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Mini-Review

Appetite-related Gut Hormone Responses to Feeding Across the Life Course

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Abstract

Appetite-related hormones are secreted from the gut, signaling the presence of nutrients. Such signaling allows for cross-talk between the gut and the appetite-control regions of the brain, influencing appetite and food intake. As nutritional requirements change throughout the life course, it is perhaps unsurprising that appetite and eating behavior are not constant. Changes in appetite-related gut hormones may underpin these alterations in appetite and eating.

In this article, we review evidence of how the release of appetite-related gut hormones changes throughout the life course and how this impacts appetite and eating behaviour. We focus on hormones for which there is the strongest evidence of impact on appetite, food intake, and body weight: the anorexigenic glucagon like peptide-1, peptide tyrosine tyrosine, and cholecystokinin, and the orexigenic ghrelin. We consider hormone concentrations, particularly in response to feeding, from the very early days of life, through childhood and adolescence, where responses may reflect energy requirements to support growth and development. We discuss the period of adulthood and midlife, with a particular focus on sex differences and the effect of menstruation, pregnancy, and menopause, as well as the potential influence of appetite-related gut hormones on body composition and weight status. We then discuss recent advancements in our understanding of how unfavorable changes in appetite-related gut hormone responses to feeding in later life may contribute to undernutrition and a detrimental aging trajectory. Finally, we briefly highlight priorities for future research.

Key Words: hunger, satiety, ghrelin, PYY, GLP-1, CCK

The gut is the largest endocrine organ in the body. Over 20 hormones are secreted from enteroendocrine cells (EECs) found on the epithelial lining of the gastrointestinal (GI) tract [1] in response to feeding-induced changes in luminal content and neurohormonal signals. Such hormone secretions signal nutrient status to other parts of the GI tract and to other tissues of the body. In doing so, these hormones play an important role in regulating not only gastrointestinal processes but also metabolic homeostasis and energy balance through controlling nutrient transit, digestion, and absorption and by influencing appetite and eating behaviour.

Appetite-related hormones are secreted from specialized EECs when ingested nutrients are sensed, primarily through G-protein coupled receptors localized on the apical cell membrane. Stimulation of these receptors results in a cascade of cellular signaling events, culminating in the secretion of gut peptides at the basolateral membrane. Through the circulation and neural pathways, these hormones signal to regions of the brain, such as the arcuate nucleus (ARC) of the hypothalamus—which has long been considered the primary appetite control region of the brain—and the nucleus of the solitary tract in the dorsal vagal complex of the brainstem—the importance of which for appetite control has received more recent acknowledgement [2, 3]. Orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) neuronal pathways then control appetite perceptions, influencing eating initiation, food choices, satiation, and satiety (see Fig. 1). The orexigenic agouti-related peptide and neuropeptide Y pathways and the anorexigenic pro-opiomelanocortin and cocaine-amphetamine-regulated transcript pathways of the ARC are well established, but more contemporary research has identified prolactin-releasing hormones and GCG neurons in the nucleus of the solitary tract as important anorexigenic pathways that respond to nutrient ingestion via vagus nerve stimulation [2]. However, the effect of gut hormones on these pathways is unclear, as stimulation of the prolactin-releasing hormones and GCG pathways may primarily be a result of orosensory signals and gut distension, respectively [2].

As our understanding of these hormones increases, it is becoming apparent that responses to feeding are not consistent

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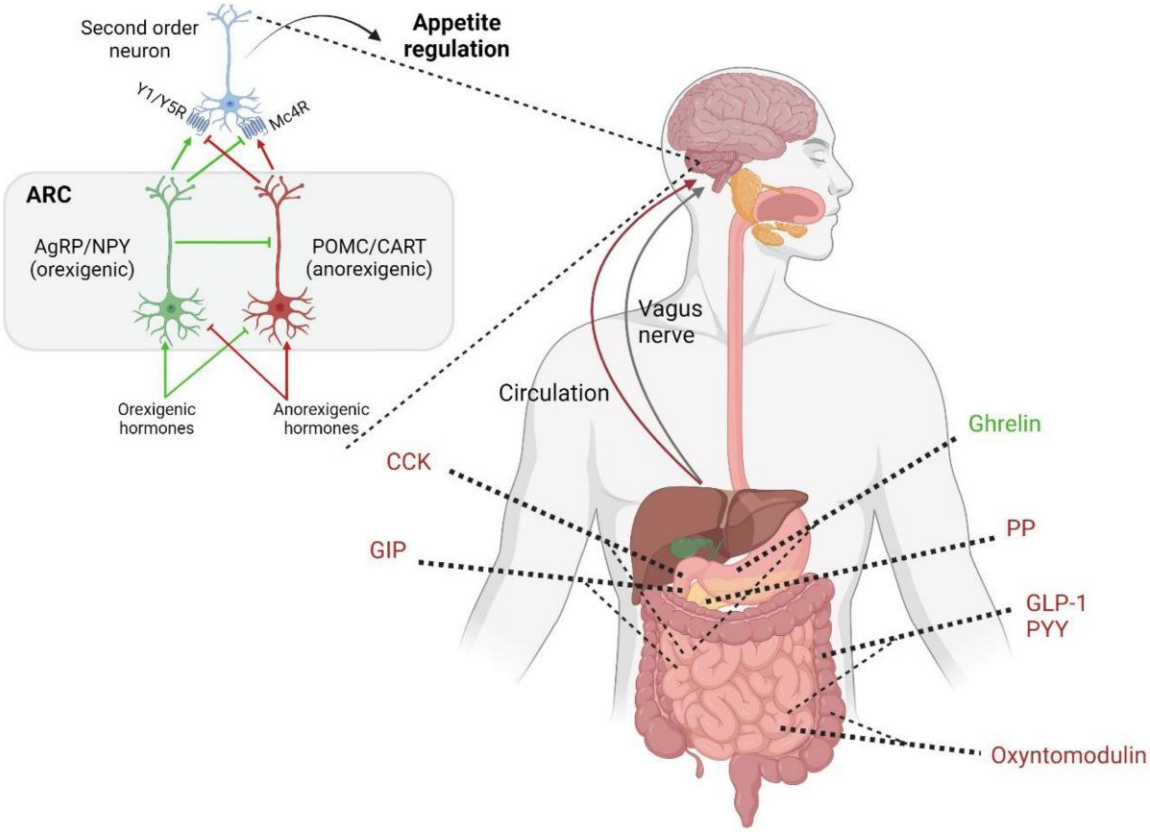


Figure 1. Appetite-related gut hormones and appetite control at their primary target region of the brain: the arcuate nucleus of the hypothalamus. Figure adapted, with permission, from Dagbasi et al [4]. Specifically, the orexigenic hormone ghrelin is secreted primarily from gastric mucosal cells of the proximal stomach. CCK is secreted primarily from I cells of the proximal small intestine. GLP-1 and PYY are secreted from L cells, primarily from the colon and ileum. These peptides signal via the circulation and vagus nerve to act upon the ARC. The orexigenic pathway signals through AgRP/NPY neurons, while the anorexigenic pathway signals through the POMC/CART neurons. Both pathways activate downstream neurons through stimulation and inhibition of Y1/Y5 and Mc4 receptors, stimulating and inhibiting food intake, through integrated brain signaling. Thick dashed line, primary site of secretion; thin dashed line, secondary site of secretion; → stimulation; ⊣ inhibition; green, orexigenic hormone or pathway; red, anorexigenic hormone or pathway.

Abbreviations: AgRP, agouti-related peptide; CART, cocaine-amphetamine-regulated transcript; CCK, cholecystokinin; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide-1; Mc4R, melanocortin 4 receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide tyrosine-tyrosine; Y1/Y5R, neuropeptide Y 1/5 receptor.

and uniform across the life course. The sensing of nutrients in the GI tract and subsequent hormone release may change purely as a function of age. Evidence also indicates that natural and lifestyle-associated transitions along the life course—such as pregnancy, menopause, and changes in body composition and physical activity levels—may coincide with changes in circulating concentrations of appetite-related gut hormones and eating behavior.

This narrative review will discuss such changes in appetite-related gut hormones and the subsequent effect on appetite and food intake across the life course. We will cover childhood and adolescence into adulthood, considering how appetite-related gut hormone responses alter with sex, sexual maturation, menstruation, and changes in both body composition and physical activity through adulthood and midlife. We will then discuss recent evidence of changes in gut hormone secretion seen in later life. Finally, we will identify gaps in current understanding and highlight areas for further investigation.

Appetite-related Gut Hormones—The Main Players

Among the gut hormones with anorexigenic properties, peptide tyrosine-tyrosine (PYY), glucagon-like peptide 1 (GLP-1), and cholecystokinin (CCK) are the 3 with the strongest evidence of their appetite-suppressing effects. For a thorough discussion on the role of gut hormones in appetite control, the reader is directed to a number of excellent reviews [5-8]. Briefly, these peptides induce anorexigenic effects via direct circulatory and indirect neuronal stimulation of anorexigenic pathways in the arcuate nucleus of the hypothalamus, resulting in suppressed appetite, meal termination, and a reduction in energy intake (see Fig. 1). Identified in 1973, CCK was the first gut-derived hormone evidenced to influence appetite [9], with CCK infusion shown to reduce food intake in humans by 23% [10]. It is secreted from I-cells, primarily in the proximal duodenum and jejunum, with plasma concentrations increasing markedly within 15 minutes of feeding [11]. Hence, it is thought that CCK is largely responsible for early onset of satiation when eating. PYY and GLP-1 are secreted from L cells in response to nutrients. Elevating plasma concentrations of PYY [12], GLP-1 [13], or both synergistically [14] through infusions exert reductions in food intake. As L cell density increases from proximal to distal components of the GI tract [15], circulating concentrations rise more slowly with eating. Initial release—thought to be the consequence of neuronal signals and/or other hormonal factors—is followed by a later increase in secretion as

nutrients transcend to the distal gut, with concentrations in plasma peaking 30 to 60 minutes after ingestion and remaining elevated for approximately 3 to 5 hours, depending on energy and nutrient content of the ingested food [16, 17]. As such, these hormones are responsible for more sustained feelings of fullness after meals [11, 16, 18].

The only known orexigenic hormone, ghrelin, is responsible for inducing feelings of hunger and increasing food intake [19] through promoting eating initiation [20]. Ghrelin is produced by mucosal cells in the stomach [21] and undergoes an acylation within the endoplasmic reticulum of the cell before release into the circulation, where this "active" acyl-ghrelin form can exert its appetite-simulating effect either directly at the hypothalamus or via the vagus nerve. There remains some uncertainty over the mechanisms by which ghrelin concentration rises during postabsorptive and fasting period, although this is thought to be via stimulation of mucosal cells by the sympathetic nervous system [22] and vagus nerve [23]. (For a thorough review of the mechanisms of ghrelin control, the reader is directed to the work of Nunex-Salces et al [7]). Ghrelin concentration gradually increases in the postprandial period and is highest immediately before feeding, coinciding with hunger and the initiation of eating [20]. Concentrations reduce sharply at the onset of food ingestion [24, 25]. The ghrelin-secreting mucosal cells of the stomach do not have direct contact with the gastric lumen, meaning direct sensing of stomach nutrient content is not the likely mechanism of suppression when eating. However, gut mucosal cells do contain membrane nutrient receptors, suggesting nutrient-sensing regulation of ghrelin suppression but via nutrient content of the blood [7]. There is also evidence that elevations in plasma concentrations of anorexigenic gut hormones [26, 27] and insulin [28] with feeding provide a feedback signal to reduce ghrelin production [7].

Appetite Control and the Role of Appetite-related Gut Hormones

Appetite control is complex and multifactorial, with both homeostatic and hedonic inputs driving appetitive perceptions and behaviors. Homeostatic control involves mechanisms to match energy intake with energy requirements, as well as the need to appropriately maintain nutrient status. The latter is mediated by episodic changes in gut hormones, as discussed earlier. Tonically, classical studies by Edholm et al [29, 30] and Mayer et al [31] first demonstrated that energy intake largely matches energy expenditure, suggesting an appetitive drive and control of food intake modulated by energy requirements. However, Mayer et al [31] proposed that this coupling between intake and expenditure is dependent on activity levels. They showed a J-shaped relationship between occupational physical activity and energy intake in Indian mill workers, suggesting a mechanism of matching energy intake with physical activity-induced energy requirements is present for those of moderate to high activity levels, but a disconnect in this relationship is experienced by those with low activity.

This may help explain why those who are active remain largely weight-stable over prolonged periods of time while others exhibit weak homeostatic control of energy balance and experience pronounced weight gain. Sedentary behavior and excess adiposity likely weaken homeostatic appetitive control mechanisms [32, 33] and may heighten sensitivity to hedonic inputs of appetite control [34], such as the pleasure and reward sensation experienced from eating (for thorough, expert reviews of "hedonic hunger," see [35, 36]). Hence, the "nonregulated" end of the J-shaped relationship between physical activity and energy intake [34] is observed, resulting in overeating and weight-gain. However, it is very feasible that evolutionary pressure promoted the development of a capacity for hedonic and cognitive systems to "override" homeostatic inputs. This would have allowed for maximizing energy intake when food was available—even when not hungry—during a time when access to food was scarce and insecure. Hence, some argue that excess consumption and excess weight, as a consequence of high hedonic control of eating, is a "natural," adapted response to environments of high availability of energy-dense foods [36, 37].

With such a capacity for hedonic inputs to override homeostatic systems, and despite seminal studies evidencing the potent effects of gut hormones on food intake, the influence of these hormones on eating behavior in humans remains somewhat contentious. Early studies that demonstrated the appetitive influence of gut hormones typically involved infusions at, or close to, nonphysiological concentrations [10, 12-14, 19, 27]. The association between hormone concentration and energy intake is not always seen with lower infusion rates [38, 39] or is weaker when plasma concentration is within the physiological range [40]. Studies that have manipulated diet and then assessed the association between concentrations of endogenous gut hormones and ad libitum intake provide more ecologically valid insights into their effect on eating behavior. In such studies, associations have been observed by some [41-44] but not by others [42-45], with inconsistencies across studies and between different hormones within the same study. As such, inferring effects on eating behavior when changes in gut hormone concentrations are observed but ad libitum feeding is not measured (a not uncommon approach in studies in this field) should be avoided.

It should also be acknowledged that the extent to which fasted concentrations of appetite-related gut hormones influence food intake is questionable, compared with the response during feeding [41, 46]. Counterintuitively, some studies have observed a negative association between fasted ghrelin concentration and ad libitum intake [47, 48]. However, it is likely that ghrelin is a more potent initiator of eating than a regulatory of energy intake once feeding has started [20]. Fasting anorexigenic hormone concentrations show little association with energy intake in healthy people [41, 49-51]. With physiological ranges, their control of eating behavior is likely more potent in the postprandial period, with the anorexigenic effects of GLP-1, in particular, appearing blunted in the fasted compared with the postprandial state [52]. The importance of fasted-state hormone concentrations may also be further limited when considering that most people spend little of their waking time in a fasted state; for those who do not experience food insecurity and follow regular eating patterns, most time will be spent in the postprandial or postabsorptive state. As such, we will focus on postprandial responses and distinguish between fasting and postprandial measures. Assertions of the effects of fasted concentrations of appetite-related gut hormones on eating behavior and energy intake should be avoided.

It is plausible that a change in the circulating concentration of a single appetite-related hormone, in isolation, has only a limited impact on eating behavior. In addition, this may be a somewhat moot point given that gut hormones do not

respond in isolation to feeding; eating a mixed meal induces alterations in numerous gut hormones, and it is the combination of these changes that likely effects food intake. In a recent study by Dagbasi and colleagues, a composite measure of the responses of ghrelin, PYY, and GLP-1 to a standardized breakfast meal was calculated—termed the "anorexigenic response score," with a higher score indicating a more anorexigenic response (ie, greater increase in PYY and GLP-1 and greater suppression of ghrelin). This response score was significantly, negatively related to energy intake at an ad libitum lunch meal. This suggests that the combined response of these hormones did influence subsequent food intake.

It is also worth considering the role of appetite-related hormones in weight management treatments. Bariatric surgery, which is currently the most effective weight loss strategy, induces an alteration in gut hormone concentrations. Postsurgery, responses of GLP-1 and PYY to feeding are amplified [53] (with typically no effect observed in fasting concentrations [54]), contributing to reduced appetite and food intake. Blocking the actions of these hormones in bariatric surgery patients increases the energy intake by 20% [49], highlighting the role of these hormones, even at physiological levels, in the reduced energy intake achieved following the surgery. GLP-1 receptor agonists have emerged as contemporary and effective antiobesity medication [55]. While these are exogenous peptide mimetics of GLP-1, often with an extended half-life and greater stability for a more potent effect, their efficacy [56], highlights the regulatory role of the GLP-1 pathway in eating behavior.

Despite the complexity of appetite control, with numerous inputs and regulatory pathways, this evidence would suggest that appetite-related gut hormones, and particularly their response to food ingestion, do influence eating behavior and food intake. The remainder of this review will focus specifically on the appetite-related gut hormones PYY, GLP-1, CCK, and ghrelin. We will discuss, primarily, the extent to which their response to feeding, and the consequences for appetite and food intake, differs across the life course.

Childhood and Adolescence

Throughout infancy, childhood, and adolescence, growth and changing body composition and energy requirements occur, which may influence or be influenced by appetite-related gut hormones. For example, in general, height increases by approximately 25 cm in the first year of life, 12 to 13 cm in the second year, and 5 to 6 cm each year until puberty [57]. Although the timing varies widely between individuals, puberty generally occurs earlier in girls than boys, with growth spurts reported as a peak height velocity of 8.3 cm·year^{-1} at age 11.5 years in girls and 9.5 cm·year^{-1} at age 13.5 years in boys [58]. These changes correspond to significant increases in fat free mass in childhood and adolescence. For example, fat free mass has been reported to increase from ~8 and 9 kg to ~15 and 16 kg between age 1 year and 5 years in girls and boys, respectively [59]. Body fat also fluctuates with total body fat reported at approximately 11% to 15% at 2 weeks old in healthy newborns, increasing to 30% at 6 months old, decreasing to ~20% at 2 years old, and ranging between ~15% and 20% at 5 to 10 years old, with lower levels in boys [57, 59]. Relative to body weight, energy requirements decrease during childhood and adolescence; however, absolute energy requirements increase with increasing age [60].

Appetite-related gut hormones may exhibit unique responses to food in very early life. Postprandial ghrelin concentrations appear to vary in childhood and adolescence and are modified by a variety of factors [61]. In neonates (2-4 days old), findings from 2 studies [62, 63] suggest that nutrient intake (breast or formula feeding) does not suppress ghrelin levels, which could play a role in growth. In contrast, in infants at 1 year of age, both babies born small and appropriate for gestational age showed a significant suppression of ghrelin between fasting and 10-minute postglucose infusion [64]. Interestingly, lower ghrelin suppression was associated with greater infancy weight gain in small for gestational age infants, which could play a role in postnatal catch-up growth [64].

Evidence in prepubertal children is mixed with some studies showing no impact of food intake on postprandial ghrelin levels [65-67] but others showing a significant ghrelin suppression [68-73]. This disparity in findings could be due to differences in the study test meals, timing/methods of sampling, different methods of ghrelin measurements, or characteristics of the population studied. Although it has been suggested that a lack of ghrelin suppression occurs in lean children but not children with obesity [74], several studies involving a direct comparison of children (age 7 to 12 years) with and without obesity (eg [68, 69, 71], have demonstrated postprandial ghrelin suppression to occur. Interestingly, ghrelin suppression was reduced in children with obesity in these studies compared to those of healthy weight [68, 69, 71] and associated with reduced insulin sensitivity [68].

In adolescents, most studies have reported a significant suppression of acyl-ghrelin and unacylated and/or total ghrelin in response to mixed meals [75-80], which appears to differ with pubertal stage [76-78] and weight status [81]. Ellis et al [77] observed lower total ghrelin suppression in early to midpubertal girls compared with adults with excess weight. In boys with obesity, lower total ghrelin suppression was observed in mid-late puberty compared with pre-early puberty [78]. Elsewhere, Prodam et al [76] reported lower unacylated ghrelin suppression during an oral glucose tolerance test (OGTT) in prepubertal compared with pubertal children with obesity, although the acyl-ghrelin response was similar. The response also appears to be modified by weight status, with evidence from a meta-analysis by Nguo et al [81] finding children (aged 6-12 years) and adolescents (aged 12-18 years) with obesity to have attenuated ghrelin responses at 60 minutes (5 studies) and 120 minutes (4 studies) after meal ingestion compared with those of a healthy weight. Others have shown the meal type modifies the extent of active and total ghrelin suppression in adolescents [79, 80].

Collectively, studies to date suggest ghrelin does not respond to nutrient intake in neonates, whereas postprandial ghrelin suppression has been demonstrated in prepubertal children and in adolescence, although the absolute reduction may be influenced by age/puberty and weight status, among other factors.

Fewer studies have examined the responses of anorexigenic hormones to nutrient intake. In neonates (4 days old), CCK was found to increase immediately after and at 30 and 60 minutes after breastfeeding, and it was proposed that it could enhance satiation despite little food in the first days of life [82]. Limited studies have examined CCK responses to food intake in older children or adolescents; however, 1 study reported the CCK response to a meal was higher in adolescent girls with obesity compared with those of healthy weight [83],

suggesting CCK was unlikely to have a role in weight gain in adolescent girls.

Studies examining PYY and GLP-1 in neonates and infants have reported primarily on concentrations prior to feeding [84-86]. There is consistent evidence of a blunted PYY response to food intake in those with obesity vs healthy weight in children (aged 7-11 years) [87] and adolescents [75, 88], including from meta-analysis [81]. There is also evidence that sex may modify the response in adolescence, with higher PYY concentrations in boys than girls in 1 study [78]. With regard to the impact of puberty, Patel et al [78] found lower PYY responses to nutrient intake in mid-late pubertal boys compared with pre- to early puberty. Although the literature is limited, these findings suggest lower postprandial PYY levels (alongside reduced postprandial ghrelin suppression) could be a potential mechanism contributing to increased food intake and facilitating growth in adolescence.

With regard to postprandial GLP-1 responses, in 1 study in 7- to 11-year-olds, GLP-1 did not increase after eating [89]. The authors speculated that, among other reasons, this finding could be due to a lack of sex hormone production in younger children. For example, there is evidence that oestrogen can increase GLP-1 secretion [90], which could explain differences in GLP-1 secretion between younger children, adolescents, and adults. In contrast to younger children [47], studies in adolescents with and without obesity have reported a significant increase in GLP-1 in response to a variety of mixed meals or OGTT, with some [83, 91, 92] but not all [79] showing the response to be attenuated in those with obesity. Elsewhere, the GLP-1 response to an OGTT was attenuated in African American compared with Caucasian adolescents despite similar adiposity and insulin sensitivity [93].

In summary, although studies examining the influence of age/puberty directly are still limited, there is evidence of alterations in postprandial gut hormone responses to nutrients throughout childhood from infancy to adolescence, which may have implications for appetite control, growth, and weight status. A variety of factors including age, pubertal stage, meal type, weight status, race, and sex may impact the response. It is possible that the change observed in these hormones may serve a purpose for a higher energy intake to facilitate growth and development; however, dysregulation in such an adaptation may contribute to excess weight gain in childhood.

Adulthood and Midlife

During adulthood (>18 years old) and mid-life (defined here as 40-64 years old, in line with the Centers for Disease Control and Prevention [94]), healthy individuals will exhibit the "typical' gut hormone response to food intake, as introduced earlier. Adults typically increase their body mass from young adulthood to midlife, with an average weight gain of ~0.4 kg·year^{-1} reported in US adults, representing a median weight increase of ~11 kg from the age of 25 to 55 years old [95] and a typical increase in body mass index (BMI) of between 3 and 10 kg m^{-2} during this period [96]. This weight gain is mainly attributable to an increase in adiposity. This change in body composition along with a reduction in activity levels (discussed in "Changes in Physical Activity") is associated with a reduction in estimated energy requirements from young adulthood to middle age [97]. It is possible that this is accompanied, or dictated, by changes in gut hormone concentrations, although data in this area are scarce. To the best of our knowledge, no longitudinal cohort study has tracked gut hormone concentrations over prolonged periods of time without manipulation.

On the other hand, there is a vast amount of evidence to highlight that gut hormone responses may differ between men and women, driven by stark hormonal differences between men and women during this stage of life. Women, in particular, experience periods of changes in food intake and energy requirements, such as during pregnancy, through menopause, and even at different stages of the menstrual cycle, and appetite-related gut hormones may play a role in regulating eating behavior to match energy intake with requirement. However, a mismatch in energy intake and expenditure can be experienced through this period of adulthood and midlife, with long-term, gradual weight gain common; dysregulation of appetite-related gut hormones may also be implicated in such a mismatch between intake and requirements for some.

Sex Differences

Sex alters fasting gut hormone levels [98-101] and postprandial responses to a variety of nutritional challenges [99-103]. Evidence in general highlights a higher level of both anorexigenic and orexigenic appetite hormones in women compared with men although conflicting evidence can be found in the literature. Greater fasting [98, 99, 104] and postprandial [99, 100] ghrelin concentrations have been observed in women compared with men, independent of body composition [104] or in the absence of sex differences in BMI [100]. However, several studies have reported no effect of sex [101-103, 105-107]. Giezenaar et al [107] found that women exhibit attenuated CCK and GLP-1 responses to nutrient intake compared with BMI-matched men, while conversely others have observed elevated postprandial GLP-1 levels in women vs men [98, 108, 109]. Though women have been shown to exhibit lower fasting PYY than men [110, 111], postprandial responses are reported to be greater [98, 105]. Conversely, Yunker et al [109] showed no sex differences in PYY response to carbohydrate ingestion, despite sex differences in GLP-1 response. Discrepant findings between studies investigating sex differences in appetite-related gut hormones could be related to menstrual cycle phase, with lower GLP-1 levels found during the follicular compared with luteal phase [112]. In addition, some studies did [105, 107, 108] and some did not [98, 106, 109-111] account for differences in body composition between men and women, which can influence gut hormone concentration (see "Changes in Body Composition"). Previous studies have reported a positive association between percent body fat and anorexigenic gut hormone concentrations in women but not men [111, 113], while menopausal status has been shown to significantly influence circulating PYY concentrations [111]. Furthermore, slower gastric emptying rates have been observed in females compared with males [100, 106], potentially mediating contrasting gut hormone responses to nutrients between sexes.

Menstruation

Contrasting findings regarding sex differences may be a result of measurements in women being obtained at different stages of the menstrual cycle. While some studies assessed hormones concentrations in the follicular phase [107, 109], others did

not control for or report the stage of the cycle [99-103, 105, 106, 110, 111, 113]. The extent to which sex differences in appetite control can be explained by menstruation and consequent sex hormone profiles is worth considering. Menstruation and the stage of the menstrual cycle can influence eating behavior. Food intake has been shown to be greater in the luteal phase than the follicular phase [114, 115], with this increase coinciding with a spike in LH [112]. Such an adaptation likely exists to prepare the body for potential pregnancy and coincides with an increased resting metabolic rate [116, 117]. Increased energy intake appears to be a consequence of greater sugar intake [118] and larger intakes at meals as opposed to an increase in eating episodes [112], which may indicate a reduction in the satiety response to ingested nutrients and carbohydrates in particular. Campolier et al [119] showed an attenuated PYY response to a standardized breakfast in the luteal phase compared with the follicular phase. However, in contrast, Brennan and colleagues [115] showed a greater GLP-1 concentration in response to a glucose load in the luteal phase. This appears somewhat paradoxical, as postprandial subjective appetite and test meal ad libitum energy intake was greater during the luteal phase, compared with the follicular phase [115]. As there appears to be changes in appetite control with the stage of the menstrual cycle, future studies exploring sex differences in appetite-related gut hormones should account for stage of the cycle, perhaps comparing men with women assessed in both the follicular and luteal phases to identify genuine sex differences and differences that result from menstrual cycle stage.

Pregnancy

In this period of childbearing age, a woman may indeed become pregnant and give birth. During the second and third trimesters of pregnancy, energy requirements are increased by approximately 300 to 350 kcal/day and 500 kcal/day, respectively [120, 121] (which is markedly less than the concept of "eating for two"). This is partly met by a decrease in energy expenditure but also by a typical increase in energy intake of ~10% [122]. Yet, managing this modest increase in energy demand can be difficult to regulate, with excess gestational weight gain experienced by approximately 43% of women [123]. As such, the role of appetite-related gut hormones in modulating appetite and food intake during pregnancy warrants discussion.

Perhaps counterintuitively, fasting GLP-1 concentration was shown to increase from the second to the third trimester in pregnant women [124], although no prepregnancy data was measured for comparison. In line with the increased energy requirements, however, Manglier et al [125] recently showed that GLP-1 response to feeding is attenuated during the second and third trimester, compared with the first trimester, favoring energy intake. Studies in rats have shown elevated fasting PYY concentrations during pregnancy [126], with no change throughout pregnancy observed in humans [124]. Similarly, and again counterintuitively, Frick et al [127] evidenced elevated fasting CCK during pregnancy compared with during the menstrual cycle in women, particularly during the second and third trimesters. However, elevated fasting anorexigenic hormone concentrations have typically not been associated with increased satiety—further questioning the influence of fasting levels on eating behavior—and have been attributed to enlargement of the GI tract during pregnancy [126].

Increases [128, 129], no change [124], and even very low [130] ghrelin concentrations have been reported during pregnancy in humans. Both Palik et al [128] and Fuglsang and coworkers [129] showed that fasting plasma ghrelin concentration increased in the second trimester but fell in the third trimester after peaking at 18 weeks of gestation. Interestingly, a study in rats showed that maternal ghrelin actives GH secretagogue receptor on fetal tissue, thought to contribute to fat accumulation and growth in the fetus, and that ghrelin treatment of the mother resulted in greater birth weight of offspring, even when controlling for maternal energy intake [131]. This suggests ghrelin plays an important role in fetal development, independent of any potential influence on maternal appetite and feeding. Cross-sectionally, women with excess weight who gained excess weight during the second trimester of pregnancy had attenuated gut hormone responses to feeding, compared with those who experienced healthy gestational weight gain [132]. From these data, it remains unclear whether appetite-related gut hormones alter in a manner to promote the matching of increased energy requirements during pregnancy, with further research in humans required, particularly with regard to hormone responses to feeding. However, the little evidence available does suggest that variation in gut hormone response to feeding may contribute to excess weight gain during pregnancy.

Menopause

At the end of this child-bearing age, menopause is characterized by important hormonal and metabolic changes that may modulate food intake. Reductions in estrogens and increases in androgens secretion [133] are believed to contribute to a dysregulation of appetite control [134], leading to weight gain [135] and an increase in body fat [136]. However, evidence for changes in gut hormones in the menopausal state is limited. Our understanding is hindered by the intricate interplay of sex-specific hormones and methodological differences between studies, with inconsistencies in methods used to determine menopause. It would appear that fasted ghrelin concentration is increased during the perimenopausal period, with no difference between pre- and postmenopausal periods [137]. Interestingly, ovariectomized rats showed an increased ghrelin concentration [138] and increased sensitivity to ghrelin [139], suggesting menopausal changes in estrogen may have resulted in elevated postmenopausal ghrelin and augmented appetite responses to ghrelin, which may explain body composition changes commonly experienced during this period. Conversely, in humans, lower fasting ghrelin concentration has been seen in postmenopausal compared with premenopausal women, with no rapid change in ghrelin after ovariectomy, despite an immediate reduction in estrogen [140]. Stojiljkovic-Drobnjak and colleagues [141] observed a minimal difference in fasted and postprandial ghrelin concentrations between pre- and postmenopausal women, while Purnell and colleagues [103] observed no differences in fasting ghrelin between premenopausal women, postmenopausal women, and postmenopausal women receiving hormone replacement therapy.

As may be the case with ghrelin, ovariectomized rats have shown reduced sensitivity to the anorexigenic effects of CCK and GLP-1 [142, 143], which again suggests neural changes to the sensitivity of gut-derived appetite signals with menopause transition. Sensitivity to anorexigenic hormones

has not been determined in differing menopausal states in humans, but studies have compared plasma concentrations, albeit with contrasting findings. No difference was seen in fasted CCK concentrations between pre- and postmenopausal women living with obesity [144], while those of postmenopausal status have been shown to exhibit contradictory lower GLP-1 [145] and higher PYY [110] concentrations, compared with those of premenopausal status. As such, the estrogen-mediated effect of menopause transition on sensitivity to appetite-related gut hormones and the role of menopausal status and transition on the secretion of these hormones remain areas for exploration in humans.

Changes in Body Composition

As was identified earlier in children and adolescents, appetite-related gut hormone response to feeding may differ with weight status and body composition. The prevalence of excess weight increases from early adulthood to midlife, with weight gain commonly experienced throughout adulthood [146, 147]. There is compelling evidence that anorexigenic hormone responses to feeding differ between those of a healthy weight and those living with obesity. In their seminal study of 2003, Batterham and colleagues [27] showed that both fasted and postprandial PYY concentrations are lower in those living with obesity, with an inverse association found between fasting PPY concentration and BMI [27]. This suggests that attenuated PYY response to feeding may contribute to reduced satiety in those with excess adiposity. However, when plasma concentration was matched to that of lean individuals through infusion, the anorexigenic response to appetite perception and feeding was restored [27], indicating that sensitivity to the appetite-suppressive effects of PYY remains in those living with obesity. Similarly, increases in GLP-1 concentration are blunted in those with excess adiposity [106, 113, 148], which coincided with lower ratings of satiety [113]. Fewer studies have compared CCK concentrations between healthy weight and those living with obesity. However, it would appear both exhibit similar CCK responses to food intake [43].

Fasting ghrelin concentration is negatively associated with body mass [101], with somewhat counterintuitive lower concentrations observed in those living with obesity [102, 149, 150]. This may be due to the ghrelin-suppressive effect of hyperinsulinemia [149, 151], although a lack of a relationship between insulin and ghrelin has also been reported [101]. There is evidence of attenuated ghrelin suppression with feeding in those with excess adiposity [149, 150, 152], but findings are inconsistent [43, 153]. A recent meta-analysis by Aukan et al [154] showed lower postprandial ghrelin concentrations in those with obesity compared with healthy-weight individuals; however, this was largely driven by lower fasted concentrations and actually masked smaller meal-induced suppressions in those with obesity [148, 155]. In another recent meta-analysis, Wang et al [156] showed a similar magnitude of ghrelin suppression in those with obesity compared with healthy-weight individuals, but the suppression was more transient, showing a quicker return to preprandial concentrations (120 minutes after meal ingestion).

Whether such dysregulation in appetite-related gut hormone responses to feeding are causes or consequences of excess weight is unclear. Cross-sectional studies do not permit the determination of causality, and there is a scarcity of longitudinal data. This contention of "cause or consequence" was addressed in the review of Lean and Malkova [157]. With a sparsity of data monitoring gut hormone changes with weight gain, they focused on the effect of calorie restriction and exercise-induced weight loss. In brief, diet-induced weight loss tends to elicit a compensatory response in appetite-related gut hormones to oppose energy deficit and promote feeding and weight regain. This, coupled with a reduction in total energy expenditure, is referred to as the "compensatory theory" [56]. In the study of Sumithran et al [158], 50 participants with excess weight followed a 10-week energy-restricted diet, inducing a 14% reduction in body mass. Immediately after the diet period, fasted and postprandial PYY and CCK were lower. At a 1-year follow-up, values remained significantly lower than before weight loss, evidencing an enduring change that prevailed even when energy balance was reestablished. Weight loss achieved through calorie restriction induces a compensatory increase in both fasted and postprandial ghrelin concentration [153, 158, 159]. As with some of the anorexigenic hormones, this response continues beyond the period of energy deficit and is maintained in a post-weight loss period of energy balance [153, 158]. Collectively, these findings suggest that alterations in appetite-related hormones in reduced-obese individuals drive weight regain; however, findings to the contrary have been reported. For example, DeBenedictis et al [160] found that basal and postprandial ghrelin concentrations increased following acute and sustained weight loss and did not differ from those of a nonobese control group. Furthermore, weight loss has been shown to elevate postprandial GLP-1 levels to concentrations comparable with those of lean controls [40]. Consequently, Martins and colleagues [56] proposed a new theory (the "normalization theory"), which, in contrast to the compensatory theory, purports that a reduction in body mass improves appetite control and that the increased orexigenic drive to eat observed in the reduced-obese state reflects a normalization toward a lower body weight. Whether changes in appetite-related hormones following weight loss represent a compensatory response or a normalization toward a lower body weight remains unclear.

As mentioned earlier, weight loss induced by bariatric surgery elicits effects on anorexigenic gut hormones [161]. Roux-en-Y gastric bypass results in augmented postprandial secretions of PYY and GLP-1 [49, 162, 163], with no change in fasted concentrations. However, this is likely a consequence of more rapid delivery of nutrients to the jejunum, rather than weight loss. Nonetheless, this favorable change in anorexigenic hormone response is likely a key factor in successful weight-loss maintenance with surgery, as acutely blocking the actions of GLP-1 and PYY in bariatric surgery patients increased food intake by 20% at a test meal [49].

As such, these data would suggest changes in appetite-related gut hormones are likely both a cause and consequence of changes in body composition and weight status. Hormonal response to weight loss appears dependent on the means of losing weight, with these influencing the success of the maintenance of weight loss. However, the role of appetite-gut hormones in gradual, long-term weight gain is less clear.

Changes in Physical Activity

A possible contributing factor to weight gain through adulthood and midlife is the observed reduction in physical activity

[164]. As discussed in "Appetite Control and the Role of Appetite-Related Gut Hormones," physical activity, as a component of energy requirement, is considered a determinant of energy intake [29-31, 33]. It would appear that a moderately to highly active lifestyle facilitates the matching of energy intake with requirements, but for those with a low activity level, there is a disconnect between energy intake and requirements, underpinned by changes in sensitivity to homeostatic and hedonic systems to promote positive energy balance and weight gain [32-34]. Consequently, a reduction in physical activity may contribute to changes in appetite control. The extent to which this is mediated by appetite-related gut hormones is somewhat unclear. This is largely due to a lack of studies assessing longitudinal changes in physical activity and gut hormone metabolism. Nonetheless, it is proposed that physical activity enhances sensitivity to appetite-related hormones [32, 165]. Martins et al [166] showed a trend for augmented GLP-1 response to feeding in those with excess weight after a 12-week aerobic exercise training program, potentially tightening the coupling between energy intake and expenditure. However, it is difficult to determine if this is a response to exercise per se or exercise-induced weight loss. As most studies exploring the effects of an increase in exercise on gut hormones are in previously inactive people with excess weight who embark on an exercise program to promote weight loss, this is a common problem. Typically, and in contrast to diet-induced weight loss, exercise-induced weight loss appears to have little effect on anorexigenic gut hormones [167] or even heightens the responses to feeding [157], as seen by Martins et al [168]. Such hormonal adaptations point to the benefit of incorporating exercise into effective weight-management strategies.

Later Life

Later life, or older adulthood, is typically considered to begin at the age of 65 years [94]. This period of the life course is accompanied by a reduction in muscle mass—known as sarcopenia—at a rate of between 0.6% and 1% per year [169] or 3% to 8% per decade [170], accelerating with increasing age. In severe cases, this can lead to a loss of up to 50% of muscle mass [169] and an even greater reduction in strength [171, 172], along with hormonal changes [173] and lifestyle alterations, including reduced physical activity [174, 175], increased sedentarism [176], and changes in dietary intake [177, 178]. In alignment with the reduction in muscle mass and activity, studies have observed lower metabolic rate [179, 180] (observed even when adjusting for fat-free mass) and total daily energy expenditure [181, 182] in older adults. Consequently, energy requirements are reduced in later life.

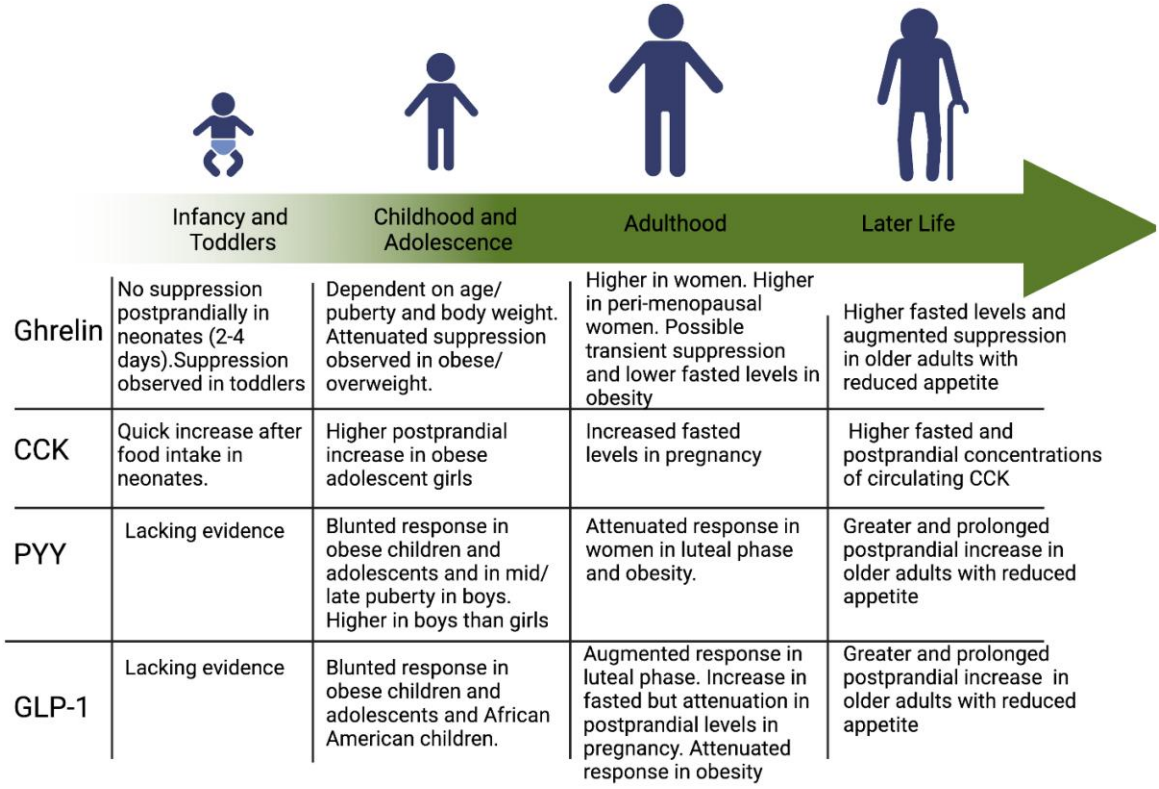
However, meeting such requirements in later life is challenging. Somewhat paradoxically, those aged 65 to 75 years are at greater risk of both excess body mass and low body mass, compared with young and mid-life adults [183]. Though it is a low body mass and a loss of mass, rather than excess body mass or gains in mass, that pose the greatest risk of mortality in older adults [184, 185] Consequently, research exploring the physiology of appetite control in later life has predominantly focused on the association between age-related alterations in appetite and the development of undernutrition, as opposed to overweight and obesity.

The etiology of undernutrition in older people is multifactorial, but one key determinant is age-related abnormalities in the balance between hunger and satiety. A meta-analysis conducted by Giezenaar and colleagues [186] determined the effect of age on appetite and reported lower fasting and postprandial hunger and greater fasting fullness in older adults compared with younger adults. Loss of appetite in later life is termed "anorexia of aging' [187] and is highly prevalent across settings, affecting approximately 15% to 30% of community-dwelling older adults and rising to over 40% in clinical settings [188-191]. However, the precise mechanisms underpinning anorexia of aging are yet to be fully elucidated.

One proposed mechanism of anorexia of aging is a change in appetite-associated gut hormone secretion with age. A comprehensive meta-analysis of circulating appetite-related hormones comparing younger to older adults by Johnson et al [192] demonstrated few differences in fasting and postprandial circulating total ghrelin concentrations. While limited studies were available for fasted acyl-ghrelin, there did appear to be a reduction in postprandial acyl-ghrelin in older adults when compared to young adults. In addition, older adults exhibited higher fasted and postprandial concentrations of circulating CCK and a trend for higher postprandial PYY when compared with their younger counterparts. There were no differences, however, found in GLP-1 and GIP. These observed changes in gut hormones between younger and older adults were in accord with decreased subjective hunger in older adults [192].

However, postprandial gut hormone responses can vary greatly in older adults [192]. Indeed, with the prevalence of anorexia of aging in community-dwelling older adults being around 30%, it is likely that study cohorts of older adults consist of some with impaired appetite and some with unimpaired, healthy appetite. Until recently, it was unclear as to whether hormonal dysregulation was causal of anorexia of aging, as studies have typically afforded little consideration as to the heterogeneity of older adult appetite control.

Research conducted by Holliday et al [47] and Dagbasi et al [41] has advanced our understanding of anorexia of aging by distinguishing between healthy-appetite and appetite-suppressed older adults when exploring age-related differences in gut hormone circulation. In both studies, a novel multicriteria classification model was used to phenotype older adults with low appetite. Older adults were considered to have suppressed appetite if 2 of the following 4 criteria were met: low weight (BMI <23 kg m^{-2} [184, 193]), score of <15 on the Simplified Nutritional Appetite Questionnaire [194], habitual energy intake $<75\%$ of estimated daily total energy requirements (as identified by the World Health Organization as indicative of undernutrition), and a laboratory-measured ad libitum lunch intake of $<25\%$ of estimated total energy requirements (based on a typical lunch energy intake of $\sim 27\%$ of total energy intake in UK adults [195]). Holliday et al [47] determined total and acyl-ghrelin concentrations in older adults with low appetite, older adults exhibiting a healthy appetite, and young adults in both the fasted and fed states. Findings demonstrated that while greater fasted ghrelin concentrations and an augmented postprandial acyl-ghrelin suppression were observed in older compared with younger adults, such differences were driven by older adults with low appetite. Dagbasi et al [41] confirmed the findings of Holliday et al [47] while also observing greater and more prolonged increases in postprandial PYY and GLP-1 levels in appetite-suppressed older adults compared with younger adults, which was not observed in older adults with a healthy appetite. In addition, Dagbasi et al [41] reported that



	Infancy and Toddlers	Childhood and Adolescence	Adulthood	Later Life
Ghrelin	No suppression postprandially in neonates (2-4 days).Suppression observed in toddlers	Dependent on age/ puberty and body weight. Attenuated suppression observed in obese/ overweight.	Higher in women. Higher in peri-menopausal women. Possible transient suppression and lower fasted levels in obesity	Higher fasted levels and augmented suppression in older adults with reduced appetite
CCK	Quick increase after food intake in neonates.	Higher postprandial increase in obese adolescent girls	Increased fasted levels in pregnancy	Higher fasted and postprandial concentrations of circulating CCK
PYY	Lacking evidence	Blunted response in obese children and adolescents and in mid/ late puberty in boys. Higher in boys than girls	Attenuated response in women in luteal phase and obesity.	Greater and prolonged postprandial increase in older adults with reduced appetite
GLP-1	Lacking evidence	Blunted response in obese children and adolescents and African American children.	Augmented response in luteal phase. Increase in fasted but attenuation in postprandial levels in pregnancy. Attenuated response in obesity	Greater and prolonged postprandial increase in older adults with reduced appetite

Figure 2. Summary of changes in ghrelin, cholecystokinin, peptide tyrosine-tyrosine, and glucagon-like peptide-1 response to feeding across the life course, from infancy to later life.

appetite-related gut hormone response to feeding proved a significant predictor of ad libitum lunch intake, with gut hormone response accounting for 18% of variance in lunch intake among the older cohort. Furthermore, the 4-criteria classification model explained 48% of the variance in gut hormone response in older adults, supporting the appropriateness of this approach for identifying those with low appetite. Holliday et al [47] and Dagbasi et al [41] have demonstrated for the first time that differences in ghrelin, PYY, and GLP-1 concentrations between young and older adults are not functions of aging per se and may be causal of impaired appetite in later life. Potential mechanisms have recently been proposed [4], including altered digestion and absorption of nutrients, inflammatory changes in the lumen environment, and dysregulated EEC cell signalling. Future studies should adopt the multicriteria classification model for identifying the anorexia of aging phenotype to explore these potential mechanisms underpinning age-related appetite loss.

Methodological Considerations

As is evident from this review of the literature, some contention and disagreement in findings persist when trying to ascertain appetite-related gut hormone responses to food and differing responses between populations. As such, it is worth considering methodological issues that may explain contrasting findings.

Measurement methods of hormones can differ between studies. The 2 most common methods deployed currently are radioimmunoassay and ELISA. However, these techniques can exhibit differences in detection. For example, Prudom et al [196] showed greater sensitivity to postprandial changes in acyl- and des-acyl ghrelin with sandwich ELISA assays, compared with radioimmunoassay, which was attributed to greater specificity. Assay specificity is particularly problematic when measuring CCK due to the likelihood of cross-reactivity of antibodies with gastrin [197]. Consequently, the lack of specificity of CCK assays, and hence the validity of some study findings, has been questioned [198]. While reliable assays with high-specificity antibodies have been developed, the discontinuation of such assay kits has presented further challenges to obtaining accurate measures of CCK. Authors are therefore encouraged to state characteristics of assays used, such as specificity, especially when measuring CCK. For authors, it is necessary to critically consider measurement method when evaluating differences in study findings, and CCK measures should be interpreted with caution. High-performance liquid/gas chromatography—mass spectrometry methods are less commonly adopted for the detection and quantification of gut hormones in plasma. These approaches do present the potential to measure hormones for which effective assays are of low availability, such as CCK and oxyntamodulin; but detection limits and specificity issues remain [198]. While good specificity and detection limits have been demonstrated for hormones such as PYY [199] and differing forms of ghrelin [200], the adoption of mass spectrometry is limited due to complexity and cost.

Conclusions and Research Priorities

Evidence reviewed here demonstrates that appetite-related gut hormone concentrations, in the fasting state and in response to feeding, are not constant across the life course. There are age-related changes, from the very first days of life until later

years, perhaps reflecting energy requirements. Such changes are summarized in Fig. 2. During periods of rapid growth and development, in the early days of life and through puberty, ghrelin response to feeding appears attenuated, possibly to favor energy intake to support growth. A similar attenuated appetite-related gut hormone response may also be present in preparation for and during pregnancy to favor energy intake; however, this requires further investigation, especially in the postprandial period. Sex differences also warrant further exploration, with specific attention to the stage of the menstrual cycle to distinguish between sex differences, per se, and those underpinned by stage of the menstrual cycle.

Dysregulation in the form of a blunted response of ghrelin and anorexigenic hormones is seen in both children and adults with excess adiposity, which likely contributes to energy surplus and weight gain. However, further longitudinal studies are required to confirm this causal relationship. Changes in gut hormones certainly appear to occur during calorie restriction, opposing an energy deficit and making sustained weight loss difficult. However, this may not be the case with exercise-induced energy deficit. This should be considered when planning weight management strategies.

It is now clear that some, but not all, older adults experience augmented responses of appetite-related gut hormones to feeding. While this may also coincide with a reduction in energy requirements in later life, this is a less advantageous adaptation, resulting in an increased risk of undernutrition. Although this has been observed in those over 65 years, what remains to be identified is at what age this dysregulation in hormonal response to feeding starts to occur. A better understanding of the onset of such an augmented appetite-related gut hormone response will help inform future interventions to delay or manage anorexia of aging.

Finally, with most if not all of these age- or stage of life-related alterations in appetite-related gut hormones, the underlying mechanisms are not known. Future studies should explore nutrient-gut interactions—such as but not limited to the luminal environment, nutrient receptor number and activity, and EEC cellular signaling—in greater depth to elucidate the mechanisms underpinning periods of attenuated or augmented appetite-related gut hormone responses to feeding.

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Data Availability

Not applicable.

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