Paediatric Endocrine Aspects of Ghrelin

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Abstract

Ghrelin is a 28 amino-acid brain-gut peptide that is well-known for its orexigenic and metabolic effects leading to an overall positive energy balance. It stimulates appetite and growth hormone release via the GHS-R1a receptors. GOAT has been identified as the enzyme that acylates ghrelin in order for its endocrine function. The ghrelin/GHS-R/GOAT system has been studied extensively in view of its association with several endocrine diseases and the potential of developing an effective treatment. These include obesity, Prader-Willi syndrome, anorexia nervosa and diabetes mellitus. Ghrelin system has also been associated with growth and stature. All these conditions can affect children and have a significant impact on the quality of health and life prognosis. In this review, we look into the association of ghrelin with appetite, growth and metabolic disorders in children.

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Key words: *ghrelin, GOAT, GHS-R, appetite, obesity, Prader-Willi Syndrome, anorexia nervosa, diabetes mellitus, stature*

Introduction

Ghrelin is a circulating brain-gut peptide that was first successfully purified from the stomach by Kojima *et al.* in 1999 (1). This endogenous hormone consists of 28 amino-acids long and the gene responsible for its synthesis is located in chromosome 3p25-26. Following its discovery, the physiological and pathophysiologic functions of ghrelin have been studied extensively. These include stimulation of growth hormone release (1-4), regulation of appetite and energy metabolism (3, 5, 6), as well as modulation of cardiopulmonary and immune functions (7-9). Ghrelin is also known to regulate cell proliferation (8-10), stimulate bone formation (11) and affect sleep duration, memory, learning and behaviour (12-14).

Ghrelin has been linked to growth and several endocrine metabolic disorders such as obesity, Prader-Willi Syndrome (PWS), anorexia nervosa and diabetes mellitus. These conditions have major impact on the quality of health of children and play a significant role as life prognostic factors for these patients.

Ghrelin, GHS-R and GOAT

Ghrelin is synthesised mainly in the endocrine X/A cells of the gastric mucosa, but it also has low-level widespread expression throughout the body (15, 16). The main mRNA synthesised from the ghrelin gene codes for the 117 amino-acid preproghrelin, which is then enzymatically cleaved into proghrelin and obestatin (**Figure 1**).

Obestatin is a peptide with anorexigenic activities supposedly opposing those of ghrelin. Proghrelin is then processed into ghrelin via loosing its signal peptide and released into the circulation.

Ghrelin binds to growth hormone secretagogue receptor (GHS-R) to exert its metabolic effects such as the stimulation of growth hormone release and the regulation of appetite and energy homeostasis. GHS-R has two variants, GHS-R1a and GHS-R1b. GHS-R1a is a type 1a G protein-coupled receptor with seven transmembrane domains and is predominantly expressed in the pituitary as well as in several nuclei of the brain, particularly the arcuate nucleus (ARC), the ventromedial nucleus (VMN) and the paraventricular nuclei (PVN) of hypothalamus (15, 17). It is also expressed in other brain areas such as the substantia nigra, the dorsal and median raphe nuclei, the ventral tegmental area and the hippocampus (17). In peripheral tissues, GHS-R1a is expressed in the pancreas, spleen, stomach, intestine, heart, thyroid, gonads,

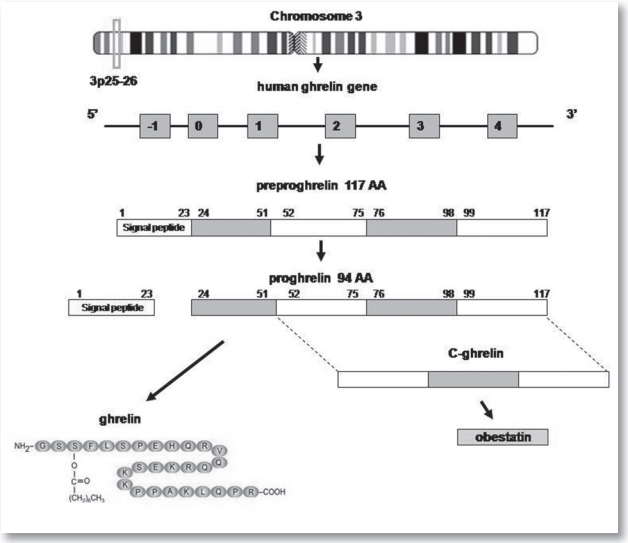

***Figure 1**: The ghrelin gene is located in chromosome 3p25-26. The main mRNA codes for the 117 amino-acid preproghrelin, which is then enzymatically cleaved to produce ghrelin and obestatin. Ghrelin is a 28 amino-acid hormone and has a unique fatty acid modification on its Ser-3.*
(Numbers above the boxes denote amino acids) (Modified from Liu et al. (116))

adrenal, kidney, adipose tissue and vasculature (15, 18). GHS-R1b is a non-spliced variant, also with wide expression throughout the body (15).

GHS-R1a was shown to transduce the GH-releasing effect of synthetic GHSs as well as ghrelin. GHS-R1a also plays a role in neuroendocrine and appetite-stimulating activities centrally. In contrast, the biological function of GHS-R1b remains unclear. GHS-R1b does not bind ghrelin or other GHSs, but it was shown to have counter-regulatory role by attenuating GHS-R1a signalling (19).

Ghrelin is known to be modified by acylation with octanoate, an eight-carbon fatty acid, for its biological functions (20). This esterification process is mediated by an acyl-transferase known as ghrelin O-acyltransferase (GOAT) (20). GOAT belongs to the super-family of membrane-bound O-acyltransferases (MBOAT4) and is able to transfer organic acids, typically long-chain fatty acids, to hydroxyl groups in membrane-embedded substrates (20, 21). Interestingly, human GOAT can acylate ghrelin with other types of fatty acids besides octanoate, such as the acetic and tetradecanoic acid (22). However, murine GOAT can only specifically binds octanoate to the Ser 3 of ghrelin covalently (23).

Using real-time reverse transcription and polymerase chain reaction, we showed widespread expression of GOAT in various human tissues: stomach, adrenal, breast, right and left colon, duodenum, jejunum, ileum, fat, fallopian tube, gallbladder, lymph node, lymphocyte cell line, kidney, liver, lung, muscle, myocardium, pituitary, oesophagus, pancreas, ovary, placenta, prostate, testis, spleen, and thyroid (24). The highest GOAT expression was in the stomach and gut but there was no direct quantitative correlation with the expression of ghrelin mRNA. Other studies have also shown GOAT expression in some of these tissues (22), further confirming the widespread expression of GOAT in various human tissues.

Recently, it is shown that the ghrelin-GOAT system does not only act as hunger signal, but also as a nutrient sensor by using readily absorbable medium-chain fatty acids to signal to the brain that high caloric food is available (25). This will then trigger the release of growth hormone and lipogenesis, leading to optimisation of nutrient partitioning and growth signals (25). More recently, a novel aspect of the effects of acylated ghrelin was revealed using a separate model of GOAT-/- animals (26). Severely undernourished GOAT-KO animals were unable to maintain blood glucose levels and died. This was due to the lack of large increase in circulating growth hormone which would help in maintaining the glucose levels in this model. Both acylated ghrelin and growth hormone injections were able to rescue this dramatic phenotype. These data bring to light a novel important role not just for ghrelin but also for growth hormone.

Ghrelin and Appetite Regulation

Ghrelin has always been popularly known as the 'hunger hormone' as its concentration in human plasma rises during fasting and falls post-prandially (27, 28), in the absence of time- and food-related cues (29). Both central and peripheral administrations of ghrelin in cause hyperphagia and increase in body weight (5, 30-32). Peripheral ghrelin translates information about nutrients and gut to the brain to determine short-term appetite and long-term body weight regulation (1, 33). It is upregulated under negative energy balance conditions and consequently initiates signal for food intake on the hypothalamus. Interestingly, a recent study showed that neither GOAT nor ghrelin expression were augmented during fasting, thus suggesting that ghrelin production may not be critical for generation of hunger signal (25).

Ghrelin reaches the brain through general circulation, crossing the blood-brain barrier, and via the stimulation of vagal afferent nerves (34). Ghrelin is also synthesized locally in the hypothalamus, where it exerts paracrine effects (35). In the hypothalamus and brain, ghrelin acts mainly by binding to its receptors in areas that are important for appetite regulation, namely in the ARC, PVN, dorsomedial region, central nucleus of amygdala and the nucleus of solitary tract (36, 37).

The ARC neurons are the main regulators of appetite and energy balance in the hypothalamus (38). The ARC neurons contain the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) and the anorexigenic peptides cocaine amphetamine-related transcript (CART) and pro-

opiomelanocortin (POMC) containing neurons. Ghrelin activates the arcuate NPY neurons and inhibits the POMC and CART neurons, leading to an increase in appetite and food intake (39, 40). ARC neurons also project to other hypothalamic nuclei, including the orexigenic orexin-containing neurons in the lateral hypothalamic area, to stimulate appetite (41).

PVN also receives projections from the anorexigenic POMC neurons as well as from the orexigenic NPY and AgRP neurons. The interactions between these two forms of projections with ghrelin in the PVN are not well known yet. Ghrelin is shown to activate AgRP-expressing cells and inhibit POMC-cells under slice preparations (35). It is proposed that ghrelin might stimulate appetite by antagonizing the inhibitory tone of the POMC neurons via the release of GABA from NPY/AgRP neurones in the PVN (35). Alternatively, ghrelin could have a direct effect on the PVN neurons via the NPY/AgRP cells (42).

Immunohistochemical analyses have revealed that ghrelin-immunoreactive neurons are localised in the hypothalamic ARC (43-45) and that ghrelin-containing axon terminals make synapses with NPY- or POMC-immunopositive dendritic processes in the ARC (35, 43, 45-47). Ghrelin-containing neurons in the ARC project to the lateral hypothalamus, where orexin- and melanin-concentrating hormone (MCH)-containing neurons are located. Ghrelin-containing axon terminals also make synapses with orexin-containing cell bodies and dendritic processes. Since the orexin neurons receive synaptic input from NPY neurons (48), it is possible that ghrelin stimulates the activity of orexin neurons via the NPY neurons. Ghrelin-containing neurons have also been shown to receive inputs from NPY-, orexin- and POMC-containing axon terminals in the ARC (47).

Interestingly, NPY gene knock-out mice showed only a slight decrease in food intake and co-administration of ghrelin and AgRP into the PVN of control rats did not produce a synergistic effect on feeding (49). AgRP-/- or NPY-/- embryo or neonate mice were also shown to be still susceptible to the effects of ghrelin (40, 50, 51), whereas the double knock-out mice were not (40). However, loss of either or both of these sets of neurons in adult animals causes a significant reduction in body weight and appetite (52-55). Activation of AgRP by ghrelin will also antagonise α-melanocyte-stimulating hormone (α-MSH) at the melanocortin receptors (MC) 3 and 4, which are the main MC receptors in the brain, leading to an increase in food intake (56). It is shown that the effects of ghrelin on food intake were reduced in MC3- and MC4-receptor knockout mice, and the circulating levels of ghrelin were also shown to be reduced in female MC4-receptor KO mice (57).

AMP-activated protein kinase (AMPK) has been shown to mediate the orexigenic effects of ghrelin (42, 58, 59). AMPK is a serine/threonine kinase with three subunits (α-, ß- and γ- subunits), forming a heterotrimeric structure. This protein plays a key role in energy homeostasis and its activity is regulated by change in AMP/ATP and ADP/ATP ratios (60, 61), leading to ultimate effects that influence the energy metabolism of the cell (61). We showed that ghrelin stimulates hypothalamic AMPK activity, leading to an increase in appetite (42, 58). However, more recently, intracerebroventricular injection of ghrelin in chickens led to inhibition of AMPKα1 and AMPK α2 mRNA expression (62).

Ghrelin has also been shown to induce Ca2+ signalling in NPY neurones in the ARC (38, 63). Recently, calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) has been shown to regulate hypothalamic production of NPY and to mediate the activation of hypothalamic AMPK by ghrelin (Figure 2) (64, 65). Activation of hypothalamic AMPK by ghrelin is achieved via the formation of a unique complex of AMPKα/ß with ACC (64, 65). This confirms CaMKK2 as the upstream kinase that mediates the effects of ghrelin on AMPK activity. Recently, uncoupling protein 2 (UCP2) was shown to mediate the effects of ghrelin on NPY/AgRP neuronal activity (39, 66). UCP2 is needed by ghrelin to activate hypothalamic mitochondrial respiration (39). This mechanism is necessary for ghrelin to induce mitochondrial proliferation, to regulate NPY/AgRP neuronal activity and ultimately to stimulate appetite (39).

The downstream effect of the ghrelin – GHS-R – CaMKK2 – AMPK axis in the regulation of appetite includes AMPK-dependent inhibition of the de novo fatty acid synthesis pathway in the VMN (**Figure 2**) (67).

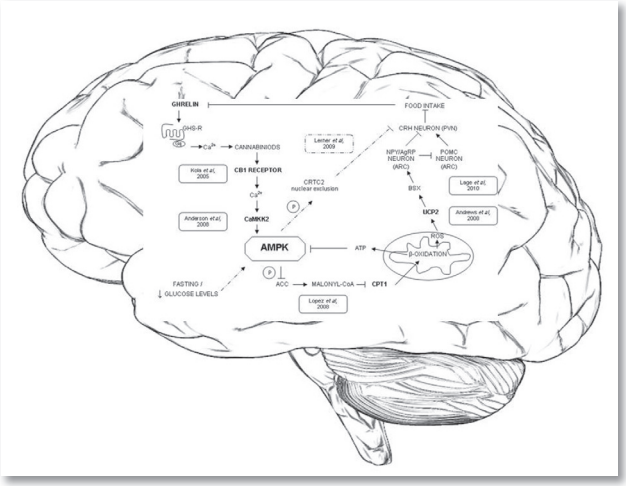

Figure 2: *Schematic diagram showing the pathway in which ghrelin stimulates appetite via AMPK (GHS-R1a, GH secretagogue receptor type 1 a; CB1, cannabinoid receptor type 1; CaMKK, calmodulin kinase kinase; AMPK, AMP-activated protein kinase; ACC, acetyl-coenzyme A carboxylase; malonyl-CoA, malonyl coenzyme A; FAS, fatty acid synthase; CPT1, carnitine palmitoyl transferase 1; ROS, reactive oxygen species; UCP2, uncoupled protein 2; NPY, neuropeptide Y; AgRP, agouti-related peptide; POMC, pro-opiomelanocortin).*

Ghrelin induces a decrease in the fatty acid synthase (FAS) mRNA levels in the VMN as well as the hypothalamic FAS activity and protein levels (67). Ghrelin also increases the phosphorylation of acetyl-coenzyme A carboxylase (ACC),

which is another downstream target. Both these events lead to the activation of carnitine palmitoyl transferase 1 (CPT1) and the degradation of malonyl-CoA in the medial basal hypothalamus (68-70). Consequently, these result in an increase in food intake and progressive weight gain.

In contrast, chronic central ghrelin administration does not induce major changes in all the enzymes of hypothalamic fatty acid metabolism in wild-type Lewis rats, but specifically decreases FAS mRNA expression in the VMH and hypothalamic CPT1 activity. These findings suggest that in the long-term setting, AMPK-induced changes in hypothalamic fatty acid metabolism have little or no role in feeding control. Secondly, quite opposite to short-term ghrelin action, chronic injection decreased CPT1 activity in the hypothalamus, which indicates that in the long-term setting ghrelin blocks hypothalamic beta oxidation, similarly to the results obtained in liver after long-term ghrelin treatment (22). The physiological relevance of this action is unclear, but the authors propose that it could be a compensatory mechanism attempting to "break" the massive orexigenic signal elicited by central hyperghrelinaemia.

Central ghrelin treatment leads to an increase in pAMPK levels in GH-deficient dwarf rats, without an effect on CPT1 activity and FAS mRNA and protein, suggesting that the effect of ghrelin on FAS mRNA expression is dependent on the GH status (71). The enhanced sensitivity of AMPK signaling to ghrelin treatment could be related to increased hypothalamic GHS-R expression in GH deficiency. Contrary to short-term administration, chronic central ghrelin treatment does not induce major changes in the overall fluxes of hypothalamic fatty acid metabolism and this effect seems to be independent of GH. Overall, these results suggest that ghrelin plays a dual time-dependent role in modulating hypothalamic lipid metabolism. As a result of this effect, short-term central ghrelin elicits a global AMPK-mediated inactivation of fatty acid metabolism pathway, an effect that promotes food intake (28, 58, 72). On the contrary, in the long-term setting, ghrelin does not induce AMPK-dependent changes in hypothalamic fatty acid metabolism, suggesting a lack of role for the ghrelin-AMPK interaction in the long-term feeding control.

Ghrelin and Obesity

Circulating ghrelin levels are altered in obesity and negatively correlate with the body mass index (BMI) in general (73). Studies have shown chronically low levels of circulating ghrelin in obese patients compared to normal subjects (74-77). Obese subjects also have blunted nocturnal plasma ghrelin levels. However, a recent study on children showed that ghrelin levels began recovery to baseline levels within three hours after food intake among the obese subjects compared to healthy children whose levels remained suppressed after three hours (78). Typically, ghrelin levels normalise with recovery to ideal body weight.

We showed that lipids are still deposited preferentially in the visceral adipose tissue of patients despite the low ghrelin levels (58). This is explained by the higher sensitivity of the visceral adipose tissue towards low levels of ghrelin compared to the subcutaneous tissue.

Insulin resistance, and thus high insulin, is commonly seen in obese patients. These subjects also experience chronically low ghrelin levels which are likely explained by the direct effect of insulin (79).

Relationships between mutations in the ghrelin or GHS-R genome and obesity have been reported (80, 81). For an example, patients with Leu72Met polymorphism in the ghrelin genome are phenotypically obese at an earlier age compared to homozygotic Leu72 allele patients (81). Arg51Gln ghrelin genome variant is seen in 6.3% of obese subjects (82). This polymorphism changes the C-terminal processing site of ghrelin and consequently results in a reduced production of ghrelin (81). Four naturally occurring GHS-R mutations, 1134T, V160M, A204E and F279L, have been reported to date and they all affect the constitutive activity of GHS-R (80). Nucleotide changes in the preproghrelin locus have also been identified in obese subjects (82, 83). All these mutations are rare.

Bariatric surgery is an effective management for obesity if the patient meets the criteria. Ghrelin levels are shown to be significantly decreased immediately after Roux-en-Y gastric bypass (84). Interestingly, ghrelin levels are also significantly decreased after weight loss with gastric bypass compared to baseline levels (85). This is different from diet-induced weight loss which does not result in decreased ghrelin levels.

Pharmacologically, there are still no effective anti-obesity drugs available that targets the ghrelin pathway. Antibodies against ghrelin and GOAT inhibitors have been studied (21, 86) and more recently, an anti-obesity vaccine that prevents ghrelin from reaching the central nervous system has also been developed (18). Exendin-4, a glucagon-like-peptide (GLP)-1 receptor agonist, has also been shown to inhibit ghrelin secretion (87). However, due to lack of efficacy, poor bioavailability, non-selectivity and lack of sustained weight loss, these drugs are still not available in the market for use as anti-obesity treatment.

Ghrelin and Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a complex genetic disorder caused by a loss of one or more paternal genes in the region 15q11-15q13 and is characterized by mild mental retardation, short stature, muscular hypotonia and obesity secondary to hyperphagia (88). Children with PWS present with rapid weight gain in childhood along with a marked

increase in appetite. In contrast to obesity, PWS patients have high ghrelin levels despite of their high BMI (89-91). The high ghrelin levels might in part contribute to their hyperphagia (89, 92) and will normalize following recovery to ideal body weight. Children with PWS were shown to have 3- to 4-fold higher ghrelin levels compared to weight matched controls (93).

PWS adults were shown to have an impaired postprandial suppression of plasma ghrelin which was associated with a blunted postprandial PYY response (94). In contrast, PWS children were shown to have a post-prandial decrease in ghrelin levels which was associated with increase in PYY levels, thereby implying that the appetite regulation of these peptides is operative during childhood and progressively deteriorates in adulthood when hyperphagia and obesity worsen (90). PWS patients also have three- to four-fold increase in mean plasma GH concentration than in reference population (81).

The negative correlation between ghrelin and adiposity is generally preserved among PWS patients (92), suggesting that although there is a shift in the relationship between ghrelin and adiposity, this condition does not represent complete ghrelin dysregulation. Additionally, the negative correlation between ghrelin and age is preserved as well.

Studies have shown that administration of octreotide, a somatostatin agonist, in PWS subjects leads to suppression of ghrelin levels, both acyl and des-acyl ghrelin (93, 95). However, these effects did not have an impact on the weight and appetite behaviour of PWS patients.

Ghrelin and Anorexia Nervosa

Anorexia nervosa (AN) patients have a distorted self and body image as well as an obsessive fear of gaining weight. The aetiology of AN is unknown and is thought to be multi-factorial. Patients suffering from AN have high levels of plasma ghrelin and growth hormone (81). This is similar to children with protein-energy malnutrition who have been shown to have high levels of serum ghrelin compared to healthy controls (96). Studies have shown increase in both active and inactive forms of ghrelin in AN patients (97, 98). It is suggested that the increased levels of ghrelin is largely due to energy deficit seen in AN subjects. The reduced food intake despite chronically increased ghrelin levels seen in AN suggests a state of ghrelin insensitivity or resistance (99, 100). This is supported by studies which showed no increase in appetite and food intake in AN subjects following exogenous ghrelin (99, 100). More recently, AN patients have been shown to have significantly lower plasma levels of acyl ghrelin IgG, IgM and IgA autoantibodies that persist even after one month of refeeding treatment (101), further supporting the theory that AN patients are resistant to ghrelin.

The degree of ghrelin suppression in AN patients following satiation is still unclear. Studies have shown significant blunting of ghrelin suppression in underweight AN patients following meal ingestion or oral glucose (102, 103). In contrast, there are also studies which showed similar degree of ghrelin suppression post-satiety compared to healthy individuals (104-106).

As expected, the elevated ghrelin levels seen in AN patients tend to normalise when patients regain their body weight following intensive weight restoration treatment (105). It is also shown in women with anorexia nervosa that hyperinsulinaemia could suppress the serum ghrelin levels (107). This might lead to an increased and more rapid feeling of satiety in patients with anorexia nervosa during feeding (107).

Ghrelin and Diabetes Mellitus

Hyperinsulinaemia is known to suppress ghrelin levels and insulin-like growth factor (IGF)-1 also has a negative correlation with ghrelin concentrations (108). Ghrelin levels have been shown to be similar in children with type 1 diabetes mellitus compared to healthy controls (109) and have no correlation with fasting glucose, insulin dose, duration of insulin therapy, glycated haemoglobin (HbA1c) and IGF binding protein (BP)-3 levels (109). Interestingly, post-prandial ghrelin levels have been shown to be significantly lower in children with Type 1 diabetes mellitus compared to healthy controls (109). In that same study, ghrelin levels were also shown to be positively correlated with serum HDL cholesterol in children with Type 1 diabetes mellitus (109). As expected, insulin treatment reduces pre-prandial ghrelin levels in children with Type 1 diabetes mellitus (110).

Ghrelin and GHS-R genes were not found to be associated with type 2 diabetes (111). The associations of Arg51Gln, Leu72Met, and Gln90Leu with type 2 diabetes were not identified in a Danish cohort (112) and in Old Order Amish members (113). The negative association for the Leu72Met polymorphism with type 2 diabetes was reinforced by work from other groups, in a separate Danish cohort (114), in two separate Japanese cohorts (115, 116), and in two separate Korean cohorts (115, 117). However, an increase in insulin sensitivity and a reduced risk for type 2 diabetes were observed in Caucasians with Leu72Met polymorphism (118). These contradicting results may be explained by the differences in the study designs and the population studied, such as the race and gender of the patients.

Genome wide studies have not identified the ghrelin or GHS-R gene as a causative factor of type 2 diabetes (119).

However, analysis study has failed to overlap the type 2 diabetes risk loci with the genome wide studies' results (120). This could be explained by the insufficient sample size in the majority of the studies and the complexity of type 2 diabetes aetiology.

Ghrelin and Stature

Ghrelin is known to stimulate the release of growth hormone via its receptor GHS-R (1-4, 121). Studies have shown that transgenic mice over-expressing GHS-R in hypothalamic GH-releasing hormone neurons undergo increased post-weaning growth rates, while rats expressing reduced level of GHS-R in the hypothalamus possess shorter nose-tail length (36, 122). Height is a highly heritable complex trait and ghrelin has been postulated as a candidate gene for stature in human because of its independent regulation of GH secretion apart from the hypothalamic control.

Several case association studies have been carried out to look into the relationship between ghrelin sequence variants and serum IGF-1 levels, a surrogate marker for GH. Ukkola *et al.* conducted a study which reported that black subjects with Leu72Met sequence variant have higher serum IGF-1 levels (123). In a different study, obese Caucasians that carries the 72M*et al*lele were also shown to have higher IGF-1 levels than 72Leu allele homozygous subjects (124). In contrast, a group of Finnish subjects who were carriers of Arg51Gln allele possesses significantly lower concentrations of IGF-1, both before and after adjustment for age, BMI, sex and study group (125). These case association studies suggest that common genetic variants of ghrelin may be involved in determination of stature via effects on the GH/IGF-1 axis.

Direct association studies did not reveal any positive findings on association between genetic variations of ghrelin and height, thus suggesting that common variations in ghrelin are not major contributors to height determination (119). The effects are likely to be subtle, as supported by a recent genome wide association study (GWAS) which showed weak associations between the genetic variants GDF5 and HMGA2 genes with the total variation (0.1-0.8%) in height in the general population studied (126, 127).

In a UK based GWAS comprising 1377 siblings with diabetes, a locus near the ghrelin gene on chromosome 3p26 was found to influence stature (LOD score 3.17) (128). We have also looked into the link between the human preproghrelin gene (GHRL) with human stature by genotyping five common SNPs which capture most of the genetic diversity of the GHRL gene (129). From the study, we showed no evidence of association between the GHRL gene with stature (129). Similar findings were then found in a subsequent case-control study in the French population (130).

Mutations in the GHS-R have also been implicated in the aetiology of short stature in humans, with variable severity and penetrance (131-134). Missense mutation p.Ala204Glu in the second extracellular loop of the GHS-R1a was shown to be associated with idiopathic short stature and isolated GH deficiency in two unrelated families from Morocco respectively (131, 133, 134). Another GHS-R mutation, p.Phe279Leu, was shown in a boy with idiopathic short stature as well as in his obese, short mother (133).

Recently, an isolated GHD patient with delayed puberty was shown to be compound heterozygous for two GHS-R mutations (p.Trp2X and p.Arg237Trp) (132). Interestingly, the father of the patient was heterozygous for the nonsense mutation but also had delayed puberty (132). All the GHS-R missense mutations described markedly decreased the constitutive activity of this receptor, but some of these mutations preserved its ability to respond to ghrelin (131, 132, 134). More recently, five different heterozygous point variations in GHS-R (c.-6 G>C, c.251G>T (p.Ser84Ile), c.505G>A (p.Ala169Thr), c.545T>C (p.Val182Ala), and c.1072G>A (p.Ala358Thr)) were identified in patients with constitutional delay of growth and puberty (135), suggesting that abnormalities in ghrelin receptor function may influence the phenotype of these patients.

We studied the association between three of the GHS-R SNPs (T171C, rs495225; C447G, rs2232169; G477A, rs572169) with IGF-1 and height in a separate UK based study and no significant associations were detected in the paediatric cohort (130). However, a larger and more recent GWAS also identified a significant association between an SNP (rs572169) located within the GHS-R gene with height (136). This finding was also confirmed in a family based analysis to prevent false positive (136).

Conclusion

Ghrelin stimulates appetite and promotes positive energy balance in the body. The discovery of ghrelin and its physiological functions have led to investigations on the association of ghrelin with growth and several metabolic disorders such as obesity, Prader-Willi Syndrome, anorexia nervosa and diabetes mellitus. These conditions have a significant impact on the health of children. More researches are needed for the development of effective treatment targeting the ghrelin/GOAT/GHS-R pathway that can be used to treat these metabolic conditions.

Disclosure

The authors declare no conflict of interest.

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