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Developmental Effects of Ghrelin

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Abstract

Ghrelin is a pleiotropic hormone that was originally described as promoting feeding and stimulating growth hormone release in adults. A growing body of evidence suggests that ghrelin may also exert developmental and organizational effects during perinatal life. The perinatal actions of ghrelin include the regulation of early developmental events such as blastocyst development and perinatal growth. Moreover, alterations in perinatal ghrelin levels result in structural differences in various peripheral organs, such as the pancreas and gastrointestinal tract. Recent data have also suggested that ghrelin acts on appetite-related brain centers in early life. Together, these observations indicate that exposure to factors that alter how ghrelin impacts development may induce lasting effects on physiological regulation.

Keywords

hormone; GHSR; brain; development; hypothalamus; proliferation; pancreas

Introduction

Ghrelin is a 28-amino-acid peptide that is primarily secreted by gastric mucosal cells and plays a key role in appetite regulation (see [1] for review). It is now widely recognized that ghrelin acts primarily on the brain to mediate its effects on feeding and energy balance. Consistent with this idea, direct intracerebroventricular administration of ghrelin produces a marked increase in food intake and body weight [31]. Among brain regions involved in ghrelin's orexigenic effects, a primary importance has been given to the hypothalamus. The hypothalamus contains the highest density of ghrelin receptors (GHSRs) of any brain region [16, 38], and administration of ghrelin induces cFos immunoreactivity (a marker of neuronal activation) in various hypothalamic nuclei involved in feeding regulation, including the arcuate (ARH), ventromedial (VMH), and paraventricular (PVH) nuclei of the hypothalamus [11, 19]. More recent work has also suggested that extra-hypothalamic sites, such as the ventral tegmental area (in the midbrain), may also be crucial for relaying ghrelin's orexigenic actions [27]. In addition to regulating feeding, ghrelin is involved in

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other physiological regulation, such as cardiovascular function [17], gastrointestinal motility [15], and growth hormone release [35]. Ghrelin has also been shown to exert more complex behavioral effects and is involved in learning and memory [7], reward/addiction [13, 20], and depression/anxiety [9]. Recent studies have demonstrated the pleiotropic nature of ghrelin by showing that it can also influence a variety of developmental processes during perinatal development.

This review summarizes the developmental and structural changes that have been observed in various organs in response to alterations in ghrelin levels during critical periods of development. In particular, this review will describe the developmental effects of ghrelin on the neural and endocrine systems involved in metabolic regulation.

Very Early Developmental Effects of Ghrelin

Following its discovery, it soon became evident that ghrelin may play a role during development. The earliest developmental event that appears to be influenced by ghrelin is blastocyst development. *Ghrelin* and *Ghsr* mRNAs are detected in embryos as early as the morula stage [14]. In addition to being expressed by the embryo, ghrelin is expressed in the uterus and secreted in uterine fluid [14]. *In vitro* experiments have indicated that ghrelin acts on GHSRs to inhibit the development of embryos from the morula to the blastocyst stage and from the blastocyst to the expanded blastocyst stage [14]. Consistent with these observations, ghrelin inhibits the proliferation of both the inner cell mass and the trophoblast, which are the two cell lineages found in the blastocyst [14]. Notably, uterine ghrelin levels are influenced by the maternal diet (*e.g.*, maternal fasting increases both the plasma and uterine ghrelin levels [14]), raising the possibility that nutritional manipulation of ghrelin secretion may affect the development of pre-implantation embryos.

Developmental Regulation of Ghrelin and GHSR Expression

As mentioned above, ghrelin is expressed in the embryo as early as the morula stage and continues to be expressed in the developing embryo and fetus. In rodents, high levels of *ghrelin* mRNA are detected in fetuses at embryonic day (E) 12, and E17 fetuses contain significant levels of acylated and deacylated ghrelin in their blood [18, 30]. A single ghrelin injection into the mother is capable of increasing the circulating ghrelin levels in the fetus within 5 minutes, indicating that maternal ghrelin can easily transfer to the fetal circulatory system and increase fetal ghrelin levels [18]. It is also worth noting that the total ghrelin levels found in fetuses are three times higher than those found in their dams [4], suggesting that the ghrelin found in a fetus may be produced by the fetus itself.

In the fetus, the pancreas appears to be a major source of ghrelin expression during perinatal life. *Ghrelin* mRNA and protein are found at high levels in the fetal pancreas, whereas low levels of ghrelin are detected in the fetal stomach [4, 33] (Fig. 1 and Table 1). These observations suggest that, in contrast to the adult, the source of circulating fetal ghrelin may be the pancreas, not the stomach. Stomach ghrelin expression increases gradually after birth to reach adult-like levels by 3–5 weeks of life [10, 30]. Meanwhile, pancreatic ghrelin expression declines progressively from birth to weaning and becomes barely detectable in the adult pancreas [33] (Fig. 1). In addition to being transiently expressed in the developing pancreas, *ghrelin* mRNA is also expressed in the pituitary gland, lung, gonads, and gut during perinatal development [4, 24, 29, 30] (Table 1).

Ghrelin acts on growth hormone secretagogue receptors (GHSRs) to mediate its effects [28]. In adult animals and neonates, GHSRs are expressed in both the central nervous system and the periphery (Table 1). In peripheral fetal organs, *Ghsr* mRNA is detected in the skin, bone, eye, heart, lung, liver, stomach, intestine, kidney, spleen, testis, ovary, and pituitary gland

[18]. Although these qualitative studies provide valuable information regarding expression sites of ghrelin and GHSR during development, further studies will be needed to quantitatively compare the expression of ghrelin and its receptor in various tissues during development. RT-PCR analysis has also indicated that *Ghsr* mRNA is highly expressed in the central nervous system during both pre- and post-natal life. *Ghsr* mRNA is found in the brain and spinal cord as early as E12 and continues to be expressed in these tissues during postnatal life [12, 18]. Unfortunately, a detailed distribution of GHSR expression in the neonatal brain has not yet been described. Similarly, whether central (and peripheral) GHSR expression is subjected to developmental regulations remains unknown. Nevertheless, we know that *Ghsr* mRNA is primarily expressed in the adult hypothalamus, specifically in the nuclei area involved in food intake and body weight regulation, such as the arcuate, ventromedial, dorsomedial, and paraventricular nuclei of the hypothalamus [16, 38]. Additionally, GHSRs are expressed in other appetite-related brain structures, such as the ventral tegmental area and the nucleus of the tractus solitarius [16, 38].

Ghrelin and Perinatal Growth

The widespread expression of ghrelin and its receptor during development suggests that ghrelin may be involved in perinatal growth. The capacity of ghrelin to influence perinatal growth has been summarized in reviews by Chanoine et al. [2, 3]. One key observation is that chronic administration of ghrelin into pregnant dams from day 14 of gestation until delivery results in higher birth weights [18]. In contrast, passive immunization against ghrelin during pregnancy results in low birth weights in the offspring [18]. Ghrelin injection into either postnatal day (P) 7 or P10 rat pups stimulates growth hormone secretion, supporting a role for ghrelin in somatic growth [10, 22]. However, a lifelong ghrelin deficiency, such as that observed in either ghrelin-knockout mice or GHSR null mice, does not impair early growth and development, suggesting that there may be compensatory pathways that can adjust for the loss of ghrelin and promote growth [26, 28, 34]. Remarkably, although adult GHSR null mice develop obesity when fed a high-fat diet, the same mutant mice appear resistant to diet-induced obesity when exposure to the high-fat diet occurs shortly after weaning [26, 28, 34]. These observations indicate that ghrelin and GHSR affect the maturation of metabolic systems involved in energy balance.

Effects of Ghrelin on Pancreatic and Gastrointestinal Development

During perinatal development, ghrelin is transiently expressed in the α islet cells in the pancreas, where it colocalizes with glucagon [5]. Recently, it has been shown that ghrelin is also produced by a distinct population of pancreatic islet cells, the ϵ cells [23]. Interestingly, insulin- and ghrelin-secreting cells appear to be derived from a common progenitor cell. In this common progenitor, both the *Nkx2.2* and *Pax4* transcription factors are involved in regulating the cell fate decision in which the progenitors differentiate into either β (*i.e.*, insulin-producing) or ϵ (*i.e.*, ghrelin-producing) cells [23]. In fact, in mice that lack either *Nkx2.2* or *Pax4*, all pancreatic endocrine cells are replaced by ϵ cells that produce ghrelin. Following the discovery that ghrelin is expressed in the endocrine pancreas during perinatal life, Dembinski et al. reported a role for ghrelin in pancreatic development. They found that newborn rats exposed to ghrelin for 7 or 14 days had reduced pancreatic weights, attenuated pancreatic DNA synthesis and reduced DNA content [6]. Remarkably, similar ghrelin injections in older rats lead to the opposite effects (*i.e.*, increased pancreatic weights, DNA synthesis and DNA content) [6]. These data highlight the ability of ghrelin to induce biphasic effects on gastric growth depending on the age of exposure. Similar effects have been observed in the stomach, in which chronic neonatal ghrelin injections reduce gastric growth, as evidenced by a decrease in gastric weight, DNA synthesis and DNA content.

Conversely, ghrelin injections in adults increase gastric weight, DNA synthesis and DNA content [32].

Ghrelin's Effects on the Developing Hypothalamus

The central function of ghrelin in adults is to promote feeding. However, accumulating evidence suggests that there are physiological differences in the regulation of energy balance between adults and neonates. In sharp contrast to the effects of ghrelin on adults, exogenous ghrelin does not significantly promote food intake in the first 2–3 postnatal weeks. More specifically, Piao and colleagues have shown that acute ghrelin injections do not induce weight gain in rats until P20 [21]. We also found that a systemic ghrelin injection does not promote weight gain in a P10 mouse neonate (Fig. 2). One possible explanation for the inability of ghrelin to promote feeding in early life is that the brain, which normally conveys the feeding effects of ghrelin, may be relatively insensitive to ghrelin during neonatal life. However, GHSRs are found in the nuclei known to regulate feeding, including in the ARH, (Fig. 2) and recent findings suggest that hypothalamic neurons can respond to exogenous ghrelin during postnatal life. For example, acute peripheral ghrelin treatment activates ARH neurons during early postnatal life, as evidenced by the presence of cFos-immunoreactive (-IR) cells in the ARH 120 minutes following ghrelin administration in P10 mice (Fig. 2). Additionally, the mRNA levels of *Proopiomelanocortin* (*Pomc*) and *Neuropeptide Y* (*Npy*) mRNA, two metabolically relevant neuropeptides in the ARH, are decreased and increased, respectively, in the ARH following ghrelin administration to mouse pups at P10 (Fig. 2). Similarly, ghrelin administration to ARH organotypic explants derived from P7-P9 rats directly increases *Npy* and *Agouti-related peptide* (*Agrp*) mRNA expression [8]. Collectively, these results provide convincing evidence that ghrelin receptors are present and functional in the hypothalamus in the postnatal period. These data further suggest that the “ghrelin insensitivity” observed in this developmental period may be due to a failure of hypothalamic neurons to relay ghrelin signals to other parts of the brain to initiate feeding.

Effects of Ghrelin on Brain Growth and Neurogenesis

The brain undergoes tremendous growth beginning early in gestation and continuing throughout the postnatal period. During this developmental period, a variety of processes shape the brain nuclei. The cellular mechanisms proposed to explain the formation of brain circuits fall into five main categories: neurogenesis, neuronal migration, cell death, axonal growth, and synapse formation. Much of what we know about the role of ghrelin in brain development has been inferred from classic studies using experimental tools such as the thymidine analog bromodeoxyuridine, which monitors cell proliferation and neurogenesis. These studies have clearly demonstrated that the exposure of neural cells derived from a variety of brain regions to ghrelin promotes cell proliferation. For example, when cells from the traditional ghrelin target areas of the adult brain (*i.e.*, the hypothalamus, dorsal motor nucleus of the vagus, and nucleus of the solitary tract) are incubated *in vitro* with ghrelin, cell proliferation increases in a dose-dependant manner [12, 36, 37]. Importantly, many of the resultant newborn cells acquire a neuronal and/or glial phenotype. Also, the neurogenic effects of ghrelin appear to be widespread, because ghrelin can also induce cell proliferation in the developing spinal cord *in vitro* [25]. These same *in vitro* studies further showed that ghrelin exerts its maximal neurogenic effect on fetal neural tissues. Exposure of either cultured spinal cord or hypothalamic cells to ghrelin markedly increases cell proliferation, but these effects were greater when the cells were taken from E17 embryos instead of P2 pups [12]. Intriguingly, both acyl and des-acyl ghrelin promote cell proliferation and neurogenesis, with the acylated form of ghrelin exerting greater proliferative effects as opposed to the acylated form of ghrelin [18, 25]. These observations suggest that the proliferative effects of ghrelin do not require the octanoic acid modification of ghrelin, and

that ghrelin acts through both a GHSR-dependent and GHSR-independent mechanisms to mediate its neurodevelopmental effects.

Conclusions

In conclusion, this relatively new area of research has provided convincing evidence that the effects of ghrelin extend well beyond those originally described in adults. It is now clear that, in addition to its regulatory role in mature animals, ghrelin acts as a signal that can influence developmental processes in a variety of organs including the pancreas, gastrointestinal tract, and brain (Fig. 1). However, more research is needed to gain a better understanding of the cellular and molecular mechanisms mediating the effects of ghrelin on perinatal growth and development, and the periods of maximal sensitivity of various organs to changes in ghrelin levels. Nevertheless, by affecting the development and function of a variety of organs, ghrelin may be a major signal mediating perinatally acquired predispositions to adult diseases

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation list

AgRP	agouti-related peptide
ARH	arcuate nucleus of the hypothalamus
E	embryonic day
GHSR	growth hormone secretagogue receptor
IR	immunoreactive
NPY	neuropeptide Y
P	postnatal day
POMC	proopiomelanocortin
PVH	paraventricular nucleus of the hypothalamus
VMH	ventromedial nucleus of the hypothalamus

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Highlights

- Ghrelin and GHSRs are expressed in the developing embryo and fetus.
- Ghrelin influences perinatal growth.
- Alterations in perinatal ghrelin levels cause structural differences in the pancreas, gastrointestinal tract, and brain.

Figure 1. Primary sites of expression and developmental effects of perinatal ghrelin

Ghrelin immunoreactivity (*green fluorescence*) is detected in both the pancreas and stomach of P10 mouse pups (A, B). Postnatal stomach ghrelin expression increases gradually to reach adult-like levels by 3–5 weeks of life (A). Meanwhile, pancreatic ghrelin expression declines progressively and is barely detectable in the adult pancreas (B). See Supplemental Online Material for detailed methods. Instead of regulating food intake, perinatal ghrelin appears to be an important signal for the growth and development of various tissues, including the pancreas, gastrointestinal tract, and central nervous system (C).

Figure 2. Ghrelin acts on appetite-related brain regions during neonatal life

In contrast to adults, acute ghrelin injection in P10 mouse pups does not result in changes in body weight (A). However, neurons located in the arcuate nucleus of the hypothalamus (ARH) contain GHSR immunoreactivity (*red fluorescence*) at P10 (B). Ghrelin increases the number of cFos-immunopositive cells (a marker of neuronal activation) in P10 ARH neurons 120 min after ghrelin injection (2 mg/kg, i.p.) (C). Acute ghrelin injection (2 mg/kg, i.p.) also increases *Npy* mRNA expression (D), while it decreases *Pomc* mRNA expression (E) in the hypothalamus of P10 mice. See Supplemental Online Material for detailed methods.

Table 1

Expression of *ghrelin* and *Ghsr* mRNA in peripheral and central tissues during perinatal development.

Organ	Ages	References
<i>Ghrelin mRNA</i>		
pancreas	E20	[4]
stomach	E20	[4]
gut	P2, P5, P10, P12	[30]
pituitary	P2, P5, P10, P12	[30]
lung	E12, E15, E17, E19, E21	[24]
gonads	P15	[29]
<i>Ghsr mRNA</i>		
skin	E14, E15, E17, E19	[12, 18]
bone	E14, E15, E17, E19	[12, 18]
eye	E14, E15, E19	[18]
heart	E14, E15, E17, E19	[12, 18]
lung	E14, E15, E19	[18]
liver	E14, E15, E17, E19	[12, 18]
stomach	E14, E15, E17, E19, P2	[12, 18]
intestine	E14, E15, E17, E19, P2	[12, 18]
kidney	E19	[18]
spleen	E19	[18]
testis	E19, P15	[18, 29]
ovary	E19	[18]
pituitary	E19	[12, 18]
spinal cord	E14, E15, E17, E19, P2	[12, 18]
brain	E14, E15, E17, E19, P2	[12, 18]