REVIEW

Appetite- and weight-inducing and -inhibiting neuroendocrine factors in Prader–Willi syndrome, Bardet–Biedl syndrome and craniopharyngioma versus anorexia nervosa

H Vlaardingerbroek[1,2], **E L T van den Akker**[1] and **A C S Hokken-Koelega**[1]

[1]Department of Pediatrics, Subdivision of Endocrinology, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands
[2]Willem-Alexander Children's Hospital, Department of Pediatrics, Division of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence should be addressed to H Vlaardingerbroek: H.Vlaardingerbroek@lumc.nl

Abstract

Obesity is reaching an epidemic state and has a major impact on health and economy. In most cases, obesity is caused by lifestyle factors. However, the risk of becoming obese differs highly between people. Individual's differences in lifestyle, genetic, and neuroendocrine factors play a role in satiety, hunger and regulation of body weight. In a small percentage of children and adults with obesity, an underlying hormonal or genetic cause can be found. The aim of this review is to present and compare data on the extreme ends of the obesity and undernutrition spectrum in patients with Prader–Willi syndrome (PWS), Bardet–Biedl syndrome (BBS), acquired hypothalamic obesity in craniopharyngioma patients, and anorexia nervosa. This may give more insight into the role of neuroendocrine factors and might give direction for future research in conditions of severe obesity and underweight.

Key Words

- neuroendocrine factors
- syndromic obesity
- Prader–Willi syndrome
- Bardet–Biedl syndrome
- craniopharyngioma
- undernutrition
- anorexia nervosa
- ghrelin
- leptin
- adiponectin

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Introduction

Worldwide, obesity is reaching an epidemic state. In a vast majority of patients with obesity, lifestyle factors, such as too much food consumption and no or infrequent exercise, play a major role; in a small percentage of children and adults with obesity, an underlying hormonal or genetic cause can be found. In the last decades, the unraveling of genetic and molecular mechanisms of obesity progresses steadily, especially due to whole-exome sequencing by which single-gene mutations that cause obesity can be detected. Hence, more and more genetic causes of monogenic and syndromic obesity are discovered.

Hunger, satiety and energy expenditure are tightly controlled homeostatic processes, in which neuroendocrine factors play an important role. Neuroendocrine factors can be produced in various tissues, such as the liver, gut, adipose tissue, pancreas, and brain (Fig. 1). These factors send signal through different pathways to the brain, mainly to the hypothalamus. In the hypothalamus, activation of different signaling cascades leads to either food intake or satiety. Since this is a complex multivariate system, the role and interplay of these neuroendocrine factors in specific circumstances still have many unraveled aspects.

For this review, neuroendocrine factors are grouped according to their main function: stimulation of food intake and/or increase in body weight vs inhibition of food intake and/or decrease in body weight. The order of presentation is based on the number of studies

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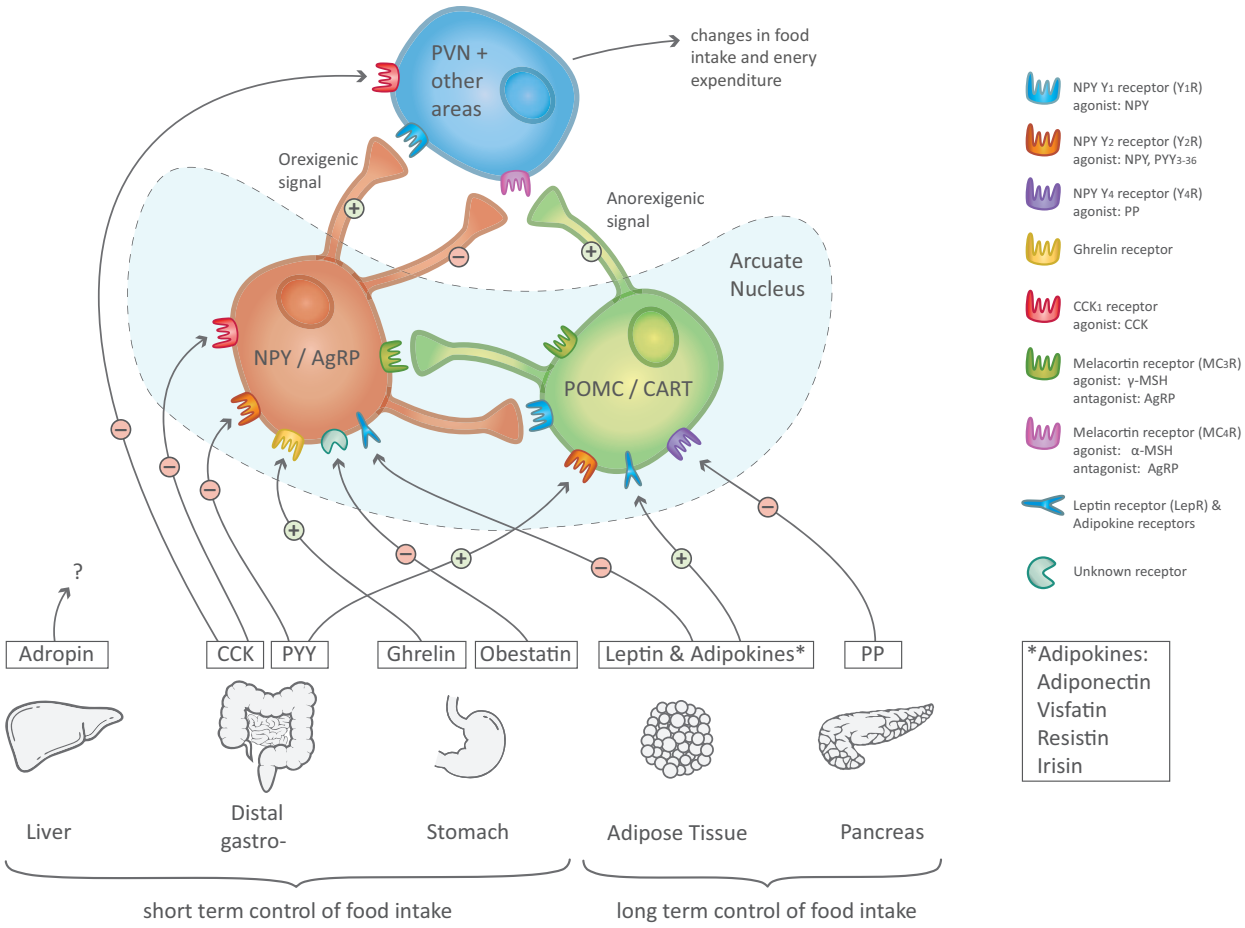

Figure 1
Neuroendocrine factors and interactions in the hypothalamus. In the gastrointestinal tract, multiple neuroendocrine hormones are produced. Ghrelin is the only gut hormone that stimulates feeding. Other hormones, including cholecystokinin (CCK), peptide YY (PYY), and pancreatic polypeptide (PP) provide information about the chemical properties of the ingested food and fullness of the stomach. Adipose tissue-related hormones are proportional to the amount of body fat. These hormones interact with postprandial gut hormones to the arcuate nucleus. In the hypothalamic region, multiple peripheral and neural signals are integrated to maintain energy homeostasis and balance between energy expenditure and food intake. The arcuate nucleus contains two types of neurons: the first type expresses the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP); the second type expresses the anorexigenic proopiomelanocortin (POMC) and cocaine-amphetamine-related transcript (CART). Both these neuron types innervate the paraventricular nucleus (PVN), which sends the signals to other parts of the brain, including the ventromedial nucleus, dorsomedial nucleus, and the lateral hypothalamic area.

available for the respective neuroendocrine factor. In Table 1, information about the main site of production, function and the site of action of the neuroendocrine factors is summarized. Background information about the functions and interactions of the neuroendocrine factors can be found in the Supplementary material (see section on supplementary materials given at the end of this article).

The aim of this review is to present data on the extreme ends of the obesity spectrum in patients with Prader–Willi syndrome (PWS), Bardet–Biedl syndrome (BBS), acquired hypothalamic obesity in craniopharyngioma patients, and compare this with anorexia nervosa. Although the pathophysiology of the psychiatric condition anorexia nervosa is not known yet, these patients have a restrictive eating pattern and a (very) low BMI. Genome-wide association studies suggest a link between genetic variants and undernutrition and obesity, suggesting that the same biological pathways and neuroendocrine factors could be affected, albeit in different directions. For example, 16p11.2 hemizygosity causes a penetrant form of obesity that is often associated with hyperphagia and intellectual disabilities, while 16p11.2 duplication is associated with being underweight with an unusually high frequency of selective and restrictive eating behaviors (1, 2, 3). Although the pathophysiology of the psychiatric condition anorexia

Table 1 Overview of neuroendocrine factors and their main actions in relation to regulation of food intake and body weight.

Neuroendocrine factor	Main site of production	Main site of action	Receptors	Action	Reference
Stimulation of food intake and increase in body weight					
Acylated ghrelin (AG), Unacylated ghrelin (UAG)	Stomach	AgRP neurons, adipose tissue	AG: GHS-R1a UAG: unknown	AG: regulates short-term food intake (↑ in hunger, ↓ after food intake) by increasing NPY/AgRP, regulates lipid metabolism by antagonizing leptin effects, increased growth-hormone secretion UAG: anti-diabetogenic, functional inhibitor of AG	(26)
Adiponectin	Adipose tissue	Pancreatic β-cells	AdipoR1 AdipoR2	Increases insulin sensitivity, chronic overexpression increases s.c. but not visceral fat	(29)
Neuropeptide Y (NPY)	Medial arcuate nucleus		Y1R, Y5R	Stimulates food intake and antagonizes POMC action	(98)
N-arachidonoyl ethanolamide (AEA), 2-arachidonoylglycerol (2-AG)	Throughout the brain	Metabolically active peripheral tissues	CB1 CB2	Stimulates food intake, stimulates energy storage, negative effect on insulin sensitivity	(99)
Beta-endorphin	Anterior pituitary gland	Anterior pituitary gland	μ-opioid	Stimulates food intake	(100)
Brain-derived neurotrophic factor (BDNF)			TrkB	Possibly related to hyperphagia and metabolism	(101)
Agouti-related peptide (AgRP)	Medial arcuate nucleus		MC3R and MC4R antagonist	Stimulates food intake	(98)
Inhibition of food intake and decrease in body weight					
Leptin	Adipose tissue	PMC and NPY neurons in arcuate nucleus	Ob-R, Ob-Rb	Inhibits NPY and AgRP, stimulates CART and POMC, hence, stimulating satiety via stimulation of MC4R	(59)
Peptide YY	Ileum, colon, rectum	Presynaptic receptor for NPY	Y2R	Induces satiety by inhibition of NPY and stimulation of POMC, thereby resulting in de-inhibition of α- and β-MSH, reduces gastric emptying and gut transit time	(12)
Pancreatic polypeptide (PP)	Endocrine pancreas		Y4R, Y5R	Inhibits food intake	(87)
Cholecystokinin (CCK)	Duodenum, jejunum	Locally; lateral hypothalamus, medial pons, lateral medulla	CCK1 CCK2	Induces satiety, reduces gastric emptying, increases secretion of bile acid and pancreatic enzymes	(67)

(Continued)

Table 1 Continued.

Neuroendocrine factor	Main site of production	Main site of action	Receptors	Action	Reference
Obestatin	Stomach (by post-translational modification of preproghrelin)	AgRP in arcuate nucleus		suppresses appetite, inhibits gastric emptying, decreases body weight	(102)
Neurotensin	Throughout the CNS	Hypothalamus, amygdala and nucleus accumbens, small intestine	NTSR1 NTSR2 NTSR3	inhibits gastric emptying	(96)
Proopiomelanocortin (POMC) α-melanotropin (α-MSH)	Arcuate nucleus		MC3R and MC4R	Inhibits food intake, stimulates basal metabolic rate, alters nutrient partitioning	(97)
CART	Arcuate nucleus			Inhibits food intake	(103)

Some data from (104). AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2; CART, cocaine-amphetamine-related transcript; CB 1, cannabinoid type 1; CB 2, cannabinoid type 2; CCK1, cholecystokinin receptor 1; CCK2, cholecystokinin receptor 2; GSH-R1a, growth hormone secretagogue type 1A receptor; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; NTSR1, neurotensin receptor 1; NTSR2, neurotensin receptor 2; NTSR3, neurotensin receptor 3; Ob-R, leptin receptor; Ob-Rb, long isoform of leptin receptor; TrkB, tropomyosin-related kinase B; Y1R, Y receptor type 1; Y2R, Y receptor type 2; Y4R, Y receptor type 4; Y5R, Y receptor type 5; α-MSH, α-melanotropin; β-MSH, β-melanotropin.

nervosa is yet unknown, these patients have a very restrictive eating pattern and a (very) low BMI. From a food intake and fat storage perspective, anorexia nervosa can be viewed as an extreme opposite condition compared to the extreme conditions of obesity. This may provide more insight into the role of neuroendocrine factors and might give direction for future research in conditions of severe obesity and underweight.

Conditions of obesity and undernutrition described in this review

Prader–Willi syndrome (PWS)

Prader–Willi syndrome (PWS) is one of the most studied syndromes of obesity and hyperphagia. It is a neurodevelopmental disorder caused due to the loss of function of the paternally derived alleles in the region of 15q11-q13 occurring in one in 10,000 to one in 25,000 live births. The loss of function can be caused by a deletion in chromosome 15 (~60%), uniparental disomy (UPD) (~36%), an imprinting defect (~2-5%), or unbalanced translocation (~1%) (4). Characteristics of PWS are hypotonia and feeding problems during the neonatal stage and early childhood and neurodevelopmental delay. In a later stage during childhood, the main characteristics are impaired satiety, hyperphagia, low energy metabolism, and neurodevelopmental disorders such as autistic behavior and obsessive-compulsive disorder. Without strict regulation of food intake, morbid obesity develops (5).

In PWS, changes in appetite and weight gain over time are described as five different nutritional phases. Phase 0 is the prenatal/birth phase characterized by decreased fetal movements and lower birth weight. In phase 1a, infants demonstrate feeding problems and decreased appetite. In phase 1b, feeding and appetite improve. In phase 2a, weight increases without increase in appetite or excess intake of calories. In phase 2b, appetite and interest in food increase. Phase 3 is characterized by hyperphagia. Some adults reach phase 4 in which appetite is no longer insatiable (6).

Bardet–Biedl syndrome (BBS)

Bardet–Biedl syndrome (BBS) is another example of syndromic obesity. It is an autosomal recessive and genetically heterogeneous ciliopathy characterized by retinitis pigmentosa, obesity, kidney dysfunction, polydactyly, behavioral dysfunction, and hypogonadism. It has a prevalence of 1 to 9 in 1,000,000. The wide clinical spectrum observed in BBS is associated with significant genetic heterogeneity. To date, mutations in 12 different genes (*BBS1* to *BBS12*) have been identified as being responsible for this phenotype (7). Data on neuroendocrine factors in other syndromic obesity conditions, such as the Prader–Willi (PW)-like conditions like Temple syndrome and 6q deletion, were too limited to contribute to this review. In addition, monogenic obesity syndromes, due to mutations in melanocortin 4 receptor (MC4R), the leptin gene (LEP), leptin receptor gene (LEPR), and proopiomelanocortin (POMC) for example,

are not described in this review due to paucity of data on neuroendocrine factors in these conditions.

Craniopharyngioma

Craniopharyngioma is a rare benign brain tumor in the sellar and suprasellar region, an area that is close to the optic chiasm, pituitary and hypothalamus. Despite its benign histological characteristics, craniopharyngioma can cause severe morbidity, including obesity. The obesity is due to hypothalamic dysfunction, leading to hyperphagia, lower resting energy expenditure, insulin resistance and a disturbed day–night rhythm with increased somnolence and decreased activity during the day. Another contributing factor can be multiple pituitary hormone deficiency, which is often present in these patients, requiring hormone supplementation (8).

Anorexia nervosa

Anorexia nervosa, a psychiatric disorder, is a condition that results in persistent low body weight with very limited food intake due to disturbed eating behavior and often increased physical activity. Due to the low body weight, many of these patients develop neuroendocrine dysfunction such as amenorrhea. The pathophysiology of anorexia nervosa is not known yet, but factors involved in eating behavior and appetite control might play a role and, therefore, might be used as a opposite model for the presented obesity conditions.

Neuroendocrine factors stimulating food intake and body weight

Data on neuroendocrine factors that stimulate food intake and induce increase in body weight are summarized in Table 2 and are briefly described below. The order of presentation is based on the number of human studies available for the respective neuroendocrine factor in the selected obesity/undernutrition conditions.

Total ghrelin, acylated ghrelin, and unacylated ghrelin

Ghrelin is mainly secreted in the stomach and increases food intake. A pitfall in most studies is that only total ghrelin is measured and not the more specific isoforms, acylated ghrelin (AG) and unacylated ghrelin (UAG). With regard to the metabolic and appetite regulating effects, AG and UAG both have distinct functional effects and can affect each other, illustrating the additional value of the AG/UAG ratio. Based on current knowledge, the measurement of total ghrelin is of hardly any relevance which is demonstrated in the contradictory results in several obesity conditions (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24). Therefore, in this review, we will only present data on AG and UAG; total ghrelin is not described.

At early age, *PWS* is characterized by feeding problems and hypotonia. In these young children, AG levels were not different and UAG levels were higher compared to controls, resulting in a lower AG/UAG ratio (25, 26). After the age of 3 years, PWS children generally become hyperphagic and obese. These older PWS children had similar high AG/UAG ratios compared to obese controls but due to different reasons; in PWS, AG was high, while in obese controls UAG was low. The AG/UAG ratio in PWS was higher compared to non-obese controls due to higher AG and similar UAG levels (26). These data suggest that the AG/UAG ratio is correlated to the nutritional phase and might have a relation with the switch from feeding problems to hyperphagia and excessive weight gain in PWS (26).

In BBS, AG was comparable to controls in a small study (20), no data were available for UAG.

For *craniopharyngioma*, no data were available in relation to AG and UAG.

In *anorexia nervosa,* AG and UAG levels were up to two-fold higher than compared to controls and returned to normal levels after normalization of body weight (27, 28), which may display a mechanism to stimulate food intake in these underweight patients.

To summarize, the AG/UAG ratio seems to be related to appetite and weight gain and might function as a switch from undernutrition or normal weight to obesity. Whether UAG could be a treatment option needs further study.

Adiponectin

Adiponectin is the most abundant peptide secreted by adipocytes and mainly plays a role in energy metabolism. Serum concentrations of adiponectin decrease with increasing body weight and are positively associated with insulin sensitivity (29).

Higher adiponectin concentrations were reported in children (14, 30, 31) and adults with *PWS* (16, 32, 33, 34, 35, 36) compared to obese controls and non-obese controls

Table 2 Neuroendocrine factors in various conditions of obesity and undernourishment compared to healthy controls.

Neuroendocrine factor	Obesity conditions					Anorexia nervosa
Stimulation of food intake and/or increase in body weight						
Acylated ghrelin (AG) Unacylated ghrelin (UAG)	PWS	<4 years: 4–15 years:	AG = AG ↑	UAG ↑ UAG = AG/UAG ↑ vs non-obese controls	AG/UAG ↓ AG/UAG = vs obese controls	AG ↑ UAG ↑
		Phase 1a, b: Phase 2b–3:	↓ vs phase 2–3; = vs controls ↑ vs controls			
	Bardet–Biedl	=				
Adiponectin	PWS	Children: During GH: Adults:	↑ = ↑ ↑			↑ (↓ =)
	Bardet–Biedl	=				
Neuropeptide Y (NPY)	PWS	=				↓ ↑ =
N-arachidonoyl ethanolamide (AEA)	PWS	Fasted: Postprandial:	= ↓			Fasted: ↑
2-arachidonoylglycerol (2-AG)	PWS	Fasted: Postprandial:	↑ =			Fasted: =
Beta-endorphin	PWS	↑				↓ ↑ =
Brain-derived neurotrophic factor (BDNF)	PWS	↓				↓ =
Agouti-related peptide (AgRP)						↑
Inhibition of food intake and/or decrease in body weight						
Leptin	PWS	<6 years: ≥6 years:	↑ = (↑)			↓
	Bardet-Biedl	↑				
	Craniopharyngioma	↑				
Peptide YY (PYY)	PWS	Fasted: Postprandial:	↓ ↑ = ↑ =			Fasted: ↑ = Postprandial: ↑ =
	Craniopharyngioma	=				
Pancreatic polypeptide (PP)	PWS	Fasted: Postprandial:	↓ = in non-obese < 5 years ↓			Fasted: = (↑) Postprandial: =
Cholecystokinin (CCK)	PWS	= (↑)				= ↓ ↑
	Craniopharyngioma	=				
Obestatin	PWS	<6 years: ≥6 years:	↑ =			↑
	Bardet–Biedl	=				
Neurotensin	PWS	↑				
α-melanotropin (α-MSH)	Craniopharyngioma	↓ with lack of postprandial increase				↓ =

If not stated otherwise, concentrations of neuroendocrine factors are measured in fasted state.. ↓,↑, =: lower, higher, not different compared to controls, respectively.

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(13), while others showed no differences with obese controls (37). The higher adiponectin concentrations in PWS were associated with the relatively lower amount of visceral adipose tissue compared to obese controls (16) and may be related to the relative lower incidence of insulin resistance and metabolic syndrome in PWS patients (31, 38).

In children with *BBS*, adiponectin levels were not different compared to controls (20). No data were available for *craniopharyngioma* patients.

In *anorexia nervosa*, data on adiponectin levels were inconsistent (27, 39, 40). Studies in severely underweight anorexia patients showed reduced adiponectin levels, which increased after weight gain (39). The lower levels in these severely underweight patients are probably a consequence of the low fat mass, rather than a causative factor.

To summarize, adiponectin levels seems to reflect the amount of body fat and higher levels might have a protective effect on metabolic syndrome. For future studies, it would be interesting to focus on the relationship between adiponectin levels and visceral vs peripheral fat and whether adiponectin might play a causative role in weight gain.

Appetite and weight stimulating brain-derived neuroendocrine factors

Several regions and neuroendocrine factors in the brain are important in processing information about food and body weight (Fig. 1). Neuropeptide Y (NPY) is one of the most abundant peptides in the hypothalamus and one of the most potent orexigenic factors. Beta-endorphin, N-arachidonoyl-ethanolamine (AEA), and 2-arachidonoylglycerol (2-AG) play a role in stimulating food intake via the hedonic system and via appetite initiation.

In *PWS* children, the fasting levels of NPY (30) and AEA (41) were not different compared to BMI)-matched controls. After a meal, AEA decreased (42). Fasting levels of beta-endorphin (43) and 2-AG (41) were higher in children with PWS compared to controls and 2-AG levels remained unchanged after a meal (42). Levels of brain-derived neurotrophic factor (BDNF) (44, 45) were lower in children with PWS compared to controls. It was suggested that the low fasting BDNF concentrations and lack of a postprandial peak may contribute to the persistent hunger after meals in PWS patients. Indeed, the loss of one copy of the BDNF gene, and, therefore, lower BDNF concentrations, due to a deletion (e.g. 11p deletion or as part of the Wilms tumor-aniridia syndrome) or by a chromosomal 11p inversion, was associated with syndromic phenotypes linked to hyperphagia, childhood-onset obesity, intellectual disability and impaired pain sensing (nociception) (46, 47, 48). Agouti-related peptide (AgRP) levels were not described in PWS.

For *BBS* and *craniopharyngioma* patients, data were lacking on appetite and weight-stimulating brain-derived neuroendocrine factors.

In *anorexia nervosa*, results on the brain-derived neuroendocrine factors NPY (27, 49), beta-endorphin (50, 51, 52), and BDNF (27, 53, 54) were inconclusive. In contrast to PWS, the cannabidoid AEA was reported higher and 2-AG was not different in anorexia patients (55). The levels of BDNF seemed to vary with the stages of illness: concentrations were higher in recovered normal weight anorexia patients compared to acute anorexia patients with underweight, and the concentrations increased with short-term weight gain (54). In addition, a BDNFp.Val66Met SNP was associated with eating disorders such as anorexia nervosa or bulimia nervosa (56). Agouti-related peptide (AgRP) was reported higher in underweight anorexia patients compared to controls. This difference disappeared after weight restoration (57, 58).

The higher beta-endorphin and 2-AG levels observed in PWS may drive eating for obtaining pleasure despite a lack of hunger or energy deficit and might be a target for future treatment. The low fasting BDNF levels and lack of a postprandial peak in PWS may contribute to the persistent hunger in these patients. However, in anorexia patients, low levels of BDNF were also described, suggesting that other factors might counterbalance or overrule BDNF.

Neuroendocrine factors inhibiting food intake and body weight

Data on neuroendocrine factors that inhibit food intake and body weight are summarized in Table 2 and are briefly described below. The order of presentation is based on the number of human studies available for the respective neuroendocrine factor in the selected obesity/undernutrition conditions.

Leptin

Leptin is mainly secreted by white adipose tissue, and leptin concentrations are positively correlated with the amount of body fat. Circulating plasma leptin

concentrations reflect primarily the amount of energy stored in fat and secondarily the acute changes in caloric intake (59).

When corrected for BMI and/or fat mass, leptin levels were higher in young children with *PWS* (<6 years of age) compared to healthy controls (13, 15, 18, 19). In older children (13, 19, 60) and adults (34, 35, 44, 60), leptin was not different compared to obese controls, although some studies show higher leptin levels in PWS (33, 61). The higher leptin levels in young children with PWS are a result of lower muscle mass and increased fat mass, which improved during growth hormone therapy (62).

In *BBS* (20) and in *craniopharyngioma* patients (21, 23, 24, 63, 64, 65, 66), fasting leptin was also higher, even after correction for BMI. In craniopharyngioma patients, higher levels are reported in patients with hypothalamic involvement compared to those without hypothalamic involvement, which may be the result of central dysregulation due to the hypothalamic damage (21, 23, 63, 66). In patients with *anorexia nervosa*, leptin concentrations were consistently lower, as expected with the low body fat mass in these patients (27, 40, 49, 53).

To summarize, leptin levels reflect the amount of fat, independent of the underlying condition. The higher leptin levels in BBS and craniopharyngioma patients after correction for BMI suggest that leptin might have a less important role in food and weight regulation than other neuroendocrine factors or might suggest leptin resistance (20) and needs further study.

Peptide YY

Peptide YY (PYY) is produced in the ilial and colonic cells and levels increase in response to a meal thereby inducing satiety.

Fasting and postprandial PYY levels in *PWS* were found to be higher, lower, or not different compared to obese and lean healthy children (9, 14, 30, 67, 68) and adults (11, 69). It was suggested that PYY concentrations in PWS decrease with age, not in association with BMI (18).

Data on PYY in *BBS* were lacking. In obesity due to *craniopharyngioma*, fasting and postprandial PYY concentrations were not different compared to controls in children and adults (12, 21, 22, 65).

In *anorexia nervosa,* PYY results were inconsistent, both during fasting and post-meal (70, 71, 72, 73, 74, 75, 76, 77, 78).

These inconclusive results might be partially due to differences in food intake, with higher responses after fat-rich meals or due to the fact that PYY concentrations changes only slowly and to a lesser extent to a meal than other gut-related neuroendocrine factors.

The lack of consistency in PYY data suggest that PYY is probably not a key factor in the explanation of obesity or undernutrition in these conditions.

Pancreatic polypeptide

The pancreatic polypeptide (PP) is secreted by specific pancreatic islet cells. PP concentrations increase postprandially and also fluctuate with the myoelectric activity of the gastrointestinal tract.

Fasting PP concentrations were reported lower in non-obese young children with *PWS* (<5 years of age) compared to healthy non-obese controls (18, 30). However, this difference disappears when children were BMI-matched. The postprandial rise in children and adults with PWS was blunted compared to obese and lean children and adults (79, 80, 81), which might be related to increased intake and hyperphagia in PWS. Indeed, short-term infusion of PP reduced food intake in adults (82) but not in children with PWS (83).

For *BBS* and *craniopharyngioma*, no data were available.

PP levels in *anorexia nervosa* were not different vs controls (40, 74, 84, 85), neither during fasting state nor after weight restoration. In two studies with a small sample size in stable anorexia patients without critical underweight, PP levels were higher (86, 87).

These inconclusive findings suggest that PP is not involved in the disturbed appetite regulation in PWS and in anorexia nervosa patients, or that its role is not of major importance.

Cholecystokinin

Cholecystokinin (CCK) is produced in the small intestine and is rapidly released locally and into the blood in response to the nutrients in the gut. It stimulates the gallbladder contraction, increases pancreatic enzyme secretion, delays gastric emptying, potentiates insulin secretion, and regulates food intake by inducing satiety (88).

Studies in children and adults with *PWS* showed no difference in fasting or postprandial CCK levels compared to obese controls (42, 67, 79, 89), although in one study a greater increase in CCK during a meal compared to control adults was observed (90). This greater increase was not related to a reduced food intake in PWS patients (90).

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No data were available for patients with *BBS*. Fasting and postprandial CCK levels were similar between *craniopharyngioma* patients and controls (65).

In *anorexia nervosa*, CCK levels were higher (91, 92), lower (93) on not different (40, 86) vs controls. Short-term refeeding did not affect CCK levels (74).

The lack of differences in CCK between obesity, undernutrition and healthy controls suggest that CCK might not be a key factor in the impaired satiety and the development of obesity or underweight in these conditions.

Obestatin

Obestatin is formed by post-translation modification of preproghrelin in the stomach. In contrast to ghrelin, it suppresses food intake.

Obestatin concentrations were higher in young children (<6 years of age) (17, 19), but not different in older children with *PWS* (≥6 years of age) (17, 19, 94) compared to BMI-matched controls. The ratio of ghrelin to obestatin declined from early to late childhood in PWS but remained higher compared to controls (19).

In children with *BBS*, fasting obestatin concentrations were not different compared to controls (20). Data on *craniopharyngioma* patients were lacking.

In patients with *anorexia nervosa*, obestatin concentrations were higher compared to controls, and an increase in calorie intake decreased obestatin (27, 95).

Changes in the ratio of ghrelin to obestatin may suggest changes in the processing of preproghrelin to ghrelin and obestatin during development and to a differential processing of preproghrelin in PWS (19). Whether this plays a role in the switch from the early nutritional phases to the next phases or whether it merely reflects the current status is unknown. However, the common finding of higher obestatin levels in young PWS children (generally with feeding problems and normal weight) and in anorexia nervosa suggests a role of obestatin in the underlying mechanism of appetite regulation.

Food intake and weight-inhibiting brain-derived neuroendocrine factors

Studies on brain-derived neuroendocrine factors with a suppressive effect on food intake and body weight are limited. Neurotensin induces various effects, including inhibition of gastric motility. The secretion of neurotensin is stimulated by food intake. α-Melanotropin (α-MSH) binds to the melanocortin 4 receptor (MC4R), a crucial receptor involved in appetite control and energy homeostasis in the paraventricular nucleus and in many other sites in the brain.

Neurotensin levels were reported higher in children with *PWS* (age 5–11 years) (96). Neurotensin was not described in *BBS*, *craniopharyngioma* and in *anorexia nervosa*.

In *PWS* and *BBS*, α-MSH was not described. Fasting α-MSH concentrations were lower in *craniopharyngioma* patients compared to obese and lean controls and also compared to patients with a MC4R mutation (monogenic obesity) (97). Postprandially, α-MSH did not increase in craniopharyngioma patients, while it increased in obese controls (97). We hypothesize that the persistently low α-MSH levels in craniopharyngioma patients are due to disturbances in the α-MSH pathway by hypothalamic and/or pituitary damage.

In *anorexia nervosa*, α-MSH levels were lower or not different compared to controls (27, 49). The levels of the anorexigenic peptides proopiomelanocortin (POMC) and cocaine-amphetamine-related transcript (CART) expressed in the arcuate nucleus are not described in patients with obesity and anorexia conditions.

To summarize, data on brain-derived neuroendocrine factors that have a suppressive effect on food intake and body weight are too limited to draw any conclusions on their role in obesity and anorexia yet.

Discussion and conclusions

With the exception of PWS and anorexia nervosa, data on neuroendocrine factors in syndromic and hypothalamic obesity are very limited.

Based on the functions of ghrelin, one would expect higher concentrations in conditions of undernourishment and low concentrations in obesity. However, AG was higher in obese PWS patients and underweight anorexia patients. The AG/UAG ratio might provide additional value compared to measuring AG or UAG alone. In patients with PWS, the switch to excessive weight seems to coincide with an increase in the AG/UAG ratio, even before the onset of hyperphagia. The AG/UAG ratio might, therefore, have a contributing role in the homeostatic disbalance, leading to obesity. It would be informative to study this ratio in other patient categories before and after the development of obesity or underweight, to prove a causative role.

Data on neuroendocrine factors related to inhibition of food intake and body weight are generally not different

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between patients with obesity and anorexia, with the exception of leptin and obestatin. Leptin is related to the amount of body fat with lower concentrations described in underweight anorexia patients and higher concentrations in obese children with PWS. The high leptin concentrations in obese patients with PWS and BBS suggest that either leptin is merely a reflection of the total body fat or that the negative feedback of leptin on appetite is lost or decreased, suggesting leptin resistance. Higher obestatin levels in young PWS children (generally with feeding problems and normal weight) and in anorexia nervosa suggest a role of obestatin in the underlying mechanism of appetite regulation.

Overall, since data are too limited or inconsistent, a comparison between the various causes of obesity or undernutrition cannot be made. To improve interpretation and to aid in the search of the causative agents in progression of obesity or undernutrition, future studies should match patients based on BMI or preferably on fat mass. In addition, longitudinal studies would be helpful to study the role of neuroendocrine factors in the switch from normal weight to obesity or underweight. The various nutritional phases in PWS and anorexia nervosa patients (underweight to weight restoration) form an interesting model for this longitudinal follow-up.

The aim of future studies could also be identification of the receptors for the various neuroendocrine factors, to investigate the effects of these factors on metabolic tissues and appetite centers in the brain. Prospective clinical studies could investigate the role of the neuroendocrine factors in the development of obesity and if these can be used as a predictive marker for the development of obesity and/or metabolic syndrome and potentially serve as a treatment option for these conditions.

Methods

Search strategy for identification of studies

A PubMed (http://www.ncbi.nlm.nih.gov/pubmed) search up to Sept 12th 2019 was conducted with the use of the following key terms (words in the title or abstract of the manuscript): 'appetite', 'appetite depressants', 'appetite stimulants', 'appetite regulating hormones', 'food intake', 'satiety', 'body weight', 'weight', 'obesity', 'obese', 'body mass index', 'BMI'. In addition, the individual appetite regulating hormones (ghrelin, acylated ghrelin, unacylated ghrelin, pancreatic polypeptide, peptide YY, obestatin, cholecystokinin, leptin, adiponectin, neuropeptide Y, Agouti-related peptide, α-melanotropin, beta-endorphin, CART, BDNF, N-arachidonoyl ethanolamide, 2-arachidonoylglycerol, neurotensin) were also added to the search. The key terms were combined with the following disorders: Prader–Willi syndrome, Bardet–Biedl syndrome, craniopharyngioma, anorexia nervosa.

No language restriction was applied in the search.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0111.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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