Ghrelin in Growth and Development

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Key Words
Ghrelin • Growth hormone secretagogue receptor • Fetal pancreas • Anorexia nervosa • Obesity • Prader-Willi syndrome

Abstract
Exogenous administration of ghrelin increases caloric intake and stimulates growth hormone (GH) secretion, two effects that are mediated through binding of ghrelin to the GH secretagogue receptor (GHS-R). In addition, ghrelin is thought to inhibit adipogenesis by GHS-R-independent mechanisms. In adults, ghrelin is mainly produced by the stomach. In contrast, in the fetal and early postnatal period, ghrelin gene expression is abundant in the pancreas but not in the stomach. While knockout animal studies demonstrate that ghrelin is not required for perinatal development under normal nutritional conditions, the characteristics of ghrelin metabolism during fetal development suggest that ghrelin could contribute to the programming of mechanisms involved in energy balance, such as β-cell maturation, orexigenic pathways and adipogenesis. In humans, ghrelin concentrations progressively decrease during childhood and adolescence, as well as with advancing puberty. In adolescents, similar to adults, ghrelin concentrations are inversely related to body mass index and to circulating insulin. One notable exception is the presence of elevated ghrelin concentrations in subjects with Prader-Willi syndrome, raising the possibility that ghrelin could be part of the etiology of excess food intake in this condition. These data raise a number of fascinating questions on the potential physiologic role of this hormone during growth and development.

Introduction

Growth hormone secretagogues (GHS) are artificial compounds with potent growth hormone (GH)-secreting properties that were first developed in the 1970s [1]. The GH secretagogue receptor (GHS-R) to which these GHS bind is a G protein-coupled receptor that was cloned in 1996 [2]. Ghrelin, the first natural ligand for the GHS-R, was isolated in 1999 [3].

Ghrelin is a 28-amino-acid peptide secreted primarily by the fundus of the stomach in adult humans [4] and animals [3]. It has the unique characteristic of having a hydroxyl group of one of its serine residues (Ser 3) acylated by n-octanoic acid. This acylation by n-octanoic acid is necessary for the binding of ghrelin to the GHS-R ([3], rev. in [5]).
Ghrelin, like synthetic GHSs, stimulates GH secretion and has potent orexigenic effects. Both effects are mediated by the GHS-R [6]. Ghrelin stimulates GH secretion in the hypothalamus, an action that requires GH-releasing hormone (GHRH) (fig. 1) [7]. The effects of ghrelin on appetite are mediated mainly in the hypothalamus through stimulation of neuropeptide Y (NPY), a potent orexigenic agent, and of agouti-related protein (AgRP), a melanocortin receptor inverse agonist (fig. 2) [8]. However, neither stimulation of NPY or AgRP by ghrelin seems to be necessary for the regulation of energy balance [9]. In addition, ghrelin also promotes a positive energy
balance through stimulation of adipogenesis independently from its effect on appetite. This effect may be mediated through GHS-R-independent pathways [10, 11].

The demonstration that ghrelin gene expression is present in the placenta [12] as well as in the fetal and/or neonatal pancreas [13–16], pituitary [17] and hypothalamus [18], raised the possibility that ghrelin may play a role in the maturation of the mechanisms implicated in energy balance. The goal of the present work is to review the animal and human data on ghrelin during development and to highlight the differences in ghrelin metabolism between the perinatal period and adulthood.

Search Methods

Articles were identified using the PubMed database (www.ncbi.nlm.nih.gov/pubmed). The key word used was ghrelin. All published or in press articles listed in the search until November 15, 2004 (n = 919) were screened for relevance to the topic of the review. Additional reports were identified from a review of references listed in the reports located through the PubMed search.

Technical Issues

Ghrelin results are reported as pg/ml or pmol/l. Using the molecular weight of deacylated human ghrelin ([Des-Octanoyl-Ser3], MW: 3,245) the conversion factor between SI and conventional units is: pmol/l = pg/ml × 0.296. The acylated form of ghrelin is responsible for the biological actions of ghrelin resulting from binding to and activation of the GHS-R and is therefore referred to as the ‘active’ form of ghrelin. It represents less than 10–20% of total (acylated and deacylated) ghrelin immunoreactivity, which is measured by most commercial assays. Deacylated ghrelin immunoreactivity is relatively stable and is well preserved if collected in chilled EDTA-aprotinin tubes. In contrast, the acylated form of ghrelin is very unstable. As the enzymatic mechanisms regulating deacetylation of ghrelin become better understood [19], more effective methods of preserving acylated (‘active’) ghrelin will become available [20, 21]. The concentration of total ghrelin reported in the literature also varies with the assay used. Two widely used commercial assays (Linco, Saint Charles, Mo., USA and Phoenix, Belmont, Calif., USA) are known to yield greatly different absolute values. In agreement with Groschl et al. [22], we demonstrated [23] that part of this difference could be accounted for by different potencies in the ghrelin standards provided by the two companies. Thus, when critically evaluating the ghrelin literature, the reader needs to keep in mind that comparison of published total ghrelin concentrations is difficult and that it is usually assumed that the concentrations of total ghrelin accurately reflect those of acylated ghrelin. This latter assumption may be correct in human umbilical cord blood [24], although it remains to be proven under specific pathological situations.

Lessons Learned from Ghrelin and Ghrelin Receptor Defects

Animal Knockout Models for Ghrelin or the Ghrelin Receptor Genes

Exogenous administration of ghrelin markedly stimulates food intake and GH secretion in rodents. It was therefore tempting to hypothesize that complete ghrelin deficiency would impair growth and development. Two ghrelin [25, 26] and one ghrelin receptor knockout models [6] were developed to test these hypotheses.

In both ghrelin knockout models, the entire coding region of the gene was deleted, resulting in a complete absence of ghrelin in all tissues tested. Ghrelin−/− mice showed normal fertility and litter size. Overall, body weight and composition, fed and fasting glucose, insulin and leptin concentrations [25, 26] as well as fasting plasma GH concentrations [26] were similar in ghrelin−/− and wild-type animals. In addition, daily food intake [25, 26], hypothalamic orexigenic (NPY, AgRP) and anorexigenic (proopiomelanocortin [POMC]) neuropeptide mRNAs [26] as well as food intake during refeeding following a 24 h fast were also unaffected by deletion of the ghrelin gene. However, a significant decrease in the respiratory quotient and a trend towards a decrease in fat mass – without changes in body weight – were reported in ghrelin−/− mice following 6 weeks on a high-fat diet [26]. These data raise the possibility that ghrelin could modulate the type of metabolic substrate (carbohydrate vs. fat) preferentially used to maintain energy balance, particularly in the presence of a high-fat diet and are consistent with the decrease in fat utilization observed in adult rats following exogenous administration of ghrelin [10].

Deletion of the ghrelin receptor gene causes a modest decrease in weight gain as well as a decrease in insulin-like growth factor-1 (IGF-1), suggesting that GHS-R plays a physiologic role in energy balance and GH regulation. A similar phenotype has also been reported by Shuto et al. [27] in transgenic rats where the synthesis of GHS-R
protein was attenuated through expression of an antisense GHS-R mRNA in the hypothalamus. These results may seem disappointing compared to the clear phenotype of massive obesity observed for instance in the ob/ob mice, a strain lacking the anorexigenic peptide leptin [28]. However, it should be remembered that they are consistent with the absence of a major phenotype observed in knockout models of NPY, a potent orexigenic peptide stimulated by ghrelin injection and modulating its action in the hypothalamus [29].

**Ghrelin and Ghrelin Receptor Mutations in Humans**

Systematic studies of large cohorts of obese children and adolescents do not support the hypothesis that single-gene mutations of the ghrelin [30] or the GHS-R genes [31] are a common cause of obesity. A polymorphism of the ghrelin gene that causes substitution of a highly conserved leucine for a methionine (Leu72Met) has been associated with earlier onset of obesity [30], although this remains to be confirmed [32, 33]. Interestingly, Pantel et al. [34] recently reported the presence of a mutation of the ghrelin receptor gene in a family where short stature is inherited in a dominant fashion. The missense mutation markedly decreased binding of ghrelin to the mutant receptor, suggesting that integrity of this pathway is required for normal growth.

Thus, the absence of ghrelin does not prevent normal fetal growth and development, at least in rodents. However, ghrelin may be required for metabolic actions that are not mediated through the GHS-R, such as adipogenesis. In addition, human and animal studies suggest that the presence of a normal GHS-R may be more important than ghrelin itself for the integrity of the GH-IGF-1 axis. In support of this hypothesis, it has recently been demonstrated that the GHS-R is constitutively activated and that it signals with 50% efficacy even in the absence of ghrelin [35]. Conditional or tissue-specific knockout models of ghrelin or GHS-R may be needed to understand the physiologic role of ghrelin.

**Animal Data**

**Different Anatomical Location of Ghrelin in the Pre- and Postnatal Periods**

Both acylated (‘active’) and deacylated ghrelin are present in fetal rat plasma on day 20 of gestation [13]. In contrast to active ghrelin, concentrations of total ghrelin are significantly higher in the fetus compared to the dam (fig. 3) [13]. Postnatally, ghrelin is present in the plasma at least by the second week of life, without clear age- or sex-related changes until weaning [36, 37].

Interestingly, tissue distribution of ghrelin greatly differs in the fetal and the postnatal periods. Ghrelin is present in the whole fetus as early as on day 12 of pregnancy [18]. Low levels of ghrelin gene expression are present in the fetal stomach by day 18 of gestation [13, 37, 38], a tissue traditionally regarded as a major source of circulating ghrelin in the adult [3, 36]. Postnatally, stomach ghrelin gene expression increases markedly and reaches adult levels by 3–5 weeks [18, 36–38]. In contrast, high levels of ghrelin gene expression are present in the fetal pancreas, suggesting that it may be a major source of circulating fetal ghrelin [13–15]. Ghrelin gene expression is 6–7 times higher in the fetal pancreas than in the fetal stomach on day 20 of gestation (fig. 3) [13] and decreases progressively during the first 2 weeks of life before reaching low levels of ghrelin gene expression in the adult pancreas [15]. Ghrelin in the fetal pancreas is produced by a novel endocrine cell type (β cell) located in the pancre-
atic islet [14, 15]. In mice lacking Nkx2.2, a transcription factor that is essential for early differentiation of insulin-producing β cells, β cells are replaced by ghrelin-producing cells in the fetal islet, raising the possibility that ghrelin (ε) and insulin (β)-producing cells derive from a common endocrine precursor [14]. Ghrelin mRNA and protein have also been reported in the rat placenta near term [12, 18]. Although placent al concentrations of total immunoreactive ghrelin are low [13], placental tissue is abundant and could potentially contribute to the fetal pool of ghrelin.

**Ghrelin and Perinatal Energy Balance**

In keeping with a different anatomical origin, the nutritional regulation of ghrelin also differs between the pre- and postnatal periods. In adult rats (including pregnant dams [13]), fasting causes a marked increase in circulating total ghrelin concentrations (fig. 3) [39]. This physiologic fasting-associated rise in plasma total ghrelin is present by the end of the first postnatal week [38]. In contrast, in the fetus, plasma total ghrelin concentrations are unaffected by maternal fasting, despite a marked decrease in fetal plasma total glucose and insulin concentrations [13], a situation known to trigger an increase in circulating ghrelin in adult animals [39]. However, acylated (‘active’) ghrelin concentrations increase in the fetal pancreas with maternal fasting raising the possibility that ghrelin may mediate the effects of maternal nutrition on the developing pancreas [13]. Interestingly, daily administration of ghrelin directly to rat pups during the first 4 weeks of life does not affect postnatal weight gain [38], a finding that contrasts with the weight gain reported in adult mice following continuous infusion of ghrelin [10, 40]. A potential explanation could be the immaturity of the efferent projections in the neonatal hypothalamus [41]. In contrast, administration of ghrelin to the mother during the last week of gestation was associated with a 10–20% increase in birth weight [38]. Similarly, exogenous administration of ghrelin in lactating dams increased milk secretion and the pups’ weight gain [42]. These data raise the possibility that maternal ghrelin could affect energy balance in the fetus and the neonate through mobilization of maternal resources.

The demonstration that GHRP-6 (a synthetic GHS) and ghrelin both regulate the expression of the transcription factor Pit-1 raises the possibility that ghrelin is involved in the differentiation of the anterior pituitary and in the development of the GH-IGF-1 axis [43]. Postnatally, pituitary ghrelin mRNA decreases progressively from birth to adulthood [18]. A single injection of ghrelin causes a 2–3-fold increase in plasma GH concentrations by 1 week of age [38], a finding consistent with the demonstration of GHS-R mRNA in the pituitary [44] and the hypothalamus [45] early in life. In contrast, the physiologic role of endogenous ghrelin on neonatal GH secretion remains unclear. Immunization-induced decrease in GHRH sufficient to cause an 80% decrease in plasma GH concentrations did not affect hypothalamic or pituitary ghrelin mRNA. Similarly, ghrelin gene expression was not affected in mice deficient in liver IGF-1, a defect associated with an increase in GH secretion [18].

Thus, ghrelin is present in the fetus and its tissue distribution differs from the adult. The abundance of ghrelin in the fetal endocrine pancreas suggests that ghrelin may regulate β-cell development. In addition, while ghrelin is not required for the survival of the fetus, it could potentially contribute to the programming of central pathways in response to perinatal environmental signals such as nutrition [46]. Such early effects have been recently suggested for leptin [47].

**Human Data**

**Ghrelin in the Fetus and the Neonate**

Immunoreactive ghrelin is present in umbilical cord blood samples as early as by the 20th week of gestation [48] in concentrations that are of the same magnitude as those reported in adults. Umbilical cord total ghrelin concentrations are higher than in maternal blood [49, 50] and are not affected by gender [51, 52] or ethnicity [51]. They are also higher in small for gestational age (SGA) compared to appropriate for gestational age (AGA) neonates [48, 52–54] (fig. 4). A modest positive correlation between gestational age and ghrelin concentrations has been reported at least in AGA neonates [50, 52]. The interpretation of a negative correlation between birth weight and ghrelin observed by several authors, including ourselves, is made difficult by the inclusion in the published series of infants with two potential confounding variables, SGA and prematurity [48, 52–54].

The source of fetal ghrelin remains unclear. Human postmortem studies have shown that ghrelin is abundant in the fetal (but not the adult) thyroid [55], lung [56] and pancreas but less so in the fetal stomach, suggesting that, like in rodents, tissues other than the stomach contribute to the pool of circulating ghrelin in the fetus [16]. Ghrelin is not detected in term human placenta [12] and ghrelin concentrations are similar [48] or only modestly higher [53] in the umbilical vein compared to the umbilical ar-
Taken together, these data do not support the existence of a major placental contribution to fetal circulating ghrelin.

The role of ghrelin on weight gain and GH secretion during the perinatal period remains unclear. Ghrelin could potentially contribute to feeding initiation and positive energy balance. In support of this hypothesis, James et al. [57] found a modest association between lower cord blood ghrelin concentrations and slower weight gain for the first 12 postnatal weeks and Iniguez et al. [58] reported a greater drop in plasma ghrelin concentrations following IV glucose load in SGA infants with a slow weight gain between 0 and 1 years.

Ghrelin could also conceptually contribute to the high GH concentrations observed in cord blood. The in vitro demonstration of GHS-R mRNA and of an increase in GH secretion in response to GHRP-6 in the human fetal pituitary supports this hypothesis [59]. However, most studies failed to observe any significant correlation between umbilical cord ghrelin and GH concentrations [51, 53].

Ghrelin in Children and Adolescents
Circulating ghrelin concentrations progressively increase during the first 2 years of life [60] before decreasing during late childhood and adolescence [61], without gender-specific differences [62, 63]. Ghrelin concentrations also decrease during puberty with advancing Tanner staging and are 30–50% lower in postpubertal compared to prepubertal subjects [60, 61]. Although gonadal steroids may seem an obvious candidate for this puberty-associated decrease, the absence of a gender difference in ghrelin concentrations does not support this hypothesis.

Ghrelin and Energy Balance
In adults, ghrelin concentrations increase prior to the 3 main meals and decrease 30–90 min following the meal [64, 65]. A temporal relationship between changes in ghrelin concentrations and hunger sensation has also been reported, raising the possibility that ghrelin may play a physiologic role in meal initiation [66]. The ontogenesis of the acute ghrelin response to caloric intake in humans is however unclear. It is present in adolescents (fig. 5) [67] and the recent report that this response may be absent in prepubertal subjects [68] suggests that it could develop progressively during childhood.

In adults, ghrelin administration induces hyperglycemia and decreases plasma insulin concentrations [69]. Conversely, hyperglycemia [70] and insulin (in the absence of hypoglycemia) [71] decrease plasma ghrelin. Similarly, a negative correlation between ghrelin and insulin concentrations has been reported in children and adolescents [62, 67, 72, 73]. A decrease in circulating ghrelin concentrations has also been observed in pediatric patients with newly diagnosed type 1 diabetes prior to initiation of insulin treatment and could be secondary to hyperglycemia [74]. Taken together, these data suggest that ghrelin is closely associated with glucose metabolism in adults as well as in children and adolescents.

Similar to adults [4, 75], ghrelin concentrations are increased in anorexic [67, 76] and decreased in obese adolescents [62, 67, 77] and there is a negative correlation between ghrelin concentrations and body mass index [61, 62]. The decrease in circulating ghrelin in response to a mixed meal [67] (fig. 5) or to a glucose load [76, 77] is preserved in anorexic and obese adolescents. Renutrition in anorexic adolescents or weight loss in obese adolescents is associated with a normalization of fasting ghrelin concentrations [73]. In a prospective study performed in Pima Indian children, Bunt et al. [62] showed that ghrelin was not an independent predictor of future weight gain.
Ghrelin and GH Physiology

Similar to adults, administration of a synthetic GHS in children without GH deficiency, or to children with GH deficiency but with intact pituitary function, causes a marked increase in plasma GH concentrations [78–80], suggesting that administration of the natural peptide ghrelin would also stimulate GH secretion in young subjects. Whether endogenous ghrelin is involved in the physiology of GH in children and adolescents remains to be demonstrated. Ghizzoni et al. [63] observed higher ghrelin and lower GH nocturnal concentrations in short children with neurosecretory dysfunction compared to short, non-GH-deficient children, suggesting that ghrelin may not be driving nighttime GH secretion. In a group of boys with constitutional delay of puberty, testosterone administration caused the expected increase in GH concentrations but did not affect the 24-hour ghrelin profile, suggesting that the testosterone-induced GH secretion was not caused by ghrelin [81]. Finally, we recently observed a decrease in ghrelin concentrations following glucagon administration in a group of non-GH-deficient short children, suggesting that ghrelin does not mediate the glucagon-induced GH secretion [23].

Ghrelin and Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a genetic disorder characterized by poor weight gain in the early postnatal period, followed by excessive weight gain by age 1–3 years. More than one third of patients with PWS weigh more than 200% of their ideal body weight [82, 83]. Obesity is thought to result mainly from hyperphagia, decreased perception of satiety and obsessive and compulsive behaviors that are primarily food related [84, 85]. Patients also present with short stature, possibly due to GH deficiency of hypothalamic origin [86, 87].

In contrast to the low ghrelin concentrations observed in obese subjects without PWS, ghrelin concentrations are markedly elevated in obese children and adolescents with PWS subjects from birth [88–90]. The physiologic decrease in circulating ghrelin following a test meal is preserved [91, 92]. The mechanism underlying these elevated ghrelin concentrations is unclear and working hypotheses include abnormal ghrelin regulation by proteins normally encoded by chromosome 15 [91], known to be abnormal in PWS or a primary hypothalamic defect [88]. Nevertheless, this unique observation raised the possibility that ghrelin might play a role in the hyperphagia and weight gain in these patients. Short-term infusion of octreotide, a somatostatin analogue, caused a marked decrease in circulating ghrelin in both young [91] and adult [93] subjects with PWS, but this was not associated with a decrease in appetite, at least in adult subjects [93]. Whether a prolonged decrease in ghrelin concentrations will be helpful in managing weight excess in these patients remains to be demonstrated. GH therapy for 1 year does not affect fasting ghrelin concentrations in patients with PWS [88, 94].

Thus, ghrelin is present in the perinatal period in humans where its role remains poorly understood. In adolescents, similar to adults, plasma ghrelin concentrations are decreased and increased in the presence of a positive and a negative energy balance, respectively. Whether these changes represent an adaptive response aiming at optimizing fat utilization as suggested in animal studies [10, 26] or whether they reflect an altered set-point for ghrelin at the hypothalamic level is presently unknown.
Conclusions

Ghrelin is present in the fetus and its tissue distribution differs from the adult. It binds to the GHS-R as early as during the fetal period. Although knockout animal studies suggest that ghrelin is not required for fetal and early postnatal growth and development under normal nutritional conditions, we speculate that ghrelin could contribute to the programming of the mechanisms involved in energy balance, such as β-cell development, orexigenic pathways and adipogenesis. Less than 5 years after the discovery of ghrelin, we are starting to understand some of the unique aspects of this hormone in the perinatal period. The characteristics of ghrelin metabolism outlined in this work raise a number of fascinating questions on the potential physiologic role of this hormone during growth and development.

Acknowledgment

This work was supported in part by grant #1637 of the Canadian Diabetes Association.

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