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Review

Ghrelin and its biological effects on pigs

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ABSTRACT

Ghrelin is a 28 amino acid peptide, which produces its marked effects through binding to the endogenous ligand of the growth hormone secretagogue receptor (GHS-R). Based on the contemporary literatures, it was shown that ghrelin was involved in a series of biological functions including regulation of food intake, body weight, gastrointestinal (GI) motility, hormone secretion, glucose release, cardiovascular functions, enzyme release, cell proliferation and reproduction in pigs through binding to GHS-R 1a or unidentified receptors. It was also observed that ghrelin induced adipocyte and hepatocyte proliferation of primary cultured piglet. In this paper, recent research on ghrelin structure, distribution, GHS-R receptor, biological functions and its regulatory mechanisms for pigs are presented.

Contents

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1. Introduction

Ghrelin can be found in rat stomach and was regarded as the endogenous ligand specific for growth hormone secretagogue receptor (GHS-R), which was then purified and reported to have stimulating effect on growth hormone (GH) release both *in vivo* and *in vitro* [68]. With the discovery of ghrelin, many scholars and their teams aimed at this peptide study on different species like humans, rodents, livestock species, birds and fish. They indicated that ghrelin was the gut hormone with direct effects [86], and it was also a multifunctional peptide including regulation of feeding behavior [8,18,81,108], neuroendocrine response to stress and hormone secretion [9], tissue growth and development [35,76,113,129], increasing GI motility [5,112], control of cell proliferation [11], energy homeostasis [70,100], hormone secretion [63,67], and modulation of the reproductive axis [32,104]. Recently, the ghrelin peptide was reported that it played an important biological role in attenuating the development of some diseases in rats [22,55,58] and was closely related to human diseases [1,57,72,74,85,110]. In pigs, ghrelin also showed its specific functions compared with other animals. Thus, relevant researches on ghrelin structure, distribution, GHS-R receptor, physiological functions and its regulatory mechanisms in pigs were reviewed in the paper.

2. Structure and distribution of ghrelin

2.1. Structure of ghrelin

Ghrelin is a peptide of 28 amino acids which has two major endogenous forms: a des-acylated form (des-acyl ghrelin) and a form acylated at serine 3 (ghrelin). Acylation is indispensable for ghrelin to bind GHS-R1a and serine 3 residue is n-octanoylated with the n-octanoylation at Ser-3 which is essential to stimulate GH release [68]. Ghrelin is found in mammalian species as well as nonmammalian species. Moreover, ghrelin structure, particularly that of the acyl-modification regions, is highly conserved throughout vertebrate species [25,69]. Porcine ghrelin is derived from a 118-residue prepro-peptide by post-translational cleavage, and it is the 25–52 peptide segment of prepro-ghrelin (Fig. 1).

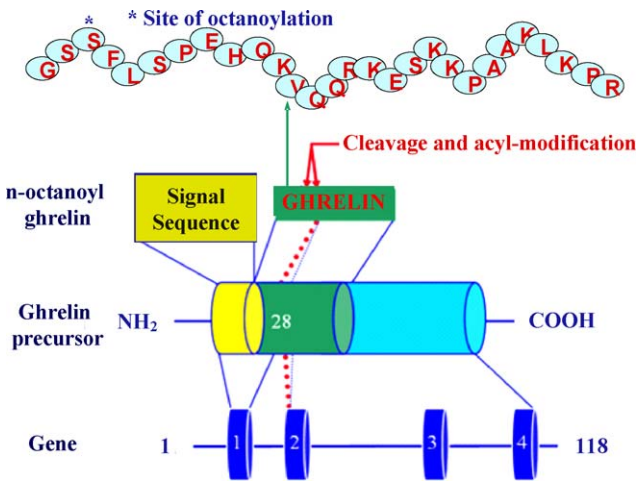

Fig. 1. Gene and amino sequences of porcine ghrelin. Porcine ghrelin derives from a 118-residue ghrelin precursor by post-translational cleavage, and is a peptide from 25 to 52 segment of ghrelin precursor. Porcine ghrelin has 28 amino acids which can be acylated at serine 3. Gene and amino sequences of porcine ghrelin are quoted from GenBank accession (no. AF308930).

2.2. Distribution of ghrelin

Ghrelin was expressed abundantly in stomach, pituitary [68] and arcuate nucleus in rats [73]. By means of semi-quantitative RT-PCR, Raghay et al. found that the ghrelin molecule was expressed in adrenal gland and pheochromocytomas in humans and rats [89]. Des-octanoylated ghrelin and n-octanoylated ghrelin were both found in rat stomach [107]. The latest reports showed that ghrelin producing cells had an abundant expression in stomachs of cow, sheep, pig and horse, especially in the cardiac and pyloric region of pig stomach [51], which was also found in porcine GI tract [117].

Ghrelin mRNA expression was up-regulated 10 days after weaning in the gastric fundus of piglets [28]. The distribution of Ghrelin mRNA was discovered in hypothalamus, stomach, duodenum, jejunum, ileum, liver, kidney, heart and pancreas of pig aged 90 days and postnatal pig [121]. Following their initial reports, Yang and his colleagues extracted a 282 bp ghrelin mRNA fragment by RT-PCR from the tissue of pigs, and they cloned this ghrelin gene [122]. Due to the wide expression of ghrelin in human and animal bodies, the ghrelin could be considered as a multifunctional peptide under many physiological conditions.

3. Regulation of ghrelin expression and secretion

3.1. Ghrelin secretion and expression in fed or fasted animals

The previous reports showed that ghrelin mRNA expression in the gastric fundus increased, but ghrelin peptide content decreased after a 48 h fast. The plasma ghrelin concentration in the gastric vein and systemic venous blood increased in 24 h and 48 h fasted rats. Both values returned to control levels after refeeding [107]. The plasma ghrelin concentration in cows decreased significantly at the moment of 1 h after feeding, and then recovered to pre-feeding levels [51]. Salfen et al. tested the weaned pigs with feed deprivation, and the evidence that while the level of ghrelin in serum became higher was provided, the expression of ghrelin mRNA tended to be lower in stomachs, pituitary glands, and hypothalami [95] of pigs. Starvation increased plasma ghrelin level in prepuberal gilts [44].

3.2. Nutrient and ghrelin secretion

Nutrient contents are much more important factors for the regulation of ghrelin expression and release. Dietary supplementation with zinc oxide enhanced ghrelin production from gastric mucosal cells of piglets at the post-transcriptional level [123]. With oral infusion of tryptophan in weanling pigs, Zhang et al. revealed that ghrelin mRNA was increased in gastrointestinal mucous membrane and ghrelin level was increased in the plasma [125]. Growing swine infused with a low dose of morrhuate sodium selectively into the left gastric artery showed a significant increase in serum ghrelin values, but at a higher dose, the mean baseline ghrelin values decreased [3]. In 2008, Arepally et al. took an intimate research and indicated that catheter-directed gastric artery chemical embolization (GACE) resulted in suppression of systemic ghrelin levels during the 4 weeks study [4].

3.3. Hormonal regulation of ghrelin expression and secretion

Hormones are important factors of regulating ghrelin expression and secretion. The ghrelin mRNA level in the rat stomach increased after the administration of insulin and leptin

[107]. Rak and Gregoraszczuk studied the effect of GH and insulin-like growth factor (IGF-I) on ghrelin synthesis and secretion in cultured whole porcine follicles, and it was demonstrated that GH stimulated both ghrelin synthesis and secretion in the ovarian follicles, whereas IGF-I showed less influence [90]. After intravenous (IV) injection of peptide YY (PYY) (3–36) in castrated male pigs, plasma acyl-ghrelin levels did not show a significant change [60].

Fig. 2. Alignment of amino acid sequences of pig, human, rat, and chicken GSH-R. GSH-R has two forms: GHSR-1a and GHSR-1b. The GHSR-1a gene sequences are quoted from GenBank accession (nos. U60178, NM198407, U94321, and AB095996), and GHSR-1b are from GenBank accession (nos. U60180, NM004122, and AB095997).

4. Ghrelin receptor

4.1. GHS-R structure

In 1996, Howard and his colleagues isolated a receptor in pituitary and hypothalamus, which was unique for GHS action on GH release [56]. The seven transmembrane GHS receptor (GHS-R) has a high degree of homology ranging from 93% to 99% identity by the molecular analysis of human, pig, dog, rat and mouse [25]. Porcine GHS-R has two forms: GHSR-1a consists of 366 amino acid peptides, and GHSR-1b encodes 289 amino acids (Fig. 2).

4.2. GHS-R activity

With this chronology, discussion on the activity of GHS-R peptides would be followed by the physiology of ghrelin focused primarily on livestock species [99]. Ghrelin endocrine activities depend entirely upon the acylation and are mediated by GHSR-1a, but des-acyl ghrelin does not bind to GHSR-1a. After acute treatment of porcine pituitary cell cultures with ghrelin, Luque et al. found that ghrelin down-regulated GHS-R expression and showed its functions through this factor [78]. Using RT-PCR and Western Blots, Rak et al. found the expression of GHS-R 1a in cultured whole porcine follicles [91]. They also indicated that ghrelin induced estradiol secretion, cell proliferation through the binding to GHS-R 1a, but it decreased caspase-3 activity which was independent of GHS-R 1a [91]. Other studies showed that ghrelin gene product might act as a survival factor for the cardiovascular system and glucose release in primary cultured porcine hepatocytes through binding to novel, yet being identified receptor, but it is distinct from GHSR-1a [11,38]. Overall, the receptor of ghrelin in pigs needs further investigation.

5. Physiological functions of ghrelin

Administration of ghrelin to pigs has been implicated in the regulation of food intake, body weight, gastrointestinal (GI) motility and growth hormone (GH) secretion, glucose release, cardiovascular functions, enzyme release, cell proliferation and reproduction *in vitro* or *in vivo* (Table 1).

5.1. Effects on food intake

Ghrelin is an appetite-stimulatory signal from stomach, with the effect of activating brain appetite centers, and participating in the control of food intake and the long-term regulation of body weight of rodents [75,109,118] and humans [10,124]. If ghrelin can decrease the period of weaning anorexia and increase body weight gain during the weaning period, pigs will potentially be able to improve resistance to pathological and environmental challenges during this period, and fewer days will be required to reach the slaughter weights [17]. Weaned pigs intravenously infused three times daily for 5 days with human ghrelin, were found to induce positive weight gain and increase eating times compared with that of the saline-infused controls [96]. In growing pigs immunized against ghrelin, the researchers concluded that ghrelin with interaction with its receptors decreased food intake by 15% and body weight gain by 10% compared with the control pigs [115]. These observations suggest that exogenous ghrelin has a variety of endocrine effects and shows potential in increasing body weight gain during weaning, but ghrelin may also negatively influence the food intake and weight gain in growing pigs at different levels.

5.2. GH secretion

Ghrelin plays an important role in GH secretion. Earlier experiments revealed that ghrelin peptide exerted very potent and specific GH-releasing activity *in vitro* and *in vivo* in rats [21,62,106,120] and humans [7,27,50,88,101]. Another study reported that central administration of ghrelin in goats dramatically increased plasma GH concentration dose-dependently [51].

More recently, the effects and mechanisms of ghrelin inducing GH secretion were studied in pigs *in vitro* and *in vivo*. *In vitro*, ghrelin showed to be potent at eliciting a GH release from porcine

Table 1
Physiological functions of ghrelin in pigs.

Model	Types of ghrelin	Experimental treatment	Physiological functions	References
Weaning piglets	Ghrelin	Intravenous infusion	Stimulate gastric acid secretion	[28]
Gastric mucosal cells	Ghrelin	Cell culture *in vitro*	Stimulate both mRNA expression and activity of H+-+-ATPase	[28]
Porcine ovarian follicles	Ghrelin	Cell culture *in vitro*	Decrease cells apoptosis Increase estradiol secretion and aromatase activity	[90]
Primary porcine hepatocytes	Ghrelin Des-acyl ghrelin	Suspension culture	Stimulate glucose output Inhibit glucose release	[38]
Weaned pigs	Ghrelin	Intravenous infusion	Increase weight gain and eating times Increase GH concentration	[96]
Growing pigs	^{125}I-ghrelin	Active immunization against ghrelin	Decrease food intake and weight gain Increase GH concentration	[115]
Porcine adenohypophyseal pituitary cells, somatotropes	Ghrelin	Cell culture *in vitro*	Induce GH release	[41,42,49,77,79,92]
Pregnant and lactating sows	Ghrelin	Validated radioimmunoassay	Unaffect GH, leptin, and IGF-1 secertion	[45]
Anesthetized Pigs	Ghrelin	Intracoronary infusion	Cause coronary vasoconstriction	[102]
Porcine coronary arteries	Ghrelin	Cell culture *in vitro*	Block Hcy-induced endothelial dysfunction Improve eNOS expression, Reduce oxidative stress	[52]
Porcine ovarian granulosa cells	Ghrelin	Cell culture *in vitro*	Reduce MAP3K5 activity Promote cell proliferation	[98]
Piglet adipose and hepatocyte	Ghrelin	Cell culture *in vitro*	Stimulate cell proliferation	Unpublished observation
Porcine dispersed pancreatic acinar cells	Pentaghrelin	Cell culture *in vitro*	Stimulate amylase release	[46]
Virginal gilts	Ghrelin	Semiquantitative RT-PCR and immunohistochemical method	Integrate energy balance and reproduction	[128]
Porcine *in vitro*- fertilized (IVF) and parthenogenetic embryos	Ghrelin	Cell culture *in vitro*	Enhance the pre-implantation development of porcine IVF and parthenogenetic embryos	[11]

adenohypophyseal cells [49] and porcine ovarian follicles. Furthermore, the effects depended on existence of GHSR-1a [90]. The findings indicated that ghrelin peptide induced GH release from pig pituitary cells through calcium channels and sodium channels [41,42] or under inositol phosphate-, and Ca2 + -dependent signaling routes [77,79], and ghrelin could increase GH secretion in cultured pig somatotropes [92] via cGMP-dependent mechanisms. Rak et al. found that ghrelin increased GH secretion but not GH synthesis by ovarian follicles. *In vivo*, the IV infusion of ghrelin increased serum ghrelin, GH, insulin and cortisol concentrations, whereas serum IGF-1 decreased in these weaned pigs [95,96]. Concentrations of GH were increased in ghrelin immunized growing pigs [115]. Ghrelin concentrations in sow maternal circulation did not play an important role in maintaining circulating GH levels during lactation [45]. Moreover, ghrelin was not associated with leptin, NEFA and IGF-1 levels [45]. The different results in sows may be produced by their special physiological stage.

5.3. Gastrointestinal activities

Produced in stomach and secreted into blood plasma, ghrelin plays a physiological role in the regulation of gastrointestinal motility. The former information showed that *in vitro* or *in vivo* ghrelin could accelerate gastric emptying and regulate gastric phase III-like contractions in rodents [6,24,65,111]. Further studies suggested that des-acyl ghrelin and acylated ghrelin, although they were derived from the same precursor, had the inverse effects on gastric emptying and small intestinal transit and motility through different receptors [19,33,34].

In weaned piglets, ghrelin acted on gastric mucosal cells to stimulate gastric acid secretion *in vivo* and *in vitro* [28]. After birth, while the gastrointestinal tract of piglets undergoes substantial developmental changes in structure and function resulting in adaptation to new dietary conditions, GI tract development is often disturbed [53,71,82], so the contribution of ghrelin to gastrointestinal tract development is of value.

5.4. Glucose release

Ghrelin or des-acyl ghrelin administration increased plasma glucose and were involved in glucose metabolism in humans and rats [14,83,114,127]. IV injection of ghrelin also increased plasma glucose concentrations in adult cows, especially in lactating cows [59]. After primary porcine hepatocyte culturing with acylated ghrelin and des-acyl ghrelin, Gauna et al. indicated that glucose output by primary hepatocytes was time- and dose-dependently stimulated by ghrelin and inhibited by des-acyl ghrelin [38]. Moreover, des-acyl ghrelin counteracted the stimulatory effect of acylated ghrelin on glucose release [38]. These findings of ghrelin in pigs are consistent with data from studies in humans and other animals, which suggest that ghrelin is likely to play a negative role in glucose metabolism, but differences for the des-acyl ghrelin indicate the further studies in this area.

5.5. Cardiovascular functions

The peptide ghrelin was linked to cardiovascular functions. Ghrelin was observed to have treatment-potential for severe chronic heart failure (CHF) and cardiac cachexia based on anti-cachectic and cardio-protective effects [2]. Schwenke et al. found that early ghrelin treatment prevented the increase in cardiac sympathetic nerve activity (CSNA) after acute myocardial infarction (MI) and improved cardiac function in rats [97]. Ghrelin either in acylated or unacylated forms showed contractile effect on guinea pig papillary muscle and renal artery [26], and affected simultaneously the function of vascular smooth muscle [84]. Intracoronary infusion of ghrelin primarily caused coronary vasoconstriction in pigs, mechanisms of the response were shown to involve the inhibition of a vasodilatory beta (2)-adrenergic receptor-mediated effects related to the release of nitric oxide [46]. The new study showed that ghrelin had a protective effect on the porcine coronary artery by blocking homocysteine (Hcy)-induced endothelial dysfunction, improving endothelial nitric oxide synthase (eNOS) expression, and reducing oxidative stress. The effect of ghrelin was dependent on its binding to GSH-R receptor [52]. The direct ghrelin involvement in cardiovascular (CV) system homeostasis suggests that ghrelin mediates CV activities in animals and humans, and ghrelin can be considered as a possible therapeutic target under many pathological conditions associated with CV damage and remodeling.

5.6. Cell proliferation and apoptosis

Ghrelin is involved in cell proliferation and apoptosis through different pathways. For example, ghrelin promotes human aortic endothelial cell (HAEC) proliferation via ERK1/2 and PI3K/Akt activation [93], but inhibits angiotensin II-induced human aortic smooth muscle cells (HASMC) proliferation and contraction via the cAMP/PKA pathway [94]. Ghrelin and des-acyl ghrelin inhibited apoptosis of primary adult and H9c2 cardiomyocytes and endothelial cells *in vitro* through activation of extracellular signal-regulated kinase-1/2 and Akt serine kinases [11]. Zhan et al. suggested that ghrelin inhibited both the proliferation and apoptosis of rat vascular smooth muscle cells (VSMCs) [130]. Ghrelin was also reported to cause a facilitative effect on cell proliferation by ovarian follicle which was dependent of its binding to GHSR-1a, while inhibitory effect on cellular apoptosis was reported to be independent of its binding to GHSR-1a [90,91]. Ghrelin reduced apoptosis-related substance-MAP3K5 accumulation and promoted the cell proliferation in porcine ovarian granulosa cells [98]. We have evaluated the effect of porcine ghrelin on cell proliferation in primary cultures of piglet adipocyte and hepatocyte. The investigation showed that this peptide could stimulate proliferation of those cells (unpublished observation). Thus, the effects of ghrelin on cell proliferation and apoptosis indicate that ghrelin may be a protective factor against damage towards body function.

5.7. Enzyme release

Ghrelin is also involved in enzyme release, but the regulatory mechanisms are unknown. Intraduodenal (ID) infusion of ghrelin stimulates pancreatic enzyme secretion in the rat [87]. Jankowska et al. tested cells from rats and pigs and found that ghrelin with maximum 10–9 M hardly inhibited the amylase release from pancreatic acinar cells in rat preparations [61]. However, ghrelin stimulated amylase release from porcine acinar cells by the doses within a range of 10^{-10} and 10^{-7} M but it had no effect on the dose related response [61]. The increase in aromatase activity was noted in ghrelin-treated whole porcine follicles [90]. These results could be implicated in the stimulatory effect of ghrelin on the pancreatic and gonadal exocrine functions.

5.8. Reproduction

The previous studies showed that ghrelin gene was expressed in human [39,43], mouse testis [102], and rat Leydig cells and ovary [15,105]. Accordingly, the mRNA and peptide of the putative ghrelin receptor GHS-R was also found in human [39,40] and rat [12,105] testis tissue. The expression of ghrelin and its receptor appear in reproductive system, which indicts that circulating

ghrelin might contribute to the functional control of the reproductive axis, but the action of ghrelin upon the axis is complex, and needs further elucidation. In rodent models, the investigations indicated that administration of ghrelin under different conditions inhibited luteinizing hormone (LH) [29–31,36,47,80,103] and gonadotropin-releasing hormone (GnRH) secretion [30] *in vivo*, whereas follicle-stimulating hormone (FSH) remained unaffected [31]. *In vitro*, ghrelin dose-dependently stimulated basal LH and FSH secretion by pituitary tissue [30,31], but this required the presence of NO and was modulated by ovarian signals [31]. Moreover, ghrelin might decrease LH responsiveness to GnRH *in vitro* [103]. In mice, ghrelin had an inhibitory role in preimplantation development of murine embryos *in vitro* [13,37,64].

In pig, ghrelin mRNA and immunoreactive cells were found in virginal gilt hypothalamo-pituitary-ovary axis by semiquantitative RT-PCR and immunohistochemical method, and the levels of ghrelin changed during the estrous cycle [128]. Ghrelin could enhance the total cell numbers of the *in vitro* fertilized (IVF) and parthenogenetic embryos of pig but decrease the proportion between inner cell mass (ICM) and total cell numbers [126]. Ghrelin increased prostaglandin F (PGF), and E (PGE) secretion in porcine ovarian granulosa cells cultured with ghrelin [98]. Rak and Gregoraszczuk demonstrated that ghrelin induced estradiol secretion, cell proliferation and decrease caspase-3 activity [91]. These findings in animals suggest that ghrelin plays a complex role in the action of the hypothalamo–gonadotropic–gonadal axis, which is relevant for reproduction.

5.9. Other functions

Furthermore, many studies have indicated that ghrelin may participate in the regulation of water intake [48], sleep [66], myometrial activity [54], intramembranous bone repair [23], immune functions [116], sympathetic nervous activity [119], memory and anxiety [16] in humans and rats, but these results are still unreported in pigs. All the findings in other species open up a new era in our understanding of the regulatory mechanisms and biological functions of ghrelin in pigs.

6. Ghrelin secretion and regulatory mechanisms in pigs

Ghrelin was first detected in stomach and was identified as a peripheral metabolic signal informing the brain about nutrient load in the stomach. Ghrelin secreted by the stomach has paracrine or endocrine effects on feeding behavior and GI motility or it circulates in the blood and acts on other target tissues. The new studies demonstrated that peripheral ghrelin induced the fasted motor activity by activating the NPY neurons in the brain, and probably it was the vagal afferent neuron with the ghrelin receptors [34]. Desacyl ghrelin decreased food intake and gastric emptying rate through an action on the paraven-

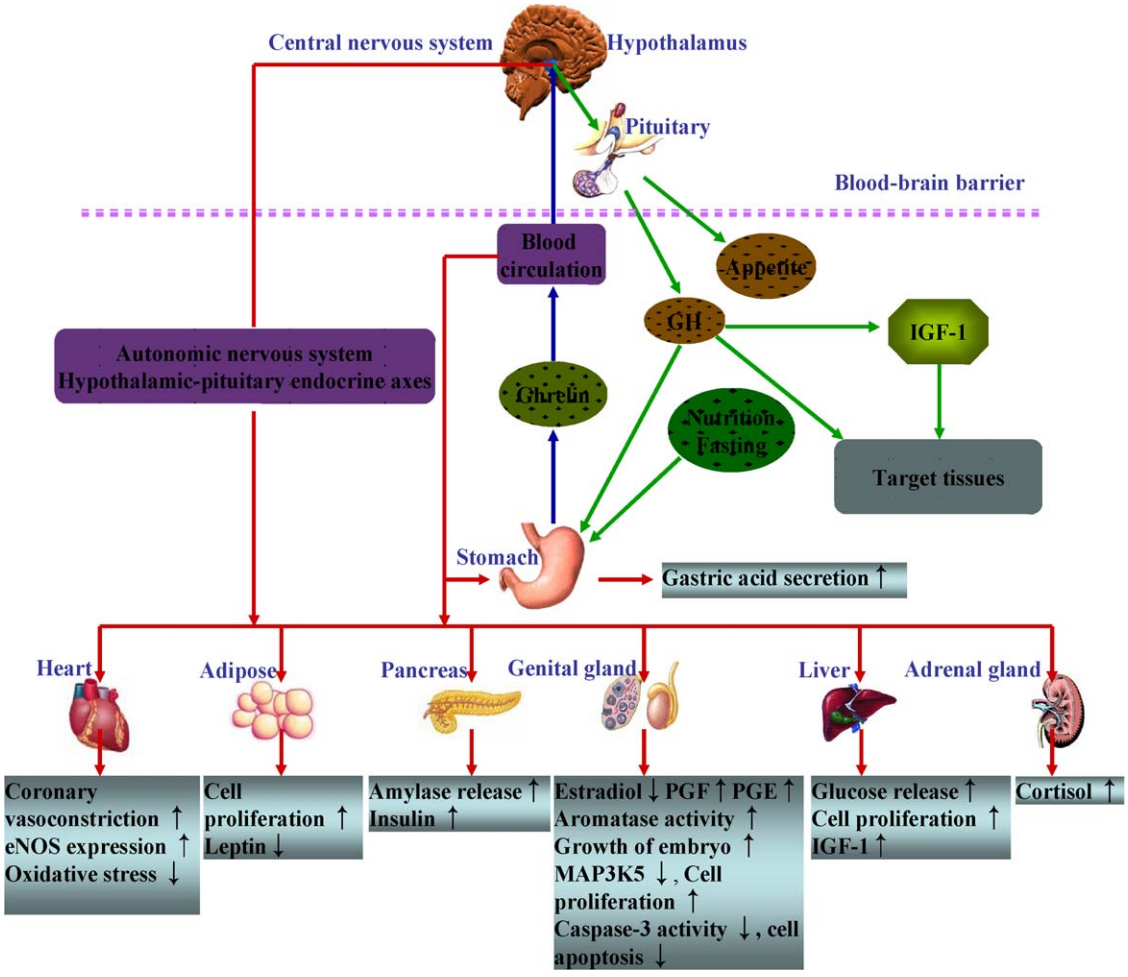

Fig. 3. Ghrelin secretion and regulation mechanisms in pigs. Apart from in the stomach, ghrelin is secreted in a variety of peripheral tissues, although at very low concentration. Paracrine ghrelin secretion from pancreatic cells might be of importance for insulin secretion and cell proliferation. Ghrelin secreted by the stomach has paracrine or endocrine effects on GI motility or circulates in the blood that acts on other target tissues. The functions of ghrelin are mediated by the autonomic nervous system as well as the hypothalamic-pituitary endocrine axis.

tricular nucleus and the arcuate nucleus in the hypothalamus [8]. Chen et al. provided compelling evidence that peripheral ghrelin acted through binding to hypothalamic neuropeptide Y (NPY)/agouti-related peptide (AgRP) and proopiomelanocortin (POMC) neurons to stimulate feeding [20]. Ghrelin exerted its effects on GI motilily through NPY Y2 or Y4 receptors in the brain, and corticotrophin-regulating factor (CRF) type 2 receptors in the brain mediated the action of des-acyl ghrelin.Vagal afferent pathways might be involved in the action of ghrelin, but not involved in the action of des-acyl ghrelin [33]. Ghrelin stimulated growth hormone release and appetite via the hypothalamus. Peripheral des-acyl ghrelin induced this function through binding to CRF 1 receptor by crossing the blood-brain barrier [19]. Without the action of hypothalamus, ghrelin peptide would induce GH release from cultured cells through calcium channels and sodium channels [41,42] or under inositol phosphate-, and Ca2 + -dependent signaling routes [77,79], or via cGMP-dependent mechanisms [92]. Ghrelin affected cell proliferation via ERK1/2 and PI3K/Akt activation [93], or the cAMP/PKA pathway [94].

Apart from the stomach, ghrelin is secreted in a variety of peripheral tissues, although it is at very low concentration in these tissues. Paracrine ghrelin secretion from pancreatic cells might be of importance for insulin secretion and cell proliferation. The functions of ghrelin are mediated by the autonomic nervous system as well as the hypothalamic-pituitary endocrine axis. Ghrelin secretion and its regulation mechanisms in pigs are shown in Fig. 3.

7. Conclusions

Ghrelin plays a crucial role in the regulation of the hypothamic–pituitary–gonadal axis of different animal species. In pigs, ghrelin also exerts great influence on the regulation of growth and development, but data on this are limited and they only focus on food intake, GH secretion, gastrointestinal activities, glucose and enzyme release, cardiovascular functions, cell proliferation and reproduction. Many biological functions and their mechanisms of action have been implicated in other species such as human, fish and bird, but they are still unknown in pigs. So, further research on this species needs to be performed in order to gain a better understanding of ghrelin peptide.

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