution of meal size with CCK administration [69], in the long-term, this CCK effect is compensated by an increase in meal frequency and no weight loss is achieved [70,71]. Other mechanisms, such as the impaired vagal sensitivity measured in HFD-fed mice, may contribute to lack of efficacy of CCK in animal models [72], as well as in patients [64]. Indeed, obese subjects who durably lose weight decrease their postprandial CCK secretion, even after a stabilization period of a year [24]. Polymorphisms in the genes coding for CCK or its receptors have been linked to body fat content [73], larger meal sizes [74], and higher risk of weight regain [75]. However, BMI and other obesity-related indicators do not seem to be related to CCK circulating levels [76], suggesting that CCK is not a major contributor to the pathogenesis of obesity.

Peptide YY

Peptide tyrosine-tyrosine (PYY) is a member of the NPY family [77], but it is mostly secreted in the gut upon lipid and protein ingestion in the form of two major forms: PYY(1–36) and PYY(3–36) [78]. PYY(1–36) binds to Y1, Y2, Y4, and Y5 receptors; PYY(3–36) is a high-affinity ligand for Y2 receptors with low affinity for Y1 and Y5 receptors [79]. Influenced by a positive control loop with CCK, PYY appears to be cosecreted and have complementary effects with GLP-1 (and OXM) [80]. Early studies proved the anorexigenic effect of central and peripheral PYY injections in various animal models, as well as in humans [81,82]. In the context of obesity, PYY variations are coherent with the hypothesis that high caloric intake is driven by an excessive appetite: fasting levels and PYY meal responses are lower in obese subjects compared with their lean counterparts and PYY levels decrease after diet-induced weight loss (for a review, see [83]). Of note, polymorphisms in the PYY gene or its regulatory regions have been linked to obesity-related phenotypes [84,85], while high circulating PYY levels are seen in restrictive-type anorexia nervosa (AN) [86]. Based on studies that confirmed comparable short-term sensitivity to PYY-induced satiation between lean and obese subjects [87], larger scale clinical studies were launched by pharmaceutical companies since the early 2000s. Merck's Nastech trial was abandoned due to a lack of results, as well as adverse effects such as constant nausea for the highest doses [88]. More recently, combination therapies of PYY(3–36) with GLP-1R agonists have been successful with less side events in primates [89] and are still under clinical investigation (Novo Nordisk trials NCT03707990 and NCT03574584).

Apolipoprotein A-IV

Apolipoproteins are a family of proteins that bind to lipids: by regulating their transport, they are key actors in lipid metabolism [90]. Among them, apolipoprotein A-IV (Apo-A4) is secreted by the small intestine in response to dietary lipids [91]. In rodents, peripheral injection of recombinant Apo-A4 suppressed appetite, while central injection of anti-Apo-A4 antibody elicited unusual food intake during the light period [92]. Mechanistically, Apo-A4 requires and interacts positively with the CCK circuits [93] and its secretion is downregulated by leptin [94].

Various human studies found associations between variations in the apo-A4 gene and obesity or obesity-related traits [95–97]. However, no general trend can be outlined from the few data available on the variation of Apo-A4 plasma levels in obesity [98,99]. This lack of consistency between studies may be explained by the influence of sexual hormones [100] but also by a retroactive mechanism in the regulation of Apo-A4. Thus, studies in rats and in humans show that Apo-A4 increases proportionally with lipid intake in the short-term, although a constant HFD diet leads to a return to Apo-A4 basal levels within weeks [101]. Moreover, the anorectic response to Apo-A4 is blunted in HFD-induced obesity of rats [102].

Bombesin-like Peptides

The bombesin-like family of peptides is comprised of two anorectic peptides: gastrin-releasing peptide (GRP) and neuromedin beta (NMB), which target specific G-coupled receptors (GRP-R and NMB-R; a third receptor, bombesin receptor subtype 3, BRS-3, has no known endogenous ligand) in order to cause systemic effects that include increased thermogenesis, decreased appetite, and inhibition of gastric emptying [103]. While GRP-R- (and BRS-3-) deficient mice tend to develop hyperphagia, metabolic imbalance, and obesity [104], NMB-R-deficient mice manifest impaired adipogenesis, which protects them from diet-induced obesity [105]. Observed in a large set of species, the anorexigenic effects of bombesin-related peptides seem to be mostly mediated by GRP through activation of hypothalamic neurons [104], while NMB regulates food intake through an effect on adipose tissue [106].

The impact of this axis on appetite is confirmed by human genetic studies: polymorphisms in NMB are more frequent in obese patients [107–109] and some sequence and copy number variations in the GRP gene have been linked to early-onset obesity [110]. Nevertheless, activation of GRP-R was able to cause food suppression in lean but not in obese women [111] and sex differences were also highlighted in the consequences of a mutation in the NMB gene on long-term caloric intake [112]. BRS-3 agonists are currently under investigation, with apparently more systematic results in obese patients, but its endogenous ligand remains unknown [113] and non-specific effects triggering adverse events will have to be taken into account [114]. Altogether, the implication of bombesin-like peptides in obesity is far from being fully understood, calling for further investigation before clinical applications can be envisioned.

Secretin

Historically seen as a digestive peptide that controls gastric acidification and motility, secretin (SCT) recently regained interest as an anorexigenic peptide. Previous studies on appetite regulation led to conflicting results: meal reduction was achieved upon central and peripheral injection of SCT in mice and was accompanied by increased lipolysis [115], but such results are inconsistent with earlier findings in rats [116] and sheep [117]. A predominant role in the regulation of lipid metabolism was inferred by the fact that SCT-receptor-deficient mice did not modify their eating patterns, but were still protected from HFD-induced obesity because of faulty lipogenesis [118]. A study by Li *et al*. reconciled the metabolic and appetite-regulatory effects of SCT with a model of SCTR-expressing brown adipocytes, which, once activated, increase thermogenesis and send hormonal signals to the hypothalamic appetite control centers [119]. This study also confirmed the effects of SCT-induced brown adipose tissue (BAT) activation on appetite and energy regulation in seven human subjects, opening the way for the use of adipose tissue-based strategies for the regulation of food intake [119]. Further studies, especially in the context of obesity, will be needed to elucidate the SCT-mediated crosstalk between intestinal and adipose tissues.

VIP/PACAP

Vasoactive intestinal peptide (VIP) and adenylate cyclase activating polypeptide 1 (ADCYAP1, hereafter referred to as PACAP) are homologous pleiotropic neuropeptides from the glucagon family. Highly expressed in the intestinal system and CNS, they target the hypothalamic centers of food regulation and decrease food intake when administered centrally to vertebrates [120]. Except for one experiment in fish [121], there is no proof that peripheral injection of VIP diminishes caloric intake. However, peripheral PACAP administration consistently inhibited food intake in mice [122]. This difference can be explained by the fact that VIP and PACAP share the VPAC1 and VPAC2 receptors, while the PAC1 receptor, which mediates appetite-inhibitory effects, is specific to PACAP [122,123].

As confirmed by genetic association studies that linked the VIP axis to obesity [124] and PACAP polymorphisms to addictive and binge-eating behaviors [125], these two peptides play a role in central control of food intake but are not strictly anorexigenic. Indeed, the knockout of both VIP and PACAP results in unexpected effects on the metabolism of mice: instead of the expected increase in caloric intake, appetite-related hormones are dysregulated, leading to a decrease in food intake and fat mass [126,127]. In a review that reconciles the opposed effects between normal and extreme conditions, Gargiulo *et al*. proposed a model in which a finely regulated feedback loop linking PACAP to the control of normal feeding cycles, is broken when overfeeding increases the basal PACAP levels [125].

Other Peripheral Anorectic Peptides

Hormones secreted by the pancreas, the liver, or multiple other cell types can participate in the regulation of the peripheral metabolic response and affect appetite and energy homeostasis.

Insulin

Insulin secretion increases in response to a meal and the concomitant hyperglycemia, which allows the body to manage caloric intake by promoting energy storage and reducing food intake. The short-term inhibitory effect of insulin on food intake was first demonstrated experimentally in the 1980s [128]. Although the molecular mechanisms have not yet been fully elucidated, it is known that peripheral insulin acts in the hypothalamus via the inhibition of NPY/AgRP/GABA neurons and the activation of POMC/CART neurons, both populations expressing the insulin receptor. Recent results indicate that insulin activates POMC neurons via transient receptor potential (TRPC)5 channels [129,130]. Conversely, insulin inhibits NPY/AgRP/GABA neurons through activation of K(ATP) channels, leading to their hyperpolarization [130].

Like leptin, insulin is believed to act as an adiposity signal, contributing to the long-term brain control of body weight in addition to its short-term effects. Thus, a change in plasma leptin or insulin levels is detected as an altered state of energy homeostasis and adiposity, to which the brain responds by adjusting food intake to restore the basal fat mass level. These long-term effects may partly explain the seasonal changes in weight and fat mass. Because of its effect on energy storage and weight gain (which is a side effect of insulin therapy for type 2 diabetics), insulin cannot be considered as an effective treatment for obesity. However, approaches combining a co-injection of amylin (see 'Calcitonin-Related Peptides') and insulin (or leptin) may act synergistically to effectively reduce food intake and body weight [131,132].

Pancreatic Polypeptide

The pancreatic polypeptide (PP) is secreted postprandially by PP cells in the islets of Langerhans. PP belongs to the family of NPY and causes central anorectic effects through Y4 and Y5 receptors. PP secretion is impaired in *ob/ob* mice [133]. PP injections limit food intake and weight gain in both leptin-competent and -deficient mice [134]. The translation of these findings to humans is not perfect, with reports of diminished food intake in the short-term [135] but no differences in hunger ratings in another study [136]. Nonetheless, consistent diminution of PP levels is confirmed in syndromic obesity such as Prader-Willi syndrome (PWS) [137], in nonsyndromic obese patients [138], and in large-scale studies, with negative correlations between PP levels and fat mass/BMI [139]. Conversely, in patients with AN, the PP response to a meal is abnormally high [140]. Despite diverging reports on its variations upon weight loss [24,141,142], in the context of obesity, PP follows a trend that fits an increase in hunger and sensitivity to PP treatment does not seem to be compromised [143]. In conclusion, PP appears as a good candidate for an anti-obesity drug, albeit with the limitations of its short half-life in circulation and the complexity of its interactions with the NPY and PYY receptor networks [144].

Calcitonin-Related Peptides

The family of calcitonin-related peptides (CRP) is comprised of peptides that are primarily secreted in the pancreas and in the brain: amylin [also called islet amyloid peptide (IAPP)], adrenomedullin (ADM), calcitonin (CT), and calcitonin gene-related peptide (CGRP). Each of them has been studied and will be presented separately, but they share two receptors, the CT-receptor (CTR) and CT-like receptor (CLR), which makes them highly interdependent [145].

Amylin is released by β-cells of the pancreas along with insulin. After an abnormal increase in the early phase of the disease, amylin blood levels are durably decreased in diabetes and amylin analogs have been approved for diabetes treatment [146]. In terms of food intake, amylin decreases meal sizes when administered centrally and peripherally, with no known long-term

resistance effects, through a direct central activation of CTR as well as the potentiation of CCK circuits [147]. Different analogs with increased effects are currently under preclinical and clinical investigation, either alone or in combination [27]. In the context of obesity, basal amylin levels tend to increase, but the postprandial rise is maintained and no desensitization to its anorexic effect has been reported [132]. Upon weight loss, amylin levels reportedly decrease [24], adding up to many other hunger signals.

ADM is a ubiquitous peptide with multiple functions, including growth, endocrine regulation, neurotransmission, and antimicrobial activity [148,149]. Evidence for altered ADM function was found in *fa/fa* obese rats [150]. Peripheral injections of ADM inhibit gastric emptying and decrease food intake in rats [151]. In human, variations in the gene for the ADM receptor were linked to a smaller BMI [150]. Long-term studies found associations between weight gain and high plasma levels of ADM in women but not in men [152]. These cues indicate a role for ADM in body weight regulation, although it is not univocally anorexigenic.

The calcitonin-related polypeptide alpha (CALCA) encodes for the last two members of the family, CT and CGRP. Elevated plasma levels of their common prepropeptide, procalcitonin, has been associated with higher BMI in the general population [153], but differential effects occur for each peptide. On one hand, CT has been most intensively studied for its calcium-related properties, but recent evidence from knockout studies in mice describes it as potentially orexigenic and lipogenic [154]. In addition, CT levels are positively correlated with BMI in elderly women [155]. On the other hand, CGRP is a neuropeptide of clinical interest for migraine treatments, which may contribute to appetite regulation [156]. CGRP neurons in the PVN are key mediators of anorexia [157,158]. Food consumption can be reduced in mice upon peripheral injection of CGRP [159] or a long-lasting analog, but these observations may result from indirect effects such as the activation of GLP-1 secretion [160].

Altogether, the CRP family definitely plays a role in appetite regulation and acts at the central and peripheral levels. Given the wide spectrum of their biological roles and the complexity of their interactions, it may be difficult to develop CRP analogs for a specific obesity treatment and further studies are required to precisely understand their appetite inhibitory effects.

Apelin

Apelin (APLN) is a 77-amino acid protein belonging to the family of adipokines. It is mainly produced by adipocytes but also by gastric mucosa and Kupffer cells in the liver [161]. Several active forms arise from this common precursor and are detected in the bloodstream (13, 17, or 36 amino acids). APLN is the ligand of the former orphan APJ receptor, a seven-transmembrane G protein-coupled receptor. APJ is widely distributed in various tissues (heart, blood vessels, stomach, etc.), including the CNS, especially in the hypothalamus. APLN appears to be pleiotropic, with evidence of dietary inhibition in rodents (mice and rats) when a synthetic analog, pyroglutamylated APLN-13, is administered centrally [162]. However, the doses and routes of administration may lead to conflicting results on dietary intake [163]. The duration of treatment may affect treatment efficacy, since peripheral administration of APLN-13 for 28 days induced a decrease in food intake and body weight in obese Swiss mice on a HFD [164].

In parallel with insulin, APLN rises in response to blood glucose increase and has a glucose-lowering effect. Recently, APLN analogs showed encouraging preclinical results, with a strong insulinotropic effect and food intake suppression in mice. [165]. Across studies, APLN plasma levels are consistently increased in obese patients compared with their lean counterparts, possibly to compensate or delay their insulin resistance [166].

Fibroblast Growth Factor 21

Fibroblast growth factor 21 (FGF21) is secreted in the liver upon sugar ingestion. It has been found to correct genetic and diet-induced obesity in mice [167], to decrease food intake, and to limit sweet preference in mice and non-human primates [168]. Metabolically, it stimulates glucose uptake and thermogenesis in the BAT and fatty acid oxidation in the liver through the activation of hypothalamic and adrenal circuits, which release corticosterone [169]. Accordingly, variants in the human FGF21 locus are associated with increased carbohydrate preference in adults [170] as well as with total macronutrient intake [171]. However, circulating FGF21 is positively correlated with BMI and high levels are associated with metabolic syndrome and type 2 diabetes [172,173]. Seen as a protective mechanism against nutrient-induced hepatotoxicity [174], the FGF21 axis seems to be overactive in obese patients. Thus, FGF21 exemplifies yet another appetite inhibitor that cannot be involved in the etiology of obesity since it is upregulated (rather than downregulated). Despite this pattern of dysregulation, many FGF21 analogs are under trial to treat obesity, diabetes, and their comorbidities. Some of them lead to moderate weight loss [168,175], but their main effect appears to be the limitation of hepatic lipid accumulation [176], establishing FGF21 analogs as candidates for the treatment of non-alcoholic fatty liver disease.

Nesfatin

Nesfatin is a broadly expressed peptide derived from the protein nucleobidin-2, the anorectic effects of which were discovered in the early 2000s when it was injected peripherally into mice and rats. These effects are leptin-independent and rely on activation of the vagus nerve and on direct hypothalamic signaling, leading to the inhibition of NPY neurons and the activation of the melanocortin system [177,178]. Metabolically, it enhances glucose-induced insulin secretion [179]. In line with this, a polymorphism of the *NUCB2* gene is associated with a decreased risk of type 2 diabetes (in heterozygosity) as well as of obesity (in homozygosity) [180,181]. However, nesfatin can be detrimental when overexpressed: in mice, genetically induced overexpression leads to insulin resistance, increased body mass, and fat deposition in the liver when fed a HFD [179]. Such a dysregulation is observed in human obesity: while nesfatin appears to be negatively correlated with BMI in normal weight subjects [182], several in obese cohort studies show either positive [183], negative [182], or no correlation [184]. The variation of the ratio between cerebral and plasma nesfatin may explain the observed differences: an exaggerated secretion in the plasma may not systematically result in the accumulation of the anorexigenic peptide in the brain [185].

Oxytocin

Oxytocin, the 'social hormone', falls into the scope of this feature review because it triggers anorectic responses when injected peripherally into rodents [186]. In humans, central and metabolic effects of oxytocin complement each other to induce weight loss: they include snacking reduction, improved insulin sensitivity, fatty acid oxidation, and increased energy consumption [187]. Oxytocin signaling is crucial for weight regulation: genetic defects in the oxytocin receptor have been linked to precocious obesity [188], while, conversely, patients with PWS have significantly lower oxytocin-expressing neurons and are moderately sensitive to oxytocin-driven weight loss [189,190]. Not all studies agree on the variations of oxytocin in obese patients, with reported positive and negative correlations between oxytocin levels and body or fat mass [191]. Nevertheless, intranasal oxytocin treatments of nonsyndromic obese patients yielded promising results, even in the case of high basal levels of this hormone [192,193].

Peripheral Appetite Stimulators

As a general rule, in pharmacology, receptor agonists/activators have more side effects than receptor antagonists/inhibitors, calling for the identification of appetite-stimulatory pathways

(Table 2 and Figure 4) that might be overactivated in obesity and hence constitute attractive targets for therapeutic intervention.

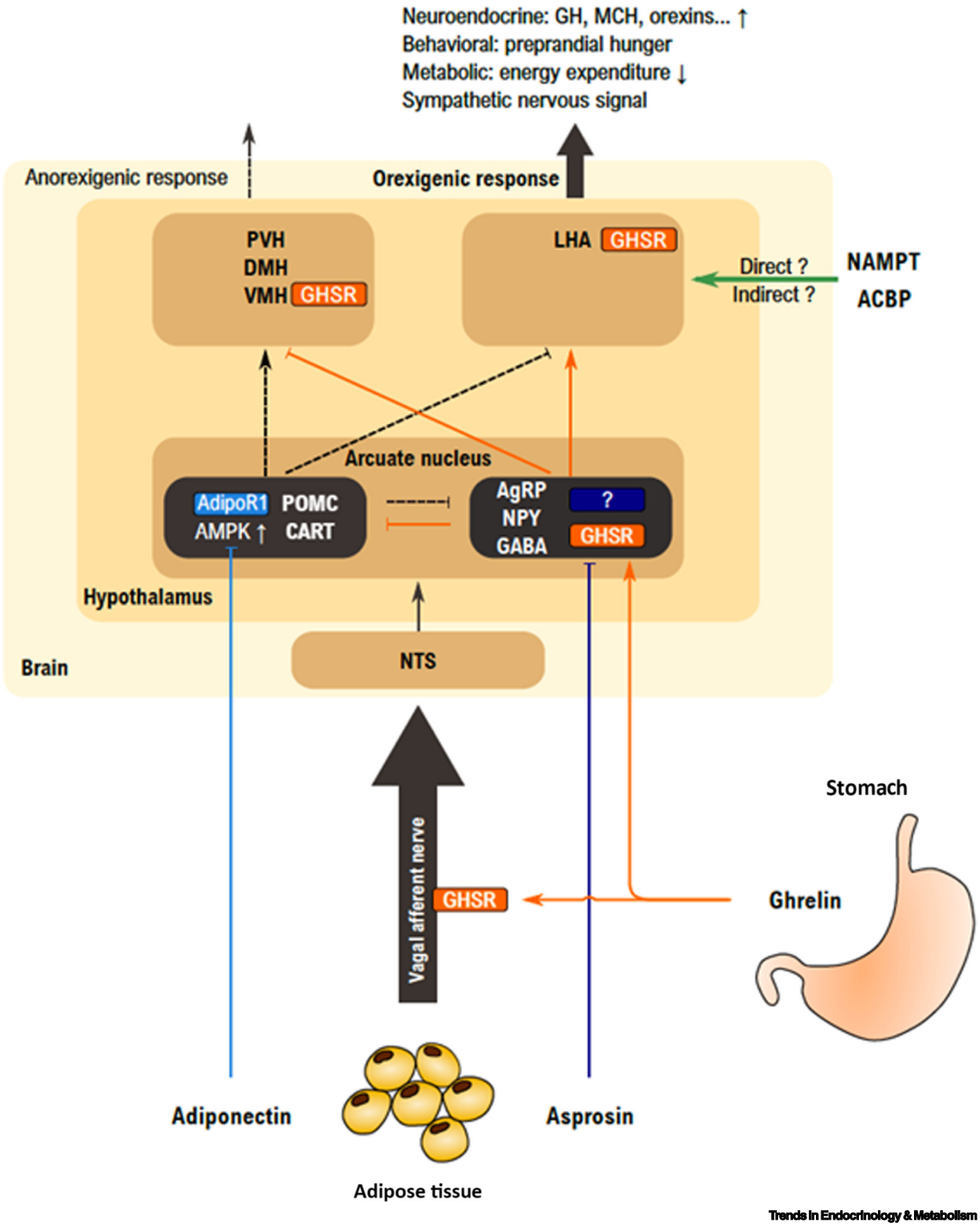
Ghrelin and Intestinal Factors

Ghrelin

The historical counterpart of leptin, ghrelin, is a hormone that apparently rises upon fasting and declines upon satiation. Its receptor [growth hormone secretagogue receptor (GHSR)] is expressed centrally, directly activating the AgRP/NPY orexigenic neurons in the hypothalamus, and peripherally, for example, in the adipose tissues where it increases fat storage. Strong orexigenic effects are seen in animal models and lead to obesity when ghrelin is chronically administrated [194], while selective

Table 2. Appetite Stimulatory Hormones with Peripheral Metabolic Effects

Hormone	*In vivo*	Genetic perturbations in human	General trend in obesity	Human studies	Refs
Acyl-CoA binding protein (ACBP)	Peripheral injections are orexigenic and obesogenic in mice. Antibody-mediated neutralization and knockout are anorexigenic.	A polymorphism (rs279858) in $GABA_A$ receptor predisposes to weight gain after treatment with antipsychotics	Increased	–	[226,233]
Adiponectin	Peripheral injections increase food intake after refeeding in mice. Adiponectin-deficient mice have decreased food intake and increased energy expenditure. Serum adiponectin levels are decreased in ob/ob mice and restored in POMC-deficient obese mice.	Adiponectin-decreasing allelic variations are associated with lower BMI and decreased appetite	Decreased	Numerous adiponectin-increasing molecules have been tested for their insulin-sensitizing properties	[210,211,283–286]
Asprosin	Subcutaneous injection into mice stimulated food intake. Its antibody-mediated neutralization decreases appetite and body weight in obese mice. Peripheral injections cause hyperglycemia and hyperlipidemia with no changes in body weight.	Mutations in the *Fbn1* gene cause the Marfan syndrome, associated with extreme thinness and hypophagia	Increased/inconsistent results in children	–	[213,215,217, 287–291]
Ghrelin	Peripheral injections increase food intake and are obesogenic at long-term in rodents. Ghrelin-receptor-deficient mice strains are hypophagic and resistant to HFD-induced obesity.	Ghrelin is upregulated in patients with Prader-Willi syndrome Rare allelic forms of preproghrelin may be protective against fat accumulation	Decreased	Appetite and food intake is increased upon high but not physiological doses Anti-ghrelin vaccination studies led to marginal weight loss	[194–200,292]
Motilin (MLN)	Peripheral injections stimulate food intake in rats. Extremely high doses inhibit feeding, probably due to nausea.	rs2274459 polymorphism in the *MLN* gene is associated with an increased odds-ratio for obesity	Absence of MLN peak during MMC phase 3 coupled to increased/decreased levels at baseline	Motilin receptor agonist erythromycin increases appetite	[206,208,209, 293–296]
Nicotinamide phosphoribosyl-transferase (NAMPT)	Central injections have orexigenic effects in chicks. *NAMPT*-deficient mice are resistant to HFD-induced obesity	rs10487818, a rare polymorphism in *Nampt*, may be protective against obesity	Increased	–	[220,222–224]



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inhibition of ghrelin signaling in the brain leads to hypophagia and resistance to HFD-induced weight gain [195]. Translation of these clear-cut observations into human treatments proved disappointing. On the one hand, ghrelin inactivation by recombinant or endogenous antibodies led to moderate weight loss [196]. On the other hand, supraphysiological doses of ghrelin are necessary to increase hunger [197,198]. Moreover, a large number of studies revealed a negative correlation between ghrelin levels and BMI in humans (reviewed in [199]). With the notable exception of PWS patients, who have abnormally high ghrelin levels [200], the (paradoxically) lower levels of ghrelin observed in nonsyndromic obesity indicate yet another feedback mechanism that is thwarted by the general hormonal deregulation associated with obesity.

Two directions may be helpful to better control ghrelin effects on appetite. The first one is the discovery that acylation by ghrelin O-acyl-transferase (GOAT) is necessary for appetite-inhibitory ghrelin activity, which led in the past decade to the development of GOAT inhibitors, that are still under study [201,202]. Importantly, only nonacylated, but not acylated, ghrelin increases with fasting, shedding doubts on the participation of ghrelin in a 'hunger reflex' [203]. The second direction is the alternative post-translational product of the ghrelin gene, obestatin. First seen as an appetite suppressor with effects opposed to ghrelin, it is now more often described as a metabolic regulator that modulates insulin sensitivity and adiposity through a GHSR-dependent mechanism [204]. Most studies report that obestatin levels are downregulated in obesity and type 2 diabetes, as well as negatively correlated with BMI, making it a possible (but controversial) target for the treatment of obesity and diabetes [205].

Motilin

Motilin is secreted between meals and stimulates peristaltic waves following the pattern of migrating motor complex (MMC) contractions: its peak provokes the entry into phase 3 (the maximum of mechanical and electrical activity causing active peristalsis for 5–10 min), which may induce the feeling of hunger through vagal nerve activation [206]. The administration of motilin or erythromycin, an antibiotic that also acts as a motilin receptor agonist, induces premature MMC phase 3 and increases the declared appetite in healthy subjects [207]. Given the potential role of motilin and gastric motility in driving hunger, plasma levels of obese patients have been compared with their lean counterparts under fasted or refed conditions, yielding alternatively higher or lower levels [207,208]. However, obese subjects seem to lack a clear motilin peak and MMC phase 3 induction across studies, indicating an impairment of gastric motility. One genome-wide association study indicated that SNPs in the motilin gene are among the mutations that are most strongly associated with extreme obesity [209].

Adipose Tissue Peptides

Adiponectin

Adiponectin is an adipocyte-secreted hormone that is obesogenic in mice and genetic inactivation of which leads to resistance to HFD-induced obesity. The absence of adiponectin led to a decrease in food intake, increased energy expenditure, insulin desensitization, and reduction in adiposity [210]. In a multiethnic meta-analysis spanning more than 45 000 subjects, alleles

Figure 4. Central Targets of Major Orexigenic Factors. Ghrelin activates orexigenic signals in the hypothalamus and inhibits the vagal nerve response though the growth-hormone secretagogue receptor (GHSR). Adipocyte-secreted factors, adiponectin and asprosin, respectively mediate proopiomelanocortin (POMC)/CART (cocaine- and amphetamine-regulated transcript) neuron inhibition though the adiponectin receptor 1 (AdipoR1) and AgRP/NPY neuron activation through a GHSR-independent pathway (unknown receptor). Soluble factors such as nicotinamide phosphoribosyltransferase (NAMPT) and acyl-coenzyme A binding protein (ACBP) have been proven to mediate the activation of the lateral hypothalamic area (LHA), but whether this activation is direct or indirect remains to be understood. Abbreviations: AgRP, agouti-related peptide; DMH, dorsomedial hypothalamic area; GABA, γ-amino butyric acid; GH, growth hormone; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; PVH, paraventricular hypothalamic; VMH, ventromedial hypothalamic nuclei.

involved in the diminution of adiponectin levels were strongly associated with lower BMI but also with an increased risk of type 2 diabetes and insulin resistance [211]. In effect, lower adiponectin levels have been consistently measured in obese patients and shown to be inversely correlated with BMI and fat mass [212]. Therefore, the obesity-associated decrease in adiponectin can be interpreted as an attempt of metabolic adaptation to increase energy intake, resulting in limited effects on feeding behavior and adipose tissue accumulation, though with deleterious consequences in terms of insulin resistance and hypertension.

Asprosin

Another adipokine, called asprosin, is secreted upon fasting. Subcutaneous injection of this factor into mice stimulated food intake, likely through central effects because peripherally injected asprosin crosses the blood–brain barrier [213]. Its main metabolic effect is to trigger glycogenolysis in the liver, thus elevating circulating glucose levels during fasting, but it is also able to directly activate orexigenic AgRP neurons [214]. Asprosin levels are associated with high BMI and insulin resistance: it was found to be upregulated in obese versus lean individuals in most recent studies, with one exception in obese children [215,216]. The Marfan lipodystrophy syndrome, associated with severe leanness, originates from mutations in the *FBN1* gene, which codes for asprosin as well as a structural protein called Fibrilin1 [217]. Other polymorphisms in the asprosin-coding part of *FBN1* have been associated with decreased asprosin plasma levels and hypophagic, extremely underweight, and lipodystrophic phenotypes [213]. Interestingly, one study on AN patients found elevated levels of asprosin in patients with bulimic behaviors, reflecting a possible detrimental adaptation to their reduced caloric intake [218]. Altogether, asprosin is a peptide whose variations reliably dictate the alimentary behavior and metabolic resilience in both lean and obese subjects, making it a new potential target for obesity treatments.

Ubiquitously Secreted Proteins

NAMPT

Nicotinamide phosphoribosyltranferase (NAMPT, also known as visfatin) is a ubiquitous intracellular enzyme that contributes to NAD^+ synthesis, conferring it with important metabolic and nutrient-sensing functions. Beyond its enzymatic activity, NAMPT is secreted by a large number of cells. Its endocrine role is the subject of much debate, especially in the pathophysiology of obesity [219]. A central effect of circulating NAMPT can be hypothesized, based on the fact that, in chicks and rats, central injections of NAMPT activate hypothalamic circuits and increase food intake [220,221]. Given that adipose tissue-specific *Nampt* knockout is sufficient to render mice completely resistant to HFD-induced obesity and to improve their glucose tolerance, adipocytes appear to contribute to the obesogenic effects of NAMPT [222]. Human studies tend to confirm the orexigenic role of NAMPT as its plasma level is increased in obesity [223]. Notably, a rare allelic form of *NAMPT* was found to be protective against extreme obesity in a cohort enrolling more than 6000 subjects [224], raising hopes for targeting NAMPT as a suitable strategy against obesity.

ACBP

Acyl-coenzyme A binding protein (ACBP), also called diazepam binding inhibitor (DBI), is a ubiquitous protein that is present in the cytoplasm of all nucleated cells, where it affects long-chain fatty acyl-CoA ester metabolism and mitochondrial fatty acid oxidation. Upon autophagy induction, for instance in response to fasting, ACBP is secreted from cells and the consequent rise in extracellular and circulating ACBP activates orexigenic and lipogenic responses in mice. Thus, the intravenous or intraperitoneal injection of ACBP causes an immediate (30 min) hyperphagic response that does not require the binding of ACBP to acyl-coenzyme A (because mutant proteins losing this function conserve their potential to stimulate appetite), yet requires the function of the GABA A receptor (GABAAR) because mice bearing a mutation in this receptor, abolishing its interactions with

ACBP, fail to mount a hyperphagic response [225]. Transgenic expression of ACBP in hepatocytes is sufficient to cause significant weight gain and an increase in adiposity in mice [226]. Conversely, antibody-mediated inactivation of circulating ACBP is anorexigenic, meaning that it reduces hyperphagy in starved mice and leptin-deficient *ob/ob* mice as it reduces weight gain of mice fed a HFD or increases weight loss when obese mice are switched from a high-fat to a normal diet [226]. Thus, the relocation of ACBP from the intracellular to the extracellular space can be viewed as a cellular sensor of nutrient scarcity that triggers appetite. It appears improbable that peripherally administered ACBP acts on the CNS to induce appetite because central injection of ACBP or its peptide fragments [in particular octadecaneuropeptide (ODN)] is anxiogenic and anorexigenic [227,228]. Thus, intracerebroventricular injection of ODN into the fourth ventricle inhibits the swallowing reflex controlled by the brainstem [229]. Similarly, intraparenchymal unilateral injection of ODN C-terminal octapeptide (OP) into the arcuate nucleus of the hypothalamus reduces food intake. These effects are not mediated by GABAAR but rather by ODN-GPCR signaling, since they are blunted by cotreatment with a selective ODN-GPCR antagonist [230,231]. Moreover, the orexigenic effects of intraperitoneally injected ACBP can be blunted by a glucose clamp, again pleading against a direct CNS effect of ACBP [226].

Dampened ACBP signals may be linked to insufficient food intake, as indicated by lower ACBP levels in patients with AN [226,232] and by a predisposition to weight gain after antipsychotic treatment for patients bearing a polymorphism in the gene coding for the γ2 subunit of GABAAR [233]. Overexpression of ACBP is found in the tissues and the plasma of rodent models of obesity [234], as well as in human obese cohort studies, in which circulating ACBP levels strongly correlate with BMI. Thus, the obesity-induced overexpression of this orexigenic factor potentially drives a feedforward mechanism to increase food consumption and to sustain the self-maintenance of obesity [235].

Concluding Remarks and Future Perspectives

Although obesity has become the most prevalent pathological condition afflicting humanity, its pathophysiology has not been elucidated to a level that would facilitate its management. Thus, a whole economic sector promises a myriad of diets or exercise regimens, psychosocial interventions, supplements of micronutrients or specific concoctions, though without tangible results. Bariatric surgery has major side effects and often provides only transient benefits. Pharmacological interventions have also been unsuccessful because anti-obesity drugs were either ineffective or produced major side effects precluding their general use [236]. In particular, anorexiants that targeted central-nervous appetite control have turned out to induce psychiatric side effects, including suicide [237]**.** For this reason, peripheral appetite regulatory circuitries may offer new opportunities for an etiological treatment of obesity.

Here, we have reviewed an extensive list of appetite regulators that are produced in peripheral locations and then regulate food intake through a variety of mechanisms that may be peripheral (for instance, by effects on vagal afferences, by effects on other (neuro)endocrine factors, or by metabolic effects on major organs, including the liver and adipose tissue) or central (by direct effects on appropriate brain centers). Of note, manipulation of some of the appetite regulators mentioned here yields ambiguous results. Thus, neutralization of GIPR and GLP-1R by systemically injected antibodies (that in principle cannot cross the blood–brain barrier) inhibits diet-induced obesity in mice, but injection of dual agonists of GIPR and GLP-1R (which reach the brain) has marked anorexigenic effects, both in preclinical and clinical settings (Table 1). Similarly, injection of ACBP/DBI into the brain has anorexigenic effects, contrasting with the orexigenic consequences of its intravenous or intraperitoneal injection. These results underscore the fact that brain-permeable and -impermeable agonists and antagonists may have rather distinct effects. Future preclinical

Outstanding Questions

A systematic longitudinal analysis of changes in the plasma concentration of neuroendocrine appetite regulators is still elusive.

It remains to be determined which appetite regulators contribute to the dynamic phase of obesity (i.e., the phase with weight gain) versus the static phase of obesity (i.e., the phase with stable weight and energy balance).

It is important to explore the question as to whether appetite regulatory neuroendocrine factors determine food preferences and hence influence the quality of ingested food items beyond the quantity of calories.

The optimal strategy to control appetite by pharmacological interventions is an open conundrum.

research should explore this conjecture, which, if correct, will affect the development of drugs for the treatment of obesity.

In this feature review, we attempted to identify those endogenous appetite inhibitors that are reduced in the circulation of obese patients as well as those appetite stimulators that are increased, driven by the belief that pharmacological manipulations of such mediators would have greater chances of being successful. Obviously, this rationale has some major caveats that result from persistent uncertainties: Are the methods used for the quantification of factors accurate? This question is particularly pertinent when distinct peptide fragments act on different receptors (as found for PYY) or post-translational modifications affect the bioactivity of appetite regulators (as illustrated for acylated ghrelin). Is the measurement of the factor in the plasma/serum physiologically relevant? This question is legitimate, considering that some of the factors mostly act as paracrine, not endocrine, factors (as gastrointestinal peptides that locally act on vagal afferences) and have a short half-live. Does the measurement occur during the dynamic phase of obesity (i.e., the phase with weight gain) or the static phase of obesity (i.e., the phase with stable weight and energy balance)? Unfortunately, longitudinal studies that would distinguish these phases are uncommon, but would be useful to distinguish possible differences in the role of appetite regulators in weight gain versus weight maintenance. Could alterations in circadian rhythms affecting peripheral appetite regulators contribute to the development of obesity? Again, the clinical exploration of disease-related, time-dependent fluctuations of appetite regulators is in its infancy. Finally, could deregulations in food preferences (for instance for high-sugar items, which likely are intrinsically obesogenic) be dictated by peripheral appetite regulators? Thus, specific factors (such as GIP and GLP) could determine a qualitative rather than a quantitative disequilibrium in food intake that contributes to the obese phenotype.

As summarized here, most factors that are generally considered as endogenous appetite inhibitors (such as leptin and many others) are increased in obese patients and most endogenous appetite stimulators (such as ghrelin and many others) are reduced in nonsyndromic obesity, likely reflecting a failing homeostatic circuitry that translates into this 'paradoxical' pattern. Thus, different to normal physiology (before obesity occurs), in which appetite stimulators or inhibitors participate in homeostatic pathways to limit caloric uptake (Figure 5A), once obesity has established, such circuitries appear to be unable to link excessive caloric intake and body mass to a reduction of appetite stimulatory hormones (or an increase in appetite inhibitor effects). Instead, they are replaced by disease amplifying feedforward loops in which excessive adiposity stimulates appetite (or suppresses appetite inhibition) (Figure 5B). Hypothetically, these latter feedforward loops would be truly pathogenic and would be accompanied by a 'coherent' pattern (i.e., an increase in appetite stimulators or a decrease in appetite inhibitors).

For this reason, it is important to identify peripheral modulators of appetite that behave in a 'coherent' rather than 'paradoxical' fashion. Thus, it may be advisable to concentrate research efforts on appetite inhibitors that are indeed reduced (not increased or unaltered) in obese subjects and to investigate whether their artificial supplementation (or, alternatively, the administration of agents that have agonistic effects on their receptors) would be able to reduce excessive caloric uptake. Similarly, it appears logical to neutralize appetite-stimulatory factors that are 'coherently' elevated (rather than 'paradoxically' reduced or unaltered) in obesity.

Apparently, only three endogenous appetite inhibitors follow a 'coherent' pattern: PP, PYY, and VIP (Table 1). Given the fact that these potential anorexiants also have multiple other functions outside of appetite control, which would yield side effects, it will be important to choose among these agents the one that is the most 'specific' appetite controller. Using this criterion, which,

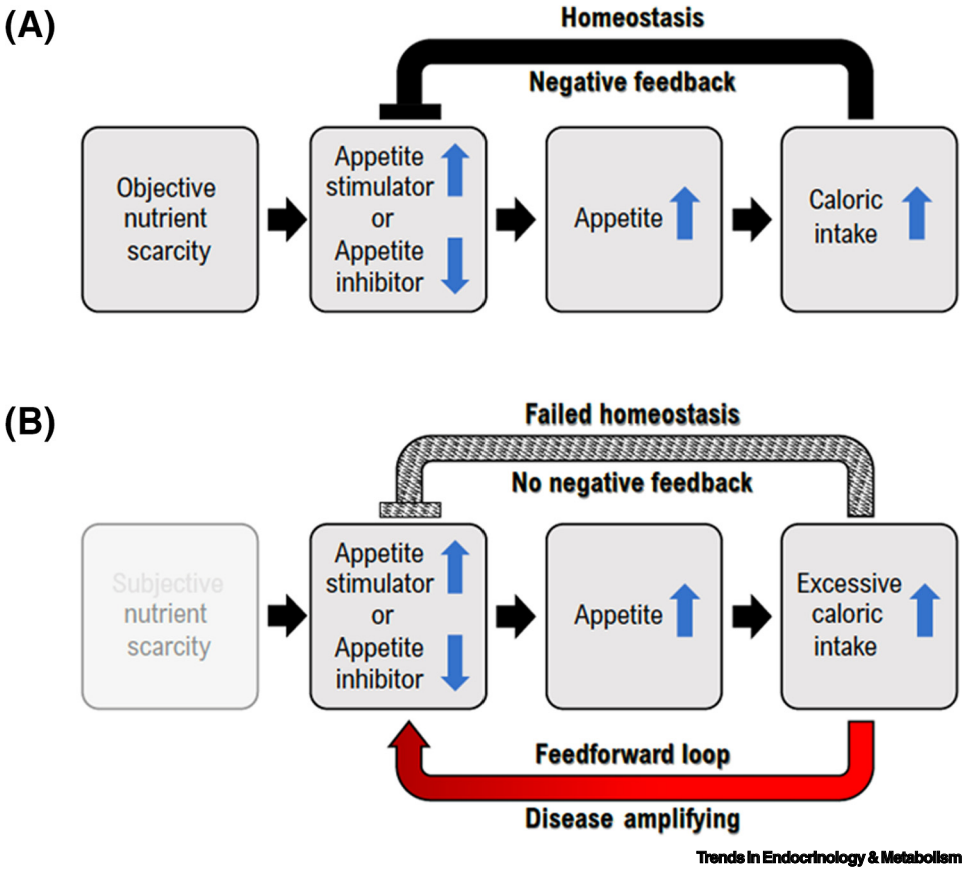

Figure 5. Peripheral Appetite-Regulatory Circuitries. (A) In the normal starvation response, appetite-stimulatory hormones are upregulated or appetite-inhibitory mediators are downregulated, causing a raise in appetite and feeding that ultimately abolishes the starvation-elicited alterations in appetite-relevant hormones, thus closing a homeostatic feedback loop. (B) In obesity, this feedback loops fails and may be superseded in importance by disease amplifying feedforward loops that involve either appetite stimulators that are upregulated or appetite inhibitors that are downregulated due to an increase in adiposity.

however, is based on scarce knowledge, it appears that PP would be the best candidate for development. Nonetheless, at this point, no active clinical trials are recruiting patients for PP administration.

Among the numerous appetite-stimulatory hormones that have been characterized over the past three decades, only three behave in a 'coherent' fashion: ACBP, asprosin, and NAMPT (Table 2). These three factors are the only appetite-stimulatory effects with a ubiquitous expression pattern (Figure 2A) and that are also phylogenetically ancient (Figure 6). Thus, ACBP is the sole protein factor secreted by yeast (*Saccharomyces cerevisiae*) upon starvation and stimulates sporulation, which is the only mechanism by which yeast cells search for new food sources. ACBP also stimulates pharyngeal pumping and nutrient uptake in the nematode *Caenorhabditis elegans* [238]. Asprosin/FBN1 possesses an ortholog in nematodes. NAMPT has a functional homolog, PNC-1, in yeast [239] and nematodes, where this protein can be secreted and has cell nonautonomous developmental functions [240]. It appears intriguing that such ubiquitous, phylogenetically ancient factors may be particularly important for the pathogenesis of human obesity.

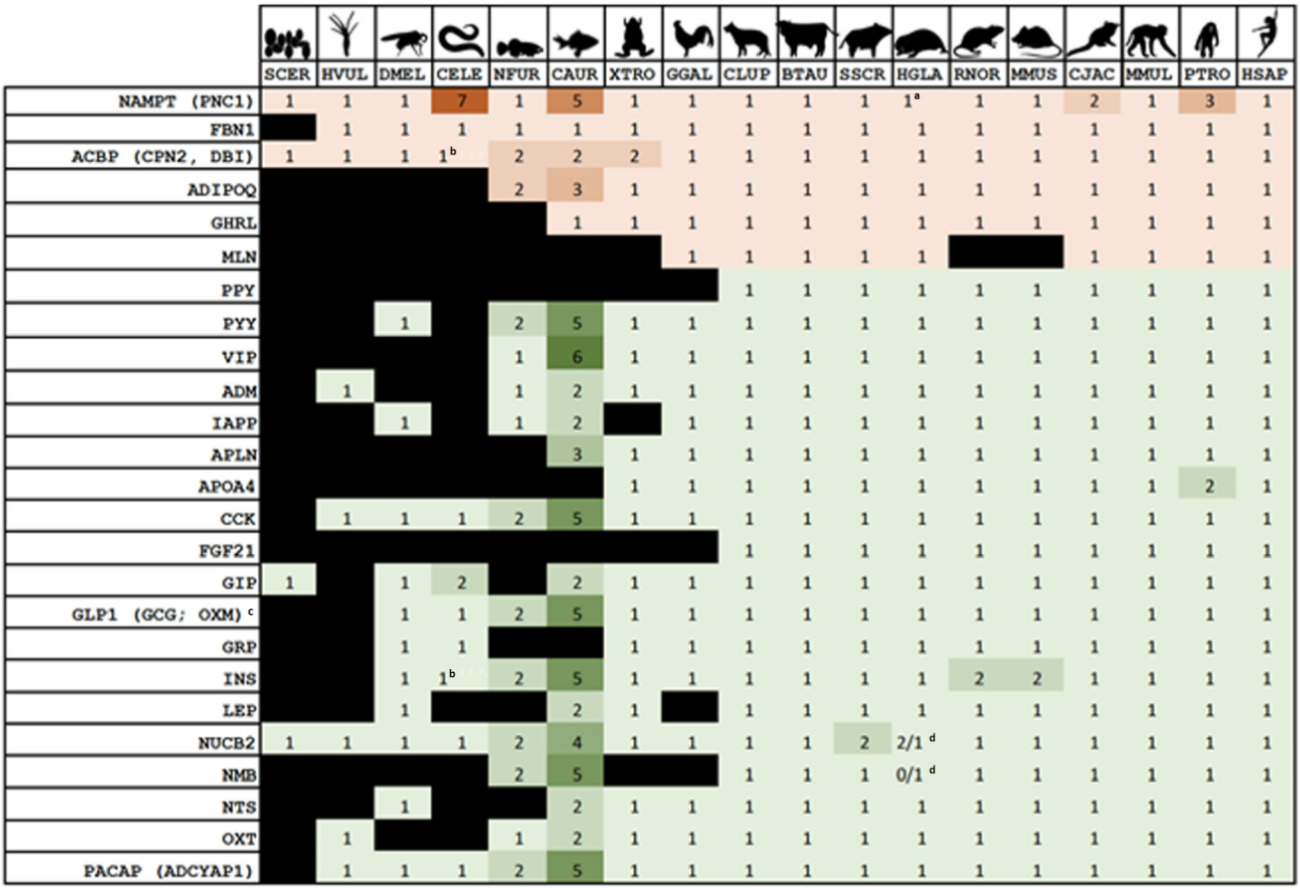

Figure 6. Phylogenomic Analysis of Genes Related to Appetite (Green for Inhibitors, Orange for Stimulators). Numbers represent functional copies of each gene. Black stands for no copies. Numbers were obtained from orthology tables at Ensembl. Where stated, these numbers were corrected using published results, manual annotation of genomic assemblies, or specific databases, such as Wormbase. Abbreviations: ACBP, acyl-coenzyme A binding protein; ADIPOQ, adiponectin; ADM, adrenomedullin; APLN, apelin; APOA4, apolipoprotein A-IV; BTAU, *Bos primigenius taurus*; CAUR, *Carassius auratus*; CCK, cholecystokinin; CELE, *Caenorhabditis elegans*; CJAC, *Callithrix jacchus*; CLUP, *Canis lupus familiaris*; DMEL, *Drosophila melanogaster*; FGF21, fibroblast growth factor 21; GGAL, *Gallus*; GHRL, ghrelin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GRP, gastrin-releasing peptide; HGLA, *Heterocephalus glaber*; HSAP, *Homo sapiens*; HVUL, *Hydra vulgaris*; IAPP, islet amyloid peptide; LEP, leptin; MLN, motilin; MMUL, *Macaca mulatta*; MMUS, *Mus musculus*; NAMPT, nicotinamide phosphoribosyltransferase; NFUR, *Nothobranchius furzeri*; OXT, oxytocin; PACAP, pituitary adenylate cyclase-activating polypeptide; PYY, peptide tyrosine-tyrosine; PTRON, *Pan troglodytes*; RNOR, *Rattus norvegicus*; SCER, *Saccharomyces cerevisiae*; SSCR, *Sus scrofa*; VIP, vasoactive intestinal peptide; XTRO, *Xenopus tropicalis*. [a]One functional copy, five additional copies seem to have undergone a pseudogenization process. [b]Wormbase annotates additional members (~7 for ACBP and ~30 for INS). Their functionality remains elusive. [c]Genetically, oxyntomodulin (OXM) and glucagon-like peptide-1 (GLP-1) are identical. [d]Values change depending on gender (male/female).

In a highly speculative scenario (see Outstanding Questions), one or several among these three factors would have evolved to generate the 'core' of appetite control, which would have been complemented during evolution by many additional factors (that do not exist in invertebrates). However, only the 'core' is indeed endowed with the capacity to impose long-term deviations from normal body mass. Among these three putative 'core' appetite stimulators (ACBP, asprosin, and NAMPT), the one that apparently has the most specific relationship to obesity is ACBP, in that it is both an orexigenic factor and stimulates lipo-anabolism. By contrast, since asprosin binds to the insulin receptor, this factor may be expected to play a major role in glucose metabolism. Moreover, NAMPT is an enzyme that participates to the biosynthesis of NAD^+, a vital cofactor of many enzymes, suggesting that NAMPT inhibition might result in major side effects. As a

Box 2. Outstanding Clinical Trials for the Modulation of Core Appetite Regulators

Clinical trials for the treatment of obesity have been hampered for a long time because obesity was only recognized by the American Medical Association as a 'disease' in 2013. For this reason, most clinical trials have been dealing with the treatment of comorbidities of obesity such as type 2 diabetes and non-alcoholic fatty liver disease. Moreover, the standards for safety are particularly stringent for clinical trials designed to achieve weight loss, because obesity (as opposed to, e.g., cancer) is not considered as an acutely life-threatening condition. The clinical management of obesity demands a combination of pharmacological treatments with nutritional and behavioral interventions (diet and exercise), requiring compliance by the patient. The problem of compliance can be overcome by monitoring drug administration (or by providing injectable drugs), as well as continuous measuring of cardiometabolic parameters. However, it is notoriously difficult to induce and maintain stable modifications of eating habits and physical (in)activity.

The notion of a 'core' of appetite-modulatory factors that exhibit a 'coherent' behavior, suggesting a causative implication in obesity, is rather new. Appetite-inhibitory agents that are reduced in human obesity have been supplemented in clinical trials. This applies to subcutaneous injections of PP (https://www.clinicaltrials.gov NCT01052493, NCT02221765), as well as oral, nasal, or intravenous administration of PYY (e.g., NCT00331175, NCT00537420, NCT00822705, NCT00940134), that were completed in the past, showing that appetite control can be achieved (see Table 1 in main text). However, specific inhibitors of appetite stimulators such as asprosin, NAMPT, and ACBP have not yet been evaluated in clinical trials for the treatment of obesity. For this, it would be necessary to develop specific receptor antagonists or humanized neutralizing antibodies that are currently not yet available.

possible strategy, 'core' appetite stimulators might be inactivated by blocking antibodies or by the blockade of their receptors. However, clinical trials that would explore this possibility are still elusive (Box 2).

In summary, well over two dozen peptide hormones participate in peripheral appetite control. However, in human obesity, the serum concentrations of only three appetite inhibitors are reduced and only three appetite stimulators are enhanced, contrasting with all the other factors that often exhibit an inverse, paradoxical behavior. We surmise that this ensemble of six hormones constitutes the short list of agents that are the best potential targets for pharmacological interventions on appetite control.

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Declaration of Interests

G.K. is listed as an inventor on a patent application dealing with ACBP/DBI as a target for therapeutic appetite control. The remaining authors have no interests to declare.

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